Regional Review

Toxoplasmosis in immunocompromised patients in Iran: a systematic review and meta-analysis

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Abstract

Although toxoplasmosis in immunocompetent individuals is generally asymptomatic, in immunocompromised patients (HIV/AIDS, cancer, and transplant patients), it can lead to serious pathological effects. This study included a systematic review and meta-analysis to comprehensively assess the seroprevalence rate of *Toxoplasma* infection in immunocompromised patients in Iran. Electronic English and Persian databases (PubMed, Google Scholar, ScienceDirect, Scopus, Magiran, Scientific Information Database [SID], IranMedex, and IranDoc), parasitology congresses, and projects and theses of Iranian medical universities, were systematically searched from 1997 to 2013 (published or unpublished data). In this paper, several studies that used serological methods for diagnosis of toxoplasmosis were selected. Analysis of seroprevalence estimates was pooled using a random-effects meta-analysis. Twenty-two studies, comprising 2,805 individuals, were included in the meta-analysis. Overall seroprevalence rate of *Toxoplasma* infection in Iranian immunocompromised patients was 50.01% (95% confidence interval, 43.85 to 56.17); however, there was significant heterogeneity among study groups. The results showed that seroprevalence rate of toxoplasmosis among transplant recipients, HIV/AIDS, and cancer patients in Iran was 55.1%, 50.05%, and 45.06%, respectively. In addition, IgM seroprevalence rate was estimated to be 4.85% (95% confidence interval, 2.22 to 8.41). This systematic review and meta-analysis identified a high seroprevalence rate of *Toxoplasma* infection among immunocompromised patients (50%).Consideration of management , design and provision of appropriate control measures of toxoplasmosis is highly recommended.

Key words: toxoplasmosis; immunocompromised; HIV/AIDS; cancer; transplant; Iran.

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Introduction

Toxoplasmosis is an infection with worldwide distribution caused by the protozoan parasite *Toxoplasma gondii* (*T. gondii*), which infects all warm-blooded vertebrates and imposes a major burden on human and animal health [1]. The global seroprevalence in humans and animals varies greatly among countries, ranging from 6.7% in Korea to 68.6% in Brazil, depending on the geographical location and differences in lifestyle [2-3]. The authors of a previous systematic review of the Iranian general population estimated that approximately 39.3% (95% CI, 33.0 to 45.7) of individuals were seropositive [4]. *Toxoplasma gondii* can pass from one host to another, through environmental transmission (food and water contaminated with oocysts), infected tissue consumption (raw or undercooked meat), or transplacental transmission. Uncommon transmission may also occur through organ transplantation and blood transfusions [1,5].

Several methods are employed for diagnosis of toxoplasmosis, which routinely relies on serological methods. Serology-based diagnosis tools such as enzyme-linked immunosorbent assay (ELISA) and indirect immunofluorescence assay (IFA) are considered to be the gold standard for the detection of *Toxoplasma*-specific antibodies (IgG or IgM) [1].

Acute infections are generally subclinical and asymptomatic in healthy individuals or cause flu-like symptoms, but may lead to chronic infection. However, toxoplasmosis can be complicated and is considered to be a serious disease in immunocompromised patients [1,5]. Results from the reactivation of a latent infection can be fatal [6-8]. *Toxoplasma* has a noted tendency to localize in the brain (neurotropism) and eye, which leads to the

formation of cysts in relevant target organs. *T. gondii* can cause repeated attacks of encephalitis in HIV/AIDS patients and in some immunocompromised individuals, which can lead to severe brain damage, long-term neurological defects, and death [6,7,9]. For appropriate diagnosis, treatment, and control of infections caused by *T. gondii*, clinicians require information concerning the seroprevalence rate of toxoplasmosis in different special populations. A systematic review of the literature was performed in order to evaluate the seroprevalence of toxoplasmosis among immunocompromised individuals in Iran.

