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Review

The seroprevalence rate and population genetic structure of human cystic echinococcosis in the Middle East: A systematic review and meta-analysis

Tahereh Mikaeili Galeh[a,1], Adel Spotin[b,1], Mahmoud Mahami-Oskouei[c], David Carmena[d], Mohammad Taghi Rahimi[e], Aleksandra Barac[f,g], Roghayeh Ghoyounchi[a], Reza Berahmat[a], Ehsan Ahmadpour[h,i,*]

[a] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Department of Parasitology, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Parasitology Service, National Centre for Microbiology, Health Institute Carlos III, Ctra Majadahonda-Pozuelo Km 2, 28220, Majadahonda, Madrid, Spain
[e] School of Medicine, Shahroud University of Medical Sciences, Shahroud, Iran
[f] Clinic for Infectious and Tropic Diseases, Clinical Centre of Serbia, Belgrade, Serbia
[g] Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[h] Research Center for Evidence Based Medicine (RCEBM), Tabriz University of Medical Sciences, Tabriz, Iran
[i] Infectious and Tropical Disease Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

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ABSTRACT

Cystic echinococcosis (CE) represents an increasing public health concern in many parts of the world, including the Middle East. The present study is the first systematic review and meta-analysis to assess the seroprevalence rate and population genetic structure of human CE in the eastern Mediterranean region. To estimate the population genetic structure, *Echinococcus* sequences of the cytochrome oxidase subunit 1 (*cox*1) gene isolated from countries from this geographical area were retrieved from the GenBank database. An electronic search for articles from 1990 until 2015 was performed using databases PubMed, ScienceDirect, and Scopus. A total of 53 articles reporting on CE seroprevalence and genotyping data met our eligibility criteria and were included in a meta-analysis. The overall CE seroprevalence rates in the general population and in individuals at high risk of infection were estimated using the random-effect model at 7.4% (95% CI = 4.8–10.6) and 10.7% (95% CI = 7.6–14.3), respectively. Risk factors including age group ($P < 0.001$), dog ownership ($P = 0.03$), residence area ($P < 0.001$), and educational level ($P = 0.04$) showed a statistically significant association with CE seroprevalence. A pairwise fixation index (*F*st), used as an estimation of gene flow, suggested a moderate level of genetic differentiation between members of the *E. granulosus* sensu stricto (G1-G3) complex from Iranian and Turkish metapopulations (*F*st = 0.171). The finding of common haplotypes may represent an ancestral transfer of alleles among populations probably during the early stages of animal domestication. The high CE seroprevalence rates found highlight the necessity of implementing appropriate public education for preventive and control strategies, particularly in individuals at high risk of infection; furthermore, our genetic findings reveal novel molecular data concerning microevolutionary events of *Echinococcus* isolates among Middle East countries.

1. Introduction

Cystic echinococcosis (CE) is one of the most important zoonotic parasitic diseases that is caused by the larval stages of the taeniid tapeworm *Echinococcus granulosus* complex, affecting humans and a variety of ungulates worldwide [1–4]. CE is transmitted between the definitive host (usually dogs or other canids) and intermediate hosts (herbivorous and omnivorous mammals) (Fig. 1). Humans act as a dead-end host, acquiring the infection after accidental ingestion of *Echinococcus* eggs, which are shed in the feces of infected canids [5–7]. Adult tapeworms develop in the small intestine of definitive hosts, while metacestodes (also called hydatid cysts) infect the internal organs, especially the liver and lungs, of the intermediate hosts [8,9]. This multi-host disease is one of the most important public health infection diseases in Middle East [7,8]. Echinococcosis is one of the leading problems not only in humans but also in traps that causes a huge

* Corresponding author. Department of Parasitology and Mycology, Tabriz university of Medical Sciences, Tabriz, Iran.
E-mail address: ehsanahmadpour@gmail.com (E. Ahmadpour).
[1] These two authors contributed equally to this work.

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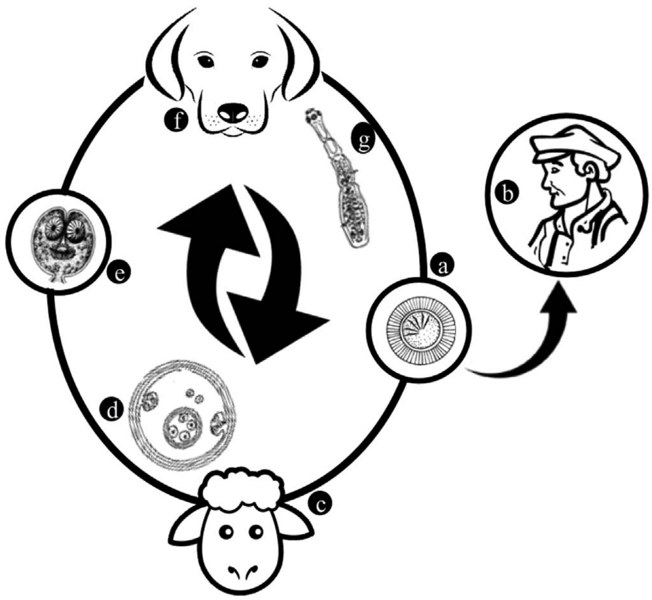

Fig. 1. The life cycle of *E. granulosus* the causative agent of cystic echinococcosis. **a:** The eggs are released from gravid proglottids and passed in the feces (infective stage for intermediate hosts), **b:** Humans can become infected accidentally (as intermediate host), **c:** Intermediate host (such as sheep, goat, swine, cattle and horses), **d:** Cystic echinococcosis, **e:** *Echinococcus* protoscolex, **f:** Dogs and other canidae (as definitive hosts), **g:** The adult worm of *E. granulosus* resides in small intestine of the definitive hosts.

economic burden for governments [8,9].

