Original Article

Spatiotemporal Variability of Zoonotic Cutaneous Leishmaniasis Based on Sociodemographic Heterogeneity. The Case of Northeastern Iran, 2011–2016

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SUMMARY: Zoonotic cutaneous leishmaniasis (ZCL) is one of the most prevalent zoonoses in Iran, especially in central and northeastern Iran. This research aimed to examine whether there were spatiotemporal clusters of ZCL cases, and if so, whether there were differences in clustering according to age, sex, area of residence, and occupation. Spatial analysis, including global and local spatial autocorrelations, inverse distance weighting, and space-time scan statistics, were used to determine potential clusters in the villages of Golestan from 2011–2016. Several spatially significant ($p < 0.05$) clusters were observed in the north and northeastern regions, and most persisted until the last year of the study period. Children (0–10 years) living in rural settings were more likely to have an infection than those living in other areas. Although the disease was centered in the northern regions, housekeepers, females, and patients aged 21–30 and 41–50 years were found to be the high-risk groups in the southern areas. The seasonal pattern indicated that the outbreak mainly began in late summer, peaked in October, and diminished in December. By exploring spatiotemporal variations of ZCL by sociodemographic information, this study was able to identify priority areas for decision-makers in healthcare and resource allocation.

INTRODUCTION

Leishmaniasis, known as the second most common vector-borne protozoa disease after malaria, is a neglected tropical disease even though it causes considerable damage to the health and economy of a number of societies (1). In Iran, the total number of cases of cutaneous leishmaniasis (CL) from 2005 to 2018 was 280,047, which ranked it the fourth highest worldwide after Syria, Afghanistan, and Brazil (2). Although this disease has been eradicated from several developed countries, it remains a considerable burden in Iran (2).

According to CL cases reported in Iran, the most common form of CL to date is zoonotic CL (ZCL). Approximately 80% of ZCL cases have been concentrated in central and northeastern rural areas of Iran (3). In the 6 years from 2011 to 2016, Golestan province was identified as a severely endemic area in Iran, and the rate of ZCL increased from 44.3 per

100,000 in 2011 to 61.6 per 100,000 in 2016 (the Center for Disease Control and Prevention, CDC), raising serious concerns for its inhabitants. In this province, the primary causative agent of ZCL is *Leishmania major* (4). *Rhombomys opimus* and *Phlebotomus papatasi* are, respectively, the main reservoir (rodent) and vector (sand fly) agents of *Leishmania major* in Golestan (5,6). To date, no vaccines have been developed for leishmaniasis (7).

The distribution of ZCL cases in Golestan is not homogeneous since it depends on environmental and climatic factors which affect the biological behavior of the sand flies and rodents (8,9). Identifying the spatially and temporally significant high-risk areas of the disease could be an effective tool for health policymakers to use to prevent, predict, and control it (10,11). To increase the discoverability of highly aggregated cases (clusters) through space and time, a requirement of health authorities, Geospatial Information Systems (GIS) can be utilized (12–17). Substantial evidence suggests that the prevalence of the disease varies by sociodemographic factors (18). One survey conducted in the south of Iran indicated that rural areas and patients aged 1 to 30 years had the highest prevalence of CL (19). Another study showed that more males were infected than females (20). In Iran, Holakouie-Naieni et al. (6) demonstrated the spatial distribution of CL using GIS, and Ramezankhani et al. (21) identified the high-risk areas for CL using spatial analysis. A study conducted in China explored spatiotemporal variations

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Fig. 1. The studied region, Golestan province located in the northeast of Iran and its counties.

in visceral leishmaniasis (16). Studies on other diseases have also suggested that future epidemiological efforts should examine potential factors that affect disease clusters (22,23). Identifying high-risk areas for susceptible groups can be used as a guideline for local health authorities to more equitably allocate health resources during ZCL epidemics to control and reduce the severity of the outbreak. Extensive studies on ZCL have examined the heterogeneity of spatial and temporal factors but have not explicitly investigated spatiotemporal differences within clusters according to the cases' sociodemographic information (16,24–26).

