Review article

Systematic Review and Meta-Analysis of Human Visceral Leishmaniasis in Iran

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SUMMARY

Visceral leishmaniasis (VL) is a protozoan disease caused by some *Leishmania donovani* complex species and is considered as an endemic zoonotic parasitic disease in Iran. This study was performed to determine the prevalence of human VL in Iran. Data were systematically gathered from 1985 to 2018 in Islamic republic of Iran from the following electronic databases: PubMed, Google Scholar, Science Direct, Scopus, Web of Science, Magiran, Irandoc, Iranmedex and Scientific Information Database (SID). In total, 29 studies reporting the prevalence of VL from different areas of Iran met our suitability criteria. The Q test and the I² statistics were applied to determine heterogeneities. The Egger's and Begg's test was used to check the presence of publication bias. The pooled prevalence of VL in Iran measured by random-effects was estimated at 1% (95% CI: 1 - 2) in urban areas, 3% (95% CI: 2 - 4) in rural areas and 2% (95% CI: 2-3) in total. The majority of VL cases during the last 33 years were reported in the northwest and south provinces of Iran. There was a high degree of heterogeneity (I² = 98.2%, Q test: p = 0.0002) and Begg's (z = 3.62, p < 0.001) and Egger's (bias = 5.9, 95% CI = 2.70 - 9.11) tests were significant for the study of publication bias. After correction, the total prevalence was estimated to be 0.3% (95% CI: 0.2 - 0.9). The prevalence of VL in Iran was 0.3%, and this rate was much higher in the northwest and south of the country. These results are desirable for managing the control programs of this disease.

Key words: black fever, *Leishmania infantum*, kala azar, prevalence, Iran

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INTRODUCTION

Leishmaniasis is one of the zoonotic parasitic diseases that occur in three forms: cutaneous (CL), mucosal (ML) and visceral (VL) (1).

Visceral leishmaniasis is caused by *Leishmania donovani* complex species. Two parasites containing *Leishmania donovani* (*L. donovani*) and *Leishmania infantum* (*L. infantum*) caused VL in the old world (the Eastern Hemisphere) and *L. chagasi* in the new world (the Western Hemisphere) (2, 3). In different countries, it is also named infantile kala-azar, tropical splenomegaly syndrome, febrile splenic anemia and ponos (4).

Endemic VL is found in tropical and subtropical regions of Africa, Asia, the Mediterranean, southern Europe, Sudan and South America, and more than 90% of cases are present in Bangladesh, India, Nepal, Sudan and Brazil (5).

The disease affects around 500,000 people each year and causes fatalities in 50,000 people around the world (6). In different parts of the world, various domestic and wild animals, and even human beings, are known to be the reservoirs of the disease; also, different sand fly species can act as vectors of this disease (7).

Currently, VL in Iran is considered an endemic disease and its prevalence is estimated at 0.092 per 100,000 people and its direct medical cost is \$ 295 per patient (8 - 10). The VL agent in Iran is *Leishmania infantum* in the Mediterranean subregion and is often reported in children under the age of 12 years and more in nomads and villagers (11, 12). Some cases of VL have been reported with disseminated CL from southern Iran, which was caused by *Leishmania tropica* (13).

In Iran, dogs are domesticated hosts and jackals, wolves and foxes as wild hosts are the main reservoirs of the disease (12, 14). Five species of sand flies are known to be the potential vectors of VL disease, four of which are from the subgenus *Larrousius* and one from subgenus *Paraphlebotomus* (8).

Visceral leishmaniasis might be found both in symptomatic and asymptomatic forms. In some regions, latent infection is more prevalent than active clinical disease. In endemic areas of Iran, latent infections are more common than in clinical forms. In the absence of diagnosis and timely treatment of the disease in humans, especially among children, death rate is about

98% (15 - 18). Treatment of this disease in Iran still relies on meglumine antimoniate whose effects are not the same in all cases.

The main symptoms are fever, splenomegaly and anemia, and abnormal laboratory findings include pancytopenia and hypergammaglobulinemia and hypoalbuminemia (12). For the diagnosis of this disease, the invasive methods of biopsy from the spleen, liver or bone marrow aspiration are set as the gold standards. Non-invasive diagnostic methods, such as antibody detection by direct agglutination test (DAT), indirect immunofluorescence assay (IFA) and enzyme-linked immunosorbent assay (ELISA) are presently used (17, 19, 20).

Given the rapid and unprogrammed development of cities, environmental changes, parasite resistance to conventional drugs, opportunistic parasites in immunocompromised individuals and a growing complexity of the disease symptoms, there is a need for more precise detection of the disease outbreak to manage the control programs. This study aimed to reveal the prevalence of human VL in Islamic republic of Iran.

METHODS

Bibliographic search

The search was done in databases including Pub Med, Google Scholar, Science Direct, Scopus, Web of Science, Magiran, Iran doc, Iran medex and Scientific Information Database (SID for the period 1985 to 2018). Duplicates and animal-based articles were excluded. All cross-sectional studies related to the human VL in Iran were considered. The research process is given in Figure 1.

