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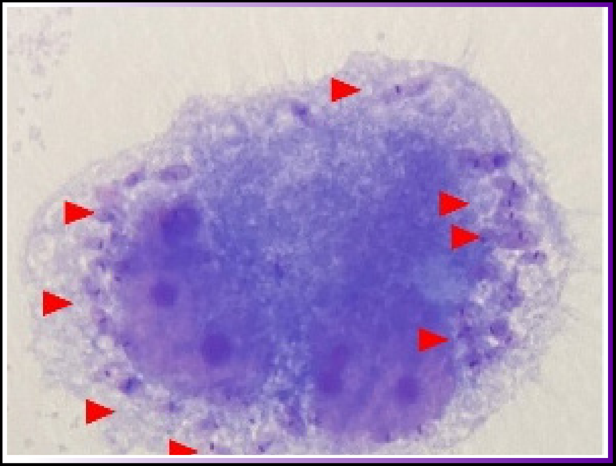

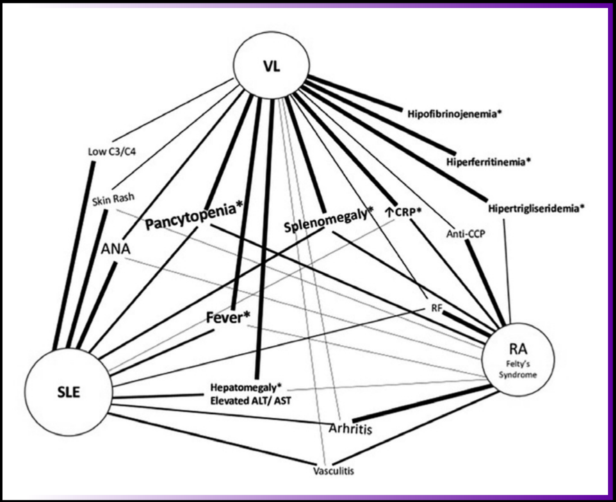

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EDİTÖRDEN

2026 yılının ikinci sayısını biri yurt dışından olmak üzere 6 özgün araştırma makalesi ve 2 derleme ile çıkarmaktayız. Özgün çalışmalar arasında, anti-leishmanial ilaçların denendiği bir laboratuvar çalışması yanı sıra, epidemiyolojik olarak da Balıkesir ilimizdeki kistik ekinokokkoz prevalansı, Sivas ilimizdeki pediatrik hastalardaki kistik ekinokokkozun durumu, Siirt ilimizde koyun ve keçilerdeki karaciğer trematodlarının yaygınlığı ile Yozgat ilindeki uyuz olguları hakkında çalışmalar bu sayımıza eklenmiştir. Ayrıca İran'da önemli bir sivrisinek türünün genetik çeşitliliğini ortaya koyan bir çalışma da yer almaktadır.

Derleme olarak ise; visseral leishmaniasis ile romatizmal hastalıklar arasındaki ilişkiyi açıklayan bir yazı ile insanlarda görülen fasciolosisin bilinenden daha yaygın olduğu konusunda yapılan araştırmaların derlendiği bir yazı sunulmaktadır.

Dergimizin ESCI için de başvurusu yeniden yapılmış olup sonucu beklenmektedir. Bu sürece büyük katkısı olan ve gönderilen makalelere özveri ile hakemlik yapan, bu sayının sonunda da listesi yayınlanan akademisyenlerimize de teşekkür etmek ve minnetlerimi sunmak isterim.

SCI/SCI-Expanded kapsamındaki dergilerde yapacağınız yayınlarda dergimizde yer alan makalelere atıf yapılmasının, dergimizin bu indekse başvuru/kabul sürecinde büyük önem taşıdığını yeniden belirtmek isterim. Bilim alanımızın en önemli unsurlarından ve bizleri güçlendiren araçlarından biri olan "Türkiye Parazitoloji Dergisi"nin bu sayısının da bilimsel çalışmalarınıza ve birikimlerinize katkı sağlamasını umuyorum.

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Quantitative Analysis of the Intracellular Efficacy of Conventional Antileishmanial Drugs Against *Leishmania tropica*: A Translational Approach Using the THP-1 Macrophage-Amastigote Model

Konvansiyonel Antileishmanial İlaçların Leishmania tropica'ya Karşı Hücre İçi Etkinliğinin Kantitatif Analizi: THP-1 Makrofaj-Amastigot Modelinde Translasyonel Bir Yaklaşım

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ABSTRACT

Objective: This study aimed to quantitatively assess the intracellular susceptibility of *Leishmania tropica (L. tropica)* to conventional antileishmanial drugs using the parasite rescue and transformation assay (PRTA), which involves controlled lysis of infected THP-1 macrophages, release of viable amastigotes, their transformation into promastigotes under defined *in vitro* conditions, and subsequent luminometric analysis.

Methods: *L. tropica* (MHOM/TR/2007/CBU001) promastigotes were cultured in Novy-MacNeal-Nicolle and Schneider's insect medium; THP-1 cells were cultured in RPMI-1640. PMA-differentiated THP-1 macrophages were infected to establish the macrophage-amastigote model. Intracellular susceptibility to five conventional drugs (amphotericin B, miltefosine, pentamidine, sodium stibogluconate, and meglumine antimoniate) was evaluated by PRTA through luminometric quantification (CellTiter-Glo®) of transformed promastigotes, with microscopic enumeration of amastigotes in Giemsa-stained slides used for validation. Inhibitory concentration 50 (IC50) values were calculated from dose-response curves and compared using Student's t-test and Pearson's correlation coefficient.

Results: Amphotericin B and pentamidine showed the highest efficacy; miltefosine demonstrated moderate activity; antimonials exhibited relatively low efficacy. IC50 values obtained by luminometric and microscopic methods were highly concordant: the paired t-test revealed no significant difference ($t=0.2172$, $p=0.8387$), and Pearson's correlation confirmed a strong positive relationship ($r=0.9944$, $p=0.005$).

Conclusion: Luminometric analysis of transformed promastigotes provides accuracy comparable to that of microscopic enumeration of intracellular amastigotes, while being more efficient in time, labor, and resources. By enabling functional assessment of parasite metabolism, supporting high-throughput and automation with low operator dependency, this standardized method represents a reliable, scalable, and translationally relevant platform with strong clinical predictive value, particularly for species-specific models such as *L. tropica*

Keywords: *Leishmania tropica*, intracellular drug susceptibility, THP-1, parasite rescue and transformation assay, translational medicine

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ÖZ

Amaç: Enfekte THP-1 makrofajlarının kontrollü lizisiyle serbest bırakılan canlı amastigotların uygun *in vitro* koşullarda promastigot forma dönüşmesine dayanan parazit kurtarma ve dönüştürme testi (PRTA) uygulanarak, dönüşen promastigotların luminometrik analizi ile konvansiyonel antileishmanial ilaçların *Leishmania tropica'ya (L. tropica)* karşı hücre içi duyarlılığının kantitatif olarak değerlendirilmesi amaçlanmıştır.

Yöntemler: *L. tropica* (MHOM/TR/2007/CBU001) promastigotları Novy-MacNeal-Nicolle ve Schneider's insect medium'da, THP-1 hücreleri ise RPMI-1640'ta kültüre edildi. PMA ile farklılaştırılan THP-1 makrofajları promastigotlarla enfekte edilerek makrofaj-amastigot modeli oluşturuldu. Hücre içi ilaç duyarlılığı, beş konvansiyonel ajan (amfoterisin B, miltefosin, pentamidin, sodyum stiboglukonat ve meglumin antimonat) için, dönüşen promastigotların (PRTA) luminometrik analizi (CellTiter-Glo®) ile kantitatif olarak belirlendi. Giemsa boyalı preparatlarda hücre içi amastigotların mikroskobik sayımı ise doğrulama yöntemi olarak kullanıldı. İnhibitör konsantrasyonu 50 (IC50) değerleri doz-yanıt eğrilerinden hesaplandı; yöntemler t-testi ve Pearson korelasyon analiziyle karşılaştırıldı.

Bulgular: Amfoterisin B ve pentamidin en yüksek etkinliği, miltefosin orta düzeyde, antimon bileşikleri ise görece düşük etkinlik göstermiştir. Luminometrik ve mikroskobik yöntemlerle elde edilen IC50 değerleri arasında yüksek düzeyde uyum saptandı; eşleştirilmiş t-testi fark olmadığını (t=0,2172, p=0,8387), Pearson analizi ise güçlü pozitif korelasyonu (r=0,9944, p=0,005) ortaya koydu.

Sonuç: Dönüşen promastigotların luminometrik analizi, hücre içi amastigotların mikroskobik sayımı ile karşılaştırılabilir doğruluk sunarken; zaman, iş gücü ve kaynak açısından daha verimli bir yöntemdir. Canlı parazitlerin metabolik aktivitesine dayalı fonksiyonel ölçüm yapabilmesi, yüksek örnekleme kapasitesi, otomasyona uyumluluğu ve düşük operatör bağımlılığı başlıca avantajlarıdır. Bu yönleriyle yöntem, standardize yapısı sayesinde *L. tropica* gibi türe özgü modellerde klinik öngörü açısından güvenilir, translasyonel araştırmalara uygun ve ölçeklenebilir bir analiz platformu olarak önerilmektedir.

Anahtar Kelimeler: *Leishmania tropica,* hücre içi ilaç duyarlılığı, THP-1, parazit kurtarma ve dönüştürme testi, translasyonel tıp

INTRODUCTION

Leishmaniasis, a zoonotic parasitic disease caused by protozoan parasites of the genus *Leishmania*, is a significant public health problem widely distributed in tropical and subtropical regions. The parasite exhibits a heteroxenous life cycle; the aflagellated amastigote form resides intracellularly within the macrophages of mammalian hosts, whereas the flagellated promastigote form develops in the digestive tract of sand fly vectors belonging to the genera *Phlebotomus* and *Lutzomyia* (1). The World Health Organization estimates that about 350 million people worldwide are at risk of infection. The clinical spectrum ranges from self-healing cutaneous lesions to the visceral form, which is fatal if left untreated (2).

Currently, there is no effective or approved vaccine against leishmaniasis; therefore, disease control relies primarily on chemotherapeutic agents. The most commonly used drugs are pentavalent antimonials, amphotericin B, miltefosine (MLT), and paromomycin (PMD) (3). However, these agents present significant limitations in clinical use due to severe systemic side effects, drug resistance, high treatment costs, and pharmacokinetic constraints. Invasive forms, such as mucocutaneous and visceral leishmaniasis, remain particularly challenging, with treatment success difficult to sustain. Thus, identifying safer, more effective, and affordable compounds, or improving current formulations, is now a major research priority (4).

The success of studies aimed at discovering new antileishmanial compounds depends on the use of highly sensitive, reliable, and translationally relevant screening methods. In this context, the promastigote-based models commonly employed in *in vitro* drug screening have limited physiological validity compared to amastigotes, the natural biological form of the parasite in mammalian hosts (5). Accordingly, intracellular amastigote-based *in vitro* models have gained prominence (5,6). However, classical methods used to apply these models, such as microscopic counting, are time-consuming, operator-dependent, and poorly reproducible. Although modern techniques using fluorescent markers, monoclonal antibodies, transgenic parasites, or colorimetric reagents have been developed, they cannot distinguish viable parasites from dead ones. Moreover, they fail to differentiate between leishmanicidal and leishmaniostatic effects. Furthermore, methods based on radioactive isotopes measure host cell activation rather than direct parasite viability and present significant operational challenges (7). In light of these limitations, there is a need for quantitative approaches capable of directly assessing viable intracellular parasite burden with improved analytical robustness. Parasite rescue and transformation assay (PRTA) has been introduced as one such strategy, based on controlled host-cell lysis, recovery of intracellular amastigotes, and subsequent transformation into promastigotes under defined *in vitro* conditions.

Because only promastigotes derived from viable amastigotes are quantified, PRTA enables selective evaluation of viable parasites. Adenosine triphosphate (ATP)-based luminometric quantification has emerged as a promising complementary approach for measuring metabolically active cells in this context (8).

The study aimed to quantitatively assess the intracellular susceptibility of *Leishmania tropica (L. tropica)*, the causative agent of cutaneous leishmaniasis (CL), to conventional antileishmanial drugs [amphotericin B (AmB), miltefosine, pentamidine (PEN), sodium stibogluconate (SSG), and meglumine antimoniate (MA)] using the PRTA, which involves transforming viable amastigotes released by controlled lysis of infected THP-1 macrophages into promastigotes under appropriate *in vitro* conditions, followed by luminometric analysis of the transformed promastigotes.

METHODS

Ethical Approval

This study was approved by the Health Sciences Ethics Committee of the Faculty of Medicine, Manisa Celal Bayar University (decision no: 20.478.486/3131, date: 07/05/2025). Patient consent was not required, as the study was performed using *L. tropica* strains and THP-1 cells obtained from a parasite bank, without direct use of human clinical specimens.

Preparation of Culture Media

Novy-MacNeal-Nicolle (NNN) medium was prepared with agar, peptone, sodium chloride, and defibrinated rabbit blood; it was supplemented with antibiotics and stabilized at 4 °C. Roswell Park Memorial Institute 1640 (RPMI-1640) (pH 7.2) was enriched with 10% fetal bovine serum (FCS) and antibiotics, stored at 4 °C, and equilibrated before use. Schneider's insect medium (SIM) (pH 5.5) was supplemented with 20% FCS, L-glutamine, and antibiotics, sterilized by 0.22 μm filtration, and stored at 4 °C for use in experiments.

Preparation of Drug Solutions

To assess antileishmanial drug susceptibility, the reference compounds SSG (Pentostam®), MA (Glucantime®), PMD (Chemcruz®), MLT (Calbiochem®), and AmB (Boc Sciences®) were employed. Stock solutions of SSG (100 mg/mL, 100 mL) and MA (1.5 g/5 mL) were prepared in their respective formulations. PMD, MTF, and AmB were solubilized in 100% dimethyl sulfoxide (DMSO) to obtain 10 mM stock solutions. For experimental use, the required working concentrations were generated by diluting the stock solutions in RPMI-1640 medium, while ensuring that the final DMSO concentration did not exceed 0.2%.

Parasite Culture and Maintenance

The *L. tropica* strain (MHOM/TR/2007/CBU001) was isolated from a CL case in Manisa, Türkiye. Parasites were first cultured in NNN medium, then adapted to RPMI-1640 with 10% FCS, 1% gentamicin, and 1% penicillin-streptomycin, and routinely maintained in SIM (pH 5.5) supplemented with 20% FCS and antibiotics at 26 °C. Experiments used promastigotes at ~1×10^8/mL, and long-term stocks were cryopreserved in RPMI-1640 with 10% DMSO in liquid nitrogen.

Culture and Differentiation of the Human Monocytic Cell Line (THP-1)

The THP-1 monocytic cell line (Parasite Bank, Manisa Celal Bayar University, Türkiye) was maintained in RPMI-1640 medium supplemented with 10% FCS at 37 °C in 5% carbon dioxide (CO_2). Cells were subcultured every three days to keep densities below 1×10^6 cells/mL. For differentiation, THP-1 cells (2.5×10^5 cells/mL) were exposed to 100 ng/mL PMA for 24 h, then seeded into 96-well plates, and incubated under standard conditions. After PMA removal and medium replacement, cultures were maintained for 96 h to obtain differentiated macrophages, which were then prepared for cytotoxicity and intracellular drug susceptibility assays (9).

Macrophage-amastigote Infection Model

Differentiated THP-1 macrophages were detached with a sterile scraper, pelleted by centrifugation, and adjusted to 5×10^5 cells/mL. Cells were seeded into flasks, incubated for 24 h at 37 °C with 5% CO_2, and then infected with *L. tropica* promastigotes at a 1:10 ratio. After washing with sterile 1x phosphate-buffered saline (PBS) to remove free parasites, fresh RPMI-1640 was added, and cultures were maintained under the same conditions for 48 h (10).

Intracellular Efficacy of Conventional Antileishmanial Drugs

This study tested MA (500-3.9 μM), SSG (500-3.9 μM), MLT (125-0.98 μM), PEN (31.25-0.24 μM), and AmB (7.8-0.06 μM) at eight concentrations. Stock solutions in RPMI-1640 (10% FCS) were serially diluted (1:2) and dispensed into 96-well plates. *L. tropica*- infected THP-1 macrophages were washed with PBS and then treated with 100 μL medium plus 100 μL drug dilution (final volume 200 μL). Infected, untreated controls were included, and plates were incubated at 37 °C with 5% CO_2 for 48 h. The intracellular susceptibility of standard antileishmanial drugs was evaluated in an *L. tropica*- infected THP-1 macrophage model using both microscopic and luminometric methods (11,12).

Microscopic Quantification of Intracellular Amastigotes

To microscopically assess the susceptibility of intracellular *L. tropica* amastigotes to reference drugs, Giemsa staining-based infection analysis was performed. Infected cells were treated with reference drugs [MA (500-3.9 μM), SSG (500-3.9 μM), MLT (125-0.98 μM), PEN (31.25-0.24 μM), and AmB (7.8-0.06 μM)] for 48 h, fixed with chilled methanol, and stained with Giemsa. Infection was evaluated by counting 100 cells in triplicate to determine the proportion of infected macrophages, the mean number of intracellular amastigotes per cell, and the reduction in infection rate. Inhibitory concentration 50 (IC50) values were subsequently derived through linear regression analysis (11).

Luminometric Assessment of Transformed Promastigotes

To assess the intracellular susceptibility of reference antileishmanial drugs, the PRTA was applied, in which parasite viability was quantified through luminescence signals (RLU) generated by the ATP-based CellTiter-Glo® assay. Infected THP-1 macrophages were treated with reference drugs: MA (500-3.9 μM), SSG (500-3.9 μM), MLT (125-0.98 μM), PEN(31.25-0.24 μM), and AmB (7.8-0.06 μM) for 48 h; they were then washed, lysed with 0.05% SDS, and cultured in SIM (20% FCS) at 26 °C for 72 h to enable amastigote-to-promastigote transformation. Viability of transformed promastigotes was quantified using the ATP-based CellTiter-Glo® assay, with RLU reflecting metabolic activity, and IC50 values calculated from dose–response curves in GraphPad Prism (9,12).

Statistical Analysis

All experiments were performed in triplicate, and data are expressed as mean ± standard deviation. IC50 values were calculated by nonlinear regression analysis of dose-response curves using GraphPad Prism 9 (San Diego, USA). Agreement between microscopy- and luminometry-derived IC50 values was evaluated using a paired t-test, while correlation between the two methods was assessed by Pearson correlation analysis. A $p<0.05$ was considered statistically significant.

RESULTS

Inverted microscopy demonstrated the presence of *L. tropica* amastigotes within differentiated THP-1 macrophages (Figure 1A). Parasites were clearly localized within the cytoplasm of host cells, confirming their intracellular persistence and reflecting their differentiation from promastigotes to amastigotes. Upon further *in vitro* cultivation, these intracellular amastigotes transformed into motile promastigote forms, which appeared as extracellular, elongated parasites (Figure 1B). The observed transition from amastigotes to promastigotes not only confirmed parasite viability but also validated the robustness of the experimental infection model employed in this study.

The intracellular susceptibility of *L. tropica* amastigotes to five conventional antileishmanial drugs—MA, SSG, MLT, PMD, and AmB—was subsequently evaluated. Two complementary and independent quantitative approaches were employed to ensure methodological reliability. First, microscopic examination following Giemsa staining enabled direct visualization and enumeration of intracellular amastigotes, thereby providing morphological confirmation of drug-induced parasite clearance. Second, luminometric quantification using the PRTA measured parasite viability indirectly via ATP-dependent RLU of transformed promastigotes. The use of dual methodologies enabled a more robust and reproducible assessment of intracellular drug susceptibility.

Microscopic evaluation involved direct counting of intracellular amastigotes in Giemsa-stained slides. Both microscopic and luminometric assays produced IC50 values that fell within comparable ranges for all tested compounds (Table 1 and Figure 2). Among the evaluated drugs, AmB (microscopy: 0.48±0.05 µM; luminometry: 0.42±0.03 µM) and PMD (1.62±0.17 µM; 1.58±0.15 µM) exhibited the highest potency, yielding nearly identical IC50 values across both quantification methods. MLT displayed intermediate activity (11.33±1.07 µM; 12.15±1.12 µM), while the antimonial compounds MA (56.12±4.31 µM; 52.78±3.45 µM) and SSG (31.55±2.17 µM; 35.42±2.45 µM) showed comparatively lower efficacy.

Statistical analyses further reinforced these findings. A paired t-test confirmed that the IC50 values obtained by the two quantification methods did not differ significantly (t=0.2172, p=0.8387). Additionally, Pearson correlation analysis revealed a strong positive association between microscopy and luminometry (r=0.9944, p=0.0005), underscoring the high concordance between the two approaches. Taken together, these results demonstrate that luminometric analysis via PRTA is not only consistent with conventional microscopic evaluation but also a reliable, quantitative, and high-throughput alternative for assessing the intracellular drug susceptibility of *L. tropica* amastigotes.

Table 1. *In vitro* intracellular susceptibility of *Leishmania tropica* amastigotes to reference antileishmanial drugs, expressed as IC50 values (µM ± SD). IC50 values were determined by two independent quantitative methods: luminometric analysis using the PRTA (PRTA; based on transformed promastigotes) and microscopic enumeration following Giemsa staining (intracellular amastigotes)

Reference drugs	**IC50 (µM ± SD)**	
	Luminometry	**Microscopy**
Meglumine antimoniate	52.78±3.45	56.12±4.31
Sodium stibogluconate	35.42±2.45	31.55±2.17
Miltefosine	12.15±1.12	11.33±1.07
Pentamidine	1.58±0.15	1.62±0.17
Amphotericin B	0.42±0.03	0.48±0.05

PRTA: Parasite rescue and transformation assay, SD: Standard deviation, IC50: Inhibitory concentration 50

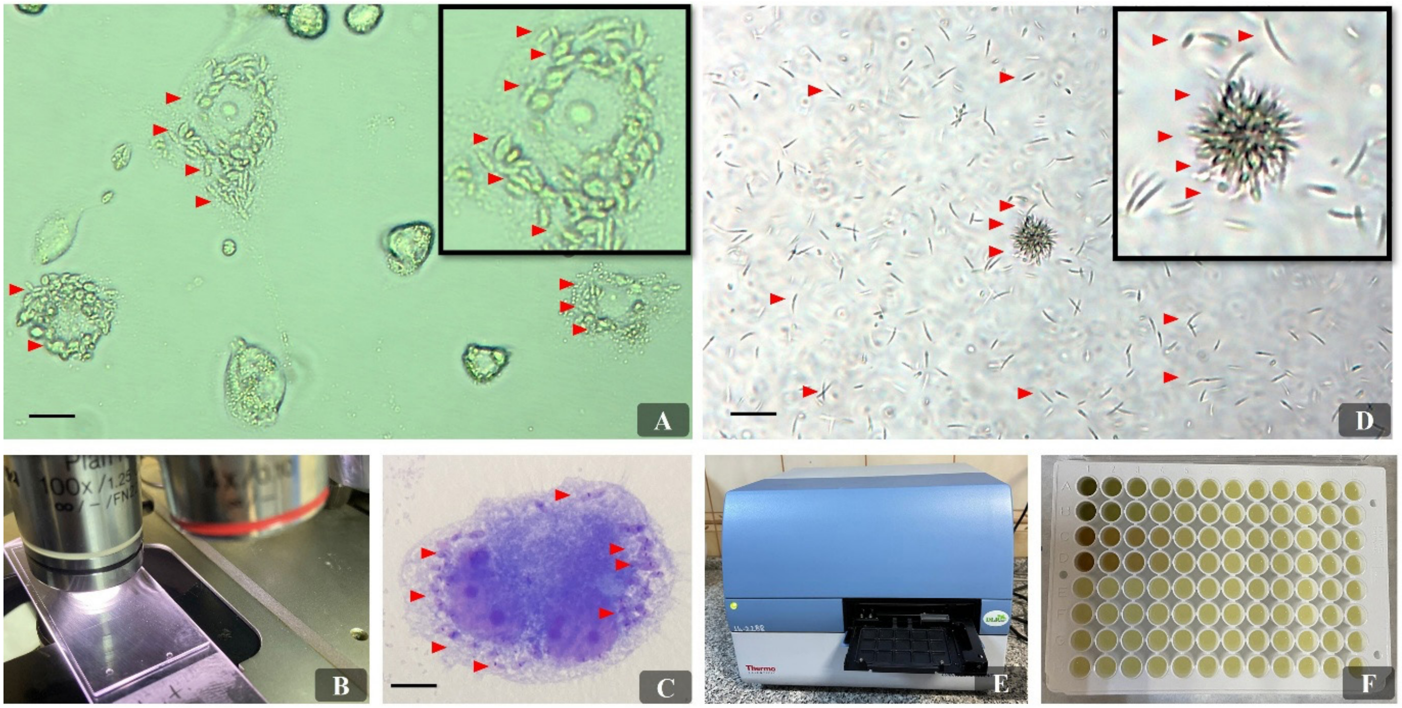

Figure 1. Representative images illustrating the *in vitro* experimental workflow of the PRTA-based intracellular susceptibility assay. (A) Intracellular *Leishmania tropica* amastigotes (red arrowheads) within differentiated THP-1 macrophages observed by inverted phase-contrast microscopy (400× magnification; scale bar=10 µm). A magnified inset is provided to enhance visualization of intracellular amastigotes under unstained live-cell conditions. (B) Slide-coverslip preparation used for microscopic examination. (C) Giemsa-stained intracellular amastigotes (red arrowheads) confirming parasite morphology at higher magnification (1000×; scale bar=5 µm). (D) Promastigotes, indicated by red arrowheads, transformed from viable intracellular amastigotes following host-cell lysis and incubation in SIM medium (200× magnification; scale bar=5 µm). A magnified inset is included to improve structural visualization despite the high density and motility of promastigotes. (E) A microplate reader used for ATP-based luminometric measurements. (F) Representative 96-well microplate layout applied in the PRTA

SIM: Schneider's insect medium, PRTA: Parasite rescue and transformation assay

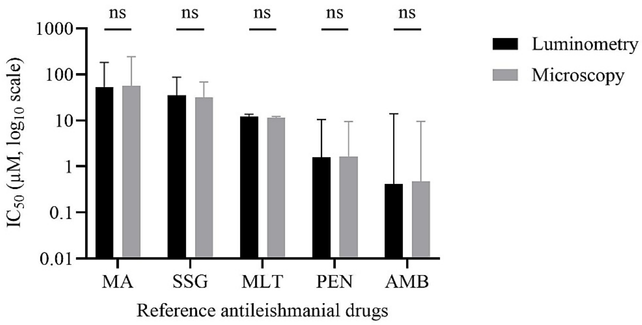

Figure 2. Comparative intracellular susceptibility of *Leishmania tropica* amastigotes to reference antileishmanial drugs, expressed as IC50 values (μM). Data were obtained using two independent methods: luminometric PRTA analysis and microscopic enumeration. Bars represent mean ± SD from independent experiments. The y-axis is presented on a logarithmic (log$_{10}$) scale to facilitate comparison across compounds with different activity ranges. Tested compounds included meglumine antimoniate, sodium stibogluconate, miltefosine, pentamidine, and amphotericin B. No statistically significant differences (ns) were observed between the two methods for any tested compound ($p>0.05$)

IC50: Inhibitory concentration 50, PRTA: Parasite rescue and transformation assay, SD: Standard deviation, MA: Meglumine antimoniate, SSG: Sodium stibogluconate, MLT: Miltefosine, PEN: Pentamidine, AmB: Amphotericin B

DISCUSSION

CL, caused by various species of the genus *Leishmania*, remains a significant public health challenge in tropical and subtropical regions. Despite the long-standing use of conventional antileishmanial agents, increasing reports of therapeutic failure and drug resistance in recent decades have considerably limited the efficacy of current treatment strategies. Field studies conducted in endemic areas such as India, Sudan, and the Middle East have documented resistance rates to pentavalent antimonials as high as 30-60%, underscoring the growing clinical concern regarding the sustainability of these compounds as first-line therapies (13). This situation has raised substantial concerns regarding the safety and efficacy profiles of many drugs, particularly pentavalent antimonial compounds. Moreover, most of the currently available therapeutic agents present major drawbacks, including the requirement for parenteral administration, the risk of systemic toxicity, and the need for prolonged treatment regimens (14,15). It has been consistently emphasized in the literature that treatment failures cannot be solely attributed to parasite resistance; host immune responses, pharmacokinetic/pharmacodynamic (PK/PD) parameters, drug penetration into cutaneous lesions, and field-related implementation factors also play critical roles in determining therapeutic outcomes (15,16). The increasing prevalence of drug resistance has called into question the efficacy of current treatment regimens. Still, it has underscored the urgent need for novel antileishmanial agents that are more effective, safer, and more accessible. The successful advancement of novel therapeutic approaches against CL depends on the establishment of reliable intracellular drug screening assays. Such assays should accurately assess intracellular drug activity, reflect parasite viability and functional status, and provide clinically meaningful predictive value. Traditional methodologies are often limited in accuracy, fail to adequately reflect clinical reality, and exhibit low throughput, thereby restricting their utility in drug development pipelines. Here, the term "translational" refers to the capacity of *in vitro* IC50 measurements to demonstrate at least a partial correlation with clinical treatment responses. However, the strength of this bridge must also be supported by PK/PD parameters, host immune responses, and field-related considerations.

