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Filarial worms: a systematic review and meta-analysis of diversity in animals from Iran with emphasis on human cases

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Review

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Abstract

Current systematic review and meta-analysis demonstrate the prevalence reports of filariasis in animals in Iran along with human cases. Studies were screened, relevant papers were selected and the random-effect model was used by forest plot with 95% confidence interval (CI). Of 17 records of human case-reports, particularly from Khuzestan province (5 cases), *Dirofilaria repens* was the most detected parasite (10 cases) with higher involvement of the right eye (7 cases) than other organs. Eleven animal species were reported to be parasitised by filarioids in Iran. The prevalence of *Dirofilaria immitis* in canids was 14.69% (95% CI: 10.33–19.67), with highest rates (20.92%; 95% CI: 13.84–29.03) in free-ranging dogs. Male (10.07%; 95% CI: 5.10–16.47) and more than 1-year old (20.77%; 95% CI: 8.66–36.42) dogs were more likely to be found infected. The frequency of other filarioids of zoonotic interest was: *Acanthocheilonema reconditum* in dogs 2.15% (95% CI: 0.71–4.33), *Dipetalonema evansi* in camels 10.16% (95% CI: 4.73–17.34), *Onchocerca cervicalis* in horses 3.63% (95% CI: 1.44–6.75%) and *Onchocerca fasciata* 16.57% (95% CI: 10.12–24.24%) in camels. Still, our knowledge on parasitic filariae in Iran is limited and more investigation is needed in both human and animal populations.

Introduction

Filarial nematodes (Spirurida, Onchocercidae) are parasitic helminths, which produce motile microfilariae (mfs), as first-stage larva (L1) in their vertebrate definitive hosts, which subsequently develop into the third-stage larvae (L3) in blood-feeding arthropods as their intermediate hosts and biological vectors (Orihel and Eberhard, 1998; Otranto and Deplazes, 2019). Adult filarial worms dwell in host's blood vessels, body cavities, lymphatic ducts and/or connective tissues (Chatterjee and Nutman, 2015). Parasitic filarioids have been isolated from most vertebrate species, except fish, but only those species found in mammals have shown to represent a zoonotic threat to human populations (Anderson, 2000). Nonetheless, humans are mainly affected by *Wuchereria bancrofti* and, to a lesser extent, *Brugia malayi* and *Brugia timori* causing the lymphatic filariasis in about 68 million people in 73 countries worldwide, as well as onchocerciasis due to *Onchocerca volvulus*, the causative agent of river blindness, which affects 40 million people mostly in Africa (Taylor *et al*., 2010; WHO, 2015; Tekle *et al*., 2016). The global health burden for both human filarial infections is approximately 3.3 million disability-adjusted life-years (DALYs) (Kwarteng *et al*., 2016). While the species above are typically anthroponotic and mainly spread in developing countries, filarioids of the genus *Dirofilaria*, particularly *Dirofilaria immitis* (*D. immitis*) and *D. repens*, cause human cases worldwide such as in the USA (Orihel and Eberhard, 1998; Theis, 2005) and Europe (Simón *et al*., 2012), highlighting their role as an emerging zoonosis for humans (Simón *et al*., 2012).

In recent years, the number of human cases associated with various filarial nematodes, particularly *Onchocerca* and *Dirofilaria* spp. have been increased in Iran (Jamshidi *et al*., 2008; Tavakolizadeh and Mobedi, 2009; Ashrafi *et al*., 2010; Mowlavi *et al*., 2014; Maraghi *et al*., 2016; Mirahmadi *et al*., 2017; Tabatabaei *et al*., 2017), due to environment changes and changing agricultural practices, leading to dwelling in the vicinity of arthropod vectors and increased contact between pet and wildlife animal species (Otranto *et al*., 2013; Otranto and Deplazes, 2019). This implicates the need for more focused studies regarding the prevalence, diversity and

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bioecological behaviour of such vector-borne diseases, particularly among different animal species (e.g. canids and herbivores) in the country.

Altogether, our better understanding of parasitic filarioids would be beneficial to alert the public and to avert cases of zoonotic human filariasis. In addition, several original prevalence studies on animal filariasis (Oryan *et al.*, 2008; Alborzi *et al.*, 2010; Akhtardanesh *et al.*, 2011; Sazmand *et al.*, 2013; Khodabakhsh *et al.*, 2016; Sazmand *et al.*, 2016; Zarei *et al.*, 2016; Solgi *et al.*, 2018; Anvari *et al.*, 2019) along with various human case-reports in Iran (Negahban *et al.*, 2007; Mowlavi *et al.*, 2014; Maraghi *et al.*, 2015; Mirahmadi *et al.*, 2017; Nabie *et al.*, 2017) highlights the importance of a review of the literature to better elucidate the filariae fauna in the country. Therefore, the current systematic review with meta-analysis was designed to assess the human filariasis case reports as well as prevalence and diversity of animal filarial nematodes in Iran.

Methods

This systematic review was accomplished on the basis of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Moher *et al.*, 2009).

Information sources and search

The systematic searching procedure was performed without time limitation until 1 December 2019. All articles on the prevalence of filarial nematodes in animals in Iran were retrieved *via* major English (Pubmed, Scopus, Web of Science and Google Scholar) and Persian databases (Scientific information database (SID), Magiran, Iran Medex, Iran Doc) using medical subject heading (MeSH) terms comprising: ('Prevalence', OR 'epidemiology'), AND ('*Dirofilaria*', '*Onchocerca*', '*Acanthocheilonema*', '*Dipetalonema*', '*Cercopithifilaria*' '*Litomosoides*', '*Stephanofilaria*', '*Suifilaria*', '*Parafilaria*', '*Brugia*', '*Mansonella*', '*Setaria*', '*Elaephora*', '(*Eulimdana*) *Pelecitus*', '*Chandlerella*', '*Cardiofilaria*') AND ('Iran'). Also, keywords required for searching infection in human individuals was: 'Filariasis', 'Filarial', 'Infection', 'Human cases', 'Case-report', 'Iran'. All searches were conducted in both English and Persian languages.

Eligibility criteria, study selection and data collection

Animal prevalence studies based on blood microscopy, necropsy, serology, Knott's test and/or histopathologic methods were eligible to undergo meta-analysis, whereas human case-reports regarding filarial infections were only included in the systematic review section. Those papers without full-text accessibility were excluded and any contradiction in the study selection process was resolved by discussion and consensus. The whole searching and extraction procedures were done by an expert researcher, and then double-checked by other colleagues.

Statistical analysis

Point estimates and their 95% confidence intervals of pooled prevalence of all included studies were calculated. Forest plots were used to visualize the heterogeneity among the included studies. The heterogeneity index among the included studies was determined using I^2 and Cochrane Q tests to show the variation in study outcomes between individual studies (Higgins *et al.*, 2003). The subgroup analysis was conducted according to year, host, location, gender, age and diagnostic method. Egger test was used to check for the presence of publication bias. This bias distorts the results and, when present, published studies are no longer a representative sample of the available evidence (Egger *et al.*, 1997). *P* value less than 0.05 was considered statistically significant. All analytical functions were applied by Stata/S.E. software version 12.0 (StataCorp, College Station, TX 77845, USA).

