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Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage: http://ees.elsevier.com/apjtm

Original research http://dx.doi.org/10.1016/j.apjtm.2016.12.007

Forecasting the number of zoonotic cutaneous leishmaniasis cases in south of Fars province, Iran using seasonal ARIMA time series method

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ARTICLE INFO

Article history:
Received 15 Oct 2016
Received in revised form 16 Nov 2016
Accepted 15 Dec 2016
Available online 27 Dec 2016

Keywords:
SARIMA model
Zoonotic cutaneous leishmaniasis
Time series analysis

ABSTRACT

Objective: To predict the trend of cutaneous leishmaniasis and assess the relationship between the disease trend and weather variables in south of Fars province using Seasonal Autoregressive Integrated Moving Average (SARIMA) model.

Methods: The trend of cutaneous leishmaniasis was predicted using Mini tab software and SARIMA model. Besides, information about the disease and weather conditions was collected monthly based on time series design during January 2010 to March 2016. Moreover, various SARIMA models were assessed and the best one was selected. Then, the model's fitness was evaluated based on normality of the residuals' distribution, correspondence between the fitted and real amounts, and calculation of Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC).

Results: The study results indicated that SARIMA model $(4,1,4)(0,1,0)_{(12)}$ in general and SARIMA model $(4,1,4)(0,1,1)_{(12)}$ in below and above 15 years age groups could appropriately predict the disease trend in the study area. Moreover, temperature with a three-month delay (lag3) increased the disease trend, rainfall with a four-month delay (lag4) decreased the disease trend, and rainfall with a nine-month delay (lag9) increased the disease trend.

Conclusions: Based on the results, leishmaniasis follows a descending trend in the study area in case drought condition continues, SARIMA models can suitably measure the disease trend, and the disease follows a seasonal trend.

1. Introduction

Leishmaniasis is a widespread zoonotic disease, which is caused by various types of intercellular leishmania parasites [1]. These parasites are transmitted to humans by the bite of female sandfly species. The main clinical forms of this disease include cutaneous, visceral, and mucocutaneous leishmaniasis [2]. Generally, leishmaniasis is a neglected tropical disease and according to the recent estimations, nearly (0.2–0.4) million cases of visceral and (0.7–1.2) million cases of cutaneous leishmaniasis occur annually. More than 90% of visceral leishmaniasis cases occur in six countries, including India, Bangladesh, Sudan, South Sudan, Ethiopia, and Brazil. On the other hand, cutaneous leishmaniasis is widely spread, with one third of the cases occurring in various epidemiological areas in the US, Mediterranean realm, and West of Asia from the Middle East to central Asia. The highest rates of this disease have also been reported in 10 countries, including Afghanistan, Algeria, Columbia, Brazil, Iran, Syria, Ethiopia, North Sudan, Costa Rica, and Peru, comprising 70%–75% of world's rate of affection [3].

Among the clinical forms of the disease, cutaneous leishmaniasis is the most prevalent in eastern Mediterranean region.

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Peer review under responsibility of Hainan Medical University.
Foundation project: The present article was extracted from the thesis written by Mehdi Sharafi and financially supported by Shiraz University of Medical Sciences (grant No. 94-01-04-10456).

In spite of considerable developments in treatment and control of this disease, leishmaniasis is still considered to be a serious health problem. According to World Health Organization (WHO), it is known as the sixth most important disease in tropical areas [4]. In Iran, the main reasons for cutaneous leishmaniasis are major and tropica leishmania [5–7]. Besides, spread of the disease in various parts of Iran depends on the spread of reservoir type, disease vector, parasite, climate, and environmental conditions such as temperature and humidity [8]. Each year, nearly 20 000 cases of two types of the disease, namely zoonotic cutaneous leishmaniasis (ZCL) and anthroponotic cutaneous leishmaniasis (ACL), are reported from various areas in Iran [9]. Similar to other vector-borne diseases, such as malaria, Lyme, and Dengue fever, the seasonal pattern and plenitude of leishmaniasis vectors depend on environmental and weather conditions. Moreover, plenitude of vectors is significantly related to the number of disease cases [10].

Fars province located in south of Iran is one of the endemic foci of ZCL. Most of its towns, such as Jahrom, Fasa, Marvdasht, Kharameh, Arsenjan, and Neiriz, are also foci for hyper endemic of this disease [11].

Up to now, various studies have been conducted on the risk factors, vectors, treatment, and spatial analysis of the disease (GIS) [8,12,13]. Time series analysis and prediction models have also been widely used to predict the required energy, traffic, and health. In fact, predicting the prevalence rate of diseases needs considerable attention and accuracy, because the obtained results play an important role in preventing the epidemic and estimating the facilities [14]. Nonetheless, no comprehensive studies have been carried out on prediction of the trend of leishmaniasis in Fars province. Therefore, this study aims at predicting the disease trend using time series analysis by taking weather variables into consideration.

