Original Article

Dynamic Relations between Incidence of Zoonotic Cutaneous Leishmaniasis and Climatic Factors in Golestan Province, Iran

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Abstract

Background: Zoonotic Cutaneous Leishmaniasis (ZCL), an important public health problem in Iran, is sensitive to climate conditions. This study aimed to examine dynamic relations between the climate factors and incidence of ZCL in Golestan Province, northern Iran during 2010–2012.
Methods: Data of monthly climatic factors, including temperature variables, relative humidity variables, evaporation, total rainfall, and number of freezing and rainy days together with monthly ZCL incidence were used. Spearman rank correlation was carried out to explain associations between the monthly ZCL incidence rate and climate factors at 0, 1, 2, 3 and 4 months lagged periods. Pearson's correlation analysis was conducted to examine the type and strength of relationships between the spatially averaged climate factors and ZCL incidence rate in district level. Stepwise multiple regression was used to find the best combination of independent climatic variables, which predict the ZCL incidence.
Results: Spearman correlation analysis indicated that the highest correlations between climate factors and monthly ZCL incidence were established when the climate time-series lagged the ZCL incidence series, especially two month prior to disease incidence. Based on the results of the both Spearman rank correlation and Pearson correlation analyses, ZCL incidences in Golestan Province tend to be more prevalent in areas with higher temperature, lower relative humidity, lower total rainfall, higher evaporation and lower number of rainy days. The results of stepwise regression analysis indicated that minimum temperature, mean humidity, and rainfall had considerable effect on ZCL incidence.
Conclusion: Climate factors are major determinants of ZCL incidence rate in Golestan Province and such climate conditions provide favourable conditions for propagation and transmission of ZCL in this endemic area.

Keywords: Zoonotic Cutaneous Leishmaniasis (ZCL), Climate factors, Correlation analysis, GIS, Iran

Introduction

Leishmaniasis is an environmental dependent disease affected by a variety of factors, amongst which climate factors are considered to play major role in frequency of the disease (Patz et al. 2005). It represents significant socio-economic burden to society and psychological disfiguring effect on patients with permanent scars, predominantly in developing countries including Iran (Yaghoobi-Ershadi et al. 2013). The disease is one of the most important health problems in Iran

and its prevention and surveillance is one of the WHO priorities (WHA 2007). Leishmaniasis in Iran has mainly three clinical forms including cutaneous leishmaniasis (CL), visceral leishmaniasis (VL) and mucocutaneous leishmaniasis (MCL), amongst which CL is the most common form of leishmaniasis. Although, CL can be seen in Zoonotic (ZCL) and Anthroponotic (ACL) forms, about 80 % of cases reported in the country are of ZCL form (Yaghoobi-Ershadi 2012). Zoonotic Cu-

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taneous Leishmaniasis due to *Leishmania major* is still a great and increasing public health problem in many rural areas of 17 out of 31 provinces of Iran (Akhavan et al. 2010). According to the published statistics by the WHO, number of CL cases in this country during the period of 1998 to 2009 generally increased from 18,560 to 24,586 patients (WHO 2012). Fig. 1 shows frequency of CL occurrence in Iran, during the period of 1998–2009. Although ZCL yearly afflicts considerable numbers of people from different parts of Iran, inadequate attention has been paid to monitoring and surveillance of the disease.

Golestan Province, an endemic province of ZCL in Iran, with several significant spatial and spatio-temporal hotspots of ZCL especially in northern and northeastern parts, is constantly at risk of infection (Mollalo et al. 2015). Previous entomological studies carried out in this province proved that ZCL is caused by the *Leishmania major* (Yakimoff and Schokhor) (Kinetoplastida: Trypanosomatidae), the main vector is *Phlebotomus papatasi* Scopoli (Diptera: Psychodidae) also the main reservoir host is *Rhombomys opimus* (great gerbil) (Rassi et al. 2008, Sharbatkhori et al. 2014).

Climate is one of the most significant factors that might affect the spatial distribution of many infectious diseases including leishmaniasis. It affects through control on host or vector physiology and behaviour directly (e.g. effect of rainfall on parasite development and vector competence) or indirectly (e.g. effect of temperature on the range and abundance of the sand fly species that act as vectors or through socio-economic changes that affect the amount of human contacts with the transmission cycle) (Ready 2008). Climate would be expected to modify the spatial and temporal distribution of the leishmaniasis (Kelly-Hope and Thomson 2008).

