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RESEARCH ARTICLE

A time series analysis of environmental and metrological factors impact on cutaneous leishmaniasis incidence in an endemic area of Dehloran, Iran

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Abstract The aim of this study was to investigate the relationship between the environmental and metrological variables and cutaneous leishmaniasis (CL) transmission and its prediction in a region susceptible to this disease prevalence using a time series model. The accurate locations of 4437 CL diagnosed from 2011 to 2015 were obtained to be used in the time series model. Temperature, number of days with temperature over 30 °C, and number of earthquake were related to CL incidence using the Seasonal Auto-correlated Integrated Moving Average (SARIMA) model according to the Box-Jenkins method. In addition, the relationship between land use and surface soil type in 500- and 1000-m radius around the CL patients were investigated. The SARIMA models showed significant associations between environmental and meteorological variables and CL incidence adjusted for seasonality and auto-correlation. The result indicated that there are need more robust preventive programs in earthquake-prone areas with high temperature and inceptisol soil type than other areas. In addition, the region with these characteristics should be considered as high-risk areas for CL prevalence.

Keywords Cutaneous leishmaniasis · Environmental factors · Earthquake · Time series analysis

Introduction

Reports indicate that leishmaniasis is endemic in 66 countries in the Old World and 22 countries in the New World. Three hundred and fifty million people are estimated to be at leishmaniasis risk, and 12 million prevalence is estimated to occur. Cutaneous leishmaniasis (CL) and visceral leishmaniasis (VL) are two types of leishmaniasis with an estimated annual incidence of 1–1.5 and 0.5 million cases, respectively (Desjeux 2001; Reithinger et al. 2007).

CL is a zoonotic skin disease which is transferred to healthy humans through the bite of infected female phlebotomine sand flies. About 90% of the total CL cases occur in eight countries around the world, one of them is Iran (Doudi 2011). The most important species of sand flies responsible for CL transmission are *Phlebotomus* spp. (in Europe, North Africa, the

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Middle East, and Asia) and *Lutzomyia* spp. (from southern USA to northern Argentina) (Killick-Kendrick 1999). Several *Leishmania* spp. can cause cutaneous leishmaniasis in human beings, although most infections probably remain symptomless (Murray et al. 2005). The common CLs in Iran are zoonotic CL (ZCL) and anthroponotic CL (ACL). ZCL is the most abundant endemic CL in rural areas of 17 out of 31 provinces in Iran, and it is considered as an important health problem in these provinces (Gholamrezaei et al. 2016; Mokhtari et al. 2016). The reservoir and vector for ZCL are recognized to be desert rodents and *Leishmania major* sand flies, respectively. Human proximity to the reservoir caused by agricultural activities and housing and residency near the active colonies of rodents can increase the chance of transmission (Gholamrezaei et al. 2016; Nadim et al. 2008; Rajabi et al. 2016).

CL is a multi-reservoir disease, and its reservoirs and consequently its spread rigorously depended on environmental factors (Mokhtari et al. 2016; Salahi-Moghaddam et al. 2015) such as temperature, humidity, land use, and other unknown environmental factors (Bavia et al. 2005; Cortes et al. 2012; Salah et al. 2007). Previous studies demonstrated that the spread of CL is negatively associated with relative humidity and has a positive relationship with the annual rainfall rate (Salah et al. 2007; Salahi-Moghaddam et al. 2015). The risk maps developed by GIS (geographic information system) in India demonstrated that the phlebotomine sand fly density infected with CL around swampy areas and regions close to rooted trees and sugar cane farms is more than other regions (Bhunia et al. 2012; Sudhakar et al. 2006). Simultaneous use of models and GIS to determine the spread regions of CL and to predict the regions that may turn into an infected situation in the future due to similar environmental conditions can be of great importance in disease control (Adegboye et al. 2016; Bavia et al. 2005; Chalghaf et al. 2016). The present study was aimed to find the relationship between the potentially predictive environmental variables (PPEVs) for the transmission of CL and prediction of the regions susceptible to the disease spread in the study region. We believe that if the health officials know the role of the environmental factors in the disease prevalence, they can prevent their spread and severe complications by doing effective interventions to control the environmental factors in the susceptible areas.