To address this research gap, this study utilized spatial analysis and space-time scan statistics to determine spatiotemporal differences within ZCL clusters according to age, sex, area of residence, and occupation in the villages of Golestan province between 2011 and 2016. In addition, unlike previous studies that have examined only a few epidemiological aspects of the disease (27–29), this study described more of the clinical signs. The findings of this study may assist health policymakers in better understanding how sociodemographic factors may affect inhabitants' health in endemic areas of the disease in order to optimize resource allocation for at-risk groups.

MATERIALS AND METHODS

Study area: Golestan province is in the northeast of Iran (lying between 36° 30' to 38° 08' northern latitude and 53° 57' to 56° 22' eastern longitude), as shown in Fig. 1. This province, which has 14 counties, 33 cities, 27 districts, 60 rural districts, and 1,024 villages, is where all our analysis was based. The topography in Golestan is extremely diverse, with a vast range in elevation from -45 m near the Caspian Sea to 3,820 m in the mountains of the Jahan-Nama Forest, resulting in various geographical conditions and climates.

Data Preparation: Demographic data on the 4,335 confirmed cases, including sex, age, occupation, travel status, area of residence, clinical symptoms, date of

onset, treatment regimen, simultaneous infections among family members, underlying diseases, and location of infection were supplied by the CDC of Golestan province. We used census data from patients who were referred to the Golestan University of Medical Sciences clinics and whose microscopic test results were positive for *Leishmania* bodies. The number of clinics in Golestan are limited; therefore, the staff are trained at one site and all data are collected in the same way, which ensures that the registration system of human ZCL is uniform throughout this province. The population of each village was obtained from the 2016 census data from the Statistical Center of Iran. Geospatial data, such as province boundaries (polygons) and the locations of villages (points), were generated from the National Cartographic Center of Iran (NCC). To identify spatial clusters, the ZCL incidence rate was calculated based on Equation 1 to analyze the spatial variation of the disease. The population at risk included people who had the potential to become infected (30). Since the disease occurs in both sexes and across all ages, all inhabitants of each village were assumed to be at risk of developing the disease (exposed population). All analyses were carried out at the village level (point layers).

$$\text{Incidence rate} = \frac{\text{number of diagnosed cases in a specified period}}{\text{population at risk in that period of time}} \times 100,000$$

For space-time analysis, ZCL records were stratified by sex (2, male and female); area of residence (2, rural and urban); age groups (9, aged 0–10; 11–20; 21–30; 31–40; 41–50; 51–60; 61–70; 71–80; > 81); and occupation (10, child, driver, employee, housekeeper, farmer, military (i.e., member of the armed forces), student, worker (i.e., a social group that consists of people who do physical work to get money), unemployed, and other).

Methodology: The epidemiological and temporal characteristics of the ZCL cases in the study area were described. Inverse distance weighting interpolation

Fig. 2. Epidemiological factors of ZCL patients. (A) Cases by year and gender. (B) Cases by age and gender. (C) Cases by age and year. (D) Cases by occupation.

was used to predict the distribution of the incidence rate across the province (31). Global and local spatial clustering approaches were carried out using the Moran's I index and Getis-Ord G_i^* statistic, respectively.

The global Moran's I index explores overall spatial autocorrelation, indicating whether a general pattern of the disease is clustered, random, or dispersed, according to the location of each village and its incidence rate at the same time (32).

Moran's I index, since it is a global approach, cannot illustrate the structure of the disease clusters locally. Therefore, the Getis-Ord G_i^* statistic was chosen to identify the spatial clusters of high and low values (hot spots and cold spots, respectively) (33).

To examine space-time clusters, the space-time scan statistic developed by Kulldorff (34) was employed. Previous studies have applied this statistic to assess clusters of influenza (35) and Ebola (36). A cylinder was used to scan high rate areas. The base of the cylinder refers to the spatial domain, and its height corresponds to the temporal dimension (37). The number of observed cases was compared to the number of expected cases through the calculation of the space-time permutation model (37). A cluster is a cylinder whose number of observed cases is statistically significantly larger than the expected value.

