Review Article

Toxoplasmosis in Patients with Cardiac Disorders: a Systematic Review and Meta-Analysis

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Abstract

Toxoplasmosis is a common and serious infection caused by an obligatory intracellular protozoan, *Toxoplasma gondii*. This study investigated the possible association between heart failure and toxoplasmosis. We searched for toxoplasmosis and heart failure patients in English databases including PubMed, Scopus, ISI Web of Sciences, Science Direct, EMBASE, and Google Scholar up to June 2018. A total of 6 studies and 1,795 participants, comprising 934 cases and 861 controls, had acceptable criteria for entering the study. Immunoglobulin G (IgG) antibodies against *T. gondii* were found in 53% (22 to 83) of patients with heart diseases and 26% (11 to 42) of healthy controls. In comparison, immunoglobulin M (IgM) antibodies were found in 0.5% (0.1 to 1) in patients with heart diseases and 0.3% (0 to 0.7) of healthy controls. The patients suffering from cardiac disorders were more significantly correlated to anti-*T. gondii* IgG (OR: 3.53; 95% CI, 2.27 to 5.47; P = 0.014) and IgM (OR: 1.80; 95% CI, 0.31 to 10.4; P = 0.028) seropositivity than healthy controls. Despite limitations such as the low number of studies, our research showed a high association between toxoplasmosis and cardiac disorders. Therefore, toxoplasmosis may be a risk factor in cardiac patients, and more studies are being done.

Keywords: Cardiac disorders, *Toxoplasma gondii***,** Heart failure, Systematic review, Meta-analysis

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Introduction

The obligate intracellular protist of the phylum Apicomplexa, *Toxoplasma gondii* (*T. gondii*), causes a neglected tropical disease called toxoplasmosis, affecting one-third of the global community, especially in low-income countries[1]. Environmental contamination of water/vegetables with sporulated oocysts, bradyzoite-infected flesh of food animals, and infected mothers during the first gestation period make large depots for parasite transmission[1, 2]. Although rare, blood transfusion and organ transplantation are

also the likely routes of transmission for toxoplasmosis[3, 4]. From a global perspective, the pooled prevalence rates of *Toxoplasma* infection have been reported in at-risk human subgroups, comprising 42.1% (95% confidence interval [CI], 34.0 to 52.0) in HIV/AIDS patients, 26.0% (95% CI, 20.5 to 31.5) in cancer patients, 42.1% (95% CI, 27.1 to 57.2) among graft recipients, 33.0% (95% CI, 28.0 to 39.0) in seemingly healthy blood donors and 0.8-77.5% in childbearing-age and pregnant women[3, 5, 6]. Some host and environmental risk factors such as soil and meteorological parameters, nutritional habits, immune status, place of residence, occupation, age, and gender signify *Toxoplasma* survival and propagation[2, 5].

In general, symptomatic *Toxoplasma* infection, as acute disease or following reactivation of latent toxoplasmosis, occurs in immunocompromised individuals, representing poor prognosis sequelae including chorioretinitis, myocarditis, and brain lesions. Notwithstanding the relatively considerable prevalence of this infection among warm-blooded animals and various human populations, there are still many open questions about its cryptic biology and pathogenesis[1, 3]. For instance, the possible correlation between chronic toxoplasmosis and neurodegenerative disorders and autoimmune diseases has been disputed recently[7, 8].

The cardiovascular system is responsible for blood circulation, implicated in nutrients, hormones, gases, and blood cell transportation. The heart muscle, the myocardium, is an appropriate place for latent *Toxoplasma* cysts. These muscular cysts may have a role in complicating cardiac disorders (CD) and matter in the case of heart donation/transplantation procedure[9]. Therefore, we designed a systematic review and meta-analysis study to reveal the pooled prevalence of chronic toxoplasmosis infection among patients with cardiac disorders.

Methods

Information sources and search strategy: Current study was based on the preferred reporting items for systematic reviews and meta-analysis (PRISMA) checklist. We explored related literature in six English databases (PubMed, Scopus, ISI Web of Sciences, Science Direct, EMBASE, and Google Scholar) to assess the prevalence of chronic Toxoplasma infection among patients with CD healthy individuals worldwide from the inception until June 2018. The following keywords were used alone or in combination with "AND" and "OR" Boolean operators for systematic searching: "Toxoplasmosis," "*T. gondii*," "*Toxoplasma gondii*," "Heart failure," "Heart disease," "Heart," and "Myocarditis." Two researchers performed a systematic literature search independently. Furthermore, a reference list of gathered full texts was sought for additional related records.