Search strategy

The search was implemented using the keywords as follows: visceral leishmaniasis, kala azar, black fever, *Leishmania infantum*, anti-*Leishmania* antibody, epidemiology, and prevalence only or in combination in Iran, both in Persian and English language.

Figure 1. A flowchart presenting the selection of the articles analyzed in this systematic review and meta-analysis

Data collection

Based on the mentioned strategy, the search was performed in nine databases. Subsequently, the collected articles were carefully evaluated for epidemiological parameters; finally, 29 articles met study inclusion criteria, including the accessibility of full text, study of human VL prevalence, as well as the selection of subjects by random or census sampling methods. Exclusion criteria were: data inconsistencies, use of inappropriate statistical methods, unspecified sampling methods, non-

random sampling method, VL in non-human cases, and articles published before 1985. The data extracted from the articles were the names of authors (s), date of study, type of study, demographic information such as age groups as well as the geographical area of the study, the number of subjects examined, the number of seropositive patients and the prevalence and laboratory method used in the study (Table 1). The findings were recorded in each database based on a search made from January to July of 2018.

Table 1. Papers that met the eligibility criteria of this systematic review and meta-analysis

NO	Type of study	Study (author and date)	Province	Sample	Number of positive tests	Percentage	Age groups	Lab method	Cut off	Ref
1	cs	Asfaram 2017	Ardabil	600	23	3.8	20-40 and 40>	DAT	1:3200	(24)
2	cs	Moheballi 2011	Northwest,Northeast,South and Southeast parts of Iran	9369	403	4.3	12≤	DAT	1:3200	(25)
3	cs	Faghihenaieini 2002	Tehran	925	1	0.1	10<	DAT	1:3200	(26)
4	cs	Ashkanifar 2016	khorestan Razavi and North	442	22	5.22	12<	DAT	1:3200	(27)
5	cs	Edrissian 2003	Ardabil, East Azarbaijan and Bushehr	19693	1274	6.47	12<	DAT	1:3200	(28)
6	cs	Mohami 2006	Ardabil	1155	7	0.6	12< and 10% of adults	DAT	1:3200	(29)
7	cs	Sarkari 2010	Booyerahmad	1628	50	3.1	10≤	DAT	1:3200	(30)
8	cs	Moheballi 2017	Ardabil	180	0	0	≥ 13	DAT	1:3200	(31)
9	cs	Fakhar 2008	Fars	802	13	1.62	5-10 and 10>	DAT	1:3200	(32)
10	cs	Fakhar 2006	Fars	321	6	1.86	10< and 10% of adults	DAT	1:3200	(33)
11	cs	Changeni Sharafi 2005	Lorestan	530	6	1.26	12< and 10% of adults	DAT	1:3200	(34)
12	cs	Fakhar 2014	Golestan	450	6	1.33	12<	DAT	1:3200	(35)
13	cs	Sarkari 2015	Fars	2003	28	1.4	adult	DAT	1:3200	(36)
14	cs	Fakhar 2010	Fars	376	32	8.5	10< and 10% of adults	PCR	-	(37)
15	cs	Fakhar 2010	Fars	376	5	1.33	10< and 10% of adults	DAT	-	(37)
16	cs	Moheballi 2011	Kerman	1476	14	0.95	12< and 10% of adults	DAT	1:3200	(38)
17	cs	Fakhar 2011	Mazandaran	402	0	0	12< and 10% of their parents	DAT	1:3200	(39)
18	cs	Hamzavi 2012	Kermanshah	1800	6	0.33	15< and adults	DAT	1:3200	(40)
19	cs	Moheballi 2015	Alborz	1007	4	0.39	10<	DAT	1:3200	(41)
20	cs	Layegh Gigloo 2018	Fars	617	17	2.75	12< and >12	ELISA		(42)
21	cs	Masoori 2018	Lorestan	800	5	0.62	12< and 10% of adults	DAT	1:3200	(43)
22	cs	Ebrahimzade-Parikhani 2017	Ardabil	776	1	0.13	12≤	DAT	1:3200	(44)
23	cs	Abadi 2015	Ilam	456	2	0.43	12≤ and 10% of adults	DAT	1:3200	(45)
24	cs	Khazaei 2017	Ilam	872	20	2.29	12≤	DAT	1:800	(46)
25	cs	Gorgipour 2017	Bushehr	1221	0	0	12≤	DAT	1:3200	(47)
26	cs	Moheballi 2003	East Azarbaijan	1252	24	1.9	10< and 10% of adults	DAT	1:3200	(48)
27	cs	Alborzi 2008	Fars	338	95	24.5	10<	PCR	-	(49)
28	cs	Alborzi 2008	Fars	388	212	54.6	1-35	IFA	ND	(49)
29	cs	Moheballi 2008	North Khorasan	1608	38	2.36	12< and 10% of adults	DAT	1:800	(50)
30	cs	Moheballi 2001	Bushehr	1496	51	3.4	10< and 10% of adults	DAT	1:3200	(51)
31	cs	Rakhshanpour 2014	Qom	1564	1	0.06	ND	DAT	1:3200	(52)

CS: Cross-Sectional, DAT: direct agglutination test, ELISA: enzyme-linked immunosorbent assay, IFA: indirect immunofluorescent assay, LST: Leishmanin skin test, ND: not defined, PCR: polymerase chain reaction. Ref - References

Statistical analysis

Point estimates and their 95% CI of seroprevalence of all involved articles were calculated. The seroprevalence (P) and standard error of mean (Se) of each study were calculated with respect to binomial distribution and studies pooled according to sample size and variance.

