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Determining endemic values of cutaneous leishmaniasis in Iranian Fars province by retrospectively detected clusters and receiver operating characteristic curve analysis

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ABSTRACT

Objective: To determine the endemic values of cutaneous leishmaniasis in different cities of Fars province, Iran.

Methods: Totally, 29 201 cases registered from 2010 to 2015 in Iranian Fars province were selected, and the endemic values of cutaneous leishmaniasis were determined by retrospective clusters derived from spatiotemporal permutation modeling on a time-series design. The accuracy of the values was assessed using receiver operating characteristic (ROC) curve. SPSS version 22, ArcGIS, and ITSM 2002 software tools were used for analysis.

Results: Nine statistically significant retrospective clusters ($P<0.05$) resulted in finding seven significant and accurate endemic values ($P<0.1$). These valid endemic scores were generalized to the other 18 cities based on 6 different climates in the province.

Conclusions: Retrospectively detected clusters with the help of ROC curve analysis could help determine cutaneous leishmaniasis endemic values which are essential for future prediction and prevention policies in the area.

1. Introduction

An epidemic is defined as a swift propagation of diseases among a specific population within a short period of time. An outbreak usually occurs when host immunity is unexpectedly degraded below the endemic equilibrium in the society and the transmission threshold is exceeded[1]. It is worth mentioning that the endemic value of the infection may change over time in the same space. So, determining the endemic equilibrium of the disease is a key point in the epidemiological approach. Since it is a dynamic measure varying according to the population, the place, and the time of disease onset, it is crucial to determine an accurate endemic score for it.

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Leishmaniasis is a significant vector-born protozoa disease. It is caused by *Leishmania* parasite and transmitted by infected sand flywith high incidence and fatality[2–5]. Human are considered to be the sole source of infection for anthroponotic sandfly insects; while for zoonotic types, animals represent reservoirs maintaining and spreading *Leishmania* parasites. Cutaneous leishmaniasis (CL) usually causes cutaneous lesions on the bare parts of the body. It can produce serious lesions that cause severe disability and generate permanent ulcers, which can be a social stigma[5–9].

Annually, CL cases account for 75% of new *Leishmania* infection cases worldwide, of which nearly 90% occur in Afghanistan, Algeria, Brazil, Iran, Peru, and Saudi Arabia[5,10,11]. With the incidence of CL ranking the fourth place in the world, the most polluted regions of southern Iran are Espahan and Fars[8]. Moreover, the most important breeding sites for sand fly insects are Arsenjan, Neireez, and Stahban cities. In recent years, one-third of CL cases occurred in urban sites and two-thirds in rural areas of Fars. The incidence of CL has been estimated to be almost 12.5 cases for each 1 000 000 dwellers.

Spatiotemporal statistical assays applied to detect significant clusters are helpful tools to forecast the relationship between CL and space and time. To make reasonable decisions on public health charge and supervision, CL space-time patterns and the transmission threshold need to be taken into account. In this framework, spatiotemporal statistical analysis of CL process that aims to find clusters (non-homogeneities) offers very beneficial knowledge for CL outbreak, prediction, and prevention and gives us an insight to estimate the endemic value of the disease. Scan statistics derived from permutation scan statistics take into account both time and space features of CL which results in finding space-time outbreaks of CL. In previous studies, the results of spatiotemporal statistical analysis proved that transmission of American CL and Persian CL followed a spatial and temporal pattern[9,12,13]. Detected clusters in spatiotemporal statistical analysis help to find a good approximation for CL endemic scores. Finally, receiver operating characteristic (ROC) curves could be informative and facilitative in order to validate the accuracy of the scores.

2. Materials and methods

2.1. Study design and area

Time-series design of CL recorded in Fars province from 2010 to 2015 was conducted retrospectively to determine the endemic value of CL. Fars province is located in the south of Iran, with an area of 122 661 km^2. Geographically, it is located on 27˚3’ and 31˚40’ northern latitude and 50˚36’ and 55˚35’ western longitude. This province is composed of 25 cities. Regarding 2011 Persian census, it has six climates and carries 4.6 million people.