New methodological advances, such as Geographic Information System (GIS) over last 30 years has provided an ability to better understand the etiology of the diseases in shorter time and less costs. GIS is a worthwhile tool in studying infectious diseases (Moore and Carpenter 1999). In spite of broad studies on the association between climate variables and incidences of different kinds of infectious diseases throughout the world, very little researches in regards of leishmaniasis has been reported from Iran. Several studies in various parts of the world had linked different forms of leishmaniasis to environmental factors. In the study region, Mollalo et al. (2014), linked the normalized difference vegetation index (NDVI), as a general proxy indicator of climate changes (Including temperature, humidity and rainfall), with incidence of CL and demonstrated that most of cases were occurred in non-vegetative or low-density vegetation areas. During 1991–2001 in Costa Rica, Chaves and Pascual (2006) studied monthly CL incidence by using mathematical models. They showed that CL has cycles of about three years related to temperature and indices of the El Niño Southern Oscillation. Using such a model, they could predict the incidence of CL up to 12 months ahead with an accuracy of between 72 % and 77 % depending on prediction time. In central Tunisia, Toumi et al. (2012), investigated temporal dynamics and impacts of climate factors (Including rainfall, temperature and humidity) on incidence of ZCL. Their results showed seasonality during the same epidemiologic year so that ZCL incidence raised by 1.8 % when there was 1 mm increase in the rainfall lagged by 12 to 14 months and by 5.0 % when there was a 1 % increase in humidity from July to September in the same epidemiologic year.

To the best of our knowledge, this is the first attempt in terms of assessing the relationship between climate factors and ZCL incidence in quantitative manner in surveyed area. Development of low-cost and efficient management tools for effective control of the

ZCL is an important objective, which requires comprehensive efforts and studies including the ecology of the disease and role of the climate change. For this purpose, this study was designed to investigate the relations between the climate factors and incidence of ZCL to gain deeper insight into the possible interactions between climate conditions and ZCL incidence in Golestan Province of Iran.

Materials and Methods

Study area

Golestan Province consists of 14 counties with 60 districts located in north-east of Iran (36° 30' to 38° 8' N and 53° 57' to 56° 22' E) bounded on the north by Turkmenistan country, on the west by Mazandaran Province and the Caspian Sea, on the south by Semnan Province, and on the east by Northern-Khorasan Province. The geographical position of this province provides a unique area with very diverse climate. As northern regions are located in the arid and semi-arid climate, southern regions represent a mountainous climate, and central and southern west regions are located in a moderate Mediterranean climate. Based on the climatic conditions of the region during the study period, the monthly maximum and minimum temperature were 30.7 °C and 5.09 °C in July 2011 and February 2012, respectively. The total annual rainfall was a minimum of 0 mm in July 2010 and its maximum of 124.18 mm in October 2011. The minimum monthly relative humidity was 51.78 % (June 2010) and the maximum was 79.64 % (March 2010) (Golestan Province Meteorological Center, unpublished data).

Data Collection

The Iranian primary health care (PHC) system was well founded especially in rural areas. More than 16,000 health houses over the country cover almost 95 % of the rural areas. Health workers are responsible to de-

liver primary healthcare and to keep health records of people to the Center for Disease Control and Prevention (CDC) of their study area. Monthly ZCL incidence records over the period of January 2010 to December 2012 (36 months) were considered for analysis of their temporal correlations and lagged effects. During the study period a total of 2,893 ZCL cases, diagnosed by direct smear examination, were officially reported by CDC of Golestan Province. The data were checked in a meticulous manner to prevent any possible mistakes and were mapped at district level using ArcGIS Desktop software version 9.3 (ESRI Inc, Redlands, CA). Fig. 3 shows the annual ZCL incidence rate at district level.

Climate data

Data of climate factors were obtained from Golestan Province Meteorological Center. The data were collected from synoptic stations in Golestan Province and synoptic stations in adjacent provinces including Northern-Khorasan and Semnan during September 2009 to December 2012 (40 months) for more accurate interpolation. Climatic factors, including the minimum, maximum and mean temperature (°C), minimum, maximum and mean relative humidity (%), mean evaporation (mm), total rainfall (mm), and number of freezing and rainy days were calculated for each district based on the observation of synoptic stations in mentioned provinces. After collection of climate data, they were entered into GIS environment for further analyses. This has been done through the following procedure:
1) The monthly average of measurements of the above factors for each synoptic station was calculated.
2) A point layer was created for observation stations and the monthly averages of factors associated with their related points.
3) For any of the factors, using inverse distance weighting (IDW) method, a raster was created by interpolating the monthly average

values of those factors between stations.

4) For each factors, its raster was overlaid with the polygon layer of the district boundaries. For each district, the average of the raster cells inside district polygon was assumed as the value of the factor in that district and analyzed to recognize possible relationships with ZCL incidence. Fig. 2 shows maps of climatic factors at district level in Golestan using IDW method.

Geographic Information System was used in conjunction with statistical analytical methods to analyze the relations between ZCL incidence and climate factors in the study area.

Spatial statistics analyses

To assess the correlation between climate factors and ZCL incidence rate, the monthly ZCL incidence was regarded as the dependent variable, while climate variables were considered as independent variables. A four-stage approach was adopted to describe and analyze the possible relations of the climatic variables on the incidence of ZCL. Firstly, the monthly and annual ZCL incidences of each district were calculated and mapped. Secondly, Spearman rank correlation was used to examine the association between the climate factors and ZCL incidence rate. In this regard, Cross correlation was performed to detect the lagged effect of climate factors on ZCL incidence rates at global (province) level at 0, 1, 2, 3 and 4 months lagged periods. Thirdly, Pearson's correlation analysis at local (district) level was conducted to examine the type and strength of relations between the spatially averaged of climate variables and annual ZCL incidence rates in districts. Finally, multivariate stepwise regression was used to establish the models to determine the contribution rate of all the climatic factors.