Results

We analysed 3012 papers from database searching, while 2561 were irrelevant (based on their title/abstract, were review papers and/or study on a non-Iranian immigrant), 450 were excluded for duplication, and one article was omitted due to lack of proper diagnosis. Finally, 17 entries relevant to case reports of human filariasis in Iran met our inclusion criteria (Fig. 1). According to Table 1, the cases were reported from 9 provinces of Iran, mostly caused by *D. repens*. The routine diagnosis was based on microscopic identification of the worm and/or examination of histopathologic sections; only three studies used polymerase chain reaction (PCR) and sequencing methods for molecular evaluation. The right eye was the most parasitised organ (7 cases), followed by left eye (2 cases), as well as single cases in the lower eyelid, cheek, forehead, spermatic cord, breast, chest, forearm and thigh. Cases were reported more frequently in men than women (64.7% *vs* 35.29%), and among adults than children (82.35% *vs* 17.64).

Information related to *Filarioidea* spp identified in various animal hosts (camel, cattle, small ruminants, dog, wild canids (jackals and red fox), horse, donkey, rodent, cat and pigeon) in Iran was illustrated as Supplementary Table 1. The systematic searching for original prevalence studies in animal hosts yielded 52 eligible papers based on our inclusion/exclusion criteria (Fig. 1). According to random-effects model meta-analysis, the pooled prevalence of *D. immitis* in canids of Iran was 14.69% (95% CI: 10.33–19.67) (Table 2; Supplementary Table 2; Fig. 2). Subgroup analysis was performed with summarized details in Table 3. Year-based analysis demonstrated a higher prevalence trend of *D. immitis* in published literature beyond 2011 [16.25% (95% CI: 10.23–23.35)] than those before 2011 [11.58% (95% CI: 7.37–16.60)] ($P < 0.001$). The higher prevalence was detected in free-ranging dogs (20.92%; 95% CI: 13.84–29.03), followed by wild canids (jackals and red fox) (10.72%; 95% CI: 6.59–15.70) and owned dogs (6.61%; 95% CI: 3.46–10.68) ($P < 0.001$). Geographical distribution showed the highest and lowest prevalence rates in western [25.29% (95% CI: 14.44–37.99)] and southern [6.10% (95% CI: 3.40–9.51)] parts of Iran, respectively ($P < 0.001$). Based on gender of dogs in Iran, *D. immitis* was more prevalent in males (10.07%; 95% CI: 5.10–16.47) than females (9.23%; 95% CI: 3.68–16.97) ($P = 0.131$). The heartworm was more prevalent in animals equal or more than 1-year old (20.77%; 95% CI: 8.66–36.42) than those younger (8.40%; 95% CI: 0.01– 32.00) ($P = 0.006$). According to the diagnostic method, the pooled prevalence of *D. immitis* in canids of Iran was as follows: microscopic 13.86% (95% CI: 9.46– 18.94), PCR 16.09% (95% CI: 3.51–35.38) and serology 16.95% (95% CI: 4.98–34.08) ($P = 0.01$).

Results revealed a strong significant heterogeneity ($Q = 661.2$, df = 35, $I^2 = 94.7\%$, $P < 0.001$) among the selected studies. Subgroup analysis revealed that there were statistically significant differences between the overall prevalence of *D. immitis* in canids of Iran and year ($X^2 = 177.1$, $P < 0.001$), host ($X^2 = 123.9$, $P < 0.001$), location ($X^2 = 123.1$, $P < 0.001$), age ($X^2 = 10.8$, $P = 0.006$) and diagnostic method ($X^2 = 110.0$, $P = 0.010$). Publication bias was checked by Egger's regression test, showed that it may not have a substantial impact on total prevalence estimate (Egger; bias: 3.0, $P = 0.266$) (Fig. 3).

Based on the random-effects model meta-analysis, the pooled prevalence, publication bias and heterogeneity of other filarioids in Iran are depicted in Table 2. Furthermore, Table 4

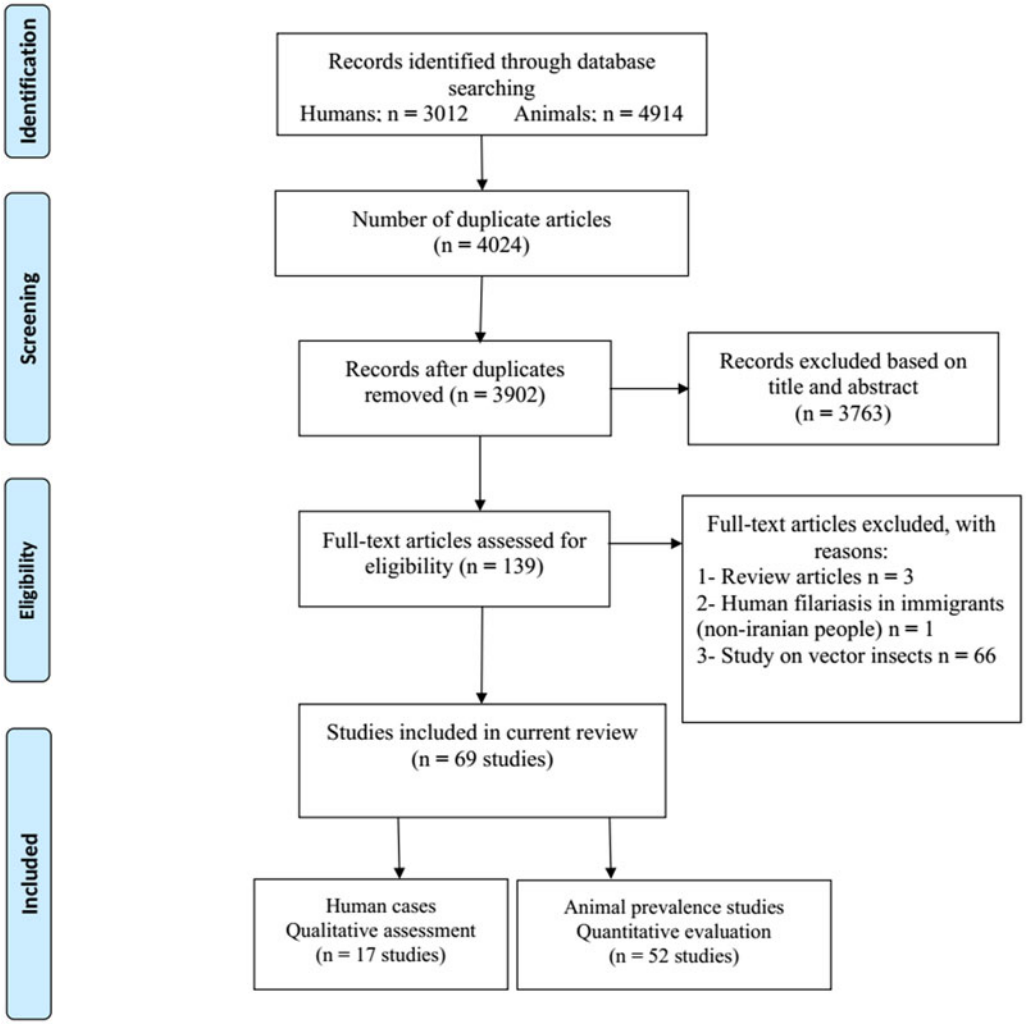

Fig. 1. PRISMA flow diagram describing included/excluded studies up to 1 December 2019 (Moher *et al.*, 2009)

demonstrates the subgroup analysis of *Dipetalonema evansi* (*D. evansi*) and *Onchocerca fasciata* (*O. fasciata*) in camels of Iran (Supplementary Figs 1–7).