Although human CE is usually asymptomatic, a substantial number of infections cause morbidity and occasional mortality with considerable economic losses in both humans and livestock [10–14]. The disease has a worldwide distribution affecting primarily rural regions where livestock rearing is the main industry [6,15]. The common signs of CE in symptomatic cases are cough, fever, chest pain, dyspnea, abdominal masses, ascites, hepatomegaly, and splenomegaly [16,17]. Cystic lesions most frequently located in the liver followed by the lung and, less frequently, in other organs, characterize CE. The disease can be fatal if inappropriate treatment is provided. In general, surgery is the treatment of choice, followed by chemotherapy being mainly used as the recommended supplementary treatment approach [18–22].

The diagnosis of CE is primarily based on imagery and serological diagnostic methods. Both serology and ultrasound (US) are used in most of the studies. Serological assays have been recommended as first-line screening tests in endemic regions [4,23,24]. However, it should be noted that these methods might have overall reduced sensitivities when used directly in endemic communities compared with those obtained in advanced symptomatic cases. These data suggest that the prevalence of CE may be higher than shown by the results reported in endemic areas [6]. Serological techniques may deliver false-negative results due to circulating immune complexes, whereas false-positive data may be associated with cross-reactivity with other parasitic infections [25,26]. Serological methods for the detection of CE antibodies include ELISA, IHA, IFA, Indirect-ELISA, EIA, WB, Casoni test, etc. [27]. As a quantitative, inexpensive, and sensitive method, ELISA is the most commonly used serological method for CE detection in the reviewed studies.

According to the World Health Organization (WHO), human CE represents a worldwide health problem and is considered a neglected disease exerting a significant impact on the economy and social welfare of people in many countries [11,28]. The infection is endemic in the Middle East, central Asia, South America, and northern and eastern Africa [29–32].

In determining the spatial genetic structuring of *Echinococcus*, computation of gene flow index (also known as gene migration) among different endemic foci can provide valuable data concerning the epidemiological drift of the parasite, allele frequencies, and speciation events. Furthermore, exploring genetic traits of *E. granulosus* populations may have a direct impact in control programs of the disease, particularly in aspects related with the efficacy of anti-helminthic treatments and their relationship with drug susceptibility/resistance [3]. In order to overcome knowledge gaps on human CE in the Middle East, we conducted a meta-analysis study to ascertain the current situation of CE seroprevalence and risk factors associated with the disease. In addition, a microevolutionary study of *Echinococcus* populations has been carried out among the studied CE patients. In this systematic review and meta-analysis study, we provide some insights into seroprevalence of CE in different countries of Middle East from 1990 to 2015 where no coordinated mass screenings have been performed in the past.

2. Materials and methods

2.1. Search strategy

Three publicly available databases, PubMed, ScienceDirect, and Scopus, were searched for publications in English (full texts and abstracts) associated with human CE infection, from 1990 to 2015. The search terms, used alone or in combination, were “echinococcosis”, “cystic echinococcosis”, “human echinococcosis”, “hydatidosis”, “hydatid cyst”, "*Echinococcus granulosus*", "*E. granulosus*", “seroprevalence”, “seroepidemiology”, “prevalence”, “serology”, “genotyping”, “genotype” and each of the Middle East countries (Bahrain, Cyprus, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Oman, Palestine, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates and Yemen).

2.2. Study selection

The eligibility of articles was evaluated against the inclusion criteria by two independent reviewers who are expert in CE field. Cross-sectional studies that estimated the seroprevalence of human cystic echinococcosis by any given immunological assay (e.g. ELISA, Western blot, indirect hemagglutination, or latex agglutination) in Middle East countries were selected, and independently evaluated for eligibility. The excluded articles were repetitive manuscripts, veterinary studies, non-serological studies, and studies with insufficient data.

2.3. Data extraction

Relevant sociodemographic, diagnostic, and molecular data were gathered from the selected studies and tabulated in a spreadsheet. Variables considered included first author, year of publication, country, sample size, number of seropositive cases, number of male and female participants and their test results, age distribution, serological diagnostic methods, sequenced gene and genotype assigned.

The individuals enrolled in the study were divided into two groups: (i) the general population and (ii) CE suspected and at risk individuals. The group of CE suspected and at risk, individuals included patients with suspected hydatid cyst, residents in endemic rural areas, nomadic population, and veterinary surgeons.

To evaluate the population genetic structure, the registered sequence numbers of *Echinococcus* cytochrome *c* oxidase subunit 1 (*Cox*1) gene in the GenBank database were retrieved and compared to measure the pairwise fixation index (*Fst*; F statistics) as a degree of gene flow. *F*st index was estimated by DnaSP software version 5.10.

2.4. Statistical analyses

Point estimates and their 95% confidence intervals (CI) of seroprevalence rates of all the included studies were calculated. The group-specific seroprevalence was calculated according to population groups (general; and CE suspected and at risk individuals), age group