Ethics approval and consent to participate: Since private information of human records was not used for our study, it was not collected. Thus, preparing ethical approval was not necessary.

RESULTS

Demographic characteristics: Over the study

period, males were infected more than females (55.98% vs. 44.02%, respectively). However, this difference was minimal in 2016 since the number of infected females increased compared to the first five years of the study period, as shown in Fig. 2-A. Around 92% of the cases were aged ≤ 50 years, and cases aged < 10 years were found to be a high-risk group (40/78%), as shown in Fig. 2-B. The age distribution of males and females was not equal. Of the females, 47.06% were aged ≤ 10 years, whereas only 35.85% of males were in this age group. Fig. 2-C shows, categorized by age group, the cases diagnosed annually. Regarding occupation, the majority of patients were children (33%), followed by housekeepers (19%) and students (17%) (Fig. 2-D). Most cases resided in rural areas (80.88%), and the rest inhabited urban regions. Less than 1% of all patients (0.39%) had a history of ulcers. Less than 50% (41.6%) of the cases had travelled to endemic areas. Regarding the number of lesions, most of the cases (92.13%) had 0–5 ulcers. A total of 2,952 cases (68.10%) were treated with a systemic glucantime regimen. Of the 4,335 patients, 1,660 (38.29%) had family members who were simultaneously infected. Most cases did not have underlying diseases (98.03%).

Temporal trends: The incidence of cases according to year and month were diverse throughout the study period (Fig. 3). From 2011 to 2013, the annual number of cases decreased, reaching a minimum of 605 in 2013 then increased to a maximum of 920 in 2016. Overall, a growth rate was observed over the 6-year study period. A seasonal trend was observed, as the ZCL outbreak started in July, peaked in October, and waned in December during the six years (Fig. 3).

Spatial analysis: The results of Moran's I and its z-scores, which ranged from 4.02 to 13.22, are displayed

Fig. 3. ZCL morbidity by year and month from 2011 to 2016, Golestan province, Iran.

Table 1. Summary of spatial autocorrelation descriptions obtained by Moran's I analysis in Golestan province, Iran, during 2011-2016

Year	Moran's Index	Expected Index	Variance	Z-score	Distance Threshold (meter)	Pattern
2011	0.022470	-0.000978	0.000010	7.252571	23516.6600	Clustered
2012	0.052465	-0.000978	0.000017	12.891738	19650.8000	Clustered
2013	0.018946	-0.000978	0.000025	4.019109	13852.0200	Clustered
2014	0.042099	-0.000978	0.000016	10.747798	19650.8000	Clustered
2015	0.075738	-0.000978	0.000034	13.080239	13852.0200	Clustered
2016	0.052595	-0.000978	0.000016	13.220044	19650.8000	Clustered
2011-2016	0.084540	-0.000978	0.000035	14.519405	13852.0200	Clustered

in Table 1. These prove the high level of ZCL clustering throughout the study area in the 6-year period. As the high z-score values suggest, the spatial pattern of the disease did not follow a stochastic distribution.

To determine high- and low-risk areas, the outputs of the hot spot analysis were interpolated using the inverse distance weighting method (Fig. 4). The results indicated that statistically significant hot spot areas (black) were located in north and northeastern Golestan. Further, statistically significant cold spot areas (white) were mainly concentrated in the south, west, and central parts of the province. Additionally, most of the hot spot regions were aggregated in rural areas.

Spatiotemporal analysis: Spatiotemporal scan

statistics for ZCL cases in the total population of the Golestan villages detected eight significant clusters (Table 2). The most likely cluster, which had the maximum likelihood ratio test statistic, consisted of 3 villages located in the northeast areas of the province (Fig. 5). The secondary clusters were mainly concentrated in the northern and northeastern regions of the province. The most likely cluster persisted for a longer period (1 year) than the other clusters (Table 2).

