Original Article

Spatiotemporal epidemiology of brucellosis in Iran from 2009 to 2018: A mixed ecological study

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Background: Brucellosis is one of the most common zoonotic diseases in the world. The present study was carried out to determine the epidemiological status of the brucellosis and identify the high-risk and low-risk clusters in different provinces of Iran. **Materials and Methods:** This was an ecological study conducted in the exploratory mixed design. The study population was the individuals with brucellosis in Iran whose data were related to the years 2009–2018. Data analysis has been done using Anselin Local Moran's I, Global Moran's I, Getis-Ord General G, Optimized Hot Spot Analysis, and Pearson correlation coefficient (PCC) in double range α and a significance level of 0.05. **Results:** The average annual incidence rate of the disease during the studied years was 19.91 per one hundred thousand. The three provinces with the highest cumulative prevalence rate included Lorestan, Hamedan, Kurdistan and the three provinces with the lowest prevalence rate involved Hormozgan, Tehran and Bushehr. Coldspots of brucellosis prevalence are in south and southwest of Iran and hotspots were observed in the west and northwest. The PCC between the prevalence rate and latitude was negative and not significant ($r = -0.253$; $P = 0.169$). However, a negative and significant correlation was found between the prevalence rate and longitude ($r = -0.358$; $P < 0.05$), indicating that as longitude increases, the prevalence of brucellosis decreases significantly. **Conclusion:** The prevalence of brucellosis in Iran is higher than developed countries and like many developing countries. High-risk areas of brucellosis were found in the western provinces and low-risk areas in the central and southern provinces of Iran. It appears essential to implement prevention and treatment measures in high-risk areas.

Key words: Brucellosis, geographical information system, incidence, Iran, prevalence

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INTRODUCTION

Brucellosis is one of the most common zoonotic diseases in the world that infects human's directly through contaminated livestock or indirectly through food products and causes high medical and economic losses every year.[1,2] The disease is caused by a pathogenic agent, which is a small aerobic Gram-negative bacillus, without capsule and motionless, called *Brucella*, of which six types are known. Two types of *Brucella melitensis* and *Brucella abortu* are very common in Iran.[3,4]

Every year, more than 500,000 cases of Malta fever occur in humans all over the world, and the annual incidence rate in some endemic areas exceeds 10 per million of the population. More importantly, according to the report of the World Health Organization (WHO), the actual cases are 10–25 times more than the declared cases, and the impact of brucellosis on national health

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and economic losses is more and more serious from what have been observed.[5]

Brucellosis is more common in Mediterranean, Latin American, and the Middle East countries and it causes considerable human effects in endemic areas.[6,7] Despite the primary healthcare systems that has been well stable in Iran, Malta fever is still an important endemic disease.[8] Iran has allocated the fourth place in the world and the first place in the Eastern Mediterranean region in terms of brucellosis prevalence.[9,10] Iran has reported the average rate of the disease prevalence 21 individuals per 100,000 populations.[11]

There is a wide range of factors affecting the incidence of Malta fever in different species of domestic animals. The incidence of brucellosis can be different according to the environment, geography, species, age as well as sex.[12]

Cognition zoning of the diseases, measurement of climatic factors affecting human health, and collection and interpretation of spatial data is so important that in some developed countries the specialized field of Geographic Information System (GIS) in Health Care has been established.[13-15] Today, GIS and SatScan software (Information Management Services Inc, Boston, Massachusetts, United States) has been concerned by decision makers and researchers as one of the new tools in examining and expressing the distribution of health-related factors.[16,17] Many studies have been conducted on diseases by means of spatial data. These studies measure and zone the influence of environmental, ecological, and social factors on health.[18,19] Considering that limited studies have been carried out about the spatial analysis of human brucellosis,[12] so the researchers aimed to conduct a study to determine the time trend and spatial distribution of brucellosis in Iran during the years 2009–2018 along with the identification of high-risk and low-risk clusters of this disease to provide clues for better control and management of the disease in Iran and to strengthen the disease surveillance system in the high risky regions.