Eligibility criteria, study selection, and data extraction: Following systematic searching, two independent reviewers checked the title, abstract, and full text of obtained entries, and irrelevant and duplicate records were excluded. Moreover, the results of each article were investigated carefully to omit duplicates and avoid reprint bias. Consensus by a third reviewer resolved any possible inconsistency. After removing duplicate entries, the below inclusion criteria were used for the assessment of the finally included article: (A) case-control studies about the relationship between chronic toxoplasmosis as exposure and CD as an outcome; (B) Published in English language without time limitation; (C) the presence of case and control groups, sample size and positive samples for each group; and (D) the studies within which toxoplasmosis was diagnosed using at least one of the methodologies such as dye test, serology and/or molecular techniques. Observational prevalence investigations, studies with only final results or raw data, and papers published in other languages were excluded. Ultimately, one author extracted the following required information from included entries, and a second researcher rechecked them: The first author's name, year of publication, country, the total number of cases and controls, number of positive and negative persons in the case, and control groups, matching, and detection method.

Meta-analysis: Meta-analysis was performed as previously described[7, 10, 11]. The OR values and their respective 95% CIs were calculated ($P< 0.05$ as significant). On this basis, OR < 1 implies the protective effect of *T. gondii* infection against CD, whereas OR > 1 demonstrates the affirmative impact of chronic toxoplasmosis on CD. A forest plot was

