Original Article

Crimean-Congo hemorrhagic fever and its relationship with climate factors in southeast Iran: a 13-year experience

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Abstract

Introduction: Crimean-Congo hemorrhagic fever (CCHF) is endemic in southeast Iran. In this study we present the epidemiological features of CCHF and its relationship with climate factors in over a 13-year span.
Methodology: Surveillance system data of CCHF from 2000 to 2012 were obtained from the Province Health Centre of Zahedan University of Medical Sciences in southeast Iran. The climate data were obtained from the climate organization. The seasonal auto-regression integrated moving average (SARIMA) model was used for time series analysis to produce a model as applicable as possible in predicting the variations in the occurrence of the disease.
Results: Between 2000 and 2012, 647 confirmed CCHF cases were reported from Sistan-va-Baluchistan province. The total case fatality rate was about 10.0%. Climate variables including mean temperature (°C), accumulated rainfall (mm), and maximum relative humidity (%) were significantly correlated with monthly incidence of CCHF ($p < 0.05$). There was no clear pattern of decline in the reported number of cases within the study's time span. The first spike in the number of CCHF cases in Iran occurred after the first surge of the disease in Pakistan.
Conclusions: This study shows the potential of climate indicators as predictive factors in modeling the occurrence of CCHF, even though it has to be appreciated whether there is any need for a practically applicable model. There are also other factors, such as entomological indicators and virological finding that must be considered.

Key words: Crimean-Congo hemorrhagic fever; climate factors; Iran; epidemiology; time series; early warning system

J Infect Dev Ctries 2014; 8(6):749-757. doi:10.3855/jidc.4020

(Received 22 July 2013 – Accepted 14 December 2013)

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a widely distributed and fatal tick-borne disease in Africa, Asia, Eastern Europe, and the Middle East. CCHF is one of the viral hemorrhagic fevers transmitted mainly through tick bites and/or contact with blood and body fluids of patients (and/or infected animals) during the viremic phase of the disease. *Hyalomma* ticks play a key role in the epidemiology of this disease as both the natural reservoir and the main arthropod vector of the disease. The domain of distribution of CCHF corresponds with the domain of distribution of *Hyalomma* ticks. The reported mortality rate of this infection has been between 3% and 50% [1].

CCHF virus (CCHFV) is a member of the *Nairovirus* genus of the family *Bunyaviridae* and circulates in an enzootic tick-vertebrate-tick cycle. There is no evidence that the virus causes disease in animals. The virus could be transferred from endemic to non-endemic areas due to large numbers of infected ticks being carried by migrating birds and livestock. This can cause the spread of the CCHFV into uninfected areas [1,2].

The time trend of CCHF occurrence follows a seasonal pattern, overlapping with the peak activity of ticks, between spring and early autumn [1,3]. Several studies have discussed the relationship between the climatic factors and the vector's lifecycle, ecological conditions, and, consequently, the occurrence of

CCHF in human populations [1,4-6]. In addition to climate variables, there are some other epidemiologic factors that influence the occurrence of CCHF that should be considered in controlling the disease [7-9].

During the period from January 2000 to September 2010, 738 confirmed cases of CCHF and 108 associated fatalities were reported in Iran [10]. CCHF has been reported from 23 out of 30 provinces of Iran. Among them, Sistan-va-Baluchistan, Isfahan, and Fars had the highest reported cases [11].

Sistan-va-Baluchistan province in southeast Iran is the most important endemic site of the disease in the country. There are several reports regarding different epidemiological aspects of the disease in the province [5,12-17]; however, none of them have considered the climate or climatic changes as one of the important variables in the epidemiology of CCHF.

In this study, we analyzed the surveillance data gathered during the past 13 years in the Sistan-va-Baluchistan province of Iran, and used climate findings and other known epidemiologic factors to create a basis for making early warnings of CCHF outbreaks possible.

Methodology

Study area

Sistan-va-Baluchistan province is located in southeast Iran and has common borders with Pakistan and Afghanistan. Its climate varies from temperate in the north to subtropical in the south of the province. Compared to the central and western parts of Iran, there is less precipitation and rainfall, especially during the dry period that begins in April and continues until the end of October or November. The southern parts of the province are under the influence of monsoon winds, and summer rainfalls every three to five years lead to floods and epidemics of malaria and other arthropod-borne diseases in the southern parts of the province. The climate condition of this province is relatively similar to border provinces of Pakistan and Afghanistan [18].

