International Journal of Biometeorology
https://doi.org/10.1007/s00484-021-02135-8

ORIGINAL PAPER

The effect of climate variables on the incidence of cutaneous leishmaniasis in Isfahan, Central Iran

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Received: 29 February 2020 / Revised: 15 February 2021 / Accepted: 14 April 2021

Abstract
In recent years, there have been considerable changes in the distribution of diseases that are potentially tied to ongoing climate variability. The aim of this study was to investigate the association between the incidence of cutaneous leishmaniasis (CL) and climatic factors in an Iranian city (Isfahan), which had the highest incidence of CL in the country. CL incidence and meteorological data were acquired from April 2010 to March 2017 (108 months) for Isfahan City. Univariate and multivariate seasonal autoregressive integrated moving average (SARIMA), generalized additive models (GAM), and generalized additive mixed models (GAMM) were used to identify the association between CL cases and meteorological variables, and forecast CL incidence. AIC, BIC, and residual tests were used to test the goodness of fit of SARIMA models; and R^2 was used for GAM/GAMM. 6798 CL cases were recorded during this time. The incidence had a seasonal pattern and the highest number of cases was recorded from August to October. In univariate SARIMA, (1,0,1) $(0,1,1)_{12}$ was the best fit for predicting CL incidence (AIC=8.09, BIC=8.32). Time series regression (1,0,1) $(0,1,1)_{12}$ showed that monthly mean humidity after 4-month lag was inversely related to CL incidence (AIC=8.53, BIC=8.66). GAMM results showed that average temperature with 2-month lag, average relative humidity with 3-month lag, monthly cumulative rainfall with 1-month lag, and monthly sunshine hours with 1-month lag were related to CL incidence (R^2=0.94). The impact of meteorological variables on the incidence of CL is not linear and GAM models that include non-linear structures are a better fit for prediction. In Isfahan, Iran, meteorological variables can greatly predict the incidence of CL, and these variables can be used for predicting outbreaks.

Keywords Iran · Forecasting · Time series analysis · SARIMA · Generalized additive model · Leishmaniasis, Cutaneous

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Introduction

The leishmaniases are a group of diseases caused by *Leishmania* parasites which come from more than 20 species. These parasites are transmitted to mammals, including humans, by the bite of infected female phlebotomine sandflies (Reithinger et al. 2007). Leishmaniasis is a neglected tropical disease, found in southern Europe and the Middle East (Wu et al. 2016). There are many forms of this disease in humans, but the most common form is cutaneous leishmaniasis (CL), which causes skin ulcers. CL is caused by the genus *Leishmania* transmitted through the bite of the female phlebotomine sand fly. Currently, there is no effective vaccine for CL (Khanjani et al. 2020).

The global number of all forms of this disease is 12 million, and 1.5–2 million new cases are diagnosed annually (Desjeux 2004; Oryan and Akbari 2016), of which 0.7–1.2 million cases are cutaneous leishmaniosis (Alvar et al. 2012; Shirzadi 2012; WHO 2017). Isfahan has one of the highest

Published online: 29 April 2021

prevalences of CL in Iran (Fig. 1). The reasons are probably its arid climate, high immigration, and other environmental and topographic factors. The incidence of CL in Isfahan province was 60.4 cases per 100,000 persons in 2007–2015 (Ramezankhani et al. 2018).

There are several risk factors that are known to impact the incidence rates of leishmaniasis (Oryan and Akbari 2016). These factors include environmental conditions, socioeconomic status, demographic characteristics (Alvar et al. 2012), and human behavioral characteristics (Reveiz et al. 2013; Votýpka et al. 2012). Some studies have suggested that the prevalence and spread of leishmaniasis is more affected by environmental conditions than economic or social factors (Yazdanpanah and Rostamianpur 2013). Environmental conditions can influence the distribution and vector reservoirs that can consequently affect the distribution and incidence of vector-borne diseases such as leishmaniasis (Toumi et al. 2012). Climate and meteorological variables can affect the distribution of leishmaniasis through three mechanisms. First, they directly affect parasite evolution and vector qualification. Second, they can indirectly affect the range and distribution of vectors. Third, they can affect people's activity