2. Materials and methods

2.1. Study location

Fars province is located in south of Iran in distances 50°55/E and 27°31/N and covers nearly 8% of Iran's entire area. This province is located 5 000 feet above the sea level. Its temperature ranges from 10 °C in winter to 30 °C in summer. This study was conducted in south of Fars province [15].

2.2. Data collection

The required information was gathered at two stages.

Information regarding the disease cases: The number of disease cases was gathered from all the healthcare centers located in southern towns of the province monthly during January 2010 to March 2016 (74 months). Then, the data were entered into Microsoft Excel 2010. Since age affects the disease trend in endemic areas [16], the data were ordered based on below 15 and above 15 years age groups.

Information regarding weather conditions: Weather information, including the means of temperature, humidity, rainfall, sunny days, rainy days, and evaporation, was gathered from the weather forecast centers of Fars province monthly during January 2010 to March 2016. Factor analysis was used in order to enter the weather variables into the model and assess the disease trend. According to the results of factor analysis, the means of temperature and rainfall showed the highest correlation and, consequently, they were entered into the model as the representative of all the other variables.

2.3. Statistical analysis

In time series analysis using Box–Jenkins' method, Seasonal Autoregressive Integrated Moving Average (SARIMA) and Autoregressive Integrated Moving Average (ARIMA) were used depending on the series structure. When observations are related to each other, the operation of the model is taken into consideration. The correlation between each observation and the previous one provides the model with a possibility to have a better prediction of the disease with seasonal trend. The SARIMA statistical models have been widely used for predicting and determining the active factors, such as weather conditions, in diseases, including malaria, hepatitis, pneumonia, and Dengue fever. Using Box–Jenkins' method, SARIMA and ARIMA models consist of the following steps: providing the series for model fitting, recognizing the primary model by estimating the model's parameters, precisely determining and fitting the model's parameters, and identifying the appropriate model [17,18].

In this study, first the disease trend was taken into account in terms of stationarity.

Stationarity in variance: The disease trend diagram and box cox regression test indicated the non-stationarity in variance. First, the data were made stationary in terms of variance and then, non-stationarity in the means was accounted in the stationary data in terms of variance. In order to assess non-stationarity in the means, Dicky–Fuller test was employed. In this test, null hypothesis (H_0) was the presence of non-stationarity and the other hypothesis (H_1) was the absence of non-stationarity. In this regard, rejection of the null hypothesis indicated the series' stationarity. In case of non-stationarity in the means, regular differencing methods were used to correct the non-stationarity. After determining the stationarity of the series in terms of variance and mean, Autocorrelation Function (ACF) and Partial Autocorrelation Function (PACF) diagrams were utilized in order to determine the parameters of ARIMA (p, d, and q) and SARIMA models (P, D, Q, and S).

P parameter (auto regressive): This index was determined through the PACF diagram and significant lags on the stationary series.

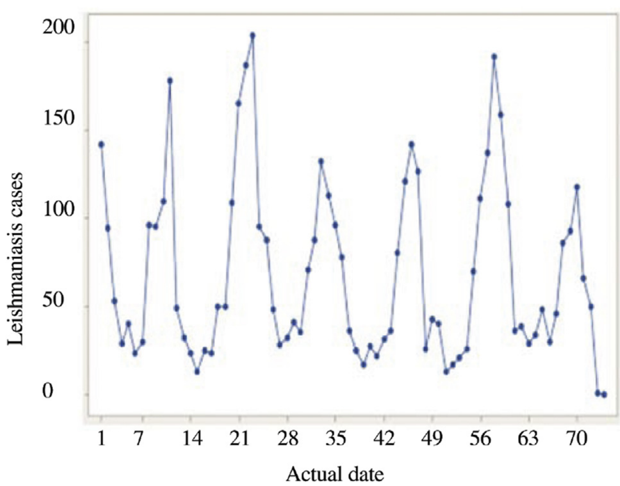

Figure 1. Time series plot for trend of leishmaniasis cases.

