An Application of Markov Switching Models in Predicting Visceral Leishmaniasis in Ardabil Province, Iran

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Abstract

Background: Visceral leishmaniasis (VL) is a neglected infection currently occurring in some regions of Europe, Asia, Africa, and America. This study was an attempt to determine the temporal patterns of VL from January 2000 to December 2019 in the Ardabil Province of north-western Iran using the Markov Switching Models (MSM).

Methods: This descriptive study used monthly data of 602 VL cases during the study period. The data were provided by the Leishmaniasis National Surveillance System (LNSS), the Iran Meteorological Organization (IMO), and Space Agency (SA), and two states were considered for such modelling. Given the Akaike and Bayesian information criterion, the two-state MSM with a five-month lag is an appropriate model.

Results: The MSM showed that the probability of staying in the non-epidemic state is 67%, (P11), while that of staying in an epidemic state is 93% (P22). The mean absolute percentage error (MAPE) was 31.63%, and the portmanteau test (Q=19.03, P=0.66) for the residuals of the selected model revealed that the data were completely modelled. The total VL cases in the next 24 months forecasted 14 cases.

Conclusion: The MSM has a relatively acceptable predictive power and is useful in planning future interventions with more information about different stages of the epidemic it provides to policymakers for early warning of epidemics.

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Introduction

Visceral leishmaniasis (VL) is a zoonotic disease common around the world and is reported from over 50 countries commonly situated in the Eastern Mediterranean and Northern America.[1] Currently, VL is an endemic infection in Iran and its prevalence is estimated at 2% and 16% in humans and dogs, respectively.[2, 3] On the other hand, VL is known as the third opportunistic disease in people with immunodeficiency, such as those living with HIV/AIDS.[4-6] According to the official reports, 1,990 cases of VL were found from 2000 to 2019, and 30.25% of those cases happened in Ardabil.[7]

VL is one of the diseases subject to compulsory reporting in the surveillance system at the Center for Disease Control of the Ministry of Health in Iran. In this surveillance, epidemiological and clinical features are completed in the reporting form of VL in health centers or hospitals, and then it is registered in the surveillance system of VL.

Several studies have reported the relationship between VL and environmental factors.[8-10] Because dogs in Iran are considered a reservoir of VL[11, 12] and its transmission to humans is carried by a vector sandfly, the occurrence of VL in humans may depend on climatic and environmental factors. A study in northern Iran showed that the most important environmental and climatic factors affecting the rate of canine visceral leishmaniasis infection include isothermal, temperature, rainfall, humidity, and vegetation.[13] These factors are associated with the occurrence of the disease in the population of the reservoir, i.e. dogs, and ultimately cause disease in the population of the reservoir and its transmission by sandflies to human hosts.[9, 14]

A few studies have considered the effect of climate and environmental factors in time series analysis for the modelling and prediction of VL in Iran, and most of the modelling done on VL so far has used spatial models.[15-17]

Creating a surveillance system is necessary for the fast discovery of leishmaniasis outbreaks, and for monitoring possible epidemics in each area. Furthermore, the surveillance system, particularly in endemic regions, should be completely ready to deal with leishmaniasis epidemics. One of the most prevalent methods used in epidemiology to predict future values is the time series model.[18] Furthermore, different models are used such as the Gray model, the general regression model, the negative binomial regression model, and the neural network model; however, each has its own assumptions and validity.[19-21]

In the previous study, Box–Jenkins SARIMA models have been used to predict infectious diseases such as brucellosis,[22] COVID-19,[5, 23, 24] influenza,[25] Crimean-Congo hemorrhagic fever (CCHF),[26] and Zoonotic cutaneous leishmaniasis (ZCL).[27-29] As infectious diseases fall into one of two stages of epidemic or non-epidemic, the use of Box–Jenkins methods for early detection of outbreaks face limitations.[30] The use of dynamic models in this case seems to be superior to static models.[26] This study aimed to determine the temporal patterns of VL in Ardabil Province, using Markov Switching Models (MSM).