A variety of *in vitro assay* systems, based on the parasite's distinct life-cycle stages, namely promastigotes and amastigotes, have been developed to evaluate the susceptibility of *Leishmania* species to conventional therapeutic agents and to newly developed compounds. Assays employing the promastigote stage are frequently used because of their practical advantages, including simple culture conditions, rapid results, and the relative ease of measurement. Nevertheless, because the promastigote represents the extracellular vector stage rather than the intracellular mammalian stage, such assays exhibit limited capacity to predict clinical treatment responses (17). As highlighted by Croft (2001), only models based on the amastigote-macrophage interaction are capable of establishing a biologically meaningful correlation between *in vitro* susceptibility data and the clinical course of the disease (13). Subsequent studies have corroborated this observation, demonstrating that IC50 values derived exclusively from amastigote-based systems exhibit greater concordance with clinical efficacy (18,19). Within the mammalian host, the intracellular amastigote form represents the pathogenic stage of the parasite, directly interacting with the immune system. Consequently, amastigote-based, macrophage-centered assay systems provide higher translational accuracy and enhanced predictive power for PD evaluations and clinical outcomes (13).

Among the *in vitro* models developed for antileishmanial drug screening, one of the most prominent is the macrophage-amastigote infection system. Primary macrophages may be derived from several sources, including peritoneal exudate cells, peripheral blood mononuclear cells, and bone marrow-derived macrophages. Alternatively, continuously proliferating cell lines are widely used, including murine lines such as J774 and RAW264.7 and human-derived lines such as THP-1, U937, and HL-60 (17,20,21). In experiments employing proliferative host cells, it must be acknowledged that the tested compounds may exert simultaneous effects on host cells and parasites, necessitating cautious interpretation of the results in light of these potential interactions. Primary macrophages are generally non-dividing, terminally differentiated cells, a feature that minimizes artifacts arising from cell proliferation during drug efficacy assessments. Nevertheless, such cells are influenced by the biological variability of donor animals and are often heterogeneous, which can compromise experimental reproducibility and data reliability. By contrast, macrophages derived from monocytic cell lines display homogeneous phenotypic characteristics and provide a higher degree of standardization across experiments (22). In the present study, the THP-1 cell line was selected as the experimental model for *L. tropica*, the causative agent of CL in Türkiye. Its homogeneous phenotype and non-proliferative nature enable standardized and reproducible results.

Macrophage-amastigote-based drug screening systems can be implemented through a variety of methodological approaches.

The most widely employed classical strategy relies on the direct microscopic enumeration of infected host cells. However, this method is labor-intensive and time-consuming, and the lack of automation significantly limits its applicability for high-throughput analyses (23). In manual systems based on host-cell and parasite counting, reliable determination of parasite viability is challenging when staining techniques are employed, as their use may lead to inaccuracies in the calculation of PD parameters such as IC50. Consequently, results derived solely from microscopic enumeration are often criticized by reviewers for possessing "limited translational value." In flow cytometry-based systems, parasites can be detected using fluorescent dyes or monoclonal antibodies; however, these approaches also demonstrate limited sensitivity and generally allow the assessment of drug activity only over short-term exposures (e.g., 24 hours) (24). This limitation hinders monitoring of long-term treatment responses. As an alternative, reporter gene-based systems have been developed that enable the quantitative tracking of intracellular amastigote proliferation. These approaches offer significant advantages in high-throughput screening studies, particularly with respect to standardization, time efficiency, and compatibility with automation (25). Green fluorescent protein-based systems are limited by their inability to distinguish between viable and non-viable parasites. Luciferase-based systems, although highly sensitive, are constrained by high operational costs, which restrict their suitability for large-scale screening applications (5). Accordingly, ATP-based viability assays represent a highly robust and scalable platform for high-throughput applications, combining exceptional analytical sensitivity with operational simplicity. Their homogeneous, rapid, and automation-compatible format minimizes procedural variability while maximizing reproducibility across large compound libraries. These characteristics support ATP quantification as a gold-standard readout for cell viability in high-throughput screening workflows. This is particularly relevant when reliable discrimination of metabolically active cells is required (26).

In the present study, the intracellular drug susceptibility of *L. tropica* amastigotes was assessed using two independent quantitative approaches: (i) direct microscopic enumeration of amastigotes within infected macrophages following Giemsa staining, and (ii) luminometric analysis based on the PRTA, which relies on the recovery of viable intracellular amastigotes and their subsequent differentiation into promastigotes. Microscopic enumeration remains a long-established standard method that provides direct visualization and quantification of the intracellular stage of *Leishmania* spp., thereby retaining its reliability for susceptibility assessments (27). The luminometric analysis of transformed promastigotes (PRTA) was first described in 2012 by Jain et al. (12), who employed the THP-1 cell line against *L. donovani* and demonstrated the reliability of this approach. Subsequent studies applied this method to other species, including *L. major* (28) and *L. martiniquensis* (29). The method has also contributed to investigations examining the impact of genetic modifications on parasite infectivity (30) In our study, luminometric analysis provided a reliable and reproducible model for evaluating intracellular drug efficacy. Strong concordance between IC50 values obtained by both methods indicates substantial clinical predictive value. Promastigote transformation was observed on approximately day 5. This finding parallels proliferation patterns previously reported for *L. major* and *L. braziliensis* and supports species- and culture-dependent variations described in the literature (31). While microscopic enumeration provides morphological validation, luminometric analysis offers a more objective and quantitative readout. Parasite subpopulations with reduced metabolic activity, such as stress-adapted, drug-exposed, or quiescent forms, may produce lower luminescent signals despite remaining viable. Metabolically attenuated yet persistent phenotypes have been described in kinetoplastid parasites and may contribute to variability in metabolic assays (32). Importantly, the strong concordance observed between luminometric PRTA measurements of transformed promastigotes and microscopic amastigote counts demonstrates that this theoretical limitation did not significantly affect quantitative outcomes under the experimental conditions employed. This methodological reliability, in turn, supports positioning luminometric analysis of transformed promastigotes as a robust alternative to classical microscopy, with clear potential to advance translational research in leishmaniasis.

CONCLUSION

In conclusion, luminometric analysis of transformed promastigotes (PRTA method) provides not only technical advantages such as quantitative accuracy and operator independence but also a human-relevant *in vitro* model with high translational validity because it uses the human monocytic THP-1 cell line. In this study, the application of the PRTA approach against *L. tropica,* the causative agent of CL endemic in Türkiye, enabled quantitative and objective monitoring of infection dynamics. The close concordance between IC50 values obtained through PRTA and those derived from conventional microscopic enumeration further substantiated the reliability of the method. Strengths of this work include the parallel application of two independent quantitative assays, the convergence of IC50 results across methods, the use of THP-1 cells, which enhance standardization, and the demonstration of PRTA's high-throughput and operator-independent measurement capacity. Together, these strengths support PRTA's predictive potential for infection dynamics. Nonetheless, several methodological limitations should be acknowledged: the study was restricted to a single species (*L. tropica*) and a limited panel of drugs; THP-1 cells, although advantageous for standardization, may not fully recapitulate the heterogeneity of primary macrophages; and microscopic enumeration is inherently labor-intensive. Taken together, luminometric analysis of transformed promastigotes offers a robust bridge between preclinical findings and clinical outcomes in therapeutic development for *L. tropica*, providing a practical, reproducible, and scalable alternative within *Leishmania*-infected macrophage models. While the method emerges as a reliable prescreening tool supported by consistent IC50 values and a standardized framework, further validation across diverse isolates, broader drug panels, primary macrophage systems, and time-dependent analyses will be essential to strengthen its clinical predictive capacity.

*Ethics

Ethics Committee Approval: This study was approved by the Health Sciences Ethics Committee of the Faculty of Medicine, Manisa Celal Bayar University (decision no: 20.478.486/3131, date: 07/05/2025).

Informed Consent: Patient consent was not required, as the study was performed using *Leishmania tropica* strains and THP-1 cells obtained from a parasite bank, without direct use of human clinical specimens.

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Footnotes

*Authorship Contributions

Surgical and Medical Practices: A.Ö., Concept: A.Y., T.A., Design: A.Y., T.A., Data Collection or Processing: A.Y., T.A., A.Ö., Analysis or Interpretation: A.Y., T.A., A.Ö., Literature Search: A.Y., T.A., Writing: A.Y., T.A.

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Prevalence of Liver Trematodes in Sheep and Goats Slaughtered in the Siirt Province Slaughterhouse

Siirt İli Mezbahasında Kesilen Koyun ve Keçilerde Karaciğer Trematodlarının Yaygınlığı

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ABSTRACT

Objective: Liver trematodes are parasites that adversely affect animal health and cause reduced productivity in ruminants in endemic areas. This study was conducted to determine the prevalence of liver trematodes in sheep and goats slaughtered in Siirt, where small ruminant breeding is widely practiced.

Methods: This study was conducted between January 1 and May 15, 2025. Fecal samples collected from animals before slaughter at the Siirt province slaughterhouse were evaluated using the sedimentation method. In addition, the livers, bile ducts, and gallbladders of the slaughtered animals were examined macroscopically for adult parasites.

Results: At the slaughterhouse, fecal samples collected before slaughter *Fasciola* spp. in 14.4% of 195 sheep, and *Dicrocoelium dendriticum (D. dendriticum)* eggs in 4.1; in 237 goats, *Fasciola* spp. was found in 9.7% and *D. dendriticum* eggs in 3%. In the 195 sheep that underwent liver examination after slaughter, *Fasciola hepatica (F. hepatica)* was found in 22.1%, *D. dendriticum* was found in 9.7%; and in 237 goats, *F. hepatica* was found in 15.6% and *D. dendriticum* adults were found in 4.2%. No statistically significant difference was found between breeds and trematode positivity in sheep. Similarly, no significant difference was found between age groups and the frequency of trematode occurrence in sheep and goat.

Conclusion: In this study conducted in Siirt province, the liver fluke infection rates we determined in sheep and goats indicate the need to combat these parasites. To prevent productivity losses and deaths in animals due to this infection, those involved in livestock farming need to be informed about this issue. Furthermore, it is crucial that animals are periodically examined and treated before being released into pasture.

Keywords: *Fasciola hepatica*, *Dicrocoelium dendriticum*, sheep, goat, Siirt

ÖZ

Amaç: Karaciğer trematodları, hayvan sağlığını olumsuz etkileyen parazitler olup endemik bölgelerde ruminantlarda verim düşüklüğüne neden olmaktadır. Bu çalışma, küçükbaş hayvan yetiştiriciliğinin yaygın olarak yapıldığı Siirt ilinde kesilen koyun ve keçilerde karaciğer trematodlarının yaygınlığını ortaya koymak amacıyla yapıldı.

Yöntemler: Bu çalışma 1 Ocak-15 Mayıs 2025 tarihleri arasında yürütüldü. Siirt ili mezbahasında, hayvanlardan kesim öncesi alınan dışkı örnekleri sedimantasyon yöntemi ile değerlendirildi. Ayrıca kesilen hayvanların karaciğerleri, safra kanalları ve safra keseleri erişkin parazitler yönünden makroskobik olarak incelendi.

Bulgular: Mezbahada kesim öncesi dışkı örnekleri alınan 195 koyunun %14,4'ünde *Fasciola* spp., %4,1'inde *Dicrocoelium dendriticum (D. dendriticum)* yumurtası, 237 keçinin %9,7'sinde *Fasciola* spp., %3'ünde ise *D. dendriticum* yumurtası saptandı. Kesim sonrası karaciğer muayenesi yapılan 195 koyunun %22,1'inde *Fasciola hepatica (F. hepatica)*, %9,7'sinde *D. dendriticum*, 237 keçinin %15,6'sında *F. hepatica*, %4,2'sinde ise *D. dendriticum*'un erişkinleri belirlendi. Koyunlarda ırklar ile trematod pozitifliği arasında istatistiksel olarak anlamlı bir fark bulunmadı. Koyun ve keçilerde yaş grupları ile trematoda rastlama sıklığı arasında da anlamlı bir fark saptanmadı.

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Sonuç: Siirt ilinde yürütülen bu çalışmada, koyun ve keçilerde belirlediğimiz karaciğer kelebeği enfeksiyon oranları bu parazitlerle mücadele edilmesi gerektiğini ortaya koymaktadır. Bu enfeksiyon nedeniyle hayvanlarda verim kayıplarını ve ölümleri önlemek için hayvancılıkla uğraşanların bu konuda bilgilendirilmesi gerekmektedir. Ayrıca hayvanların otlağa salınmadan önce periyodik olarak muayene edilip tedavi edilmesi önem arz etmektedir.

Anahtar Kelimeler: *Fasciola hepatica*, *Dicrocoelium dendriticum*, koyun, keçi, Siirt

INTRODUCTION

Fascioliasis is a freshwater snail-borne, zoonotic, parasitic disease. The adult stage of *Fasciola* spp. infects the bile ducts in the livers of herbivorous mammals such as sheep, goats, and cattle (1-3).

During the migration of *Fasciola* spp. in the liver, inflammation, edema, hemorrhage, congestion, fibrosis, cholangitis and mechanical damage, and after the migration of adults into the bile ducts, impaired bile flow and related findings may be observed (2,4-6). The distribution of fasciolosis is dependent on the ecology of aquatic snail intermediate hosts that inhabit both tropical and temperate climatic zones (7).

Dicrocoelium dendriticum (D. dendriticum) usually inhabits the hepatobiliary tract and gallbladder of ruminants. This parasite is known to be less pathogenic than *Fasciola* species. Dicrocoeliosis is mostly prevalent in areas with dry pastures that favor the development of the intermediate hosts (5,8). The relevance of dicrocoeliosis is often underestimated due to its often-subclinical course in domestic ruminants, and because clinical signs can be masked by other parasitic infections (8).

Liver flukes cause economic losses due to reasons such as decrease in milk and meat production, unusable livers infested with parasites, abortion, increased mortality rates and the cost of control measures (4,9).

According to the 2025 data of the Turkish Statistical Institute, there were 786,415 sheep and 541,325 goats in Siirt province in 2024 (10). This study aimed to determine the prevalence of liver trematodes in slaughtered sheep and goats from Siirt province, where small ruminant farming is common.

METHODS

Prior to the study, approval was obtained from the Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee (decision number: E-27552122-604.01-622088, date: 10.12.2024). The study was conducted between January 1 and May 15, 2025, on 195 sheep (144 Akkaraman and 51 Morkaraman) and 237 Angora goats, all slaughtered at the Siirt provincial slaughterhouse. Age, breed, and gender information of all animals included in the study was recorded. The collected samples were evaluated at the Parasitology Research Laboratory, Department of Parasitology, Faculty of Medicine, Van Yüzüncü Yıl University.

Parasitological Examination of Stool Samples

Collected stool samples were stored in a refrigerator at +4 °C until processing and were evaluated using the sedimentation method. The preparations were examined under a light microscope at 10x and 40x magnifications.

Postmortem Examination

The livers, bile ducts, and gallbladders of the slaughtered animals were examined macroscopically. The liver was incised perpendicular to the bile ducts to remove trematodes, and both the gallbladder and the collected parasites were taken to the laboratory for examination.

Statistical Analysis

Descriptive statistics for the study variables were presented as numbers (n) and percentages (%). Differences in trematode positivity between animal species, breeds, and age groups were analyzed using the two-proportion Z test. A significance level of 5% was adopted, and all statistical analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 26.0) and Minitab (Version 17, Minitab Statistical Software LLC).

RESULTS

In this study, fecal examination revealed *Fasciola* spp. in 14.4% of sheep and 9.7% of goats, and *D. dendriticum* in 4.1% of sheep and 3% of goats (Table 1). On macroscopic examination of the bile ducts and gallbladders, *Fasciola hepatica (F. hepatica)* adults were detected in 22.1% of sheep and 15.6% of goats, while *D. dendriticum* adults were detected in 9.7% of sheep and 4.2% of goats (Table 2). Fecal examination results showed no statistically significant difference between sheep and goats in trematode positivity (Table 1). Considering the results of postmortem organ examinations, a significant difference in *D. dendriticum* positivity between sheep and goats was observed (p=0.027) (Table 2).

Adults of *F. hepatica* were detected by liver examination in 15 sheep and 14 goats, and adults of *D. dendriticum* were detected by liver examination in 11 sheep and 3 goats; no eggs were detected in the fecal samples (Table 1, Table 2).

Both *F. hepatica* and *D. dendriticum* adults were detected in three sheep and five goats. In sheep, *F. hepatica* was found at higher rates in the Akkaraman breed, whereas *D. dendriticum* was found at higher rates in the Morkaraman breed. No statistically significant difference was found between breeds and trematode positivity in sheep. Similarly, no significant difference in the frequency of trematode occurrence was found between age groups of sheep and goats (Table 3). Since most of the slaughtered sheep and goats were female, parasite positivity could not be compared statistically by gender.

Table 1. Trematode positivity determined by fecal examination in sheep and goats

Animal type	*Fasciola* spp.		*Dicrocoelium dendriticum*	
	Positive (%)	p-value	Positive (%)	p-value
Sheep (n=195)	28 (14.4)	0.141	8 (4.1)	0.522
Goat (n=237)	23 (9.7)		7 (3)	
Total (n=432)	51 (11.8)		15 (3.5)	

DISCUSSION

D. dendriticum and *F. hepatica* are two of the well-known trematodes of the livestock worldwide including Türkiye (11). Liver trematode infections cause serious losses in livestock production. Also, it might adversely affect the development and live-weight gain of animals and damage the national economy by causing the loss of economically significant organs such as the liver (6,7).

In studies conducted on small ruminants worldwide and in Türkiye, the frequency of liver fluke infection was determined by fecal examination, post-slaughter organ examination, or serological methods.

Using fecal examination, Eke et al. (9) in Nigeria detected fascioliasis in 12.5% of sheep and 7.25% of goats; Cringoli et al. (12) in Italy detected fascioliasis in 4.1% of sheep and *D. dendriticum* in 52.3%; Alstedt et al. (8) in Germany detected fascioliasis in 2.7% of sheep and 5.6% of goats; *D. dendriticum* in 21.1% of sheep and 7% of goats. In Türkiye, using the same method, Gül and Günyaktı Kılınç (13) in Bingöl detected fascioliasis in 27% of sheep and 21% of goats; *D. dendriticum* in 14% of sheep and 12% of goats; and Denizhan (14) in Van city center and some districts detected fascioliasis in 15.63% of sheep. The results of our study were similar to the rate found in two studies determining the frequency of fascioliasis in sheep and goats (9,14).

By post-slaughter organ examination, Oljira et al. (7) detected *Fasciola* species in 20.7% of sheep and 1.6% of goats in Ethiopia; Ezatpour et al. (5) detected *Fasciola* species and *D. dendriticum* in 7.1% and 5.6% of sheep and 3.9% and 2.6% of goats in Iran, respectively; Kruchynenko et al. (15) detected *D. dendriticum* in 28.42% of sheep and 24.5% of goats in Ukraine. In the Thrace region of Türkiye, Gargılı et al. (16) detected *F. hepatica* in sheep as 3.99% and *D. dendriticum* as 23.52%; Pekağırbaş et al. (6) detected *F. hepatica* in sheep as 0.02% and *D. dendriticum* as 0.3% in Aydın; Kara et al. (11) detected *F. hepatica* in sheep as 4.42% and *D. dendriticum* as 3.85% in Malatya; Kaplan et al. (17) detected *F. hepatica* in sheep as 7.89% and *D. dendriticum* as 1.15% in Elazığ; *F. hepatica* in goats as 5.64% and *D. dendriticum* as 0.47%. The rates determined in our study are similar to the frequency of *F. hepatica* detected in sheep in one study (7), in goats in another study (5), and *D. dendriticum* detected in sheep in another study (11).

Table 2. Trematode positivity in liver examination of sheep and goats

Animal type	***Fasciola hepatica***		***Dicrocoelium dendriticum***	
	Positive (%)	**p-value**	**Positive (%)**	**p-value**
Sheep (n=195)	43 (22.1)	0.089	19 (9.7)	**0.027**
Goat (n=237)	37 (15.6)		10 (4.2)	
Total (n=432)	80 (18.5)		29 (6.7)	

p<0.05 indicates significant differences

In one serological study conducted in Türkiye, fascioliasis was detected at a rate of 49.43% in sheep in the center of Van and some of its districts (14). In another study, *F. hepatica* seropositivity was found at a rate of 7.5% in sheep and 14.14% in goats in Siirt province (3). In our study, the *F. hepatica* positivity detected by liver examination was higher than the rate detected in sheep in this serological study conducted in 2018, and was similar to the rate detected in goats. This situation indicates that the control of liver flukes in small ruminants in the region is inadequate.

The rates we found in our study differed significantly from those found globally and in Türkiye. We believe that this is due to differences in environmental conditions, intermediate host availability, and parasite control practices. Furthermore, the diagnostic methods may contribute to these differences.

In this study, no statistically significant difference in trematode positivity (positive result on liver examination) was found between breeds of sheep. However, comprehensive studies with larger numbers of animals are necessary to fully demonstrate the effect of breed on fascioliasis.

Several studies have statistically evaluated the relationship between age and trematode frequency. In one study, a significant difference was found in the frequency of *F. hepatica* and *D. dendriticum* in sheep and goats (5), in another study in the frequency of *D. dendriticum* in sheep and goats (15), and in three studies in the frequency of *Fasciola* in sheep (7,11,14). In one study (15), similar to our study, no statistically significant difference was found between age groups in terms of *D. dendriticum* positivity in sheep and goats.

In our study, the prevalence of liver flukes was determined by both fecal examination and postmortem organ examination. The markedly higher rate of trematode positivity detected by liver examination suggests that fecal examination is insufficient for diagnosing these parasites. Organ examination detects a higher positivity rate than stool analysis, possibly because trematodes do not regularly lay eggs, trematodes in the liver have not yet reached adulthood, and eggs are not found in every region of the stool even if the animal is positive.

Our study provides insight into the prevalence of liver fluke infection among sheep and goats in the Siirt region. However, studies involving a larger number of animals are needed in the region. Although the number of animals evaluated was limited, our results clearly demonstrate that liver fluke is a problem in small ruminants in the region.

Table 3. Trematode positivity in bile ducts and gall bladders according to breed and age groups

Species			***Fasciola hepatica***		***Dicrocoelium dendriticum***	
			Number (%)	**p-value**	**Number (%)**	**p-value**
Sheep	**Breed**	Akkaraman (144)	32 (22.2)	0.923	12 (8.3)	0.313
		Morkaraman (51)	11 (21.6)		7 (13.7)	
	Age	0-2 (54)	9 (16.7)	0.231	3 (5.6)	0.158
		>2 (141)	34 (24.1)		16 (11.3)	
Goat (Angora)	**Age**	0-2 (81)	12 (14.8)	0.806	2 (2.5)	0.281
		>2 (156)	25 (16)		8 (5.1)	

CONCLUSION

In this study conducted in Siirt province, the liver fluke infection rates we determined in sheep and goats indicate the need to combat these parasites. To prevent productivity losses and deaths in animals due to this infection, those involved in livestock farming need to be informed about this issue. Furthermore, it is crucial that animals are periodically examined and treated before being released into pasture.

*Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from Van Yüzüncü Yıl University Ethics Committee (decision number: E-27552122-604.01-622088, date: 10.12.2024).

Informed Consent: The study was conducted between January 1 and May 15, 2025, on 195 sheep (144 Akkaraman and 51 Morkaraman) and 237 Angora goats, all slaughtered at the Siirt provincial slaughterhouse.

Footnotes

*Authorship Contributions

Concept: M.A., H.Y., Design: M.Y., H.Y., Data Collection or Processing: M.A., M.Y., Analysis or Interpretation: Z.T.C., H.Y., Literature Search: M.A., Z.T.C., Writing: M.A.

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Original Investigation
Özgün Araştırma

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Evaluation of the Seroprevalence of Cystic Echinococcosis by the Indirect Hemagglutination (IHA) Method at Balıkesir University Faculty of Medicine: A Seven-year Analysis

Balıkesir Üniversitesi Tıp Fakültesi'nde İndirekt Hemaglütinasyon (IHA) Yöntemi ile Kistik Ekinokokkoz Seroprevalansının Değerlendirilmesi: Yedi Yıllık Analiz

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ABSTRACT

Objective: Echinococcosis is a zoonotic infection caused by cestodes of the *Echinococcus* genus. The most common form, cystic echinococcosis, is a chronic parasitic disease caused by the *Echinococcus granulosus sensu lato* species complex. The aim of our study is to determine the prevalence of cystic echinococcosis in our hospital and to reveal the regional epidemiological characteristics of the disease based on the obtained data.

Methods: In this study, 526 serum samples sent to the medical microbiology laboratory from various hospital departments and outpatient clinics with suspected cystic echinococcosis between 01.07.2018 and 01.07.2025 were evaluated. A commercial ELI.H.A *Echinococcus* (ELITech Microbio, France) kit was used. The clinical diagnosis, gender, age, delivery department, and demographic characteristics of the patients were retrospectively analyzed.

Results: Among the 526 patients evaluated in the study, 302 (57.4%) were female. Of the total applications, 60.5% originated from the general surgery outpatient clinic. Using the IHA test, seropositivity was detected in 21.5% of the 526 patients. When the distribution according to antibody titers was examined, the antibody levels detected in the serum samples were as follows: 6.8% (n=36) at 1/80, 6.1% (n=32) at 1/160, 4% (n=21) at 1/320, 4.9% (n=26) at 1/640, 3.8% (n=20) at 1/1280, 2.8% (n=15) at 1/2560, and 5.9% (n=31) at 1/5120. Among the 90 patients with available clinical data for cystic echinococcosis, the liver was identified as the most frequently involved organ (95.5%). Among 76 patients with available cyst size measurements, most cysts measured 51-100 mm (48.6%). According to the World Health Organization-IWGE classification, CE3b was the most common stage (23.6%).

Conclusion: The obtained data indicate that cystic echinococcosis remains an important public health problem in Balıkesir. Therefore, in light of these findings, it is necessary to strengthen healthcare services for the diagnosis and follow-up of the disease and to place greater emphasis on preventive measures.

Keywords: Echinococcosis, prevalence, zoonotic

ÖZ

Amaç: Ekinokokkoz, *Echinococcus* türlerine ait sestodların yol açtığı bir zoonotik enfeksiyondur. En yaygın görülen form olan kistik ekinokokkoz, *Echinococcus granulosus sensu lato* tür kompleksi tarafından oluşturulan, kronik seyirli ilerleyen bir paraziter hastalıktır. Çalışmamızın amacı hastanemizdeki kistik ekinokokkoz sıklığını belirlemek, elde edilen veriler doğrultusunda hastalığın bölgesel epidemiyolojik özelliklerini ortaya koymaktır.

Yöntemler: Çalışmada, 01.07.2018 ve 01.07.2025 tarihleri arasında kistik ekinokokkoz şüphesiyle çeşitli servis ve polikliniklerden tıbbi mikrobiyoloji laboratuvarına gönderilen 526 serum örneği incelendi. Ticari bir ELI.H.A *Echinococcus* (ELITech Microbio, Fransa) kiti kullanıldı. Hastaların klinik tanısı, cinsiyet, yaş, örneğin gönderildiği bölüm ve demografik özellikleri retrospektif olarak değerlendirildi.