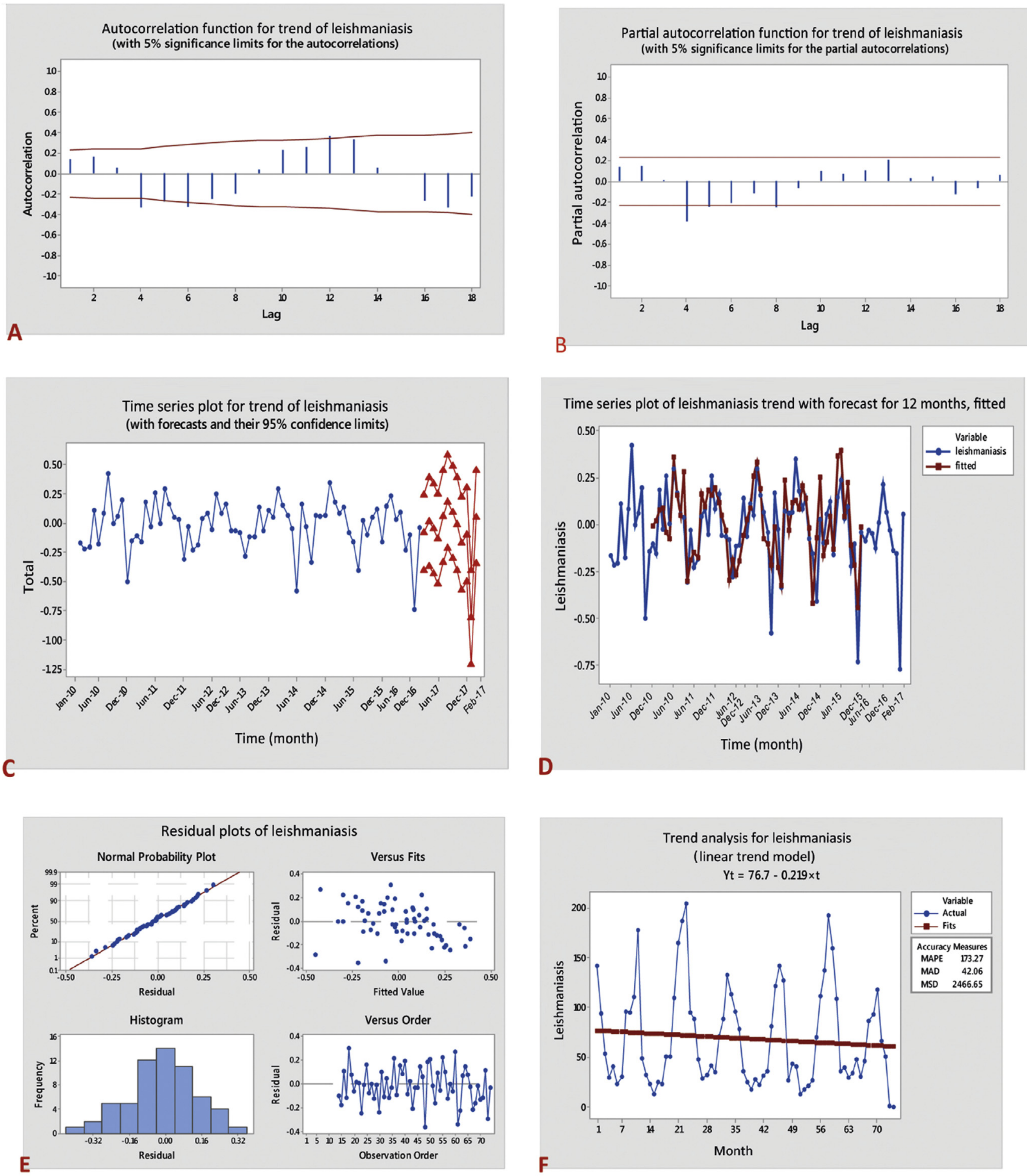

Figure 2. Autocorrelation, partial autocorrelation function, time series plot for trend, residual plots, and trend analysis for leishmaniasis.
A. Autocorrelation function for trend of leishmaniasis (with 5% significance limits for the autocorrelation); B. Partial autocorrelation function for trend of leishmaniasis (with 5% significance limits for the autocorrelation); C. Time series plot for trend of leishmaniasis (with forecasts and their 95% confidence limits); D. Time series plot of leishmaniasis trend with forecast for 12 months, fitted; E. Residual plots of leishmaniasis, with a. Normal probability plot, b. Versus fits, c. Histogram, d. Versus order; F. Trend analysis for leishmaniasis (linear trend model), Yt = 76.7–0.219 × *t*.

Q parameter (moving average): This index was determined through the ACF diagram. The ACF diagram was also used in order to determine the seasonal trend of the disease. In this respect, the sinus waves in the ACF diagram indicated the seasonal trend. In order to control the seasonal trend, ranked differencing (D = 1) was used. In doing so, the deviation of the series' value from its mean in the data related to 12 months ago was used to predict the variable size in this month.

D parameter (difference): This represented the number of differencing performed for making the mean stationary. This index is represented by D in seasonal data.

S Parameter: Since the data were gathered monthly, S was equal to 12.

In order to determine the relationship between the trend of independent variables (temperature and rainfall) and the disease trend, cross correlation diagram and Poisson regression test were utilized. Additionally, model residuals' normality test and their independence were used for evaluating the model. If a model is appropriately fitted, its residuals distribution will be normal and independent. Then, the model can be evaluated by determining the fitted and real values and drawing their diagram. Besides, the fitted amount will correspond to the real amount. Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) were also employed in this study in order to choose the best model. The following formulae were used to compute AIC and BIC [19].

$$AIC = -2 \times \ln(\text{likelihood}) + 2 \times k$$

$$BIC = -2 \times \ln(\text{likelihood}) + \ln(N) \times k$$

Where k was the number of the estimated parameters and N was the number of observations. Finally, the data were analyzed using Mini tab software, version 17.