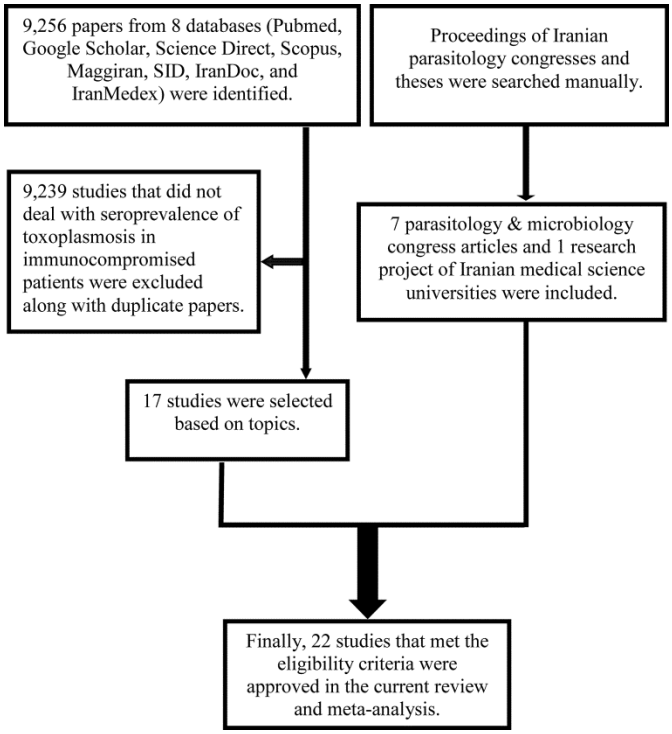
Database search

English databases, including PubMed, ScienceDirect, Scopus, Google Scholar; and Persian databases, including Magiran, SID, IranMedex, and IranDoc, were searched for publications related to infection with *T. gondii*, from 1997 to 2013. Furthermore, the gray literature searched included the abstracts of parasitology conference proceedings and projects of Iranian research centers and medical universities (published or unpublished). Keywords included toxoplasmosis, *Toxoplasma gondii*, *T. gondii*, Iran, Islamic Republic of Iran, cancer, transplant, HIV, AIDS, immunocompromised, and seroprevalence (alone or combined). Papers written in Persian or English were selected.

Data collection

To provide comprehensive awareness, all studies that were based on serological methods and carried out to estimate the seroprevalence of *T. gondii* infection in immunocompromised patients in Iran were included in this review. Eligibility of identified studies was assessed independently by two authors. Discrepancies were resolved by discussion and consensus. In addition, studies that did not use random sampling methods or that were performed in other groups of people, such as pregnant women and the general population, were excluded. Included papers were carefully investigated, and information about year of publication, first author, study location, total sample size, number of male and female participants, number of seropositive patients, age distribution, and laboratory methods of *T. gondii* diagnosis were extracted using a data extraction form. Figure 1 briefly shows the search process in this review article.

Figure 1. Flow diagram describing the study design process.



Statistical analysis

Point estimates and their 95% confidence intervals of seroprevalence of all included studies were calculated. An overall seroprevalence and group-specific seroprevalences were calculated among the patient groups (HIV/AIDS, malignancies, and transplantation). A forest plot chart was used to visualize the heterogeneity among studies. The I^2 and Cochran's Q tests were used to quantify the variations between studies (with significance of $p < 0.01$). For this meta-analysis, the included studies were assumed to be random samples from a population, and the random effect model was employed. Proportions of individual studies and overall seroprevalence were presented by forest plots. The meta-analysis was performed separately for IgG and IgM using the trial version of StatDirect statistical software (http://statsdirect.com).

Results

Out of 9,256 studies from literature searches, 22 records were eligible for inclusion in this systematic review and meta-analysis. In total, 2,805 individuals were included in the analysis, which contained 1,326 IgG seropositive cases. The baseline characteristics of the studies included in this literature search are shown in Tables 1 and 2.