Methods

Study Site

Ardabil province is located in northwestern Iran, and according to the General Population and Housing Census (GPHC), the province had a population of 1,270,420 in 2016 (866,034 urban and 404,386 rural). Ardabil has four warm Mediterranean, temperate Mediterranean, cold, and temperate mountainous climates. This province is famous as one of the coldest districts in Iran. The average minimum and maximum annual temperatures in this province are -4 and 30 degrees Celsius, respectively. The average annual rainfall is 260mm, and the humidity is 17-100%.[13]

Data Collection

This descriptive study applied monthly data of 602 VL cases from January 2000 to December 2019. The data were provided by the Leishmaniasis National Surveillance System (LNSS) at the Ministry of Health. All climate data such as the average monthly temperature, average monthly maximum and minimum temperature, average monthly pressure, average monthly relative humidity, average maximum, and minimum relative humidity, total hours of sunshine per month, total number of rainy days per month, total monthly rainfall, and maximum and minimum monthly wind speed were gathered from the meteorological organization of Ardabil province. The data were collected from five synoptic centers in Ardabil province, which shows the highest incidence of VL. The vegetation information was extracted from the Moderate Resolution Imaging Spectroradiometer (MRISR) (16-day composites) satellite. MRISR uses remote sensing data of the Normalized Difference Vegetation Index (NDVI), for analysis, measurement, and evaluation of the presence or absence of vegetation in an area. NDVI changes range from +1 to -1, where positive values indicate more vegetation and negative values indicate a lack of green vegetation.[31] The NDVI data of the province were accessible via the Iranian Space Agency (ISA) for the period from January 2000 to December 2019.

Statistical Analysis

The simple time series models are not capable of explaining the nonlinear occurrence of outcomes such as the data of surveillance systems of infectious diseases. Therefore, the MSM model is used due to the problem of structural failure and nonlinearity of the series.[26] The MSM is one of the most famous models for nonlinear time series models that shows the occurrence of outcomes in different states.[30] Since the VL series has a switching state from epidemic and non-epidemic and vice versa (as the name of the switching suggests), the model was found suitable for analyzing and predicting such data. In this study, modelling was carried out separately for the epidemic and non-epidemic states (number of states: 2).

A simple MSM model can be written as follows (in this model, S_t=1 means epidemic state and S_t=0 means non-epidemic state):

$$yt = a_{0.0} + a_{0.1}s_t + (a_{1.0} + a_{1.1}s_t)y_{t-1} + e_t \quad (1)$$

$$P(s_t = j/s_{t-1} = i) = p_{ij} \quad (2)$$

$$s_t \in \{0.1\} \quad (3)$$

$$e_t \sim N(0.\sigma^2). \quad (4)$$

The model shows that in the non-epidemic state S_t=0 and the value of y_t is determined based on the $\alpha_{0,0}$ constant and the autoregressive parameter with $\alpha_{0,1}$. If an epidemic happens (S_t=1), the constant value increases to $\alpha_{0,0+}\alpha_{0,1}$, and the autoregressive parameter value increases to $\alpha_{1,0+}\alpha_{1,1}$ (see Equation 1).

Equation 2 shows that the hidden states S_t is a function of Markov significant with the transition probability; *Pij* is the probability of state *j* at time *t* conditional to state *i* at time *t–1:*

$$p''_{ij}\left(s_t = \frac{j}{s_{t-1}} = i.\, s_{t-2} = k.\, \ldots\, s_{t-k} = n\right)$$

$$= p\left(s_t = \frac{j}{s_{t-1}} = i\right) = p''_{ij} \quad (5)$$

$$p''_{ij} + p + \cdots + p_{in} = 1'' \quad (6)$$

The transition probability is also an N*N matrix consisting of *Pij*. After fitting the model and estimating the parameters, the values of ρ_{00} and ρ_{10} were also estimated. According to the values of these parameters, the matrix of transition probabilities can be formed as follows:

$$p'' = \begin{bmatrix} p00 & p01 \\ p10 & p11 \end{bmatrix} = \begin{bmatrix} p00 & 1-p00 \\ 1-p11 & p11 \end{bmatrix}, \quad (7)$$

In this matrix, the sum of the probabilities of each row is equal to one. Here, $\rho_{0,0}$ means that the regime is likely to be at the non-epidemic state at time *t*, provided it is at a non-epidemic state at time *t-1*. The ρ_{11}, means the probability that the regime will be in a state of the epidemic at time *t* provided that it is also in a state of the epidemic at time *t-1*. The ρ_{01} means the probability that the regime is in a state of the epidemic at time *t*, provided that it is at a non-epidemic at time *t-1*. The ρ_{10} means the probability that the regime is in a non-epidemic state at time *t*, provided that it is in a state of the epidemic at time *t-1*.