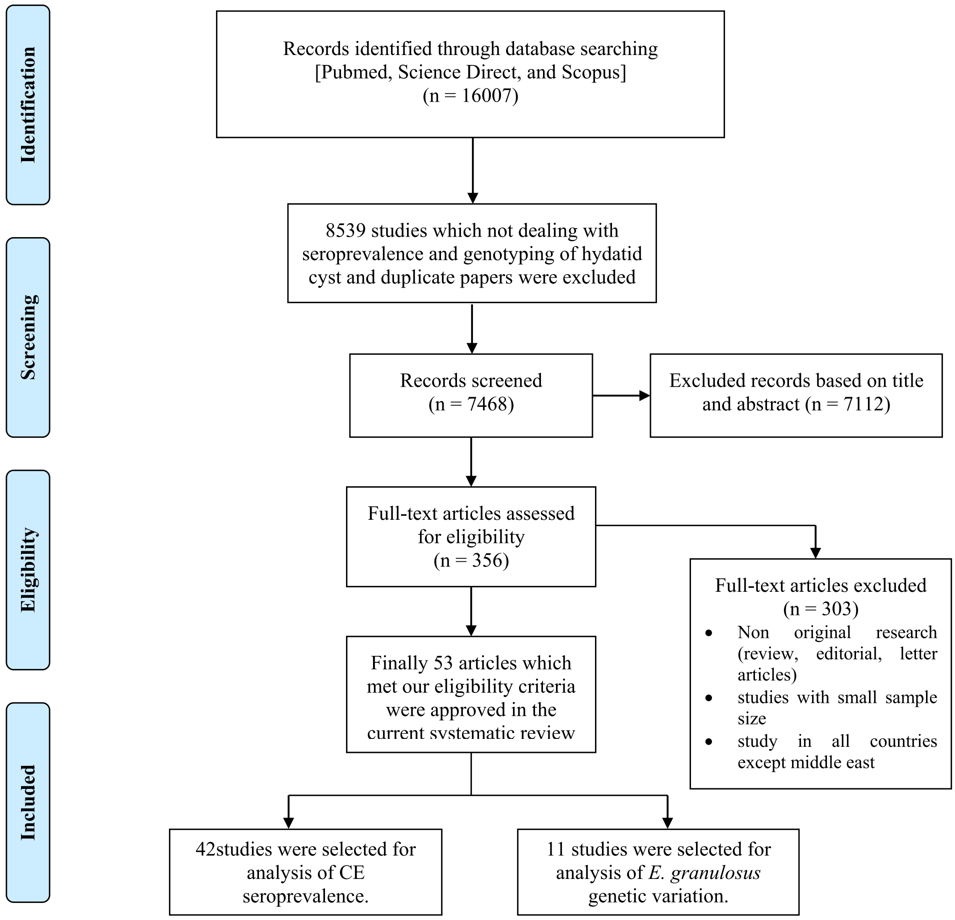

Fig. 2. Flowchart describing the study design process.

(≤19, 20–39, and ≥40 years), gender, and geographical region of origin. The forest plot diagrams were used to visualize the heterogeneity among the studies. The heterogeneity was expected in advance, and statistical methods (I^2 and Cochrane Q statistics, P value < 0.1) were used to quantify the observed variations. For meta-analysis purposes, we assumed that the included surveys were a random sample from a population of studies, and a random effect model was used. Forest plots presented overall seroprevalence and proportions of individual studies. The meta-analysis was performed with Stats Direct statistical software (www.statsdirect.com). To appraise the phylogenetic information provided by *cox1* sequences, a UPGMA tree was built by Splits Tree 4.0 based on genetic distances calculated according to nucleotide substitutions [33]. *Taenia mustelae* (GenBank accession No: AB732957) was considered as an out-group branch.

3. Results

3.1. Search results

Out of 16.007 studies from literature searches, 53 records were eligible for inclusion in this systematic review and meta-analysis. Fig. 2 shows the search approach followed in this review article. The different serological diagnostic tests used in the studies were based on enzyme-linked immunosorbent assay/ELISA (28 studies), followed by indirect haemagglutination/IHA (13 studies), indirect fluorescent antibody/IFA (four studies), Indirect-ELISA (one study), enzyme immunoassay/EIA (one study), Western Blot/WB (one study) and Casoni test (one study). The baseline characteristics of the selected studies in the literature review are shown in Table 1.

3.2. Serological data in the general population

In the group of the general population, 22 publications were included. In total, 17.775 individuals were evaluated, of which 1.073 subjects were IgG seropositive using different serological diagnostic tests. In the general population, there was a wide variation in the seroprevalence among different studies (Q = 1115.8; df = 21, $p < 0.0001$; $I^2 = 98.1\%$). The overall seroprevalence of CE among general population in the Middle East was 7.44% (95% CI = 4.82–10.58) using the random-effect model meta-analysis (Fig. 3).

3.3. Serological data in the CE suspected and at risk population

Data analysis revealed that 10.4% (1.881/18.008) participants from 20 studies including CE suspected and at risk population, were seropositive to *E. granulosus* antigens. The Q statistic was very large (Q = 962.7; df = 19, $P < 0.0001$; $I^2 = 98\%$). In addition, the overall seroprevalence in CE suspected and at risk was 10.7% (95% CI = 7.6–14.3). The forest plot diagrams of this review are shown in Fig. 4.

3.4. Hydatid cyst seroprevalence and risk factors

There were no statistically significant differences between male and female individuals (male 9.3% and female 9.2%). Considering age, IgG seropositive rate in the age groups of ≤19, 20–39, and ≥40 years were 2.7%, 8.3%, and 7.2%, respectively ($P < 0.001$). Fig. 5 shows that the 5-year seroprevalence of CE in the Middle East was the lowest and highest in the period of 1990–1995 and 1996–2000, respectively. The seroprevalence of CE was significantly higher among dog owners ($P = 0.03$); illiterate individuals ($P = 0.04$); farmers and shepherds

Table 1
Baseline characteristics of the included human studies.