Results

The monthly trend of climate factors and ZCL incidence rate is shown in Fig. 4. With regard to the lagged effects, it can be visually seen positive associations between average temperature and evaporation with increase of ZCL incidence rate, and negative associations between relative humidity, and rainfall with increase of ZCL incidence rate. However, statistical analyses needs to formally test whether the results are statistically significant or not.

Associations between monthly ZCL incidence rate and climate factors were observed at global (province) level at 0, 1, 2, 3 and 4 months lagged periods. Besides, local correlation at district level between ZCL incidence rate and climate factors was observed using the Pearson correlation analysis. Based on the results of the Spearman rank correlation at the province level, positive associations were observed between the monthly ZCL incidence rates with all temperature variables and evaporation. In addition, negative correlations were seen between the monthly ZCL incidence rates with all humidity variables, rainfall, number of rainy days and number of freezing days. The time lag(s) of climatic factors preceding ZCL incidence at which the series showed that the strongest correlation were obtained by cross-correlation analysis of monthly ZCL incidence series and monthly climatic data time-series. Among ten climate factors used in this study, except minimum humidity and rainfall, highest correlations were found with 2-months lagged period. Moreover, lowest correlations were found 0-month (for all temperature variables, evaporation, rainfall and number of freezing days) and 4-month (for all humidity variables and number of rainy days). Among the climate factors, temperature variables showed the highest correlation with the monthly ZCL incidence rate whereas rainfall showed the least correlations with the monthly ZCL incidence rates. Detailed information of the results of Spearman rank correlation between the

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monthly ZCL incidence rates and climate factors at 0, 1, 2, 3 and 4 months lagged periods has presented in Table 1.

Pearson's correlation analyses revealed that positive associations were observed between annual ZCL incidence rates in all 60 districts of province with all temperature variables, evaporation, and number of freezing days. While negative associations were observed with all relative humidity variables, rainfall and number of rainy days. These results indicate that ZCL incidences in Golestan Province tend to be more prevalent in districts with the lowest average relative humidity values as an indicator of drought. However, all the variables except number of freezing days showed similar signs in both analyses. Among the climate factors, relative humidity showed the highest correlation, while minimum temperature showed the least correlations with ZCL incidence rates. Table 2 represents results of the Pearson correlation between the monthly ZCL incidence rates and climate factors.

Results of the multivariate stepwise regression showed the best model among others, with highest R, R^2, and lowest standard error, was the regression model with equation Y= 4.015+0.739* (minimum temperature)-0.841* (mean humidity)-0.7631* (rainfall) (Table 3). The multiple regression showed 0.536 changes of monthly ZCL incidence contributed to the average monthly minimum temperature, mean humidity, and total rainfall.

Table 1. Spearman rank correlation between the monthly ZCL incidence rates and climate factors at 0, 1, 2, 3 and 4 months lagged periods, between September 2009 and December 2012

Monthly ZCL Incidence	Temperature	Min. Temperature	Max. Temperature	Relative Humidity	Min. Relative Humidity
0-Month	.403*	.399*	.368*	-.505**	-.492**
1-Month	.735**	.695**	.723**	-.764**	-.712**
2- Month	.895**	.858**	.854**	-.776**	-.649**
3-Month	.800**	.780**	.749**	-.625**	-.445**
4-Month	.472**	.502**	.398*	-0.278	-0.088
Monthly ZCL Incidence	Max. Relative Humidity	Evaporation	Rainfall	No. Rainy Days	No. Freezing Days
0-Month	-.514**	0.314	-0.166	-.493**	-0.306
1-Month	-.736**	.695**	-.383*	-.604**	-.540**
2- Month	-.759**	.893**	-.497**	-.611**	-.670**
3-Month	-.636**	.853**	-.551**	-.469**	-.646**
4-Month	-.411*	.574**	-.336*	-0.138	-.451**

    **.Correlation is significant at the 0.01 level
    *.Correlation is significant at the 0.05 level

Table 2. Results of Pearson correlation analysis between climate factors and ZCL incidences in 60 districts of Golestan Province, Iran, between September 2009 and December 2012

Monthly ZCL Incidence	Temperature	Min. Temperature	Max. Temperature	Relative Humidity	Min. Relative Humidity
Yearly ZCL incidence	.150	.035	.106	-.326**	-.272*
Monthly ZCL Incidence	Max. Relative Humidity	Evaporation	Rainfall	No. Rainy Days	No. Freezing Days
Yearly ZCL incidence	-.320**	.249	-.210	-.128	.122