Eight significant clusters were detected for males (Table 2). The most likely cluster for males consisted of 6 villages located at the common border of Gonbad Kavus, Maraveh Tappeh, and Kalaleh counties (Fig. 5). This cluster closely mirrored that of the total population

Fig. 4. Hot spot analysis of ZCL incidence rate, resulting from Getis-Ord Gi* statistic, Golestan province, Iran from 2011 to 2016. Black and white regions show clusters of high and low values (hot and cold spot), respectively.

in terms of location, time, and size. The first secondary cluster for females persisted from late-2011 to mid-2014 and encompassed a large area in some highly populated counties in the south of the province (Fig. 5).

According to the area of residence, the clusters for the rural population were similar to the clusters for the total population, albeit with a slight difference. This can be attributed to the density of the rural areas. Only two significant urban clusters were observed in highly populated cities in the north and south of the province (i.e., Gonbad Kavus and Gorgan, respectively).

Clusters related to age groups 0–10, 11–20, and 31–40 were mostly concentrated in the northern and northeastern regions of the province, whereas clusters for age groups 21–30 and 41–50 were observed in the south of the province. There were no significant clusters observed for the age groups older than 50 years because there were very few ZCL cases in these groups.

The most likely cluster observed for children consisted of 39 villages in Gonbad Kavus county, which persisted from late-2014 to mid-2015. The most likely cluster for drivers was found in Aq Qala county in late 2016. The most likely cluster for the employee group was detected in the same region as the worker group, but persisted for different periods (Fig. 5 and Table 2). A most likely cluster was also observed for the military group, which consisted of 68 villages located in the north of the province where most of the province's garrisons were located. The most likely cluster for housekeepers was similar to the first secondary cluster for females. Students had a most likely cluster that was reasonably concordant with the most likely cluster for the total population. No significant spatiotemporal clusters were detected for the unemployed group or the other occupations.

Table 2. Summary of statistically significant spatiotemporal clusters of ZCL cases in the study area, during 2011-2016 by demographic characteristics