Regarding the fact that the seroprevalence of the three articles included in this meta-analysis was zero, the continuity correction method was used. In this method, in all groups, $k = 0.5$ was added to the number of subjects in all studies (21, 22) and then all calculations, including seroprevalence and standard error, were recalculated based on new data. The mean error when using $k = 0.5$ was zero (23).

The Egger's and Begg's test were used to assess the presence of publication bias and whereas trim-and-fill method was used to correct the publication bias. Forest plot was used to visualize the heterogeneity among papers. The heterogeneity was predictable in advance and I^2 and Q test (with significance of $P < 0.05$) were used to measure the variations. With the aim to perform meta-analysis, we assumed that the included papers were random samples of the population under study and a random effects model was used. Proportions of separate studies and prevalence pool were shown by forest plots. Statistical analyses were implemented using Stata, version 12.0 (Stata Corp, College Station, TX, USA). Furthermore, the Arc GIS 10.3 software was applied to map the distribution of VL cases.

RESULTS

In total, 939 articles were obtained by searching the databases with reference to the period from July 15,

1985 to 2018; after reviewing the inclusion criteria, 29 papers met the eligibility criteria of this systematic review and meta-analysis (Table 1). All 29 articles included in this study evaluated the seroprevalence of VL in children under 12 years of age as a cross-sectional type and in adults as an active type. A total of 55,311 people were evaluated during 33 years, of which 2,498 were seropositive (Table 1).

There was a high degree of heterogeneity in estimating the prevalence of studies in meta-analysis, in which the heterogeneity was $I^2 = 88.2\%$ (Q test: $p = 0.0001$) in urban areas, $I^2 = 99.2\%$ (Q test: $p = 0.0002$) in rural areas and $I^2 = 98.2\%$ (Q test: $p = 0.0002$) in total.

The pooled prevalence of VL in Iran measured by random-effects meta-analysis was estimated at 1% (95% CI: 1 - 2) in urban areas, 3% (95% CI: 2 - 4) in rural area and 2% (95% CI: 2-3) in total (Figure 2).

In addition, a schematic image of the VL distribution was made based on studies conducted over the past 33 years in 14 provinces of Iran (Figure 3)

Publication bias

The Egger's and Begg's tests were applied to check the presence of publication bias. The Begg's test ($z = 3.62$, $p = 0.001$) and the Egger's test (bias = 5.9, 95% CI = 2.70 - 9.11) indicated a significant publication bias of studies (Figure 4). The Trim-and-fill method was used to correct the meta-analysis results, and the hypothetical values of 14 censored studies were estimated using non-parametric methods and then were reported as corrected values in the final meta-analysis. The corrected seroprevalence after correction of publication bias was estimated to be 0.3% (95% CI: 0.2 - 0.9) by random-effects method (Table 2).

Figure 2. Forest plot showing the proportion of human VL in urban and rural population in the Islamic Republic of Iran (random-effects)

Figure 3. Plan of the total distribution of human VL in the states of the Islamic Republic of Iran

Figure 4. Egger's plot for the detection of publication bias in the review

Table 2. Comparison of common and corrected meta-analysis results for publication bias

Number of study	95% CI		Pooled seroprevalence	Method	Type of meta-analysis
	Upper	Lower			
29	0.003	0.002	0.002	Fixed	Usual meta-analysis
	0.030	0.020	0.025	Random	
43	0.002	0.001	0.002	Fixed	Filled meta-analysis
	0.009	-0.002	0.003	Random	

DISCUSSION

Visceral leishmaniasis is one of the most malignant types of leishmaniasis that is considered to be a deadly parasitic infection in the endemic parts of the world, which affects annually from about 50,000 to 90,000 new cases. In 2015, more than 90% of patients described to the world health organization were reported in seven countries, including Brazil, Ethiopia, India, Kenya, Somalia, South Sudan, and Sudan (53).

The aim of the current study was to determine the seroprevalence of human VL in Iran since no meta-analysis related to this issue have been available so far.

Based on the results of this study, it seems that most of the VL cases have been recorded in the northwest (Ardebil, East Azerbaijan) and south (Fars and Bushehr) provinces of Iran over the past 33 years (Figure 3). These areas in Iran have already been known as endemic areas of visceral leishmaniasis (20, 51, 54, 55). These foci seem to be expanding in other parts of Iran (56) and major studies on the VL seroprevalence in these areas have also been conducted. The sporadic incidence of disease in other regions of Iran has also been reported in recent years (20).