Discussion

Nowadays, the complex interaction between humans and animals has subjected to revolutionary changes in several aspects including human behaviour, demographics, land use and environment changes (Otranto and Deplazes, 2019). This also leads to an unprecedented encounter between humans and infectious agents and the problem of the emergence of infectious zoonotic diseases. Regarding filariasis, this occurs in those areas of the world where insect vectors inhabit, particularly in developing countries, inflicting significant threat to human and animal health (Thompson *et al.*, 2010). With respect to the importance of this issue and increased number of human cases in recent years, we sought to extend our knowledge on poorly-known filarial infections in the human and examined animals in a vast Middle Eastern country, Iran.

Regarding human cases, most reports were from Khuzestan province, southwestern Iran. This territory is located in the vicinity of the Persian Gulf and possesses favourable milieu such as abundant dams and lagoons as well as tropical temperatures throughout the year, required for the colonization of blood-sucking arthropod vectors (Hamidinia *et al.*, 2016). The eyes or the conjunctiva are a frequent site of choice for filarioids (Otranto and Eberhard, 2011), as we also found most Iranian cases in right and left eyes, respectively. Dirofilariasis due to *Dirofilaria* spp. were the most abundant filarial infection in humans in Iran. Despite remarkable seroprevalence of antibodies to *Dirofilaria* in human societies of endemic areas (Simon *et al.*, 1991; Espinoza *et al.*, 1993; Vieira *et al.*, 1998; Tasić-Otašević *et al.*, 2014), human dirofilariasis is underdiagnosed, though the substantial increase in cases has been recorded worldwide mainly as subcutaneous/ocular form (Simón *et al.*, 2012). In the current review, it was realized that *D. repens* was the most isolated species, commonly from subcutaneous tissue and right eye. Iranian cases with *D. immitis* had an eye infection as well as an interesting case removed from the spermatic cord in relation to testicular hydrocele (Salahi-Moghadam and Banihashemi, 2016). There was only a single case of intraocular involvement (anterior chamber/vitreous body) among Iranian dirofilariasis cases (Mirahmadi *et al.*, 2017), similar to some cases from other countries including Turkey and Brazil (Gungel *et al.*, 2009; Otranto *et al.*, 2011*a*). Cases of human pulmonary dirofilariasis, which has been predominantly reported from Japan and USA (Simón *et al.*, 2012), were not detected in Iran, which could be due to lack of available serological assessment, though clinicians should be alerted to it (Khedri *et al.*, 2014). In an international scale, human infections by *D. repens* are prevalent in Eurasia region, with the highest incidences of subcutaneous/ocular dirofilariasis occurring in Europe particularly in Russia and Italy (Simón *et al.*, 2012). In Asia, Sri Lanka and India are predominant regarding subcutaneous/ocular dirofilariasis (Simón *et al.*, 2017). Subcutaneous nodules due to *D.*

Table 1. Characteristics of human filariasis case report studies in Iran up to 1 December 2019

Reference	Sex/ age/ city or province/ year of report/ ref	Symptoms/signs	Genus and species of parasite	diagnostic methods	Outcome
Subcutaneous Dirofilariasis					
Ashrafi *et al.* (2010)	F/ 39 y/Rasht, Guilan/ 2010/	1. Itching 2. Highly erythematous subcutaneous 3. Tender nodule on her right thigh.	*Dirofilaria repens*	1. A dermatologist as a suspected case of cutaneous fascioliasis 2. Microscopic examination of the excised nodule revealed the presence of *D. repens*.	Cure
Subcutaneous Dirofilariasis					
Negahban *et al.* (2007)	M/ 40 y/ Shiraz, Fars/ 2007	1. Firm mass, $2.5 \times 2.5\ cm^2$, at the lateral aspect of his right forearm. 2. History of mosquito bite and swelling of forearm 3. Antibiotic therapy resolved swelling but firm, painless mass was remained at dorsolateral.	*Dirofilaria repens*	1. Fine needle aspiration (FNA); was performed on 2 occasions using a 22-gauge needle. Three ethanol-fixed and 1 air-dried smear were stained by Papanicolaou and Wright stain, respectively. Many well-preserved microfilariae on the first attempt and eggs with microfilariae on the second occasion were detected in the FNA smears. 2. Surgical excision; the presence of adult worms in tissue sections confirmed the diagnosis. 3. MRI: Oval, hypersignal nodule in subcutaneous tissue in T2-weighted images associated with surrounding oedema.	Cure
Subcutaneous Dirofilariasis					
Athari (2003)	M/ 22 y/ Chalus, Mazandaran/ 2003/	1. With a transient nodule measuring 2 cm within the 2. Subcutaneous tissues of the forehead 3. Mild headache, weakness and paraesthesia of both lower limbs	*Dirofilaria repens*	1. Surgical excision; the nodule was surgically removed under local anaesthesia and a living and coiled filarial worm, more than 12 cm long, emerged intact from the lesion. 2. Microscopic examinations: characteristics are typical of the genus *Dirofilaria* and suggest a mature female of *D. repens.*	Cure
Subcutaneous Dirofilariasis					
Maraghi *et al.* (2006)	M/ 34 y/ Ahvaz, Khuzestan/ 2006/	1. A single, firm and moveable nodule on the right cheek	*Dirofilaria repens*	1. Excisional biopsy; an adult *Dirofilaria* measured 120 mm in length with white colour was removed. 2. Nodule histopathology showed intense inflammatory cell reaction.	Cure
Subcutaneous Dirofilariasis					
Maraghi *et al.* (2006)	M/ 37 y/ Ahvaz, Khuzestan/ 2006/	1. A single and moveable nodule measuring 15 mm in diameter on his chest.	*Dirofilaria repens*	1. The patient pressed the nodule and a white worm 130 mm in length was observed and identified as *D. repens* 2. No microfilaria was observed in peripheral blood, in nodule or inside worm.	Cure
Ocular Dirofilariasis					
Jamshidi *et al.* (2008)	M/ 49 y/ Tehran, Tehran/ 2010/	1. Redness, tearing, blepharospasm, swelling of lids 2. Photophobia 3. Cystic swelling on the temporal side of bulbar conjunctiva of right eye.	*Dirofilaria repens*	1. Histopathologic examination: extracted worm was recognized as immature *D. repens* of 18 mm length and 280-μm width based on longitudinal ridges.	NR
Ocular Dirofilariasis					
Mirahmadi *et al.* (2017)	M/ 2 y/ Chabahar, Sistan & Baluchistan/ 2017/	1. Redness, irritation, pain and foreign body sensation in the right eye. 2. Presence of anaemia and history of pica. 3. Visual acuity and fundus were normal.	*Dirofilaria immitis*	1. Slit lamp examination demonstrated a thread-like whitish nematode in the anterior chamber of the right eye that twisted around it. 2. PCR amplification and sequence analysis of mitochondrial 12S rDNA confirmed that recovered worm was D. *immitis.*	Cure