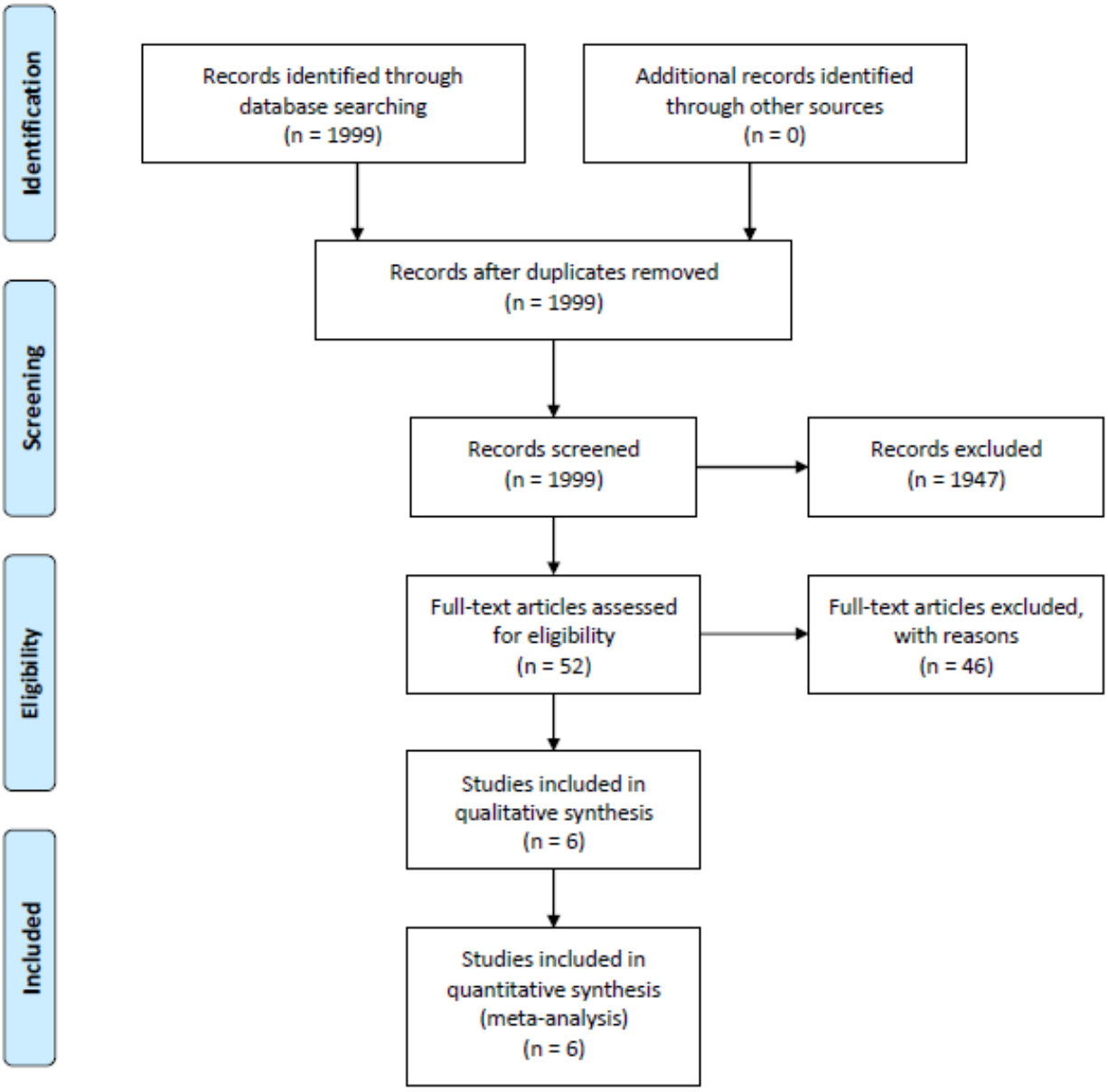

Figure 1. Flowchart describing the study design process

depicted to show the approximated estimates with 95% CIs of individual studies. Also, heterogeneity and inconsistency among eligible studies were evaluated using Cochran's Q and I^2 index. According to Egger's regression test, publication bias and minor study effects were discerned via Begg's funnel plot diagram. Either Mantel-Haenszel's fixed-effects or Der Simonian and Laird's random-effects methods were exerted to pool the estimations (Stata Corp, College Station, TX, USA).

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Results

Of the 1999 explored records, six records were

Table 1: Baseline characteristics of included studies.

Reference	Country	Year	Group	Sample size (n)	Positive samples		Method	Age range or mean age	Matching
					IgG^+ n	IgM^+ n			
Ludlam and Somers (1966)	Uganda	1966	Case	120	27	-	Sabin-Feldman dye test	-	NR
			Control	94	11	-		>25	
Sibalić et al. (1986)	Yugoslavia	1986	Case	183	157	5	Sabin-Feldman dye test and IFAT	14-54	Age and gender
			Control	183	94	-		14-54	
Yazar et al. (2006)	Turkey	2006	Case	97	66	1	ELISA	63.64 ± 11.46	Age
			Control	50	18	0		62.91 ± 12.14	
Hamidinejat et al. (2013)	Iran	2013	Case	48	32	11	ELISA	40-55	Age
			Control	48	14	2		40-55	
Alvarado-Esquivel et al. (2016)	Mexico	2016	Case	400	55	13	ELISA	58.87 ± 14.59	Age and gender
			Control	400	32	19		58.76 ± 14.54	
Gohari and Dalimi (2017)	Iran	2017	Case	86	53	-	ELISA	NR	Age and gender
			Control	86	21	-			

qualified for our meta-analysis[12-17] study, with the baseline characteristics being described in Table 1. Also, Figure 1 represents the study selection process. Out of 6 included case-control investigations, 1795 participants, comprising 934 cases and 861 controls, were examined for chronic toxoplasmosis. Concerning detection methods, enzyme-linked immunosorbent assay (ELISA) (4 studies), Sabin-Feldman dye test (2 studies), and an indirect fluorescent antibody test (IFAT) (one study) were the most employed diagnostics, respectively. Despite IgG, which was evaluated in all studies in both case and control groups, IgM was only assessed in 4 cases and three control groups. Furthermore, the odds of IgM seropositivity for toxoplasmosis in CD patients were merely appraised in 3 studies.