MATERIALS AND METHODS

Study type and design

This methods study was an ecological study that was carried out by the Exploratory Mixed Methods design on all people with brucellosis in Iran during 2009–2018. The term exploratory means that these types of studies explore and describe the time trends and spatial patterns of the incidence of the diseases. Furthermore, the meaning of the word mixed is that in these studies, the effect of location (multiple-group study) and the effect of time (time-trend study) is simultaneously evaluated and measured.[20-22]

Sources of data collection

Three types of data were used in this study, including: (1) Data related to the patients' characteristics; these data were related to the years 2009–2018, which were obtained from the Department of Infectious Diseases of the Ministry of Health and Medical Education; (2) Data related to the population of the provinces: These data were related to the total population of the provinces during the years 2009–2018, which were taken from the Statistical Center of Iran; and (3) Data related to the geographic coordinate of the patients: These data were collected from the latest information available in the Google Map software and Digital Elevation Model (DEM) of Iran. DEM is basically a raster layer that contains the information of the coordinate and digital elevation (X, Y, and Z).

Statistical analysis

Statistical analysis included the three main parts of descriptive analysis, time trend and spatial pattern of the disease incidence as follows. In the present study, all statistical tests were performed in two-sided alpha of 0.05.

Descriptive analysis

In this study, in order to analyze the data descriptively, first the indicators of central tendency and dispersion of the disease were obtained, then the average annual incidence rate disease in Iran and the Cumulative Prevalence Rate (CPR) of brucellosis in each of Iran's provinces from 2009 to 2018 were calculated. The rates in the present study were calculated per 100,000 people.

Analysis of the disease time trend

To check the time trend of Brucellosis disease, first the annual incidence rate was calculated and then using the 10.2.0.329 version of GraphPad Prism software (GraphPad Software Inc, Boston, Massachusetts, United States), the time trend was drawn.

Spatial pattern analysis and cluster identification

In order to evaluate the spatial pattern of the disease, first, the prevalence rate of brucellosis in each of the provinces of Iran was calculated from 2009 to 2018, and then the CPR zoning in Iran was drawn using ArcGIS 10.3 environment. Thereafter, this model was evaluated using Getis-Ord General G (GOGG) and optimized hot spot analysis (OHSA) indices.

Prevalence rate is the result of dividing the number of the total number of disease cases in a population during a certain period of time to the number of people in that population in the same period of time.

Furthermore, in order to evaluate the degree of spatial autocorrelation of the disease, Global Moran's I index was used by ArcGIS 10.3. The range of this statistic varies from +1 to −1. The closer the value of this statistic is to +1, it indicates that it is clustered, and the closer to −1, it indicates the dispersion, and if its value is zero, it indicates that the spatial distribution of the investigated phenomenon investigation random. In this study, the null hypothesis states that the distribution of brucellosis disease is completely randomly scattered in Iran. Finally, in order to identify the exact location of high-risk and low-risk clusters of brucellosis in Iran, the Anselin local Moran's I index was used. This index divides polygons into five splits of "Low-Low," "Low-High," "High-Low," "High-High" and "Not Significant." "High-High" indicates the areas that have a high rate of disease incidence in and around them, and in fact shows high-risk clusters or hotspots, but "Low-Low" indicates the low rate of disease incidence in these areas and around; they actually show clusters of low risk of disease or coldspots.[23,24]

Getis-Ord general G

This index was developed by Getis and Ord as one of the global statistics for measuring spatial patterns.[25] GOGG shows the degree and value of clustering of high and low values. If the GOGG value obtained by this method is higher than the expected value and the *Z*-score is positive, it indicates that high values have tendency to clustering, and if the obtained GOGG value is lower than the expected value and the *Z*-score is negative, it indicates the tendency of low values to create clusters. Null hypothesis in GOGG, it mainly expresses the absence of spatial clustering in the region.[26-28] In the next step, Getis-Ord Gi*index was used in optimized mode to identify hot spots and cold spots in different regions of Iran used by ArcGIS 10.3.