Fars province has moderate winters with annual average rainfall of 400 to 600 mm. Affected by its topographic factors, there are 3 main climatic regions including mountainous areas of North, Northwest and West with cold winters and annual rainfall of 400 and 600 mm; the central part with mild winters, dry and warm summers and annual rainfall of 200 to 400 mm; and the South and Southeast part covered by vast plains with hot summers and annual rainfall of 100 to 200 mm which is mostly seen in spring and fall.

Fars is the fourth most populated province in Iran including 204 villages. Shiraz, the capital of Fars province with 1 869 001 people, is the most crowded city followed by Marvdasht, Jahrom, Kazerun and Fasa. Although metropolitans are industrialized, most people are farmers and ranchers with outdoor activities.

2.2. Subjects and population data

This investigation was performed on 29 201 confirmed CL cases, which were from 25 different cities of Fars. CL cases confirmed by polymerase chain reaction, culture, or smear selected as study participants. In addition, patients whose symptoms began from January 1, 2010 to December 31, 2015 were involved, and there were no exclusion criteria. As it was a retrospective study, there was no need to take consent form, all clinical ethics have been supposed to be considered. The medical decision of CL was derived from the patient’s clinical documents. All ethical steps, including data collection and analysis as well as reporting the results were in accordance with the standards approved by the Ethics Committee of the Ministry of Health, Treatment and Medical Education under ethics number: IR.SUMS.REC.1396.S755. Indeed, the process of work was completely anonymous and the results were reported to the study participants.

2.3. Information processing and statistical analysis

Several software tools were used including SPSS version 22, ITSM version 2002, ArcGIS version 9, and SaTScan version 9.4.4. To explain any scale and categorical variables, median (interquartile range, IQR) and relative frequency were used, respectively. Kolmogorov–Smirnov test was used to assess normality assumption; *Chi*-square test was used to evaluate equal frequency of CL occurrence over time and place; Kruskal–Wallis tests were performed to assess equality of median of cases through different time periods and places. Moreover, moving average method was used to explore the general trend of CL occurrence over time, and ROC curve procedure was carried out to verify the validation of endemic scores. Significance level was considered to be 0.05 for all statistical tests, but 0.1 for estimating cutoffs in ROC procedure[14–18].

Spatiotemporal permutation methodology with clusters within a cluster analysis was performed to explore past clusters of CL during 2010-2015. This methodology is deeply explained by Martin Kulldorff, and examines if the cases were distributed randomly over time and space[19]. In the current research, the space variation, which was imported to the analysis, was considered as zero to fifty percent of the total population at risk as default and the related time variation was set to zero to a month. The statistical significance of retrospectively found clusters was tested using Monte-Carlo hypothesis testing.

2.4. Accuracy of estimated endemic values

Monthly recorded 29 201 CL cases during 2010 and 2015 were considered as continuous variables and past clusters detected from permutation scan modeling were regarded as dichotomous variables in ROC process. ROC procedure was used to approximate the endemic points and verify if the estimated endemic values were accurate. The asymptotic significance was considered as 0.1.

Coordinates of the curve offer various cutoffs, of which those with the maximum sensitivity multiplied by specificity were selected as our most accurate cutoffs for CL endemic points. Regarding the under reporting range of CL in Iran offered by WHO, two endemic scores were given for each city, namely lower and upper estimated endemic values[10, 20].

3. Results

A total of 29201 CL cases during 2010-2015 are selected, and the information about city and month is shown in Table 1 and Table 2.

Incidence rate accompanied by the largest numbers of CL cases during 2010-2015 is shown in Figure 1. Frequency of CL occurrence over time and place, and equality of median of cases in different times and places, and increasing linear trend of CL incidence rate (moving average of new cases divided by population at risk in each year) during study time were statistically significant (P<0.05).