Category	Cluster	Start Date	End Date	No. of Villages	Radius	No. of Observed Cases	No. of Expected Cases	Test Statistic	P-value ¹⁾
All populations	Most likely cluster	2013/10/1	2014/10/31	3	5.472603341	88	27.5727797	42.12331459	1.67E-15
	Secondary cluster 1	2014/11/1	2015/1/31	69	16.21769292	55	13.05190311	37.36809313	2.2704E-13
	Secondary cluster 2	2015/6/1	2015/8/31	23	13.32524377	47	11.73587082	30.09247092	4.01848E-10
	Secondary cluster 3	2016/8/1	2016/11/30	11	20.2653098	119	56.79584775	26.26984541	2.04451E-08
	Secondary cluster 4	2015/10/1	2015/10/31	75	24.13707438	55	20.01822376	20.74836565	5.96391E-06
	Secondary cluster 5	2012/11/1	2012/12/31	2	7.227451164	15	1.972318339	17.42453044	0.000181696
	Secondary cluster 6	2016/9/1	2016/11/30	6	7.330180005	55	22.70634371	16.48545239	0.000476993
Male	Secondary cluster 7	2012/10/1	2013/1/31	39	43.63176139	30	8.879584775	15.45450209	0.001375822
	Most likely cluster	2013/10/1	2014/10/31	6	7.407412297	46	13.70580964	23.62065021	1.10172E-07
	Secondary cluster 1	2014/11/1	2015/1/31	59	16.88396952	28	6.172229089	20.61097779	2.75444E-06
	Secondary cluster 2	2015/6/1	2015/8/31	23	13.32524377	28	6.21631644	20.45537892	3.25318E-06
	Secondary cluster 3	2012/9/1	2012/9/30	4	3.723674117	7	0.339925834	14.52363942	0.00184988
	Secondary cluster 4	2012/3/1	2012/7/31	93	19.45117283	19	4.03461063	14.52197719	0.001853169
	Secondary cluster 5	2015/9/1	2015/10/31	23	14.69695987	41	16.31644005	13.22059787	0.007433221
Female	Secondary cluster 6	2014/12/1	2015/6/30	15	29.610101	9	0.883395138	12.78785276	0.013
	Secondary cluster 7	2013/2/1	2013/9/30	30	8.955285042	19	4.54223321	12.77484652	0.013
	Most likely cluster	2014/9/1	2014/10/31	8	12.1577576	30	6.210691824	23.60785788	4.73035E-08
	Secondary cluster 1	2011/10/1	2014/6/30	340	57.98402996	126	66.98113208	21.55314959	4.62104E-07
	Secondary cluster 2	2014/11/1	2015/1/31	46	14.70286038	26	6.112159329	17.85973308	2.77984E-05
	Secondary cluster 3	2012/11/1	2013/9/30	7	18.80007231	27	8.452830189	12.89973335	0.006792107
	Secondary cluster 4	2015/7/1	2015/8/31	23	13.32524377	19	4.635220126	12.49391332	0.010633256
Rural	Secondary cluster 5	2015/10/1	2015/10/31	73	23.57141058	26	8.254716981	12.16795987	0.013
	Secondary cluster 6	2015/9/1	2016/11/30	8	17.64603857	77	41.94968553	12.04569923	0.014
	Secondary cluster 7	2013/1/1	2013/7/31	83	14.38458463	5	0.187106918	11.62074775	0.027
	Most likely cluster	2013/10/1	2014/10/31	3	5.472603341	88	27.35111238	42.71791291	1E-17
	Secondary cluster 1	2014/11/1	2015/1/31	69	16.21769292	55	12.91043925	37.87637309	3E-15
	Secondary cluster 2	2015/6/1	2015/8/31	23	13.32524377	47	12.70678836	27.35219594	5.76935E-10
	Secondary cluster 3	2016/8/1	2016/11/30	11	20.2653098	99	44.00656018	25.71300638	3.84067E-09
Urban	Secondary cluster 4	2011/9/1	2014/7/31	205	40.66201301	175	102.4346834	21.93690785	3.02655E-07
	Secondary cluster 5	2012/11/1	2012/12/31	2	7.227451164	15	2.032230462	17.04000013	8.71753E-05
	Secondary cluster 6	2016/9/1	2016/11/30	6	7.330180005	55	23.58471192	15.29723707	0.000653989
	Secondary cluster 7	2012/10/1	2012/12/31	34	43.01088978	20	4.668568169	13.79978049	0.003689825
	Secondary cluster 8	2012/10/1	2013/11/30	16	8.601771154	29	9.381061038	13.16568928	0.007666718
	Secondary cluster 9	2011/6/1	2011/9/30	3	15.45398796	22	5.845978323	13.03965996	0.008864325
	Most likely cluster	2014/9/1	2016/12/31	259	71.92025948	161	106.3908323	14.20821573	6.23756E-05
Urban	Secondary cluster 1	2011/12/1	2014/9/30	486	68.48755296	187	134.9831122	10.93739207	0.002876629