Materials and methods

Ethics statement

All necessary agreements for this study were obtained from the Ethics Committee of Ilam University of Medical Sciences (No: IR.MEDILAM.REC.1394.173).

Study area

Dehloran is located in western Iran at 47′ 10″ longitude and 32′ 41″ latitude with a population of about 60,000 and total surface area of 6229 km^2. It has about 220-km common borderline with Iraq. This city is recognized as one of the endemic regions of CL in the Middle East (Nejati et al. 2014). Figure 1 shows the location and land use of this city in Iran. The land use map was taken from Ilam province Geology Center. Its temperature varies from moderate in the north to warm and dry in the south. The annual mean rainfall in the northern and southern regions of the city is 700 and 150 mm, respectively. The lack of possibility to provide appropriate hygienic services during the Iran-Iraq war in 1981–1989 and movements of Iranian and Iraqi military forces beside the environmental conditions have contributed to the prevalence of some contagious diseases such as CL in this region (Nejati et al. 2014).

Collection and preparation of disease data

Exact postal addresses of all the CL patients with CL recognized from 2011 to 2015 were obtained from Healthcare and Therapeutic Centers of the Dehloran city. Since the first symptoms of the disease appear about 2 months after the biting by phlebotomine sand flies (Ali-Akbarpour et al. 2012; Salahi-Moghaddam et al. 2015; Yoosefi and Vakil 2007), therefore, morbidity time was assumed 2 months before in order to adjust the morbidity time with the environmental variables. For example, if the time of the first symptoms was recorded in July, the morbidity time was assumed in May. Based on their postal addresses, the exact geometric locations of their residence were allocated according to latitude and longitude in the Universal Transverse Mercator system. Mobile GPS device (eTrex 20 Garmin, USA) was used to record the latitude (*Y*) and longitude (*X*) of the locations. On this basis, the exact locations of 4437 CL patients for each month and year were prepared for use in GIS.

Potentially predictive environmental variables (PPEVs)

The meteorological and rainfall data were obtained from the Ilam Meteorological Organization and the information related to the earthquake was provided by Iranian Seismological Center, Institute of Geophysics of Tehran University. Then, the temperature was classified into two forms: monthly mean temperature and number of days per month with a daily mean temperature more than 30 °C. The number of earthquakes with the intensity of 3.5 Richter and more occurred in the study area from 2011 to 2015 was arranged based on monthly and yearly scale. The annual mean of rainfall in the whole county during 5 years was obtained and classified. Other PPEVs for the incidence of CL such as land use, elevation, surface soil type, and rainfall isohyets were prepared as vector