Table 1. Baseline characteristics of included studies (based on IgG assessment)

No.	First author	Year	Province	Patient group	Number of cases	IgG-positive cases	Sero-prevalence (%)	Age range	Serological test	Design	Ref
1	Gharavi MJ	1997	Tehran	Malignancy	36	10	27.77	NA	IFA	Descriptive	15
2	Gharavi MJ	1997	Tehran	Transplant	64	58	90.62	NA	ELISA	Descriptive	15
3	Jalallo N	2001	Tehran	Transplant	80	54	67.5	NA	IFA	Cross-sectional	16
4	Jalallo N	2001	Tehran	Malignancy	80	54	67.5	NA	ELISA	Cross-sectional	16
5	Fallah E	2003	East Azerbaijan	Malignancy	100	48	48	NA	ELISA	Cross-sectional	17
6	Mardani A	2004	Ghom	HIV/AIDS	75	46	62.33	20 – 50	ELISA	Cross-sectional	18
7	Ghasemian M	2007	Khozestan	Malignancy	252	114	45.23	<10 – 50<	ELISA	Cross-sectional	19
8	Davarpanah MA	2007	Fars	HIV/AIDS	208	38	18.26	39 ± 7.6	ELISA	Descriptive	20
9	Afrasiabian S	2008	Kurdestan	HIV/AIDS	64	30	46.87	32.1 ± 6.73	ELISA	Cross-sectional	21
10	KhayatNouri MH	2009	East Azerbaijan	Malignancy	150	61	40.66	<10 – 70<	IFA	Cross-sectional	22
11	Vejdani M	2009	Kermanshah	Transplant	50	27	54	40 – 86	ELISA	Quasi-experimental	23
12	Kavakeb P	2009	Tehran	Transplant	31	17	54.83	NA	ELISA	Cross-sectional	24
13	Ebrahimisadr P	2010	Tehran	Malignancy	200	95	47.5	NA	ELISA	Descriptive	25
14	Mohraz M	2010	Tehran	HIV/AIDS	201	100	49.75	36 ± 1	ELISA	Cross-sectional	26
15	Shafiei R	2011	Khorasan-Razavi	HIV/AIDS	121	46	38.01	35.83 ± 6.75	ELISA	Cross-sectional	27
16	Daryani A	2011	Mazandaran	HIV/AIDS	62	48	77.41	32.6 ± 7.4	ELISA	Cross-sectional	9
17	Foroughi M	2011	Tehran	HIV/AIDS	201	96	47.76	36 ± 0.65	IFA	Cross-sectional	28
18	Raeghi S	2011	West Azerbaijan	Transplant	83	36	43.37	35/4 ± 14/5	ELISA	Cross-sectional	29
19	Gharavi MJ	2011	Tehran	Transplant	102	65	63.72	15 – 65	ELISA	Cohort	30
20	Gharavi MJ	2011	Tehran	Transplant	102	49	48.03	15 – 65	ELFA	Cohort	30
21	Saburi E	2012	Tehran	Malignancy	81	29	35.8	NA	ELISA	Cross-sectional	31
22	AnvariTafti MH	2012	Yazd	Malignancy	172	74	43.02	NA	ELISA	Cross-sectional	32
23	Soltani S	2012	Khozestan	Transplant	100	34	34	NA	ELISA	Cross-sectional	33
24	Abdollahyar F	2012	Kerman	Transplant	90	32	35.55	16 – 72	ELISA	Case-control	34
25	Abdollahi A	2013	Tehran	HIV/AIDS	100	65	65	36.04 ± 1.04	ELISA	Case-control	35

Table 2. Baseline characteristics of included studies (based on IgM assessment)

No.	First author	Year	Province	Patients group	Number of cases	IgM positive cases	Sero-prevalence (%)	Laboratory method	Ref
1	Jalallo N	2000	Tehran	Transplant	80	0	0	ELISA	16
2	Mardani A	2004	Ghom	HIV	75	0	0	ELISA	18
3	Ghasemian M	2007	Khozestan	Cancer	252	26	10.31	ELISA	19
4	Afrasiabian S	2008	Kurdestan	HIV	64	7	10.93	ELISA	21
5	KhayatNouri MH	2009	East Azerbaijan	Cancer	150	23	15.33	ELISA	22
6	Vejdani M	2009	Kermanshah	Transplant	50	3	6	ELISA	23
7	Mohraz M	2010	Tehran	HIV	201	1	0.49	ELISA	26
8	Shafiei R	2011	Khorasan-Razavi	HIV	121	3	2.47	ELISA	27
9	Daryani A	2011	Mazandaran	HIV	62	6	9.67	ELISA	9
10	Foroughi M	2011	Tehran	HIV	201	2	0.99	ELISA	28
11	Raeghi S	2011	West Azerbaijan	Transplant	83	4	4.81	ELISA	29
12	Gharavi MJ	2011	Tehran	Transplant	102	3	2.94	ELFA	30
13	Gharavi MJ	2011	Tehran	Transplant	102	2	1.96	ELISA	30
14	Soltani S	2012	Khozestan	Transplant	100	18	18	ELISA	33
15	Abdollahyar F	2012	Kerman	Transplant	90	0	0	ELISA	34