Independent variables as external regression with different lags were used about VL cases using cross-correlation coefficients to detect the best predictor and its best lag(s) to be included in the final model. To eliminate autocorrelation and seasonal trend of each series, we performed the pre-whitening method. For this end, we used a Box–Jenkins model for each separate series[29] and then evaluated the correlation between the residuals of the univariate model of VL and those of climatic variables over a range of lags.

Afterward, the achieved model was used to forecast the incidence cases. The predicting accuracy was assessed by the Mean Absolute Percentage Error (MAPE), which was calculated by equation 8:

$$MAPE = \frac{1}{N}\sum_{t=1}^{n} \frac{\text{Actual cases} - \text{Predicted cases}}{\text{Actual cases}} \quad (8)$$

Where N is the number of predictions.

Analysis of data was performed using Stata software (version 14) and package time series analysis. To assess the seasonal trend, stationary in variance and mean, we used the chi-square for trend, Box-Cox regression, and Dickey-Fuller tests, respectively. The validity of the MSM was examined by fitting the data for the period of the study. Nonetheless, the portmanteau test for white noise graphically checked the normality of the residuals. The alpha level was 0.05.

Results

Descriptive Analysis

Figure 1 shows that the trend of VL cases from 2000 to 2019 has reduced significantly since 2005

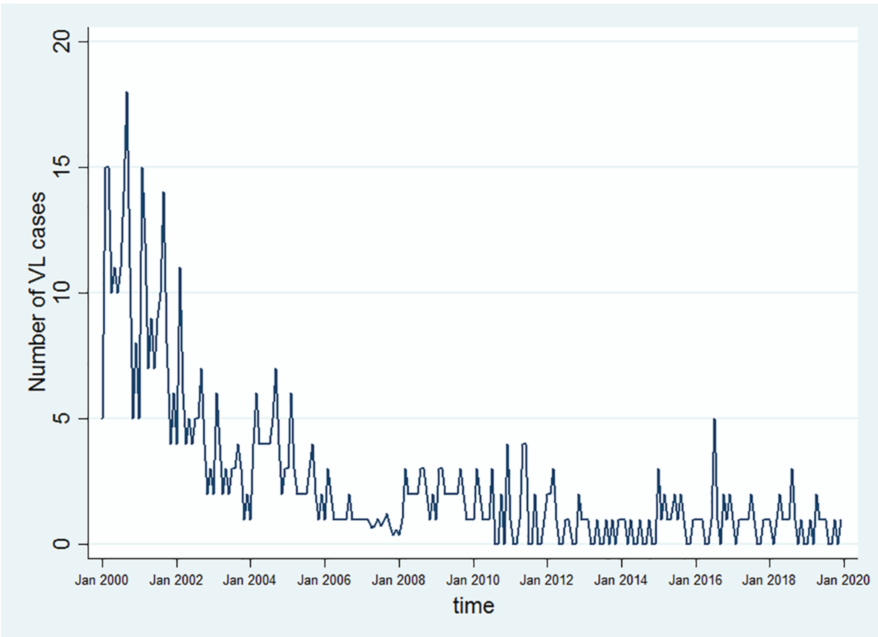

Figure 1: The trend of 602 Visceral leishmaniasis cases from January 2000 to December 2019 in Ardabil Province

and since August 2010, there have been reports of zero cases in some months of the year; therefore, we used smoothing methods for eliminating series noise, reducing fluctuations in the data and improved presentation of series patterns (Figure 2). Chi-Square for trend showed that the occurrence of VL did not have a seasonal trend (X2=5497.28, P=0.411).

Table 1 shows the correlation between environmental variables with the number of cases of VL during the years 2000- 2019. There was a correlation between the minimum monthly wind speed and the occurrence of the disease (Figure 3).