No.	Country	Author/Year	No. of participants			Positive cases			Method	Age (yr.)	Ref
			Total	Male	Female	Total (%)	Male (%)	Female (%)			
General population											
1	Jordan	(Abo-Shehada et al., 1993)	1656	NA	NA	60 (3.6)	NA	NA	IHA	NA	[34]
2	Jordan	(Abo-Shehada et al., 1993)	1085	NA	NA	56 (5.2)	NA	NA	IHA	18–24	[34]
3	Jordan	(Abo-Shehada et al., 1993)	176	NA	NA	5 (2.8)	NA	NA	ELISA	5–24	[34]
4	Jordan	(Moosa et al., 1994)	104	NA	NA	6 (5.8)	NA	NA	ELISA	NA	[35]
5	Jordan	(Moosa et al., 1994)	2006	NA	NA	48 (2.4)	13 (NA)	35 (NA)	ELISA	NA	[35]
6	Iran	(Kooroush et al., 1998)	406	NA	NA	87 (21.4)	NA (24.2)	NA (19.7)	Casoni	> 10	[36]
7	Oman	(Idris et al., 1999)	306	NA	NA	1 (0.3)	NA	NA	IHA	NA	[37]
8	Turkey	(Karaman et al., 2004)	511	NA	NA	177 (34.6)	NA	NA	IHA/IFA	NA	[38]
9	Iran	(Akhlaghi et al., 2005)	1114	NA	NA	81 (7.3)	NA	NA	IFA	NA	[39]
10	Iraq	(Yacoub et al., 2006)	181	73	108	47 (26)	19 (26)	28 (26)	EIA	< 5 – > 45	[40]
11	Turkey	(Apan et al., 2006)	50	26	24	11 (22)	NA	NA	ELISA	20–70	[41]
12	Turkey	(Sönmez et al., 2008)	388	NA	NA	30 (7.7)	NA	NA	ELISA	NA	[42]
13	Iran	(Sarkari et al., 2010)	500	252	248	36 (7.2)	21 (8.3)	15 (6)	ELISA	≤19 - ≥50	[43]
14	Iran	(Mirzanejad-Asl et al., 2010)	1003	434	569	84 (9.2)	NA	NA	ELISA	5 - > 80	[17]
15	Iran	(Heidari et al., 2011)	670	194	476	13 (1.8)	5 (2.6)	8 (1.7)	ELISA	0–69	[44]
16	Iran	(Garedaghi, 2011)	1500	NA	NA	19 (1.3)	NA (0.8)	NA (1.8)	ELISA	NA	[45]
17	Iran	(Dadkhah et al., 2011)	250	NA	NA	8 (3.2)	NA	NA	IFA	NA	[46]
18	Iran	(Rakhshanpour et al., 2012)	1564	800	764	25 (1.6)	18 (2.2)	7 (0.9)	ELISA	< 30 – > 60	[47]
19	Iran	(Jahangir et al., 2013)	1200	500	700	27 (2.3)	15 (3)	12 (1.7)	ELISA	4–90	[48]
20	Iran	(Zibaei et al., 2013)	617	234	383	95 (15.4)	57 (24.4)	38 (9.9)	ELISA	3–97	[32]
21	Turkey	(Karadag et al., 2013)	454	NA	NA	114 (25.1)	NA	NA	ELISA	NA	[49]
22	Turkey	(Kilimcioğlu et al., 2013)	2034	NA	NA	43 (2.1)	NA	NA	ELISA	NA	[50]
CE suspected & At risk population											
1	Jordan	(Qaqish et al., 2003)	2388	880	1508	185 (7.7)	70 (8)	115 (7.6)	ELISA	> 5	[51]
2	Turkey	(Özkol et al., 2005)	483	NA	NA	43 (8.9)	NA	NA	ELISA	7–17	[52]
3	Turkey	(Cetinkaya et al., 2005)	611	278	333	89 (14.6)	30 (10.8)	59 (17.7)	IHA	10–85	[53]
4	Egypt	(Dyab et al., 2005)	100	NA	NA	5 (5)	NA	NA	IHA	NA	[54]
5	Turkey	(Delibaş et al., 2005)	465	NA	NA	78 (16.8)	NA	NA	ELISA	NA	[55]
6	Iran	(Arbabi, 2006)	500	NA	NA	12 (2.4)	NA (0.9)	NA (3.5)	IHA	< 20 – > 50	[56]
7	Turkey	(Yazar et al., 2006)	2242	NA	NA	61 (2.7)	NA	NA	ELISA/IFA	10–90	[26]
8	Turkey	(Eşgin et al., 2006)	85	NA	NA	46 (54.1)	NA	NA	IHA	NA	[57]
9	Iran	(Rafiei et al., 2007)	3448	1281	2167	475 (13.8)	176 (13.7)	299 (13.8)	ELISA	0 - > 50	[6]
10	Turkey	(Kilic et al., 2007)	93	NA	NA	2 (2.2)	NA	NA	ELISA	NA	[58]
11	Turkey	(Karadam et al., 2008)	946	392	554	5 (0.5)	NA	NA	ELISA/IHA	1–94	[59]
12	Iran	(Harandi et al., 2011)	1062	187	875	77 (7.3)	4 (2.1)	73 (8.3)	ELISA	< 19 – > 80	[5]
13	Turkey	(Ertabaklar et al., 2012)	209	NA	NA	24 (11.5)	NA	NA	ELISA	7–88	[60]
14	Turkey	(Aydin et al., 2012)	186	NA	NA	66 (35.5)	NA	NA	ELISA	NA	[61]
15	Turkey	(Yazici et al., 2012)	225	74	151	18 (8)	NA	NA	IHA	NA	[62]
16	Iran	(Fotoohi et al., 2013)	100	NA	NA	3 (3)	NA	NA	ELISA	NA	[63]
17	Turkey	(Yilmaz et al., 2013)	558	255	303	143 (25.6)	65 (25.5)	78 (25.7)	ELISA/IHA	NA	[64]
18	Turkey	(Akalin et al., 2014)	1133	530	603	78 (6.9)	29 (5.5)	49 (8.1)	ELISA	18–90	[65]
19	Turkey	(Gureser et al., 2015)	253	105	148	32 (12.6)	9 (8.6)	23 (15.5)	IHA	NA	[66]
20	Turkey	(Beyhan et al., 2015)	2921	NA	NA	439 (15)	NA (13)	NA (16.4)	ELISA/IHA/WB	NA	[67]

($P < 0.001$); residents of rural areas ($P < 0.001$) and nomadic population ($P < 0.001$) (Table 2). The overall prevalence of CE antibodies in the Middle East countries for each 5-year period (during 1991–2015) is presented in Fig. 6. The highest and the lowest seroprevalence of CE was obtained in the general population group in Iraq (26%) and Oman (0.3%), respectively. In addition, the highest seroprevalence in CE suspected and at risk, individuals were observed in Iran (11.1%).