From 9 statistically significant clusters, 6 subclusters were tracked. The results of permutation scan statistics and subcluster analysis of all 9 statistically significant clusters are presented in Table 3.

The longest cluster was seen in Zarindasht from 1/4/2014 to 31/12/2015 (almost 21 month outbreak), and the shortest one occurred in Farashband from 1/1/2015 to 31/1/2015 (a month outbreak). Using 9 significant CL space-time clusters, the ROC analysis revealed 7 statistically significant endemic values of CL as shown in Table 4.

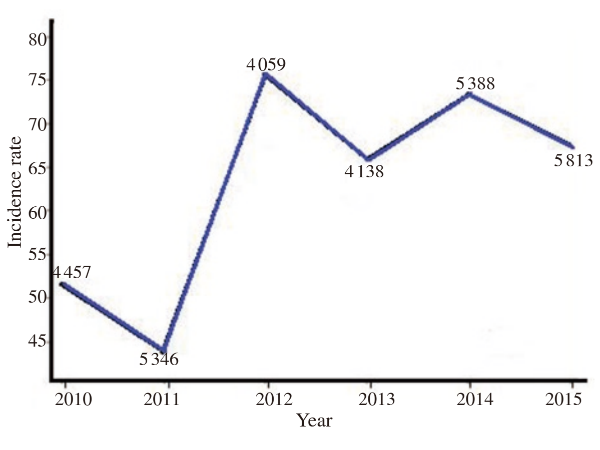

Figure 1. Incidence rate of cutaneous leishmaniasis in Fars province, Iran from 2010 to 2015. Note: Incidence rate=Annual cases/1 000 000 inhabitants. A total of 29201 cutaneous leishmaniasis cases were reported for the period. The number of cutaneous leishmaniasis cases is shown for each year in the graph.

Table 1. Descriptive measures of 29 201 cutaneous leishmaniasis cases per city between 2010 and 2015 in Fars province, Iran.

City	Median (lower quartile, upper quartile)	Min	Max	Relative frequency
Arsenjan	7.00 (1.00, 17.75)	0.00	53.00	2.7%
Stahban	4.00 (2.00, 11.75)	0.00	75.00	2.3%
Eghlid	1.00 (0.00, 3.00)	0.00	9.00	0.4%
Abade	5.00 (1.25, 20.00)	0.00	65.00	2.7%
Bavanat	1.50 (0.00, 4.00)	0.00	20.00	0.6%
Pasargad	2.00 (0.00, 6.00)	0.00	16.00	0.9%
Jahrom	11.00 (5.00, 21.75)	1.00	76.00	3.9%
Kharame	12.50 (3.25, 35,75)	0.00	142.00	6.0%
Khonj	4.00 (2.00, 9.00)	0.00	45.00	1.8%
Darab	4.00 (2.00, 8.00)	0.00	19.00	1.5%
Rostam	0.00 (0.00, 0.75)	0.00	7.00	0.1%
Zarindasht	7.00 (3.00, 12.75)	0.00	29.00	2.1%
Sepidan	3.50 (0.00, 22.00)	0.00	131.00	4.2%
Sarvestan	1.00 (0.00, 7.00)	0.00	38.00	1.4%
Shiraz	59.00 (29.25, 152.5)	9.00	384.00	26.5%
Farashband	1.00 (0.00, 2.00)	0.00	41.00	0.6%
Fasa	7.50 (0.00, 22.75)	0.00	69.00	3.5%
Firoozabad	0.00 (0.00, 2.00)	0.00	6.00	0.3%
Ghirkarzin	1.00 (0.00, 3.00)	0.00	16.00	0.6%
Kazerun	4.00 (2.00, 6.00)	0.00	13.00	1.1%
Lar	15.50 (8.25, 26.50)	3.00	76.00	5.2%
Lamerd	1.00 (0.00, 2.00)	0.00	6.00	0.4%
Marvdasht	88.50 (12.00, 185.25)	0.00	499.00	29.7%
Mamasani	0.00 (0.00, 1.75)	0.00	6.00	0.2%
Neireez	2.00 (0.00, 7.75)	0.00	83.00	1.3%

Table 2. Descriptive measures of 29 201 cutaneous leishmaniasis cases per month between 2010 and 2015 in Fars province, Iran.