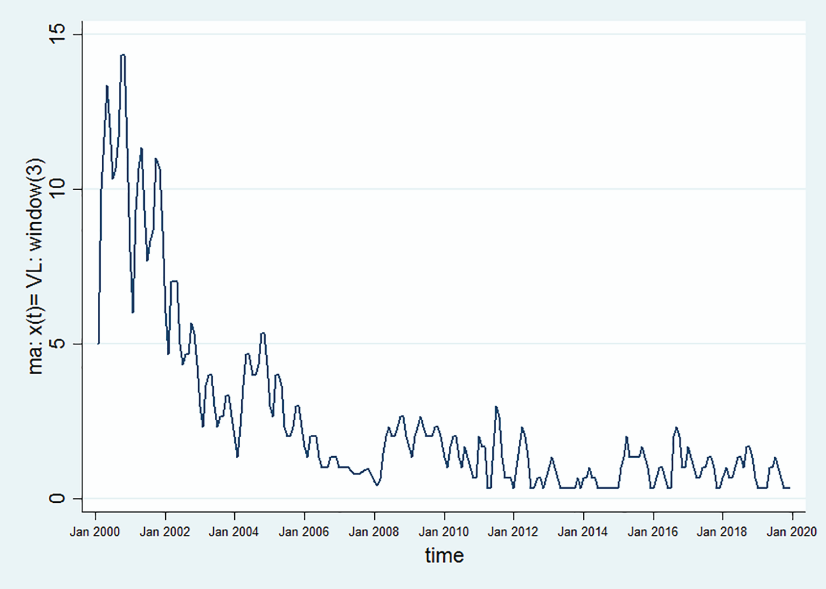

Figure 2: The smoothing trend and distribution of 602 Visceral leishmaniasis cases from January 2000 to December 2019 in Ardabil Province.

Table 1: Correlation of environmental variables with Visceral leishmaniasis cases in Ardabil province during 2000-2019

Variable	Average temperature (°C)	Maximum temperature(°C)	Minimum temperature(°C)	Average relative humidity (%)	Maximum relative humidity (%)	Minimum relative humidity (%)	Average air pressure	Minimum wind speed	Maximum wind speed	Total monthly rainfall	Number of rainy days	Total hours of sunshine	Mean NDVI
Pearson correlation coefficient	-0.01	0.02	-0.03	-0.05	0.16	-0.04	-0.16	-0.13	-0.43	-0.09	-0.11	0.08	-0.08
Significance	0.81	0.71	0.56	0.41	0.08	0.45	0.008	0.03	<0.001	0.13	0.06	0.11	0.21

NDVI: Normalized Difference Vegetation Index

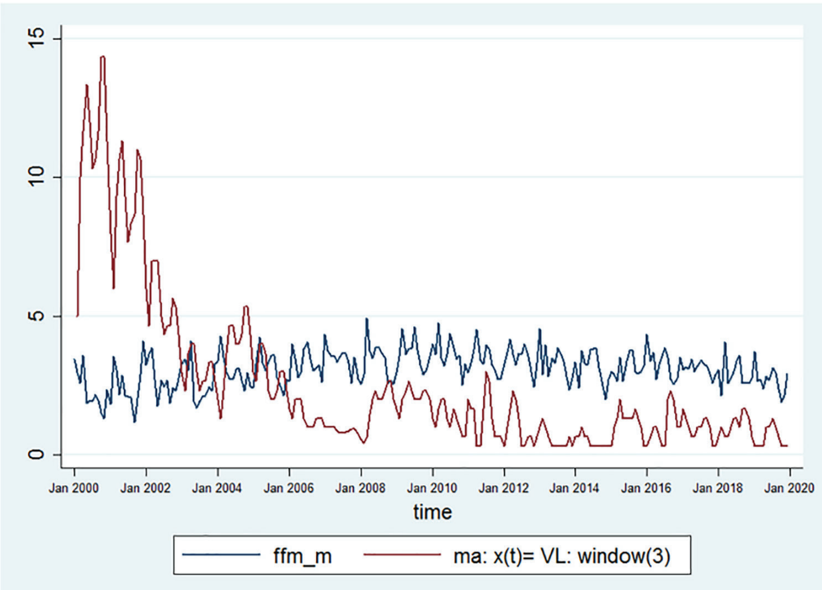

Figure 3: Number of cases of visceral leishmaniasis and minimum monthly wind speed in Ardabil Province during 2000-2019

Table 2: Cross-correlation coefficients of environmental variables in Ardabil Province from zero lag (communication without delay) to 12 months' lag