According to the Center for Infectious Diseases Control at the Ministry of Health in 2017, 58 definite cases of kala-azar were reported in Iran, with the highest frequency in East Azerbaijan (9 cases), Ardebil (8 cases) and Fars (6 cases) provinces, which confirms the results of this study. In the endemic form, the highest rate of infection is among the children, and out of 29 studies included in this review, only three studies have investigated the seroprevalence of VL in adolescents (25, 31, 36), whereas other studies focused on the target group of children. Based on the results of some studies, the frequency of VL is associated with age (14, 51, 57, 58).

The results of the present study showed that the prevalence of VL in Iran was 1% (95% CI: 1 - 2) in urban areas and 4% (95% CI: 3 - 5) in rural areas, indicating a higher incidence of disease in rural areas of Iran compared with urban areas. The pooled prevalence of VL was estimated to be 3% (95% CI: 3 - 5) in Iran though Mohebbi (20) reported a total incidence of VL to be 4.7% in five regions of Iran. Different seroprevalence has been reported in other studies based on the location of study, type of diagnostic method and sample size. Meta-analysis provides valuable results on the magnitude of the effects of the evaluated studies. However, if the results of a meta-analysis are an example of a bias in the studies in that field, then this bias will also have affected the results of meta-analysis (58).

Since the publication bias was significant in the current meta-analysis, after statistical correction, the Trim-and-fill method was used to correct the meta-analysis results, and the hypothetical values of 14 censored studies were estimated using non-parametric methods and then were reported as corrected values in the final meta-analysis. Finally, the corrected prevalence after the correction of publication bias was estimated to be 0.3% (95% CI: 0.2 - 0.9) by random-effects method. It can be seen that the estimated prevalence after the correction has decreased significantly, indicating that 14 censored studies are likely to be studies with low sample size or with negative results that have not been reported and published and therefore have resulted in publication bias.

However, the genetic factors probably accompanied with the infection should not be ignored. The results of a meta-analysis in the United States demonstrated a close association between VL and the life in poverty, the absence of urban substructure and sustainable services and a low educational level. This relationship between low socioeconomic conditions

and VL risk can be described by the fact that the poor economic status is associated with more vectors, the irresponsibility of domesticated owners and the areas with a vegetation density suitable for the presence of vectors and possible reservoirs (58).

Lastly, although in a small number of studies, the variables linked to the geography of the environment and vegetation confirmed that the VL occurs more frequently in regions where the urbanization level is lower and the vegetation density is higher, possibly generating adequate habitats for breeding the vector population (59).

The infection rate in our bordering countries was as follows: in Pakistan (0.03 cases/10 000 population) (60) and in Saudi Arabia (0.01 cases/10 000 population) (61), which is less than the infection rate in Iran. Two other studies have reported the infection rate of 1.62% and 47.21% in suspected patients who were positive for visceral leishmaniasis, in Turkey (62) and Iraq (63), respectively.

Success in VL control programs requires the knowledge of the infection rate among human populations and reservoirs, as well as the awareness of active disease foci (64). Dogs are considered as the most important source and reservoir for VL in Iran. Shokri et al. (65), on the basis of a meta-analysis and systematic review, reported that the prevalence of VL in dogs, jackals, wolves and foxes in Islamic republic of Iran was 16.4% (95% CI: 15 - 20%), 10% (95% CI: 5 - 15%), 10% (95% CI: 5 - 15%) and 10% (95% CI: 1 - 19%), respectively. The highest prevalence was in dogs of Ardebil province with the prevalence of 43.6%. In the present study, Ardabil province has been also identified with high prevalence of human VL.

According to various studies, the use of direct agglutination test is one of the desirable, simple and practical methods for investigating VL seroepidemiology and animal reservoirs (3, 54, 66, 67). The most widely used diagnostic test in the majority of papers included in this study was DAT with a cut-off point of 1:3000, and only Faghar et al. (37) applied PCR in addition to DAT, whereas Alborzi et al. (49) employed two methods of PCR and IFAT to determine the VL separately in all of their subjects and reported the prevalence according to individual diagnostic methods.

If a target antigen is available, DAT test can be performed by a trained technician in remote areas with minimal laboratory facilities. The sensitivity of this method has been reported to be 92% - 100% in endemic areas. Additionally, the patients with clinical signs

suspected of kala-azar could undergo specific VL treatments without bone marrow or spleen puncture if this test is positive (68, 69).

It is necessary to mention some limitations in this study. Such an analysis is limited due to the heterogeneity among the results of various studies. Although an extensive search was done for doctoral theses done on this subject, it is possible that many of them have not been published at all, which may be one of the reasons for the publication bias in the present study.

Also, an unequal sample size due to the demographic features in some studies caused this bias. A possible conclusion is that the small sample size in some studies, therefore the infection rate, appears higher than the true rate.

CONCLUSION

The results of this meta-analysis showed that, after correcting the publication bias, the prevalence of VL in Iran was 0.3% (95% CI: 0.2 - 0.9). The incidence rate of the VL over the past 33 years was higher in the northwest (Ardebil and East Azerbaijan) and south (Fars and Bushehr) provinces of Iran and these provinces have been considered as endemic VL foci in Iran.