3. Results

A total of 5069 cases were entered into the study monthly. Among the cases, 51% (2584) were male and the rest were female. Besides, 55% of the cases (2811) belonged to the below 15 years age group, while the rest were related to the above 15 years age group. The means of temperature and rainfall in the study area during six years were (23.74 ± 8.30)°C and (16.16 ± 27.14) mm, respectively.

Time series plot for trend of leishmaniasis cases indicated the seasonal trend of leishmaniasis in the study area (Figure 1). Therefore, the SARIMA model was used. After controlling for the non-stationarity and seasonal trend, the ACF and PACF diagrams have been shown in Figure 2A and B. ACF showed that q = 4 and PACF revealed that p = 4. (p and q in lag4 are significant).

In order to control the non-stationarity in the means and seasonal trend, regular differencing methods (d = 1), ranked differencing (D = 1) were used. Since the data were gathered monthly, S was equal to 12. Determination of parameters from ACF and PACF diagrams are approximate and the exact values of parameters were obtained by assessed fitted values. Various SARIMA models were assessed and the best one was selected.

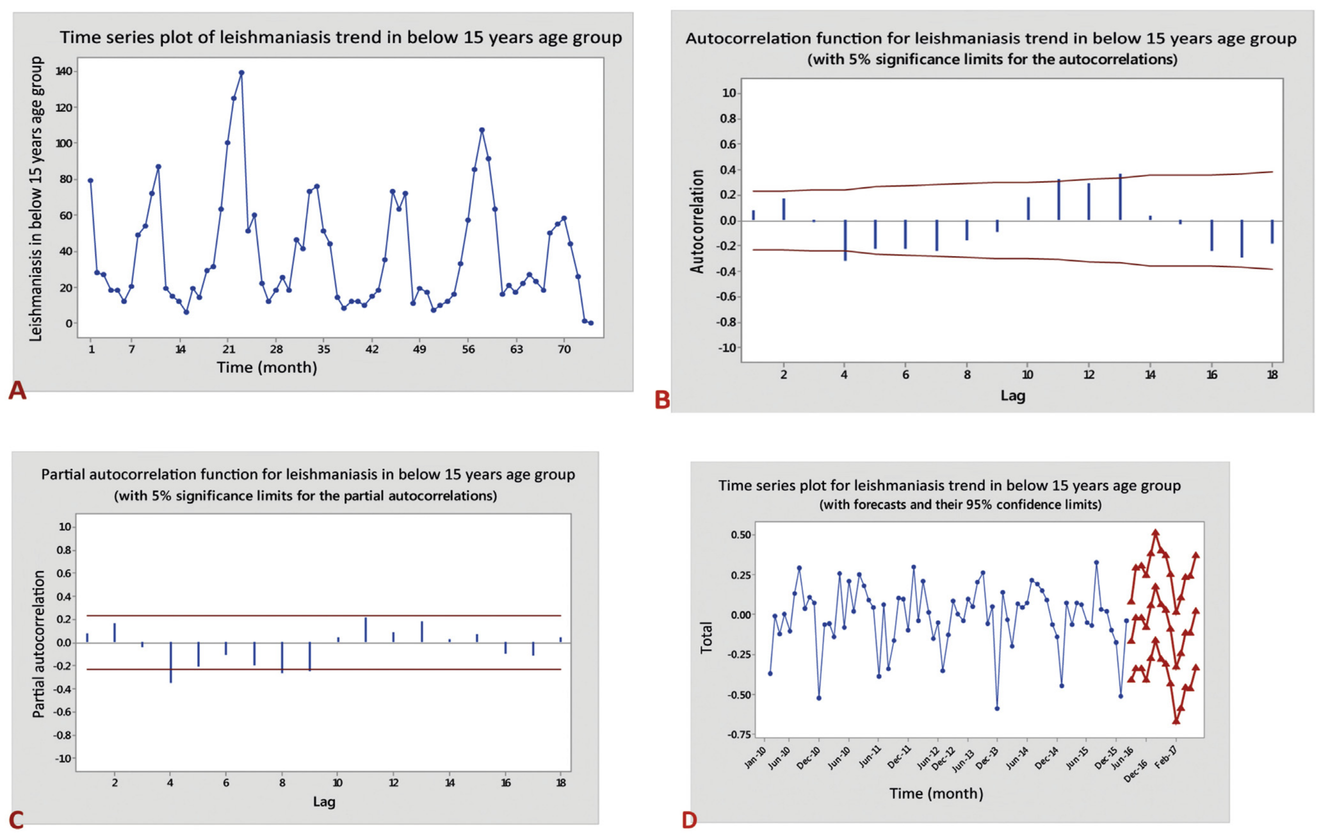

Figure 3. Time series plot, autocorrelation function, partial autocorrelation function for leishmaniasis in below 15 years age group.
A. Time series plot of leishmaniasis trend in below 15 years age group; B. Autocorrelation function for leishmaniasis trend in below 15 years age group (with 5% significance limits for the autocorrelations); C. Partial autocorrelation function for leishmaniasis in below 15 years age group (with 5% significance limits for the autocorrelations); D. Time series plot for leishmaniasis trend in below 15 years age group (with forecasts and their 95% confidence limits).