Optimized hot spot analysis

A more accurate, more valid and newer method to detect clusters is OHSA, which is actually the use of Getis-Ord Gi*statistics in a state that the value of the distance band is optimized to detect hotspots and coldspots. One of the strengths of OHSA is that after implementation, it identifies and prioritizes high-risk and low-risk clusters at different confidence intervals (CIs) of 90%, 95%, and 99%.

Correlation analysis

In this study, we aimed to evaluate the correlation between the CPR of brucellosis and the geographic coordinates of patients. To achieve this, we employed the Pearson correlation coefficient (PCC), which quantifies the strength and direction of the linear relationship between the two continuous variables. The PCC is denoted as RR and ranges from −1 to +1, where values closer to 1 indicate a strong positive correlation, values closer to −1 indicate a strong negative correlation, and values around 0 suggest no linear correlation. The analysis was conducted using GraphPad Prism software, which facilitates both calculation of the PCC and generation of scatter plots with a line of best fit. The software also provides CIs for the estimated correlation, enhancing the robustness of our findings.

RESULTS

Time trend results

In this research, the total number of patients over 10 years was 155,059. The average annual incidence rate of the disease in Iran during the years 2009–2018 was obtained 19.91 per 100,000 people. The 10-year time trend of the annual incidence of the disease is shown in Figure 1.

Spatial distribution results

To analyze the spatial pattern of brucellosis, at first CPR of the disease was calculated during the years 2009–2018 and then the CPR zoning of the disease was drawn in GIS [Figure 2]. The three provinces with the highest rate of prevalence included Lorestan (CPR = 703.10), Hamedan (CPR = 599.25), Kurdistan (CPR = 581.30), and the three provinces with the lowest rate of prevalence included Hormozgan (CPR = 14.63), Tehran (CPR = 23.34), and Bushehr (CPR = 27.73).

Spatial autocorrelation results and identifying clusters

The value of Moran's index is 0.252, which indicates the severity of autocorrelation and the high tendency of brucellosis to cluster. The value of *Z* score and *P* value shows that the degree of spatial autocorrelation of the disease was statistically significant ($P < 0.001$).

After knowing about the high spatial autocorrelation and clustering of the spatial distribution of the disease, it was decided to identify the hotspots and coldspots in Iran. In order to achieve this goal, Anselin local Moran's I index was used and its zoning was drawn in Figure 3. According to the results, the provinces of Kurdistan, Hamedan, Lorestan,