IgG *T. gondii* antibodies were reported in 53% (95% CI, 22 to 83) of the CD patients and in 26% (95% CI, 11 to 42) of the healthy controls (Figures 2 and 3). In addition, IgM antibodies were detected in 0.5% (95% CI, 0.1 to 1) of the CD patients and in 0.3% (95% CI, 0 to 0.7) of the healthy individuals (Figures2 and 3). On the basis of Figure 4, patients suffering from CD were more significantly correlated to anti-*T. gondii* IgG (OR: 3.53; 95% CI, 2.27 to 5.47; P = 0.014) and IgM (OR: 1.80; 95% CI, 0.31 to 10.4; P = 0.028) seropositivity than healthy controls. Our results showed that publication bias for both IgG (P = 0.553) and IgM (P = 0.586) antibodies is not statistically significant (Figure 5).

Discussion

T. gondii is one of the most frequent organisms worldwide, with severe complications in the unborn child and immunocompromised individuals[1, 3, 5]. In the latter, the clinical course of toxoplasmosis may involve the brain with the subsequent pernicious encephalitis and the heart with various manifestations such as acute heart failure, myocarditis alone or in combination with pericarditis[12, 18, 19]. Infections with *T. gondii* are systemic, and the parasite can persist in the heart muscles. Very little is known about the impact of *T. gondii* on patients with heart disease[12].

Toxoplasma-induced myocarditis may represent life-threatening symptoms of constrictive pericarditis, pericardial effusion, arrhythmias, and congestive heart failure[12-14]. Regarding such possible consequences, we contrived a systematic review and meta-analysis study to reveal the possible association between chronic toxoplasmosis infection as the exposure and CD as the outcome. The present meta-analysis assessed the seroprevalence of *T. gondii* infection in patients with cardiac disorders worldwide. The results demonstrated a relatively high prevalence (53%) of *T. gondii*

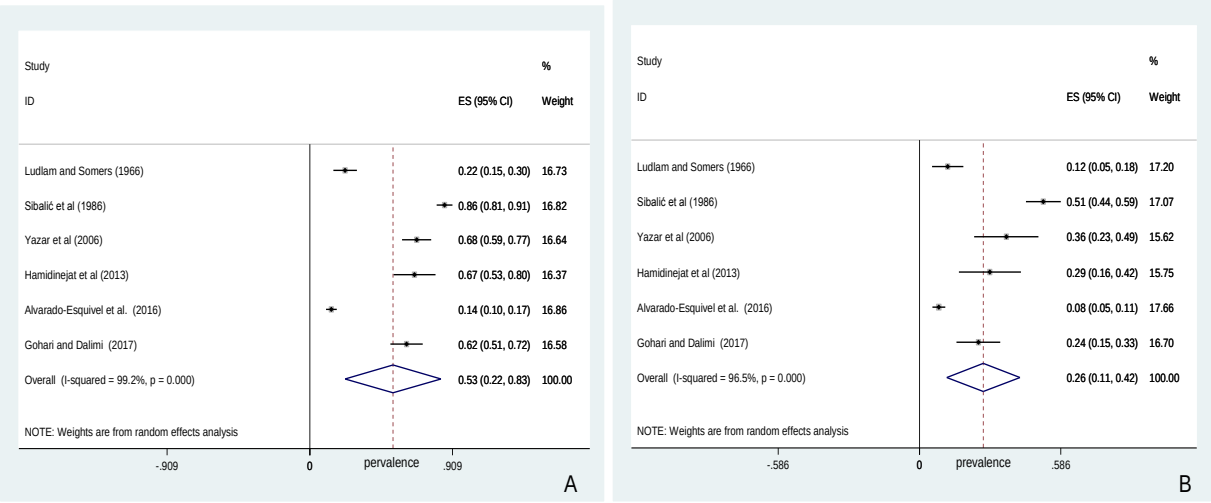

Figure 2. Forest plot diagram of the present systematic review and meta-analysis based on immunoglobulin G antibodies in case (A) and control (B) groups. ES, effect size; CI, confidence interval.