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Bulgular: Çalışmada değerlendirilen 526 hastanın 302'si kadın (%57,4) olarak belirlenmiştir. Toplam 526 başvurunun %60,5'i genel cerrahi polikliniğindendir. IHA testi ile 526 hastanın %21,5'inde seropozitiflik saptanmıştır. Titrelere göre dağılım incelendiğinde, serum örneklerinde saptanan antikor düzeyleri 1/80 titrede %6,8 (n=36), 1/160 titrede %6,1 (n=32), 1/320 titrede %4 (n=21), 1/640 titrede %4,9 (n=26), 1/1280 titrede %3,8 (n=20), 1/2560 titrede %2,8 (n=15) ve 1/5120 titrede %5,9 (n=31) bulunmuştur. Kistik ekinokokkoz için klinik verilerine ulaşılabilen 90 hasta arasında en sık tutulan organ karaciğer (%95,5) olarak saptanmıştır. Kist boyutu ölçümleri mevcut olan 76 hastada ise kistlerin çoğunluğunun 51-100 mm (%48,6) arasında olduğu belirlenmiştir. Dünya Sağlık Örgütü-IWGE sınıflamasına göre en sık görülen evre CE3b (%23,6) olmuştur.

Sonuç: Elde edilen veriler Balıkesir'de kistik ekinokokkozun önemli bir halk sağlığı sorunu olduğunu ortaya koymaktadır. Bu nedenle, bu veriler ışığında hastalığın tanı ve takibine yönelik sağlık hizmetlerinin güçlendirilmesi ve koruyucu önlemlere daha fazla önem verilmesi gerekmektedir.

Anahtar Kelimeler: Ekinokokkoz, prevalans, zoonotik

INTRODUCTION

Echinococcosis in humans is a zoonotic infection caused by cestodes belonging to the *Echinococcus* species. The most commonly observed form, cystic echinococcosis, is a chronic parasitic disease caused by the *Echinococcus granulosus sensu lato* species complex. Alveolar echinococcosis, on the other hand, is associated with *Echinococcus multilocularis*. Additionally, two species endemic to the New World—*Echinococcus vogeli* and *Echinococcus oligarthrus*—are responsible for a form referred to as "neotropical echinococcosis". Among these, *Echinococcus vogeli* causes a disease with polycystic structures, whereas *Echinococcus oligarthrus* leads to a rare clinical presentation with a single cyst (1).

For the detection of antibodies in the serum samples of patients with cystic echinococcosis, commonly used serological methods include indirect hemagglutination assay (IHA), indirect fluorescent antibody test, and enzyme-linked immunosorbent assays (ELISA) (2). These tests exhibit high sensitivity, generally ranging from 60% to 90%, depending on the disease stage and the type of antigen used (3). ELISA or IHA tests can be employed for screening purposes; however, it is recommended that positive results be confirmed by methods such as immunoblotting (4).

The aim of our study is to determine the prevalence of cystic echinococcosis in our hospital, to identify the epidemiological characteristics of the disease based on the obtained data, and thereby to contribute to diagnosis, follow-up, and preventive healthcare services.

METHODS

Between 1 July 2018 and 1 July 2025, a total of 526 serum samples were analyzed in this study. These serum samples were obtained from patients who presented to Balıkesir University Health Practice and Research Hospital were sent to the Medical Microbiology Laboratory from various clinics and departments with a preliminary diagnosis of cystic echinococcosis. Patient data were retrospectively analyzed from the hospital information system records. The study included adult patients aged between 18 and 90 years, and only the first test result for each patient was considered. The clinical diagnosis, sex, department from which the sample was sent, demographic features, and clinical parameters of the included patients were retrospectively evaluated. For statistical analysis, patients were categorized into six age groups: 18-30,31-40,41-50,51-60,61-70, and 71 years and above.

As part of the study, specific antibodies against *Echinococcus granulosus* were semi-quantitatively detected in serum samples using the commercial kit ELI.H.A *Echinococcus* (ELITech Microbio, France), based on the principle of indirect hemagglutination. The test is based on the reaction of sheep erythrocytes coated with antigen and serum samples. The serum samples were diluted at a ratio of 1:40 using buffer solution. Fifty microliters (50 µL) of buffer solution was added to each of the nine wells. Subsequently, 50 µL of diluted serum and antigen-coated erythrocyte suspension (R1 reagent) was added to the first seven wells. Serial dilutions ranging from 1/80 to 1/5120 were prepared for each sample, and the test was applied accordingly. The eighth well served as a control for natural anti-sheep agglutinins and contained a mixture of serum and uncoated erythrocytes (R2 reagent). The nineth well, containing only buffer and R1 reagent, was used as a reagent control. After a 2-hour incubation at room temperature, the results were evaluated macroscopically. In the presence of specific antibodies, agglutinated sensitized erythrocytes formed a reddish, homogeneous layer on the microplate surface, indicating a positive reaction. In contrast, a ring-shaped sediment at the bottom of the well indicated a negative result. Serologically, titers below 1/80 were considered negative, titers of 1/80 and 1/160 were classified as borderline or equivocal, and titers of 1/320 or higher were accepted as positive (5). The validity of the test was confirmed using both positive and negative control sera (Figure 1).

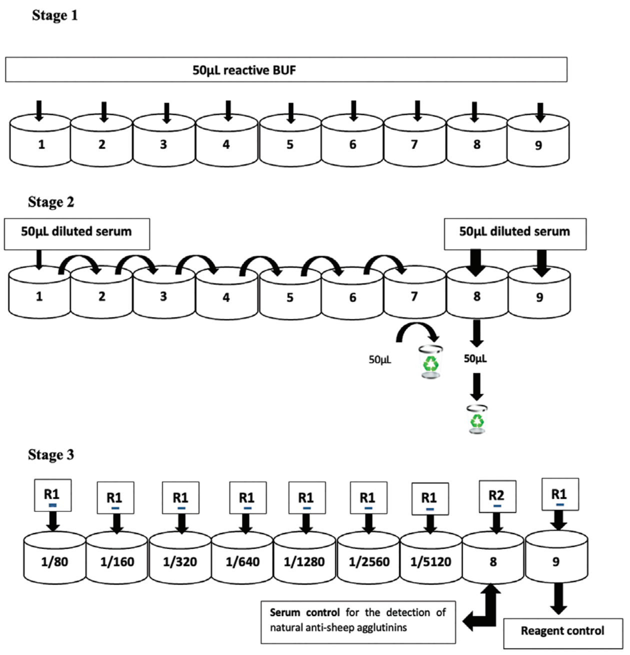

Figure 1. Schematic abstract of the working principle of the indirect hemagglutination test
BUF: Buffer solution

Statistical Analysis

The data obtained in the study were recorded and statistically analyzed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Numerical data were presented as percentages and mean ± standard deviation. Categorical data were expressed as percentages. The chi-square test was used to compare independent groups containing categorical variables. A p-value of less than 0.05 was considered statistically significant.

Ethical Approval

Ethical approval for this study was obtained from the Non-Interventional Clinical Research Ethics Committee of Balıkesir University, dated June 3, 2025, with the approval number E.526429, decision number 2025/220.

RESULTS

Of the 526 patients tested for cystic echinococcosis using the ELI.H.A *Echinococcus* IHA, 302 (57.4%) were female. The mean age of the patients included in the study was 55.5±16.3 years. Among the total 526 cases evaluated, 60.5% were referred from the general surgery outpatient clinic, followed by internal medicine (12.7%), gastroenterology (6.6%), inpatient wards (5.1%), and infectious diseases (4.9%).

The distribution of antibody titers in the serum samples was as follows: 1/80: 6.8% (n=36), 1/160: 6.1% (n=32), 1/320: 4.0% (n=21), 1/640: 4.9% (n=26), 1/1280: 3.8% (n=20), 1/2560: 2.8% (n=15), 1/5120: 5.9% (n=31) (Figure 2). According to the results of the indirect hemagglutination test, 21.5% (n=113) of the patients had seropositivity at a titer of 1/320 or higher. The mean age of seropositive patients was 50.2±16.5 years. When positivity rates were compared across age groups, the highest rates were observed in the 41-50 and 61-70 age groups, each with 19.5% (n=22), while the lowest rate was seen in patients aged 71 and older, with 11.5% (n=13). A statistically significant difference in positivity rates was found between age groups (p=0.003). Among the patients who tested positive, 58 (51.3%) were female. There was no statistically significant difference in seropositivity rates between females and males (p=0.086).

The cyst characteristics and demographic features of patients with cystic echinococcosis with antibody titers ≥1:320 are presented in Table 1. Radiological findings were available for a subset of patients. The liver was the most frequently involved organ (95.5%) among 90 patients with available localization data. Among 76 patients with available cyst size measurements, most cysts measured 51-100 mm (48.6%). According to the World Health Organization (WHO)-IWGE classification, CE3b was the most common stage (23.6%).

Between 2018 and 2025, serological evaluations for cystic echinococcosis revealed variations in seropositivity rates across the years. When examined by year, the seropositivity rates

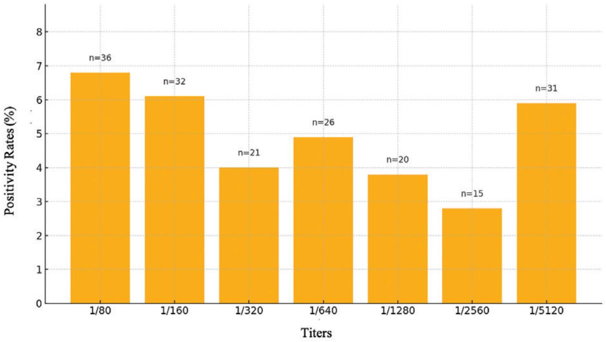

Figure 2. Distribution of positivity rates and titers in serum samples studied by *Echinococcus* indirect hemagglutination test

Table 1. Clinical evaluation of patients with cystic echinococcosis with IHA seropositivity ≥1/320

			n (%)
Demographic characteristics	**Gender**	Female/male	58 (51.3)/55 (48.7)
	Age distribution	18-30	19 (16.8)
		31-40	16 (14.1)
		41-50	22 (19.5)
		51-60	21 (18.5)
		61-70	22 (19.5)
		≥71	13 (11.5)
	Department	General Surgery	84 (74.3)
		Gastroenterology	4 (3.5)
		Infectious Diseases	4 (3.5)
		Internal Medicine	3 (2.6)
		Pulmonology	2 (1.7)
		Other	16 (14.1)
Cyst characteristics*	**Location (site)** (n=90)**	Liver	86 (95.5)
		Lung	7 (7.7)
		CNS	1 (1.1)
		Spleen	4 (4.4)
		Bone	2 (2.2)
		Heart	2 (2.2)
	Dimensions (mm) (n=76)	0-10	1(1.3)
		11-30	11 (14.4)
		31-50	15 (19.7)
		51-100	37 (48.6)
		>100	12 (15.7)
	Stage (WHO-IWGE)* (n=76)	CE1	6 (7.8)
		CE2	5 (6.5)
		CE3a	10 (13.1)
		CE3b	18 (23.6)
		CE4	13 (17.1)
		CE5	6 (7.8)
		Unspecified/ suspected	18 (23.6)

*: The evaluation was performed based on patients whose radiological findings were available, **: More than one category may be present in the same patient, CNS: Central nervous system, WHO-IWGE: The World Health Organization Informal Working Group on Echinococcosis, mm: Millimeter

were 50% in 2018 (4/8), 18.8% in 2019 (17/90), 19.6% in 2020 (11/56), 18.6% in 2021 (11/59), 36.7% in 2022 (18/49), 24.5% in 2023 (25/102), 16.8% in 2024 (18/107), and 19.5% in 2025 (9/46) (Table 2). A statistically significant difference was found among the annual seropositivity rates (p=0.049). These findings indicate marked fluctuations in positivity rates over the years, with a noticeable upward trend in 2022 compared to previous years. In our study, the seropositivity rate during the coronavirus disease 2019 (COVID-19) period (2020-2022) was found to be 32.2% for cystic echinococcosis.

DISCUSSION

Cystic echinococcosis is classified as a neglected tropical disease by the WHO (6). Although cystic echinococcosis is prevalent globally, it is recognized as a significant public health problem particularly in endemic regions such as South America, the Mediterranean Region, Central Asia, Türkiye, Western China, and East Africa (7,8).

In our study, seropositivity rates varied by age group, with high positivity rates detected in the 41-50 and 61-70 age groups. No statistically significant association was found between gender and test results (p=0.086), indicating that positive test results were observed at similar rates in both male and female patients, and that gender did not significantly influence test outcomes. Several studies in Türkiye have shown that cases of cystic echinococcosis typically present with clinical symptoms after the age of 40, with a peak incidence observed between the ages of 50 and 60 (9). In the study conducted by Taşbent et al., (10) the highest IHA positivity was observed in the 41-65 age group, at a rate of 37.7%. In contrast, Başer et al. (11) reported the highest seropositivity in the 21-40 age group.

Table 2. Cystic echinococcosis seropositivity rates between 2018 and 2025 years*

Year	Positive	Negative	Total	Positivity rate (%)
2018	4	4	8	50.0**
2019	17	73	90	18.9
2020	11	45	56	19.6
2021	11	48	59	18.6
2022	18	31	49	36.7
2023	25	77	102	24.5
2024	18	89	107	16.8
2025	9	37	46	19.5
Total	113	413	526	21.5

*: A statistically significant difference was found in the chi-square test, in which the results were compared according to the years (p=0.049), **: In 2018, the positivity rate was found to be high due to the low number of total patients

In our study, the seroprevalance of cystic echinococcosis was found to be 21.5% at Balıkesir, using the IHA method. According to studies conducted in Türkiye, the prevalence of cystic echinococcosis ranges between 5% and 25%. An overview of publications using the IHA method for detecting seropositivity in cystic echinococcosis is presented in Table 3. In a study conducted by Özkeklikçi and Cirit, (12) a seropositivity rate of 28.6% was reported among patients presenting with suspected cystic echinococcosis to the parasitology laboratory in Gaziantep between 2015 and 2022. In another study by Çelik et al., (13) 1,607 serum samples submitted to Adıyaman University Training and Research Hospital between 2013 and 2020 showed a seropositivity rate of 15.1% via the IHA method. Bağcı and Akarsu (14) evaluated serum samples sent to the Central Laboratory of Ankara University Hospital between 2023 and 2024 using the IHA method and reported a seropositivity rate of 5.9% (14). Taşbent et al. (10) also reported a seropositivity rate of 15.2% (n=143) among 938 patients in Konya. In the study by Alver et al., (15) 19.9% (n=213) of the 1,072 patients who presented to Bursa Uludağ University Hospital with suspected cystic echinococcosis were found to be seropositive using the IHA method. Çiftçi et al. (16) reported a seropositivity rate of 25.1% (n=221) in 879 patient serum samples sent to the microbiology laboratory of Selçuk University Faculty of Medicine between 2010 and 2014 with a preliminary diagnosis of cystic echinococcosis. In the study by Behçet and Avcıoğlu (17), which evaluated patients with suspected cystic echinococcosis using the IHA method, a seropositivity rate of 10.6% was observed among 644 patients. In another study by Başer et al., (11) a seropositivity rate of 21.6% was reported among 1,543 patients who presented with suspected cystic echinococcosis at Selçuk University Faculty of Medicine Hospital between 2015 and 2020. In a study conducted at Balıkesir Atatürk State Hospital, 19.8% of 823 serum samples collected between 2011 and 2013 showed positivity at a titre of 1/320 or higher (18).

In the present study, the liver was the most frequently involved organ (95.5%), followed by the lung (7.7%). This finding is consistent with previous studies conducted in Türkiye (19,20). Regarding cyst size, the majority of cysts in our study measured 51-100 mm (48.6%). Similarly, in a multicenter study evaluating 170 patients with cystic echinococcosis in Türkiye, most cysts were reported to measure between 5 and 10 cm (47.1%) (21). In terms of WHO-IWGE classification, CE3b was the most common stage (23.6%) in our study. These findings suggest that many patients are diagnosed when cysts reach moderate to large sizes, likely due to the slow-growing nature of the disease.

The seropositivity rate during the COVID-19 period (2020-2022) was found to be 32.2% for cystic echinococcosis in our study. In the study by Ulusan Bağcı (22), a comparison of pre-pandemic (2019 and earlier) and pandemic (2020-2022) periods in İzmir showed that the seropositivity rate decreased from 18.4% to 14.6% during the pandemic period when evaluated using the IHA method.

Table 3. Analysis of publications containing IHA method for cystic echinococcosis

Researcher	Interval	Province	Positivity rates (%)	Sample number	Methods
Çiftçi et al. (16)	2010- 2014	Konya	25.1	879	IHA (Hydatidose, Fumouze Laboratoires, France)
Şafak (18)	2011-2013	Balıkesir	9.8	823	IHA (Hydatidose, Fumouze Laboratoires, France)
Behçet and Avcıoğlu (17)	2013-2018	Bolu	10.6	644	IHA (Fumouze Diagnostics, France)
Çelik et al. (13)	2013-2020	Adıyaman	15.1	1607	IHA (Fumouze Laboratoires, France)
Taşbent et al. (10)	2014- 2018	Konya	15.2	938	IHA (Hydatidose, Fumouze Laboratoires, France)
Başer et al. (11)	2015-2020	Konya	21.6	1543	IHA (Fumouze Laboratoires, France)
Özkeklikçi and Cirit (12)	2015-2022	Gaziantep	28.6	1811	IHA (ELITech Microbio, France)
Alver et al. (15)	2017-2018	Bursa	19.9	1072	IHA (Siemens Healthcare Diagnostics, Germany)
Ulusan Bağcı (22) Pre-COVID	10.09.2017-10.03.2020	İzmir	18.4	1444	IHA (Hydatidose, Fumouze Laboratoires, France)
Ulusan Bağcı (22) COVID	11.03.2020-11.09.2022	İzmir	14.6	877	IHA (Hydatidose, Fumouze Laboratoires, France)
Bağcı and Akarsu (14)	01.01.2023-01.09.2024	Ankara	5.9	636	*Echinococcus* IHA (Fumouze Diagnostics, France)
Present study	2018-2025	Balıkesir	21.5	526	IHA (ELITech Microbio, France)

IHA: Indirect hemagglutination assay

A total of 6.8% of the serum samples included in the study showed a suspicious reaction at a 1/80 titre, and 6.1% at a 1/160 titre. The IHA method can be used for the screening and diagnosis of cystic echinococcosis. In cases of low-titre suspicious positivity detected by IHA, it is recommended that the test be repeated after two or three weeks (5). As a secondary confirmatory test, Western blot or immunoblot methods are preferred to verify the diagnosis when IHA results are borderline or suspicious (23).

Study Limitations

The limitations of this study include its retrospective design and being conducted at a single center, which restricts the generalizability of the results. The sensitivity and specificity of the indirect hemagglutination test used in the study may vary depending on laboratory conditions and the stage of the disease. In our study, no secondary confirmatory method was used for samples with suspicious titres. In addition, radiological data for some patients could not be accessed. Therefore, multicenter and prospective studies are needed for a more robust analysis of epidemiological data at regional or national levels.

CONCLUSION

The findings of this study indicate that cystic echinococcosis remains a significant public health issue in Balıkesir, a region with intensive agricultural and livestock activities. Consequently, it is essential to strengthen healthcare services related to the diagnosis and follow-up of the disease and to place greater emphasis on preventive measures. For effective control of cystic echinococcosis, early diagnosis, efficient monitoring, and increased public awareness initiatives are of critical importance.

*Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Non-Interventional Clinical Research Ethics Committee of Balıkesir University, dated June 3, 2025, with the approval number E.526429, decision number 2025/220.

Informed Consent: Informed consent was no received due to the retrospective nature of the study.

Footnotes

*Authorship Contributions

Concept: N.İ., Design: N.İ., Data Collection or Processing: N.İ., Y.Ö., Analysis or Interpretation: N.İ., Y.Ö., T.K.A., A.G.Ş., Literature Search: N.İ., Y.Ö., T.K.A., Writing: N.İ., Y.Ö., T.K.A., A.G.Ş.

Conflict of Interest: No conflict of interest was declared by the authors.

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Original Investigation
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Cystic Echinococcosis in Pediatric Patients in Sivas Province: Clinical, Laboratory, Surgical, and Radiological Findings

Sivas İlindeki Pediatrik Hastalarda Kistik Ekinokokoz: Klinik, Laboratuvar, Cerrahi ve Radyolojik Bulgular

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ABSTRACT

Objective: This study aimed to retrospectively evaluate the serological, clinical, and radiological findings in the diagnosis of cystic echinococcosis (CE) in pediatric patients. The relationship between serological test results and clinical and radiological findings was also investigated.
Methods: The study included 216 pediatric patients (under 18 years old) who underwent indirect hemagglutination assay (IHA) testing for CE differential diagnosis between January 2016 and December 2023. Demographic data, clinical symptoms, radiological imaging results, and surgical status were obtained from the hospital information management system. IHA tests were performed using a commercial kit (Hydatidose, Fumouze Laboratoires, France) following the manufacturer's protocol. A titer of ≥1/320 was considered positive, 1/160 as borderline, and <1/160 as negative. Statistical analysis was performed using SPSS 23.0, and a p-value <0.05 was considered significant.
Results: CE was diagnosed in 40 (18.5%) of 216 patients based on combined clinical, laboratory, and radiological evaluations. The mean age of the patients was 11.92±4.14 years, and 52.5% were male. IHA test results were positive in 31 (77.5%) patients and negative in 9 (22.5%). Radiological imaging showed a single cyst in 67.5% of patients and multicystic appearance in 32.5%. The most common cyst localizations were liver (67.5%), lung (22.5%), spleen (7.5%), and brain (2.5%). Surgery was performed in 42.5% of patients, while 22.5% were followed non-surgically. No statistically significant relationship was found between cyst number, localization, and IHA positivity (p>0.05).
Conclusion: The findings emphasize the importance of evaluating clinical, laboratory, and radiological data together for accurate and early diagnosis of CE. Due to the variable sensitivity of the IHA test, negative results should be confirmed with additional diagnostic methods. While radiological imaging provides critical information about cyst localization, further studies are needed to investigate the correlation between cyst number, localization, and clinical course. Larger patient series would help improve the diagnostic process and clinical management of pediatric CE.
Keywords: Cystic echinococcosis, serological diagnosis, indirect hemagglutination, cyst hydatid

ÖZ

Amaç: Bu çalışma, pediatrik hastalarda kistik ekinokokkoz (KE) tanısında serolojik, klinik ve radyolojik bulguların retrospektif olarak değerlendirilmesini amaçlamaktadır. Çalışmada, serolojik test sonuçları ile klinik ve radyolojik bulgular arasındaki ilişkiler incelenmiştir.
Yöntemler: Ocak 2016 - Aralık 2023 tarihleri arasında hastanemizde KE ayırıcı tanısı için indirekt hemaglütinasyon (İHA) testi çalışılan 18 yaş altındaki 216 hastanın verileri retrospektif olarak analiz edildi. Hastaların demografik verileri, klinik belirtileri, radyolojik görüntüleme sonuçları ve cerrahi durumları hastane bilgi yönetim sisteminden elde edildi. İHA testleri, üretici firmanın protokolüne uygun olarak ticari bir kit (Hydatidose, Fumouze Laboratoires, Fransa) kullanılarak çalışıldı. Test sonuçlarında ≥1/320 pozitif, 1/160 şüpheli ve <1/160 negatif olarak değerlendirildi. İstatistiksel analizler SPSS 23,0 yazılımı ile yapıldı ve p<0,05 değeri anlamlı kabul edildi.

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Bulgular: Toplam 216 hastanın 40'ında (%18,5) klinik, laboratuvar ve radyolojik bulguların birlikte değerlendirilmesiyle KE tanısı konuldu. Hastaların yaş ortalaması 11,92±4,14 yıl olup, %52,5'i erkekti. İHA testi 31 hastada (%77,5) pozitif (≥1/320), 9 hastada (%22,5) negatif (<1/320) olarak bulundu. Radyolojik görüntülemeler sonucunda hastaların %67,5'inde tek kist, %32,5'inde ise multikistik görünüm tespit edildi. Kistlerin en sık yerleşim bölgeleri karaciğer (%67,5), akciğer (%22,5), dalak (%7,5) ve beyin (%2,5) olarak saptandı. Hastaların %42,5'i opere edilmiş, %22,5'i cerrahi dışı takip edilmişti. Kist sayısı, kist yerleşim yeri ile İHA pozitifliği arasında istatistiksel olarak anlamlı bir ilişki saptanmadı (p>0,05).

Sonuç: Elde edilen veriler, KE tanısının doğru ve erken konulabilmesi için klinik, laboratuvar ve radyolojik bulguların birlikte değerlendirilmesi gerektiğini vurgulamaktadır. İHA testinin duyarlılığı değişkenlik gösterebildiğinden, negatif sonuçların kesin tanı için ek testlerle desteklenmesi önerilmektedir. Radyolojik görüntüleme yöntemleri, hastalığın lokalizasyonu açısından önemli bilgiler sunsa da, kist sayısı ve yerleşiminin klinik seyirle ilişkisi daha fazla araştırılmalıdır. Daha geniş hasta gruplarıyla yapılacak çalışmalar, tanısal süreçlerin geliştirilmesine katkı sağlayacaktır.

Anahtar Kelimeler: Kistik ekinokokkoz, serolojik tanı, indirekt hemaglütinasyon, kist hidatik

INTRODUCTION

Cystic echinococcosis is a zoonotic parasitic disease caused by *Echinococcus* species (1,2). The parasite is transmitted to humans through ingestion of food or water contaminated with parasite eggs shed in the feces of infected dogs, or through direct contact with contaminated environments (3). Humans are intermediate hosts for *Echinococcus*, meaning they are not the parasite's primary targets (4). In Türkiye, the disease is a significant public health issue, particularly in the Eastern and Central Anatolian regions and in rural areas (5). The liver is the most commonly affected organ, followed by the lungs. In pediatric cases, pulmonary involvement is more frequent than hepatic involvement (4). Due to the possibility of hematogenous spread, the parasite can affect various organs and, although rare, may localize in virtually any part of the body (5,6).

The clinical presentation of the disease varies depending on factors such as the location, size, pressure effects, and possible rupture of the cyst. However, the disease may remain asymptomatic for many years (4,7). A definitive diagnosis requires a combination of methods, including serology, histology, nucleic acid detection, and imaging techniques (3). Serological diagnosis is typically established using a screening test such as indirect hemagglutination assay (IHA) or ELISA, followed—if positive—by confirmation with Western blot testing (8). Treatment options for cystic echinococcosis include medical treatment, surgery, percutaneous interventions, and a watch-and-wait strategy, depending on the size, location, and clinical presentation of the cyst (4,9).

The aim of this study was to evaluate the clinical findings, IHA results, surgical status, and radiological characteristics of patients diagnosed with cystic echinococcosis and to investigate the relationships among these variables.

METHODS

Study Design and Sample Collection

This study was approved by the Sivas Cumhuriyet University Ethics Committee with decision number 2024-12/06, dated December 19, 2024. A total of 216 samples from patients under 18 years of age, submitted between January 2016 and December 2023 from various departments of our hospital for the differential diagnosis of hydatid cyst, were retrospectively analyzed.

Clinical signs and symptoms, surgical status, radiological imaging findings, and demographic data of the patients were obtained from the hospital information management system. Repeated test results performed for treatment follow-up after an initial positive result were excluded from the study.

Serological Analysis

In the routine practice of our laboratory, sera were separated from blood samples and tested using a commercial kit (Hydatidose, Fumouze Laboratoires, France) according to the manufacturer's instructions. Upon arrival at the laboratory, the samples were stored at +4 °C and processed within 48 hours. The IHA was performed using U-bottom microplates.

Serum dilutions (1/80, 1/160, 1/320, and 1/640) were prepared and mixed with antigen-coated erythrocyte suspension. The absence of sedimentation or the presence of irregular lace-like sedimentation was considered a positive reaction. A negative result was defined as the formation of a compact button-like sediment in the center of the wells due to gravity.