It is worth mentioning that CCHF is also endemic in both Afghanistan and Pakistan; without a doubt, livestock trading, traveling, and the movement of nomadic populations between the two sides of the border influences the epidemiology of the disease in both the animal and human sectors [7,14,19,20].

Case definition

A confirmed CCHF case was defined as one with a positive IgM or IgG serologic test (enzyme-linked immunosorbent assay method) and/or positive by reverse transcription polymerase chain reaction (RT-PCR) detection of viral RNA in the serum sample sent to the Laboratory of Arboviruses and Viral Hemorrhagic Fevers, Pasteur Institute of Iran, Tehran, Iran [10]. In Iran, CCHF is an urgently notifiable disease; upon diagnosis, its reporting is a high priority for the surveillance system. All cases are reported and registered according to the surveillance and control program of CCHF in Iran [21].

Data collection

The data of all confirmed cases of CCHF registered from 2000 to 2012 by the surveillance system of the Province Health Centre of Zahedan University of Medical Sciences (ZUMS) were extracted from the computerized data banks and analyzed. This data bank is under supervision of the Centre for Management of Communicable Diseases in Iran.

The records of two synoptic centers located in the east and northeast of the province were used. From 18 climate variables, the data for accumulated rainfall (millimeters), minimum, maximum and average relative humidity (%), minimum, maximum and average temperature (°C), sunny hours per day, and barometric pressure were obtained.

Statistical analysis

The statistical software STATA version 10 was used for all analyses. The descriptive statistics, Spearman correlation coefficient, and cross-correlation charts were used for analyzing and presenting the results.

Due to the seasonality of dependent (CCHF number) and independent (climate factors) variables, the seasonal autoregressive integrated moving average (SARIMA) model was applied to each series [22]. The variance of the series was stabilized by natural logarithm transformation. The dependent variable and accumulated rainfall were log transformed. A seasonal component was removed by a seasonal differencing: $Zt - Zt\text{-}s$ (Zt = values of the time series at time [t]; $Zt\text{-}s$ = values of the time series at time [t]-12 month) and the trend was removed by a regular differencing: $Zt - Zt\text{-}1$ ($Zt\text{-}1$ = values of the time series at time [t]-1 month). After fitting the best SARIMA model to each dependent and independent time series individually, the residuals of each time series, *i.e.*, the difference between an observation and its fitted value according to the model were observed. The cross-correlation coefficients between the residuals of CCHF incidence and the residuals of each climate time series over a range of lags were then computed. The climate variables with different lags (delayed effects), found to correlate with CCHF cases under this analysis, were tested as additional regressors in an alternative regression-SARIMA model. The regression-SARIMA model was fitted with climate variables as external regressors to CCHF incidence. The smallest value of Akaike's information criterion (AIC) was set as the standard to identify the best-fit model and the Ljung-Box test confirmed that the residuals of time series were statistically not dependent ($p > 0.05$). It should be noted that correlation at lag 1 is the correlation between each observation and the previous one, correlation at lag 2 is the correlation between each observation and previous observation but one (lag two), and so on.

Results

Between 2000 and 2012, 647 confirmed CCHF cases were reported from Sistan-va-Baluchistan Province to the Centre for Disease Management (CDC) of the Ministry of Health (MOH).

Of the reported cases, 80.53% were male and 19.47% were female. The mean age of the patients was 31.8±1.4 years (range: 7–82 years), and 94.75% were older than 15 years of age. The distribution of patients according to occupation showed that in all years, most were butchers and abattoir workers (37.7%), followed by sheep handlers (28.1%). There was no considerable variation in job and age distribution of patients during the years of the study period. Most of the cases were from rural areas (79.4%). The case fatality rate showed a decreasing trend during these years, from 34.7% in 2000 to 8.3% in 2012; the total case fatality rate was 10.0% (65/647) (the last row of Table 1). Of all cases, 6.9% had a history of close contact with CCHF patients and 96.7% had a history of close contact with livestock (Table 1).