These results are desirable for managing the control and prevention programs.

To control VL in Iran, it is recommended to manage stray dogs, to detect suspicious dogs of the disease by periodic DATs and to deal with them if serologically positive. It is also necessary to control the vectors, to diagnose quickly and timely human cases using serological tests, to treat infected people for reducing mortality and to develop the public health education.

Conflict of interest

The authors declare that they have no conflict of interest.

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References

1. Rahmanian V, Rahmanian K, Sarikhani Y, et al. Epidemiology of Cutaneous Leishmaniasis, West South of Iran, 2006-2014. *J Res Med Dent Sci* 2018; 6:378-83. doi: 10.5455/jrmds.20186258
2. Palatnik-de-Sousa CB, dos Santos WR, Franca-Silva JC, et al. Impact of canine control on the epidemiology of canine and human visceral leishmaniasis in Brazil. *Am J Trop Med Hyg* 2001; 65:510-7.
<https://doi.org/10.4269/ajtmh.2001.65.510>
3. Bokai S, Mobedi I, Edrissian GhH NA. Seroepidemiological study of canine visceral leishmaniasis in Meshkin-Shahr, northwest of Iran. *Arch Inst Razi* 1998; 41:48-9.
4. Bokaei S, Sharifi L, Mamishi S, et al. Clinical And Epidemiologic Characteristics Of Children With Kala-Azar Hospitalized In Children's Medical Center(1991-2003). *Iran J Epidemiol*.1:21-6.
5. Desjeux P. Leishmaniasis: current situation and new perspectives. *Comp Immunol Microbiol Infect Dis* 2004;27:305-18.
<https://doi.org/10.1016/j.cimid.2004.03.004>
6. Chappuis F, Sundar S, Hailu A, et al. Visceral leishmaniasis: what are the needs for diagnosis, treatment and control? *Nat Rev Microbiol* 2007;5: 7.
<https://doi.org/10.1038/nrmicro1748z>
7. Mohebbali M, Hajjaran H, Hamzavi Y, et al. Epidemiological aspects of canine visceral leishmaniosis in the Islamic Republic of Iran. *Vet Parasitol* 2005;129:243-51.
<https://doi.org/10.1016/j.vetpar.2005.01.010>
8. Yaghoobi-Ershadi M. Phlebotomine sand flies (Diptera: Psychodidae) in Iran and their role on Leishmania transmission. *J Arthropod Borne Dis* 2012;6:1.
9. Heydarpour F, Akbari Sari A, Mohebbali M, et al. Economic burden of cutaneous and visceral leishmaniasis in Iran in 2013. *Iran J Epidemiol* 2017;13:1-13.
10. Heydarpour F, Sari AA, Mohebbali M, et al. Incidence and Disability-Adjusted Life Years (Dalys) Attributable to Leishmaniasis In Iran, 2013. *Ethiop J Health Sci* 2016;26:381-8.
<https://doi.org/10.4314/ejhs.v26i4.10>
11. Asgari Q, Fakhar M, Motazedian H. Nomadic kala-azar in South of Iran. *Iran J Public Health* 2006;35:85-6.
12. Edrissian G, Hajjaran H, Mohebbali M, et al. Application and evaluation of direct agglutination test in ser-diagnosis of visceral leishmaniasis in man and canine reservoirs in Iran. *Iran J Med Sci* 1996;21:119-24.
13. Alborzi A, Pouladfar GR, Fakhar M, et al. Isolation of Leishmania tropica from a patient with visceral leishmaniasis and disseminated cutaneous leishmaniasis, southern Iran. *Am J Trop Med Hyg* 2008;79:435-7.
<https://doi.org/10.4269/ajtmh.2008.79.435>
14. Nadim A, Navid-Hamidid A, Javadian E, et al. Present status of kala-azar in Iran. *Am J Trop Med Hyg* 1978;27:25-8.
<https://doi.org/10.4269/ajtmh.1978.27.25>
15. Motazedian H, Noyes H, Maingon R. Leishmania and Sauroleishmania: the use of random amplified polymorphic DNA for the identification of parasites from vertebrates and invertebrates. *Exp Parasitol* 1996;83:150-4.
<https://doi.org/10.1006/expr.1996.0059>
16. Alborzi A, Pouladfar GR, Aelami MH. Visceral leishmaniasis; literature review and Iranian experience. *Iran J Clin Infect Dis* 2007;2:99-108.
17. Fakhar M, Ahmad Pour E. An Overview of the Laboratory Diagnostic Procedures of Visceral Leishmaniasis (Kala-Azar). *Med Lab J* 2013;7:45-54.