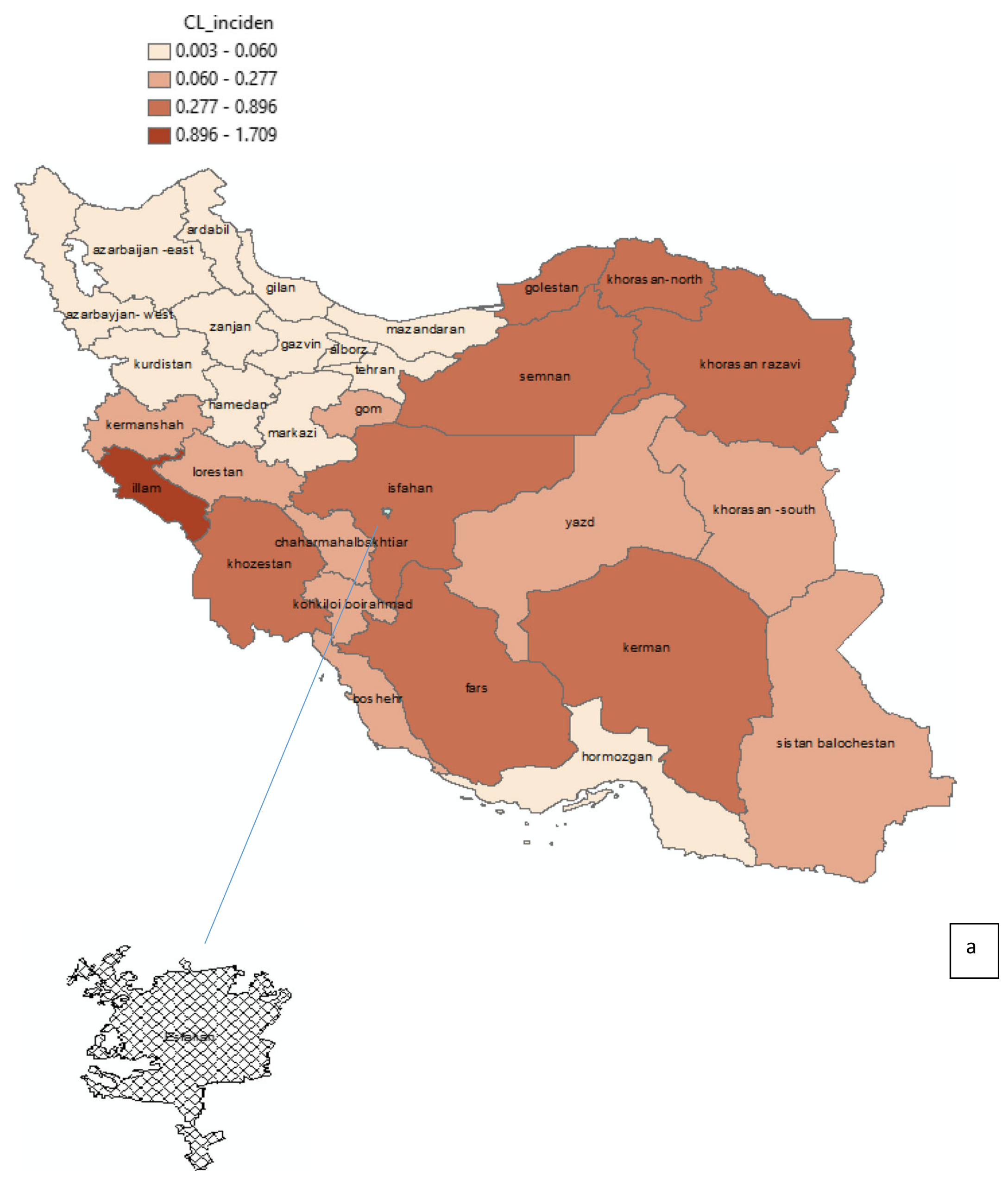

Fig. 1 The distribution of cutaneous leishmaniasis according to province in Iran (**a**) and Isfahan City (**b**)

pattern which can increase exposure to vectors (Ready 2008). The proliferation and growth of the sandflies is influenced by vegetation and climatic factors including temperature and precipitation (Mozafari and Bakhshizade Koloche 2011; Chaves and Pascual 2006, 2007). There is emerging evidence from Iran that shows CL is moving to higher latitudes (Hatami et al. 2018), which may be in response to increased temperatures and climate change (Elnaiem et al. 2003).

In recent years, several studies conducted in Iran and other countries have used statistical models to evaluate the effect of environmental factors on CL (Talmoudi et al. 2017; Azimi et al. 2017; Lewnard et al. 2014; Sharafi et al. 2017; Selmane 2015; Shirzadi et al. 2015; Tohidinik et al. 2018; Nikonahad et al. 2017; Ramezankhani et al. 2018). We built on these prior studies by (1) estimating non-linear relations between climatic factors and CL and (2) building predictive models to estimate the burden of CL in Isfahan, Iran. The choice of model has a great impact on quantifying these relations (Talmoudi et al. 2017). One of the reasons for using time series models in this study is that it provides the possibility of estimating the trend by taking into account previous observations and trends (Talmoudi et al. 2017). However, considering the fact that time series considers the linear relation between the response variable and the prediction variables, GAM was used to assess non-linear relations as well. GAM allows for a rather flexible specification of the dependence of the response on the covariates (Wood 2017). GAM is a semi-parametric model that, unlike parametric models, does not impose the form of the trend, and allows the data to determine the trend (Nkurunziza et al. 2010). However, due to the autocorrelations between the observations, in this study the generalized additive mixed model (GAMM) was used in data analysis.

Predictive models are critical for decision-making processes such as reallocation of resources, if CL epidemics are foreseen (Chaves and Pascual 2007). The aim of this study was to assess the effect of climatic variables on the incidence of CL.

Material and methods

Study population and area

Isfahan is the third largest city in Iran with a population of about 2 million people and with the highest incidence of CL in the country (Fig. 1). Its geographical location is 32° 39′ N and 51° 43′ E and is located in Central Iran. Isfahan has a semi-arid climate with relatively cold winters. The average annual precipitation is between 110 and 160 mm and the average annual temperature is between 10 and 16°C (IRIMO 2015). This city has an arid climate based on the De Martonne classification with an average temperature of 2.2°C in the coldest month (January) and 28.2°C in the warmest month of the year (Akbari 2017).