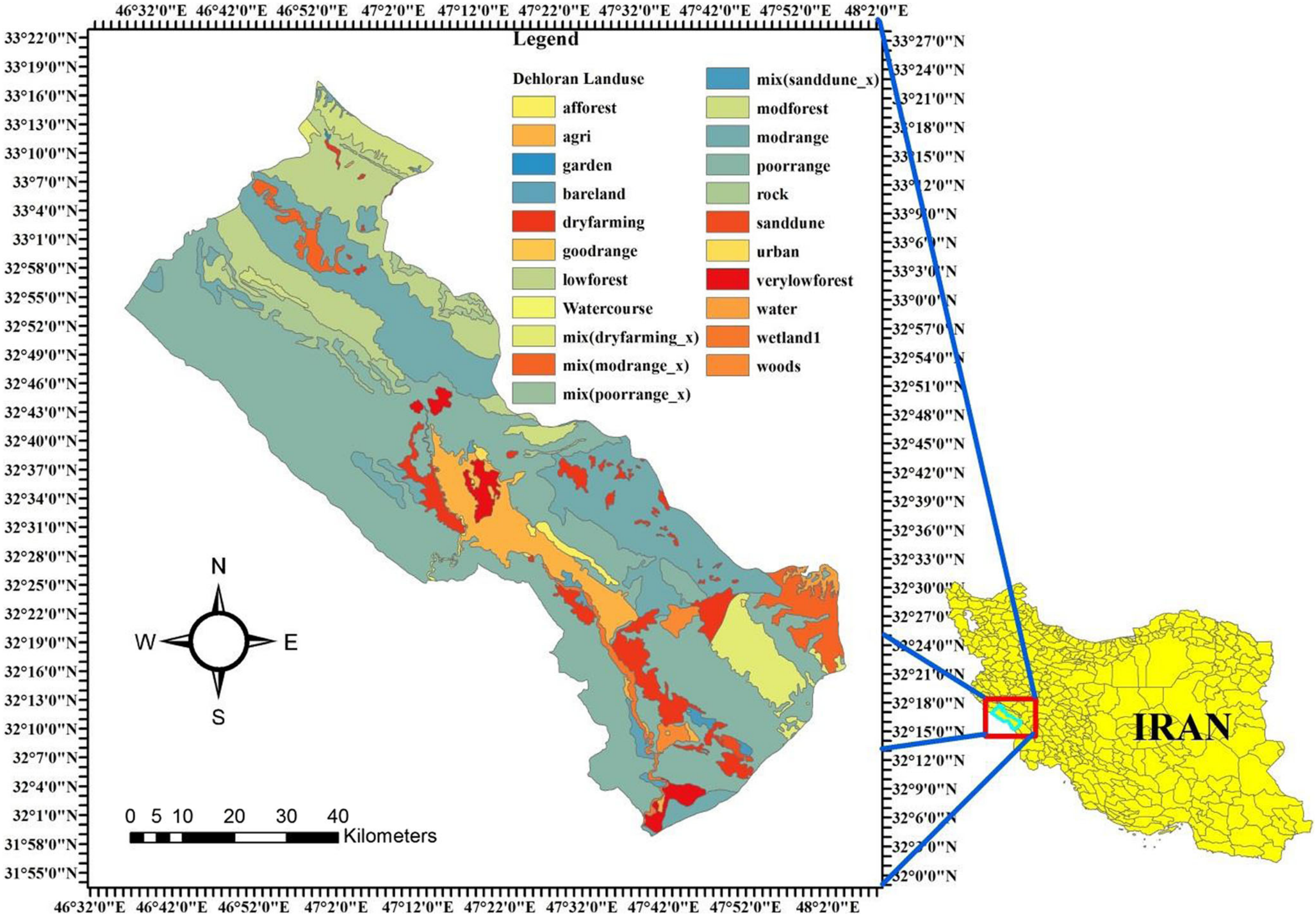

Fig. 1 Dhloran county location and land use type in Iran

layers and converted into a raster layer with the pixel size of 5 × 5 m after entering into the GIS software version 10.1 (Mokhtari et al. 2016; Orshan et al. 2016).

Considering the flight radius of phlebotomine sand flies as the only agent of disease transmission as well as the movement area of the rats as the main reservoir of the disease, two buffers with the radii of 500 and 1000 m were drawn around the patients' residency site using GIS software to investigate PPEVs. Previous studies have reported that the activity radius of phlebotomine sand flies and rats is from 500 to 1000 m (Nejati et al. 2014; Yoosefi and Vakil 2007). Finally, the descriptive tables of the buffers were drawn using GIS and applied to extract the PPEVs existing at 500- and 1000-m distance from the patients' residency site.

Statistical analysis

The time series models were generated to analyze the relationship between PPEVs and monthly CL incidence. The order of moving average (MA) and auto-regression (AR) parameters was identified by examining the structure of temporal dependence of time series using auto-correlation (AC) and partial auto-correlation (PAC) functions, respectively.

The Seasonal Auto-correlated Integrated Moving Average (SARIMA) model with the Box-Jenkins method was used to determine the relationship between environmental factors (temperatures, days with temperatures more than 30 °C, and number of earthquakes) and CL incidence. In time correlation between series, cross-correlation was used. Logarithmic transformation was used for all variables to become stationary input series. For every series, the SARIMA model using AC and PAC functions was fitted to explain better the parameters of p, q, and I. The Akaike's information criterion (AIC) is used to select the best model with the minimum parameters. In the analysis, the statistically significant level was set at 0.05. In addition, the relationship between CL incidence and environmental factors were assessed using Spearman rank correlation. All statistical analyses were done using STATA software version 13.1.