Ocular Dirofilariasis					
Rouhani and Athari (2003)	M/ 20 y/ Mazandaran/ 2003/	1. A nodule in his right eye. The nodule measured approximately 5 × 5 mm^2, and had grown slowly in the past year. 2. Complain of itching, epiphora and mild pain in right eye	*Dirofilaria,* but the species could not be identified	Microscopically; the presence of longitudinal cuticular ridges, a thick muscle cell layer, the presence of internal organs, consisting of intestine and reproductive organs and the presence of nuclei per histological section in the lateral cord, led to identify the specimen as a *Dirofilaria*, without species identification.	NR
Ocular onchocerciasis					
Mowlavi *et al*. (2014)	M/ 20 y/ Qom, Qom/ 2013/	1. Yellowish conjunctival nodular lesion in the left eye. 2. The lesion had been present for 1 year and caused a mild foreign body sensation with a minor conjunctival hyperemia over the affected part of the eye. 3. No history of travel to other cities. 4. Uncorrected visual acuity (20/20) with normal intraocular pressure and eye movements.	*Onchocerca lupi*	1. Microscopic examination of the worm revealed a multilayered cuticle with typical prominent undulated ridges on the external layer and transverse striae on the internal layer. Absence of striae might be due either to inappropriate preparation of tissue samples or lack of fine contrast adjustment. The distances between annular outer ridges were 38–40 mm on a segment of worm 210 mm wide, with two striae per ridge interval. These features are indicative of female worms of the genus *Onchocerca*. 2. PCR assay: The 12S rRNA gene showed 99% homology with O. *lupi* of canine onchocerciasis from Portugal and O. *lupi* involved in human eye infection from Turkey.	Cure
Orbital Dirofilariasis					
Tavakolizadeh and Mobedi (2009)	F/ 24 y/ Tehran, Tehran/ 2009	1. Complaining of a slightly painful mass near the temporal area of the right eye 2. Unresponsive to topical steroids and palliative therapy. 3. No history of trauma or insect bite.	*Dirofilaria repens*	1. Histological examinations: revealed multiple sections of a nematode with central eosinophilic and neutrophilic infiltration surrounded by granulomatous and fibrous tissues. 2. Morphologic evaluation: showed a nematode with multilayer thick cuticles, indistinct intestinal cells, numerous external ridges, distinct dorsal and ventral fields of divided coelomyarian somatic musculature, internal longitudinal ridges with broad lateral chords, heavy musculature, and didelphic uterine tubes with a small extra branch empty of microfilariae. These findings suggested it to be a mature female *D. repens*.	Cure
Ophthalmic Dirofilariasis					
Maraghi *et al*. (2016)	F/ 54 y/ Abadan, Khuzestan/ 2016/	1. Tearing, irritation, swelling and itching of the right eye	*Dirofilaria repens*	1. In ophthalmoscopy, a live worm was observed in sub-conjunctival space. The worm was removed and sent to the laboratory. The worm was white in colour with a length of 105 mm. Based on morphological characterization identified as *Dirofilaria repens*	NR
Subconjunctival Dirofilariasis					
Tabatabaei *et al*. (2017)	M/ 59 y/ Tabriz, East Azerbaijan/ 2017/	1. Diurnal foreign body sensation, localized tenderness and eye redness during the day in right eye since 5 days ago. 2. No history of travel, trauma, allergy and visual acuity was normal.	*Dirofilaria immitis*	1. Ocular examination showed moderate chemosis and injection at that temporal conjunctiva. After careful slit lamp examination, a U-shaped moving lesion was visible under the conjunctiva at the site of redness and injection. In fact, when the light focused on the conjunctival surface, the worm started to move. 2. Parasitological examination: extracted worm was reported to be an immature female worm with 100 mm length and 0.5 mm width belonging to *D. Immitis* family. 3. Proof of identity was based on the morphological appearance and reliable diagnostic clues were completed with observing smooth laminated cuticle, narrow hypodermal lateral cords and long muscle cells	Cured, except for faint temporal conjunctival scar.

(*Continued*)

Table 1. (*Continued.*)

Reference	Sex/ age/ city or province/ year of report/ ref	Symptoms/signs	Genus and species of parasite	diagnostic methods	Outcome
Subconjunctival Dirofilariasis					
Maraghi *et al.* (2006)	M/ 35 y/ Ahvaz, Khuzestan/ 2006/	1. Itching, swelling and redness of the right eye.	*Dirofilaria repens*	1. Examination noticed a living worm with the length of 110 mm which was removed from the subconjunctival space.	Cure
Subconjunctival Setariasis					
Nabie *et al.* (2017)	F/ 15 y/ Tabriz, East Azerbaijan/ 2017/	1. A 24 h history of redness, itching, swelling and foreign body sensation in her left eye. 2. History of insect bite 1-year ago without history of travel.	*Setaria equina*	1. Slit lamp examination: a thread-like cylindrical worm was moving in the subconjunctival area. The worm was extracted, stained and measured 110 mm in length 510 μm in width. The isolated worm was identified as adult female *S. equina* based on morphometric criteria. 2. PCR: identification of the species of the worm was confirmed using molecular methods.	Cure
Periocular Dirofilariasis					
Jamshidi *et al.* (2008)	F/ 27 y/ Bandar Abbas, Hormozgan/ 2008	1. Redness and swelling of the left eye since 10 years ago. 2. Redness and swelling of right eye and frontal area since 2 days ago. 3. No history of bites and normal haematological and biochemical parameters.	The worm was diagnosed as, likelihood, *Dirofilaria immitis*	1. Microscopic examinations: live worm (126×0.75 mm^2) was surgically extracted from the lower lid subcutaneous tissue. The parasite was sent to Department of Parasitology, Tehran University of Medical Sciences for further identification. The worm was at a juvenile stage, body was smooth, and the tail was round. The whole oesophagus from the anterior end measured 1.25 mm. The vulva opening was situated in the anterior part of the esophagus 2.2 mm from the frontal region behind the muscular esophagus. Microfilariae were detected in the uterus, and the worm was possibly *D. immitis.*	Cure
Dirofilaria in Hydrocele					
Salahi-Moghadam and Banihashemi (2016)	M/ 5 y/ Bandar Abbas, Hormozgan/ 2016/	1. Main compliant of left inguinal pain 2. Ultrasonography of testes was normal. 3. A well-defined heterogeneous lesion was seen in superior aspect of left testis.	*Dirofilaria immitis*	1. According to ultrasonic imaging, diagnosis was based on incarcerated inguinal hernia and hydrocele. During surgery, a worm was removed from spermatic cord. 2. Macroscopic features: 60 mm long milky nematode, with conic head and end, and without other notable macroscopic features 3. Microscopy: overview of worm body indicated a kind of filarial; and seeing vulva in anterior portion and bifurcate uterus terminal and the form of oesophagus and cuticle caused the detection of *D. immitis*. Large amount of cells were seen in this worm's uterus.	Cure
Breast Dirofilariasis					
Maraghi *et al.* (2015)	F/ 40 y/ Abadan, Khuzestan/ 2015/	1. A nodule on her right breast	*Dirofilaria repens*	1. Ultrasound and mammography revealed a nodule diagnosed as parasitic lesion. 2. Histopathological examination, cross-section of a worm surrounded with necrotic tissue, associated with infiltration of Neutrophils, Eosinophils and foreign body giant cells observed which was morphologically compatible with *Dirofilaria repens*	Cure