    **.Correlation is significant at the 0.01 level
    *.Correlation is significant at the 0.05 level

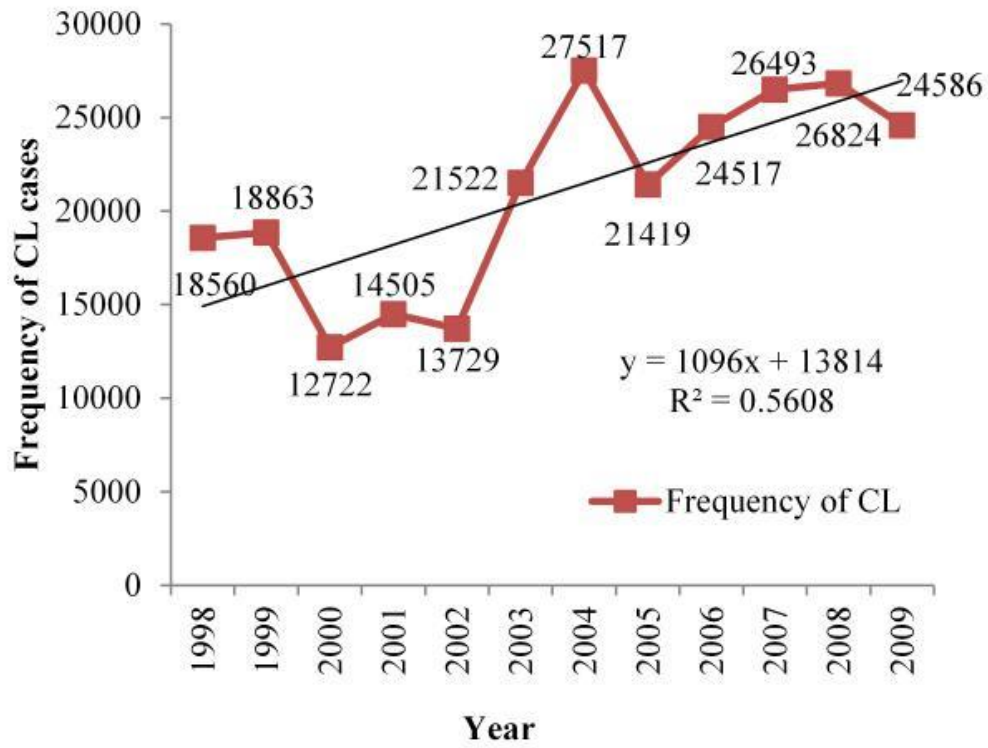http://jad.tums.ac.ir
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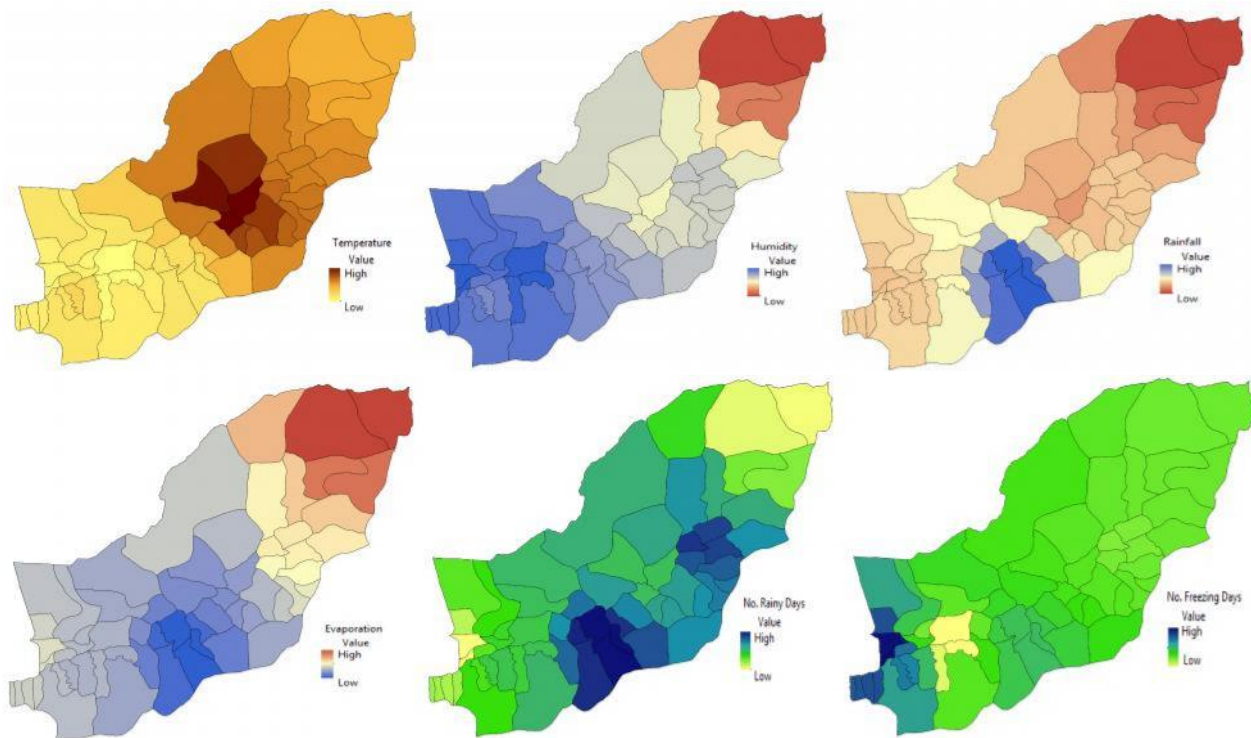**Fig. 1.** Frequency of CL cases in Iran, between 1998 and 2009