18. Fakhar M, Rahmati B. Visceral leishmaniasis in Mazandaran province and Review on its current situation in Iran. *J Babol univ med sci* 2011;13:68-75
19. Sakkas H, Gartzonika C, Levdiotou S. Laboratory diagnosis of human visceral leishmaniasis. *J Vector Borne Dis* 2016;53:8.
20. Mohebbali M. Visceral leishmaniasis in Iran: review of the epidemiological and clinical features. *Iran J Parasitol* 2013;8:348.
21. Spittal MJ, Pirkis J, Gurrin LC. Meta-analysis of incidence rate data in the presence of zero events. *BMC Med Res Methodol* 2015;15:42.
<https://doi.org/10.1186/s12874-015-0031-0>
22. J. Sweeting M, J. Sutton A, C. Lambert P. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat med* 2004;23:1351-75.
<https://doi.org/10.1002/sim.1761>
23. Cox D. The continuity correction. *Biometrika* 1970;57:217-9.
<https://doi.org/10.1093/biomet/57.1.217>
24. Asfaram S, Fakhar M, Mohebbali M, et al. Asymptomatic human blood donors carriers of *Leishmania infantum*: potential reservoirs for visceral leishmaniasis in northwestern Iran. *Transfus Apher Sci* 2017;56:474-9.
<https://doi.org/10.1016/j.transci.2017.06.001>
25. Mohebbali M, Edrissian GH, Shirzadi MR, et al. An observational study on the current distribution of visceral leishmaniasis in different geographical zones of Iran and implication to health policy. *Trop Med Infect Dis* 2011;9:67-74.
<https://doi.org/10.1016/j.tmaid.2011.02.003>
26. Faghinaeini F, Mohebbali M, Javadian E. Epidemiology of visceral leishmaniasis in the Kordan region of Savojbolagh, Tehran province. *J Shahid Beheshti Unive Med Sci* 2002;7:9-15.
27. Ashkanifar S, Fata A, Aalami M, et al. Seroepidemiological Study Of Asymptomatic Visceral Leishmaniasis Among Children Living In Rural Areas Of North And Central Khorasan ,Iran. *J Mashhad Univ Med Sci* 2016;59:283-92.
28. Edrissian G, Mohebbali M, Hajjarian H, et al. Kala-Azar Case Finding Using Direct Agglutination. *J Public Health Res* 2003;1:9-16.
29. Mohami M, Mohebbali M, Keshavarz H, et al. Seroepidemiologic study of visceral leishmaniasis in Garmsi county of Ardabil province. *J Public Health Res* 2006;4:45-55.
30. Sarkari B, Pedram N, Mohebbali M, et al. Seroepidemiological study of visceral leishmaniasis in Booyerahmad district, south-west Islamic Republic of Iran. *East Mediterr Health J* 2010;16:1133-6.
<https://doi.org/10.26719/2010.16.11.113>
31. Shirmohammad S, Mohebbali M, Ghalehbin BM, et al. Human visceral leishmaniasis: Seroprevalence survey of asymptomatic adults in an endemic area of Northwestern Iran. *J Biostat Epidemiol* 2017;2:136-42.
32. Fakhar M, Motazedian M, Hatam G, et al. Asymptomatic human carriers of *Leishmania infantum*: possible reservoirs for Mediterranean visceral leishmaniasis in southern Iran. *Ann Trop Med Parasitol* 2008;102:577-83.
<https://doi.org/10.1179/136485908X337526>
33. Fakhar M, Motazedian M, Asgari Q, et al. A New Endemic Focus of Visceral Leishmaniasis in Southern Iran. *Armaghane Danesh J* 2006;11:103-13.
34. Chegeni-Sharafi A, Urmazdi H, Mohebbali M, et al. Seroepidemiology of Visceral Leishmaniasis (Human Infection) by Direct Agglutination Method in the Miankoo Region of Poldokhtar, Lorestan. *J Lorestan Univ of Med Sci* 2005;7:31-5.
35. Fakhar M, Kia AA, Gohardehi S, et al. Emergence of a new focus of visceral leishmaniasis due to *Leishmania infantum* in Golestan Province, north-eastern of Iran. *J Parasit Dis* 2014;38:255-9.
<https://doi.org/10.1007/s12639-013-0307-4>
36. Sarkari B, Gadami F, Shafiei R, et al. Seroprevalence of *Leishmania* infection among the healthy blood donors in kala-azar endemic areas of Iran. *J parasit dis* 2015;39:545-9.
<https://doi.org/10.1007/s12639-013-0393-3>