Figure 2. Forest plot diagram of studies showing IgG seropositivity rates to *T. gondii*in HIV/AIDS patients from Iran

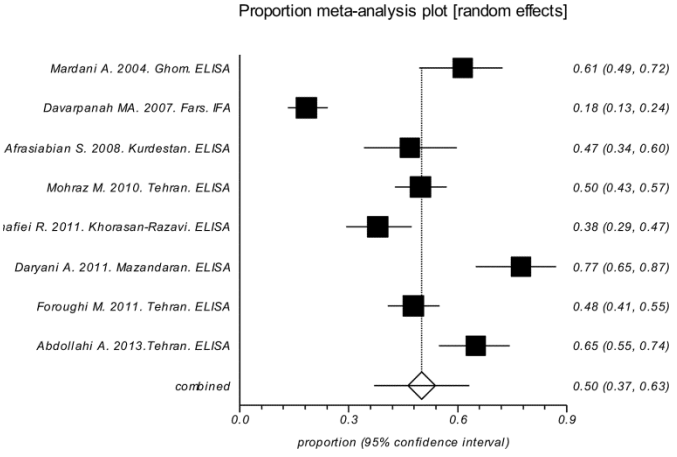
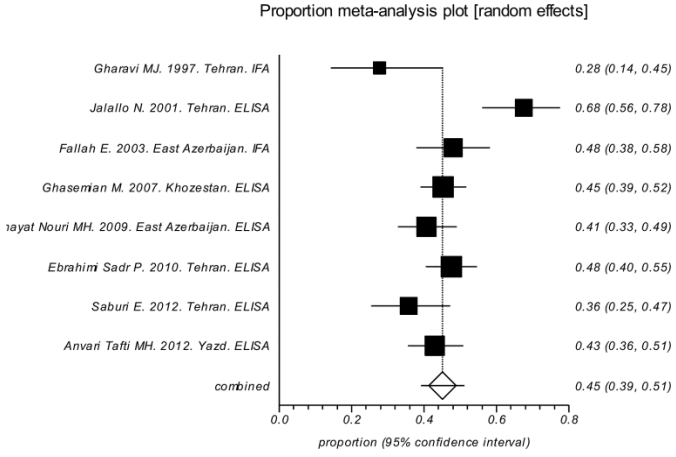


Figure 3. Forest plot diagram of studies showing IgG seropositivity rates to *T. gondii* in cancer patients from Iran



There was a wide variation in the seroprevalence estimation among different studies; the *Q* statistic was very large (*Q* = 260.37, degrees of freedom [df] = 24, p < 0.0001), and the I^2 obtained was 90.8%. The overall seroprevalence of *T. gondii* infection among Iranian immunocompromised individuals using the random-effect model meta-analysis was 50.01% (95% CI, 43.85 to 56.17).

HIV/AIDS patients

In this study group, eight publications that included 1,032 HIV/AIDS patients were evaluated. The *Q* statistic and the pooled seroprevalence were 128.75 (df = 7, p < 0.0001) and 50.05%, (95% CI, 36.9 to 63.2), respectively (Figure 2).

Cancer patients

Eight studies that included 1,071 patients were evaluated. In this group, the *Q* statistic was 26.11 (df = 7, p = 0.0005) with inconsistency (I^2 = 73.2%), and the pooled seroprevalence was 45.06% (95% CI, 39.12 to 51.06) (Figure 3).