Time lag (Months)	Average temperature (°C)	Maximum temperature(°C)	Minimum temperature(°C)	Average relative humidity (%)	Maximum relative humidity (%)	Minimum relative humidity (%)	Average air pressure	Minimum wind speed	Maximum wind speed	Total monthly rainfall	Number of rainy days	Total hours of sunshine	Mean NDVI
-12	0.009	0.02	0.004	-0.07	0.11	-0.1	-0.01	0.09	-0.10	-0.01	0.02	0.04	-0.01
-11	-0.04	-0.03	-0.08	-0.01	0.06	-0.04	0.07	-0.09	0.03	0.03	0.03	0.04	0.001
-10	-0.02	0.01	-0.01	0.11	0.05	-0.03	-0.01	0.10	-0.03	-0.08	-0.09	0.12	0.09
-9	0.08	0.07	0.05	-0.005	0.04	-0.01	0.001	-0.05	-0.01	-0.04	0.02	0.007	0.007
-8	0.11	0.011	0.11	-0.05	0.15	-0.06	-0.11	0.04	0.03	-0.04	-0.01	0.01	-0.04
-7	0.03	0.04	0.0002	-0.05	0.03	-0.07	-0.05	-0.002	0.03	-0.02	-0.04	-0.01	-0.02
-6	0.03	0.03	-0.01	-0.05	-0.08	-0.03	0.06	0.02	0.008	-0.02	-0.01	-0.08	-0.07
-5	0.04	0.04	-0.0006	0.01	0.01	-0.02	0.007	-0.06	0.01	0.03	-0.005	0.01	0.02
-4	-0.06	-0.06	-0.02	0.02	0.03	0.07	-0.01	-0.05	0.07	0.12	0.08	-0.09	-0.04
-3	-0.09	0.10	-0.13	0.11	0.04	0.12	0.05	-0.006	0.02	0.05	0.09	-0.08	0.008
-2	0.14	0.12	0.11	0.07	0.04	-0.07	0.005	-0.03	0.04	-0.09	-0.09	0.04	-0.07
-1	-0.03	-0.01	0.004	-0.001	-0.04	0.005	-0.03	0.05	0.003	0.01	0.02	-0.006	-0.01
0	0.04	0.06	0.03	-0.07	0.009	-0.002	0.005	-0.02	-0.03	-0.04	-0.08	0.05	0.01

NDVI: Normalized Difference Vegetation Index

Table 3: Regression coefficients of Markov Switching Models for Visceral leishmaniasis cases in Ardabil Province

Parameters	Coefficient	S.E	95% CI	P value
AR(5)	0.94	0.02	0.89,0.98	<0.001
Constant(1)	-0.53	0.31	-0.88,-0.19	0.002
Constant(2)	0.37	0.31	0.20,0.88	0.002
Sigma	0.27	0.01	0.24,0.30	-
P11	0.67	0.09	0.48,0.82	-
P21	0.06	0.09	0.03,0.11	-
AIC	0.81	-	-	-
BIC	0.90	-	-	

AR: autoregressive, AIC: Akaike information criteria, BIC: Bayesian information criterion

As can be seen, there was a correlation between the minimum monthly wind speed and the occurrence of the disease, but this type of relationship is not our concern and may be due to justifiable patterns. In time series analysis, these patterns should be eliminated and any trend, decrease or increase in the number of cases of the disease, should be identified for reasons other than justifiable patterns because failure to remove these patterns leads to false connections.

Cross-correlation Function

Due to the nature of VL and reviewing previous studies,[26, 29] the number of time lags was considered 12. Table 2 shows the cross-correlation coefficient of the VL incident as well as the climate and environmental factors in different lags. However, there was no significant correlation between the variables and the incidence of VL in any of the lags. Zero lags were not considered due to their insignificance and non-applicability.

Markov Switching Model (MSM)

At the beginning of preparing the series or data to fit the model, the Box-Cox regression test was used to check the stationary variance of the data. This test showed that there were non-stationary variances, and log transformation was used. in the next step, to evaluate the stationary in the mean, the Dickey-Fuller test was performed; it was revealed that the data were stationary (P=0.02).

Since the VL series has a switching state from epidemic and non-epidemic, two states were considered for modelling. State 1 was considered as the non-epidemic state, and state 2 was selected as the epidemic one. Table 3 shows the coefficients for the MSM model.