Age 0-10	Most likely cluster	2013/10/1	2014/10/31	6	7.407412297	53	16.83257919	24.99837638	4.45603E-09
	Secondary cluster 1	2016/8/1	2016/11/30	11	20.2653098	87	45.45475113	15.43943012	0.000213579
	Secondary cluster 2	2011/4/1	2011/8/31	154	26.92268145	32	10.25	14.81578558	0.000431407
	Secondary cluster 3	2015/10/1	2015/11/30	11	9.600069333	26	7.496606335	13.9289856	0.001172085
	Secondary cluster 4	2012/7/1	2013/9/30	6	17.53060201	96	54.31561086	13.50225189	0.001895646
	Secondary cluster 5	2013/2/1	2013/9/30	32	8.959035381	10	1.191176471	12.48960868	0.005925604
Age 11-20	Secondary cluster 6	2011/11/1	2012/4/30	147	23.17099613	8	0.778280543	11.43393453	0.018
	Most likely cluster	2015/10/1	2015/10/31	14	10.99970004	14	2.804347826	11.40645432	0.013083839
	Secondary cluster 1	2013/10/1	2013/11/30	22	6.217657759	11	1.739130435	11.09132681	0.013
Age 21-30	Secondary cluster 2	2014/11/1	2014/12/31	39	13.04810148	13	2.555072464	10.78412074	0.025
	Most likely cluster	2012/10/1	2013/4/30	72	20.86048721	15	3.034438776	12.09693136	0.005225098
Age 31-40	Secondary cluster 1	2011/11/1	2011/12/31	50	13.48948081	7	0.505102041	11.93443166	0.006361212
	Most likely cluster	2011/5/1	2011/9/30	46	28.73899283	15	3.221006565	11.4505681	0.00429725
Age 41-50	Secondary cluster 1	2013/12/1	2015/1/31	39	19.29725235	18	5.133479212	9.9010109	0.026
	Most likely cluster	2013/2/1	2014/5/31	265	42.57193848	21	6.98630137	9.44860142	0.029
Childhood	Most likely cluster	2014/10/1	2015/7/31	39	21.11933579	44	15.79081272	17.166602	2.32909E-05
	Secondary cluster 1	2013/10/1	2014/9/30	6	7.407412297	30	8.662897527	16.09003068	7.84104E-05
	Secondary cluster 2	2012/7/1	2013/9/30	8	16.71033049	83	47.03038869	11.6535591	0.01157535
	Secondary cluster 3	2011/12/1	2012/4/30	92	17.12080151	5	0.207773852	11.11961399	0.018
Driver	Most likely cluster	2016/10/1	2016/11/30	32	15.29351313	6	0.685714286	7.837763669	0.011
	Secondary cluster 1	2012/6/1	2012/7/31	18	8.07446983	5	0.476190476	7.332406106	0.033
Employee	Most likely cluster	2013/9/1	2013/10/31	49	37.60357058	6	0.965517241	6.155663729	0.018
Farmer	Most likely cluster	2011/12/1	2013/11/30	194	27.04182376	19	5.507614213	10.522361	0.002779992
Housekeeper	Most likely cluster	2011/9/1	2013/10/31	346	65.65921493	91	47.11217184	17.2609094	1.38553E-05
	Secondary cluster 1	2014/9/1	2014/10/31	17	15.1949038	15	2.718377088	13.42934213	0.00124714
Military	Most likely cluster	2011/4/1	2012/9/30	68	52.19161851	29	7.827715356	17.69620782	2.03796E-07
Student	Most likely cluster	2013/10/1	2014/10/31	3	5.472603341	34	10.2367688	17.45296961	4.09126E-06
	Secondary cluster 1	2014/11/1	2014/12/31	39	13.04810148	13	1.516713092	16.53848114	1.26753E-05
	Secondary cluster 2	2015/11/1	2016/10/31	43	39.1372527	59	28.66295265	12.93450682	0.001091803
Worker	Most likely cluster	2012/11/1	2012/12/31	29	32.5333749	6	0.502793296	9.421290301	0.047

¹⁾: Statistical significance was calculated based on a Monte Carlo simulation of 999 repetitions and statistical significance at 0.05.

Fig. 5. Spatiotemporal patterns of ZCL cases among the villages of Golestan province by demographic factors.

DISCUSSION

This study indicates the existence of spatiotemporal agglomerations of ZCL cases according to sociodemographic factors in Golestan. The result of Moran's I index revealed that the ZCL incidence rate in villages of Golestan province had global spatial autocorrelation (clustered) over the study period. In addition, the hotspot analysis highlighted high and low endemic areas, which local health authorities can utilize as a substantial guideline to more equitably allocate health facilities to endemic areas during epidemics.

Based on the results of the space-time scan statistics, most most likely clusters were significantly associated with areas in the north and northeastern regions of the province, confirming the results of the hot spot analysis. Previous investigations in this province have had similar findings (26,38). Moreover, these clusters were found to occur in the last months of a year, especially in October, which is in line with the temporal trend observed in this study.