The seroprevalence of CE in low risk individuals (general population) was 8.2% (95% CI = 7.5–9.0) and significantly lower than that observed in the at risk population with 12% (95% CI = 10.9–13.2) ($P < 0.001$). The highest and the lowest seroprevalence rates in the general population of Middle East were observed in Turkey (34.6%) and Oman (0.3%), respectively. The highest seroprevalence in CE suspected and at risk population was recorded in Turkey (54.1%). Meanwhile, in the Iranian and Jordanian general populations, the seroprevalence of CE was found to be 5.4% and 3.5%, respectively, lower than CE suspected and at risk population in these countries, 11.1%, and 7.7%, respectively.

3.5. Molecular data

As a result of the lack of deposited sequences of *Echinococcus granulosus* sensu lato isolates in the GenBank database from countries including Jordan, Iraq, Palestine, Egypt, and Oman, only Iranian and Turkish sequences were retrieved and subsequently used in molecular analyses. A *F*st value as a degree of gene flow was the high value between Iranian and Turkish populations (0.171), while the number of migrants (Nm) was 1.18. The taxonomic status of understudied genotypes including *E. granulosus* sensu stricto complex (G1-G3) and *E. canadensis* (G6) are shown at constructed phylogeny tree (Fig. 7).

The retrieved sequences used to determine gene flow between Iranian and Turkish isolates were: Accession nose: JN048504-JN048513: AB677815-AB677822: KP859559-KP859571 for Iranian isolates and accession no: EF689726: EF693891, EF693892: EU006774-EU006784 for Turkish isolates.

4. Discussion

This is the first systematic review and meta-analysis of the seroprevalence of human CE and genetic structure of *E. granulosus* in the Middle East. CE is an emerging neglected disease and one of the major public health problems in the Middle East, which results in substantial economic resource loss [23,68]. Our results present a comprehensive view of the seroprevalence of CE in the Middle East and illustrate how

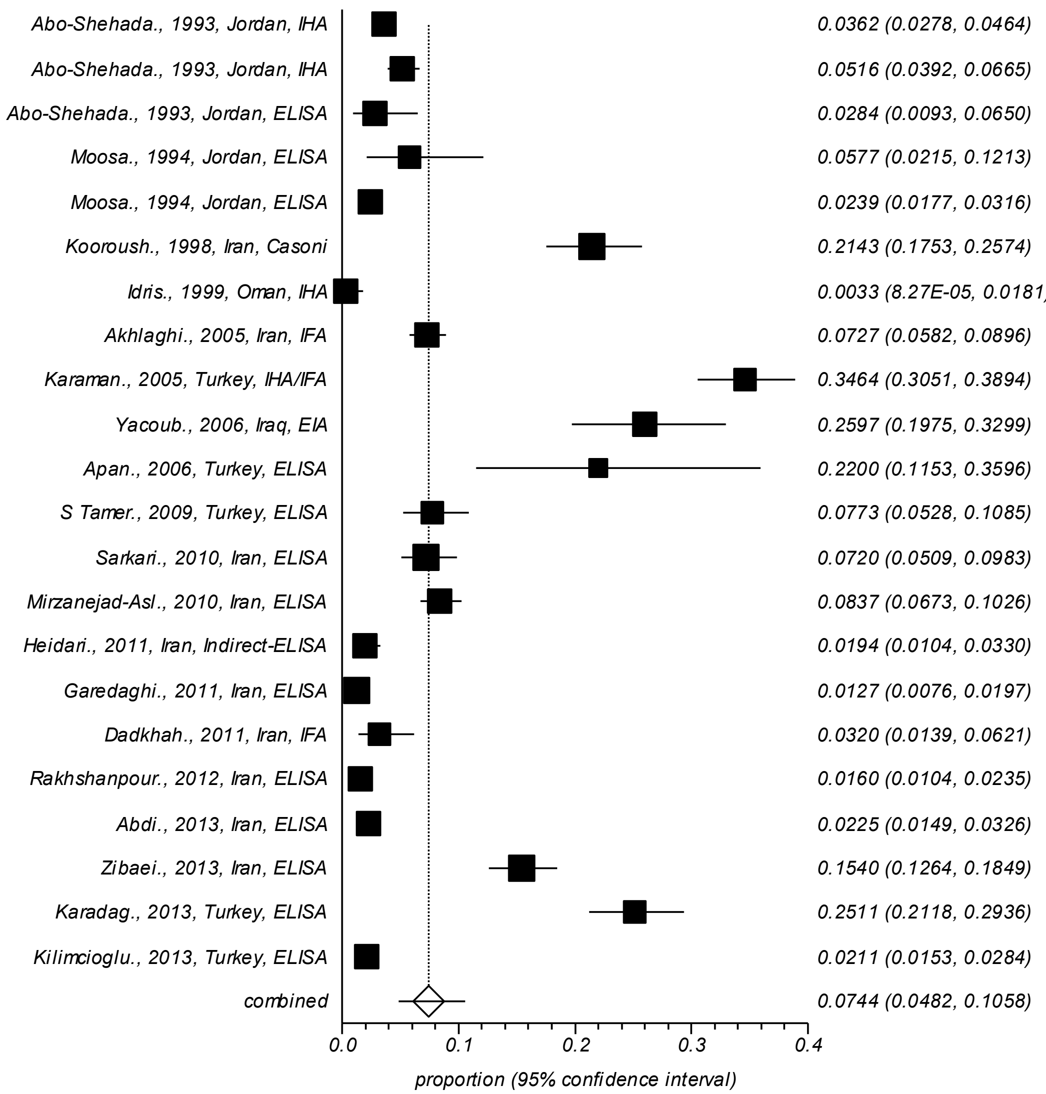

Fig. 3. Forest plot of random effect meta-analysis displaying the pooled IgG seroprevalence rates of Cystic Echinococcosis in general population of the Middle East from 22 studies (first author, year and country and diagnostic method). The black square (■) represents the prevalence of each study and solid lines (—) are 95% confidence interval. The combined estimate from the random-effects meta-analysis is labeled (◊). Diagnostic methods: IHA (indirect haemagglutination), ELISA (enzyme-linked immunosorbent assay), IFA (immunofluorescence assay), EIA (enzyme immunoassay). Further details of each included study are given in Table 1.

the *Echinococcus* isolates have epidemiologically drifted among the Middle East countries.