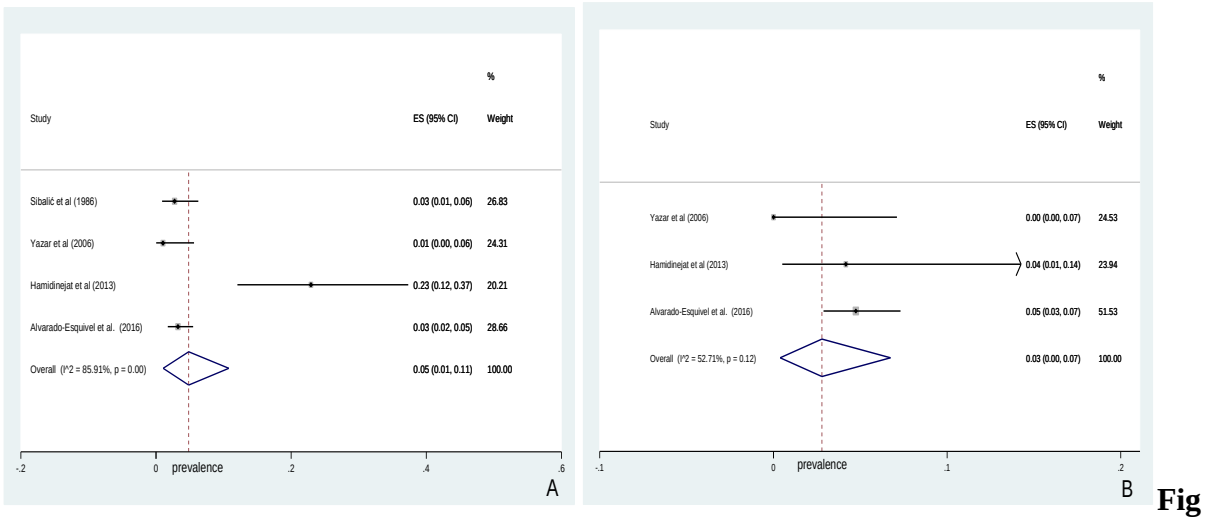

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Figure 3. Forest plot diagram of the present systematic review and meta-analysis based on immunoglobulin M antibodies in case (A) and control (B) groups. ES, effect size; CI, confidence interval.

infection in patients suffering from heart disease, which was significantly higher than was observed in healthy controls. Results indicate that patients with heart diseases represent a risk group for *T. gondii* infection. Toxoplasmosis is probably the only parasitosis that persists for the whole life without any remarkable manifestations. Although *Toxoplasma* interaction inside the skeletal muscle was recently explained, it is unknown how *T. gondii* may manipulate the microenvironment of the muscle cells toward subsequent inflammation and/or disease condition[9, 12-14].

There are some reasons why *Toxoplasma* is present in patients with heart diseases, including chronic heart failure (CHF) involves interactions between cardiovascular, neurological, and immune systems. Natural killer cells (NK) are essential immune cells. These cells contribute to the first line of non-antigen-specific defense against infections, and there is evidence that they play a crucial role in tumor surveillance[20]. A study reported that a subgroup of patients with heart failure exhibited NK cell anergy to activation by interleukin (IL-2) and interferon gamma[21]. Therefore, it seems likely that suppressed immune systems in patients with CHF increased the risk of incredibly opportunistic infections.

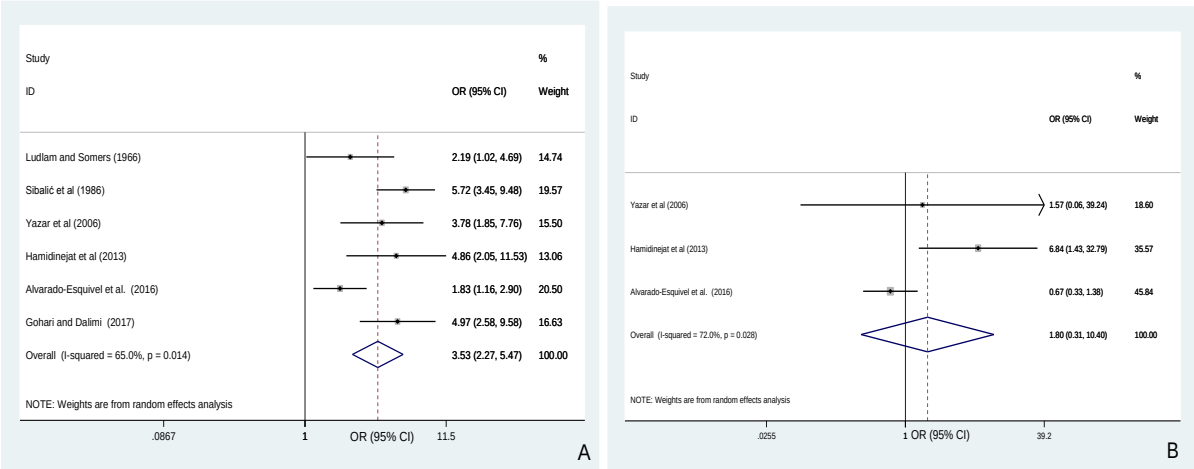

Figure 4. Forest plot of ORs related to the immunoglobulin G (A) and immunoglobulin M (B) groups. OR, odds ratio; CI, confidence interval.