Outcome data

The diagnosis of leishmaniasis is basically inactive, which means patients who visit health centers with suspected lesions are identified and referred to the city's leishmaniasis laboratory (Shirzadi 2012). CL case definition in Iran is based on confirming the presence of the parasite in the tissue sample by direct smear, culture, or clinical and epidemiologic criteria. Cases which were diagnosed between April 2010 and April 2017, in Isfahan, were inquired from the Iranian Ministry of Health and Medical Education's Center for Communicable Disease and were included in this study. The recorded time of disease onset was the time that the first symptoms appeared, not the time the diagnosis was made. The number of cases diagnosed monthly was used in this study.

Meteorological data

Weather variables from 2010 until 2017 were obtained from the Isfahan City meteorological station. Meteorological data included average, minimum, and maximum monthly temperature, relative humidity, monthly cumulative rainfall, and the sum of sunshine hours per month. In case data was not available for some days, the monthly average was calculated based on data from the available days. In this study, spring included April, May, and June; summer included July, August, and September; autumn included October, November, and December; and winter included January, February, and March.

Modeling approach and evaluation

We used seasonal autoregressive integrated moving average (SARIMA) models to investigate the seasonality and time pattern of CL incidence (Helfenstein 1991). SARIMA models are used for time series data and take care of the correlation between adjacent points. It can be considered a combination of complex and simple statistical models (Shumway and Stoffer 2017). Initially, we used the autocorrelation function (ACF) and partial autocorrelation function (PACF) graphs to identify trend, stationary, and seasonality. Points exceeding the 95% CI were considered as target lags. In order to assess non-stationary of the mean, the Dicky-Fuller test was used. In case the data was non-stationary, the first-order non-seasonal difference (d=1) and the first-order seasonal difference (D=1) were calculated. The moving average (MA) (P, p) and autoregressive (AR) (Q, q) parameters were obtained by checking the ACF and PACF plots. We used Box-Cox transformations to stabilize the variance. If the transformation is done properly, residuals must be independent and have a normal distribution. Investigation of normality can be accomplished visually by looking at a histogram of the residuals, or using a normal probability plot or a Q-Q plot (Khorrami and Bozorgnia 2008). We used "tseries" package version 0.10-47 designed by Trapletti (Trapletti et al. 2019) in R software (R version 3.5.3) to do the statistical analysis.

We used multivariate time series analysis to investigate the dynamic relation between temperature, humidity, rainfall, and sunshine, with leishmaniasis incidence. This modeling technique allowed several dependent series to be modeled together and while accounting for both cross- and within-correlations of the series. At first, the pre-whitening process was used to eliminate the autocorrelation and seasonal trends of the variables and the SARIMA model was run for each of the meteorological variables. Then, they were added to the univariate model to assess the impact of meteorological variables. The variance inflation factor (VIF) was used to test collinearity between variables. In the case of high collinearity (VIF≥10) between variables, they were separately entered into the competing models and their effect was evaluated separately, and finally, the best variable and its most significant lag were retained in the model, based on the Bayesian information criterion (BIC) and Akaike information criterion (AIC). In these indices, a lower number indicates a better fit.

Generalized additive models (GAM) can be used to analyze non-linear relations (Helfenstein 1991). GAM transforms the standard linear model of each of the variables into a model with non-linear functions. The general form of the linear regression model is $yi = \beta 0 + \beta 1xi1 + \beta 2xi2 + \bullet\bullet\bullet + \beta pxip + \_i$, in which simple variables (xi) are replaced by non-linear functions $fj\ (x_{ij})$.

$$yi = \beta 0 + \Sigma fj\ (xij) + \varepsilon i = \beta 0 + f1\ (xi1) + f2\ (xi2) + \_ + fp\ (xip) + \varepsilon i$$

The reason for naming this model additive is that fj is calculated for each variable, and then, they are summed together (James et al. 2013). Unlike the GLM, GAM automatically identifies and estimates the best degree of non-linearity according to the effective degree of freedom (Toumi et al. 2012; Wood 2017). The cross-correlation function (CCF) between the residuals of the Y and Xi series was computed with 95% confidence intervals (cut-off at $1.96n^{-1/2}$), where n was the length of the time series in months.

GAMM, used in this study, is an expanded form of GAM that is used to control for high dispersion and autocorrelation in observations and allows the response variable to have a flexible dependence on the independent variables. It also considers the correlation between observations, using random effects. Independent variables in non-parametric additive functions are considered fixed effects (James et al. 2013).

The "mgcv" package version 1.8-7, designed by Wood (Wood 2017), available in the R statistical software (version 3.5.3), was used for analysis.

Ethics statement

This project was approved by the ethics committee of Kerman University of Medical Sciences, Kerman, Iran (Ethics Code: IR.KMU.REC.1397.233). All health data were deidentified.

Results

Overall, there were 6798 cases of CL recorded between 2010 and 2017 in Isfahan City. The mean age of all cases with CL was 24.1±17.6 years at the time of diagnosis. The mean age in men was 23.6±14.2 and in women was 24.7±18.6, which was significantly different (p-value=0.007). The majority of cases (66%) were male, the median age at onset of symptoms was 22, the skewness was 4.98, and the incidence was higher in younger ages. Table 1 illustrates the demographic characteristic of CL cases in Isfahan City. In this study, 89% of the cases were infected with L. major. Therefore, the number of *Leishmania tropica* cases was too low to do a separate analysis.