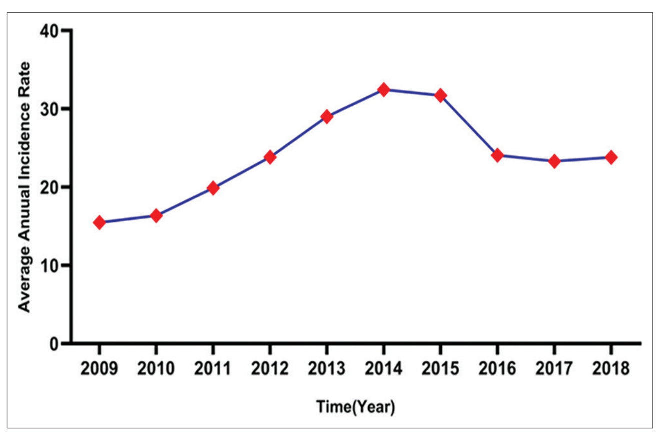

Figure 1: Annual incidence rate of brucellosis during 2009–2018

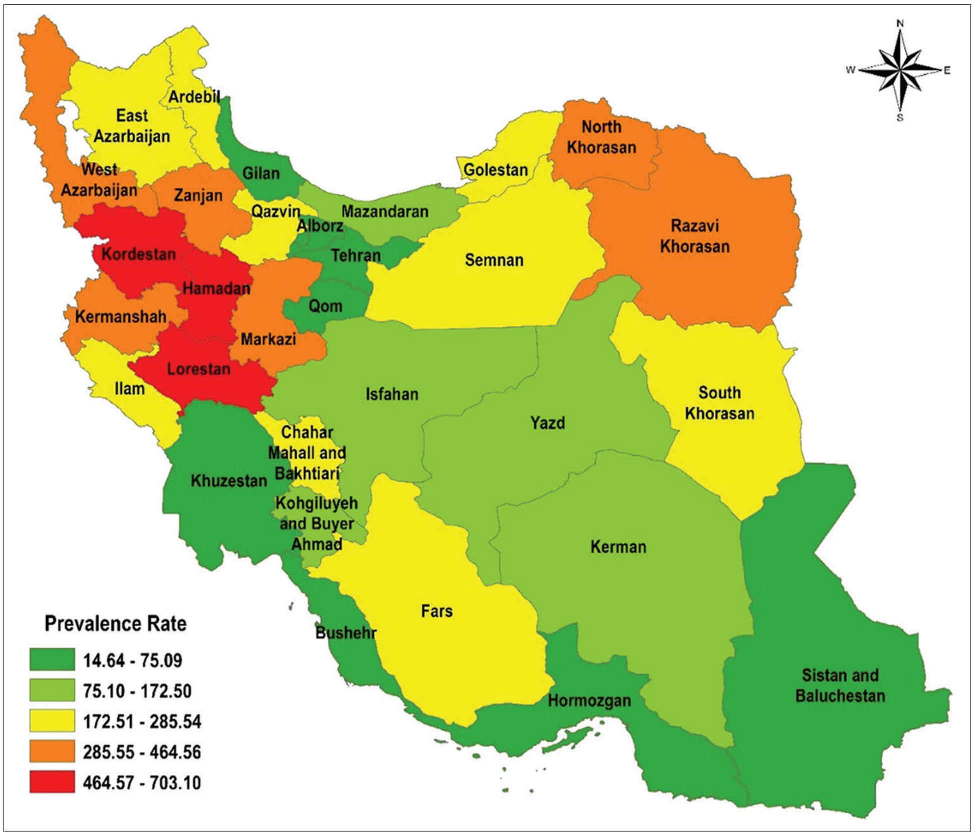

Figure 2: Cumulative prevalence rate of brucellosis during 2009–2018

and Kermanshah are hotspots, which indicate the spatial clusters of high values and the high risk of prevalence of the disease in these areas. On the other hand, the rest of the provinces were in "Not Significant" status, which indicates that the distribution of the disease in these provinces does not have a specific pattern and is scattered randomly.

The optimal value of the estimated distance band based on OHSA was 216 km. Based on the results of OHSA, high-risk clusters (hotspots) and low-risk clusters (coldspots) of brucellosis incidence are shown in Figure 4 at 90%, 95%, and 99% CIs. By observing the zoning of brucellosis clusters, it can be realized that the coldspots were identified in the South and Southwest of Iran in the provinces of Sistan and Baluchistan, Bushehr, Hormozgan, Khuzestan (99% CI), Kohgiluyeh and Boyer Ahmad (95% CI), Yazd and Kerman (90% CI), and hotspots were observed in the west and northwest of the country in Kurdistan, Lorestan, Hamedan and Kermanshah provinces (99% CI), Zanjan, Makarzi and Ilam (95% CI) and West Azerbaijan (90% CI).

To evaluate whether the prevalence of brucellosis is really related to the geographical coordinates of the patients' residence, PCC was used between CPR and the latitude and longitude of the patients' residence. According to the obtained results, PCC between CPR and latitude was negative and not statistically significant ($r = -0.253$; $P = 0.169$). On the other hand, there is a negative and significant relationship between CPR and PCC longitude ($r = -0.358$; $P < 0.05$). Therefore, it can be said with more certainty that the prevalence of the disease will increase significantly with the decrease in latitude and moving from the western regions to the eastern regions of Iran [Figure 5].