Table 2. Prevalence, publication bias, and heterogeneity of *Dirofilaria immitis*, *Dipetalonema* spp, *Onchocera* spp, *Setaria* spp and *Parafilaria multipapillosa* in animal hosts in Iran up to 1 December 2019

Species	Host	Prevalence, % (95% CI)	Cochran *Q*	df	I^2 (%)	*P* value	Egger bias	*P* value
D. immitis	Canids	14.69 (10.33–19.67)	661.2	35	94.7%	$P < 0.001$	3.0	0.266
D. evansi	Camel	10.16 (4.73–17.34)	339.4	10	97.1%	$P < 0.001$	9.0	0.010
D. reconditum	Dog	2.15 (0.71–4.33)	6.3	3	52.7%	$P = 0.095$	1.9	0.050
O. cervicalis	Horse, Donkey	3.63 (1.44–6.75)	0.1	1	–	$P = 0.658$	–	–
O. fasciata	Camel	16.57 (10.12–24.24)	60.8	6	90.1	$P < 0.001$	5.8	0.009
Setaria equina	Horse, Donkey	12.15 (0.04–40.70)	16.8	1	–	$P < 0.001$	–	–
***Setaria* spp**	Cattle	45.47 (14.45–78.61)	2677.7	5	99.8	$P < 0.001$	−50.4	0.016
P. multipapillosa	Horse, Donkey	5.85 (3.75–8.37)	5.9	3	49.7%	$P = 0.113$	−2.0	0.164

repens usually emerge over a period of weeks or months, with rigid, elastic solidity (Simón *et al.*, 2012). Approximately, 30–35% of *D. repens*-related infections involve ocular sites, entailing considerable consequences such as floaters, damaged vision, glaucoma, crystalline lens, the opacity of the vitreous humor and blepharedema (Pampiglione and Rivasi, 2000; Stringfellow *et al.*, 2002). Altogether, the spread of human dirofilariasis due to *D. repens* may be the result of vector habitat outreach, impaired immune responses to subcutaneous parasites and inadequate diagnosis and therapy in the primary hosts, i.e. dogs (Otranto and Deplazes, 2019).

Among Iranian case reports, subconjunctival infection to *Onchocerca lupi* (*O. lupi*) in a 20-year-old male commuter inhabiting Qom province was interesting, since it was the first human case of *Onchocerca* infection in the country (Mowlavi *et al.*, 2014). Mowlavi *et al.* mentioned that the patient with multiple parasitic nodules in his eye may have got infected by blackflies in northern Tehran or *Culicoides* species in Qom suburbs (Mowlavi *et al.*, 2014). *Onchocerca lupi* was first described in a wolf (*Canis lupus cubanensis*) in Russia in 1967 (Rodonaja, 1967). Otranto *et al.*, in 2011 confirmed the first certain case of ocular *O. lupi* in a human by morphological and molecular analysis in Turkey where there was no report of canine onchocerciasis before (Otranto *et al.*, 2011*b*, 2012). Based on a published systematic review, there have been increasing reports of human infections with *O. lupi*, especially during last decade, raising the zoonotic potential of this nematode in Europe, Middle East and USA (Grácio *et al.*, 2015). Although ocular cases are more common, *O. lupi* has occasionally been recovered from the spinal cord or subcutaneous nodules of infected humans (Grácio *et al.*, 2015). Notwithstanding reported infections in dogs and cats from some European countries (Hermosilla *et al.*, 2005; Faísca *et al.*, 2010; Maia *et al.*, 2015; Tudor *et al.*, 2016; Hodžić *et al.*, 2018) as well as USA and Canada (Labelle *et al.*, 2011; Otranto et al., 2015*b*), there exist paucity of data about *O. lupi* prevalence in canid population of Iran and its potential blackfly (Simuliidae) or Culicoides vectors.

Setaria spp. are parasites of some herbivores, with adults causing fibrinous peritonitis and immature forms aberrantly migrating in accidental hosts (Ahmad and Srivastava, 2007). A subconjunctival setariasis due to *Setaria equina* (*S. equina*) in the left eye of a 15-year-old girl was reported from northwestern Iran (Nabie *et al.*, 2017). So far, only few cases of human infection to adult *Setaria* spp. has been reported globally. Panaitescu *et al.*, documented four human cases of subconjunctival *S. labiatopapillosa* infection in Romania with photophobia, swelling and tearing signs (Panaitescu *et al.*, 1999). Another report from Romania emphasized subconjunctival infection of an old man with *Setaria* sp. (Țălu *et al.*, 2012). Despite a wide array of Culicidae mosquito vectors for setariasis around the world, comprising *Aedes*, *Anopheles*, *Armigeres*, *Culex* and *Mansonia* (Azari-Hamidian *et al.*, 2019), less is understood about the possible vectors in Iran. Azari-Hamidian *et al.*, in 2009 did the only present survey and found *Anopheles maculipennis* mosquitoes in northwestern Iran infected to *Setaria* (Azari-Hamidian *et al.*, 2009).

Dirofilaria immitis, agent of cardiopulmonary dirofilariasis in canids, was the predominant species of filarioids among all examined animals in Iran. The highest detection rate was obtained by serology (16.95%; 95% CI = 3.51–35.38%) as convenient techniques for screening or field-based appraisal, while the lowest prevalence was determined using microscopy (13.86%; 95% CI = 9.46–18.94%). Serological methods are appropriate, especially for the diagnosis of amicrofilaremic infections (Simón *et al.*, 2012). Geographically, both *D. immitis* and *D. repens* are sympatric in most territories (Simón *et al.*, 2017), although the latter was only detected in a recent multiplex-PCR study in Iran with 26% prevalence in dogs (Pedram *et al.*, 2019). Globally, several studies have reported the prevalence of canine *D. immitis* infection. In continental Portugal where heartworm is endemic, 4–9% prevalence was reported (Alho *et al.*, 2018). The prevalence in Turkey, neighbouring Iran, was zero to 18% (Köse and Erdoğan, 2012). In Greece, canine *D. immitis* prevalence ranged between 0.7% and 25% (Angelou *et al.*, 2019; Diakou *et al.*, 2019). In Poland, Eastern Europe very low prevalence (<1%) was observed (Krämer *et al.*, 2014). The highest canine heartworm prevalence was reported from Madeira Island with 40% (Genchi and Kramer, 2019). Reports from the Far East countries are rare, with 2–15% and 18% in China (Liu *et al.*, 2013)and Thailand (Boonyapakorn *et al.*, 2008), respectively. Moreover, 4.7–29.5% prevalence rates were observed in India (Borthakur *et al.*, 2015). A few studies have reported *D. immitis* and *D. repens* in African countries including Algeria (Tahir *et al.*, 2017), Tunisia (Rjeibi *et al.*, 2017), Mozambique (Schwan and Durand, 2002) and Tanzania (Mukendi *et al.*, 2016) with 1.4–14.5% prevalence rates. The highest prevalence of *D. immitis* in the Americas has been reported in US Eastern states, Caribbean Islands and some parts of Argentina and Brazil (20.4–74%) (Lee *et al.*, 2010; Little *et al.*, 2014; Barrett and Little, 2016; Simón *et al.*, 2017).