The result of our investigation showed that the seroprevalence of CE in the Middle East, during three decades, is 7.4% (95% CI = 4.8–10.6) and 10.7% (95% CI = 7.6–14.3) in the general population and in CE suspected and at risk group, respectively. This systematic review included general population as well as CE suspected and at risk group, in aim to better understand an epidemiological scenario of the disease in the region. Several studies have been conducted to assess the seroprevalence of CE in general population in different parts of world. Reported prevalence rates were between 0% and 25.8% [69–72]. ELISA was used in most of the studies because this method is acceptable, easy, efficient, and affordable and has a high level of sensitivity and specificity. Applying of different kinds of serological methods could be the reason for controversy of reported results. ELISA test by means of local antigens could help in getting rid of the controversy results obtained from different groups.

The global distribution of the disease has been related to various risk factors including contact with dog, geographical climate, the abundance of dogs, nutrition behavior (consumption of water, food and raw vegetables contaminated with parasite eggs), residence area (urban, rural or nomad), education level, occupation, etc [4,5,65,73].

As mentioned above, analysis of the data indicated a statistically significant difference in CE prevalence between high-risk groups (such as farmers and shepherds) and low-risk groups (general population). This discrepancy may be justified by the presence of dogs in the household of most farmers and consequently their close exposure to *Echinococcus* eggs [32].

Additionally, there is a risk of infection from direct contacts with dogs and dogs' feces, and indirectly through food or water contaminated with *Echinococcus* eggs [43]. As expected, the prevalence rate in dog owners was 12.2%, while in people who do not have dogs was 10.1% ($P = 0.03$). Our findings showed that the seroprevalence of infection is similar in both genders and there was no statistically significant difference between sexes, what is in accordance with results of authors from Iran [24].

Regarding residency, a significant difference was observed among urban, rural, and nomadic populations, with seroprevalence rates 4.3%, 6.5%, and 13.8%, respectively ($P < 0.001$). This finding indicates that the nomadic people are at higher risk for CE infection than urban and rural populations. This higher seroprevalence rate could be associated with the free movement of dogs between the nomadic community, as

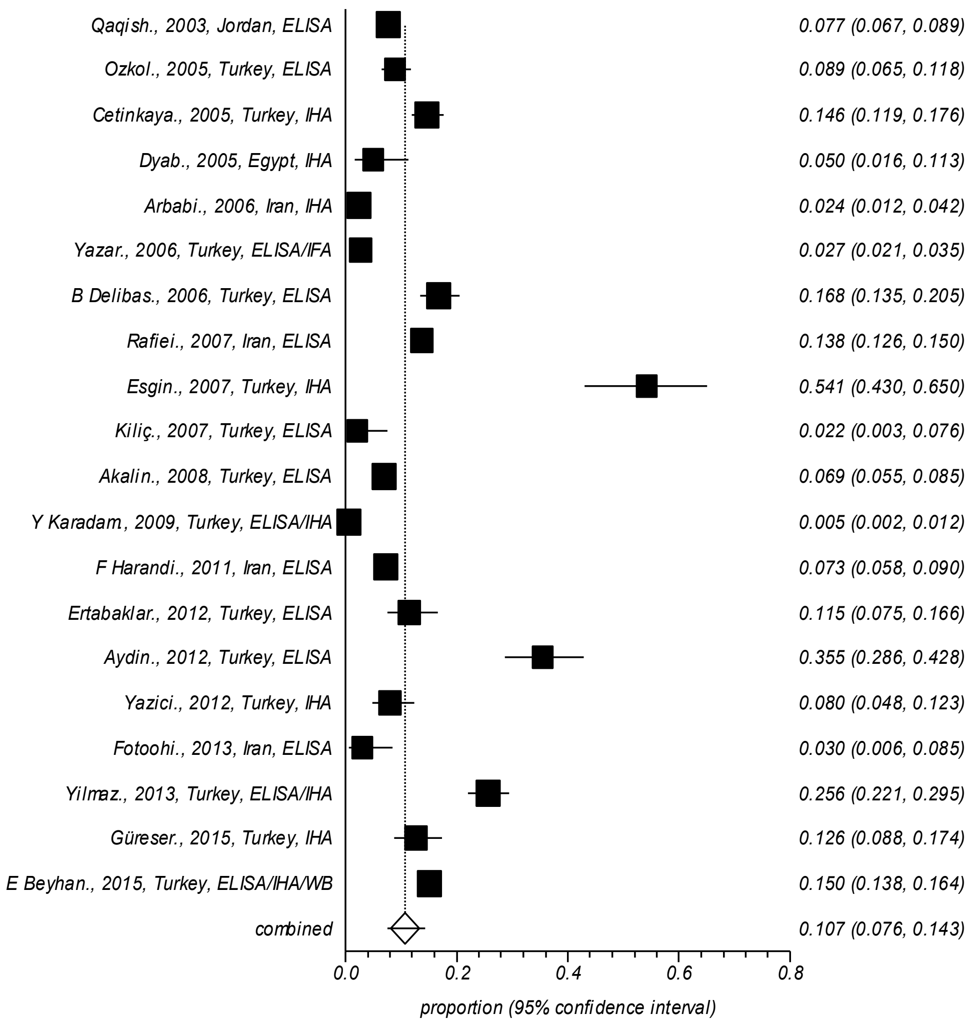

Fig. 4. Forest plot of random effect meta-analysis displaying the pooled IgG seroprevalence rates of Cystic Echinococcosis among CE suspected & At risk population of the Middle East from 20 studies (first author, year and country and diagnostic method). The black square (■) represents the prevalence of each study and solid lines (—) are 95% confidence interval. The combined estimate from the random-effects meta-analysis is labeled (◊). Diagnostic methods: IHA (indirect haemagglutination), ELISA (enzyme-linked immunosorbent assay), IFA (immunofluorescence assay), WB (western blot). Further details of each included study are given in Table 1.

well as the lifestyle and the cultural traits of the nomads, who live in close contact with their dogs from their early childhood [6]. Our Meta-review also indicates a significant association between CE seropositivity and age group ($P < 0.001$). CE is a chronic disease and hydatid cyst develops very slowly in human. It takes years for hydatid cyst to bring on the clinical disease in humans. This fact might explain the high rate of CE infection in the older ages in the present study [43].