Results

The number of CL in the study period (January 2011–December 2015) was 4437 cases. Figure 2 demonstrates the morbidity based on a monthly scale. It can be seen from the

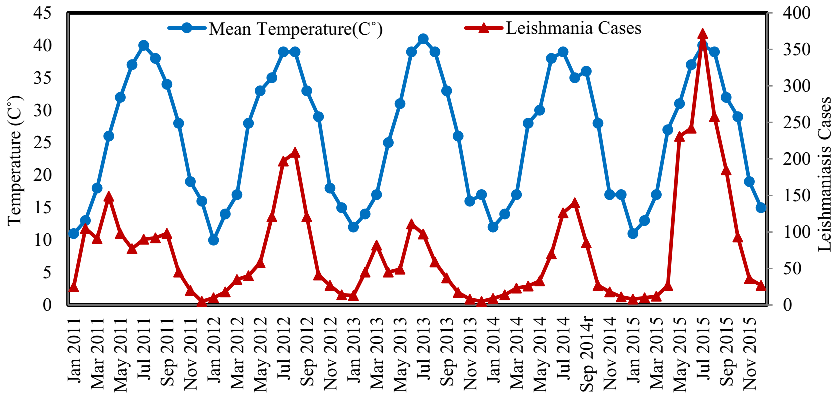

Fig. 2 Trend of CL incidence with the changes in monthly mean temperature

figure that the minimum rates of morbidity were related to the cold months from January to December and the maximum rates occurred in July which is one of the warmest months of the year with the daily mean temperature of 40 °C in the study area. Spearman rank correlation coefficient indicated a significant relationship between the increase in CL incidence and monthly temperature ($r = 0.77$; P value = 0.01; CI 95%). Also, a significant relationship was found between the increase in CL incidence and the number of days per month with temperature more than 30 °C ($r = 0.81$; P value = 0.01; CI 95%).

Figure 3 indicates the trend of CL incidence and the number of earthquakes of 3.5 Richter and more in every month from 2011 to 2015. As seen from this figure, the most of the earthquakes have occurred in warm months (April to November): 3 cases in 2011, 11 cases in 2013, 2 cases in 2014, and 48 in 2015. In 2015, there were more earthquakes in comparison to the previous 4 years. An increase in the number of earthquakes was paralleled to significant increase ($r = 0.683$; P value = 0.01; CI 95%) in the rate of CL incidence in this year. There was a strong correlation between the increased CL incidence and the occurrence of earthquakes ($r = 0.683$; P value = 0.01; CI 95%). No significant relationship was found between the annual mean rainfall and CL incidence (P value = 0.56).

Land use, elevation, surface soil type, and rainfall rate within the radius buffer (500 and 1000 m) around the residency patients' locations were shown in Table 1. According to Table 1, all the patients were living in the regions with the elevation of 100 to 400 m. The maximum percentage of land use in radius buffers were bare land and dry farming, and the maximum percentage of surface soil type was Inceptisols. Sixty eight percent of annual mean rainfalls in the reigns of CL incidence were less than 300 mm.

The SARIMA models (1, 0, 1) $(1, 0, 0)_{12}$ including independent variables were significantly relevant. Table 2 summarizes the time series regression models fitted to the CL incidence data. As it can be seen from the table, model 2 is the best fitting one according to the monthly time series. The MA and AR parameters are 0.698 and 0.513, respectively, and the seasonal AR is 0.518. CL incidence is positively associated with warm days (over than 30 °C) at a lag of 1 month ($\beta = 0.620$, $p = 0.000$) and earthquakes per month at a lag of 2 months ($\beta = 0.184$, $p = 0.036$) and negatively associated with warm days (over than 30 °C) at a lag of 2 months ($\beta = -0.430$, $p = 0.014$). Model 1 also shows that the inclusion of earthquakes per month at a lag of 1 month is not statistically associated with CL incidence and does not improve the fitness of model, ($\beta = 0.020$, $p = 0.914$).

Figure 4 compares CL incidence during the study period and predicted values based on the final model. As it can be seen from the figure, the pattern of predicted monthly values is very close to actual CL incidence.