The disease was most common in the months of May, June, July, and August, and there was no clear pattern of decline during these years. The years 2002, 2008, and 2010 were the worst with regard to the number of cases and occurrence of outbreaks (Figure 1). The mean incubation period (the time interval from a potentially infective contact with an animal or another case to the onset of fever) was 4.4±2.6 days (range: 2–13 days). Fatigue, fever, and thrombocytopenia were the most common clinical findings. Hemorrhagic findings were detected in 46% of the patients.

Climate variables and CCHF

Since the data from the two mentioned synoptic centers were mostly in agreement with each other, the mean of the variables was used in analysis. Both the surveillance data of the Province Health Center and the data from the synoptic centers were gathered on a monthly basis.

Figure 2 shows the relationship between the number of cases with average temperature (Spearman $r = 0.6$, $p = 0.002$) (Figure 2A) and with accumulated rain fall ($r = -0.37$, $p = 0.007$) (Figure 2B) during the study period based on seasonally aggregated data.

To adjust the periodical effect of seasons, the data was analyzed separately for each season for all the 13 years. The relationship between number of cases and temperature for 13 springs of the 13 years were analyzed separately from the other seasons. Further analysis of the data in different seasons separately showed that the relation between the average temperature and number of CCHF cases was significant in all seasons: winter ($r = 0.56$; $p = 0.046$), spring ($r = 0.7$; $p = 0.007$), summer ($r = 0.65$; $p = 0.016$), and autumn ($r = 0.59$; $p = 0.033$); however, the relation between the accumulated rainfall and number of CCHF cases was significant only in autumn and spring: winter ($r = -0.21$; $p = 0.49$), spring ($r = -0.57$; $p = 0.041$), summer ($r = -0.19$; $p = 0.53$), and autumn ($r = -0.56$; $p = 0.046$). Based on these findings, it might be deduced that the number of cases in warmer summers was higher than the relatively cooler ones, and also that the warmer the winters, the higher the number of cases. No relationship was found among other variables and the number of CCHF cases in seasonal analysis.

As the focus in this study was on short-term associations, the correlations between residuals of CCHF incidence and those of meteorological variables over a range of 24 month lags were analyzed. The weather variables were significantly associated with the incidence of CCHF by cross-correlations. The most significant associations, based on the value of correlation coefficients for monthly mean temperature ($r = 0.32$; $p = 0.000$) and maximum monthly relative humidity ($r = 0.5$; $p = 0.000$) were found at a lag of one month. Monthly accumulated rainfall was inversely correlated with incidence of CCHF ($r = -0.23$; $p = 0.003$) at a lag of one month. Moreover, significant correlations for monthly mean temperature ($r = 0.36$; $p = 0.000$) and maximum monthly relative humidity ($r = 0.38$; $p = 0.000$) were found at a lag of two months.

Table 1. Epidemiological characteristics of all 647 confirmed CCHF cases in Sistan-va-Baluchistan province, southeast Iran, over thirteen years (Jan 2000 – Dec 2012).