According to the manufacturer's instructions, titers of 1/320 and above were reported as positive. A titer of 1/160 was considered borderline, and repeat testing was recommended 2-3 weeks later.

Statistical Analysis

The collected data were analyzed using the SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as numbers and percentages. Descriptive statistics were expressed as mean ± standard deviation, minimum-maximum values, numbers, and percentages. Comparisons between categorical variables were performed using the Pearson chi-square test. When expected cell counts were less than five, Fisher's exact test or Fisher-Freeman-Halton exact test was used as appropriate. A p-value of <0.05 was considered statistically significant.

RESULTS

In this study, cystic echinococcosis was identified in 40 patients based on laboratory, clinical, and radiological findings. Of these patients, 21 were male (52.5%) and 19 were female (47.5%), and the mean age was 11.92±4.14 years (range: 4-17). A positive IHA result (≥1/320) was detected in 31 patients (77.5%), while nine patients (22.5%) had negative IHA results (<1/320). Imaging modalities used for diagnosis included ultrasonography, computed tomography, and magnetic resonance imaging. A single cyst was observed in 27 patients (67.5%), whereas multiple cysts were present in 13 patients (32.5%).

Regarding cyst localization, the liver was the most commonly affected organ (67.5%), followed by the lungs (22.5%), spleen (7.5%), and brain (2.5%). Seventeen patients (42.5%) underwent surgical treatment, nine patients (22.5%) were followed without surgery, and the surgical status of 14 patients (35%) could not be determined.

At presentation, 34 patients (85%) had at least one symptom, whereas six patients (15%) were diagnosed incidentally during imaging studies performed for unrelated conditions. Abdominal pain was the most frequently reported symptom among patients with hepatic cysts, while cough was observed in patients with pulmonary involvement. No statistically significant association was found between cyst localization and presenting symptoms (p>0.200). Detailed demographic and clinical characteristics of the patients are presented in Table 1.

The distribution of IHA titers among patients was also evaluated. Five patients (12.5%) had titers below 1/160, four patients (10.0%) had a titer of 1/160, seven patients (17.5%) had a titer of 1/320, and twenty-four patients (60.0%) had titers of 1/640. Nine patients had negative IHA results. Despite negative serology, these patients were diagnosed with cystic echinococcosis based on compatible clinical findings and characteristic radiological features.

The relationship between cyst number and IHA positivity was also evaluated. IHA positivity was detected in 20 of 27 patients (74.1%) with a single cyst and in 11 of 13 patients (84.6%) with multiple cysts. No statistically significant association was found between cyst number and IHA positivity (Fisher's exact test, p=0.690).

Regarding cyst localization, the liver was the most commonly affected organ (27/40, 67.5%), followed by the lungs (9/40, 22.5%), spleen (3/40, 7.5%), and brain (1/40, 2.5%). The distribution of cyst localization according to affected organs is illustrated in Figure 1. The association between cyst localization and IHA positivity was analyzed by grouping cyst localization as pulmonary, hepatic, and other sites. IHA positivity was observed in 7 of 8 patients (87.5%) with pulmonary cysts, 21 of 26 patients (80.8%) with hepatic cysts, and 3 of 6 patients (50.0%) with cysts located at other sites. No statistically significant association was found between cyst localization and IHA positivity (Pearson chi-square test, χ^2=3.22, df=2, p=0.200) (Table 2).

Surgical management according to cyst localization was also evaluated. Surgical treatment was performed in patients with pulmonary, hepatic, and other organ involvements. However, no statistically significant association was found between cyst localization and surgical status (Fisher-Freeman-Halton exact test, p=0.413). The distribution of surgical status and presenting symptoms according to cyst localization is shown in Table 3. The location of the cyst and the most common associated symptoms are shown in Table 4.

Table 1. Demographic and clinical characteristics of patients with cystic echinococcosis (n=40)

Variable	n (%)
Sex	
Male	21 (52.5)
Female	19 (47.5)
Age (years)	11.92±4.14
Cyst number	
Single cyst	27 (67.5)
Multicystic	13 (32.5)
IHA result	
Positive	31 (77.5)
Negative	9 (22.5)
IHA titers	
<1/160	5 (12,5)
1/160	4 (10)
1/320	7 (17.7)
1/640	24 (60)
Surgical status	
Operated	17 (42.5)
Follow-up without surgery	9 (22.5)
Unknown	14 (35)
Clinical presentation	
Symptomatic	34 (85)
Incidental diagnosis	6 (15)

n: Number of patients, IHA: Indirect hemagglutination assay

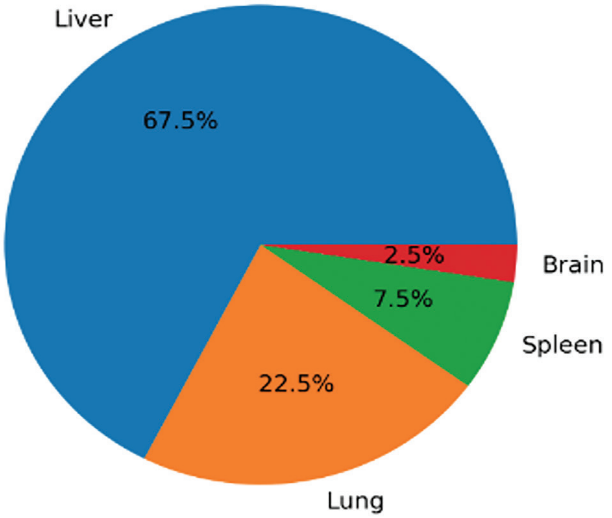

Figure 1. Distribution of cyst localization according to affected organs in patients with cystic echinococcosis.

Table 2. Relationship between cyst characteristics and IHA positivity

Variable	IHA positive, n (%)	IHA negative, n (%)	p
Cyst number			
Single cyst	20 (74.1)	7 (25.9)	0.69
Multicystic	11 (84.6)	2 (15.4)	
Localization			
Lung	7 (87.5)	1 (12.5)	0.2
Liver	21 (80.8)	5 (19.2)	
Other	3 (50)	3 (50)	

Pearson chi-square test was used for comparisons; Fisher's exact test was applied when expected cell counts were less than five
IHA: Indirect hemagglutination assay

Table 3. Distribution of surgical status and symptoms according to cyst localization

	Surgical status			**p**
Localization	**Operated, n (%)**	**Follow-up, n (%)**	**Unknown, n (%)**	
Lung	3 (17.6)	1 (11.1)	4 (28.6)	0.413
Liver	10 (58.8)	7 (77.8)	9 (64.3)	
Brain	1 (5.9)	0	0	
Lung + liver	2 (11.8)	0	0	
Spleen	1 (5.9)	1 (11.1)	1 (7.1)	

Due to small expected cell counts, comparisons were performed using Fisher-Freeman-Halton exact test

Table 4. Presenting symptoms by localization (main symptoms)

	Localization			
Symptom	**Lung**	**Liver**	**Brain**	**Spleen**
Abdominal pain	1	17	0	1
Cough	2	0	0	0
Fever	1	0	0	0
Febrile convulsion	0	0	1	0
No complaint	1	4	0	1

DISCUSSION

Cystic echinococcosis remains an important zoonotic and public health problem in Türkiye, as reported by the Ministry of Health and several epidemiological studies (10,11). Although infection may be acquired during childhood, the disease is often diagnosed later in life because hydatid cysts grow slowly. Previous studies have reported that only 10-20% of cases are diagnosed in individuals younger than 16 years (12). In the present study, 40 of 216 pediatric patients were diagnosed with cystic echinococcosis, indicating that the disease continues to represent a significant health concern in children and emphasizing the importance of early recognition and diagnosis.

In our study, no statistically significant difference in IHA positivity was observed between male and female patients. Similar findings have been reported in previous studies, suggesting that sex may not represent a major determinant of serological response in cystic echinococcosis (13,14).

The reported localization sites in various studies are summarized in Table 5. In addition to hepatic and pulmonary involvement, splenic and cerebral hydatid cysts were also identified in our study. In several studies (15-19), the lungs have been reported as the most frequently involved organ in pediatric cases, whereas other studies have identified the liver as the most commonly affected organ, similar to adult populations (11,16,20,21).

Table 5. Various cyst localization sites reported in the literature

Localization Site	**Age, sex**	**Reference**
Spleen	Child, female	Mansour et al. (22)
Thyroid	Adult, female	Zorluoğlu et al. (23)
Pelvis	Adult, female	Arac et al. (24)
Kidney	Adult, female	Yeşil et al. (25)
Iliac bone	Child, female	Çelebi Çongur et al. (26)
Heart	Child, male	Mutlu et al. (27)
Brain	Child, case series	Assamadi et al. (28)
Ovary	Adult, female	Mohammed and Arif (29)
Bone, eye, bladder, spinal cord, pancreas, colon	Child, case series	Anadol et al. (18)

In our study, the liver was the most frequently involved organ (67.5%), followed by the lungs (22.5%). The mean age of the patients in our study was 11.9 years. However, the age at diagnosis does not necessarily reflect the timing of infection or the onset of symptoms. The predominance of hepatic involvement observed in our study may be explained by the anatomical and physiological role of the liver as the first filter in the portal circulation, where parasites entering the bloodstream after intestinal absorption are most likely to be trapped.

In a study evaluating 57 pediatric hydatid cyst cases (20), abdominal pain was reported as the most common presenting complaint, followed by cough, nausea, vomiting, fever, and dyspnea. Another study analyzing 100 cases of hepatic hydatid cysts (30) found that fever, hepatomegaly, and abdominal pain were the most frequent symptoms. In pediatric patients with pulmonary involvement (19), cough, chest pain, and fever were reported as the predominant symptoms. Similarly, studies evaluating 38 pulmonary cystic echinococcosis cases (31), as well as other studies including 41 (16), 50 (15), and 376 (18) patients, have consistently reported cough, fever, and abdominal pain as the most common presenting complaints.

In the present study, the most frequent presenting symptom was abdominal pain, followed by cough and fever. Differences reported in the literature may be explained by variations in the localization of cyst involvement. Patients with hepatic cysts tend to present with abdominal pain, whereas pulmonary cysts are more commonly associated with cough. Although abdominal pain was more frequently observed among patients with hepatic cysts in our study, no statistically significant association was detected between cyst localization and presenting symptoms (p>0.05). This finding may be related to the relatively small sample size and suggests that clinical manifestations may overlap depending on multiple factors.

In line with our findings, varying rates of IHA positivity at the time of diagnosis have been reported in the literature, including 86.7% (18), 48% (32), 54.8% (16) and 58% (11). In our study, IHA positivity was 77.5%, and 15% of the patients were diagnosed incidentally during investigations performed for unrelated conditions. Although serological tests such as IHA are frequently used in the diagnostic evaluation of cystic echinococcosis, their sensitivity may vary depending on several factors. The host immune response may differ according to cyst location, stage, and integrity. In our study, some patients had negative IHA results despite radiologically compatible findings. Possible explanations for seronegativity include early-stage infection, intact cysts that do not induce a strong immune response, or variability in individual immune responses. Therefore, serological results should be interpreted together with clinical findings and imaging studies in the diagnostic evaluation of cystic echinococcosis.

CONCLUSION

The findings of this study highlight the importance of integrating clinical, serological, and imaging findings in the diagnostic evaluation of cystic echinococcosis in pediatric patients. Given the variable diagnostic sensitivity of the IHA, negative serological results should not exclude the disease, and further diagnostic evaluation may be required. Imaging modalities play a crucial role in identifying the localization of cysts and supporting the diagnostic process.

The relatively small sample size represents a limitation of the present study and may have influenced the statistical significance of some analyses. Nevertheless, the findings provide useful clinical and serological insights into pediatric cystic echinococcosis and emphasize the need for larger and prospective studies to better clarify the relationship between cyst characteristics and clinical manifestations.

*Ethics

Ethics Committee Approval: This study was approved by the Sivas Cumhuriyet University Ethics Committee with decision number 2024-12/06, dated December 19, 2024.

Informed Consent: Retrospective study.

*Authorship Contributions

Surgical and Medical Practices: L.C., Concept: K.F.T., L.C., M.H., Design: K.F.T., L.C., Data Collection or Processing: K.F.T., M.H., Analysis or Interpretation: K.F.T., L.C., M.H., Literature Search: K.F.T., Writing: K.F.T., L.C., M.H.

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Original Investigation
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Epidemiological Evaluation of Scabies Cases Presenting to a Tertiary Healthcare Facility Over a Five-year Period

Üçüncü Basamak Bir Sağlık Kuruluşuna Başvuran Skabiesli Olguların Beş Yıllık Süreçte Epidemiyolojik Olarak Değerlendirilmesi

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ABSTRACT

Objective: This study aimed to evaluate the demographic characteristics and annual trends of scabies cases before, during, and after the coronavirus disease-2019 pandemic.
Methods: All patients diagnosed with scabies at the Dermatology Outpatient Clinic of Yozgat Bozok University between January 2019 and December 2023 were retrospectively analyzed. Demographic data, including age, sex, nationality, and admission date, were retrieved from the hospital database.
Results: Two thousand ten of 50,887 patients (3.9%) were diagnosed with scabies during the five-year study period (2019-2023). The frequencies of scabies from 2019 to 2023 were 1.66%, 2.9%, 3.12%, 5.99%, and 5.82%, respectively, and a statistically significant difference was observed across the years ($p<0.001$). Males represented 54.5% of the total cases. The lowest frequency was in the second quarter of 2019, and the highest in the first quarter of 2023 (1.31% and 7.84% respectively). The fourth quarter exhibited the highest overall case count ($p<0.001$). The patient's mean age was 29.4±21.9 years, with significant annual variation ($p=0.002$). The prevalence of scabies was significantly higher among foreign patients than among Turkish nationals ($p<0.001$). Treatment failure and reinfestation peaked in 2020. Scabies was present in 1.71% (257/14,989) of patients prior to the pandemic, compared to 3% (261/8,687) during the pandemic ($p<0.001$).
Conclusion: The incidence of scabies has increased gradually since 2019, with a marked rise observed in 2022, coinciding with the post-pandemic period. This may be linked to treatment resistance, poor compliance, limited healthcare access during the pandemic, and the lifting of restrictions thereafter. Reinfestation rates fell to their lowest level once oral ivermectin became available in early 2023. Public education and effective treatment strategies are essential for outbreak control.
Keywords: Scabies, epidemiology, outbreak, COVID-19

ÖZ

Amaç: Çalışmamızda koronavirüs hastalığı-2019 pandemisi öncesi, pandemi dönemi ve pandemi sonrası skabies olgularının demografik özellikleri ve yıllara göre değişimlerinin değerlendirilmesi amaçlandı.
Yöntemler: Ocak 2019 ve Aralık 2023 tarihleri arasında Yozgat Bozok Üniversitesi Dermatoloji Kliniği'nde skabies tanısı alan tüm hastalar retrospektif olarak değerlendirilerek çalışmaya alındı. Yaş, cinsiyet, vatandaşlık ve başvuru tarihleri hastane veri tabanından elde edildi.
Bulgular: Beş yılda (2019-2023) polikliniğe başvuran toplam 50887 hastanın 2010'u (%3,9) skabies tanısı aldı. 2019-2023 yıllarındaki skabies sıklığı sırasıyla %1,66, %2,9, %3,12, %5,99 ve %5,82'ydi. Yıllar arasındaki skabies sıklığı farkı anlamlıydı ($p<0,001$). Çalışmaya dahil edilen hastaların %54,5'ü erkekti. Skabies sıklığının en düşük olduğu dönem 2019 yılının 2. çeyreklik dilimiyken, en yüksek olduğu dönem 2023 yılının 1. çeyreklik dilimiydi (%1,31'e karşı %7,84). Fakat toplamda en sık 4. çeyrekte hasta izlendi ve bu fark diğer çeyreklere göre anlamlıydı. Yaş ortalaması 29,4±21,9 yıl olup, yıllara göre yaş ortalamalarında anlamlı fark mevcuttu ($p=0,002$). Yabancı uyruklu hastalarda skabies görülme oranı Türk vatandaşlarına göre anlamlı derecede yüksekti ($p<0,001$). Tedavi başarısızlığı ve reinfestasyon oranı 2020 yılında en yüksek seviyeye ulaştı. Reinfestasyon oranları 2023 yılında en

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düşük seviyede izlendi. COVID-19 pandemisi öncesinde toplam 14.989 hastanın 257'si (%1,71) skabies iken, pandemi döneminde başvuran 8.687 hastanın 261'i (%3) skabiesti ve bu fark anlamlı saptandı (p<0,001).

Sonuç: Skabies sıklığı, 2019'dan itibaren kademeli olarak artmış ve pandemi sonrası döneme denk gelen 2022'de belirgin bir artış göstermiştir. Bu artışın tedavi uyumsuzluğu, tedavi direnci, pandemi nedeniyle tedaviye ulaşamama, pandemi sonrası sosyal kısıtlamaların kalkmasına bağlı olabileceği değerlendirilmiştir. 2023 yılının başında oral ivermektinin ülkemizde ruhsat almasıyla reinfestasyon oranları bu yılda en düşük seviyede izlenmiştir. Skabies epidemisinin kontrolü için toplumun bilgilendirilmesi ve etkili tedavi stratejileri önemlidir.

Anahtar Kelimeler: Skabies, epidemiyoloji, salgın, COVID-19

INTRODUCTION

Scabies is an infestation characterized by nocturnal pruritus and polymorphic eruptions. Transmission primarily occurs through direct skin-to-skin contact, with occasional indirect transmission via contaminated fomites. Contributing factors include migration, inadequate healthcare, communal living, and poor hygiene. The incidence frequently increases during the fall and winter. Scabies is caused by an obligate parasite that completes its life cycle on humans, surviving outside the body for 2-3 days (1-5).

Symptoms typically manifest 3-6 weeks post-infestation. Clinically, patients present with nocturnal pruritus, particularly around the abdomen, genital region, wrists, and ankles, but sparing the interscapular and facial areas. This pruritus represents a hypersensitivity reaction to mite proteins and feces. Dermatological examination reveals non-specific lesions such as excoriated papules, secondary infections, and eczematization, together with specific findings such as burrows and vesicle perles (6).

The diagnosis is usually clinical, based on typical presentation, nocturnal pruritus, and the presence of a household scabies infection (7). In 2020, the International Alliance for the Control of Scabies (IACS) established diagnostic criteria involving three main levels: confirmed (A), clinical (B), and suspected (C), which are further divided into eight subcategories. Level A involves the observation of mites, eggs, or feces via microscopy (A1), high-magnification devices (A2), or dermoscopy (A3). Level B includes scabies burrows (B1), typical male genital lesions (B2), or typical lesions with a typical distribution and two history features (B3). Level C involves either a typical clinical distribution with one history feature (C1) or an atypical lesion or distribution with two history features (C2). History features include pruritus and close contact (8).

Scabies is a significant public health concern due to its outbreak potential, treatment costs, and impact on patient quality of life (4). Recent Turkish epidemiological studies suggest a correlation between an increased incidence and the coronavirus disease-2019 (COVID-19) pandemic (9,10). This study evaluated the frequency of scabies and the demographic characteristics of cases in our region over a five-year period spanning pre-pandemic, pandemic, and post-pandemic phases.

METHODS

Patients who presented to the Yozgat Bozok University Research and Training Hospital Dermatology Clinic, Türkiye, between January 1, 2019, and December 31, 2023, and who were diagnosed with scabies (ICD-10 code B86) according to the International Classification of Diseases, 10th revision (ICD-10) were included in the study. All were diagnosed according to IACS criteria (levels A, B, or C), with the majority classified as level A. Diagnosis was based on patient history, clinical examination, dermoscopic observation of mites, feces, or eggs, and, in selected cases, light microscopy. Dermoscopy was the most commonly used diagnostic tool, particularly in level A cases. Demographic data such as age, gender, nationality, and admission dates were anonymized and retrieved from the electronic registration database. Patients diagnosed with scabies outside the dermatology clinic were excluded. All patients diagnosed with scabies were enrolled, and no exclusion criteria were applied. However, repeat visits occurring within 10 days were considered clinically insignificant and therefore excluded. Recurrent presentations between 10 and 30 days were regarded as treatment failures, whereas those occurring after 31 days were considered reinfestation. Approval for the study was obtained from the Yozgat Bozok University Faculty of Medicine Ethics Committee (decision no: 2025-GOKAEK-2510_2025.05.21_460, date: 21.05.2025). Due to the retrospective nature of the study, written informed consent could not be obtained from patients. However, the research was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

All statistical procedures were conducted using SPSS version 27.0 for Windows. The annual distributions of scabies diagnoses and of patients' gender and age were analyzed using frequency and percentage distributions. Mean and standard deviation were used to describe age. Where appropriate, categorical variables were analyzed using Pearson's chi-square test. For chi-square tests with degrees of freedom greater than 1, post-hoc analyses were performed using the z-test. Once the normality of the scale variables had been confirmed with the Kolmogorov-Smirnov test, independent samples were compared using appropriate significance tests (the Kruskal-Wallis H and Mann-Whitney U tests). Two-sided p-values <0.05 were considered statistically significant. A Bonferroni correction for alpha inflation was applied post-hoc after the Kruskal-Wallis H and chi-square tests.

RESULTS

Two thousand ten (3.9%) out of 50,887 dermatology clinic outpatient cases between 2019 and 2023 were diagnosed as scabies. Table 1 shows the quarterly proportions of scabies cases among the total admissions. The frequency increased progressively from 2019 to 2022 (1.66%, 2.9%, 3.12%, and 5.99%) before declining slightly in 2023 (5.82%) (Figure 1). The frequency also exhibited a statistically significant difference across the years (p<0.001), with no significant differences observed between 2020 and 2021 or between 2022 and 2023.

The lowest frequency was in the second quarter of 2019 (1.31%), and the highest in the first quarter of 2023 (7.84%). All quarters exhibited significant interannual variation (p<0.001) (Table 1). The distribution across quarters was 25% in the first, 21.7% in the second, 22% in the third, and 31.2% in the fourth (Figure 2). The differences among the quarters were significant (p<0.001),

Table 1. Frequency distribution of scabies according to years and quarters

		2019	2020	2021	2022	2023	p
Quarter 1	Scabies n (%)	43 (1.35)	45 (2.04)	52 (2.18)	152 (6.36)	211 (7.84)	**p<0.001**
	All outpatients n	3196	2208	2390	2391	2691	
Quarter 2	Scabies n (%)	40 (1.31)	47 (4.01)	59 (3.36)	129 (5.1)	161 (5.64)	**p<0.001**
	All outpatients n	3042	1173	1755	2530	2854	
Quarter 3	Scabies n (%)	63 (1.89)	38 (2.58)	84 (3.21)	124 (4.64)	134 (4.73)	**p<0.001**
	All outpatients n	3337	1473	2620	2673	2831	
Quarter 4	Scabies n (%)	66 (2.06)	66 (3.48)	83 (3.86)	246 (7.50)	167 (5.23)	**p<0.001**
	All outpatients n	3205	1897	2148	3280	3193	
Total	Scabies n (%)	212 (1.66)	196 (2.9)	278 (3.12)	651 (5.99)	673 (5.82)	**p<0.001**
	All outpatients n	12780	6751	8913	10874	11569	

Quarter 1: January-March, Quarter 2: April-June, Quarter 3: July-September, Quarter 4: October-December. Data were expressed as the number of patients (percentage). The chi-square test was used, followed by a Bonferroni correction as a post-hoc analysis. Significant values are shown in bold

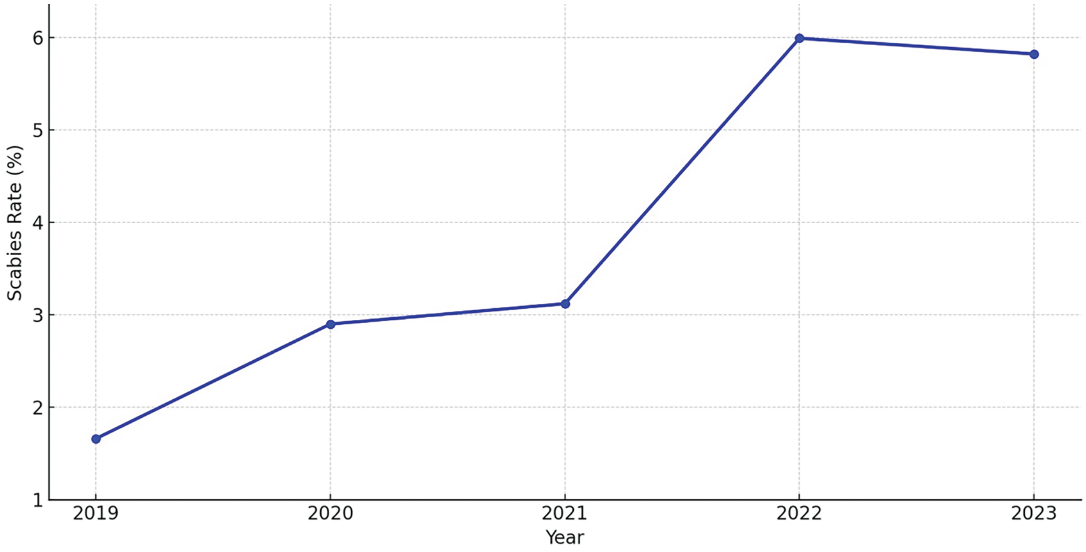

Figure 1. Frequency distribution of scabies by year

except between the first and second quarters and between the second and third quarters. In 2020, the frequency of scabies in the first quarter was significantly lower than in the second and fourth quarters (p<0.001 and p=0.004, respectively).

Males represented 1,096 (54.5%) of the scabies cases and females represented 914 (45.5%); the difference was significant (p<0.001). Although a male predominance was observed in all five years, the difference was not significant in 2019 or 2021 (p=0.68, p=0.01, p=0.905, p=0.002, and p=0.028, respectively). The overall gender distribution did not differ significantly across the five years of the study (p=0.26) (Table 2).

The mean age of the scabies patients was 29.43±21.90 years. Yearly mean ages from 2019 to 2023 were 35.79±24.04, 27.11±19.72, 28.32±21.28, 28.69±21.49, and 29.28±22.16 years, respectively. A significant difference was found in both overall mean age and female mean age across the years (p=0.002 and p=0.001, respectively). Although females were significantly older in 2019 than in other years, the male age distribution exhibited no significant variation over time (p=0.48). Females were significantly older than males in 2019 and 2023 (p=0.005 and p=0.023, respectively) (Table 2).

Patients were categorized into six age groups: infants (0-1), preschool (1-6), school-age (7-14), young adults (15-44), middle-aged (45-65), and elderly (65+). Scabies was present in all groups, but was significantly more frequent among preschool boys than girls (p=0.002). A significant difference in age group distribution was observed across the years (p=0.003), principally due to the higher proportion of elderly patients in 2019 (p<0.0004). No significant changes were noted in other age groups (Table 2).

Ninety-nine (13%) of the 725 (1.4%) foreign nationals were diagnosed with scabies. The incidence was significantly higher among foreign patients (p<0.001). Overall, 4.9% of scabies patients were foreign nationals; the highest rate (11.7%) was observed in 2020 (p<0.001).

Three hundred forty-one (69.9%) of the 488 patients with recurrent visits underwent two consultations for scabies, while 147 (30.1%) were treated more than twice. The number of recurrent visits differed significantly across years (p=0.002). Foreign nationals with scabies exhibited higher recurrence rates than Turkish citizens (p=0.008). The overall rate of recurrent visits among scabies patients peaked in 2020 at 36.7%. Treatment failure, as a proportion of total visits, also exhibited significant annual variation (p=0.022), with the highest level occurring in 2020 (7.1%), although pairwise year comparisons revealed no significant differences. Reinfestation rates also varied significantly (p<0.001), reaching 29.6% in 2020 and dropping to 15.2% in 2023, which was significantly lower than in 2019, 2020, and 2021 (Table 2).

Because this study covered the COVID-19 pandemic, frequencies of scabies were compared between the pre-pandemic period (before April 2020) and the pandemic period (April 2020-July 2021). Scabies was diagnosed in 1.71% (257/14,989) of patients before the pandemic and in 3% (261/8,687) during the pandemic, a significant increase (p<0.001).