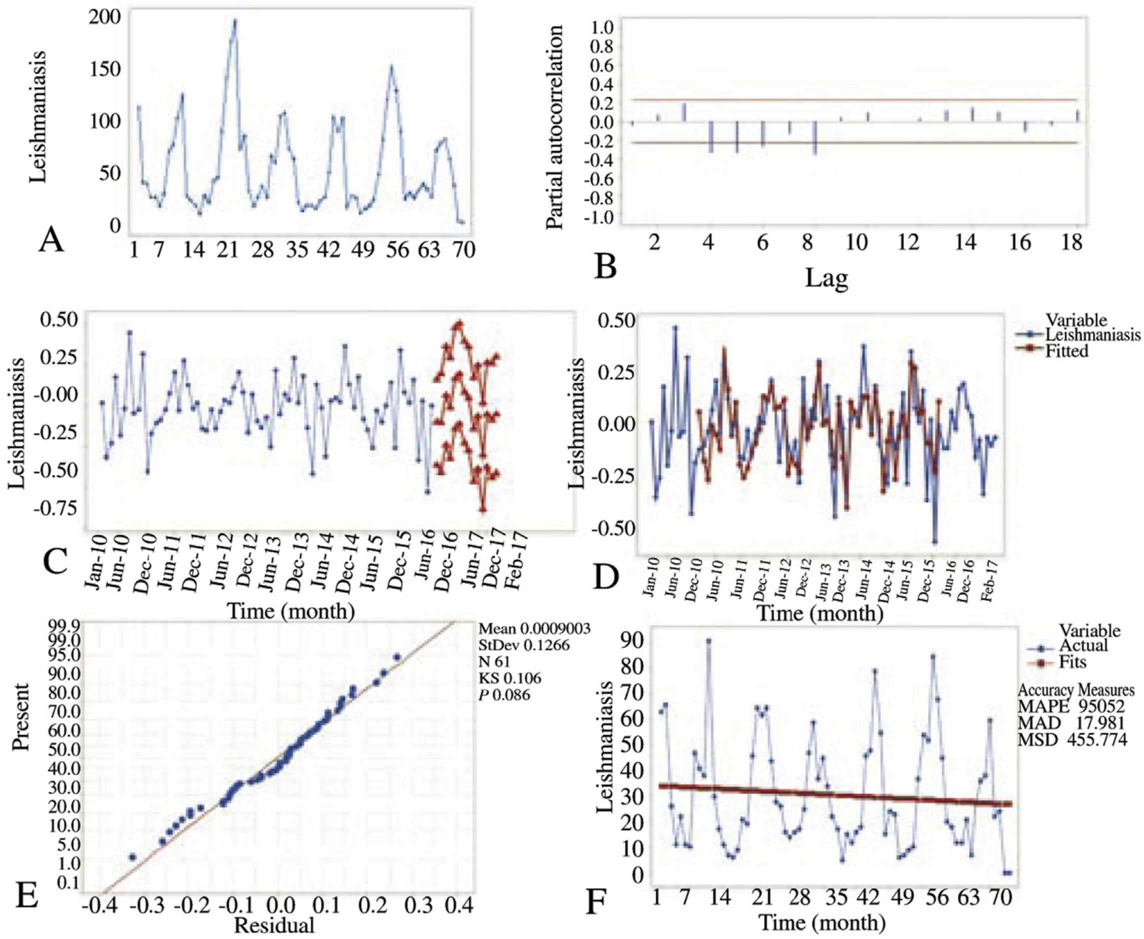

Figure 4. Time series plot, autocorrelation function, partial autocorrelation function, test of residuals' normality, and trend analysis for leishmaniasis in above 15 years age group.
A. Autocorrelation function for leishmaniasis trend in above 15 years age group (with 5% significance limits for the autocorrelations); B. Partial autocorrelation function for leishmaniasis in above 15 years age group (with 5% significance limits for the partial autocorrelations); C. Time series plot for leishmaniasis trend in above 15 years age group (with forecasts and their 95% confidence limits); D. Time series plot of leishmaniasis trend in above 15 years age group, fitted; E. Test of residuals' normality; F. trend analysis for leishmaniasis in above 15 years age group (linear trend model), Yt = 34.27–0.100 × *t*.

The prediction results of the SARIMA model $(4,1,4)(0,1,0)_{(12)}$ with 95% confidence interval have been depicted in Figure 2C ($P < 0.05$). The results indicated that the disease followed a descending trend.