The GOGG analysis yielded a result of 0.323. This value suggests a significant clustering of high disease incidence areas, referred to as "hotspots," compared to areas with low disease incidence, known as "coldspots." Specifically, the analysis indicates that regions with higher disease rates are more likely to be grouped together than those with lower rates ($P < 0.001$).

DISCUSSION

The purpose of the present study was to determine the 10-year prevalence of brucellosis along with evaluating the spatial pattern and identifying high-risk and low-risk clusters in order to have a more correct judgment than the hypothesis of the effect of infectious and environmental pathogens on the spread of the disease.

In the present study, the prevalence rate of brucellosis during 2009–2018 was obtained 200.09 per 100,000 people. According to the WHO, the prevalence of brucellosis widely

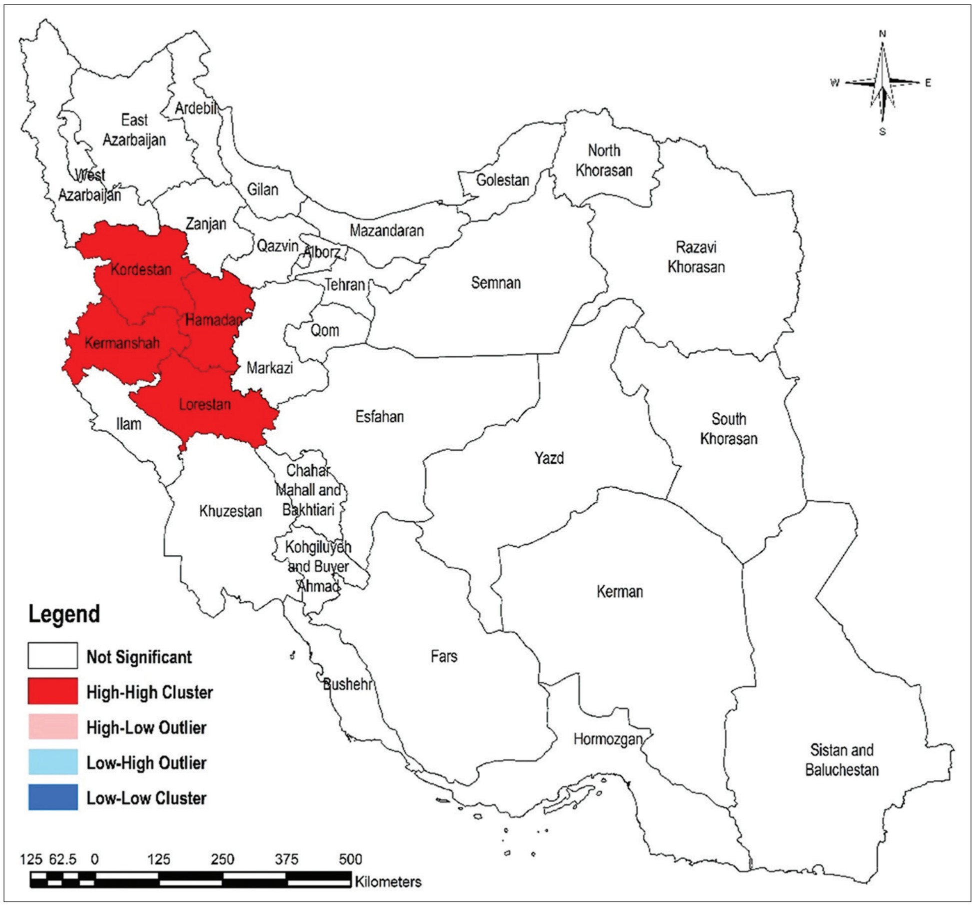

Figure 3: Hotspots (clusters of high values) and coldspots (clusters of low values) of brucellosis in Iran using Anselin local Moran's I index

varies from 0.01 to 200 per 100,000 populations, such that in the endemic areas of America is 1 per 100,000, in Britain, 0.3 per a million, in Germany, it is 0.03 per 100,000 and in Greece, it is 0.3 per 100,000.[29] Studies also show that Malta fever has a high prevalence in developing countries.[30] It is endemic in some of these regions, including the Western Mediterranean, the Middle East (including Syria, Iraq, Turkey, and Iran), Central and South America, as well as India.[31] In the endemic areas, the prevalence rate varies from <0.03 to more than 200 per 100,000 people.[32] The prevalence of the disease has a significant difference in the different parts of the country and its rate varies from 98 to 130 cases per 100,000 people.[33] The study of seroprevalence in Northeast of Iran showed that the prevalence of brucellosis in human was 37 per 100,000 people during 2002–2006.[34]