Transplant patients

In 702 cases from nine studies, the *Q* statistic was 90.62 (df = 8, p < 0.0001), and the pooled seroprevalence was 55.1% (95% CI, 42.63 to 67.25) (Figure 4).

Also, among 1,733 immunocompromised patients, 98 (5.1%) cases were seropositive for IgM antibodies (Table 2); the corresponding forest plot diagram is shown in Figure 5. In the included studies, three different serological diagnostic tests were used. The most used diagnostic method was ELISA (20 studies), followed by IFA (4 studies) and enzyme-linked fluorescent assay (ELFA) (1 study).

Figure 4. Forest plot diagram of studies showing IgG seropositivity rates to *T. gondii* in transplant recipients from Iran

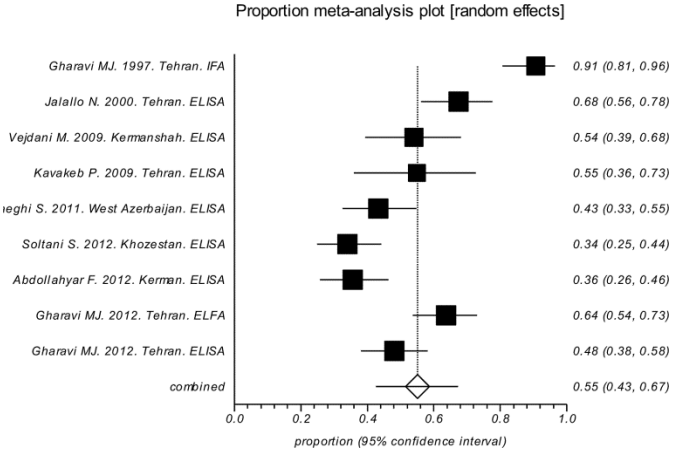
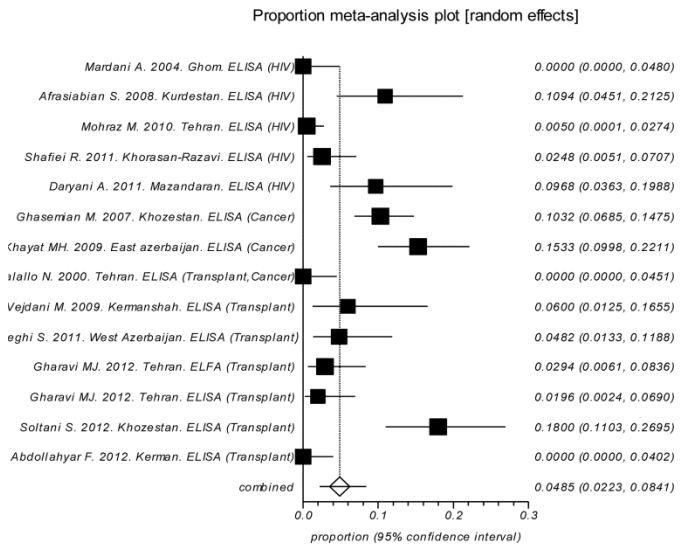


Figure 5. Forest plot diagram of studies showing IgM seropositivity rates to *T. gondii* in immunocompromised patients from Iran



Discussion

This is the first systematic review and meta-analysis of toxoplasmosis in immunocompromised individuals from Iran. Findings of the meta-analysis show that seroprevalence rates are noticeable and that more than half of immunocompromised patients in Iran are at risk for reactivation of a *T. gondii* infection and the development of a fulminant disease. Among the 2,805 immunocompromised patients in Iran, the highest seroprevalence rate of *T. gondii* was observed in patients who had received transplants (55%) followed by HIV-infected individuals (50%) and patients with cancer (45%).

An efficient immune system often can control disease and usually keeps the parasite from causing illness in immunocompetent persons [5]. In immunocompromised patients, however, disease can occur in two circumstances. In the first, patients with a positive IgM titer were infected recently with *Toxoplasma*. This was considered to be acute *Toxoplasma* infection that is more likely to develop into a severe infection. In the second circumstance, individuals with a positive IgG, who were infected previously (before they become immunosuppressed), were at a great risk for developing a reactivated infection [3-6,10].