37. Fakhar M, Motazedian M, Asgari Q, et al. The efficacy of PCR for early diagnosis and detection of asymptomatic cases of visceral leishmaniasis in human and dog. *J Jahrom Univ Med Sci* 2010;8:1-7.
<https://doi.org/10.29252/jmj.8.2.1>
38. Mahmoudvand H, Mohebbali M, Sharifi I, et al. Epidemiological aspects of visceral leishmaniasis in Baft district, Kerman Province, Southeast of Iran. *Iran J Parasitol* 2011;6:1.
39. Fakhar M, Rahmati B, Gohardehi S, et al. Molecular and seroepidemiological survey of visceral leishmaniasis among humans and domestic dogs in Mazandaran province, north of Iran. *Iran J Parasitol* 2011;6:51.
40. Hamzavi Y, Hamzeh B, Mohebbali M, et al. Human visceral leishmaniasis in Kermanshah province, western Iran, during 2011-2012. *Iran J Parasitol* 2012;7:49.
41. Heidari A, Mohebbali M, Kabir K, et al. Visceral leishmaniasis in rural areas of Alborz province of Iran and implication to health policy. *Korean J Parasitol* 2015;53:379.
<https://doi.org/10.3347/kjp.2015.53.4.379>
42. Layegh Gigloo A, Sarkari B, Rezaei Z, et al. Asymptomatic Leishmania Infected Children: A Seroprevalence and Molecular Survey in a Rural Area of Fars Province, Southern Iran. *J trop med* 2018;15:1-6.
<https://doi.org/10.1155/2018/8167247>
43. Masoori L, Kheirandish F, Haghighi A, et al. Molecular-Based Detection of Leishmania infantum in Human Blood Samples in a New Focus of Visceral Leishmaniasis in Lorestan Province, Iran. *J Arthropod Borne Dis* 2018;12:67.
44. Ebrahimzade-Parikhani H, Mohebbali M, Zarei Z, et al. Seroprevalence of visceral leishmaniasis in children up to 12 years old among nomadic tribes from rural areas of Pars Abad, northwestern Iran: an observational study in 2015. *J Arthropod Borne Dis* 2017;11:331.
45. Jahangir A, Akhoundi B, Mohebbali M, et al. Seroepidemiological survey of human visceral leishmaniasis in Ilam province, west of Iran in 2013. *Iran J Parasitol* 2015;10:56.
46. Khazaei S, Mohebbali M, Akhoundi B, et al. Seroprevalence survey of visceral leishmaniasis among children up to 12 years old and domestic dogs in rural areas of Dehloran District, Ilam Province of west part of Iran, 2014. *Novelty in Biomedicine* 2017;5(2):78-84.
<https://doi.org/10.22037/nbm.v5i2.13047>
47. Gorgipoor M, Mohebbali M, Akhoundi B, et al. Human Visceral Leishmaniasis: a Serological Survey in Rural Areas of Dashti District of Bushehr Province, Southern Iran. *Novelty in Biomedicine* 2017;5:54-8.
<https://doi.org/10.22037/nbm.v5i2.13491>
48. Mirsamadi N, Mohebbali M, Atari M, et al. Serological survey of Visceral leishmaniasis (kala-azar) in Azarshahr, Azarbaijan province, northwest of Iran. *Hakim Res J* 2003;6:17-25
49. Alborzi A, Pourabbas B, Shahian F, et al. Detection of Leishmania infantum kinetoplast DNA in the whole blood of asymptomatic individuals by PCR-ELISA and comparison with other infection markers in endemic areas, southern Iran. *Am J Trop Med Hyg* 2008;79:839-42.
<https://doi.org/10.4269/ajtmh.2008.79.839>
50. Torabi V, Mohebbali M, Edrissian G, et al. Seroepidemiology Of Visceral Leishmaniasis By Direct Agglutination Method In Bojnourd City Of North Khorasan Province In 2007. *Iran J Epidemiol* 2008;4:43-50.
51. Mohebbali M, Hamzavi Y, Edrissian GH, et al. Seroepidemiological study of visceral leishmaniasis among humans and animal reservoirs in Bushehr province, Islamic Republic of Iran. *East Mediterr Health J* 2001 ;7:912-7
52. Rakhshanpour A, Mohebbali M, Akhondi B, et al. Serological Survey and Associated Risk Factors of Visceral Leishmaniasis in Qom Province, Central Iran. *Iran J Public Health* 2014;43:50.
53. Visceral leishmaniasis [Internet]. who.int. [cited 1 August 2018]. Available from:

<http://www.who.int/news-room/fact-sheets/detail/leishmaniasis>.

54. Mohebbali M, Edrissian G, Nadim A, et al. Application of direct agglutination test (DAT) for the diagnosis and seroepidemiological studies of visceral leishmaniasis in Iran. *Iran J Parasitol* 2006;1:15-25.

55. Edrissian GH, Ahanchin A, Gharachahi A, et al. Seroepidemiological studies of visceral leishmaniasis and search for animal reservoirs in Fars province, southern Iran. *Iran J Med Sci* 1993;18:99-105.

56. Fakhar M, Mohebbali M, Barani M. Introduction of an endemic focus of kala-azar in Ghom province and seroepidemiological survey on visceral leishmaniasis in human and animal reservoirs (dogs) in this area. *Armaghane-danesh J* 2004;33:43-52.

57. Mohammadi-Kheyraabadi K, Mohebbali M, Mamishi S, et al. Epidemiological Characteristics Of Kala-Azar In Hospitalized Patients In Ardebil Province. *J public Health Res* 2004;2:11-24.