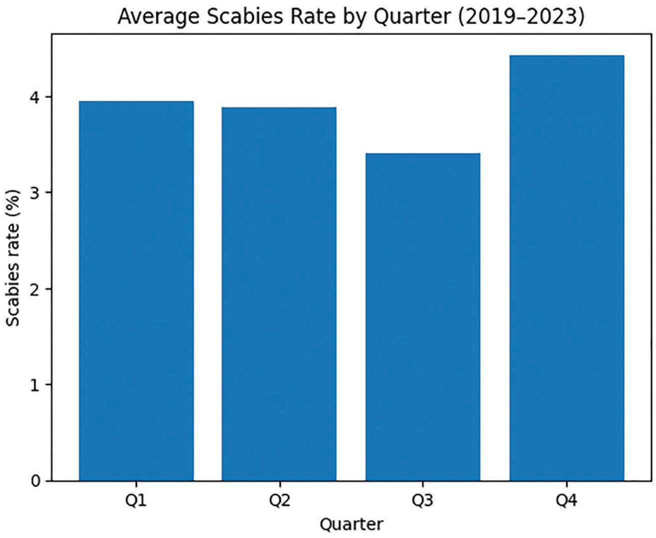

Figure 2. Frequency distribution of scabies according to quarters

Q1: January-March, Q2: April-June, Q3: July-September, Q4: October-December

Table 2. Changes in the demographic characteristics of scabies patients by year

	2019 (n=212)	**2020 (n=196)**	**2021 (n=278)**	**2022 (n=651)**	**2023 (n=673)**	**Total (n=2010)**	**p**
Age	35.79±24.04	27.11±19.72	28.32±21.28	28.69±21.49	29.28±22.16	29.43±21.90	**0.002**
Female-age	41.07±24.35	29.33±20.24	29.67±20.38	29.71±21.56	31.25±22.40	31.47±22.12	**0.001**
Male-age	30.81±22.74	25.58±19.29	26.98±22.13	27.90±21.42	27.62±21.84	27.74±21.57	0.48
p	**0.005**	0.197	0.149	0.272	**0.023**		
Sex (F/M)	103/109	80/116	138/140	285/366	308/365	914/1096	0.26
Refugee n (%)	15 (7.1)	23 (11.7)	11 (4)	21 (3.2)	29 (4.3)	99 (4.9)	**<0.001**
Recurrent presentations n (%)							**0.002**
Treatment failure	6 (2.8)	14 (7.1)	7 (2.5)	30 (4.6)	18 (2.7)	75 (3.7)	**0.022**
Re-infestation	55 (25.9)	58 (29.6)	64 (23)	134 (20.6)	102 (15.2)	413 (20.5)	**<0.001**
Age groups n (%)							**0.003**
Infants (0-1)	7 (3.3)	18 (9.2)	18 (6.5)	33 (5.1)	43 (6.4)	119 (5.9)	0.10
Preschool children (1-6)	12 (5.7)	12 (6.1)	22 (7.9)	56 (8.6)	44 (6.5)	146 (7.2)	0.45
School children (7-14)	33 (15.6)	27 (13.8)	57 (20.5)	106 (16.3)	111 (16.5)	334 (16.6)	0.35
Young adults (15-44)	74 (34.9)	93 (47.4)	116 (41.7)	290 (44.5)	293 (43.5)	871 (43.3)	0.086
Middle-aged persons (45-65)	49 (23.1)	35 (17.9)	42 (15.1)	111 (17.1)	118 (17.5)	355 (17.6)	0.21
Aged persons (65+)	37 (17.5)	11 (5.6)	23 (8.3)	55 (8.4)	64 (9.5)	190 (9.4)	**0.0004**

Data were expressed as mean ± standard deviation or patient number (percentage). Kruskal-Wallis H, Mann-Whitney U, and chi-square tests were used. Following the Kruskal-Wallis H and chi-square tests, Bonferroni correction was applied as a post-hoc analysis. Significant values are shown in bold

DISCUSSION

According to World Health Organization (WHO) data, scabies affects approximately 400 million individuals annually, with an estimated 200 million active cases worldwide and a prevalence ranging from 0.2% to 71%. The WHO classified scabies as a neglected tropical disease in 2017 (11,12). In the past two decades, more than 20 countries have reported rising prevalence, particularly in Papua New Guinea, Panama, and Fiji. Scabies remains a worldwide public health concern, affecting individuals of all ages, ethnicities, genders, and socioeconomic backgrounds, and one that primarily impairs quality of life due to severe pruritus (10,12). In Türkiye, scabies continues to represent a serious health issue. Prior to 2000, the reported prevalence ranged from 0.001% to 11.5%. After 2000, rates generally fell below 1%, and until 2018, no study reported a prevalence exceeding 1% (13-15). However, in recent years, there has been a marked rise in prevalence, consistent with the present study (1,3,6,15-18).

A Turkish-based study conducted between 2018 and 2022 reported a frequency of scabies of 3.14%, aligning with the findings of the present research, while another study covering 2019 to 2021 reported a rate of 1.99% (6,19). Notably, the upward trend in scabies incidence is not confined to the 2019-2023 period examined in the current study. Aktaş and Cebecik (1) reported that the frequency rose from 0.4% in 2013 to 1% in 2018. Similarly, a study examining 2010-2018 data noted an increase from 0.14% in 2010 to 0.91% in 2014, maintaining similar levels through 2018 (1,17). In Turan et al.'s (3) study (2017-2019), the frequency rose from 0.55% in 2017 to 0.94% in 2019. Baykal et al. (15) also identified a significant increase starting in the fourth quarter of 2018 (1.5%), which continued into 2019 (3.0%). Our 2019 rate of 1.66% is consistent with the findings of these studies.

In a study conducted in Italy, a decrease in scabies incidence was observed in 2020, followed by a progressively increasing trend through 2023, similar to the pattern identified in our study (20). In the Netherlands, a threefold increase in scabies incidence was observed between 2011 and 2021, while a study from Germany reported a ninefold increase during the period from 2009 to 2018 (21,22).

A multicenter study by Özden et al. (16) using data from 12 tertiary dermatology centers between 2014 and 2019, revealed a seven-fold increase from 2017 to 2018 and a 30-fold increase by 2019. Importantly, resistance to topical treatments was first reported in 2018; this may partially explain the sustained nationwide rise in scabies incidence reflected in the present findings through 2023 (16).

Çetinkaya et al. (7) reported 3,908 scabies cases between January 2006 and April 2017 in Kayseri and its surrounding regions. The lowest prevalence was noted in 2016, followed by a two-fold increase in the first four months of 2017 compared to the previous year. In contrast to our results, a female predominance was observed in that study (7).

In a study spanning a similar timeframe to the current research, Kara et al. (19) documented a marked increase in frequency between 2018 and 2022, the highest rate being observed in 2022, a finding consistent with our own findings. Similarly, Göçer Gürok (6) reported a steady rise from 2019 to 2021, although at slightly lower frequency rates (0.95-1.66%, 1.75-2.90%, and 1.99-3.12%, respectively). The author also noted a significant time-dependent decrease in the mean age of female patients, which is consistent with our results. Further similarities include significant differences in all quarterly comparisons and the highest case numbers occurring in the fourth quarter (6). Likewise, Turan et al. (3) observed the majority of cases in the fourth quarter, with a notable year-over-year increase during that period. International research also supports an uptick in the incidence of scabies during winter (13,18,23). The increased number of cases observed in the final quarter of this and other studies may be attributable to increased indoor contact during colder months. However, this seasonal trend is not seen in tropical regions, likely due to consistently warm climates that limit changes in daily routines and social behavior (12,24).

Studies conducted during similar periods have reported a significant decrease in the mean age of scabies patients, consistent with our findings. Aktaş and Cebecik (1) reported that the mean age decreased from 49.7 in 2013 to 31.4 in 2019. Initially, middle-aged and elderly individuals were most affected, but a notable rise in younger patients was observed over time. Other Turkish studies have also reported a downward trend in mean age (1,3,6). Consistent with the results of the present study, young adults (15-44 years) were identified as the most frequently affected group. While the prevalence of scabies in developed countries is generally low and evenly distributed across age groups, it tends to peak in infancy and school-age children in underdeveloped and developing countries (3,6,7,13). The association between a rising incidence of scabies and decreasing mean age may reflect greater social and sexual activity among younger individuals and increased transmission risk in communal settings, such as dormitories and hostels.

Gender-based frequencies have varied across studies. Some Turkish studies have reported a female predominance (1,7,17,19,25), while others, including the current research, indicate higher rates in males (3,6,26). Gender differences within specific age groups have also been observed. Turan et al. (3) reported that scabies was more common in males among young adults and infants, but more frequent in females in the middle-aged group, with no significant difference in other groups. An Ethiopian study also noted a higher, though not statistically significant, prevalence among school-aged boys. Another Turkish study observed a slight male predominance in the 0-18 age group (3,27,28). In the present study, although males exhibited a higher overall frequency, a significant difference was found only in preschool boys. These disparities may reflect population structure, lifestyle, and cultural differences. We suggest that men in our region who have more active social lives may contribute to this pattern. The higher frequency among preschool boys, despite the absence of any difference in school-aged children, might be explained by preschool boys having closer social interactions outdoors during playtime. This difference may diminish as children of different genders enter school, leading to similar social conditions.

Recent studies suggest that the increasing incidence of scabies may be due to treatment failure, drug resistance, or reinfestation. A multicenter study from Türkiye reported resistance to topical agents in 13% of patients during 2018-2019 (16), while another study reported that 42.5% of patients did not benefit from treatment. In addition to publications reporting permethrin resistance (29), some studies have proposed that treatment unresponsiveness is attributable to incorrect drug use, rather than permethrin to resistance itself (30). Turan et al. (3) also examined suspected reinfestation and treatment failure, and reported that the failure rate rose from 3.2% in 2017 to 6.2% in 2019, although this increase was not statistically significant. Reinfestation rates were 2.2%, 2.1%, and 1.4% for 2017, 2018, and 2019, respectively (3). In the present study, recurrent visits did not exhibit a linear increase but instead peaked in 2022. The average treatment failure rate was 3.7%, increased to 7.1% in 2020 and exhibited a fluctuating pattern. A decline was observed from 4.6% in 2022 to 2.7% in 2023. In contrast, reinfestation averaged a notably high rate of 20.5%, far exceeding that reported in the study cited above. This disparity may reflect regional differences in education, awareness, treatment adherence, and household compliance. Similar to treatment failure, reinfestation declined in 2023, likely due to the introduction of oral ivermectin in January 2023. Ivermectin's ease of use may have enhanced adherence among patients and households, thereby reducing both treatment failure and reinfestation. Additionally, if permethrin resistance were present, these cases may have been managed more effectively with ivermectin.

Refugee patients have been included in numerous studies, their proportions among total scabies cases reported being as follows: Özden et al., (16) 2.42%; Baykal et al., (15) 2.94%; Göçer Gürok (6), 27.6%, 8.7%, and 7.9% in 2019, 2020, and 2021, respectively; Turan et al., (3) 4.2%, 1.7%, and 3.3% in 2017, 2018, and 2019; and Kara et al., (19) 2.9%. Both Turan et al. (3) and Kara et al. (19) found no significant difference in repeat visits between refugees and Turkish nationals. In the present study, although refugees represented only 1.4% of the total patient population, they accounted for 4.9% of all scabies cases and had significantly higher rates of repeat visits. This may be attributed to regional variations in refugee density, education levels, language barriers, crowded living conditions, and hygiene standards. In Bener's (31) 2020 study of 767 Syrian refugees, scabies was present in 16.9%. The present study determined a scabies rate of 13% among refugees, compared with 3.8% among Turkish patients, which supports the effect of these factors.

Since this study spans the pre-pandemic, pandemic, and post-pandemic periods, the relevant literature was also reviewed. A cross-sectional study from April 2021 reported a scabies prevalence of 10.9%. Kara et al. (19) reported that the frequency rose from 2.02% before the pandemic to 5.30% after it. The frequency increased from 1.71% pre-pandemic to 3% during the pandemic, which demonstrates partial alignment. Kutlu and Metin (32) reported a rise in cases from 1.23% in April 2019 to 6.23% in April 2020, representing the early pandemic onset. Similarly, the present study determined scabies frequencies of 1.31% in the second quarter of 2019 and 4.01% in the second quarter of 2020. Additionally, a multicenter study on the pandemic's impact on dermatology outpatient services observed a decline in absolute scabies cases but an increased proportion relative to total visits (1.18% vs. 2.03%, respectively) (33).

A notable increase in scabies cases had already been documented in Türkiye prior to the COVID-19 pandemic (16). Although several studies conducted during periods overlapping with the present study reported rising case numbers during the pandemic, the extent to which this increase was directly attributable to the pandemic remains debatable (9,10). A UK-based study noted that scabies cases tend to surge approximately every 20 years, and the sharp increase reported in 2018 and 2019 had already raised questions about the role of the pandemic in this trend (15,34). One Turkish study examining the effect of the pandemic reported that although the absolute numbers of scabies cases were similar in 2019 and 2020, the frequency rose from 0.94% to 1.91% due to a significant reduction in total outpatient visits. No significant changes were observed across the first three quarters of 2020. The comparable scabies frequencies in the last quarter of 2019 (pre-pandemic) and the first quarter of 2020 (early pandemic) suggest an ongoing rise that is independent of the pandemic. However, despite a stable frequency, the sharp decline in diagnosed cases from 442 to 154 between the first and second quarters of 2020 raises questions. The authors attributed this to decreased outpatient visits due to social distancing policies or public reluctance to seek care during the initial pandemic shock (9). Similarly, Porsuk and Cerit (26) reported a peak incidence in January 2020, followed by a sharp decline in March and April. In the present study, the frequency increased significantly in the second and fourth quarters of 2020 compared to the first quarter. In 2021, the frequency rose slightly but did not reach statistical significance. During the post-pandemic phase in 2022, however, both the number and the frequency of cases surged dramatically following the easing of restrictions. These findings suggest that while scabies remained stable during the pandemic, containment measures such as social distancing may have temporarily curbed transmission.

In the study by Spaziante et al., (20) which analyzed data from 2017 to 2023, the authors suggested that the lowest number of scabies cases observed in 2020 compared with other years may be attributable to the negative impact of the COVID-19 pandemic on reporting activities. In contrast to many other studies, a Korean study covering the period from 2010 to 2021 reported a decline in scabies incidence, from approximately 50,000 annual cases in 2010 to 30,000 in 2021. The decrease persisted during the pandemic period, and it was proposed that increased social isolation and public health restrictions contributed to this decline (35).

Another study examining scabies cases between 2017 and 2022 observed a gradual time-dependent increase, with significant peaks in 2019 and 2021. The authors attributed this to close human contact under quarantine conditions and limited access to healthcare services. Considering the reported rise in sexually transmitted infections during that period, they also suggested that increased sexual activity during the COVID-19 pandemic may have contributed to the transmission of scabies (10). Conversely, another study attributed the progressively decreasing incidence observed in 2019-2020 and 2021 to social isolation and public health restrictions during the COVID-19 pandemic (35). In the present study, a notable surge was identified not during the peak of the pandemic in 2021, but rather in 2022, following the easing of pandemic restrictions. Two studies from Türkiye reported the lowest incidences of scabies during lockdowns (6,26), while another observed an increase in both scabies and COVID-19 as normalization began (9). These findings support the view that stay-at-home policies and social restrictions may have prevented—or at least reduced—the increase in incidence.

Study Limitations

The primary limitation of this study is its retrospective design. In addition, data from internal medicine, pediatric, and emergency departments and from primary healthcare centers were not included. Socioeconomic status, living conditions, household size, and treatment methods were not assessed. This study was designed to provide a scientific explanation for the recent increase in scabies incidence in Türkiye and to serve as a guide for future research. Because of the study methodology, the results cannot be generalized to the entire country, although they provide useful insights.

CONCLUSION

Scabies remains a significant public health problem worldwide and in Türkiye, with a notable increase in incidence since 2018, which persisted during the COVID-19 pandemic. In our study, scabies rates increased gradually from 2019 onward and showed a marked surge in 2022, which corresponded to the post-pandemic period. Migration, the growing refugee population, the COVID-19 pandemic, poor adherence to topical therapies, and potential resistance to scabicidal agents may have contributed to this trend. The impact of the COVID-19 pandemic on scabies epidemiology remains controversial; our data are insufficient to establish causality. However, our findings may inform future studies.

*Ethics

Ethics Committee Approval: Approval for the study was obtained from the Yozgat Bozok University Faculty of Medicine Ethics Committee (decision no: 2025-GOKAEK-2510_2025.05.21_460, date: 21.05.2025).

Informed Consent: Due to the retrospective nature of the study, written informed consent could not be obtained from patients. However, the research was conducted in accordance with the principles of the Declaration of Helsinki.

Peer-review: Internally and externally peer reviewed.

Footnotes

*Authorship Contributions

Surgical and Medical Practices: N.E.K., Concept: N.E.K., E.Ç., Design: N.E.K., E.Ç., Data Collection or Processing: N.E.K., Analysis or Interpretation: N.E.K., E.Ç., Literature Search: N.E.K., E.Ç., Writing: N.E.K., E.Ç.

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Original Investigation
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Investigating the Genetic Diversity of *Culiseta longiareolata* Populations in Southern Iran: Insights from the *COI* Gene

Güney İran'daki Culiseta longiareolata Popülasyonlarının Genetik Çeşitliliğinin Araştırılması: COI Geninden Elde Edilen Bulgular

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ABSTRACT

Objective: *Culiseta longiareolata (Cs. longiareolata)*, a mosquito species found in Europe, Asia, and North Africa, is an important vector for various diseases like West Nile encephalitis, and malaria. This study aimed to assess the genetic diversity of the *Cs. longiareolata* mosquito population in Fars province, southern Iran due to the critical role of genetic diversity in shaping the adaptability and survival of mosquito populations and also adaptation of mosquitoes to environmental changes, insecticides, and pathogens.

Methods: In this study, samples of *Cs. longiareolata* mosquitoes were collected from 12 locations in Fars province, Iran. Larval stages were collected using the dipping method, while adults were captured with aspirators and mosquito nets, then stored at -20 °C for later DNA extraction. The *COI* gene was amplified via polymerase chain reaction (PCR) for genetic analysis. The sequencing was done by Bioneer Company in South Korea, and the results were analyzed using bioinformatics tools like Chromas, ClustalW2, and MEGA7. The final sequences were registered in GenBank for further analysis.

Results: The phylogenetic analysis using the maximum likelihood method revealed that *Cs. longiareolata* samples from Iran clustered with populations from various countries. The analysis involved 17 nucleotide sequences with 504 positions, using the Tamura-Nei model. The genetic diversity index was 0.0165, with 6 haplotypes and a haplotype diversity of 0.721. Demographic expansion indices suggested a potential expansion event in the population. A total of 274 mosquitoes were collected, with 18 examined by PCR and 6 sequenced for the study.

Conclusion: This study provides the first comprehensive genetic assessment of *Cs. longiareolata* populations in southern Iran using the *COI* gene which contributes valuable baseline data for future molecular and ecological studies. The findings reveal a moderate level of genetic diversity and clear genetic connections with Mediterranean and Middle Eastern populations, highlighting possible regional gene flow. The research highlights the significance of genetic diversity in comprehending mosquito dynamics and enhancing disease control efforts. Ongoing genetic monitoring is essential for managing vector-borne diseases.

Keywords: *Culiseta longiareolata,* genetic diversity, *COI* gene, phylogenetic analysis, vector-borne diseases

ÖZ

Amaç: Avrupa, Asya ve Kuzey Afrika'da bulunan bir sivrisinek türü olan *Culiseta longiareolata (Cs. longiareolata)*, bruselloz, kuş gribi, Batı Nil ensefaliti ve sıtma gibi çeşitli hastalıklar için önemli bir vektördür. Bu çalışma, Güney İran'ın Fars eyaletindeki *Cs. longiareolata* sivrisinek popülasyonunun genetik çeşitliliğini değerlendirmeyi amaçlamıştır.

Yöntemler: Bu çalışmada, İran'ın Fars eyaletindeki 12 lokasyondan daldırma yöntemi kullanılarak *Cs. longiareolata* sivrisinek örnekleri toplandı. Yetişkin sivrisinekler aspiratörler ve sivrisinek ağları kullanılarak toplandı ve daha sonra DNA ekstraksiyonu için -20 °C'de saklandı. Genetik analiz için *COI* geni polimeraz zincir reaksiyonu (PCR) yoluyla çoğaltıldı. Dizileme işlemi Güney Kore'deki Bioneer Şirketi tarafından yapıldı ve sonuçlar Chromas, ClustalW2 ve MEGA7 gibi biyoinformatik araçlar kullanılarak analiz edildi. Nihai diziler daha ileri analizler için GenBank'a kaydedildi.

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Bulgular: Maksimum olabilirlik yöntemi kullanılarak yapılan filogenetik analiz, İran'dan alınan *Cs. longiareolata* örneklerinin çeşitli ülkelerden gelen popülasyonlarla kümelendiğini ortaya koydu. Analiz, Temura-Nei modeli kullanılarak 504 pozisyonlu 17 nükleotid dizisini içeriyordu. Altı haplotip ve 0,721 haplotip çeşitliliği ile genetik çeşitlilik indeksi 0,0165 idi. Demografik genişleme indeksleri, popülasyonda potansiyel bir genişleme olayına işaret etti. Çalışma için toplam 274 sivrisinek toplandı, 18'i PCR ile incelendi ve 6'sı dizilendi.

Sonuç: Bu çalışma, İran'daki *Cs. longiareolata* popülasyonlarının küresel popülasyonlarla genetik olarak bağlantılı olduğunu ortaya koymuştur. Araştırma, sivrisinek dinamiklerini anlamada ve hastalık kontrol çabalarını geliştirmede genetik çeşitliliğin önemini vurgulamaktadır. Vektör kaynaklı hastalıkların yönetimi için devam eden genetik izleme şarttır.

Anahtar Kelimeler: *Culiseta longiareolata*, genetik çeşitlilik, *COI* geni, filogenetik analiz, vektör kaynaklı hastalıklar

INTRODUCTION

Mosquitoes are among the most important insects in the field of medicine and public health, known as vectors of numerous human and animal diseasefs (1-6). To date, more than 3,500 species of mosquitoes have been reported worldwide. Species belonging to the four genera *Culiseta*, *Anopheles, Aedes*, and *Culex* play a key role in the transmission of significant diseases such as malaria, filariasis, encephalitis, and arboviral diseases (7-16). Among these, *Culiseta longiareolata (Cs. longiareolata)* has attracted special attention as one of the important mosquito species. This species was first reported in Algeria (North Africa) (17) and is now found in diverse natural habitats such as ponds, valleys, streams, and even stagnant water in plastic containers, tires, and fountains (18-20). The geographic distribution of this mosquito includes the southern Palearctic, Mediterranean, European, and Asian regions (18-20).

Cs. longiareolata is easily distinguished from other species of the genus *Culiseta* by its distinctive white stripes on various parts of its body (21). This species is not only known as a nuisance pest, but also plays an important role in the transmission of various diseases to humans and animals. *Cs. longiareolata* is one of the mosquito species that directly and indirectly affects human and animal health and acts as an intermediate host for the transmission of several pathogens and is involved in the spread of diseases such as West Nile encephalitis, and malaria (22,23). Some aspects of the medical importance of this species are mentioned. First, West Nile Encephalitis: This viral disease caused by the West Nile virus is usually transmitted to humans and animals by mosquitoes. *Cs. longiareolata* is one of the mosquito species that can play a role in the transmission of this virus (24). This disease can cause severe neurological symptoms such as inflammation of the brain (encephalitis) and, in severe cases, death. Second, role in the transmission of parasitic diseases; avian malaria: *Cs. longiareolata* is known as a potential vector for the *Plasmodium* parasite in birds. This parasite causes avian malaria, which can have a significant impact on wild and domestic bird populations (24). While this disease does not directly affect humans, it can lead to a decrease in biodiversity and disruption of ecosystems. Third, role in the transmission of Malta fever; although Malta fever is mainly transmitted through the consumption of water or food contaminated with the bacterium *Brucella*, *Cs. longiareolata* can also play a role in the transmission of this disease (24). By transmitting the bacteria between different hosts, this mosquito can contribute to the spread of the disease in different areas. Fourth, human harassment; in addition to its role in the transmission of diseases, *Cs. longiareolata* also act as a nuisance pest for humans. The bite of this mosquito can cause itching, inflammation, and allergic reactions in people. This can lead to a decrease in quality of life and disruption of daily activities, especially in areas with high densities of this mosquito.

Considering the medical importance and wide geographic distribution of this species, studying the genetic diversity of *Cs. longiareolata* can provide valuable information about the population structure, genetic patterns, and phylogenetic relationships of this species. The *cytochrome c oxidase subunit I (COI)* gene is a common molecular marker in genetic and phylogenetic studies, widely used for species identification and evolutionary relationship analysis. Due to its relatively constant evolutionary rate and ability to distinguish species, this gene is a suitable tool for studying genetic diversity in different populations.

This study aims to investigate the genetic diversity of *Cs. longiareolata* in Fars province based on the *COI* gene due to the critical role and importance of genetic diversity in shaping the adaptability and survival of mosquito populations. This research seeks to analyze the population structure, identify haplotypes, and determine the phylogenetic relationships of this species in the region. The findings of this study can enhance our understanding of the distribution patterns, ecology, and role of this mosquito in disease transmission. Additionally, they provide essential information for control and management programs targeting this species.

METHODS

Study Area

The collection of Culiseta samples was carried out using the stratified sampling method. For this purpose, Fars province was initially divided into four regions: north, south, west, and east, and three sampling locations were selected from each region. In total, 12 locations were selected for sampling from Fars province for this project (Figure 1 and Table 1). This study was conducted with the approval of the Ethics Committee of Shiraz University of Medical Sciences (number: IR.SUMS.SCHEANUT.REC.1403.078, date: 10.11.2024).

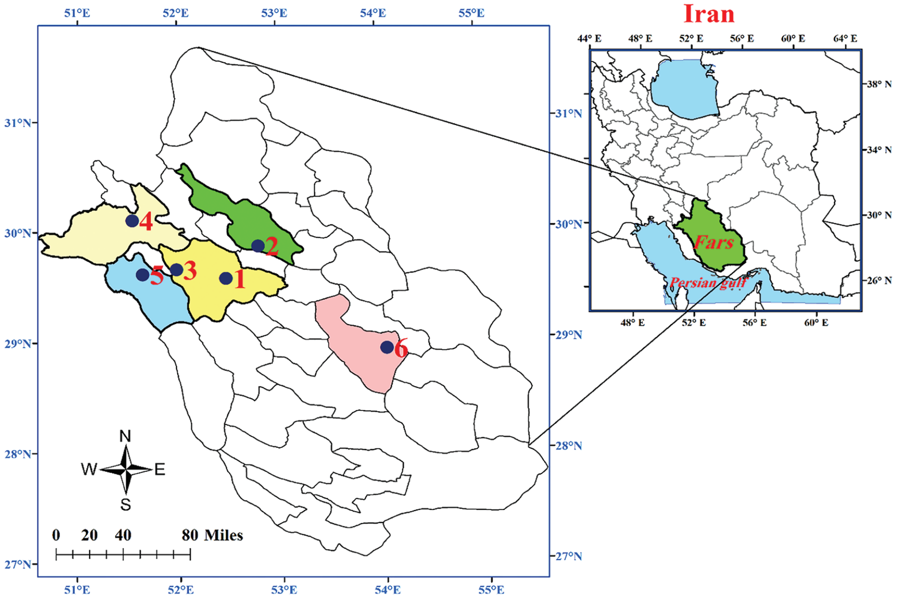

Figure 1. The geographical locations of the collection sites were mapped using ArcGIS Pro software, version 3.3.0 (Environmental Systems Research Institute). The collected samples were then identified based on valid keys and recorded in standard forms, and finally stored in a -20 °C freezer until DNA extraction (25-27). There are total of 6 location of study: Shiraz: 1, Marvdasht: 2, Dasht Arjan: 3, Nurabad: 4, Kazerun: 5, Vakilabad: 6 from Fars province, Iran

Table 1. Geographic characteristics of the collection sites for adult *Culiseta longiareolata*, detailing the number of adults collected at each location

Map codes for sampling sites	Sampling sites	Geographic coordination		Altitude (ma.s.l.)	Collected samples (n)	Adults analyzed by PCR (n)	Adults included in sequencing analysis (n)	Accession number in GenBank
		Latitude (N)	Longitude (E)					
1	Shiraz	29.579	52.475	1553	54	3	1	OR250657
2	Marvdasht	29.868	52.797	1599	42	3	1	OR250658
3	Dasht Arjan	29.660	51.984	2027	37	3	1	OR250659
4	Nurabad	30.107	51.547	978	44	3	1	OR250660
5	Kazerun	29.616	51.649	834	36	3	1	OR250661
6	Vakilabad	28.927	54.051	1383	61	3	1	OR250662
-	Total	-	-	-	274	18	6	-

PCR: Polymerase chain reaction, ma.s.l.: Meters above sea level

Mosquito Collection

Collecting adult samples at dusk to determine abundance, conduct genetic diversity studies, and analyze phylogenetic relationships in each of the study sites where no spraying was done, such as human, animal, and outdoor spaces, was carried out using an mouth aspirator and mosquito net.