Global Moran's I index value = 0.252 and the results of Z-score and P value showed that the spatial autocorrelation and tendency to spatial clustering of brucellosis is very high. In other words, the areas that were close to each other in terms of distance were also similar in terms of the incidence of disease. Other studies have also reported the cluster behavior of brucellosis. In the study of Mollalo *et al*. in 2014 that was carried out on the spatial and spatio-temporal analysis of human brucellosis in Iran, the distribution of human brucellosis cases in both city and province levels in the form of clusters ($P < 0.05$) was reported with a relatively stable annual pattern throughout the country.[6]

The results of the study by Abdullayev *et al*. in 2012, which was conducted on the spatial and temporal analysis of human brucellosis in Azerbaijan (1995–2009), showed that statistically significant spatial clusters in each of the 3-year and 5-year periods with accumulation incidence rates from 101.1 (95% CI: 82.8, 124.3) to 203.0 (95% CI: 176.4, 234.8) were identified.[35]

In the study by Karimi *et al*. in 2020 on the spatial and temporal analysis of brucellosis cases in Golestan province from 2015 to 2017 using GIS showed that the geographical distribution of Malta fever in Golestan province had been influenced by several spatial and spatio-temporal clusters and had various pattern in the cluster and noncluster areas, contact with livestock, indirect dairy products consumption and hospitalization; and the exposure to nonpasteurized dairy products had a significant difference between cluster and noncluster areas.[36]

In 2020, Liang *et al*. examined the spatial and temporal distribution of human brucellosis in China from 2007 to