In this review, the *E. granulosus* (G1-G3) complex was identified as the most dominant *Echinococcus* species circulating in Middle East metapopulations. This shows that synanthropic cycles of *Echinococcus* are unequivocally circulating between canids and herbivores hosts in the Middle East countries. Furthermore, the camel strain (G6) was

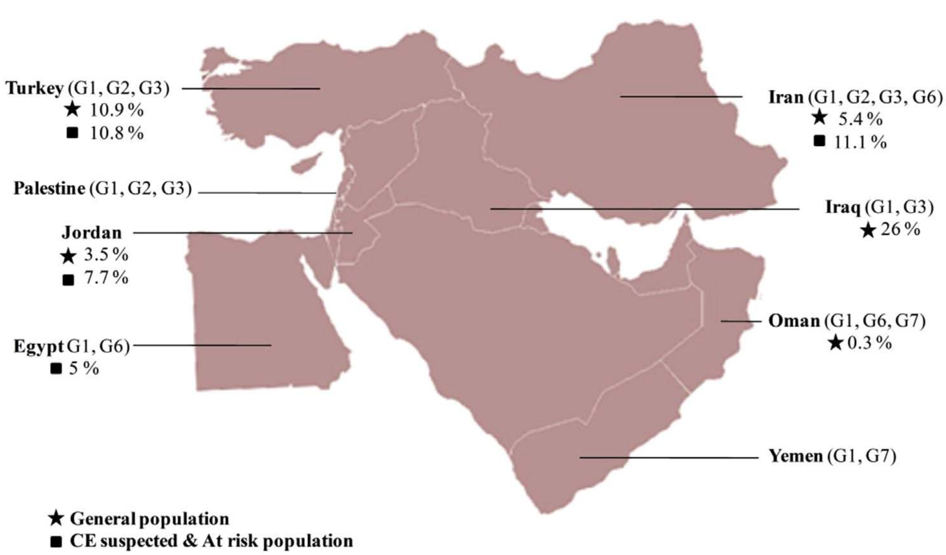

Fig. 5. Seroprevalence of CE in the Middle East according to IgG antibody seropositivity and isolated genotypes (The source of image: https://commons.wikimedia.org/wiki/Atlas_of_the_world).

Table 2
Risk factors associated to CE seropositivity in human population of the Middle East.

Demographic factors	Total individuals	Positive cases	Overall prevalence (%)	P-value	References
Sexes				P = 0.87	Qaqish et al. (2003), Cetinkaya et al. (2005), Yacoub et al. (2006), Rafiei et al. (2007), Akalin et al. (2008), Sarkari et al. (2010), Heidari et al. (2011), F. Harandi et al. (2011), Rakhshanpour et al. (2012), Yilmaz et al. (2013), Zibaei et al. (2013), Abdi et al. (2013).
Male	5464	509	9.3 (95% CI = 8.6–10.1)		
Female	8468	781	9.2 (95% CI = 8.6–9.9)		
Age group (years)				P < 0.001	Arbabi et al. (2006), Akalin et al. (2008), Sarkari et al. (2010), Mirzanejad-Asl et al. (2010), Heidari et al. (2011), F. Harandi et al. (2011), Zibaei et al. (2013).
19	514	14	2.7 (95% CI = 1.6–4.5)≥		
20–39	2094	173	8.3 (95% CI = 7.2–9.5)		
≥40	2872	207	7.2 (95% CI = 6.3–8.2)		
Dog ownership				P = 0.03	Cetinkaya et al. (2005), Rafiei et al. (2007), Akalin et al. (2008), F. Harandi et al. (2011).
Yes	4168	508	12.2 (95% CI = 11.2–13.2)		
No	2084	211	10.1 (95% CI = 8.9–11.5)		
Residence				P < 0.001	Qaqish et al. (2003), Cetinkaya et al. (2005), Ozkol et al. (2005), Arbabi et al. (2006), Yazar et al. (2006), Rafiei et al. (2007), Akalin et al. (2008), Mirzanejad-Asl et al. (2010), F. Harandi et al. (2011), Garedaghi et al. (2011), Ertabaklar et al. (2012), Rakhshanpour et al. (2012), Zibaei et al. (2013).
Urban	3006	130	4.3 (95% CI = 3.7–5.1)		
Rural	11420	740	6.5 (95% CI = 6.0–6.9)		
Nomad	3448	475	13.8 (95% CI = 12.7–15.0)		
Educational				P = 0.04	Cetinkaya et al. (2005), Akalin et al. (2008), Zibaei et al. (2013).
Illiterate	357	54	15.1 (95% CI = 11.8–19.2)		
Primary school	1399	138	9.9 (95% CI = 8.4–11.5)		
Secondary school & college	605	70	11.6 (95% CI = 9.3–14.4)		
Occupational group				P < 0.001	Cetinkaya et al. (2005), Rafiei et al. (2007), F. Harandi et al. (2011), Rakhshanpour et al. (2012), Zibaei et al. (2013).
At risk[a]	3359	404	12.0 (95% CI = 10.9–13.2)		
Low risk[b]	5074	416	8.2 (95% CI = 7.5–9.0)		
Knowledge of the disease				P = 0.06	F. Harandi et al. (2011), Rakhshanpour et al. (2012).
Knowledge	251	4	1.6 (95% CI = 0.06–4.0)		
Lack of knowledge	2375	98	4.1 (95% CI = 3.4–5.0)		

[a] Farmers and Shepherds.
[b] Students, Housewives, Children under 6 years, Retired, jobless, Employees, etc other than farmers and shepherds.