DNA Extraction

DNA extraction from adult mosquitoes to determine genetic diversity was performed using the method described by Collins et al. (28). After DNA extraction, to determine the genetic diversity of the Culiseta DNA genome, we used a 721-bp region of the mitochondrial DNA-encoded *COI* gene amplified in a thermal cycler using forward primers (GGTCAACAAATCATAAAGATATTGG) and reverse primers (TAAACTTCAGGGTGACCAAAAAATCA) (29).

The polymerase chain reaction (PCR) reaction was carried out in a total reaction volume of 20 μL (4 mM of magnesium chloride, 1.5 μM of forward primer, 1.5 of reverse primer, 2 mM buffer, 150 mM of each deoxynucleoside triphosphate, 1 U Taq DNA polymerase, 40 ng of DNA and deionized water to correct volume). The thermal conditions for the PCR reaction consisted of an initial denaturation at 95 °C for 10 min; followed by 30 cycles of amplification (denaturation at 95 °C for 1 min, annealing at 54 °C for 1 min and expansion at 70 °C for 1 min; with a final extension at 70 °C for 10 min (30).

Then, this amplified DNA was loaded onto a 1% agarose gel along with a 100 bp ladder marker. Staining with green viewer solution was performed to visualize the bands formed on the ultraviolet trans-illuminator. The PCR product was purified and sequenced (30).

Phylogenetic Analysis

For sequencing and analysis of the *COI* gene, we sent 30 microliters of the gene amplification product from those of suitable quality through the Takapouzist Institute to Bioneer Company in South Korea, and sequencing was performed using the primers used in the PCR reactions (29). The results obtained from the sequenced samples were reviewed and edited using the bioinformatics software Chromas (31). To examine the similarity of the obtained sequences with each other, ClustalW2 software was used, and to compare with the sequences registered in GenBank, the NCBI BLAST server available in the GenBank databasewas used. The MEGA7 software was used to examine phylogenetic relationships and draw the phylogenetic tree, and subsequently, the obtained sequences were submittedto GenBank (32).

Statistical Analysis

Genetic diversity indices, including nucleotide diversity (π), the number of segregating sites, haplotype diversity (Hd), and the average number of pairwise nucleotide differences (K_a, K_b), were calculated using DnaSP version 6.12.03. Population expansion was assessed through Fu and Li's D and F tests, Tajima's D, Fu's Fs, Strobeck's S, and Harpending's raggedness index (*r*) to infer potential demographic events. These tests were used to evaluate deviations from neutrality and detect signs of population expansion or selection. All analyses were based on *COI* gene sequences and performed using default parameters. Phylogenetic relationships were examined using the maximum likelihood (ML) method in MEGA X, applying the Tamura-Nei model with a gamma distribution (+G) to account for evolutionary rate heterogeneity across sites. A total of 504 aligned positions were used in the final dataset, excluding gaps and missing data from the analysis.

RESULTS

The evolutionary history was inferred using the ML method based on the Tamura-Nei model. The tree with the highest log-likelihood value (-943.91) is shown, with branch percentages indicating related taxa clustering. The initial tree was obtained using the Neighbor-Join and BioNJ algorithms on pairwise distances. The analysis included 17 nucleotide sequences, with 504 positions after removing gaps. The substitution model included a discrete gamma distribution for rate variation across sites, with estimated nucleotide frequencies of A=30.33%, T/U=39.29%, C=15.59%, and G=14.79%.

ML values were estimated based on an automatically calculated tree topology. Molecular phylogenetic analysis using the ML method showed that the *Cs. longiareolata* samples from Iran (codes OR250657 to OR250662) are clustered with other populations of this species from Türkiye, Malta, Portugal, Croatia, Spain, Greece, the Netherlands, Germany, and the United Arab Emirates. The genetic distance between these samples indicates a moderate genetic diversity among the different populations of this species. Based on the provided tables, 274 adult mosquitoes were collected from 6 regions in southern Iran, of which 18 samples were examined by PCR and 6 samples were sequenced. π was 0.0165, and 6 haplotypes with a Hd of 0.721 were observed. Demographic expansion indices (such as Fu and Li's D and F, Tajima's D, and R2) indicated that the population of this species may have experienced a demographic expansion event (Tables 2 and 3, Figure 1).

All genetic variability indices were computed using DnaSP v6.12 for a 504bp mitochondrial COI fragment from 17 *Cs. longiareolata* specimens.

π : Average number of pairwise nucleotide differences per site (unit: substitutions/site).

K_a and K_b: Average number of pairwise nucleotide differences per sequence (unit: substitutions/sequence); their identical values indicate they represent the same metric (likely duplicated in labeling).

Θs (theta, per site): Population mutation rate estimate based on the number of segregating sites, scaled per site (unit: substitutions/site).

Θg (theta, per sequence): Same as Θs, but scaled to the full sequence length (unit: substitutions/sequence).

Hap (number of haplotypes): Count of distinct mitochondrial haplotypes observed.

Hd: Probability that two randomly chosen haplotypes differ (dimensionless, range 0-1).

Variance of Hd: Sampling variance of haplotype diversity.

Population expansion indices were calculated using DnaSP v6.12 based on 17 mitochondrial COI haplotypes (504 bp).

Table 2. Genetic variability indices for *Culiseta longiareolata* samples from Southern Iran

Number of sequences	Number of sites	Number of segregating sites (polymorphic)	π	K_a	K_b	Θs	Θg	Number of haplotypes	Haploid diversity	Variance of haploid diversity
17	504	67	0.0165	8.353	8.353	0.0393	19.818	6	0.721	0.0075

π: Nucleotide diversity

Table 3. Population expansion indices for *Culiseta longiareolata* samples from Southern Iran

D^+	F^+	F_s	S	D	R_2
-3.571	-3.759	4.313	0.048	-2.437	0.2525

D^+: Fu and Li's D, F^+: Fu and Li's, F_s: Fu's Fs, S: Segregating sites, D: Tajima's D

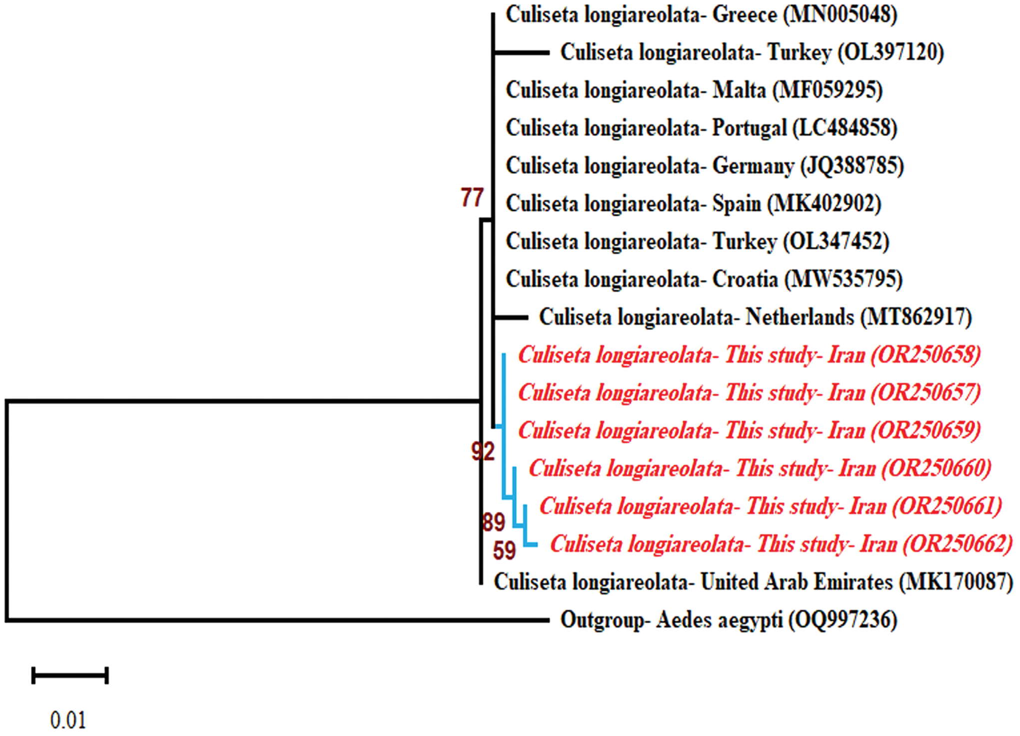

Figure 2. The evolutionary history was inferred by using the maximum likelihood method and Hasegawa-Kishino-Yano model. The tree with the highest log likelihood (-1244.36) is shown. Initial tree(s) for the heuristic search were obtained automatically by applying Neighbor-Join and BioNJ algorithms to a matrix of pairwise distances estimated using the maximum composite likelihood approach, and then selecting the topology with superior log likelihood value. The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. This analysis involved 17 nucleotide sequences. Codon positions included were 1st+2nd+3rd+non-coding. There were a total of 671 positions in the final dataset. Evolutionary analyses were conducted in MEGA X

D^+ and F^+: Fu and Li's tests comparing singleton vs. internal mutations (negative values suggest recent expansion or positive selection).

Fs: Fu's statistic; strongly negative values indicate excess of haplotypes, consistent with population expansion.

S: Strobeck's statistic (ratio of segregating sites to pairwise differences); lower values support expansion.

D: Tajima's D; negative values reflect an excess of low-frequency variants, typical after demographic expansion.

R_2: Harpending's raggedness index; low values (e.g., <0.3) indicate a smooth mismatch distribution, supporting recent expansion.

DISCUSSION

Previous studies have shown that *Cs. longiareolata* has a wide geographical distribution in Asia, Europe and Africa (18-20). The findings of this research are also consistent with these data and indicate that the populations in Iran have a genetic connection with global populations. The medium to high level of genetic diversity indicates that the populations of this species are not completely isolated in different regions. Phylogenetic data indicate that the populations in Iran are likely interacting genetically with other regions, which could be due to natural migration or environmental influences. Population expansion indices (such as Fu and Li's D, Tajima's D) indicate a probable increase in population size in the past, and this growth could be due to climatic changes, the expansion of suitable habitats, and an increase in water resources in the environment. *Cs. longiareolata* is a vector of important viral and bacterial diseases such as West Nile encephalitis, brucellosis, and avian influenza (7-11,24). Considering these factors, studying the genetic diversity of this species can help predict population changes and provide more effective control measures to reduce diseases transmitted by this mosquito. This research is one of practical comprehensive studies on the genetic diversity of *Cs. longiareolata* in Iran and provides valuable information for environmental management and vector control programs.

Genetic studies on mosquito populations have shown that environmental factors, including temperature, humidity, and available breeding sites, significantly impact genetic variation (33). The phylogenetic relationships of *Cs. longiareolata* populations in Iran suggest possible genetic exchange with populations from neighboring countries, further supporting the role of migration in maintaining genetic diversity (34). Studies on mosquito-borne disease transmission emphasize that genetic diversity in vector populations can influence pathogen susceptibility and transmission efficiency (35). Genetic studies on mosquito populations in Iran have demonstrated that environmental heterogeneity—including regional variation in temperature, precipitation, and larval habitat availability—shapes population structure and genetic diversity. For instance, analyses of mosquito species across Iranian ecozones revealed significant genetic differentiation correlated with altitude and aridity gradients (34).

Notably, phylogeographic work on *Cs. longiareolata* in southern and western Iran identified shared haplotypes with populations from Iraq and Türkiye (35), providing direct molecular evidence of cross-border gene flow. Such migration likely counteracts genetic drift and sustains diversity in peripheral populations. Furthermore, studies on *Aedes caspius* and *Culex pipiens* in Iran have linked higher mitochondrial Hd with increased vector competence for West Nile virus and *Dirofilaria immitis* (1-3,11-12.36-38) underscoring the epidemiological relevance of genetic variation in local vector populations.

Additionally, research indicates that climatic shifts have historically played a role in mosquito population dynamics, leading to fluctuations in genetic diversity due to changes in habitat suitability (39). The presence of genetically distinct yet interconnected populations suggests that movement between regions may be more frequent than previously assumed, potentially facilitated by human activities and natural dispersal mechanisms (40). Such findings highlight the need for continuous surveillance and genetic monitoring of mosquito populations to mitigate the risks associated with emerging infectious diseases (41).

Incorporating molecular tools for vector surveillance can aid in identifying cryptic species and understanding their role in disease ecology, improving vector control strategies (42-44). Future research should focus on the impact of anthropogenic factors on genetic variation and how these changes may influence disease transmission dynamics. Strengthening collaborative research efforts across different geographical regions will enhance our ability to predict and manage vector-borne disease risks effectively. New studies suggest that genetic changes in mosquito populations are influenced by environmental factors, especially in areas with unstable climates (33). This adaptability may explain the persistence of *Cs. longiareolata* across diverse habitats, supporting their role as efficient disease vectors (37). The application of genomic sequencing in mosquito surveillance programs has provided novel insights into the evolutionary trajectories of different populations (38). Such approaches are essential for identifying emerging threats and assessing the impact of control measures (39). Furthermore, ecological studies have revealed that competition with other mosquito species, as well as interspecies hybridization, may also contribute to genetic differentiation in *Cs. longiareolata* (40). This underscores the need for integrated vector management programs that incorporate ecological, genetic, and epidemiological data (41).

Study Limitations

This study was limited by the small number of sequenced samples (n=6) due to budget and logistical constraints. Additionally, only one genetic marker (*COI*) was analyzed, which may not capture the full extent of genetic variation. Future research using multilocus approaches and larger datasets is recommended.

CONCLUSION

This study confirms that *Cs. longiareolata* populations in Iran share genetic connections with global populations, showing medium to high genetic diversity and this represents the first COI-based phylogenetic assessment of *Cs. longiareolata* in southern Iran that can show critical role of genetic diversity in shaping the adaptability of mosquito populations. The genetic exchange likely occurs through migration or environmental factors, with population expansion possibly driven by climatic changes and habitat availability. The research highlights the importance of genetic diversity in predicting mosquito population dynamics and improving disease control measures. Environmental factors and migration are key in maintaining genetic variation, which can affect disease transmission. Continued genetic monitoring is crucial for managing vector-borne diseases and improving surveillance strategies.

*Ethics

Ethics Committee Approval: This study was conducted with the approval of the Ethics Committee of Shiraz University of Medical Sciences (number: IR.SUMS.SCHEANUT.REC.1403.078, date: 10.11.2024).

Informed Consent: Consent was not required to participate.

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Footnotes

*Authorship Contributions

Concept: S.S., A.P., Design: A.H.R., Data Collection or Processing: R.S., Analysis or Interpretation: A.P., Literature Search: S.S., Writing: A.H.R.

Conflict of Interest: No conflict of interest was declared by the authors.

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Clinical and Immunological Overlap Between Visceral Leishmaniasis and Rheumatic Disorders: A Comparative Review on Diagnostic Challenges

Visseral Leishmaniasis ve Romatizmal Hastalıklar Arasındaki Klinik ve İmmünolojik Örtüşme: Tanısal Zorluklar Üzerine Karşılaştırmalı Bir Derleme

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ABSTRACT

Rheumatic diseases are complex systemic disorders characterized by multi-organ involvement and diverse laboratory abnormalities. The diagnostic approach involves a comprehensive evaluation of clinical and serological markers and the exclusion of conditions with overlapping presentations, such as other rheumatic diseases and systemic infections. Visceral leishmaniasis (VL) is a protozoan infection that primarily affects the reticuloendothelial system. Direct effects of parasite infiltration of the reticuloendothelial system, combined with the subsequent host immune response, produce clinical and laboratory findings that mimic those of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Furthermore, the exaggerated immune response observed in a subset of VL patients overlaps clinically with primary hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS). VL can mimic SLE and Felty's syndrome and may trigger secondary HLH. Furthermore, in endemic regions, VL can present as a coexisting condition in patients with SLE and RA, often mimicking disease flares. In these vulnerable patient groups who are receiving immunosuppressive therapies, delayed diagnosis can significantly worsen the clinical course and prognosis of VL. This review explores the clinical and immunological manifestations of VL, providing a detailed comparative evaluation of its diagnostic overlap with HLH, MAS, SLE, and Felty's syndrome.

Keywords: Visceral leishmaniasis, rheumatic diseases, hemophagocytic lymphohistiocytosis, systemic lupus erythematosus, rheumatoid arthritis

ÖZ

Romatizmal hastalıklar, çoklu organ tutulumu ve çeşitli laboratuvar anomalileri ile karakterize, kompleks sistemik bozukluklardır. Tanısal yaklaşım, klinik bulguların ve serolojik belirteçlerin kapsamlı bir şekilde değerlendirilmesi ve diğer romatizmal hastalıklar ve sistemik enfeksiyonlar gibi benzer özelikler gösteren durumların dışlanmasını içerir. Visseral leishmaniasis (VL), öncelikle retiküloendotelyal sistemi etkileyen bir protozoon enfeksiyonudur. Retiküloendotelyal sisteme parazit infiltrasyonunun doğrudan etkileri, ardından gelen konakçı immün tepkisi ile birleştiğinde, sistemik lupus eritematozus (SLE) ve romatoid artriti (RA) taklit eden klinik ve laboratuvar bulguları üretir. Ayrıca, VL hastalarının bir alt grubunda gözlemlenen abartılı immün yanıt, klinik olarak primer hemofagositik lenfohistiyositoz (HLH) ve makrofaj aktivasyon sendromu (MAS) ile örtüşmektedir. VL, SLE ve Felty sendromunun klinik bir taklitçisi olarak hareket eder ve ikincil HLH için tetikleyici görevi görebilir. Ayrıca, endemik bölgelerde VL, SLE ve RA hastalarında sıklıkla hastalık alevlenmelerini taklit eden bir durum olarak ortaya çıkabilir. İmmünosüpresif tedaviler alan bu hassas hasta gruplarında gecikmiş tanı, VL'nin klinik seyrini ve prognozunu önemli ölçüde kötüleştirebilir. Bu derlemede, VL'nin klinik ve immünolojik belirtilerini açıklanmış, HLH, MAS, SLE ve Felty sendromu ile örtüşen tanısal özellikleri hakkında ayrıntılı, karşılaştırmalı bir değerlendirme yapılmıştır.

Anahtar Kelimeler: Visseral leishmaniasis, romatizmal hastalıklar, hemofagositik lenfohistiyositoz, sistemik lupus eritematozus, romatoid artrit

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INTRODUCTION

Leishmaniasis is a complex parasitic disease with a global distribution, affecting both human and animal populations. *Leishmania* species belong to the order Trypanosomatidae in the eukaryotic supergroup Excavata (Excavata; Discicristata; Euglenozoa; Kinetoplastea; Trypanosomatidae). Leishmaniasis is one of the world's most neglected tropical diseases according to the World Health Organization (WHO). It is caused by more than 20 protozoan parasites and is transmitted by the bite of an infected female sandfly of species *Phlebotomus* in the Old World and Lutzomia in the New World (1,2).

Its epidemiology is determined by multifaceted interactions among *Leishmania* species, sandfly vectors, host immune responses, and environmental factors. Leishmaniasis presents a broad clinical spectrum, ranging from asymptomatic and latent infections to cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis, and visceral leishmaniasis (VL), traditionally known as kala-azar. VL, the most lethal form of the disease, is mainly caused by *Leishmania donovani* and *Leishmania infantum* (2). In a subset of VL patients, a clinical syndrome mimicking hemophagocytic lymphohistiocytosis (HLH) emerges, driven by the profound activation of the reticuloendothelial system (RES) (3).

We recently encountered two patients in our clinic: the first was diagnosed with macrophage activation syndrome (MAS) triggered by adult-onset Still's disease (AOSD), and the second with systemic lupus erythematosus (SLE). Both patients had been initiated on systemic corticosteroids and immunosuppressive agents prior to their current presentation. Subsequent comprehensive investigations confirmed the diagnosis of VL, and a complete clinical recovery was achieved following the administration of antiparasitic therapy. In contrast, another patient managed in the intensive care unit for MAS received a delayed diagnosis of VL. Despite subsequent initiation of treatment, the patient died. Consequently, we aimed to review the literature to re-emphasize the clinical and laboratory characteristics and the differential diagnosis of VL.

Clinical Masquerade: Leishmaniasis

WHO data indicate that the annual incidence of newly diagnosed leishmaniasis cases is approximately one million. VL, the most severe clinical manifestation of the disease, accounts for an estimated 50,000 to 90,000 new cases annually. The highest disease burden is reported in Brazil, East Africa, and India, which remain the most heavily affected regions (1). Environmental factors such as temperature, precipitation, vegetation, and humidity affect the development of vectors and parasites; socioeconomic conditions such as poverty, malnutrition, conflicts, population displacement, and rapid urbanization; and factors affecting the host's immune system such as human immunodeficiency virus (HIV) infection, organ transplantation, rheumatological diseases, and drugs determine the epidemiology of the disease (4,5). It is stated that global warming may cause the disease to spread to more temperate regions and become endemic in a wider geography (6). It is endemic in the Southeastern provinces of Türkiye and the number of cases is increasing due to recent Middle Eastern migration (7). Özbel et al. (8) reported that CL cases are unexpected increasing in Türkiye, posing a risk for its spread to Europe.

The systemic inflammatory response elicited by VL pose a diagnostic challenge by mimicking the clinical manifestations and laboratory abnormalities of HLH, MAS, AOSD, SLE, and Felty's syndrome, which occurs in the context of severe seropositive rheumatoid arthritis (RA). Such clinical mimicry often leads to misdiagnosis and the initiation of inappropriate therapies (5,9). Furthermore, VL may present as a coexisting condition in patients with SLE and RA, in whom it frequently masquerades as a disease flare. While the cases published in the literature are clinically interesting, many involve patients in non-endemic regions, where diagnosis is challenging. Clinicians practicing in endemic regions are likely more proficient in diagnosing and managing VL, potentially leading to underreporting of routine cases deemed "unremarkable". Furthermore, most published cases describe successful therapeutic outcomes. It is highly probable that patients with poor ultimate outcomes, as well as those who died without being diagnosed with VL, were not reported in the literature. Because of the high mortality risk (exceeding 95%) if VL is untreated, a rapid and accurate differential diagnosis in a patient presenting with rheumatic symptoms is not merely a medical procedure but a life-saving intervention. The key factors in differential diagnosis VL and rheumatic diseases are the in-depth analysis of clinical and laboratory findings by the consultant (10-13). Similar symptoms, findings, and laboratory abnormalities are summarized in Table 1. Furthermore, Figure 1 illustrates the strength of the associations between VL and HLH, SLE, and RA-Felty's syndrome, based on their shared clinical and laboratory features.

- **Clinical Features:** Typically irregular fever, marked weight loss, hepatosplenomegaly (usually massive), and lymphadenopathy are observed in VL.
- **Laboratory Abnormalities:** Pancytopenia is a consequence of RES and spleen sequestration rather than of simple bone marrow suppression. Elevated levels of ferritin, triglycerides, and C-reactive protein (CRP) are observed, alongside increases in liver enzymes, mainly alanine transaminase and aspartate transaminase. Hypergammaglobulinemia is common in VL.
- **Immunologic Mechanisms for Mimicking Rheumatic Diseases:** By manipulating the host's immune system, VL acquires a serological profile resembling that of a full-blown autoimmune disease. *Leishmania* infection triggers autoimmunity through polyclonal B-cell activation driven by tissue damage and molecular mimicry, in which parasite antigens resemble human proteins. These processes, combined with the formation of immune complexes that cause inflammation and complement depletion, lead to a clinical profile that closely mimics systemic autoimmune diseases like SLE.

The diagnosis of leishmaniasis involves various methods, including microscopy, culture, and polymerase chain reaction (PCR); however, it is recommended that laboratories employ a multimodal approach rather than relying on a single diagnostic tool (2). In the diagnosis of VL, tissue aspiration smears are used for histopathological examination, parasite culture, and molecular testing. While bone marrow is the most commonly preferred site, liver, spleen, enlarged lymph nodes, and whole blood (buffy coat) samples are also viable options (14). While splenic puncture in VL offers a high diagnostic yield, it carries a significant risk of splenic rupture. The sensitivity of microscopic evaluation varies between 15% and 70% as it is observer-dependent (2). Serological methods are widely utilized in the diagnosis of VL. Currently, the rK39-based immunochromatographic rapid test is the most commonly employed diagnostic tool for VL (3). Cunningham et al. (15) evaluated multiple commercial rK39- and rKE16-based immunochromatographic rapid diagnostic tests for VL using serum samples from the Indian subcontinent, Brazil, and East Africa. While most tests showed high sensitivity and specificity in the Indian subcontinent, their sensitivity was considerably lower in Brazil and East Africa, indicating substantial regional variability and reduced reliability of some rapid diagnostic tests when used alone in these settings. In a meta-analysis of diagnostic tests for VL, the direct agglutination test (DAT) and ELISA exhibited higher sensitivity (93.0-93.8%) than rapid diagnostic tests (89.1%) and immunofluorescence assays (82.0%). Notably, all methods maintained high specificity, ranging from 95.5% to 96.9%. Furthermore, the overall diagnostic performance of DAT was found to be comparable to that of molecular assays (16). Antibody-based tests must always be used in combination with a standardized clinical case definition for the diagnosis of VL. While the sensitivity and specificity of PCR vary depending on the methodology employed (median: 78.9-97.0% and 98.4-99.4%, respectively), these molecular techniques generally surpass microscopy, culture, and histology in diagnostic yield. However, their clinical utility remains constrained by a lack of standardization and the ongoing need for validation, particularly within large hospital and clinical settings (2,16).

Rheumatological Disorders Mimicked by or Overlapping with VL

a) VL and HLH: Clinical Overlap and Differential Diagnosis

HLH involves excessive inflammation characterized by immune activation and uncontrolled cytokine release, which can lead to multiorgan failure. HLH develops as a result of inherited genetic mutations that disrupt the function of immune system cells—especially cytotoxic T-cells and natural killer cells; this form is called primary or familial HLH. Secondary HLH is triggered by infections, malignancies, or rheumatic diseases. HLH, which develops on the basis of rheumatic diseases such as AOSD and systemic juvenile idiopathic arthritis, is also described in the literature as MAS. VL shows many similarities to HLH due to its clinical presentation, which is characterized by the triad of persistent fever, splenomegaly, and pancytopenia. Numerous case reports emphasize that VL patients often fully meet the HLH-2004 diagnostic criteria, making the two diseases clinically indistinguishable (17-34). Table 2 presents a summary of case reports and case series published in the PubMed database since 2015. In a study involving pediatric VL patients in Brazil, 35 out of 127 children (27.5%) were found to meet the diagnostic criteria for HLH (35). Another Brazilian study reported that 39 out of 258 children (15.1%) diagnosed with VL met the HLH criteria, with the majority of these cases residing in urban areas (36). Diagnostic confusion represents a critical clinical threshold that directly impacts patient survival. In cases of VL misdiagnosed as primary or secondary HLH, the initiation of aggressive immunosuppressive therapy without first ruling out underlying VL can lead to uncontrolled parasite proliferation and fatal outcomes (19-21). However, with appropriate and timely antiparasitic treatment, survival rates in VL-associated HLH cases are significantly higher than those observed in primary HLH.