Month	Median (lower quartile, upper quartile)	Min	Max	Relative frequency
January	6.50 (2.00, 17.25)	0.00	170.00	9.4%
February	3.00 (0.00, 8.00)	0.00	280.00	5.6%
March	2.00 (0.00, 5.00)	0.00	45.00	2.3%
April	1.00 (0.00, 4.00)	0.00	48.00	2.0%
May	1.00 (0.00, 3.00)	0.00	48.00	1.6%
June	1.00 (0.00, 3.00)	0.00	45.00	1.8%
July	2.00 (0.00, 6.00)	0.00	190.00	3.6%
August	3.00 (1.00, 10.25)	0.00	323.00	7.6%
September	6.50 (1.00, 18.00)	0.00	347.00	13.2%
October	9.50 (3.00, 30.25)	0.00	401.00	18.9%
November	10.00 (4.00, 31.25)	0.00	499.00	20.3%
December	10.00 (3.00, 27.00)	0.00	294.00	13.7%

Based on locating on each different climate; namely: arid, absolutely arid, half semi arid, moderate semi arid, severe semi arid, and semi wet, the endemic scores were generalized to the other 18 cities. If there were more than one estimated endemic values in a particular climate, the average of the endemic scores was generalized to all cities located in that climate. Based on mild CL under reporting considered for Iran which was 2.8-4.6 by WHO, the generalized estimated endemic scores are depicted in Figure 2. Farashband had the largest reported range between 88 and 145, followed by 56-92 in Kharame, Abade, Khonj, Zarindasht, Lar, and Lamerd.