The monthly distribution of CL cases is depicted in Fig. 2. The peak of CL mainly occurred from August to October. The incidence was significantly different in different months (Kruskal-Wallis=76.66, df=11, p<0.001). Time series graphs of the number of cases indicated that CL incidence had a seasonal pattern. The stationary trend indicated that differencing was not required (Fig. 3, top). There was a significant

Table 1 Distribution of the cutaneous leishmaniasis (CL) cases by age, sex, and job in Isfahan City, 2010–2017

Characteristics		No. of cases (%)
Age	0–4	729 (10.72)
	5–14	1090 (16.03)
	15–24	2141 (31.49)
	25–59	2586 (38.04)
	≥60	252 (3.70)
Sex	Male	4524 (66.55)
	Female	2274 (33.45)
Job	Child	995 (14.63)
	Student	1115 (16.40)
	House keeper	1145 (16.84)
	Driver	95 (1.39)
	Ranch	51 (0.75)
	Clerk	338 (4.97)
	Farmer	86 (1.26)
	Military	1472 (21.65)
	Manual worker	443 (6.52)
	Unemployed	33 (0.48)
	Others	1025 (15.08)

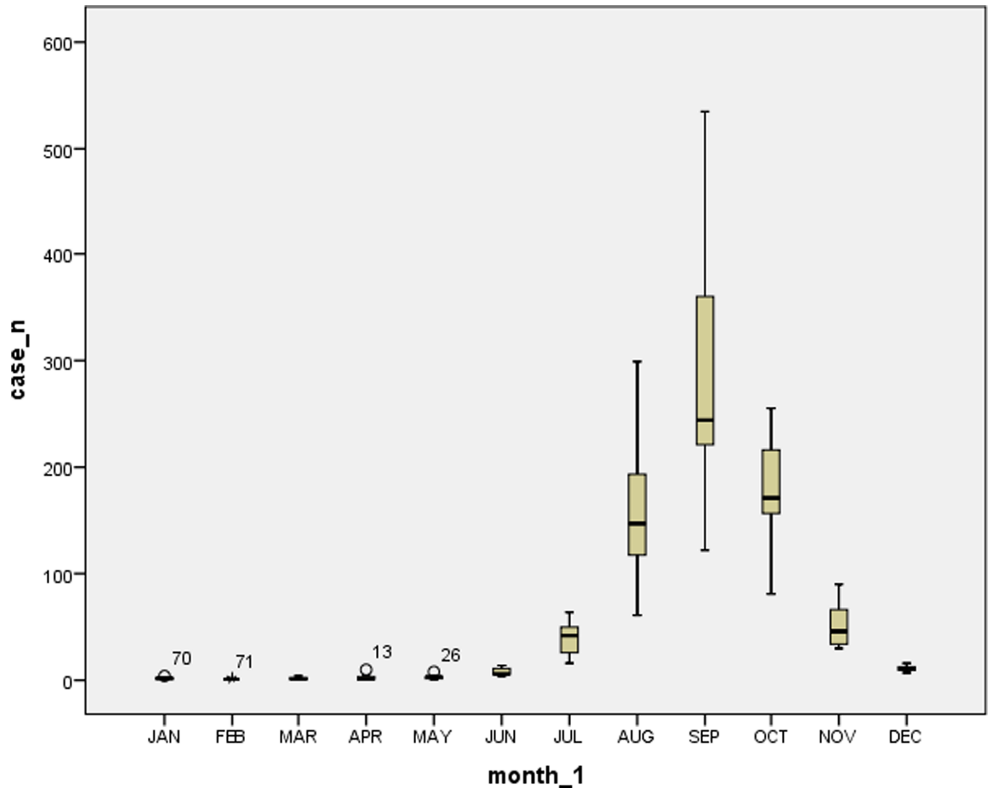

Fig. 2 Box plot of monthly CL incidence

dependence on the first lag, according to the ACF and PACF graphs (Fig. 3, bottom). AIC and BIC were calculated for different models and the models with the least values were considered the best models.