If we consider the constant estimated by the model in the epidemic state as the epidemic threshold, according to the model, the number of cases above two for VL in the province per month can be taken as the outbreak threshold. This is because log transformation was used for stationary of the variance of the series, and the exponential of this coefficient was used to reach the real value, so that expression (0.37)=1.45.

In addition, according to the MSM, the transition probabilities were calculated as follows:

$$p" = \begin{bmatrix} p11 & p12 \\ p21 & p22 \end{bmatrix} = \begin{bmatrix} p11 & 1-p11 \\ 1-p22 & p22 \end{bmatrix} ” = \begin{bmatrix} 0.67 & 0.33 \\ 0.07 & 0.93 \end{bmatrix}$$

Where P11 is the non-epidemic state, it is 67% likely to stay in the non-epidemic state, and only 33% is likely to change from a non-epidemic to an epidemic state. *P21* indicates a 7% chance of regime change from the epidemic to a non-epidemic state. In other words, if the regime is in an epidemic state,it is 93% likely to stay in the epidemic state.

Table 4 showed the average period in each regime; that is, when the regime is in the non-epidemic state, it lasts an average of three months (95%CI: 1.92-5.73), and when it enters the epidemic state, it lasts an average of 15.38 months (95%CI: 8.44-28.77) and then enters a non-epidemic state.

Figures 4 and 5 show the smoothed probabilities for both regimes. The vertical axis indicates the probability that its value is between zero and one,

Table 4: The average time in each state

Expected Duration	Estimate	Standard error	CI 95%	
			Lower	Upper
State1	3.09	0.87	1.92	5.73
State 2	15.38	4.82	8.44	28.77

CI: Confidence interval

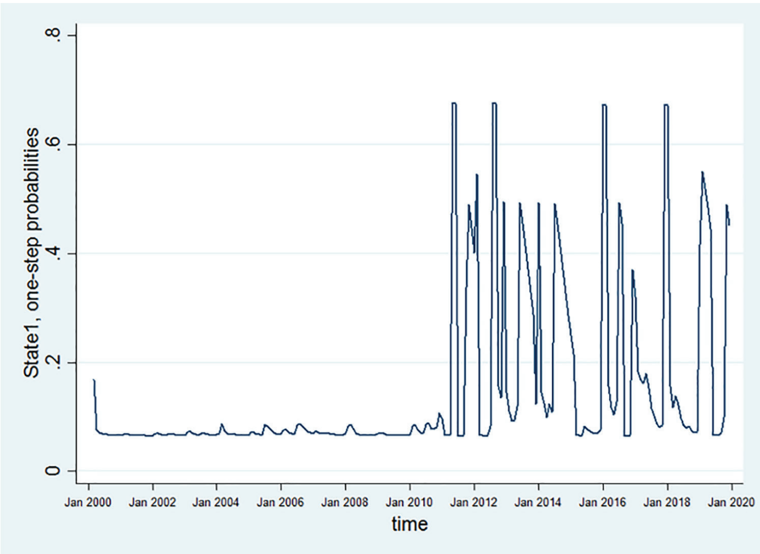

Figure 4: Smoothed probabilities for state 1 in the Markov Switching Models

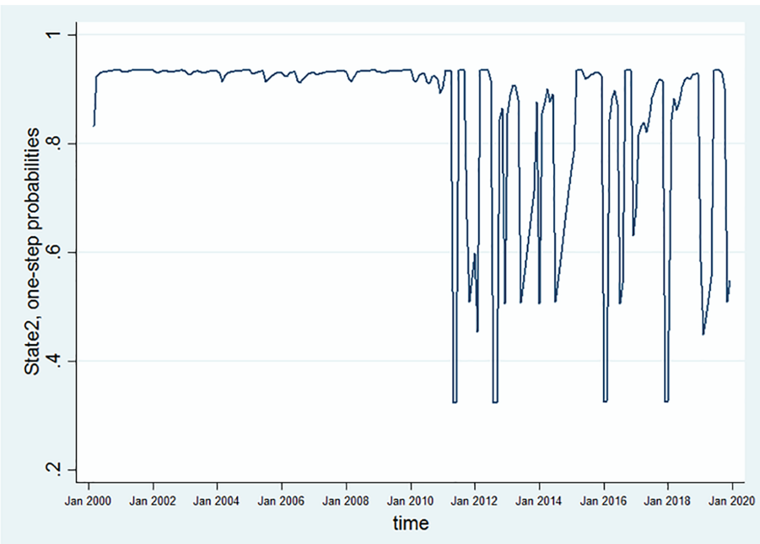

Figure 5: Smoothed probabilities for state 2 in the Markov Switching Models

and the horizontal axis of time is monthly. These two graphs are opposites and from which, until 2010, the VL situation was mainly in a state of the outbreak, and the following years, periods of relaxation and outbreak were repeated.