58. Belo VS, Werneck GL, Barbosa DS, et al. Factors associated with visceral leishmaniasis in the americas: a systematic review and meta-analysis. *PLoS Negl Trop Dis* 2013;7:e2182. <https://doi.org/10.1371/journal.pntd.0002182>

59. Lainson R, Rangel EF. *Lutzomyia longipalpis* and the eco-epidemiology of American visceral leishmaniasis, with particular reference to Brazil: a review. *Mem Inst Oswaldo Cruz* 2005;100:811-27. <https://doi.org/10.1590/S0074-02762005000800001>

60. Ertaabklar H, Ozensoy Toz S, Taylan Ozkan A, et al. Serological and entomological survey in a zoonotic visceral leishmaniasis focus of North Central Anatolia, Turkey: Corum province. *Acta Trop* 2005;93:239-46. <https://doi.org/10.1016/j.actatropica.2005.01.002>

61. Rahi AA, Ali MA, Valian HK, et al. Seroepidemiological studies of visceral leishmaniasis in Iraq. *Sch J App Med Sci* 2013;1:985-9. <https://doi.org/10.11648/j.ajbio.20130101.11>

62. Leishmaniasis in Pakistan. [Internet]. who.int. [cited 2 August 2018]. Available from: http://www.who.int/leishmaniasis/resources/Pakistan_CP_2014.pdf?ua=1&ua=1.

63. Leishmaniasis in Saudi Arabia. [Internet]. who.int. [cited 2 August 2018]. Available from: http://www.who.int/leishmaniasis/resources/SaudiArabia_CP_2014.pdf.

64. Ashford DA, David JR, Freire M, et al. Studies on control of visceral leishmaniasis: impact of dog control on canine and human visceral leishmaniasis in Jacobina, Bahia, Brazil. *Am J Trop Med Hyg* 1998;59:53-7. <https://doi.org/10.4269/ajtmh.1998.59.53>

65. Shokri A, Fakhar M, Teshnizi SH. Canine visceral leishmaniasis in Iran: a systematic review and meta-analysis. *Acta Trop* 2017;165:76-89. <https://doi.org/10.1016/j.actatropica.2016.08.020>

66. Cardoso Ls, Rodrigues M, Santos H, et al. Sero-epidemiological study of canine *Leishmania* spp. infection in the municipality of Alijó (Alto Douro, Portugal). *Vet Parasitol* 2004;121:21-32. <https://doi.org/10.1016/j.vetpar.2004.02.008>

67. Edrissian GhH, Hajjarian H, Mohebbali M, et al. Application and evaluation of direct agglutination test in ser-diagnosis of visceral leishmaniasis in man and canine reservoirs in Iran. *Iran J Med Sci* 1996;21:119-24.

68. Andrade C, Silva O, Andrade P, et al. A direct agglutination test discriminative toward Chagas' disease for the diagnosis of visceral leishmaniasis in Brazil: preliminary results. *Ann Inst Pasteur Immunol* 1987;138:457-9. [https://doi.org/10.1016/S0769-2625\(87\)80056-9](https://doi.org/10.1016/S0769-2625(87)80056-9)

69. Boelaert M, Lynen L, Desjeux P, et al. Cost-effectiveness of competing diagnostic-therapeutic strategies for visceral leishmaniasis. *Bull World Health Org* 1999;77:667.

Sistematični pregled i metaanaliza humane visceralne leišmanijaze u Iranu

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SAŽETAK

Visceralna leišmanijaza je parazitska bolest izazvana vrstom *Leishmania donovani* i smatra se endemskom zoonozom u Iranu. Cilj ove studije bilo je određivanje prevalencije humane visceralne leišmanijaze u Iranu. Podaci su sistematično prikupljeni za period od 1985. godine do 2018. godine u islamskoj republici Iran, iz sledećih elektronskih baza: PubMed, Google Scholar, Science Direct, Scopus, Web of Science, Magiran, Irandoc, Iranmedex and Scientific Information Database (SID). Naše kriterijume zadovoljilo je ukupno 29 studija, koje su izveštavale o prevalenciji visceralne leišmanijaze u različitim delovima Irana. Za određivanje heterogenosti korišćeni su Q test kao i I² statistika. Egerov i Begov test primenjen je kako bi se utvrdila pristrasnost publikovanja. Zbirna, prosečna prevalencija visceralne leišmanijaze merena modelom slučajnog efekta procenjena je na 1% (95% CI: 1 - 2) u gradskim sredinama, 3% (95% CI: 2 - 4) u ruralnim sredinama i 2% (95% CI: 2 - 3) ukupno.

Najveći broj slučajeva visceralne leišmanijaze u poslednje 33 godine zabeležen je u severozapadnim i južnim provincijama Irana. Utvrđen je visok stepen heterogenosti (I² = 98.2%, Q test: p = 0,0002); Begovi i Egerovi testovi bili su značajni kod utvrđivanja pristrasnosti publikovanja. Nakon korekcije, ukupna prevalencija procenjena je na 0,3% (95% CI: 0,2 – 0,9). Prevalencija visceralne leišmanijaze u Iranu bila je 0,3%. Ova stopa bila je znatno viša u severozapadnim i južnim delovima zemlje. Ovi podaci su korisni za uvođenje programa kontrole bolesti.

Ključne reči: crna groznica, *Leishmania infantum*, prevalencija, Iran