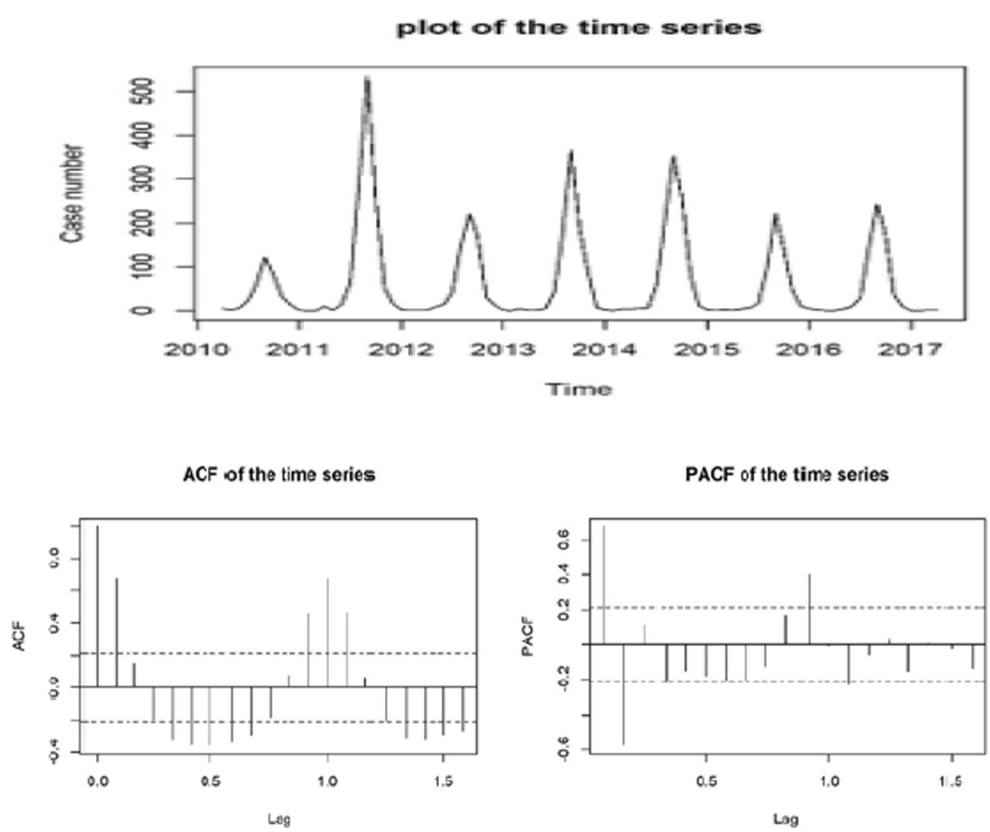

Fig. 3 The time series plot of leishmaniasis trend in 2010–2017, in Isfahan City (upper graph). Autocorrelation function and partial autocorrelation function for leishmaniasis cases (lower graphs)

As seen in Table 2, several models were run on the data, and the SARIMA (1,0,1) $(0,1,1)_{12}$ model (AIC=8.09, BIC=8.32) was the best fit for the data. Residuals from the null models did not have significant temporal autocorrelations based on the Ljung-Box test.

Meteorological predictors

In the multivariate SARIMA (1,0,1) $(0,1,1)_{12}$ model (AIC=8.87, BIC=9.12), meteorological variables with zero-lag were the best fit for the data, but none of the meteorological variables was significant (Table 3). Figure 4 shows the best-fitting model according to AIC/BIC.

Based on the variance inflation factor (VIF) index, there was collinearity between some meteorological variables. Therefore, the impact of the variables on disease incidence was evaluated in separate models. The best model was selected according to the cross-correlation table in the evaluation model, and the AIC and BIC values. The SARIMA (1,0,1) $(0,1,1)_{12}$ model was found to be the best fit, with mean humidity at 4-month lag significantly related to the incidence of CL (AIC= 8.53, AIC_C = 8.53, BIC=8.66, log likelihood=−353.1) (Table 4).

The GAMM results which include the autocorrelations between observations, as a random effect inside the model, were used. Several models were examined using the VIF and CCF. Then, the R^2s were used to compare the statistical performance of different models. The result showed significant associations between CL incidence and average temperature (2-month lag), mean of monthly relative humidity (3-month lag), monthly cumulative rainfall (1-month lag), and monthly sunshine hours (1-month lag) (Table 5).

There was an increase in the number of CL cases that started in June, reaching peak level in September, followed by a rapid decline. The relation between meteorological variables and CL incidence was significant and non-linear. Mean relative humidity higher than 35%, with 3-month lag, was positively correlated with CL cases (edf=3.93). Also, mean temperature, with 2-month lag, until 6°C, had a direct relation; from 7 to 12°C had an inverse relation; from 12° to 27°C had a direct relation; and from temperatures above 27°C had a negative (inverse) relation with number of CL cases (edf=7.08). There was a positive relation between rainfall and the number of cases, with 1-month lag, from 3 to 8 mm, but above 15 mm, the relation was negative (edf=8.03). The hours of sunshine in a month, with 1-month lag, until 170 h, had a positive relation with the incidence of CL, with small fluctuations (edf=8.12) (Fig. 5).

$$
\begin{aligned}
E(ZCLi) = \beta 0 &+ f1(\text{month}, i) \\
&+ f2(\text{average tempreture}, 2) \\
&+ f3(\text{mean relative humidity}, 3) \\
&+ f4(\text{rainfall}, 1) + f5(\text{sunshine}, 1)
\end{aligned}
$$

Table 2 Test results comparing the performance of the constructed models

Model	AIC	BIC
MA (1)	11.39	11.47
MA (2)	11.19	11.31
SARIMA (0,1,1) (0,1,1)	9.21	9.29
SARIMA (1,0,1) (0,1,1)	8.09	8.32
SARIMA (1,0,2) (0,1,1)	9.06	9.22
SARIMA (1,2,2) (0,1,1)	9.39	9.56
Multivariate SARIMA (0,1,1) (0,1,1)	9.37	9.67
Multivariate SARIMA (1,0,1) (0,1,1)	8.87	9.12
Multivariate SARIMA (1,0,2) (0,1,1)	8.95	9.11
Multivariate SARIMA (1,2,2) (0,1,1)	9.50	9.86

Discussion

In this study, we investigated the relation between meteorological variables and CL incidence using SARIMA and GAM/GAMM models, in Isfahan City. The results showed that the peak of CL mainly occurred from August to October.