Based on the findings of this current review, the highest prevalence of *D. immitis* was observed in stray dogs (20.92%; 95% CI = 13.84–29.03%), whereas 10.72% (95% CI = 6.59–15.7%) and 6.61% (95% CI = 3.46–10.68%) prevalence rates were reported in wild canids (jackals and red fox) and owned dogs, respectively, in Iran. An increasing trend has been shown of heartworm infection among European populations of jackals (7.7–23.3%), foxes (3.7–35%) and raccoon dogs (31.1%) (Marconcini *et al.*, 1996; Cirovic *et al.*, 2014; Simón *et al.*, 2017). A recent study in Canada showed 4.8% prevalence of *D. immitis* in wild canids

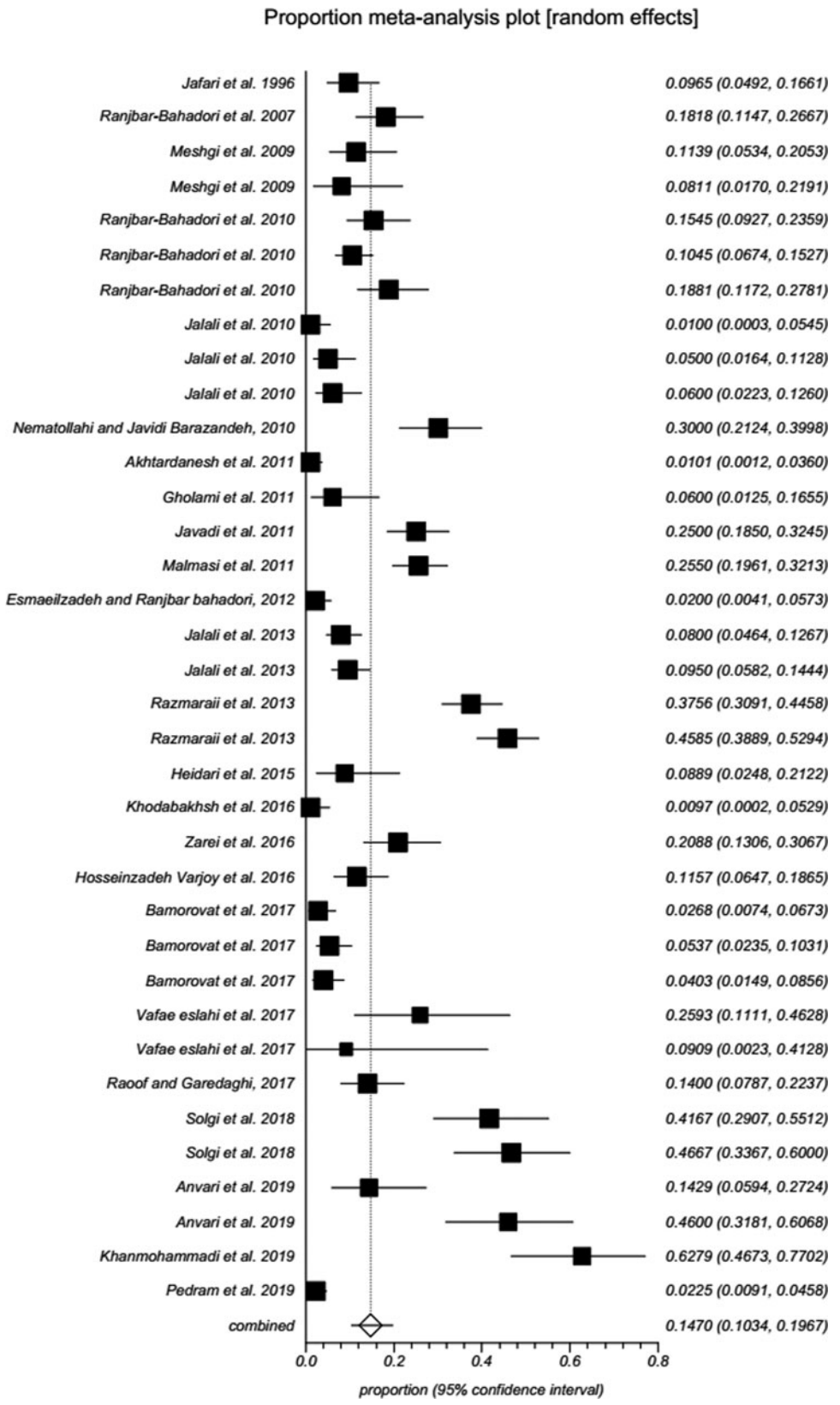

Fig. 2. Forest plot of the prevalence of *D. immitis* in canids of Iran up to 1 December 2019. A square is appointed to each individual study with a horizontal line as confidence intervals and the area of each square is proportional to the study's weight in the meta-analysis. Also, a diamond is assigned to the meta-analysed measure of effect. A vertical line representing no effect is also plotted. If the confidence intervals for individual studies overlap with this line, it demonstrates that at the given level of confidence their effect sizes do not differ from no effect for the individual study.