Fig. 2. Climatic maps of Golestan Province during 2010–2012, generated by IDW method
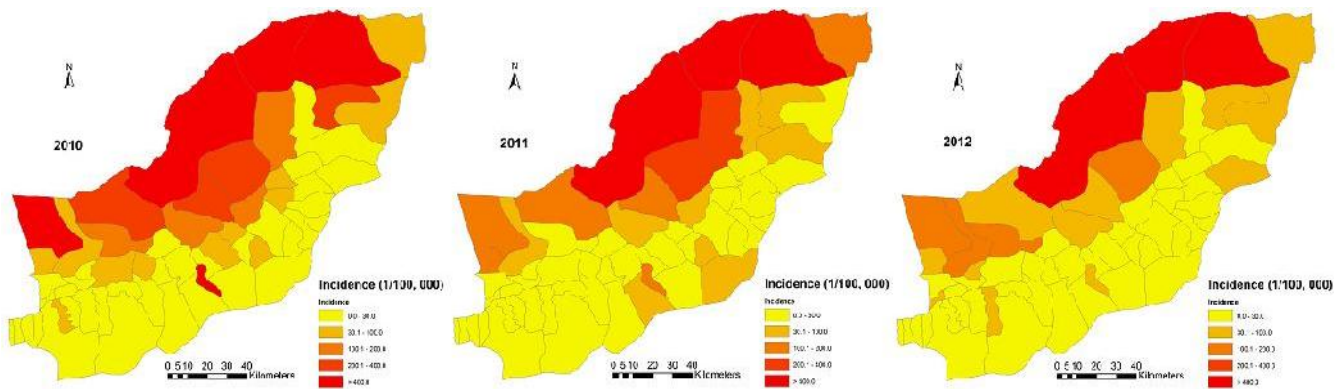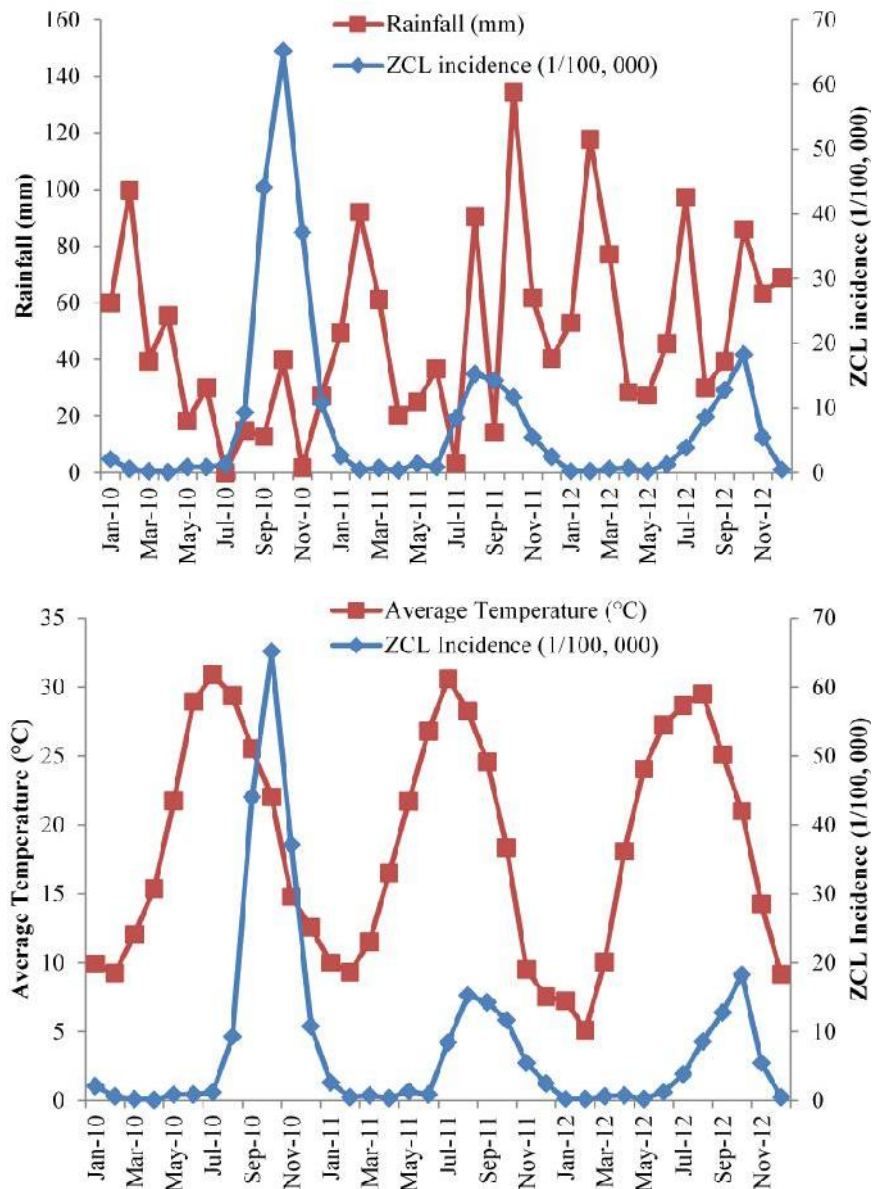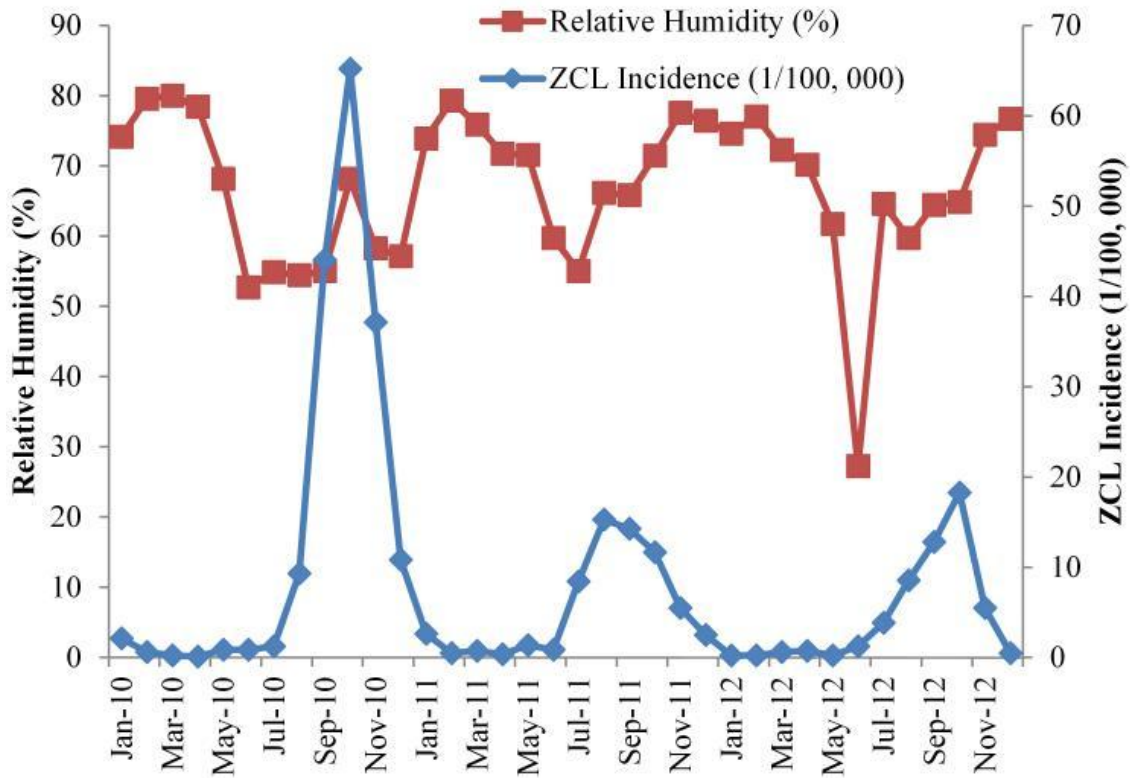