The fitted and real amounts of the disease cases have been presented in Figure 2D. In addition, Figure 2E showed the normal distribution of the model's residuals. Besides, the results of trend analysis in Figure 2F indicated the descending trend of the disease. After making the series stationary and controlling for the seasonal trend in below and above 15 years age groups, SARIMA models $(4,1,4)(0,1,1)_{(12)}$ were selected for these two groups. The model results have been shown in Figures 3 and 4. Accordingly, the disease followed a descending trend in both age groups.

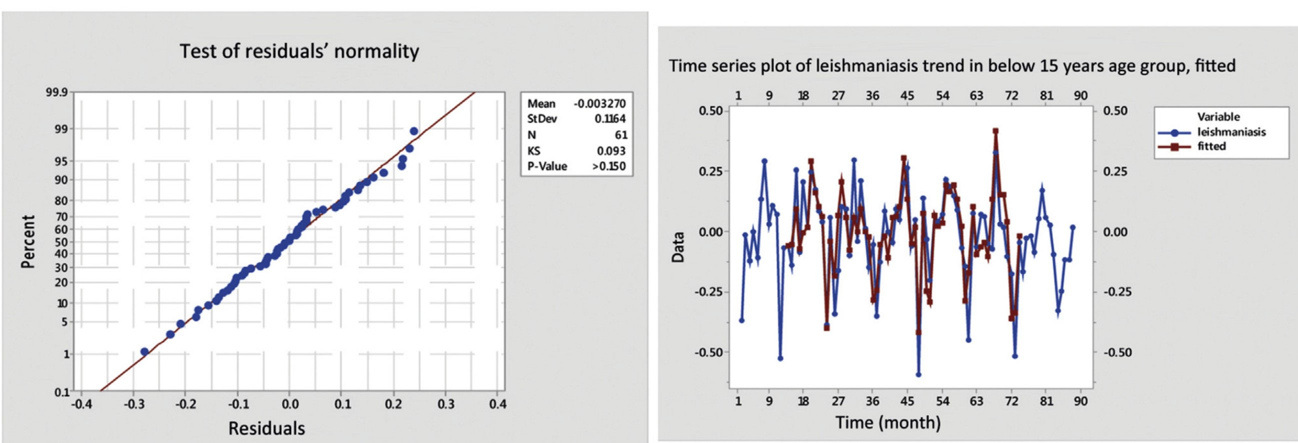

Figure 5. Test of residuals' normality and time series plot of leishmaniasis trend in below 15 years age group.
A. Test of residuals' normality; B. time series plot of leishmaniasis trend in below 15 years age group, fitted.

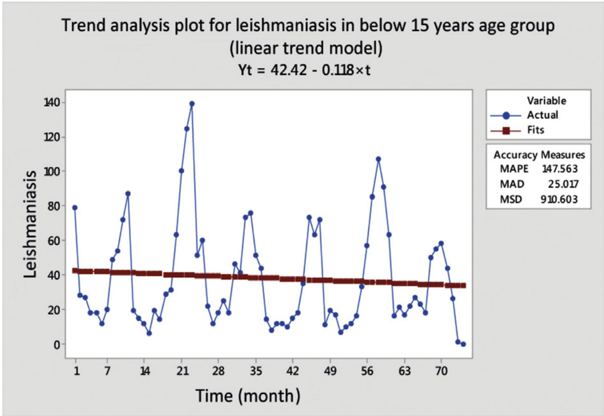

Figure 6. Trend analysis plot for leishmaniasis in below 15 years age group.
Linear trend model, Yt = 34.27–0.100 × *t*.

Table 1
The characteristics of SARIMA models.

Model	Group	AIC	BIC	Variance	Likelihood
SARIMA $(4,1,4)(0,1,0)_{(12)}$	Total	600.11	619.11	717.4	−291.05
SARIMA $(4,1,4)(0,1,1)_{(12)}$	<15 years	532.58	553.69	213.1	256.29
SARIMA $(4,1,4)(0,1,1)_{(12)}$	>15 years	510.57	531.68	162.5	−245.28

Table 2
Poisson regression for the relationship between rainfall and temperature means and leishmaniasis trend.

Variable		IRR	95% CI	*P*
Mean of temperature	Lag0	0.9800	0.9776–0.9842	<0.001
	Lag3	1.0630	1.0590–1.0670	<0.001
Rainfall	Lag0	1.0050	1.0030–1.0080	<0.001
	Lag4	0.9602	0.9575–0.9628	<0.001
	Lag9	1.0350	1.0334–1.0375	<0.001

The normality of the model residuals' distribution and correspondence of the fitted amount with the real amount in Figure 5 showed that the model was well-fitted. Moreover, the trend analysis in age groups indicated the descending trend of the disease (Figures 6 and 4F).