Characteristics		**2000 n = 23**	**2001 n = 28**	**2002 n = 83**	**2003 n = 48**	**2004 n = 14**	**2005 n = 14**	**2006 n = 39**	**2007 n = 53**	**2008 n = 94**	**2009 n = 65**	**2010 n = 104**	**2011 n = 45**	**2012 n = 37**
Age (years)		30.6 ± 13.7 [8-61]	33.7 ± 12.6 [12-56]	33.7 ± 14.5 [12-68]	30.0 ± 13.3 [8-60]	31.1 ± 10.9 [16-56]	33.9 ± 12.6 [19-64]	31.3 ± 13.7 [4-70]	32.1 ± 11.3 [13-60]	30.1 ± 13.0 [10-80]	27.6 ± 11.2 [6-59]	31.4 ± 14.3 [10-82]	33.6 ± 15.0 [6-78]	33.2 ± 16.4 [6-81]
Gender (M/F)		13/10	24/4	71/12	38/10	11/3	10/4	29/10	45/8	73/21	48/17	92/12	37/8	30/7
Location of residence (village/town)		17/6	20/8	65/18	34/14	8/6	10/4	30/9	41/12	71/23	55/10	92/12	41/4	30/7
Occupation N (%)	Butcher/ abattoir worker	4 (17.4)	8 (28.6)	33 (40)	20 (41.7)	6 (42.8)	6 (42.8)	11 (28.3)	20 (37.8)	33 (35.1)	26 (40)	50 (48.1)	14 (31.1)	13 (35.2)
	Sheep handler	7 (30.4)	7 (25)	26 (31.2)	15 (31.2)	6 (42.8)	4 (28.6)	9 (23)	17 (32)	23 (24.4)	16 (24.6)	30 (28.8)	12 (26.7)	10 (27)
	Farmer	0	2 (7.1)	1 (1.2)	1 (2.1)	0	1 (7.1)	2 (5.1)	2 (3.8)	4 (4.25)	2 (3.1)	5 (4.8)	1 (2.2)	1 (2.7)
	Student	4 (17.4)	2 (7.1)	2 (2.4)	2 (4.2)	0	0	3 (7.7)	4 (7.5)	7 (7.45)	4 (6.1)	6 (5.7)	6 (13.3)	2 (5.4)
	Clerk	0	2 (7.1)	8 (9.6)	2 (4.2)	0	0	1 (2.6)	3 (5.7)	3 (3.2)	3 (4.6)	3 (2.9)	4 (8.9)	4 (10.8)
	Housewife	8 (34.8)	4 (14.3)	12 (14.4)	8 (16.6)	2 (14.4)	3 (21.5)	10 (25.6)	5 (9.4)	19 (20.2)	14 (21.6)	10 (9.7)	8 (17.8)	5 (13.5)
	Military	0	3 (10.8)	1 (1.2)	0	0	0	3 (7.7)	2 (3.8)	5 (5.4)	0	0	0	2 (5.4)
History of contact with patient		13 (56.5)	2 (7.1)	3 (3.6)	3 (6.2)	2 (14.4)	0	2 (5.1)	5 (9.4)	5 (5.3)	3 (4.6)	3 (2.8)	4 (8.9)	0
History of contact with livestock		22 (95.6)	26 (92.8)	81 (97.6)	47 (97.9)	13 (92.6)	14 (100)	38 (97.4)	47 (88.7)	91 (96.8)	65 (100)	102 (98.1)	45 (100)	35 (94.6)
CFR (%)[1]		34. 8	28.5	19.2	18.7	14.3	14.3	12.8	7.5	9.5	7.6	12.5	13.3	8.1

[1]CFR: case fatality rate
Data are presented as mean ± 1SD [min-max], number, and number (percent)

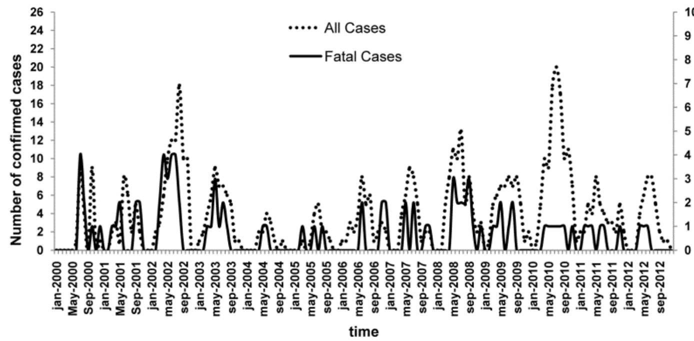

Figure 1. Trend and distribution of confirmed CCHF cases and number of fatal cases by month and year, in southeast Iran. The X axis gives the years and months, from January 2000 to December 2012 (Jan: January, May: May, Sep: September. The other months are not shown).