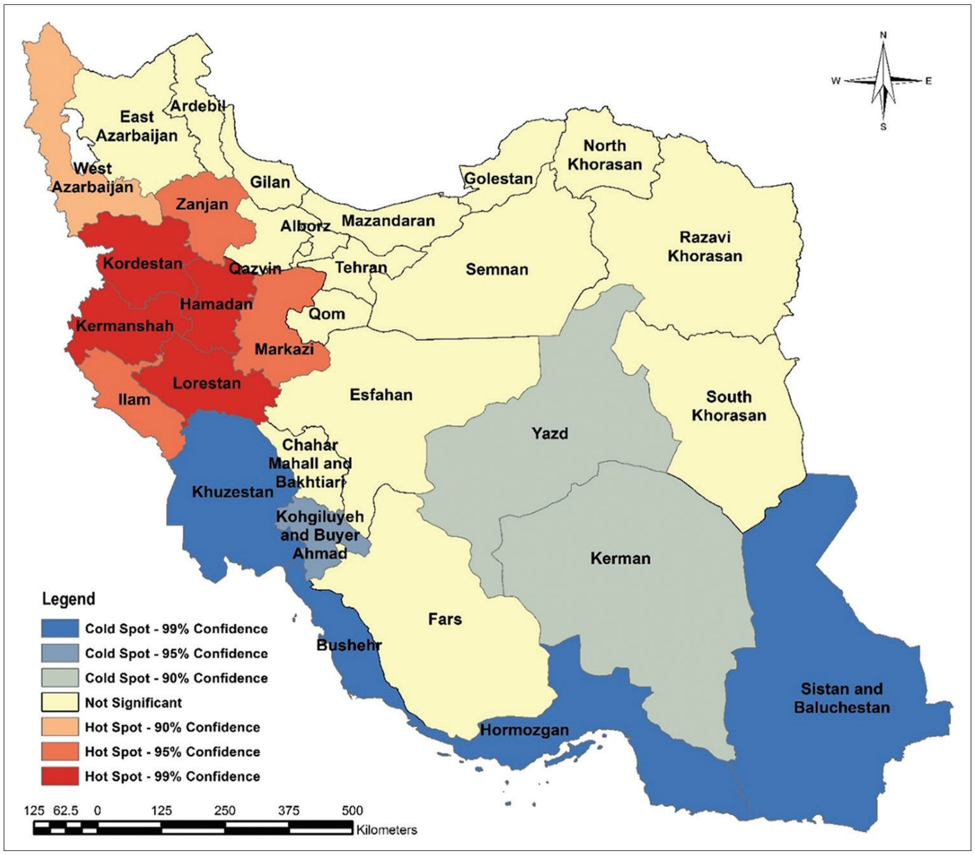

Figure 4: Hotspots and coldspots of brucellosis incidence in Iran at 90%, 95%, and 99% confidence intervals

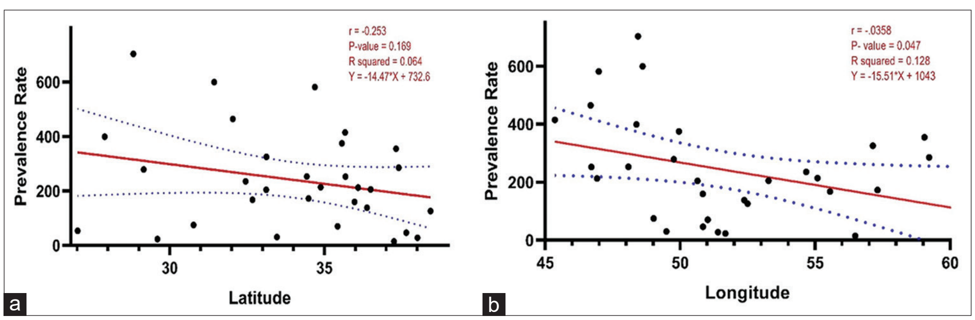

Figure 5: Scatter plot and line of best fit (95% confidence interval) for correlation between PR brucellosis with latitude (a) and longitude (b)

2016. In global autocorrelation analysis, brucellosis in China between 2013 and 2014 had a nonrandom distribution with spatial autocorrelation ($Z > 1.96$, $P < 0.05$) and showed a clustering trend.[37]

In 2018, Pakzad *et al*. analyzed the spatial and temporal analysis of brucellosis incidence in Iran from 2010 to 2013 using GIS. One of the findings of this study was the clustering pattern of the disease: the areas with a high incidence rate were located in the vicinity and had cluster distribution patterns. This clustering of the disease occurred in the northwest and west of the country.[38]

Because brucellosis is not a contagious disease, spatial clusters of human cases are likely the result of shared food sources, animal processing, areas of more intensive agricultural production, or similar sociocultural practices also the behavior of the disease may be due to environmental factors or be geographical. Low altitudes and moderate humidity create areas with vegetative cover and the weather conditions provide a suitable environment for the survival and spread of the disease. In fact, underdevelopment or lack of health infrastructure as well as traditional lifestyle can also be important factors in disease transmission.[38-40]

Hotspot of brucellosis was in Kurdistan, Hamedan, Lorestan and Kermanshah provinces, and Coldspot was not significant in the provinces. The high incidence rate of the disease in these areas has been observed in several studies that have been mentioned in this study. Based on the results of Shirzadi's study in 2021, the highest incidence of Malta fever in the years 2006–2015 was in the provinces of Lorestan, Hamedan and Kurdistan, Markazi, Kermanshah, East and West Azarbaijan and North Khorasan, South Khorasan and Razavi Khorasan.[29] In the western provinces of Iran, due to the proximity to the Zagros Mountain and the presence of clump oak forests and fertile soil, the main economic activities of the people are farming and ranching. Furthermore, due to the movement of nomads, these areas have a higher rate of Malta than other parts of Iran.[41]