The amounts of each model's BIC, AIC, variance, and likelihood have been presented in Table 1. Additionally, the cross correlation diagrams of temperature and rainfall means and leishmaniasis trend have been depicted in Figure 7. The results revealed that leishmaniasis trend had the highest correlation with lag3 temperature and the Incidence Rate Ratio (IRR) in lag3 decreased from 0.9800 to 1.0630 ($P < 0.001$). In lag4, the disease trend showed a reverse relationship with the mean of rainfall and IRR increased from 1.0050 to 0.9602 ($P < 0.001$). In lag9, on the other hand, the disease trend showed a direct relationship with the mean of rainfall and the IRR increased from 0.9602 to 1.0350 ($P < 0.001$) (Table 2).

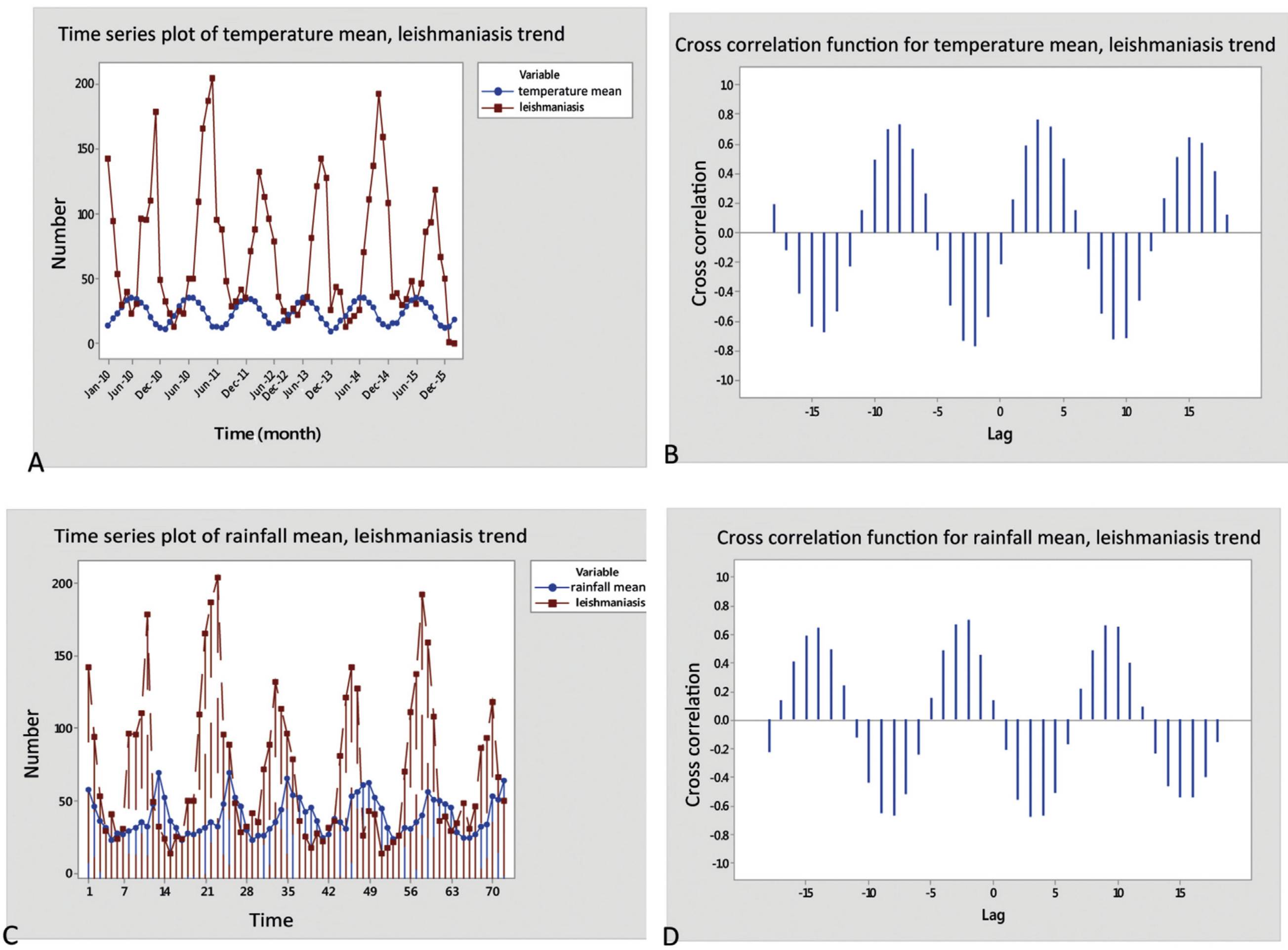

Figure 7. Time series plot for temperature and rainfall mean, and cross correlation functions for leishmaniasis trend.
A. Time series plot for temperature mean, leishmaniasis trend; B. Cross correlation functions for temperature mean, leishmaniasis trend; C. Time series plot of rainfall mean, leishmaniasis trend; D. Cross correlation function for rainfall mean, leishmaniasis trend.