Figure 6 shows the number of observed and predicted VL cases for the period from January 2000 to December 2019 based on the MSM. To evaluate the validity of the MSM, a fitted model with real data of VL from January 2000 to December 2019 was used, and then forecast the number of VL cases from January 2020 to December 2021. The total VL cases in the next 24 months were forecast for 14 cases.

The residuals were investigated to check the goodness of fit. The residual histogram showed that the residues had a normal distribution (Figure 7). The MAPE quantity was 31.63%. The portmanteau test (Q=19.03, P=0.66) for the residuals of the choice model revealed that the data were completely fitted.

Discussion

In this study, we have introduced the Markov Switching Model as a good tool to reflect the trend of visceral leishmaniasis incidence in Ardabil Province. The findings of this study revealed that the incidence of VL had no seasonal distribution, and none of the climatic factors studied was associated with the incidence of VL. The occurrence of VL mainly depends on the distribution of cases that occurred in previous months, and the correlation of each observation with the previous observation can predict the course of VL.

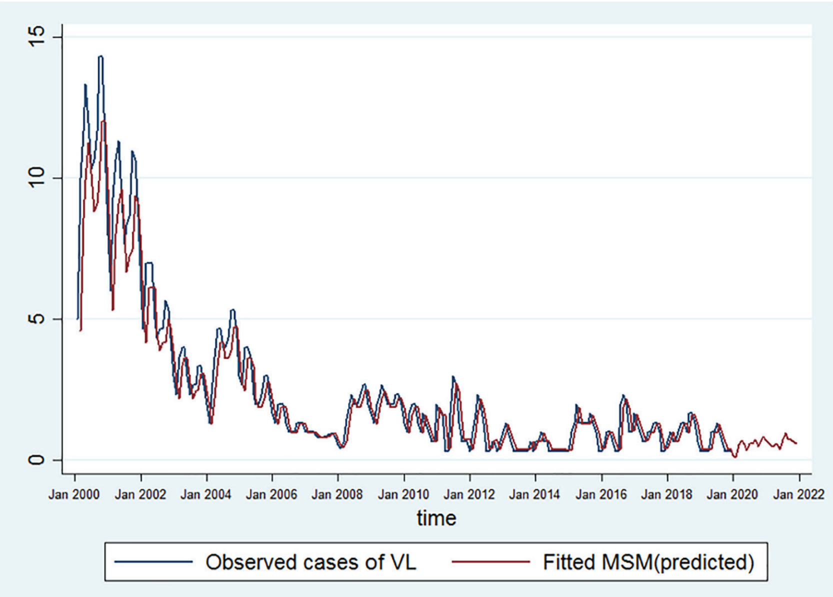

Figure 6: Observed Visceral leishmaniasis cases for the period from January 2000 to December 2019 and 1-step ahead forecast from January 2020 to December 2021 based on the Markov Switching Models