Pathophysiology: Immune Evasion and Cytokine Storm

The pathogenesis of VL-associated HLH is driven by a complex interplay between the survival strategies of *Leishmania* and a dysregulated host immune response. Immune response to VL has been discussed in detail by Lodi et al. (3). The immunopathophysiology of VL is characterized by the parasite's sophisticated evasion of host defenses, resulting in systemic infection involving the spleen, liver, and bone marrow. *Leishmania* creates a protected niche for replication within macrophages by manipulating Toll-like receptors, inhibiting phagosome-lysosome fusion, and utilizing a "Trojan horse" strategy via apoptotic neutrophils. While approximately 70% of individuals mount an effective Th1/M1 pro-inflammatory response that confines the parasite within granulomas, disease progression is driven by a shift toward an interleukin (IL)-10-dominant anti-inflammatory milieu (M2/Th2 polarization). This environment, exacerbated by B-cell-mediated hypergammaglobulinemia and programmed death-ligand 1expression, results in T-cell exhaustion and impaired microbicidal capacity. Ultimately, the failure of these regulatory mechanisms can precipitate an "HLH-like" state, characterized by uncontrolled macrophage activation, a cytokine storm, and high mortality, particularly in immunosuppressed patients (3).

Hemophagocytosis is the most frequently observed pathological feature in bone marrow smears from VL patients. This finding raises a critical diagnostic question: should it be interpreted as a component of VL-associated dyserythropoiesis or as a distinct HLH syndrome triggered by the infection? Lodi et al. (3) reported that it would be more accurate to define the condition called VL-HLH as "VL-related HLH-mimic". Indeed, clinical and laboratory abnormalities often resolve completely with anti-parasite therapy alone, without the need for specific HLH-directed treatment (Table 2). This suggests that the presence of histopathological hemophagocytosis may represent a reactive bone marrow phenomenon within the natural course of VL, rather than a separate, self-sustaining syndrome.

In patients with HLH or MAS, serum sCD25 (soluble IL-2 receptor) levels are significantly increased. Its association with elevated ferritin levels yields approximately 100% diagnostic accuracy for MAS. Additionally, sCD25 levels were increased in VL cases. In endemic regions, while sCD25 exhibits high sensitivity, its specificity remains limited. Consequently, differentiating between "isolated VL" and "VL-associated HLH" based solely on sCD25 elevation can be clinically challenging. Nevertheless, markedly elevated levels of both ferritin and sCD25 should strongly suggest the presence of a secondary HLH syndrome (37).

The identification of the parasite in bone marrow remains the most common and definitive diagnostic standard for VL. A primary challenge in reporting VL cases that mimic HLH is the frequent failure to detect amastigotes on initial bone marrow aspiration. In 36% to 64.7% of cases, the parasite is not identified in the first examination; detection is often only achieved through repeat aspirations or more exhaustive diagnostic evaluations (19). Liver biopsies are used for diagnosis only in rare instances. Serological assays are essential for diagnosing leishmaniasis in endemic areas. In the majority of cases presented in the literature, these tests were used in conjunction with bone marrow aspiration (Table 2).

The treatment of HLH is tailored to its underlying etiology. In primary HLH, the standard induction regimen follows the HLH-94/2004 protocols, primarily utilizing corticosteroids and etoposide; hematopoietic stem cell transplantation remains the definitive cure. Rituximab is highly effective in managing HLH triggered by Epstein-Barr virus because it targets infected B-cells. In MAS secondary to systemic inflammatory diseases, corticosteroids and intravenous immunoglobulin (IVIG) constitute the mainstays of therapy and are often supplemented by calcineurin inhibitors. Finally, in the cytokine storm induced by coronavirus disease 2019, targeted biologicals such as anti-IL-1 (e.g., anakinra) and anti-IL-6 (e.g., tocilizumab) therapies have proven effective (38). However, in the presence of VL and associated HLH, the primary therapeutic approach must be anti-parasitic therapy. With appropriate treatment strategies, mortality rates remain remarkably low. Recovery was achieved in 27 of 30 cases (90%), as summarized in Table 2. Studies conducted in Brazil have reported cures in nearly all VL-HLH patients, emphasizing that early diagnosis is life-saving and that liposomal amphotericin B is the treatment of choice. While anti-parasitic therapy is paramount, corticosteroids may still be required at anti-inflammatory doses in some patients, or at immunosuppressive doses in a limited number of cases (35,36). According to the literature, in certain cases where clinical improvement is not achieved despite anti-parasitic therapy, clinicians have resorted to agents included in the standard HLH protocols—such as glucocorticoids, IVIG, and cyclosporine A—and have observed therapeutic efficacy (Table 2).

b) VL and SLE: Comparative Evaluation

SLE is a multisystemic autoimmune disease characterized by a broad spectrum of clinical manifestations, often mimicking various systemic conditions due to its diverse organ involvement. VL is also recognized as a "great mimicker" due to its diverse clinical presentation. Both SLE and VL can manifest with overlapping features such as fever, splenomegaly, and cytopenias, often leading to significant diagnostic confusion-particularly in cases where VL triggers secondary immunological phenomena that mirror autoimmune disorders (5,39-45). Table 3 summarizes some cases of concurrent SLE and leishmaniasis reported in the literature since 2015. Notably, in five of eleven patients (45.5%), SLE was the provisional diagnosis. However, following diagnosis and successful treatment of VL, all clinical and serological abnormalities resolved, and the diagnosis of SLE could not be confirmed during follow-up. In another six patients (54.5%) with a pre-existing diagnosis of SLE, VL emerged as a comorbid infection, presenting with a clinical profile that closely mimicked an acute SLE flare (Table 3).

Shared Symptoms and Clinical Findings, Distinct Phenotypes: The involvement of the RES in both conditions accounts for their overlapping clinical presentations, characterized by hepatosplenomegaly, lymphadenopathy, and cytopenias. While splenomegaly in VL is typically massive (often exceeding 20 cm) and characterized by firm consistency, it is generally mild in SLE and only rarely reaches such significant proportions (Table 1 and Figure 1).

Irregular or high fever, significant weight loss and weakness common features of both VL and SLE (5,39-42). High-grade fever is more frequently associated with VL; however, significant thermal elevations may also occur in a subset of SLE patients during acute flares.

Arthralgia is common in VL, but arthritis/synovitis is rare, whereas non-erosive arthritis is a significant clinical finding in SLE (5). SLE is characterized by photosensitive skin rashes, such as malar rash, discoid rash, and subacute cutaneous lupus dermatitis. CL can present with facial lesions that closely mimic discoid lupus erythematosus. Specifically, lupoid leishmaniasis—a distinct clinical variant of CL—is characterized by its striking resemblance to lupus vulgaris or discoid lupus, as its nomenclature implies. In immunocompromised individuals, including SLE patients, CL can present as unusual or widespread lesions, such as ulcerated nodules and crusted plaques, which can be confused with cutaneous lupus. In some VL cases, skin lesions mimicking malar rash and vasculitis, combined with fever, pancytopenia, and antinuclear antibody (ANA) positivity, may lead clinicians to initially consider SLE as a provisional initial diagnosis (39-45).

Laboratory Overlap and Diagnostic Challenges: Cytopenias are common in both SLE and VL, but the mechanisms by which these reductions in cell lines develop are different. In VL, cytopenias are primarily due to parasitic bone marrow infiltration and RES activation, whereas in SLE they result from peripheral immune-mediated destruction. Bone marrow examination provides a definitive distinction. Bone marrow findings in SLE vary but may present as hyper- or normocellular, often reflecting peripheral immune-mediated destruction. Conversely, VL is characterized by macrophages containing intracellular amastigotes and the presence of hemophagocytic histiocytes—indicative of associated HLH—which demonstrate the phagocytosis of erythrocytes and neutrophils (5,10,12,40).

VL causes polyclonal B-cell activation, leading to positive results for many autoantibodies used in the diagnosis of SLE. ANA, which is essential for the diagnosis of SLE, can also be detected in 82% to 94% of VL patients. In addition, rheumatoid factor (RF), anti-

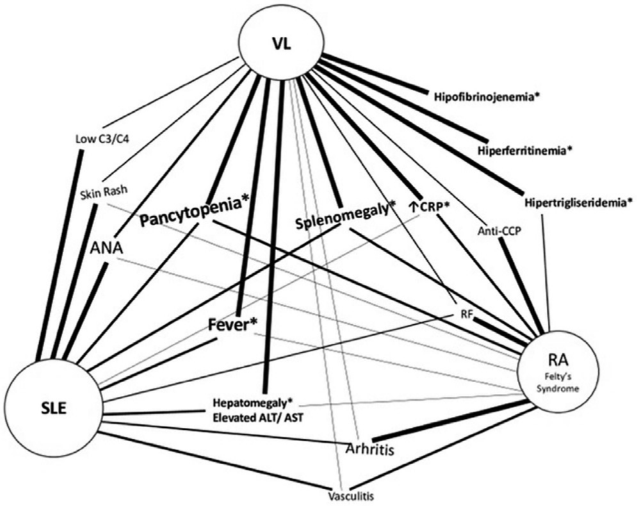

Figure 1. The figure illustrates the overlapping clinical and laboratory features of visceral leishmaniasis (VL), systemic lupus erythematosus (SLE), and Felty's syndrome. The thickness of the lines and writings represents the strength of the association between these conditions and their shared findings. Features marked with an asterisk (*) also serve as diagnostic criteria for hemophagocytic lymphohistiocytosis

RA: Rheumatoid arthritis, CRP: C-reactive protein, Anti-CCP: Anti-cyclic citrullinated peptide, ALT/AST: Alanine aminotransferase/aspartate aminotransferase, ANA: Antinuclear antibody dsDNA (to a lesser extent), anti-Sm, and a positive direct Coombs test can be detected in both diseases (5,11-13,40).

A significant disparity exists in inflammatory markers: VL is characterized by markedly elevated CRP levels (often >100 mg/L), whereas SLE typically presents with only mild-to-moderate CRP levels. In the context of SLE, a disproportionately high CRP should alert the clinician to concomitant infections or serositis (5,13). Serum ferritin levels are also extremely high in VL (>4000 ng/mL), but usually normal in SLE (<500 ng/mL). Serum ferritin levels may not reach characteristically high levels in the presence of concurrent iron deficiency, and conversely, low ferritin measurements may still be observed despite a systemic inflammatory state.

Serum complement levels (C3 and C4) are normal in VL. They are usually low in patients with active SLE, especially lupus nephritis (5,41,42). Hypergammaglobulinemia and low albumin levels are observed in both SLE and VL patients (10,12,41).

Due to symptom overlap with other autoimmune diseases, the diagnosis of SLE relies on specific classification criteria that combine clinical and immunological markers and are anchored by mandatory ANA positivity. Even if the patient fully meets the SLE classification criteria, in a newly diagnosed SLE patient—or one undergoing follow-up—who receives high-dose corticosteroids or immunosuppressive therapy the persistence of fever and lack of hematological improvement should strongly raise suspicion of underlying other diseases, including VL (10,40). Misinterpreting an underlying VL infection as an SLE flare and subsequently intensifying immunosuppressive therapy can lead to the rapid dissemination of the parasite, potentially resulting in fatal outcomes. Consequently, in SLE cases presenting with refractory fever and pancytopenia, particularly in endemic regions, VL should be considered before increasing the dose of immunosuppressive therapy (5,11,12,39-42). In conclusion, because leishmaniasis can act as a mimic, a trigger, or a co-infection with SLE, it must remain a high-priority consideration in the differential diagnosis of patients presenting with multisystem inflammatory features.

c) VL and RA/Felty's Syndrome: Comparative Analysis

RA typically presents with a clinical picture dominated by erosive arthritis. Its autoimmune pathogenesis is characterized by the development of RF and anti-cyclic citrullinated peptide (CCP) positivity. Diagnosis is established based on the evaluation of the distribution of affected joints, symptom duration, acute-phase reactant levels, and serological markers (RF and/or anti-CCP). A fundamental requirement of these criteria is that the observed synovitis cannot be better explained by an alternative diagnosis. Felty's syndrome is characterized by the triad of splenomegaly, neutropenia, and typically severe seropositive RA, which often precedes systemic symptoms by over a decade. Furthermore, compared with isolated RA, this syndrome is associated with a significantly higher prevalence of extra-articular manifestations, including rheumatoid nodules, vasculitis, and persistent skin ulcers. Rather than being a primary differential diagnosis for RA, VL is more frequently confused with Felty's syndrome. In a patient with established RA, the emergence of hepatosplenomegaly and pancytopenia strongly suggests Felty's syndrome; however, these findings also necessitate the exclusion of VL, especially in endemic regions (46-50) (Table 3).

Table 1. Comparison of clinical and laboratory features in visceral leishmaniasis and its mimics (hemophagocytic lymphohistiocytosis, systemic lupus erythematosus, and rheumatoid arthritis-Felty's syndrome) (Ref. 9,11,12,13,17,19,35,36,47-50)

	VL	**HLH**	**SLE**	**RA**
Fever	Irregular, persistent	Persistent and prolonged	Sometimes (>38.3 °C)	Rarely (subfebrile)
Splenomegaly	Massive	Massive	Mild/moderate	If Felty's syndrome present
Pancytopenia	Bone marrow infiltration by parasite and RES activation-related pancytopenia	RES activation, overstimulation of lymphocytes and macrophages, pancytopenia associated with cytokine storm	Immune cytopenias (isolated or combined) -Autoimmune hemolytic anemia -Immune thrombocytopenia, -Immune neutropenia or lymphopenia	Chronic disease anemia Leukocytosis Bicytopenia and pancytopenia in Felty's syndrome
Arthralgia arthritis	Artralgia (generally)	Arthritis associated with triggering diseases; AOSD, sJIA	Non-erosive arthritis	Erosive arthritis accompanied by synovitis involving symmetrical, small joints
Elevated liver enzymes	Often accompanied by hepatomegaly (~60%)	Oftenly (~80%)	Rarely	Rarely
Skin lesion	If cutaneous Leishmaniasis present	Non-pathognomonic	Typical photosensitive; malar rash, discoid lesion	None OR vasculitic lesions
Ferritin level	Very high (>4000 ng/mL)	Very high (>4000 ng/mL)	Normal*	Normal*
CRP	Very high (>100 mg/L)	Very high	Normal/mild	Moderately
Serum C3/C4	Normal	Normal	Normal/low (in active disease and nephritis)	Normal
RF/anti-CCP	Both are measurable as positive	None	RF (+) (20-60%) Anti-CCP(+), (2-15%)	RF (+) (70-80%) Anti-CCP (+) (60-70%)
Triglycerides	High	Very high	Normal/mild	Normal/mild
Fibrinogen	Normal/high	Very low	Normal	Normal

*: It is measured as low in the presence of iron deficiency, VL: Visceral leishmaniasis, HLH: Hemophagocytic lymphohistiocytosis, SLE: Systemic lupus erythematosus, RA: Rheumatoid arthritis, CRP: C-reactive protein, Anti-CCP: Anti-cyclic citrullinated peptide antibody, RES: Reticuloendothelial system, AOSD: Adult-onset Still's disease, sJIA: Systemic juvenil idiopathic arthritis, RF: Rheumatoid factor, OR: Odds ratio

Table 2. Summary of cases representing visceral leishmaniasis-associated hemophagocytic lymphohistiocytosis (HLH)$^{\delta}$

N	Age	Sex	Country*	Diagnosis	Ferritin	Treatment	Outcome	Ref.
1	1	F	Italy	A/BM+PCR (BM)	912	Lipo. Amp. B	Cure	17
2	16	F	Italy	A/BM+PCR (BM)	593	Lipo. Amp. B	Cure	17
3	2	M	Ethiopia	rK39	1500	Lipo. Amp. B+Dex	Cure	18
4	58	M	China	A/BM+ rK39	>500	Sodium stibogluconate+MP	Cure	19
5	58	M	China	A/BM+rK39	>500	Sodium stibogluconate	Died	19
6	38	M	China	A/BM+rK39	>500	Sodium stibogluconate+MP	Cure	19
7	43	M	China	A/BM+rK39	>500	Sodium stibogluconate+MP	Cure	19
8	47	M	China	A/BM+rK39	>500	Sodium stibogluconate	Cure	19
9	27	M	China	A/BM+rK39	>500	Sodium stibogluconate+MP	Cure	19
10	60	M	China	A/BM+rK39+mNGS	>1650	Pentavalent antimonial	Died	20
11	46	M	China	PCR+rK39	>1650	Pentavalent antimonial	N/A	20
12	26	M	Brazil	A/BM+rK39	NA	Lipo. Amp. B	Died	21
13	20	F	Brazil	rK39	10770	Lipo. Amp. B+MP+IVIG	Cure	21
14	41	F	Brazil	A/BM	577	Lipo. Amp. B+MP	Cure	21
15	48	F	Saudi Arabia	A/BM	5324	Lipo. Amp. B+MP	Cure	22
16	50	F	Türkiye	A/BM+IFAT+PCR	764	Lipo. Amp. B	Cure	23
17	83	F	Greece	A/BM+PCR+anti-*Leishmania* Ab	7146	Lipo. Amp. B+MP	Cure	24
18	64	M	Belgium	PCR	13418	Lipo. Amp. B	Cure	25
19	22	M	Armenia	A/BM+Anti-*Leishmania* Ab	2563	Lipo. Amp. B	Cure	26
20	1	M	Armenia	A/BM	>2000	Lipo. Amp. B+Dex+IVIG	Cure	26
21	6	M	Russian	rK39+Anti-*Leishmania* Ab	>3000	Lipo. Amp. B+Dex	Cure	26
22	7	M	Greek/Bulgarian	A/BM+IFAT	>2000	Lipo. Amp. B	Cure	27
23	40	F	Bulgaria	A/BM	NA	Meglumine antimoniate+ MP+IVIG+Cs	Cure	28
24	2	M	Türkiye	A/BM	14000	Lipo. Amp. B	Cure	29
25	3	N/A	Türkiye	IFAT	573	Lipo. Amp. B+IVIG	Cure	30
26	35	M	Deutschland/Spain	A/BM+PCR	896	Lipo. Amp. B	Cure	31
27	2	F	China	A/BM+rK39	40000	Antimony	Cure	32
28	1	F	China	A/BM+rK39	69445	Antimony	Cure	32
29	21	F	Portugal	A/BM	32573	Lipo. Amp. B	Cure	33
30	14	M	Ethiopia	A/BM+rK39	30000	Lipo. Amp. B+Dex	Cure	34

δ : Includes case reports and case series published in PubMed since 2015, *: The country where the case was published and/or where the potential transmission occurred, N: Number, F: Female, M: Male, BM: Bone marrow, A/BM: Amastigotes on bone marrow, PCR: Polymerase chain reaction, mNGS: metagenomic next-generation sequencing test, IFAT: Indirect fluorescent antibody test, Lipo. Amp. B: Liposomal amphotericin B, Dex: Dexamethasone, MP: Methylprednisolone, IVIG: Intravenous immunoglobulin, Cs: Cyclosporin-A, N/A: Not available

Constitutional symptoms, including malaise, fatigue, anorexia, and weight loss, can manifest in both VL and RA. However, fever is one of the primary symptoms in VL and is usually irregular, higher, and prolonged, it is rare and mild levels in RA (9,46). In patients with active RA who have not progressed to Felty's syndrome, anemia of chronic disease is a common finding, whereas hepatosplenomegaly remains rare (see Table 1 and Figure 1).

The clinical picture of RA is typically dominated by symmetrical small-joint polyarthritis, characterized by active synovitis and erosive changes, with the latter being an infrequent feature of VL. Nevertheless, in endemic regions, the presence of polyarthralgia or polyarthritis combined with RF and/or anti-CCP positivity can create significant diagnostic ambiguity between these two conditions. The release of self-antigens resulting from parasite-induced tissue destruction may trigger an autoimmune response. Specifically, this process can initiate the citrullination of proteins—a key factor in RA pathogenesis—thereby potentially acting as a catalyst for the development of RA (14). In patients with VL, RF positivity occurs at remarkably high rates (63-90%), primarily due to polyclonal B-cell activation. Furthermore, anti-CCP antibodies—traditionally regarded as having up to 95% specificity for RA—may also yield positive results in VL cases. This phenomenon is attributed to the citrullination of host proteins induced during the course of the infection. Consequently, both diseases share a common laboratory profile characterized by ANA positivity, hypergammaglobulinemia (predominantly elevated immunoglobulin G), and significantly increased acute-phase reactants, such as erythrocytes sedimentation rate and CRP (11-13).

Table 3. Characteristics of patients with SLE and RA coexisting with or mimicking leishmaniasis$^{\delta}$

N	Age	Sex	Country*	Drugs	Disease	Diagnosis	Treatment	Outcome	Ref.
SLE									
1	25	F	Brazil	MP	Not confirmed	A/BM	Lipo. Amp. B	Cure	5
2	27	F	Brazil	MP	6 years prior	A/BM	N/A	Died	5
3	18	F	Brazil	MP, MMF	1 year prior	A/BM+rK39	Lipo. Amp. B	Cure	5
4	53	M	Brazil	-	Not confirmed	A/BM+IFAT	Lipo. Amp. B	Cure	14
5	73	M	India	MP, HQ, MMF, Belimumab	Not confirmed	A/BM+anti *Leishmania Ab*	Sodium stibogluconate Lipo. Amp. B	Cure	39
6	36	F	India	MP, Cs, HQ, Tofasitinib, Telitacicept	Not confirmed	A/BM+PCR	Lipo. Amp. B	Cure	40
7	60	F	Portugal	MP, Mtx	40 years prior	PCR (blood, BM)	Lipo. Amp. B	Cure	41
8	48	F	Türkiye	MP, MMF	20 years prior	A/BM	Lipo. Amp. B	Cure	42
9	21	M	Türkiye	MP	Not confirmed	A/BM	Lipo. Amp. B	Cure	43
10	22	M	Greece	MP	Prior	N/A	N/A	Cure	44
11	40	M	Colombia	-	7 years prior	A/BM	Miltefosine Pentamidine	Cure	45
RA									
1	50	M	Brazil	Mtx, ABA	3 years prior	A/BM (+liver)+PCR+anti-*Leishmania* Ab	Lipo. Amp. B	Cure	9
2	72	N/A	Deutschland	Mtx, MP, ETA	9 years prior	Amastigotes (liver)+PCR+ELISA	Unknown	N/A	46
3	64	F	Spain	Mtx, MP	14 years prior	A/BM	Lipo. Amp. B	Cure	47
4	71	F	Greece	Mtx, MP	5 years prior	A/BM +IFAT+PCR	Lipo. Amp. B	Cure	48
5	66	M	Spain	Mtx, ADA	7 years prior	A/S+ PCR (BM)+serology	Lipo. Amp. B	Cure	49
6	79	M	Spain/Türkiye	Mtx, MP	Several years	A/BM+serology	Lipo. Amp. B	Relaps/died	49
7	83	M	Spain	Mtx, MP	6 month prior	Amastigotes (spleen)+PCR (blood and spleen)+serology	Lipo. Amp. B	Cure	49
8	84	M	Spain	Mtx	6 years prior	A/BM+serology+PCR	Lipo. Amp. B	Cure	50

δ : Includes case reports and case series published in PubMed since 2015, *: The country where the case was published and/or where the potential transmission occurred, N: Number, F: Female, M: Male, SLE: Systemic lupus erythematosus, RA: Rheumatoid arthritis, MP: Methylprednisolone, MMF: Mycophenolate mofetil, HQ: Hydroxychloroquine sulfate, Cs: Cyclosporin-A, Mtx: Methotrexate, ABA: Abatacept, ETA: Etanercept, ADA: Adalimumab, BM: Bone marrow, A/BM: Amastigotes on bone marrow, A/S: Amastigotes on skin, IFAT: Indirect fluorescent antibody, Ab: Antibodies, PCR: Polymerase chain reaction, Lipo. Amp. B: Liposomal amphotericin B, N/A: Not available

It is crucial to emphasize that drugs used to treat RA—including corticosteroids, disease-modifying antirheumatic drugs such as methotrexate, and biological agents, particularly anti-tumor necrosis factor (TNF) drugs (e.g., adalimumab, infliximab)—can significantly impair host immunity. Such treatments may trigger the reactivation of latent *Leishmania* infections or exacerbate atypical or severe clinical presentations of VL. Compared to immunocompetent individuals, those who are immunosuppressed may lack typical VL findings—such as fever, splenomegaly, and pancytopenia—or exhibit these symptoms in much milder form. Furthermore, because immunosuppressive drugs inhibit antibody production, serological tests for VL may yield false-negative results, leading to significant diagnostic delays. If immunosuppressive therapy is mistakenly intensified under the assumption of an underlying disease flare, the parasitic load increases rapidly, resulting in severe clinical deterioration. TNF-α antagonists, in particular, disrupt granuloma formation—a critical mechanism for sequestering the parasite—thereby triggering latent infections. This effect is notably more pronounced with monoclonal antibody-based agents, such as infliximab and adalimumab. In contrast, the risk appears to be lower with etanercept, which acts via soluble receptor blockade rather than direct monoclonal binding (9,46,49).

Secondary prophylaxis with liposomal Amphotericin B is indicated for patients co-infected with HIV and leishmaniasis, provided that CD4^{+} T-cell counts are less than 200 cells/mm^{3}. A definitive consensus has yet to be established regarding the necessity of prophylactic treatment for patients with a history of leishmaniasis who require ongoing immunosuppressive therapy for rheumatic diseases. Specifically, it remains unclear whether prophylaxis is mandatory upon the resumption of immunosuppression. Nevertheless, regular monitoring via PCR assays is strongly recommended in this high-risk group to ensure the early detection of reactivation (1).

* Ethics

*Footnotes

*Authorship Contributions

Concept: H.Y., V.Y, Design: H.Y., V.Y., Data Collection or Processing: H.Y., V.Y., Analysis or Interpretation: H.Y., V.Y., Literature Search: H.Y., V.Y., Writing: H.Y., V.Y., Literature Search: H.Y., V.Y., Writing: H.Y., V.Y.

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Review
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Human *Fasciola hepatica* Infection in Türkiye is More Then We Knew: A Systematic Review

Türkiye'de İnsan Fasciola hepatica Enfeksiyonu Bildiğimizden Daha Fazladır: Sistematik Bir İnceleme

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ABSTRACT

Fasciola hepatica is a trematode that is easily visible to the naked eye. It infects sheep and cattle, but can sometimes be an accidental host in humans. This review was carried out to review the published studies on human *Fasciola hepatica* in Türkiye and to systematically examine the data obtained from the studies. Literature search was conducted using keywords such as "*Fasciola hepatica*, Fascioliasis, Türkiye (Turkey)" from "Pubmed, Google Scholar, Google" databases. In addition, poster presentations presented at congresses of national infectious disease societies on the subject were also included in the study. Eighty-four studies published in Türkiye between 1993-2022 and 183 cases examined in these studies were included in the evaluation. In this review, it was found that *Fasciola hepatica* infection is not rare in Türkiye, but clinicians were not aware of this and did not consider this infection in the differential diagnosis. It is seen that diagnostic methods such as serological and stool microscopy are not used adequately due to the fact that *Fasciola hepatica* infection is not considered in the differential diagnosis and the diagnosis methods is not available in every center. As *Fasciola hepatica* infection is not considered in the preliminary diagnosis and these diagnostic methods are not used sufficiently, we see that cases are often confused with primary or metastatic liver tumors in abdominal imaging, and therefore unnecessary invasive procedures are performed. In regions where *Fasciola hepatica* infection is endemic, *Fasciola hepatica* infection should be considered before performing a major surgical procedure in patients with typical clinical findings, elevated liver and cholestasis enzymes, and eosinophilia, and characteristic computed tomography or ultrasonography findings, and noninvasive diagnostic methods should be used first.