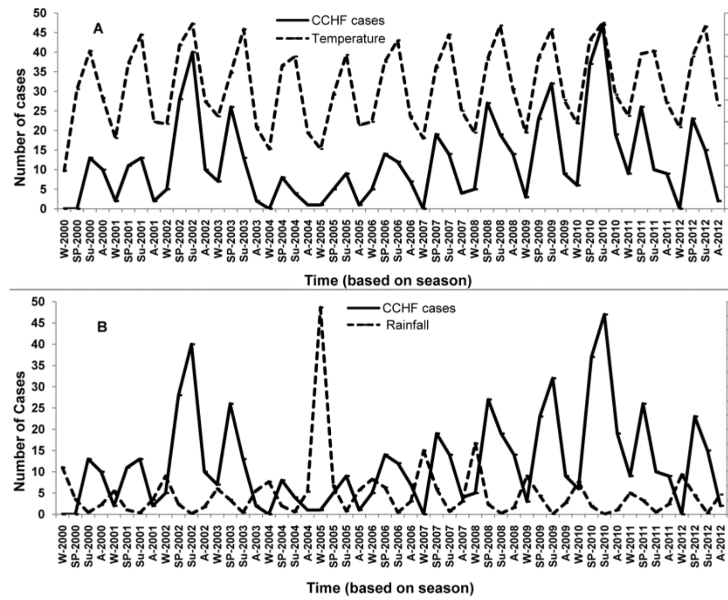

Figure 2. Distribution of seasonally CCHF cases in southeast Iran, according to A) average temperature (°C), and B) accumulated rainfall (mm).The X axis gives the years (2000-2012) and seasons. W: winter (January, February, March), SP: spring (April, May, June), Su: summer (July, August, September), and A: autumn (October, November, December).

Table 2. Cross-correlation coefficients between climate variables and monthly number of CCHF cases in Sistan-va-Baluchistan province, southeast Iran

Time-lag (months)	Average temperature	Maximum temperature	Minimum temperature	Average relative humidity	Maximum relative humidity	Minimum relative humidity	Rainfall	Sunny hours	Barometric pressure
-5	-0.43*	-0.15	-0.12	0.11	0.15	0.15	0.27*	-0.19	0.11
-4	-0.14	-0.13	0.15	0.12	0.13	0.15	0.04	0.01	0.02
-3	0.09	0.1	0.08	0.14	0.39*	0.13	0.15	0.12	0.07
-2	0.36*	0.12	0.1	0.09	0.38*	0.09	-0.05	0.01	0.05
-1	0.32*	0.11	0.09	0.11	0.5*	0.11	-0.23*	0.14	0.12

Table 3. Regression coefficients of weather variables on the monthly incidence of CCHF in Sistan-va-Baluchistan province, southeast Iran, based on the final model

Variables	Coefficients (β)	Standard error	95% confidence interval	P value
Mean temperature_lag2	0.43	0.117	0.2 to 0.66	0.001
Mean temperature_lag5	-0.74	0.097	-0.93 to -0.55	0.000
Maximum relative humidity_2	0.58	0.212	0.16 to 0.99	0.01
Accumulated rainfall_5	0.68	0.104	0.48 to 0.89	0.000
Intercept	1.45	1.33	-1.15 to 4	0.27

Akaike's information criterion =288, root mean square error = 0.65

This study also showed that maximum monthly relative humidity was correlated with disease incidence at lag of three months (r = 0.39; p = 0.000). The monthly mean temperature was found to be inversely correlated (r = -0.43; p = 0.000), and accumulated rainfall directly correlated (r = 0.27; p = 0.000) with disease incidence at lag of five months. There was no significant correlation between CCHF incidence and the following variables: monthly mean barometric pressure, accumulated sunny hours per month, minimum monthly relative humidity, monthly mean relative humidity, and minimum and maximum monthly temperature (Table 2).

The best-fitted regression-SARIMA model after removing seasonality contained four variables; the incidence of CCHF was significantly associated with monthly mean temperature (β = 0.43; p = 0.001) and maximum monthly relative humidity at a lag of two months (β = 0.58; p = 0.01) and accumulated rainfall at a lag of five months (β = 0.68; p = 0.001). On the other hand, as the fourth variable in the model, the incidence of CCHF was inversely associated with the monthly mean temperature at a lag of five months (β = -0.74; p = 0.001). The AIC and root mean square error (RMSE) of the model were 288 and 0.65, respectively (Table 3).

Discussion

Based on our findings in this study, there was no clear pattern of decline in the reported number of CCHF cases during the past 13 years; a fluctuation was seen in the occurrence of this disease with three peaks in 2002, 2008, and 2010. This result is somewhat similar to a previous study conducted in Bulgaria that described the trends of CCHF between 1997 and 2009 [6]. However, in a Turkish study, the number of cases increased dramatically from 2004 to 2007 [3].