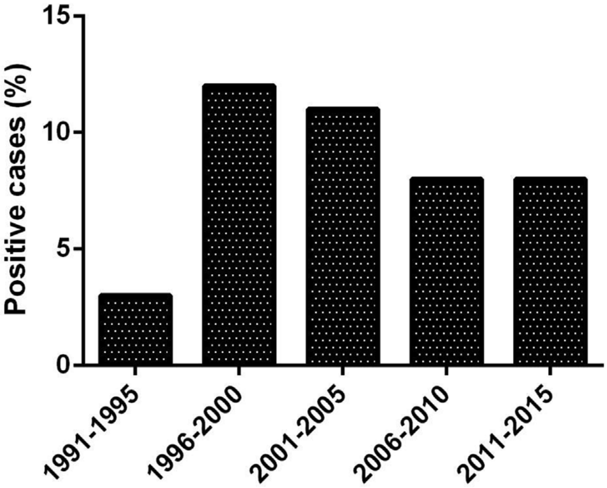

Fig. 6. Overall prevalence of CE antibodies in the Middle East during 1991–2015 (for each 5-year period).

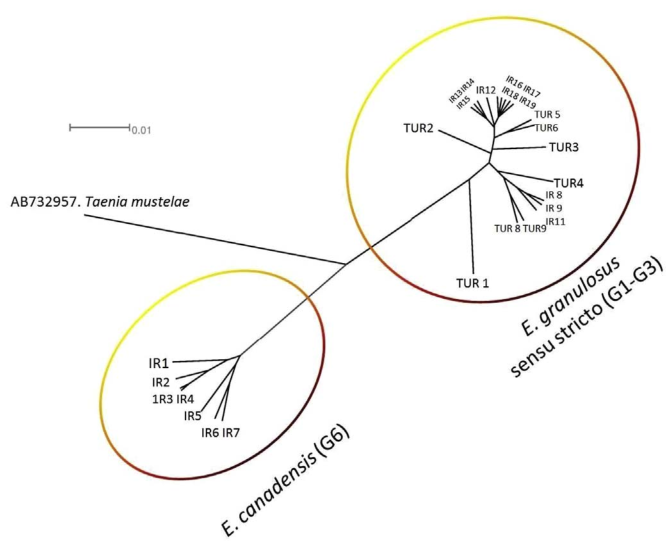

Fig. 7. The phylogeny of *E. granulosus* sensuo latu sub-populations according to UPGMA model inferred by genetic distances calculated according to nucleotide substitutions. *Taenia mustelae* was considered as an out group branch (Accession No: AB732957).

reported in the studies from Iran, Oman, and Egypt. One of the recent interesting records was that of the first occurrence of G7 genotype (pig strain) of two human isolates in Egypt [74], while so far, no report of G7 has been reported in the Middle East region.

Understanding the genetic diversity and population structure of *Echinococcus* can assist infection control programs and prevent parasite transmission. So far, several researchers have been locally focused their molecular experiments on inter-intra divergence levels of *E. granulosus* complex in different regions of the Middle East [2,3,7,15]. Nevertheless, no comparative epidemiological study on genetic population genetic structure of *E. granulosus* complex was carried out aimed to investigate how the *Echinococcus* isolates are epidemiologically drifted among Middle East countries. The *F*st statistically value indicates that *Echinococcus* s.s. (G1-G3) complex are genetically moderate differentiated among Iranian and Turkish isolates. Findings of common haplotypes explain that there is probably the dawn of domestication due to the epidemiological drift of alleles from one population to another through the diffusion of stock raising or anthropogenic mobility. The presence of common sequences among Iranian and Turkish populations proposed that the mitochondrial DNA (*Cox*1) haplotypes have an extensive distribution between two distinct countries.

In this systematic review, the *Cox*1 gene was indicated as appropriate evolutionary marker for calculation of the population genetic structure of *E. granulosus* complex (G1-G3) among Iranian and Turkish isolates since this marker frequently evolve more rapidly than nuclear marker do. Haploids and absence of recombination events are also important features of this marker [3,7].

There are several strategies that aid in the prevention and control of CE: (i) public educational programs aimed to inform the individuals about the disease; (ii) preventing feeding of the dogs with the carcasses of infected sheeps; (iii) control of stray dog populations, (iv) avoiding the consumption of any food or water that may be contaminated by fecal matter from dogs, (v) washing hands with soap before and after handling dogs, and (vi) teaching children about the importance of washing hands in aim to prevent infection.

The main limitation of this systematic review is that the epidemiology of the disease remains unknown in the most countries of the Middle East, although comprehensive review was conducted. Additionally, the different diagnostic methods with different sensitivities and specificities were used in reviewed studies. The majority of studies were focused on the seroprevalence instead on surgical reports. Seroprevalence report about previous contact with the parasite, but not necessarily infection. On the other side, a few studies such as those from Yemen, and Palestine authors, are performed using surgical methods only [74,75].

These limitations affect on the results in this review and might have biased the overall seroprevalence rate estimation of CE in the Middle East. Thus, extensive studies are required to investigate the epidemiology of the disease in all countries of Middle East, particularly in unstudied parts, to organize a persistent and purposeful control program.

In conclusion, this is the first systematic review and meta-analysis of CE seroepidemiology and genetic structure of *E. granulosus* in the Middle East. The considerable seroprevalence of CE among studied populations show that the surveillance and suitable preventive strategies should be broadly addressed for EC. Additionally, we made step into the genetic investigation and our results reflect the novel achievements about microevolutionary events of *Echinococcus* isolates among the Middle East countries.

Conflicts of interest

There is no conflict of interest.

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Author contribution

Tahereh Mikaeili Galeh, Roghayeh Ghoyounchi1, Reza Berahmat searched the databases for potentially eligible articles. All authors contributed in study design, and analysis, and writing the manuscript.

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