(Kotwa *et al.*, 2019). Wild canids, directly or indirectly, possibly play a critical role in the maintenance and transmission of *D. immitis* (Simón *et al.*, 2017). Distribution patterns of *D. immitis* in canids may be influenced by different ecosystems, such that foxes in agricultural regions of Europe were more infected than those foxes in semiarid or mountainous territories. High interactions among wildlife, pets and humans in suburban/agricultural areas could affect the transmission dynamics

Table 3. Prevalence of *Dirofilaria immitis* in canines according to year, host, location, gender, age and diagnostic method in Iran up to 1 December 2019

Subgroup variable	Prevalence (95% CI)	I^2 (%)	Heterogeneity (*Q*)	*P* value	Interaction test (X^2)	*P* value
Year						
<2011	11.58 (7.37–16.60)	84%	62.5	*P* < 0.001	177.1	*P* < 0.001
⩾2011	16.25 (10.23–23.35)	96%	596.4	*P* < 0.001		
Host						
Wild Canines	10.72 (6.59–15.70)	0%	0.2	*P* = 0.963	123.9	*P* < 0.001
Owned dogs	6.61 (3.46–10.68)	88.1%	84.2	*P* < 0.001		
Stray dogs	20.92 (13.84–29.03)	95.6%	453.7	*P* < 0.001		
Location						
North	13.59 (7.29–21.46)	88.3%	59.6	*P* < 0.001	123.1	*P* < 0.001
South	6.10 (3.40–9.51)	65.1%	11.4	*P* = 0.021		
East	9.03 (3.15–17.52)	92%	74.5	*P* < 0.001		
West	25.29 (14.44–37.99)	95.4%	173.1	*P* < 0.001		
Centre	20.60 (5.93–41.13)	96.7%	121.1	*P* < 0.001		
Gender						
Male	10.07 (5.10–16.47)	87.9%	99.4	*P* < 0.001	89.1	*P* = 0.131
Female	9.23 (3.68–16.97)	87.3%	86.9	*P* < 0.001		
Age						
<1 Year old	8.40 (0.01– 32.00)	77%	13.0	*P* = 0.004	10.8	*P* = 0.006
⩾1 Year old	20.77 (8.66–36.42)	90.1%	40.5	*P* < 0.001		
Diagnostic method						
Serological	16.95 (4.98–34.08)	96.6%	146.9	*P* < 0.001	110.0	*P* = 0.010
Microscopic	13.86 (9.46– 18.94)	92%	286.0	*P* < 0.001		
PCR	16.09 (3.51–35.38)	97.7%	215.8	*P* < 0.001		

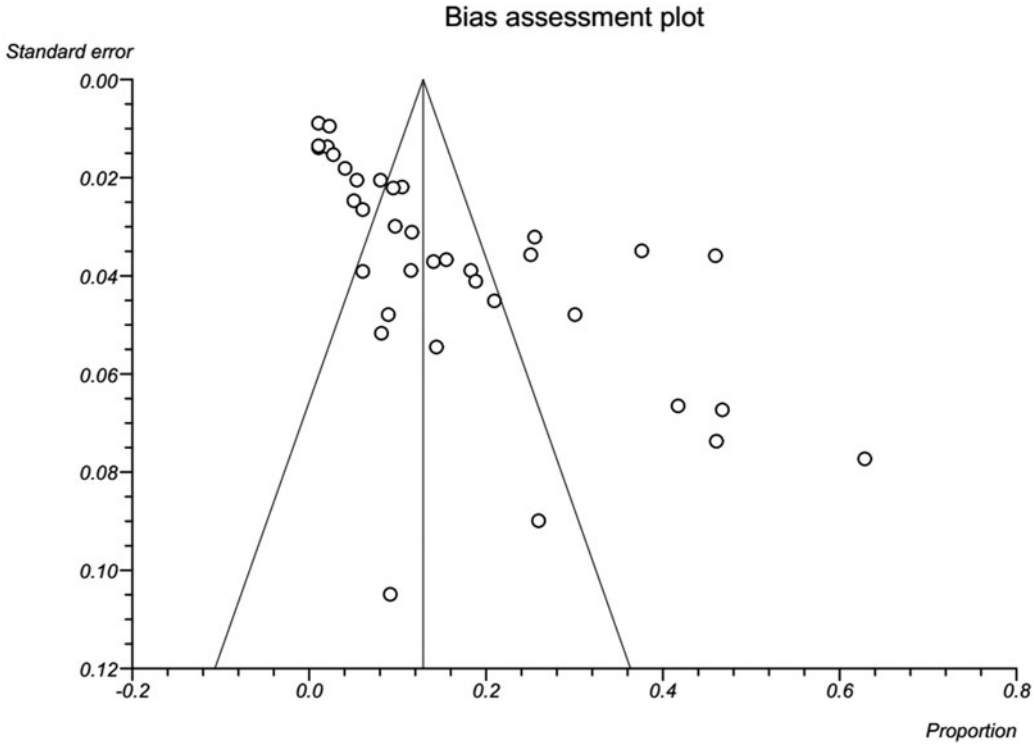

Fig. 3. A bias assessment plot from Egger for the prevalence of *D. immitis* in canids of Iran up to 1 December 2019. In the absence of publication bias, it assumes that studies with high precision will be plotted near the average, and studies with low precision will be spread evenly on both sides of the average, creating a roughly funnel-shaped distribution. Deviation from this shape can indicate publication bias.

Table 4. Subgroup analysis of *Dipetalonema evansi* and *Onchocerca fasciata* in camels of Iran up to 1 December 2019

Subgroup variable	Prevalence (95% CI)	I^2 (%)	Heterogeneity (Q)	P value	Interaction test (X^2)	P value
Dipetalonema evansi						
Gender						
Male	10.62 (3.13–21.82)	92.2%	25.7	$P < 0.001$	2.9	$P = 0.084$
Female	8.01 (5.00–11.64)	0%	0.2	$P = 0.903$		
Diagnostic method						
Microscopic examination	9.94 (2.63–21.21)	97.1%	172.4	$P < 0.001$	13.2	$P < 0.001$
Modified Knott test	7.24 (0.15–23.46)	98.4%	127.1	$P < 0.001$		
Onchocerca fasciata						
Gender						
Male	11.52 (4.56–21.12)	80.9%	10.4	$P = 0.005$	4.4	$P = 0.035$
Female	18.54 (8.77–30.91)	84.2%	12.6	$P = 0.001$		
Diagnostic method						
Microscopic examination	18.56 (9.87–29.23)	84.2%	12.6	$P = 0.001$	6.1	$P = 0.013$
Histopathologic methods	15.28 (6.54–26.84)	92.7%	41.1	$P < 0.001$		

of dirofilariasis (Gortázar *et al.*, 1994; Marks and Bloomfield, 1998).

Based on our findings, *D. immitis* prevalence was prevalent in western (25.29%; 95% CI = 14.44–37.99%) and northern (13.59%; 95% CI = 7.29–21.46%) Iran. From a historical perspective, the first observation of the heartworm in Iran dates back to 1969 when Sadighian reported necropsy documentation of stray dogs in Caspian Sea littoral, northern Iran (Sadighian, 1969). Climate and environment are important extrinsic factors for survival and development of vector mosquitoes and subsequent occurrence of dirofilariasis. Regarding the ectothermic nature of mosquitoes and their reliance on water supplies, climatic parameters including humidity/precipitation and temperature substantially impact their colonization, population density, diversity and activity (Simón *et al.*, 2017). Also, from a parasitic standpoint, extrinsic incubation (8–20 days with 22–30°C temperatures) is influential for L3 larvae development (Simón *et al.*, 2012). Such favourable circumstances are provided in the western and northern parts of Iran, where there exist huge water resources, irrigation systems and high precipitation rates annually. In contrast, low prevalence rates in eastern and southern parts of Iran are observed, where weak water supplies and low annual precipitation exist. An expedient exemplary of climate impact on the prevalence of dirofilariasis is represented in Grand Canary Island, where various altitudes possess different semitropical climates. Accordingly, *D. immitis* prevalence among canines of various zones differ significantly, from 30.4% in mild climate zone to 10% in the temperate cold climate zone (Montoya-Alonso *et al.*, 2010). Although not significant, the prevalence in males was partly more than females in our review (10.07% *vs* 9.23%; $P = 0.131$), which is consistent with findings of other investigations (Reifur *et al.*, 2004; Simsek *et al.*, 2008). Also, canids over 1-year old were over 2-fold more susceptible than younger (<1-year old) ones (20.77% *vs* 8.40%; $P = 0.006$), in agreement with another study in Brazil (Reifur *et al.*, 2004). Adult animals had probably accumulated more exposure time to insect bites, thus had a higher prevalence of infection.