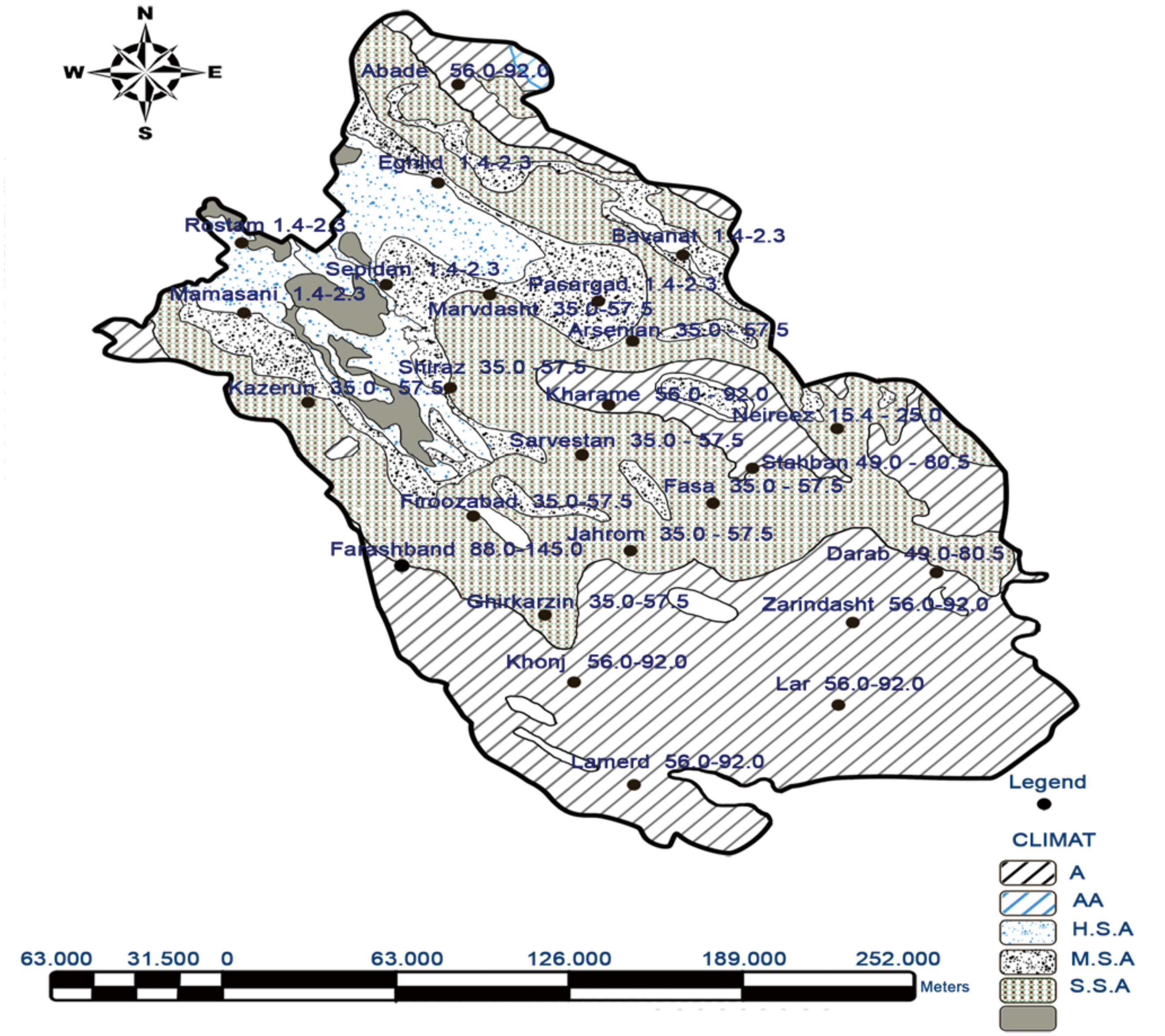

Figure 2. Estimated lower and upper endemic values of cutaneous leishmaniasis in Fars province regarding 6 climates based on 9 retrospectively detected clusters from 2010 to 2015. A: Arid, A.A: Absolutely arid, H.S.A: Half semi arid, M.S.A: Moderate semi arid, S.S.A: Severe semi arid, S.W: Semi wet. Note: Scores are lower and upper endemic values derived based on the under reporting range of cutaneous leishmaniasis in Iran cracked by WHO in 2012.

Table 3. Spatiotemporal permutation scan statistics and subcluster analysis of cutaneous leishmaniasis in Fars province, Iran from 1 January 2010 to 31 December 2015.

Cluster	Location	Radius (km)	Observed/expected	Time frame	Test statistic	*P*-value*
1	Neireez	0.00	3.88	1/7/2010 to 31/12/2010	105.31	0.01
2	Farashband	0.00	16.05	1/1/2015 to 31/1/2015	75.34	0.01
3	Arsenjan	0.00	1.63	1/6/2010 to 30/11/2011	36.59	0.01
4	Rostam	0.00	3.09	1/11/2012 to 28/2/2014	6.83	0.01
5	Kharame	0.00	1.79	1/7/2015 to 31/10/2015	47.84	0.01
6	Fasa	0.00	1.64	1/9/2011 to 28/2/2013	47.55	0.01
7	Stahban	0.00	1.62	1/5/2014 to 31/3/2015	27.77	0.01
8	Darab	0.00	2.47	1/3/2010 to 31/5/2010	16.19	0.01
9	Zarindasht	0.00	1.42	1/4/2014 to 31/12/2015	13.06	0.01

*Statistical significance was evaluated using Monte Carlo hypothesis testing.

Table 4. Receiver operating characteristic curve analysis of endemic values of cutaneous leishmaniasis cases in Fars province.