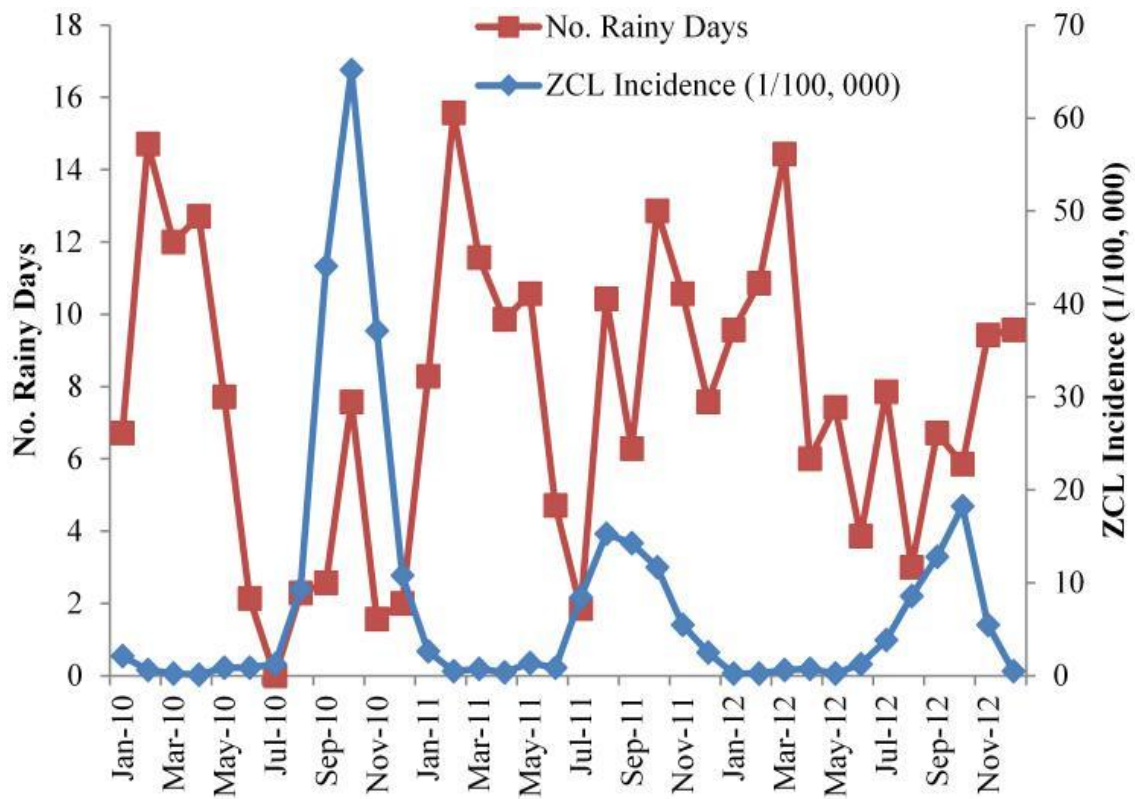
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Fig. 3. Annual ZCL incidence rate at the district level per 100,000 individuals in Golestan Province, Iran, 2010–2012