In the study by Pakzad *et al*. in 2018, based on the hotspot analysis, at the beginning of this study, the high-risk areas were mostly in the cities of the northeast, west, and northwest of Iran, but at the end of the study, most of the high-risk areas of brucellosis were located in the west and northwest of the country, and the towns with the highest incidence rate were in the vicinity of the Zagros mountains. Furthermore, due to the thick oak forests and fertile soil, the main economic activity of the region is ranching, and the Zagros mountain range is also the seasonal migration route of the nomads.[38]

In the study conducted by Norouzinezhad *et al*. in 2021, the results of their 9-year research indicated the highest rate of infection in the provinces of Hamedan, Lorestan, Kurdistan, and Kermanshah in Iran. The classification carried out in 2019 showed that among all the provinces, Kermanshah, Lorestan, Kurdistan, and Hamedan had the highest incidence of Malta fever.[32]

With a general look at the zoning of the clusters, we found that coldspots are in the south and southwest of the country (lower latitude and higher longitude) and hotspots are in the west and northwest of the country (higher latitude and lower longitude). Furthermore, according to the results PCC between prevalence rate (PR) and latitude was negative and not statistically significant ($r = -0.253$; $P = 0.169$). On the other hand, there is a negative and significant relationship between PR and PCC longitude ($r = -0.358$; $P < 0.05$). As the results show, the prevalence of the disease increases with decreasing longitude, but with decreasing latitude, which was not statistically significant, we see areas with low prevalence.

In the study of Mollalo *et al*., the spatial hotspots of human brucellosis in each year were identified mainly in the west, northwest, and northeast of the country and pointing out that the distribution of human Malta fever is more in cities with a higher average altitude from 2000 m above mean sea level (SL); the reason is the possibility of indirect effects of environmental conditions in these areas and the existence of climatic conditions such as lower temperatures, more raining and the steeper slopes provide appropriate conditions for the transmission of human brucellosis in these areas.[6] Finally, previous researches have also reported a higher rate of this disease in fertile and green lands at an altitude of 800–1600 m above SL, which is also in this region of Iran.[42]

Environmental or geographical factors, low and medium altitudes, humidity, and vegetation and climatic conditions in the west and northwest of the country have provided an appropriate environment for the survival and spread of brucellosis. Therefore, the influence of geographic factors on the occurrence of common diseases between humans and animals is inevitable.[43] The lack of development or lack of traditional health infrastructure and traditional lifestyle, low education and low socioeconomic status in the western and northwestern regions of Iran can be also one of the main factors of transmission of this disease in these areas, which can turn them into high-risk areas in the region in future.[44,45]

Limitations

The effect of climatic factors on the incidence of common diseases between humans and livestock is inevitable. However, the researchers did not have access to the necessary data, so it is suggested that researchers investigate these variables in future.

CONCLUSION

The prevalence of brucellosis in Iran is higher than developed countries and like many developing countries. Hotspots of brucellosis were identified in Kermanshah, Hamedan, Lorestan, and Kurdistan provinces. In the western provinces of Iran, due to the proximity to the Zagros Mountains and the presence of dense oak forests and fertile soil, the main economic activities of the people are farming and ranching. Furthermore, due to the movement of nomads, these areas have a higher incidence of Malta fever compared to other parts of Iran (48). Moreover, the geographical location of Iran and its vicinity to endemic countries such as Iraq, Pakistan and Afghanistan are important risk factors for the increase of brucellosis prevalence. Although proper veterinary services have been provided for these countries to control livestock diseases, there is still a risk of disease spreading from country to country (38). In general, it can be concluded that there are fundamental differences in the spatial distribution of this disease in Iran. The high prevalence of Malta fever is observed in the western and northwestern cities of the country, and this disease has caused many problems for the residents of these areas as a health issue. Therefore, it is very necessary to accurately identify the environmental, economic, and social factors affecting the disease to prevent new cases of the disease. On the other hand, understanding the spatio-temporal aspects of Malta fever can help health professionals and policy-makers to take appropriate actions to control it.

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Conflicts of interest

There are no conflicts of interest.

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