City	Endemic value	Cutoff[$]	ROC curve results		
			Area under ROC	Std.Error	*P* value[*]
Arsenjan	12.05	0.05	0.07	0.08	0.01
Stahban	17.05	0.54	0.75	0.09	0.01
Kharame	20.00	0.04	0.07	0.08	0.07
Darab	17.05	0.02	0.08	0.01	0.02
Rostam	0.05	0.05	0.07	0.01	0.09
Farashband	31.05	1.00	1.00	0.00	0.08
Neireez	5.05	0.08	0.93	0.04	0.01

ROC: Receiver operating characteristic. [*]significance level was considered at 0.1. [$]a cutoff with maximum sensitivity multiplied by specificity was considered the best potential accurate endemic values.

4. Discussion

Based on the results of the previous work, CL is proved to be a space and time dependent outcome, there were 9 spatiotemporal clusters detected in the area. ROC analysis using detected clusters revealed 7 statistically significant endemic scores in Farashband, Kharame, Stahban, Darab, Arsenjan, Neireez, and Rostam with maximum value of 31.05 in Farashband and minimum value of 0.05 in Rostam. As a correlated factor to CL, 6 main climates in the site; namely, arid, absolutely arid, half semi arid, moderate semi arid, severe semi arid, semi wet were considered to generalize the estimated endemic values to the other cities in the province.

Farashband had the largest reported range between 88 and 145 CL score, meaning that if the observed frequency of CL becomes more than 88, there could be a potential outbreak in Farashband for the next coming year. The next largest range was 56-92 in Kharame, Abade, Khonj, Zarindasht, Lar, and Lamerd. Range of 49.0-80.5 was detected in Stahban and Darab.

Arsenjan, Jahrom, Sarvestan, Shiraz, Fasa, Firoozabad, Marvdasht, Ghirkarzin and Kazerun displayed 35.0-57.5 scores followd by Neireez with 15.4-25.0 score, and the lowest range was detected in Rostam, Eghlid, Bavanat, Mamasani, Sepidan and Pasargad with 1.4-2.3.

The basic reproduction number of infection, R_0 which is used to examine if there is an outbreak or not is useful because it helps determine whether an infectious disease can spread through a population or not. When $R_0<1$, the infection will die out in the long run. But if $R_0>1$, the infection will be able to spread in a population. R_0 is affected by several basics like the infectivity span of the infected person, the infectiousness of the agent and the number of at-risk people in the population, which the infected persons are in touch with. There are plenty of mathematical theories involved in computing R_0, but few of them constantly render the exact value of R_0. This is particularly problematic if there are intermediate vectors between hosts, like CL vector-born infection. Hence, the values of R_0 should be interpreted cautiously[14,21]. In most health centers, the mean of the five past years of disease frequency is considered as an endemic value[14]. Since the distribution of such diseases is not always symmetrical, and it was highly skewed in our case, we had to use another metric to determine the endemic score. Introducing new, innovative ways to estimate an infection endemic value has always been beneficial especially in endemic areas, hereby, we tried to present a method to estimate the endemic score regarding the outcome as a two dimensional phenomenon, a value which is free from any pre-defined distribution and also free from any necessary parameters that need to be approximated in the population.

This study has some limitations that could impact the results severely. Though the under reporting was given into account, the incidence rate of CL might still be underestimated. This could adversely affect the disease burden, the health services forecasts and endemic values estimates. Moreover, related factors like participants' background and environmental elements could result in more accurate endemic score[20,22].

Severe health concern; namely CL endemicity, has been evaluated with only traditional methods of comparing the case occurrences with the average of CL over the past five years. Derived endemic scores based on results of ROC procedure and spatiotemporal analysis could be trustworthy endemic value estimation for CL, especially in Fars province known to be an endemic site in the area.

This method is suggested to apply to countries outside Iran with climatic characteristics close to those of the province of Fars, and the endemic countries such as Afghanistan, Algeria, Brazil, Peru, and Saudi Arabia.

Conflict of interest statement

Authors declare that there are no competing interests.

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