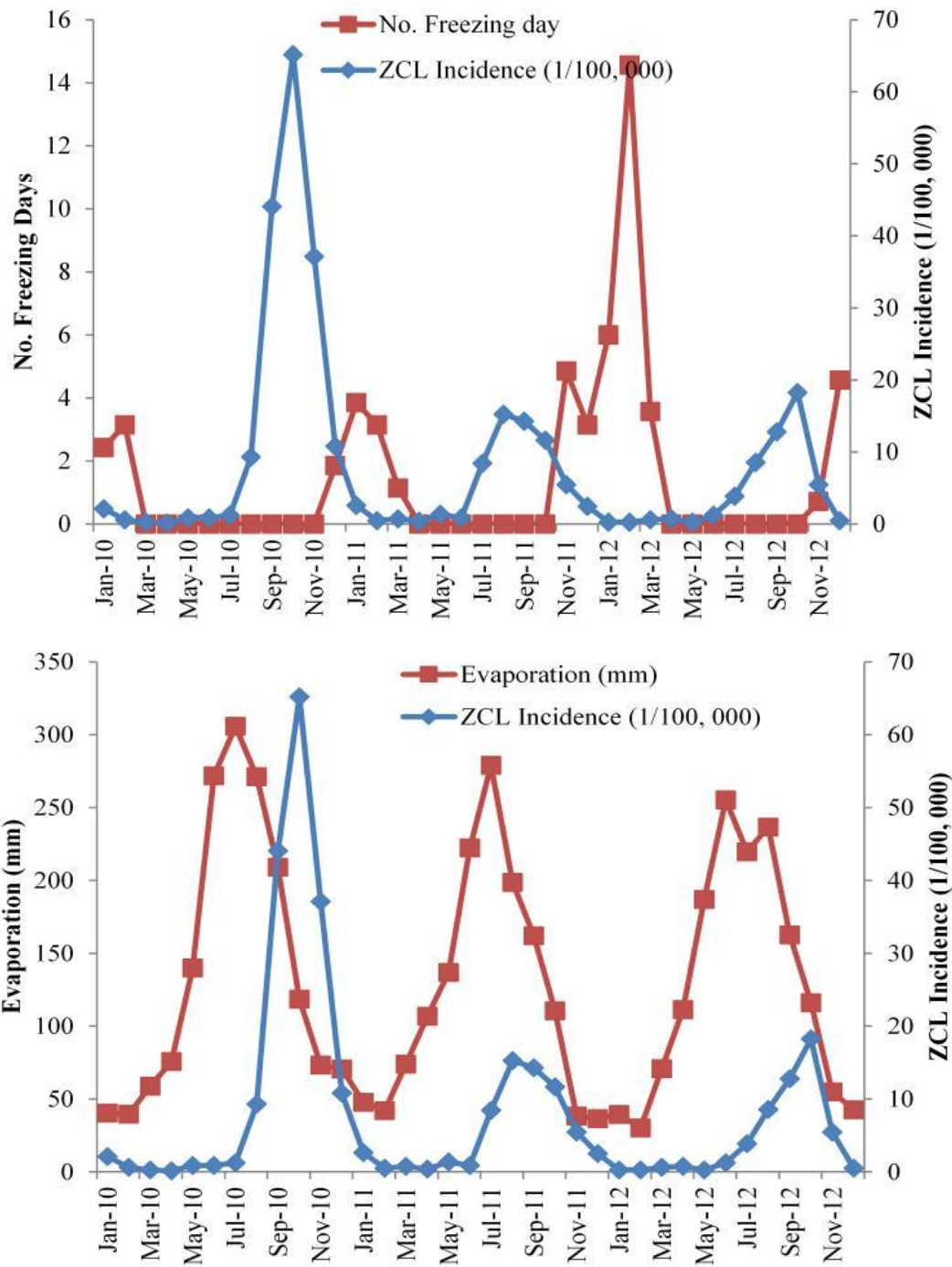
Fig. 4. Temporal trend of ZCL cases incidence (per 100, 000) concerning mean of climate factors, Golestan Province, Iran, 2010–2012