Keywords: *Fasciola hepatica*, obstructive jaundice, eosinophilia

ÖZ

Fasciola hepatica çıplak gözle kolayca görülebilen bir trematodtur. Koyun ve sığırları infekte etmekle birlikte, bazen insanlarda tesadüfi konakçı olabilmektedir. Bu derleme, Türkiye'de insan *Fasciola hepatica* ile ilgili yayımlanmış çalışmaları incelemek ve çalışmalardan elde edilen verileri sistematik olarak incelemek amacıyla yapılmıştır. Literatür taraması, "Pubmed, Google Scholar, Google" veri tabanlarından "*Fasciola hepatica,* Fascioliasis, Türkiye (Turkey)" gibi anahtar kelimeler kullanılarak konu ile ilgili tarama yapıldı. Ayrıca konuyla ilgili ulusal enfeksiyon hastalıkları derneklerinin kongrelerinde sunulan poster sunumları da çalışmaya dahil edilmiştir. Türkiye'de 1993-2022 yılları arasında yayımlanan 84 çalışma ve bu çalışmalarda incelenen 183 olgu değerlendirmeye alındı. Bu derlemede *Fasciola hepatica* enfeksiyonun Türkiye'de nadir olmadığı ancak klinisyenlerin bunun farkında olmadıkları ve ayırıcı tanıda bu enfeksiyonu düşünmedikleri bulunmuştur. Ayırıcı tanıda *Fasciola hepatica* enfeksiyonun düşünülmemesi ve her merkezde tanı imkanının olmaması gibi nedenlerle, serolojik ve gayta mikroskopisi gibi tanı yöntemlerin yeterince kullanılmadığı görülmektedir. *Fasciola hepatica* enfeksiyonunun ön tanıda düşünülmemesi ve bu tanı yöntemlerinin yeterince kullanılmaması nedeniyle, abdominal görüntülemede olguların sıklıkla primer veya metastatik karaciğer tümörleri ile karıştırıldığını ve bu nedenle gereksiz invaziv işlemlerin yapıldığını görmekteyiz. *Fasciola hepatica* enfeksiyonun endemik olduğu bölgelerde tipik klinik bulgusu olan, karaciğer ve kolestaz enzim yüksekliği ile birlikte eozinofilisi olan ve karekteristik bilgisayarlı tomografi ya da ultrasonografi bulguları olan hastalarda majör bir cerrahi girişim yapmadan önce *Fasciola hepatica* enfeksiyonu düşünülmeli ve öncelikle invaziv olmayan tanı yöntemleri kullanılmalıdır.

Anahtar Kelimeler: *Fasciola hepatica*, obstrüktif sarılık, eozinofili

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INTRODUCTION

Fascioliasis has recently been recognized by the World Health Organization as an important zoonotic disease that has been neglected in humans. This disease is a parasitic zoonosis caused by two liver fluke species *[Fasciola hepatica (F. hepatica), Fasciola gigantica*] (1). *F. hepatica* is a treamatode about 30 mm x 15 mm in size and easily visible to the naked eye. Although it primarily infects sheep and cattle but can accidentally infect humans due to its similar life cycle in both animals and humans (2). The socio-economic and medical significance of fascioliasis is undeniable, with an estimated global prevalence of 2.4 to 17 million infections, predominantly in Europe and Asia, with sporadic cases in other regions including North Africa, Central and South America, the Middle East, and occasionally the USA and the Caribbean (2). There is no comprehensive seroprevalence study for *F. hepatica* in Türkiye. Diagnosis can be made by serology, clinical improvement associated with reduced eosinophilia after treatment with triclabendazole, or detection of parasite eggs in stool samples. In some cases, the diagnosis is made incidentally during unnecessary procedures such as open surgery, laparoscopic cholecystectomy, or endoscopic retrograde cholangio-pancreatography (ERCP) (3). However, the diagnosis of fascioliasis can be challenging due to its many differential diagnoses and low incidence rates (4).

The main research questions in this review are:

1. Is *F. hepatica* common in Türkiye?
2. Which methods are used in the diagnosis of *F. hepatica* in Türkiye?
3. Is *F. hepatica* considered in the differential diagnosis of hepatobiliary diseases in Türkiye?

This review was conducted to examine the prevalence and regional distribution of *F. hepatica*, its clinical and laboratory findings, diagnostic methods used, treatments administered, and whether *F. hepatica* is considered in the differential diagnosis, by reviewing published studies on *F. hepatica* in Türkiye.

METHODS

Literature Search

Literature search was conducted using keywords such as "*Fasciola hepatica, F. hepatica*, Fascioliasis, Turkey" from "Pubmed, Google Scholar, Google" databases. Case reports and original human studies published in national and international journals from Türkiye were included in the evaluation. In addition, poster presentations presented at congresses of national infectious disease societies on the subject were also included in the study.

Inclusion or Exclusion Criteria from the Study

All reported human *F. hepatica* cases and prevalence studies from Türkiye were included in the study. Cases reported from outside Türkiye, a case presented in two different places (journal or poster presentation) were not included in the study. In addition, only one of the multiple studies conducted at the same university on overlapping dates was included in the study.

Characteristics of the Study

Between 1993-2022, 84 studies (5-88) published in Türkiye and 183 cases examined in these studies were included in the evaluation. One of these studies was a retrospective original article including 39 cases (49), and another one was the abstract that examined 46 cases and presented at a congress (50). Seventy-six studies were case reports (5-48,57-88). Of the case reports, 59 were studies published in national and international journals, and 17 were poster presentations presented at congresses. In a case report study, there were at least one and at most 6 cases. A total of 98 cases were analyzed in these 76 case reports. Six studies were prevalence studies (51-56).

Classification

In order to analyze the study better, the retrospective original article including 39 cases was classified as the first study (49), the summary of the papers examining 46 cases was the second study (50), and the data of 98 cases in the other 76 case studies were analyzed and classified as the third study (5-48,57-88).

Data Analysis

Demographic characteristics, complaints, laboratory and imaging findings, parasite localization, diagnostic methods and invasive procedures, treatments and recovery status of 98 cases presented in the 76-case study were recorded in the SPSS program. Continuous variables were defined as mean ± standard deviation and categorical variables were defined as numbers and percentages.

RESULTS

Demographic Data

In the first study; 77% of the patients were female, mean age was 45.77±16.53 (18-83) (49), in the second study; 60.8% of the cases were female (50), in the third study; 68,3% of the patients were female, mean age was 40.5 (4-76) (5-48,57-88) (Table 1). In the first study (49), 59% of the patients lived in rural areas, and in the third study, there was information that the patients lived in rural areas in seven cases (7,11,18,40,41,46,48).

Epidemiology

The prevalence of *F. hepatica* varies between 0.79-10.3% in six studies reported from different provinces of Türkiye (Adana, Mersin, Isparta, Kayseri, Elazig, Van) (Table 2) (51-56). In addition, of the 183 cases examined in this study, 33.3% were reported from the Mediterranean Region (19,23,42,50,67,69,74,76,80,81,83,87,88), 25.1% from the South East Anatolian Region (9,11,22,36,49,75,85), 15.3% from the Eastern Anatolia Region (5,7,10,17,18,20,24,48,57,60,61,63-65,71,76,84), 10.3% from the Central Anatolia Region (13,25,33,35,38,40,45,58,62,66,68,70,77-79,86), 7.1% from the Marmara Region (16,21,26,27,31,34,37,39,43,44,46,59), 6.5% from the Aegean Region (6,8,12,15,28,30,32,41,72), and 1% from the Black Sea Region (14,29) (Figure 1). In the study of Ulger et al. (49), 72% of the cases applied between March and June.

Clinic

The mean duration of symptoms was 508 days (49) in the first study and 233 days in the third study (5-48,57-88). In the first study (49) disease stage was not reported and the most common symptoms were abdominal pain (90%), fever (28%), and weight loss (20%). In the second study (50), 54.3% of the cases were classified as acute infections and 36.9% as chronic infections. Epigastric pain was present in 61% of acute cases, fatigue in 43%, right upper quadrant pain in 41% and fever in 40%. Epigastric pain was present in 64% of chronic cases, right upper quadrant pain in 59%, and nausea in 47%. In the third study (5-48,57-88), 48.9% of the cases were acute, 39.7% were chronic cases, and 11.2% did not report disease stage. Abdominal pain was present in 86% of acute cases, nausea and vomiting in 25%, anorexia in 33.3%, and fever in 25%. In chronic cases, 94.7% had abdominal pain, 57.8% had nausea and vomiting, 26.3% had anorexia, 23.6% had fever (Table 1). Four cases (8.6%) in the second study (50) and six cases (6.1%) (32,39,45,59,62,69) in the third study were evaluated as latent (asymptomatic) infections.

Laboratory Finding

In the first study, 79% of the cases had eosinophilia, 38% had an increase in liver enzymes, and 1% had an increase in total bilirubin (49). In the second study, eosinophilia was found in 63% of all cases and 100% of acute cases (50). In the third study, 75.9% of all cases had eosinophilia, 43.5% had aspartate aminotransferase (AST), 40.5% had alanine aminotransferase (ALT) and 26.7% had total bilirubin elevation (Table 1) (5-48,57-88).

Diagnosis

In the first study, enzyme-linked immunosorbent assay (ELISA) test was performed for *F. hepatica* in 12 patients and it was found positive in 11 (91.6%) patients. Diagnosis was made by clinical, laboratory and radiological findings in 27 patients (69.2%), by pathological examination of samples in 8 (20.5%) patients, and by removal of live parasites during the ERCP procedure in 4 (10.3%) patients. No parasite eggs were detected in the stool of any of the patients (49). In the second study, ELISA test was positive in all patients, except for one patient who was not examined. While *F. hepatica* eggs were detected in the stools of three patients and in 3 of 4 patients who underwent ultrasonography (USG)-guided fine needle aspiration. In 5 patients who were operated on with various preliminary diagnoses, the diagnosis of *F. hepatica* was confirmed by pathological examination of the samples (50). In the third study, serological tests for *F. hepatica* were performed in 60 patients, and it was found positive in 59 (98.3%) patients (ELISA test in 38 cases, indirect hemagglutination test in 22 cases) (8,11,12,15,18,20,21,23,25,29,31-34,36-45,47,57,58,65,67-69,71-75,77,82,83,85-88). Stool microscopy was performed in 45 patients (8,11,12,18,20,21,23,28,30-32,34,36-39,41,43,45,47,57,58,65-67,69,71,73-77,79,83,84,86), and *F. hepatica* eggs were observed in 14 (31.1%) patients (11,12,18,20,21,30,47,57,65,67,79,84), *F. hepatica* eggs were seen in the bile aspiration fluid in five patients (6,66,73,81,87), in the duodenal aspiration fluid in one patient (18), and in the colon biopsy sample in one patient (30). Pathological examination of the liver was performed in 36 of the cases yapılmış (5,7,12,17,19,20,24,25,28,30,32,34,44,57-59,61,62,64,66,67,72,76,78,81-83,85,86) and in 24 (66.6%) patients *F. hepatica* was diagnosed. ERCP was performed in 25 of the cases (5,6,9-11,14-16,22,26,27,35,46-48,61,63,65,66,70,73,81) and diagnostic findings were observed in 23 (92%) patients. The diagnostic methods used are shown in Table 3.

Table 1. Distribution of cases in acute and chronic phase in the third study by age, gender, symptom duration and laboratory values of fascioliasis cases between 1993-2022, Türkiye

	Acute phase (liver period), n=48	**Chronic phase (biliary period), n=39**	**Total, n=98**
Age median (min-max)	44 (4-76)	40 (9-75)	40.5 (4-76)
Gender-female (%)	67.2	69.0	71.4
Symptoms	**Acute phase (liver period), n=43 (%)**	**Chronic phase (biliary period), n=38 (%)**	**Total, n=91 (%)**
Stomach ache	37 (86.0)	18 (94.7)	81 (89.0)
Nausea-vomiting	12 (25.0)	22 (57.8)	36 (39.5)
Anorexia	16 (33.3)	10 (26.3)	28 (30.7)
Fever	12 (25.0)	9 (23.6)	22 (24.1)
Weight loss	11 (22.9)	8 (21.0)	23 (25.2)
Jaundice	1 (2.0)	9 (23.6)	10 (10.9)
Urticaria	4 (8.3)	2 (5.2)	7 (7.6)
Average symptom duration/day	208	311	233
Lab	**Acute phase (liver period) %**	**Chronic phase (biliary period) %**	**Total %**
Eosinophilia	73.3	66.0	75.9
ALP elevation	40.8	58.4	48.3
AST elevation	37.2	52.7	43.5
Leukocytosis	44.7	31.6	41.6
ALT elevation	30.3	52.7	40.5
GGT elevation	18.8	48.0	32.4
Total bilirubinemia	8.3	49.0	26.7

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, ALP: Alkaline phosphatase

Table 2. Prevalence of *Fasciola hepatica* by provinces in between 1993-2022, Türkiye

Provinces	Year	Scope of work n	Looked test	Prevalence (%)	Source
Mersin	2009	884	ELISA	0.79	(51)
Kayseri	2008	374	ELISA/UAV	3.5	(52)
Van	2004	500	Stool microscopy	1.8	(53)
Adana	2005	291	UAV	10.3	(54)
Isparta*	2003	756	ELISA	6.1[#]	(55)
Isparta*	2003	320	ELISA	0.9[a]	(55)
Elazığ	2002	540	ELISA	2.78	(56)

*: Same study, [#]: Included group of patients with eosinophilia, [a]: Included group of patients without eosinophilia, ELISA: Enzyme-linked immunosorbent assay

Figure 1. Regional distribution of cases fascioliasis between 1993-2022, Türkiye

Table 3. Diagnostic methods used for diagnosis of fascioliasis between 1993-2022, Türkiye

	n=98 (%)	Diagnostic finding rate
Serology*	60 (61.2)	59/60 (98.3%)
Stool microscopy	45 (45.9)	14/45 (31.1%)
ERCP	25 (25.5)	23/25 (92.0%)
Pathology	36 (36.7)	24/36 (66.6%)

*: ELISA test in 38 cases, IHA test in 22 cases, ERCP: Endoscopic retrograde cholangio-pancreatography, ELISA: Enzyme-linked immunosorbent assay

Imaging Findings

In the cases reported in the first arm of the study, diagnostic imaging modalities were USG in 94.8%, abdominal computed tomography (CT) in 74.3%, magnetic resonance imaging (MRI) in 59%. The most frequently reported radiological finding was the appearance of masses with irregular borders around the bile ducts in the subcapsular area of the liver (49). In the third arm of the study, USG was performed in 78.5%, abdominal CT in 51%, and abdominal MRI in 22.4%. The most frequently reported USG findings were enlargement of the common bile duct (31.1%), cholelithiasis (22%), hypoechoic appearance in the liver (20.7%), and heterogeneous appearance in the liver (12.9%). The most common abdominal CT findings were hypodense nodule in the liver (40%), enlargement of the common bile duct (18%) and heterogeneous appearance in the liver (16%), and the most common abdominal MRI findings were hypodense nodule in the liver (50%) and enlargement of the common bile duct (45.4%) (5-48,57-88).

Treatment

All patients in the first arm of the study were given triclabendazole for two consecutive days. While clinical and laboratory findings of the patients were generally improved in the 1st month, improvement in the radiological findings was observed after the 3rd month. After 12 months of treatment, 88.6% of the patients showed radiological improvement in liver lesions, and 11.4% did not change the size of the lesions. Five (12.8%) patients showed no clinical or laboratory improvement in their follow-up, and therefore triclabendazole was given again (49). In the third arm of the study, triclabendazole was given to 73 patients (5,6,8,10-13,15,16,18,20,23,25-27,29-34,36-48,57,58,60-64,67-69,71,74,75,77,81-83,86-88), bithionol to four patients (9,35,65,72), praziquantel to four patients (28,66,73), metronidazole to two patients (59,79), albendazole to two patients (76), ornidazole to one patient (78), and emetine chlorohydrate to one patient (66). Eleven cases (7,14,17,24,70,80,84,85) had no treatment information. There was no improvement in one patient (47) receiving triclabendazole, and two patients (76,77) had no treatment response information, while all other patients improved.

DISCUSSION

F. hepatica is a liver parasite that has been infecting humans for over 5,000 years (89). It is a rare parasitic infection that spreads mostly in tropical, subtropical and temperate climate regions of the world and is frequently reported from sheep and cattle breeding countries (90). The main source of infection is the consumption of raw vegetables contaminated with metacercariae. Familial and regional outbreaks have been reported in the literature due to watercress consumption (91-94). The non-embryonic eggs excreted with the feces of the host become embryonic when they come into contact with water, then return to the form called "miracidium" and invade the snail tissue. In the snail tissue, respectively; they revert to sporocyte, redia and cercaria forms. Then they float freely in aquatic plants in the form of cercariae in cysts. The metacercariae form in aquatic plants is eaten by humans and transmission occurs (3). Fascioliasis has recently been recognized by the World Health Organization as an important zoonotic disease that has been neglected in humans (1). But, increased focus on human fascioliasis over the past 30 years has led to the discovery of major endemic regions in China, Southeast Asia (such as Vietnam), Egypt, Türkiye, and northern Iran (89). The prevalence of *F. hepatica* varies between 0.79-10.3% in 6 studies reported from different provinces of Türkiye (Table 2) (51-59). When we examine the reported cases, we see that *F. hepatica* cases have been reported from every region of Türkiye. The cases were mostly reported from the two neighboring regions, the Mediterranean and Southeastern Anatolia Regions (Figure 1). These studies show that *F. hepatica* infection is not very rare in our country. Comprehensive serological studies should be conducted in different regions of Türkiye to determine the exact prevalence of the disease.

It is seen that the cases examined in this study are mostly women (5-50,57-88). Similarly,in other previous studies, it was found that *F. hepatica* was more common in women (95,96). However, Parkinson et al. (97) did not find a significant relationship between infection and gender in their study in Bolivia. Another study of more than 21,000 children in Egypt showed that *F. hepatica* infection was more common in women (98). This situation may be related to cultural, hygiene and behavioral factors such as more contact with raw water plants, as well as an unexplained physiopathological mechanism that increases the susceptibility of women to this infection. Comprehensive studies are needed to explain this situation.

Fascioliasis is divided into two main stages, acute (liver stage) and chronic (biliary stage), each showing different clinical signs and symptoms (99). Some authors consider asymptomatic *F. hepatica* infection as a latent infection apart from the chronic stage (32,39,45,50). However, asymptomatic infection is generally considered in the chronic stage (3,99,100). The acute stage (liver period) begins 3-5 months after infection, it is the period when immature forms in the duodenum reach the liver and finally, they pass into the bile ducts. The chronic stage (bile duct period) begins after about the sixth month and is the period when the parasites mature in the bile ducts. This stage can last for several years (>10 years) and half of the patients are asymptomatic (3). When the reported cases were examined, most of the cases were in the acute stage (48.9%, 54.3%) (5-48,50,57-88). However, in a study of 24 cases by Karahocagil et al., (94) most of the cases were evaluated as chronic stage (54%). *F. hepatica* is a parasite that usually settles in the liver and biliary system, but cases with atypical localization have also been reported. It was reported that *F. hepatica* was localized in the colon in three cases (30,36,44), both in the colon and liver in 2 cases (17,24), in the peritoneum in one case (86), in the ovary in one case (83), and in the lung in another case (85). Abdominal pain, nausea-vomiting, weakness, fever are the most common in both stages, and diarrhea, weight loss, urticaria, jaundice, itching, headache, and sweating have also been reported (5-50,57-88,94).

The most common laboratory finding of *F. hepatica* is eosinophilia (5-50,57-88,93,94). Eosinophilia is an important laboratory finding in fascioliasis. Saba et al. (50) reported the percentage of eosinophilia as 100% in acute patients. Karahocagil et al. (94) reported eosinophilia in 70.8% of 24 seropositive patients. However, normal eosinophil count does not exclude the diagnosis. Turhan et al. (101) reported that only 11% of seropositive patients had eosinophilia. In addition, AST, ALT, total bilirubin, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP) elevation and leukocytosis can be seen (5-50,57-88,94). Hyperbilirubinemia is a more common finding in the chronic stage because the parasite obstructs the bile duct (5-48,57-88). The presence of eosinophilia along with elevated bilirubin and cholestasis enzymes (ALP, GGT) or elevations of AST and ALT in the endemic area should suggest *F. hepatica* infection.

Fascioliasis has no specific signs and symptoms. Diagnosis and treatment are not easy because physicians rarely encounter this disease, and effective drugs are not available in many countries. However, patients with a history of living in an endemic area and eating watercress, as well as symptoms such as abdominal pain, nausea-vomiting, weakness, fever, diarrhea, weight loss, urticaria, jaundice, and eosinophilia should be evaluated for *F. hepatica* infestation with parasitological, radiological and serological tests. Definitive diagnosis of fascioliasis is made by detection of *F. hepatica* eggs in stool or gallbladder sample or radiological findings suggestive of fascioliasis together with a positivity of serological test (102). Serology has been the fastest and most effective diagnostic method in the diagnosis of fascioliasis in recent years. Antibodies are detectable 2 to 4 weeks after initial exposure, undetectable in approximately 65% of patients one month after successful treatment, but low levels of positive titers may persist for years in some patients (2). ELISA is the most commonly used serological diagnosis method, in the literature it is stated that the sensitivity of this method is 78.9-100% and the specificity is 97% (103,104). ELISA positivity was reported to be 91.6% in the case series of Ulger et al., (49) and 100% in two studies by Saba et al. (50) and Karahocagil et al. (94). Stool microscopy is another useful diagnostic method still used in the diagnosis of chronic infections in countries with scarce resources. An adult *F. hepatica* parasite can lay more than 20,000 eggs per day. Because this release is intermittent, multiple stool samples should be examined (2). It takes 5 to 7 weeks after initial infection for adult worms to mature enough to produce eggs, so there are no eggs in the stool in the acute phase of infection, so serological testing is of greater importance (2). In the 39 case study of Ulger et al., (49) it was stated that stool microscopy of all patients was examined and no parasite eggs were observed. In the 46-case study of Saba et al. (50), parasite eggs were found in the stool of only 3 cases. In the 24-case study of Karahocagil et al. (94), parasite eggs were observed in the stool of 11 patients. The presence of *F. hepatica* eggs in the stool is diagnostic, but the absence of parasite eggs does not exclude infection. In addition, diagnosis can be made by detecting *F. hepatica* eggs in the bile fluid obtained through invasive procedures performed with various preliminary diagnoses (66,73,80,81). Sometimes the diagnosis is made as a result of invasive procedures such as open surgery, laparoscopic cholecystectomy and ERCP. Live adult *F. hepatica* parasite can be detected in the biliary tract during ERCP in patients with biliary obstruction (5,6,9-11,14-16,22,26,27,35,46-49,61,63,65,66,70,73). In addition, *F. hepatica* can be identified in open surgical operation and pathological examination of biopsies (5,7,17,19,20,24,28,30,34,44,49,50,58, 59,61,64,67,72,78,82,83,85).

The differential diagnosis of *F. hepatica* includes liver abscess, malignancy, viral hepatitis, cholecystitis, cholangitis, ruptured hydatid cyst, toxocariasis, acute schistosomiasis, ascariasis, and strongyloidiasis (2,105-107). The diagnosis of fascioliasis may be overlooked due to the many differential diagnoses and low incidence (4). The most common diagnostic imaging modalities are abdominal USG, CT, and MRI, respectively (5-50,57-88). USG findings are focal areas of the liver with increased echogenicity, multiple nodules of varying echogenicity, irregular lesions or a single complex mass, enlargement of the common bile duct, and cholelithiasis (Table 4). The most common liver CT or MRI findings are heterogeneous appearance and hypodense nodule in the liver, enlargement of the common bile duct, and multiple metastasis-like lesions (Table 4) (5-50,57-88,94). The most common mistake in the interpretation of imaging methods is confusion with malignancy. As a result of the evaluation of the imaging, we see that *F. hepatica* is often confused with malignancy (8,17,19,22-25,30,34,36,39,40,44,57-59,61,62,72,75,81-83,94), in one case (61) chemotherapy was given considering liver metastasis of colon cancer, and hepatobiliary diseases such as liver abscess (31,49), choledochelelithiasis (6,10,14,20,27,66), cholecystitis (13,57,66,75) and cholangitis (7,9,15,16,65) are considered in the preliminary diagnosis. With these preliminary diagnoses, we see that 82 of 183 cases (44.8%) underwent at least one invasive procedure such as ERCP, open surgery, and liver biopsy (5-50,57-88).

Table 4. Radiological findings of the fascioliasis cases between 1993-2022, Türkiye

USG findings (77 patients)	**n (%)**
Enlargement of the common bile duct	24 (31.1)
Cholelithiasis	17 (22)
Hypoechoic appearance in the liver	16 (20.7)
Heterogeneous appearance in the liver	10 (12.9)
Intrahepatic bile duct dilatation	9 (11.6)
Cholecystitis	6 (7)
Abdominal CT findings (50 patients)	**n (%)**
Hypodense nodule in the liver	20 (40)
Enlargement of the common bile duct	9 (18)
Heterogeneous appearance in the liver	8 (16)
Mass appearance in the colon	7 (14)
Stone in the choledoch	4 (8)
Hypoechoic appearance in the liver	2 (4)
Normal view	3 (6)
Abdominal MRI findings (22 patients)	**n (%)**
Hypodense nodule in the liver	11 (50)
Enlargement of the common bile duct	10 (45.4)
Intrahepatic bile duct dilatation	4 (18.1)

USG: Ultrasonography, CT: Computed tomography, MRI: Magnetic resonance imaging

Appropriate treatment for both stages is triclabendazole 10 mg/kg daily for 2 days. The cure rate is 90% (2). The first drug therapy recommended by the CDC for fascioliasis since 1998 is triclabendazole. The recovery rate was reported as 79.4% in the first dose and 94% in the second dose (108). In another study, similar cure rates of 79.2% at the first dose and 100% at the second dose were reported (103). In the study conducted by Ulger et al., (49) 2 doses of triclabendazole were given to 39 patients and treatment response was obtained in 34 patients (87.1%). There are also other medical treatment options other than triclabendazole. It has been reported in the literature that some cases were successfully treated with alternative drugs such as bithionol, praziquantel, albendazole, metronidazole and ornidazole (9,28,35,59,65,66,72,73,76,78,79). When a patient is diagnosed with fascioliasis, other family members should be checked with serological testing. When the patient has a positive test, treatment should be given regardless of whether he is symptomatic or not (94).

CONCLUSIONS

Contrary to popular belief, *F. hepatica* is not rare in Türkiye and is more common in all regions of Türkiye, especially in the Mediterranean and Southeastern Anatolia regions. When we examine the reported cases in Türkiye, we see that diagnostic methods such as serological examinations and stool microscopy are not sufficiently used due to the fact that *F. hepatica* infection is not considered in the differential diagnosis and diagnostic facilities are not available in every center. As a result of not considering *F. hepatica* infection in the preliminary diagnosis and the insufficient use of these diagnostic methods, we see that patients are often misdiagnosed as having primary or metastatic liver tumors based on abdominal imaging. Consequently, invasive procedures or even open surgery have been performed on these patients for diagnostic purposes. This is an unacceptable situation, both for the patients and considering the economic burden it places on the country. In areas where *F. hepatica* infection is endemic, *F. hepatica* infection should be considered in patients with clinical findings, elevated liver and cholestasis enzymes along with eosinophilia, and characteristic CT or USG findings, before major surgical intervention. Non-invasive diagnostic methods such as stool microscopy and serological tests should be used first. The most appropriate treatment for *F. hepatica* is triclabendazole at 10 mg/kg daily for 2 days. However, triclabendazole is not available in Türkiye and must be obtained from abroad. To prevent *F. hepatica* infection, especially in endemic areas, individuals should avoid consuming raw water plants and stay away from areas where food and water may be contaminated or where hygiene conditions are inadequate.

1. *F. hepatica* infection is not uncommon in Türkiye, and *F. hepatica* infection should be considered in patients with elevated liver and cholestasis enzymes along with eosinophilia and characteristic imaging findings, and non-invasive diagnostic methods (stool microscopy and serological tests) should be used first.
2. In Türkiye, serological tests for *F. hepatica* are performed in certain reference laboratories. However, *F. hepatica* is an endemic infectious disease in Türkiye. Therefore, providing serological diagnostic facilities in healthcare centers will increase awareness and diagnosis rates of *F. hepatica*.
3. The unavailability of triclabendazole, the primary treatment option for *F. hepatica* infection, in Türkiye can cause difficulties for clinicians in treatment and patient followup, leading to patient suffering. Therefore, healthcare administrators should pay more attention to this issue.

*Authorship Contributions

Concept: N.M., F.C., A.T.Ö., Design: N.M., F.C., A.T.Ö., Data Collection or Processing: N.M., F.C., A.T.Ö., Analysis or Interpretation: N.M., F.C., A.T.Ö., Literature Search: N.M., F.C., A.T.Ö., Writing: N.M., F.C., A.T.Ö.

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