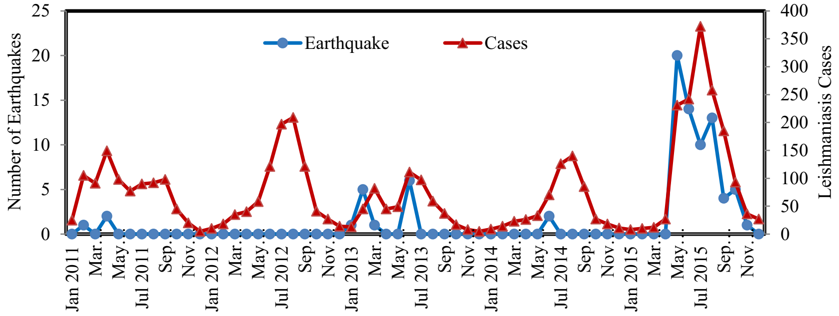

Fig. 3 Trend of CL incidence with change in monthly number of earthquakes more than 3.5 Richter scale

Table 1 Type of surface soils, elevation, land use, and rainfall in radius of 500 and 1000 meters around the CL patients' locations

Variables	Sub-Variables	Percentage in 500 meters buffers	Percentage in 1000 meters buffers
Elevation	100-400m	100	100
	>400m	0	0
Land use	Dry Farming	23.5	37.7
	Irrigated	21.4	17.2
	Residential	8.4	3.6
	Forest	1	2.8
	Bare land	43	35.7
	Others	2.7	3
Type of surface soils	Inceptisols [a]	44.7	51
	Aridisols [b]	29	22.1
	Rocks	0	0
	Others	26.3	26.9
Rainfall (mm)	100-300	68	68
	>300	32	32

[a] Inceptisols developed than Entisols, but these soils are in the beginning stages of soil profile development

[b] Aridisoils (or desert soils) have a very low concentration of organic matters

Discussion

The meteorological parameters, environmental factors, and the number of earthquakes were related to CL incidence for the first time in Dehloran, Iran, as an endemic region of CL. The trend of monthly temperature and CL incidence data showed that an increase in temperature more than 30 °C resulted in increase in CL incidence. With beginning warm day in March, the increasing trend of the disease morbidity is started and reached to its peak in July and then gradually slow down in September. This result is in agreement with some previous studies in which the increasing trend was found in CL incidence according to the increase in temperature (Chretien et al. 2015; Garni et al. 2014; Karagiannis-Voules et al. 2013; Lewnard et al. 2014; Toumi et al. 2012; Yoosefi and Vakil 2007). Ali-Akbarpour et al. (2012) has shown a statistically significant relationship between the prevalence of this disease and the temperature in different regions of Iran (*P* value = 0.007; *r* = 0.45). Results of a similar research in 2010 in Meshkinshahr, Iran, demonstrated a significant relationship between the temperature of the region and the prevalence of visceral leishmaniasis (*P* value = 0.007) (Salahi-Moghaddam Abdoreza et al. 2010). In general, the results of this study indicated that the annual peak of cutaneous leishmaniasis occurred in those months of the year for which the mean temperature was above 30 °C.

Although the rainfall rate of the study region was 100–700 mm, about 68% of patients was residing in the areas where the annual mean rainfall was 100–300 mm. In contrast to these results, some studies have reported that the increase in rainfall resulted in the increase in CL incidence (Elnaiem et al. 2003; Thomson et al. 1999). The most probable explanation for this difference is colder weather and higher elevation of study area in this research. Most of the rainy regions in the study area have cold regions and are located at the elevations higher than 700 m; therefore, the elevation and coldness could

Table 2 SARIMA regression of the logarithmic monthly CL incidence on environmental factors

Variables	Model 1			Model 2		
	β	S.E.	*P*	*β*	S.E.	*P*
Auto-regression	0.499	0.19	0.007	0.513	0.18	0.003
Moving average	0.701	0.12	0.000	0.698	0.12	0.000
Seasonal auto-regression	0.514	0.14	0.000	0.518	0.14	0.000
Earthquake per month at lag 1	0.020	0.19	0.914	–	–	–
Earthquake per month at lag 2	0.199	0.17	0.252	0.185	0.09	0.036
Warm days (over than 30 °C)	0.633	0.12	0.000	0.620	0.12	0.000
Warm days (over than 30 °C)	–0.434	0.17	0.012	−0.430	0.18	0.014
AIC		101.11			97.07	