Children less than 10 years old living in the northern and northeastern regions of the province have more exposure to infection. Although the disease is more common in the northern areas of the province, the existence of highly significant clusters for housekeepers, females, and patients aged 21–30 and 41–50 years in the southern regions requires further attention from health officials. Consistent with the literature (18,26), the rural population was found to be at higher risk of exposure to the disease than urban inhabitants. Although there are studies that have identified clusters of the disease in space and time (16,24–26), many of them have not explicitly examined space-time clusters for patients based on sociodemographic factors.

By tracking the hotspots, this study demonstrated the

dynamics of ZCL throughout the study area, as shown in Fig. 4. Infection aggregation moved from the north toward the northeast and east in the first three years of the study period, and then emerged in the northern and central regions of the province. The displacement of high infection areas was likely a result of environmental changes, which caused vectors and reservoirs to migrate, and, in turn, caused movement in case aggregation (39).

The temporal pattern found in this study was partially consistent with the seasonal trend of ZCL found in previous studies (9,40). Since the incubation period of the disease is approximately four months, and the maximum activity of sand flies in the studied area lasts from mid-spring to the end of summer (9), it was expected that most cases would occur in the Fall. This can be observed in the seasonal pattern obtained in this study. It is worth noting that preventive measures to control and reduce the number of cases, such as using insecticides and protective nets, should be taken at the beginning of the warm season, since this corresponds to the significant increase in sand flies in the study area.

Based on demographic results, children aged ≥ 10 years were identified as the most at-risk group. This could be because older people are likely to have been exposed to the infection at least once during their lifetime and thus obtained lifelong resistance and higher herd immunity (41). This partially corresponds to the results of the ulcer history in this study. During the study period, ZCL was more common in males than in females, but this difference reached its minimum in the last year of the study period (18,42,43). Although sex hormones can affect immunity to the disease (44), there is no convincing explanation for this difference. However, behavioral characteristics, such as men's habit of covering less of their bodies than women in the warm months, may make them more susceptible to

sand fly bites than women (26). The proportion of ZCL cases aged ≤ 10 years gradually increased from 32% in 2011 to 51% in 2016, suggesting that health authorities should pay close attention to this high-risk group.

This study may help epidemiologists and public health officials to understand where, when, and why this disease occurs in order to fine-tune screening programs, which highlights the value of epidemiological surveillance in the field of medical geography. To extend previous studies, this detailed investigation not only described the spatial and temporal trends of ZCL by demographic factors, but also explained the epidemiological aspects of the disease in the studied area. According to the results of the present study, it can be concluded that ZCL is becoming a grave public health problem in Golestan province, especially in the north and northeast areas identified as hot spots. The clusters detected by sociodemographic characteristics varied significantly, revealing areas where health center resources may be inadequate. More studies need to be carried out to explore the reasons the detected clusters exist, especially in the southern regions of the province where high-risk clusters were observed for housekeepers, females, and patients aged 21–30 and 41–50 years. Meanwhile, to establish control strategies, this research could serve as a foundation to detect how the behavior of this disease changes over time, space, and demographic factors. In addition, the seasonal pattern observed can serve as an efficient tool for early warning systems to be developed to prevent outbreaks. Additionally, by identifying disease-prone regions, health insurance institutions can adjust payment plans for high-risk groups.

The current study has limitations that may impede the explicit characterization of the spatiotemporal pattern of the disease. First, the healthcare surveillance system for ZCL patients in Iran is passive, and only information concerning cases who refer to health centers for treatment are recorded, thus the underreporting of cases in our study is a concern. Since ZCL spread depends on determinants related to climate, the ecology of the area, environmental changes, the culture (45), and information about reservoirs and vectors, exploring these may provide a more realistic viewpoint of the spatial and temporal nature of ZCL to mitigate spatial inequalities caused by the disease.

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Conflict of interest None to declare.

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