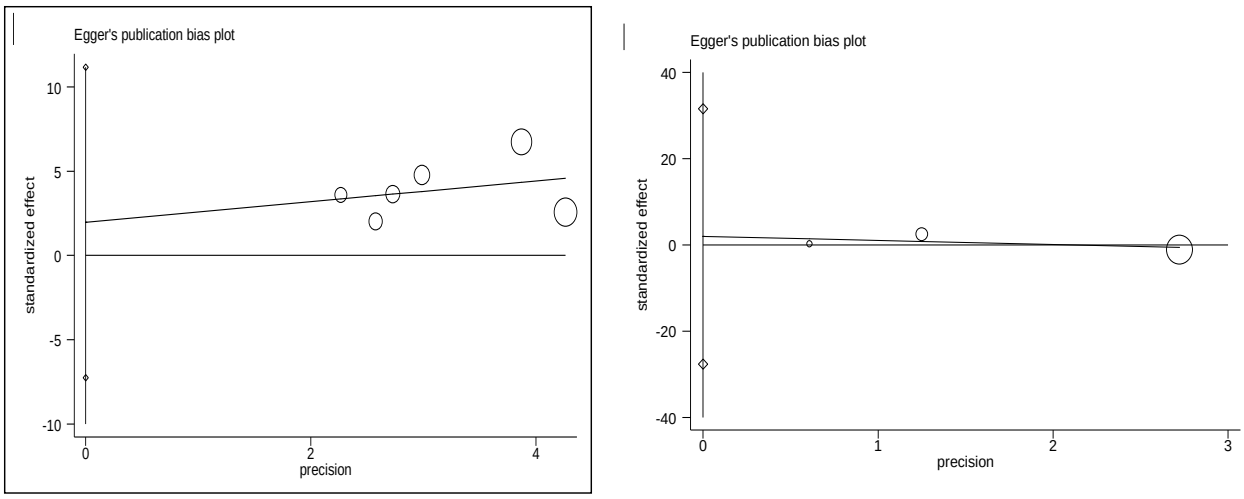

Figure 5. Egger plot for detecting publication bias. The parentheses indicate the inverse of sample size.

Several limitations confined our deductions in the current meta-analysis: 1) we included only case-control studies on the prevalence of *T. gondii* as the exposure and heart diseases as the anticipated outcome, instead of longitudinal cohort investigations; 2) Mostly serology tests such as ELISA with various cutoff values were employed for identification of anti-*T. gondii* antibodies and molecular techniques were neglected; 3) however, the weak immune status would be a predisposing factor for the parasite to revive from latent form and provoke clinical disease, other probable risk factors involved in the parasite-derived CD aren't recognized; 4) the relationship between CD duration and *Toxoplasma* seropositivity was not assessed; and 5) the insufficient number of relevant papers would have biased our findings.

These studies indicate that *Toxoplasma* may be associated with heart disease, so further studies are recommended. In addition to serological tests, molecular tests should also be used. Also, consider other factors affecting the relationship between heart disease and parasitic infections, such as the duration of heart disease and the time of parasitic infections.

Conclusion

Humans are an intermediate host for *T. gondii. Since* the heart muscle is a suitable site for *Toxoplasma*

cysts, patients with cardiac disorders may be a high-risk group for this infection. Concerning our findings, the prevalence of heart disease is higher than that of healthy controls. Thus, it appears that serological tests for *T. gondii* should be incorporated into the routine clinical care of these patients. Finally, we believe that there is a great need for more seroepidemiological studies to understand better overlaps between *Toxoplasma* and heart disease in endemic countries.

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Conflict of interest

The authors further declare that they have no conflict of interest.

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