Table 3. The results of stepwise regression analysis in which 3 out of 10 climate factors were selected

Model	R	R-square	Adjusted R^2	P-value
6	0.732	0.536	0.534	<0.01

Final regression model: Y=4.015+0.739*(minimum temperature)-0.841*(mean humidity)-0.7631*(rainfall)

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Discussion

The results of this study both support and extend the findings of previous works where temporal series of climate variables had associated with other vector-borne infectious diseases such as Malaria (Nath and Mwchahary 2012, Zhao et al. 2014) and dengue fever (Goto et al. 2013). Examining of correlations showed statistically significant association between climate factors behind ZCL incidence time series by Spearman rank correlation. According to results of the Spearman rank correlation, monthly climate factors dynamically correlated with monthly ZCL incidence rate during three years period of study. However, climate factors generally did not show strong correlation with ZCL incidence rates in the same months. The best correlations between the climate factors and monthly ZCL incidence rates were observed when climate factors time-series were lagged the ZCL incidence rates. This indicates that climate change prior to the disease active period is an important influencing factor and at least one-month time is needed for climate factors to effect on occurrence of ZCL in humans.

It should be noted that the above temporal relationship might vary by different geographic areas due to different seasonal patterns in different ecological zones. Previous studies have debated the association between leishmaniasis epidemic and climatic factors in some areas of Iran. Comparison the results of correlation analysis between incidence of cutaneous leishmaniasis and climate factors with studies of Yazdanpanah and Rostamianpur (2013) in Ilam Province, west of Iran, and Mozafari and Bakhshizadeh-Kolooche (2011) in Yazd-Ardakan plain in central part of Iran, indicates that although positive correlation between the average temperature and CL incidence was observed in Ilam, this relation was negative in Yazd. In contrast, both of the studies reported that the association be-

tween CL epidemic and relative humidity was not significant, while in our analyses in both local (district) and global (province) levels, relative humidity appeared to be the most significant factor. Therefore, results of this study are not valid for other study areas of Iran. Moreover, results of our study were consistent with findings of other researchers around the world including Roger et al. (2013) in French Guiana located in South America, and Sing (1999) in Rajasthan, India. Both of the studies showed that incidence of disease increased with rise of temperature and decreased with decline of rainfall, and relative humidity, respectively.

The results of this study are also consistent with the previous findings of Mollalo et al. (2014), at the same study area, who observed significant association between vegetation cover and CL incidence in Golestan Province. Because low vegetation covers almost accompanies by higher temperature, evaporation, lower rainfall, and relative humidity. Moreover, it is clear from Fig. 3 that districts with high incidence rate of ZCL were almost located at northern parts of the province with arid and semi-arid climate conditions indicating that such climate conditions provide favorable circumstances for ZCL transmission in this province.

The main limitations of this study are related to current surveillance system in Iran, which yearly loses considerable numbers of the cases. Official reports are probably underestimated due to many reasons such as the not reported, not diagnosed or misdiagnosed cases. Therefore, it is possible that incidence of the disease is underestimated in this study. However, there are few published empirical evaluations of reported and underestimated CL cases, the degree of underreporting CL cases in Iran was found to be 2.8 to 4.6 fold (Alvar et al. 2012). Since the registration system is uniform throughout the

Iran, these errors are evenly distributed. In addition, short period of this study (three years) may not lead to robust and reliable results. Besides, it should be noted that this study examined only climate factors on ZCL epidemics, without taking socio-economic conditions, and other elements influencing the number of new cases, such as herd immunity or individual factors influencing the number of asymptomatic carriers into account. Therefore, it is necessary to perform further studies to other environmental factors (such as construction of roads, building dams, etc.) and even culture and life style of people in the study area, which might influence on disease pattern.

Since the geographical and seasonal distributions of ZCL is closely linked to the climate conditions, using climate factors together with the other influencing factors as predictive indicators can be used to establish early warning systems (EWSs) to forecast ZCL incidence in managing the next epidemic.

Conclusion

Climate factors have been greatly caused or affected on the spatial distribution of ZCL in Golestan Province, so that areas with higher temperature and evaporation, and in contrast lower humidity, rainfall, and num- ber of rainy days were more susceptible to disease occurrence. These findings can provide essential guidelines for public health policy makers to monitor and predict the disease based on the climate factors for future control measures. This means that the budget, personnel, and resources can be allocated more efficiently by concentrating on major determinants of ZCL epidemic in Golestan Province.

Acknowledgments

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