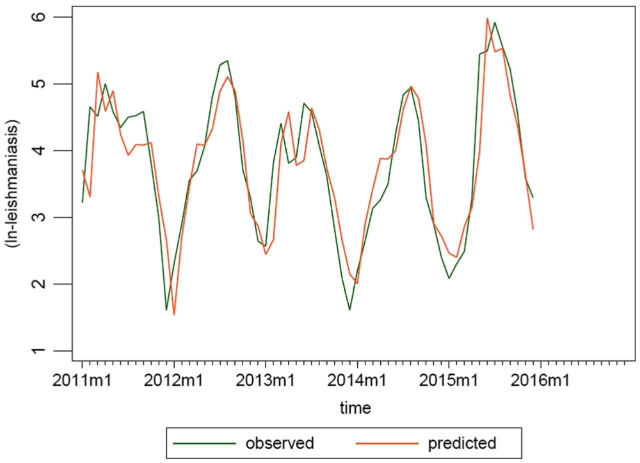

Fig. 4 Comparison of predicted and observed values of CL incidence

be probably the preventive factors for the CL incidence (Mokhtari et al. 2016).

The peak of warmth, the occurrence of earthquakes, and the incidence of CL have been found to be almost simultaneous in the time period from April to September. It makes it difficult to separate the role of the warmth and earthquake factors in the incidence of the disease. However, the correlation coefficient between the disease incidence and earthquake occurrence was about 0.15% more than the one between the disease incidence and temperature increase. Furthermore, as can be seen from Fig. 3, the disease prevalence peak happened after the earthquake occurrence and the biggest peak of the CL morbidity in 2015 occurred exactly after the occurrence of 48 continuous earthquakes, while the status of rainfall and temperature in 2015 was almost similar to those of the previous 4 years. It can be concluded that, therefore, the outbreak of the cutaneous leishmaniasis morbidity in 2015 was most likely related to the occurrence of multiple earthquakes. These results can be explained by the fact that peoples spend most of the night time out of their houses after each earthquake because of concerns about the earthquake recurrence and probable aftershocks. Resting and sleeping in outdoors at the nights following the earthquake could provide suitable conditions for infected phlebotomine sand flies to bite peoples and consequently increase the number of the individuals infected with CL.

Table 1 demonstrates that within 500- and 1000-m radius from the patient's locations, there were, respectively, 43 and 35.7% bare lands, 23.5 and 37.7% dry farmlands, and 21.4 and 17.2% irrigated farmlands. Although most of the patients were residing in the rural areas with irrigated farming lands, the maximum number of bare lands were located within 500 and 1000 m radius. Therefore, it can be concluded that agricultural activities especially irrigation farming in which land plowing is done for several times per year can destroy the rodents' lairs and consequently reduce the possibility of contact between phlebotomine sand flies and rodents. It can finally end in the decrease in CL incidence. In addition, in agricultural regions, rodents rarely return to their old lairs after digging some new ones (Wasserberg et al. 2003). Therefore, consecutive plowing of farms can remarkably reduce the abandoned lairs of rodents as a shelter for phlebotomine sand flies and as a result influence the reduced population of phlebotomine sand flies. A study in Tunisia indicated that increase in the irrigated farmland area in dry and bare lands can reduce most of phlebotomine sand flies species and only a limited number of the species is increased (Barhoumi et al. 2015).

Surface soils at 500- and 1000-m radius of the patient's location were, respectively, 44.7 and 51% inceptisols and 22.1 and 29% aridisols. At these radii, there was no rocky land. Some organic material content in inceptisol soils can be the most probable reason for the increase in rodents and phlebotomine sand flies in such types of soils because they maintain soil moisture and help the plants growth better than aridisol soils (Adegboye et al. 2016; Mokhtari et al. 2016).

The most important limitations of the present study are related to registration system in which some cases can be lost due to unreported, undiagnosed, and misdiagnosed cases. Also, some cases do not go to health care centers. Cases of slight or impaction usually do not. In addition, the study period is short (4 years) and may lead to unreliable and robust results. Another limitation is that socio-economic conditions in the study area were not investigated.

Conclusion

A time series analysis and Spearman rank correlation coefficient were applied to investigate the impact of meteorological and environmental factors on CL incidence. There were positive correlations between these variables and CL incidence. There was a strong relationship between the number of earthquakes and increasing CL incidence. The most abundant land around CL patients was bare lands, and the most abundant type of surface soil was inceptisols. The results indicated that in earthquake-prone areas with high temperature and inceptisol soil type, more robust preventive programs are needed than other areas and the region with these characteristics should be considered as high-risk areas for CL incidence.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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