The seasonal pattern of CL incidence has been shown in some other studies (Tohidinik et al. 2018; Sharafi et al. 2017; Lewnard et al. 2014; Nikonahad et al. 2017) as well. In a study conducted in central Tunisia, the incidence of CL from October to March was significantly higher than other months of the year (Toumi et al. 2012). In a study conducted in Isfahan, the highest incidence of CL was seen in summer and then in autumn (Karami et al. 2013), which is probably because the evolution period of the sandflies in Isfahan occurs in spring and early summer (Nadim and Faghih 1968). But in Pakistan, most cases were reported in winter (Ayub et al. 2003). In a study conducted in Aran and Bidgol in central Iran, the highest frequency of cases was in autumn (Moein et al. 2019). The increase in the number of cases in summer and early autumn is probably because of the 1–3-month lag time after increased humidity and rainfall in winter and spring, which causes sandfly abundance and increased rates of infection among the rodent host. The time of incidence of CL also depends on the type of leishmaniasis, and the prevalence of the vectors and reservoirs (Karami et al. 2013); and this might explain the differences in peaks of incidence reported from different geographical locations. The main vector and reservoir of zoonotic cutaneous leishmaniasis in Iran and Isfahan are *Phlebotomus papatasi* (*Ph. papatasi*) and *Rhombomys*

Table 3 Comparison of candidate SARIMA models for number of CL cases and covariate lag selection in Isfahan City, Iran

Model	Variables		Lag	Estimate	SE	T	Sig.
[A]	Monthly patients	Constant		61.27	17.33	3.53	0.000
		MA	Lag 1	1.13	0.088	12.77	0.000
			Lag 2	0.47	0.09	5.16	0.000
[B]	Monthly patients	Constant		−0.037	0.39	−0.96	0.92
		AR	Lag 1	0.48	0.13	3.67	0.002
		MA	Lag 1	0.38	0.14	2.71	0.0005
		Seasonal difference		1			
		MA, seasonal	Lag 1	−1	0.13	−7.47	0.0000
[C]	Monthly patients	AR	Lag 1	0.45	0.15	3.04	0.0034
		MA	Lag 1	0.40	0.17	2.33	0.02
		Seasonal difference		1			
		MA, seasonal	Lag 1	−1	0.13	−7.22	0.0000
	Maximum temperature			1.98	4.28	0.46	0.64
	Minimum temperature		Lag 0	1.76	4.24	0.41	0.67
	Mean temperature		Lag 0	−2.46	5	−0.50	0.62
	Rain fall		Lag 0	−0.25	0.40	−0.62	0.54
	Maximum Humidity		Lag 0	0.11	0.29	0.38	0.69
	Minimum Humidity		Lag 0	0.67	1.13	0.59	0.57
	Mean humidity		Lag 0	−0.14	0.78	−0.18	0.85
	Sunshine		Lag 0	0.04	0.09	0.46	0.64

[A]: MA (2), [B]: univariate SARIMA (1,0,1) (0,1,1), [C]: multivariate SARIMA (1,0,1) (0,1,1); *SARIMA* seasonal autoregressive integrated moving average

opimus (*R. opimus*), respectively (Karami et al. 2013; Parvizi et al. 2012). The most suitable months for breeding and activity of *Phlebotomus papatasi* in Iran are May and September (Karimi et al. 2014). In a study conducted in Isfahan in 1996, the highest rate of infection among sandflies was seen from mid-August to September, which coincided with sandfly

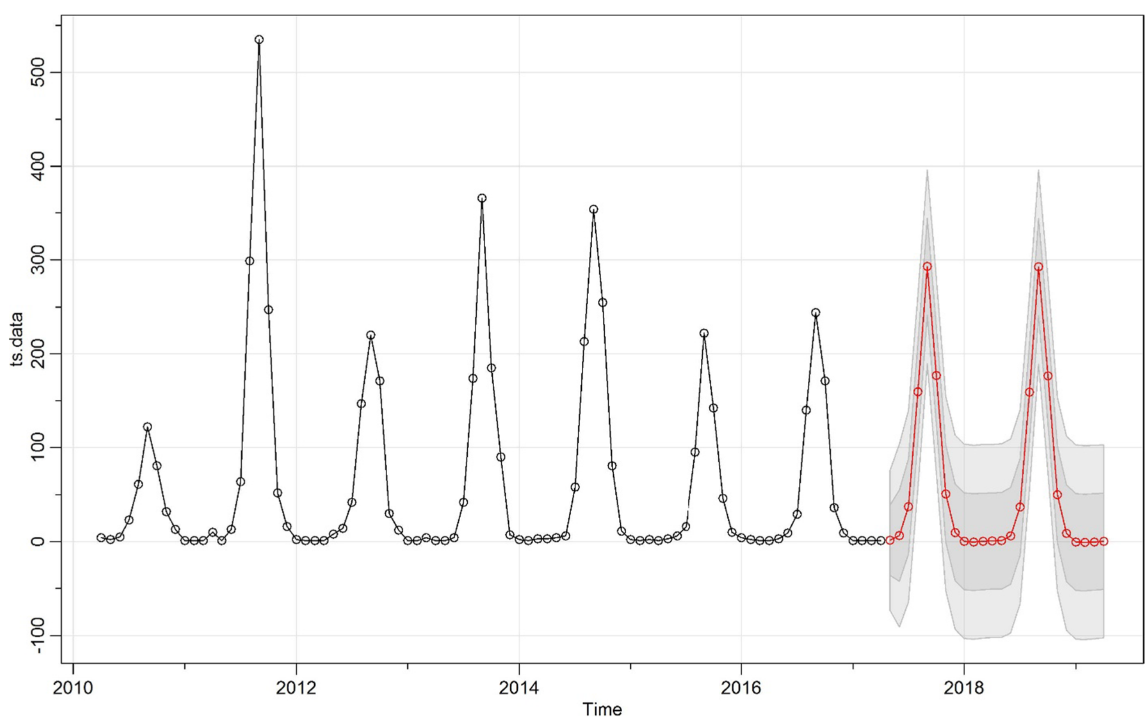

Fig. 4 The best-fitting model according to AIC/BIC

Table 4 The best fitted SARIMA model for meteorological variables in Isfahan City, Iran