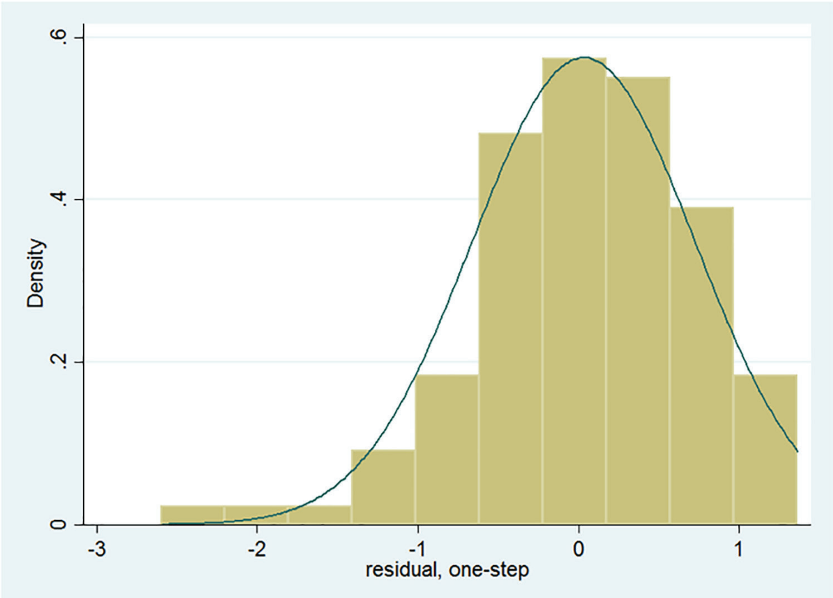

Figure 7: Histogram of the residuals in Markov Switching Models

Based on the transition probabilities calculated in the MSM, it can be concluded that VL has been in the epidemic state for 10 years, and since 2011, epidemic periods have been shortened, which may be related to control measures taken such as disease control programs in reservoirs and vectors, improving public awareness of the disease in recent years in the study area.

Other results of this study revealed that there was no significant association between environmental variables and the occurrence of VL in different time lags. However, in a study of the associations between meteorological factors and VL epidemics in China using generalized estimating equations analysis, it was shown that temperature and relative humidity had very significant associations with the VL risk, and there were interactions between these factors.[32] Our results are not in the same line with those of other studies probably because we performed pre-whitening to evaluate the relationships between the incidence of VL and the environmental data at different lags. Then, the cross-correlation between the residuals in different series was investigated.[26, 27] In time series analysis, cross-correlation on the original data is not suggested because without pre-whitening, the significant correlations observed between the one lag of different variables may be due to the auto-correlation in seasonal time series.[33] In addition, the statistics such as Pearson and Spearman's correlation assume that the data are independent, whereas this assumption is not true in time series data. Each observation is correlated with its previous values, so using such statistics without pre-whitening can result in misleading outcomes.[29]

On other hand, some studies have shown the association of climatic variables with the occurrence of canine visceral leishmaniasis (CVL); however, such studies showed that the most important environmental factors affecting CVL included isothermality, temperature seasonality, rainfall, humidity, and normalized difference vegetation index (NDVI).[8] In Brazil, most cases of CVL occur in areas with high-density vegetation and rivers as well as houses with vegetation and high debris.[34] In France, however, there was a negative correlation between CVL cases and NDVI.[9] Given that in Iran canines are the reservoir for the disease and its transmission to humans is carried out by the sandfly, it can be inferred that the occurrence of VL in humans does not depend on climatic factors. It is associated with canines and eventually causes an abundance of disease in the reservoir population, and its transmission by vectors to human hosts.[35]

The results of a meta-analysis showed that there was an association between VL and bad living conditions, absence of urban substructure, sustainable services, and low levels of education. Another study explains the greater frequency of carriers and the lack of responsibility of pet owners and the location of houses in regions where vegetation density is appropriate for the presence of carriers and maybe reservoirs.[14]

Using Markov models in epidemiological surveillance of infectious diseases was first introduced by Le Strat and Carrat.[36] The use of MSM in medicine and public health has increased; however, such a model has been used to forecast the occurrence of brucellosis.[37] Furthermore, MSM has been used to forecast new cases of tuberculosis.[38, 39] One study in Iran applied MSM to forecast Crimean–Congo haemorrhagic fever (CCHF).[26] Meanwhile, a study in the United States used MSM to determine hospital infection.[40]

One of the strengths of this study is that the time unit was considered much longer, i.e. 240 months, which reveals more accurate and detailed information about the trend of the disease and its link with environmental factors. On the other hand, our study had several limitations. First, the use of the existing data in a surveillance system of disease may indicate a systematic underestimation. Second, there are other factors such as host-related factors, vectors, reservoir variety, and health interventions than the climatic factors in the epidemiology of VL which are effective and should be considered for future studies.

Conclusion

The MSM has a relatively acceptable predictive power and is useful in planning future interventions with more information about different stages of the epidemic; it provides the policy-makers with early warning of epidemics.

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Authors' Contribution

The authors contributed equally to this work.

Ethical Consideration

This research was approved by the Faculty of Veterinary Medicine, University of Tehran, Iran, (Project identification code (Ref: 7265130).

Conflict to Interest: None declared.

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