4. Discussion

This study focused on time series analysis of cutaneous leishmaniasis and predicting the disease trend in future based on weather changes in south of Fars province during January 2010 to March 2016. The study results revealed that SARIMA model $(4,1,4)(0,1,0)_{(12)}$ and SARIMA model $(4,1,4)(0,1,1)_{(12)}$ appropriately predicted the disease trend in this area, particularly in above 15 and below 15 years age groups. According to the model's results, the disease followed a descending trend in general and in both age groups. Additionally, the model's fitted amounts and normality of the model residuals' distribution demonstrated the model's fitness.

The study results also indicated that the mean of temperature with a three-month delay (lag3) caused an increase in the disease trend. However, rainfall with a four-month delay (lag4) caused a decrease in the trend of the disease. On the other hand, rainfall with a 9-month delay (lag9) led to an increase in the disease trend. The descending trend of the disease in the area could be attributed to implementation of disease controlling programs, including fighting against the reservoirs (rodents) and vectors (various types of *Phlebotomus papatasi*) and improving the environment, which have been conducted in all the areas of the province during the disease transmission season (from April to November) since 2008. In Iran, several studies have been conducted on the effectiveness of rodenticide programs with P_2ZN_3 poison in decreasing the incidence of ZCL. Therefore, implementation of the programs leading to a decrease in disease reservoirs could finally decrease the incidence rate of the disease [20–22]. Smearing mosquito nets with permethrin poison could also disrupt the chain of disease transmission to humans and, consequently, decrease the number of vectors (*Phlebotomus papatasi*) [23]. Furthermore, increasing individuals' level of knowledge regarding the disease and its prevention methods that has been continuously implemented by healthcare centers could affect the disease trend. These issues have been proved in various studies [24]. Moreover, the incidence rate of the disease is higher in children than in adults in endemic areas. Due to their infection with this disease during childhood, the prevalence of this disease is lower among adults and they are immune against the disease. Additionally, considering the decreasing trend of childbearing (decrease in sensitive population), the descending trend of this disease can be attributed to the decrease in the sensitive population. It can also be related to draught trend and decrease in vegetation due to the impact of environmental conditions, especially weather, on plenitude of the disease vectors and reservoirs.

The relationship between cutaneous leishmaniasis and temperature, Normalized Difference Vegetation Index (NDVI), rainfall, humidity, wind, and El Niño has been indicated in various studies. Accordingly, warm and humid conditions providing appropriate conditions for vectors could increase the number of cases affected by the disease after humid seasons [10,25–27]. In these areas, continuation of drought trend and decrease in rainfall, which affect the environmental factors could lead to the disease descending trend. It should also be noted that each area has its own weather conditions, hosts, and disease vectors and the disease trend can change based on such conditions. Therefore, assessment of the disease trend should be specific to each area's conditions. The findings of the current, similar to other studies, revealed that temperature and rainfall were significantly related to the disease trend. In these areas, temperature with lag3 had a direct relationship, rainfall with lag4 showed a negative relationship, and rainfall with leg9 had a direct relationship with the disease trend.

In French Guiana, Amaury Roger *et al.* concluded that temperature with lag8 and El Niño with lag4 had a direct relationship, while rainfall with lag2 had a negative relationship with the disease trend [28]. Furthermore, the results of a study conducted in North Africa revealed that cutaneous leishmaniasis was related to a 2-year delay (lag2) after rainfall and NDVI index. In addition, temperatures above the critical range could decrease the incidence of ZCL by limiting the vectors reproducing activities [26]. In this regard, we can refer to the El Niño phenomenon that results in arid conditions through warming the ground. This will lead to rapid growth of plants, eventually increasing the number of disease cases with the peak occurring after 4 or 5 months. On the other hand, the La Nina phenomenon causing humid and cold conditions will decrease the number of disease cases [25].

The present study was conducted during the draught condition. Since weather condition affects the disease, the results of prediction depend on continuation of this weather condition. In addition, the healthcare system of cutaneous leishmaniasis in Iran is relatively passive and individuals with small ulcers may not refer to healthcare centers. On the other hand, the strong point of the current study was that the weather variables were taken into account, while they were ignored in the previous studies.

Predicting the trend of diseases, as an important issue in the early warning system, plays a key role in preventing the epidemic, providing facilities, and controlling diseases. In diseases with seasonal trend, the SARIMA model can be used for appropriate prediction of the disease trend due to deletion of the seasonal component.

In the present study, different SARIMA models were assessed and the best one was selected. SARIMA model $(4,1,4)(0,1,0)_{(12)}$ in general and SARIMA model $(4,1,4)(0,1,1)_{(12)}$ in below and above 15 years age groups could appropriately predict the disease trend in the study area.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Acknowledgments

The present article was extracted from the thesis written by Mehdi Sharafi and financially supported by Shiraz University of Medical Sciences (grant No. 94-01-04-10456). Hereby, the authors would like to express their gratitude to the Center for Disease Control (CDC) in the health centers of Shiraz University of Medical Sciences for providing the required information about the disease. They would also like to appreciate Ms. A. Keivanshekouh at the Research Improvement Center of Shiraz University of Medical Sciences for improving the use of English in the manuscript.

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