The total case fatality rate for the study period (13 years) was about 10.0%, which is similar to findings in the adjacent areas on the other side of the border in Pakistan (9.6%) over a five-year time period (1997 to 2002) [20]. It is worth mentioning that the case fatality rate in Turkey from 2002 to 2007 was been about 5% [3]. Since ribavirin is an effective treatment for the hemorrhagic form of CCHF [23], the relative decrease in the fatality rate may be due to early detection of cases with mild to moderate clinical findings and the relatively better treatment with ribavirin in southeast Iran.

Evaluation of the epidemiological characteristics of cases showed that the male-to-female ratio was about 4:1, and also that the disease was most common in rural areas (79.4%) and among actively working age groups (15-44 years). Most of the patients were butchers and sheep handlers (65.8%). All these findings are in accordance with the mode of transmission of the disease that dominates an occupational disease pattern of distribution, *i.e.*, among those whose jobs are related to livestock.

The majority of cases were reported between the months of April and August, with peak levels in June and July. This result is similar to previous studies in Iran, Turkey, and Bulgaria [3,6,11] and corresponds closely with the months that the temperature is between 30°C and 40°C and maximum humidity is between 20% and 50% (the favorite condition of *Hyalomma* ticks) in southeast Iran. It should be noted that the pattern of CCHF distribution on the other side of the border (in the Baluchistan province of Pakistan) is somewhat different from the results of our study, with two annual surges in April and August [20] and very few cases seen during the rest of the year. In Baluchistan province of Pakistan, the tick fauna is not unknown [7], but ixodid ticks were found throughout the year with high activity from April to August in Iran [24]. Therefore, reports of the disease throughout the year in southeast Iran, with peak levels from April to August, are expected. We observed that the yearly peak number of cases in Sistan-Balochistan province of Iran was between two surges of the disease in Baluchistan province of Pakistan. This is probably due to the transmission of infected immature ticks by rodents, small animals, and birds [1], and of infected mature ticks by livestock imported from Pakistan to Iran [7,8]. Transmission of infected mature and immature ticks by rodents and birds and also by skin and hide trades from Sistan-Balochistan province of Iran to Pakistan may be the reason for the second surge in Baluchistan province of Pakistan. It must be mentioned that as in the results of previous studies, infestation with *Hyalomma* among wild rodents is more common than with other tick species in southeast Iran [8] and that the CCHFV genome isolated from Iranian patients is similar to Afghanistan and Pakistan, which have a close relationship with the CCHF Matin strain [7,11,13,25,26].

The migration of CCHFV is free and unrestricted between Iran and Pakistan [9]; this virus circulates between three adjacent provinces in three neighboring countries – Iran, Afghanistan, and Pakistan. This could be due to transmission of infected ticks by rodents and migratory birds and infected livestock by unlawful animal trade and uncontrolled population movements (*e.g.*, nomadic populations) between Baluchistan province of Pakistan and Afghanistan (through Quetta city) [7] and consequently between Baluchistan province of Iran and Afghanistan (through Nimroz province).

The effect of climate factors on tick activity and occurrence of CCHF have been discussed in other studies [2,4,5,16,27,28]. Indeed, understanding the relationship between climate factors and the occurrence of CCHF could be helpful in the establishment of early warning and even forecasting systems in the surveillance of this disease.

In the present study, higher numbers of reported cases in warmer seasons and seasons with low rainfall show that the temperature and precipitation may have an important role in the activity of ticks and, consequently, the occurrence of CCHF.Although these results imply the seasonal pattern of this disease, they could not be used as predictive indicators in an early warning system (EWS). Therefore, we analyzed the data on a monthly time scale to identify short-term associations between weather conditions and incidence of CCHF, using univariate and multiple regression-SARIMA models [22].

We found that temperature and maximum relative humidity were affecting factors in the fluctuation of CCHF. This result is similar to previous studies conducted in Iran and Europe [5,6]. The predominant effect of these variables was observed after a one- and two-month lag for the mean temperature and one-, two- and three-month lags for the maximum relative humidity in univariate analysis (using cross-correlations). However, the regression-SARIMA model showed that these variables could explain fluctuations in the number of CCHF cases, with a time lag of two months.