Model	Variables		Lag	Estimate	SE	T	Sig.
	Monthly patients	AR	Lag 1	0.46	0.13	3.38	0.0012
		MA	Lag 1	0.52	0.13	3.74	0.0004
		Seasonal difference		1			
		MA, seasonal	Lag 1	−1	0.14	−6.87	0.0000
	Mean humidity		Lag 4	1.6	0.34	4.73	0.0000

Log likelihood=−353.1

AIC=8.53, AICc (AIC corrected for sample size) =8.53, BIC=8.66

abundance, and the highest rate of infection among the rodent hosts. The increase in disease incidence in November and December indicates an average incubation period of 1 to 3 months (Yaghoobi-Ershadi and Javadian 1996).

In this study, we identified the SARIMA (1,0,1) $(0,1,1)_{12}$ time series model as the preferred model to illustrate the trend of CL incidence in Isfahan City. This model showed that the number of CL cases can be estimated by the number of cases 1 month ago, but it was not seasonally related to the number of cases in the past 12 months ($AR_{seasonal}$=0).

Accounting for meteorological factors improved the SARIMA model and found a relation between relative humidity, lagged 4 months, and the number of CL cases; and GAMM results showed that monthly mean relative humidity after 3-month lag could predict the incidence of CL in Isfahan City, and when above 37% showed a positive relation. This is in agreement with the findings of Talmoudi et al. from central Tunisia that also used GAM models and showed that relative humidity with 4-month lag was associated non-linearly with the incidence of CL (Talmoudi et al. 2017). A study conducted in eastern Fars Province, which also used multivariate SARIMA models, suggested that humidity had a significant direct relation with the number of CL cases, after 8-month lag (Tohidinik et al. 2018). A study from Biskra province in Algeria, about the relation between leishmaniasis cases and climatic variables, showed that an ARMA (3,3) model, which included relative humidity (without lag), could predict the incidence of CL (Selmane 2015). Also, in Southern Iran, maximum relative humidity was directly related with CL incidence (Ali-Akbarpour et al. 2012). In Golestan, one of the northern provinces of Iran, the highest correlations were reported between relative humidity and monthly CL incidence, especially after 2-month lags, and the relation was inverse; also, stepwise regression analysis showed that mean humidity had a negative association with CL incidence (Shirzadi et al. 2015). Another study conducted in northeastern Brazil showed a week positive association between relative air humidity (monthly mean) and the number of CL cases per month (p=0.04) (Oliveira et al. 2020). Compared to other arthropod vectors, sandflies do not have an aquatic life phase and do not lay their eggs in water; however, sufficient humidity is essential for egg survival (Kasap and Alten 2006; Kasap and Alten 2005). Relative humidity can increase the incidence of CL through several mechanisms. It increases the survival of the sandflies' eggs, the biting behavior of female adults, egg hatchability, adult feeding, and survival. Low relative humidity decreases egg laying and increases adult sandflies' mortality, and relative humidity above 75% also inversely affects the eggs (Talmoudi et al. 2017).

Table 5 GAMM estimates of effects of environmental variables on CL incidence

Smooth terms	Edf	F
S(month)	8.13	148.87***
s (Lag (average temperature, -2))	7.67	15.76***
s (Lag (relative humidity, -3))	3.93	134.74***
s (Lag (rainfall, -1))	8.55	15.21***
s (Lag (sunshine hours, -1))	7.67	14.65***
	Estimate	Std. error
Intercept	2.61	0.054***
R-sq. (adj)	0.94	

***Significant at the 0.000 level

edf effective degrees of freedom of the smooth function term (edf>1 indicate non-linear association)

F value is an estimate of *F*-test

In this study, GAMM results showed that rainfall above 15 mm with 1-month lag had a negative effect on the incidence of CL in Isfahan City. Talmoudi et al. showed that monthly cumulative rainfall with 1-month lag was non-linearly associated with the incidence of CL (Talmoudi et al. 2017). In another study done in Fars Province by incorporating seasonal ARIMA time series analysis, cumulative monthly rainfall with 9-month lag increased CL incidence, but monthly rainfall with 4-month lag reduced CL incidence (Sharafi et al. 2017). In Brazil, multivariate time series models showed rainfall after a 5-month lag had a significant inverse relation with CL incidence (Lewnard et al. 2014). In the Andean region, annual rainfall was a direct (positive) predictor for CL incidence (Pérez-Flórez et al. 2016). Heavy rainfall can negatively affect the sandfly by limiting the sites for