Toxoplasmosis is recognized as an opportunistic infection in immunocompromised patients and has a poor prognosis. Also, it is a life-threatening disease responsible for a high mortality rate, causing encephalitis, pneumonitis, and myocarditis (common clinical manifestations of toxoplasmosis in immunocompromised patients) due to recrudescence and reactivation of chronic (latent) disease followed by rupture of tissue cysts [3-6]. Moreover, acquired acute infection may occur through, for example, solid organ transplantation (*Toxoplasma*-seronegative recipients who receive *Toxoplasma*-seropositive organs) [5,6,10].

Toxoplasma infection in vulnerable clinical groups, such as immunocompromised patients, is usually more severe and often requires specialist investigation. There are limited data on *Toxoplasma* infection in immunocompromised patients, and studies do not reflect the actual incidence of disease. Awareness about toxoplasmosis in different population groups is gradually rising, and the surveys provide health information, but there are gaps in the studies' knowledge about patients. In general, a remarkable paucity of data on seroepidemiological surveys has been observed, and studies have not provided sufficient information. Overall, a number of gaps such as patient's age, sex, risk factors, and sources of *T. gondii* infection, have remained and cannot be explained. Hence, future studies should be well defined and should consider the risk factors and epidemiological aspects.

At this time, serological tests are regarded as the gold standard and are used for diagnosis of *T. gondii* infection, but this infection is doubtlessly undervalued because these methods are not conclusive, though they do provide critical information [1]. Diversity of the sensitivity and specificity of diagnostic methods is one of the most important factors that cause wide variation in *T. gondii* prevalence [1,6]. For instance, in transplant patients, large differences were observed between IFA (91%) and ELISA results (highest seroprevalence of 68%), while the results of ELFA and ELISA methods were close to each other. The majority of studies in Iran used ELISA and IFA tests, except for one study that used ELFA test with 102 individuals, the results of which could not be compared.

The accurate incidence of toxoplasmosis among immunocompromised patients and various organ transplant recipients has not been identified in various regions, including Asia, Europe, and America [4,11]. Indeed, numerous studies have been conducted to determine the relationship between toxoplasmosis and special groups of diseases; however, insufficient data have been published on the global or regional incidence of *Toxoplasma* infection in these groups. Recently, Galvan-Ramirez *et al*. systematically reviewed prevalence of *T. gondii* infection in a Mexican population. They reported a 28.54% prevalence rate in 627 immunocompromised patients from seven studies [12].

The incidence of *T. gondii* infection is not well defined and most infections are probably not recognized. In addition, the incidence and prevalence of *T. gondii* infection varies depending on geographic areas, weather conditions, and age groups, so the frequency of seropositivity in the Iranian general population ranges from 12% in Khuzestan and Azarbaijan to 86% in Gilan [13,14]. The seroprevalence of *T. gondii* infection in the general population in Iran was found to be 39.3% [4], whereas the rate of infection was higher among the immunocompromised patients (50%). The cancerous patient group had lower specific *Toxoplasma* IgG antibodies among the immunocompromised patients. In the eight studies focused on cancerous patients, the seroprevalence was 45% among 702 patients. Also, among the mentioned groups, the highest rate of *T.*

gondii infection was observed in transplant recipients (55%). The presence of pre-transplantation *T. gondii* antibodies is a major risk factor for infection in transplant recipients. Therefore, to reduce *Toxoplasma* infection and prevent the acute phase of infection, transplant recipients and donors should be screened for toxoplasmosis.

Conclusions

To the best of our knowledge, this is the first systematic review and meta-analysis that provides a comprehensive view of the seroepidemiology of toxoplasmosis in Iranian immunocompromised patients. Our data indicate that researchers must pay more attention to seroprevalence of toxoplasmosis in immunocompromised patients. Hence, more information focused on *Toxoplasma* seroprevalence and its risk factors must be collected to improve prevention strategies for control of the disease in immunocompromised patients. Also, strengthened educational efforts are needed to avoid a relapse and to stop the spread of *T. gondii* infection that cannot be adequately controlled by drugs alone in immunosuppressed patients.

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