High temperatures and high humidity, especially in the spring and summer, accelerate the *HyalommaMarginatum*'s life cycle by hastening the molting stages, trans-stadial virus transmission, and host questing activity [24,27,29]. It might be concluded that climatic variables do not directly influence the incidence of the disease; rather, they influence it only indirectly through their effect on the life-cycle dynamics of both vector and virus. On the other hand, the several successive phases from tick hatching to human case appearance led to global cumulative lags in our study (especially in univariate analysis using cross-correlations). Furthermore, rising temperature and humidity increases vector survival rate and prolongs the time ticks can feed effectively on an infective host. All these situations will lead to an increase in the tick population, which has a dual role in the circulation of CCHFV, both as a reservoir and vector. The activity of *Hyalomma* is not limited to one specific month; they can be found throughout the year [24]. Therefore, there is a positive relationship between maximum humidity and temperature in different lags. This result indicates that increasing heat and moisture in a specific month could not predict the number of cases in a specific later month. The temperature and humidity involved in all biological cycles of ticks take more time to influence viremia and infection in animals and, consequently, the occurrence of CCHF in humans.

This study demonstrated an inverse relationship between CCHF incidence and average temperature at a lag of five months in both univariate and multiple regression SARIMA models. This means that the increasing average temperature in October to November decreased the likelihood of CCHF cases in the following year. A similar finding had previously been observed in Turkey and Bulgaria [6,30]. The warmer temperatures in winter and shorter annual cold periods limit development and increase mortality of tick stages [31]. Therefore, we could use this result as a predictive indicator to establish the early warning signs of CCHF.

Some studies have noted that a decrease in rainfall might produce a more suitable condition for higher tick activities [16,27]. We also observed such a finding in the univariate analysis of the relationship between CCHF incidence and rainfall with a lag of one month. There were higher numbers of cases in the months and years with low rainfall – even from March to September when rainfall is negligible – than in the months and years with high rainfall. We also observed a positive relationship between accumulated rainfall amount and the number of CCHF cases at a lag of five months in the regression-SARIMA model. It can be said the increasing rainfall (possibly along with decreasing temperature) in October to November increased the likelihood of CCHF cases in the following year. This result could be in line with the finding that was previously observed in Turkey and Bulgaria [6,28].

Globally, we examined the ecological association between change in average climate variable and change in occurrence of CCHF in one geographically defined area. There were, nonetheless, other confounders such as change in agricultural activities, ranching, nomadic populations, and illegal livestock trading that might also lead to bias in causal inference in this study.

However, near the borders, the weather conditions in neighboring countries is the same as Sistan-va-Baluchistan province in Iran (data not shown), and the results of this study (correlation between climate factors and CCHF incidence) could be generalized to Pakistan (Baluchistan province) and Afghanistan (Nimroz province).

It should be noted that there are several other factors that either independently, or in connection with the climate factors, affected the incidence of CCHF. These factors included agricultural activities, ranching, movements of nomadic populations, buying, selling, and illegal trading of livestock, and activities of wild rodent populations.Awareness and evaluation of these factors might help the health system in the early detection of CCHF outbreaks. Generally, the results of the present study can be used as predictive indicator in EWS and could help the health system to plan and have an efficient CCHF control program in this region. Nonetheless, to achieve an EWS and better control of this disease in the most prevalent region in Iran and adjacent provinces in neighboring countries, we suggest the establishment of independent research groups in every adjacent province. These groups should combine and argue the results of their evaluations and describe the role of climate factors, reservoir hosts, and vectors. Entomologists could evaluate and monitor the tick infestation of wild rodents and livestock periodically. Virologists could evaluate and monitor the CCHFV among ticks, humans, and livestock. Epidemiologists, using ecological and climate factors, could integrate the entomology and virology data and finally evaluate the epidemiological aspects of outbreaks for early detection.

Climate factors could not be used alone as predictive indicators in EWS, and the following factors could be used together for early warning of CCHF occurrence: rising temperatures and/or decreasing rainfall in late autumn, rising humidity synchronized with temperature in any month, peak levels of CCHF in Baluchistan province of Pakistan, and an increase in tick-infested wild rodent populations.

Acknowledgements

The authors wish to thank Mr. Hasanzehi, Zahedan University of Medical Sciences, Iran, and Mr. Mohammadzadeh, Zabol University of Medical Sciences, Iran, for their help in data registering. This work was supported by research deputy of Tehran University of medical sciences.

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Conflict of interests: No conflict of interests is declared.