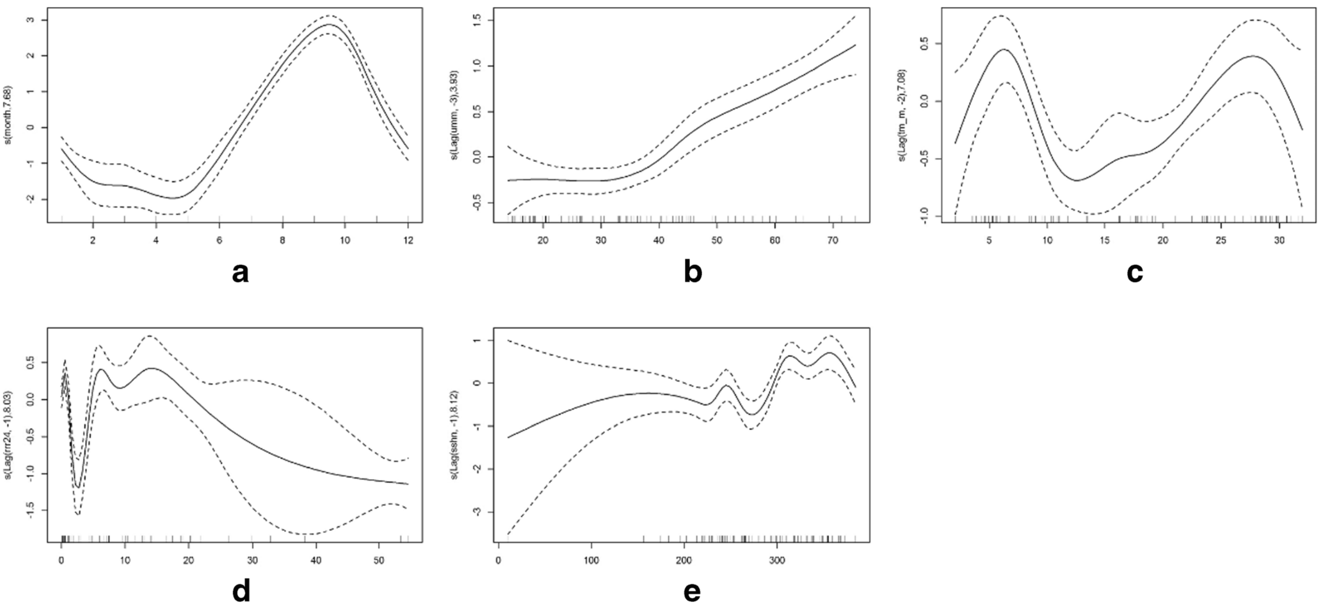

Fig. 5 GAM-estimated relation between the number of CL cases and month (**a**), monthly humidity mean (**b**), monthly temperature mean (**c**), monthly average rainfall (**d**), and sunshine hours in month (**e**)

resting, restricting sandfly flight and killing immature sandflies (Simsek et al. 2007). Rainfall can also affect the vector life cycle by affecting the humidity, temperature, and vegetation of the area, and can increase the reservoirs of leishmaniasis through increasing vegetation and plant growth (Simental and Martinez-Urtaza 2008), and this can increase CL transmission and incidence (Talmoudi et al. 2017). The inverse relation between humidity and rainfall after 3- to 5-month lag, with CL incidence, indicates that CL is more likely to occur after dry periods (Lewnard et al. 2014; Wu et al. 2014).

In this study, GAMM results showed that average temperature with 2-month lags and sunshine with 1-month lag predicted the incidence of CL in Isfahan City. In the Golestan, Iran, study, CL incidence was more prevalent in regions with higher temperature (Shirzadi et al. 2015). Talmoudi et al. suggested that mean temperature with 4-month lag was non-linearly associated with the incidence of CL (Talmoudi et al. 2017), but in Southern Iran, minimum temperature was inversely related to CL incidence (Ali-Akbarpour et al. 2012). Another study conducted in Nicaragua showed that mean annual temperature had a significant negative association with CL incidence (Hernandez et al. 2020). A study done in Fars Province, Iran, showed that mean temperature with 3-month lag increased CL incidence (Sharafi et al. 2017), and a study from Algeria showed that temperature with 5-month lag was directly associated with the incidence of CL (Selmane 2015). In a study conducted in the Andean region of Colombia using spatial-temporal analysis and conditional autoregressive Poisson random-effects modeling in a Bayesian framework, annual temperature was a risk factor for CL incidence; and in multivariate analysis, temperature and seasonal temperature were introduced as the best predictors for disease incidence (Pérez-Flórez et al. 2016). Ramezankhani et al. suggested average temperature was positively related to CL incidence (Ramezankhani et al. 2018). One of the requirements for the survival of sandflies is warm temperature; for example, in the case of *Phlebotomus papatasi*, at temperatures below 15°C, survival is not possible (Kasap and Alten 2006). One other reason for the direct effect of temperature on the incidence of CL is that the development of the infective forms of *Leishmania* happens in the sandfly guts in warm weather (Bates 2007).

In this study, we found non-linear relations between meteorological variables and CL incidence, which might be partly related to the role of various biological factors (vectors and reservoirs), in disease occurrence.

Conclusion

Meteorological variables including average temperature, relative humidity, rainfall, and sunshine hours can affect CL incidence and can be used for predicting the incidence of CL in Isfahan, Iran.

Availability of data The number of cases was inquired from the Iranian Ministry of Health and Medical Education. Weather variables were inquired from the Isfahan City Meteorological Organization.

Code availability R statistical software (version 3.5.3).

Author contribution NK suggested the topic and was the main supervisor, and helped in writing and editing the manuscript. SN acquired the data, cleaned the data, analyzed the data, and prepared the initial draft. YJ supervised data analysis, provided statistical consultation, and edited the final manuscript. BB, AS, and GM provided scientific advice and edited the final article. All authors read and approved the final manuscript.

Funding This study was supported by Grant No. 97-433, from Kerman University of Medical Science, Kerman, Iran.

Declarations

Ethic approval This project was approved by the Ethics Committee of Kerman University of Medical Sciences, Kerman, Iran (Ethics Code: IR.KMU.REC.1397.233). All human data was inquired without identity.

Competing interests The authors declare no competing interests.

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