Besides canine *Dirofilaria* infection in Iran, we only found two studies regarding feline dirofilariasis in Ardabil and Khuzestan provinces. Heartworm infection is a subclinical condition in domestic/wild felids and only a few worms reach maturity; hence, there may be a limited number of blood microfilariae, which, in turn, substantially reduces the chance of transmission (Simón *et al.*, 2012; Penezic *et al.*, 2014). Otranto *et al.* (2015*a*) also corroborate our findings, highlighting the lower contribution of felids in the epidemiology of heartworm disease (Otranto et al., 2015*a*). In the USA, 3–19% prevalence ranges have been reported regarding feline dirofilariasis. Studies in Europe have shown a 7–27% (Italy) and 33% (Canary Islands) seroprevalence rates. In Japan, 2–5.2% of cats were seropositive for dirofilariasis (Simón *et al.*, 2012).

Other known, but less frequent filarioid nematodes found in Iran are *D. evansi* (syn. *Deraiophoronema evansi*) in camels, and *Acanthocheilonema reconditum* (*A. reconditum*) in dogs. The camel parasite was isolated from 7 provinces with a total prevalence of 10.16% (95% CI = 4.73–17.34%). Male dromedaries were more parasitised than females (10.62% *vs* 8.01%), consistent with Mahran study (Mahran, 2004), although it was not significant ($P = 0.084$). A significant association was observed between the prevalence of *D. evansi* in Iranian camels and diagnostic method ($X^2 = 13.2$; $P < 0.001$). It seems that using a microscope examination is more appropriate for identifying *D. evansi* than the Knott test. One-humped camel (*Camelus dromedarius*) is the dominant species in Iran, with particular tolerance to the harsh desert environment and some pathogens, although *D. evansi* induces clinical disease (Sazmand and Joachim, 2017). Adult worms accumulate in large number in various affected organs, comprising spermatic cord, epididymis, testicles, heart and lungs. The acute disease could lead to emaciation, orchitis, heart failure, arteriosclerosis and nervous impairment (Oryan *et al.*, 2008). Our knowledge on this parasite is limited to prevalence studies in arid, semi-arid countries of the world, including Egypt, Nigeria, Saudia Arabia, Iran and India (Pathak and Chahabra, 2010; Sazmand *et al.*, 2013; Egbe-Nwiyi *et al.*, 2016; El-Khabaz *et al.*, 2019). Globally, the estimated prevalence in adult camels was 2.5–4%, while it was 47.5% in less than 1-year-old camels (Muhammad and Athar, 2000). A molecular study by PCR and sequencing methods in 2016 revealed paraphyly of *D. evansi* and *D. gracile*, which deserves further investigations (Sazmand *et al.*, 2016). *Acanthocheilonema reconditum* living in canine subcutis and on muscle fascia develops mild parasitism in dogs with no major damages (Saari *et al.*, 2019). Approximately, 2.15% (95% CI = 0.71–4.33%) of the dog population in Iran was reported to have this infection. In a multispecies survey in Romania on filarioid infections, *A. reconditum* DNA was only detected in a red fox (0.33%) (Ionică *et al.*, 2017).

Diagnosis is important only to differentiate their mfs from the life-threatening species, *D. immitis* (Otranto and Deplazes, 2019).

With respect to other filarioids infecting domestic livestock in Iran, we could only estimate the weighted prevalence of *Parafilaria multipapillosa* (*P. multipapillosa*) (referred to as *Filaria haemorrhagica*) in equids (5.85%; 95% CI: 3.75–8.37%), *S. equina* in equids (12.15%; 95% CI: 0.04–40.7%) and *S. digitata* in ruminants (45.47%; 95% CI: 14.45–78.61%). Several *Onchocerca* spp. parasitise livestock including, *O. fasciata* (camel; connective tissue, ligamentum nuchae) (16.57%; 95% CI: 10.12–24.24%), *O. cervicalis* (horse and donkey; cervical ligament) (3.63%; 95% CI: 1.44–6.57%) and *O. reticulata* (horse and donkey; connective tissue, flexor tendon) which are found in Iran. We found a statistically significant association between prevalence of *O. fasciata* in Iranian camels and gender ($X^2 = 4.4$: $P = 0.035$) and diagnostic method ($X^2 = 6.1$; $P = 0.013$). It seems that using microscopic examination may be more likely to detect *O. fasciata* than histopathologic methods. Prevalence studies are actually rare on *P. multipapillosa*, while there is more on *P. bovicola* of cattle (not found in Iran) (Bech-Nielsen *et al.*, 1982; Solismaa *et al.*, 2008; Borgsteede *et al.*, 2009). Setariosis is a benign infection and even high rates of microfilaraemia could be well tolerated (Hornok *et al.*, 2007). Survey of filarial nematodes of 188 donkeys in Egypt showed a total infection rate of 86.7% mostly in males (86.73%), regarding *O. cervicalis* (82.98%), *O. reticulata* (4.26%), *S. equina* (36.17%) and *P. multipapillosa* (5.32%) (Radwan *et al.*, 2016). In Hungary, 18 of 195 (9.2%) horses had mfs by Knott technique for *S. equina* (Hornok *et al.*, 2007). In a Finnish study, 209 skin biopsies of cattle revealed 78 (37%) positive for *Onchocerca* sp. mfs (Solismaa *et al.*, 2008). Altogether, the above information obtained from current systematic review and meta-analysis represents that there is a gap in our knowledge and understanding in the field of filariasis in livestock that needs global collaboration for better realization of such arthropod-borne helminths.

Concluding remarks

As we stated in the current systematic review and meta-analysis, *Dirofilaria* spp. infections (*D. repens* cases in humans and *D. immitis* in canids) were the most frequently found species of all filarioid nematodes in Iran. Most cases have been reported from rainy provinces with favourable temperatures for vector hosts. Also, most cases were detected during the last two decades, which indicates increased prevalence, and/or improved diagnostics or awareness in the public and clinical understanding of *Dirofilaria* infections. In this context, there is an urgent need to nationwide epidemiological surveys, e.g. serodiagnosis to detect human pulmonary cases, as well as preventive therapy of, at least pet dogs. Regarding less evident, but existing filarioids, such as the interesting human case of *O. lupi* in Qom province and those being found in herbivores much large-scale studies in the context of the host-parasite-vector axis are recommended to be done in the future for better understanding of the epidemiology of these filarioid infections.

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