Strategic Understanding of Symptom Variation and Long-Term Risks: A Data-Driven Perspective

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Abstract

Understanding how individuals respond to infectious exposure and how symptom patterns evolve over time is critical for developing effective long-term management strategies. This study examines data from northern China to analyze symptom variation and the risk of chronic progression associated with delayed response. We apply data-driven models to explore how individual characteristics—such as occupation, age, and gender—are associated with different symptom profiles and long-term outcomes. Our findings suggest that individuals engaged in agriculture, animal handling, and related sectors are significantly less likely to experience high-fever symptoms. Additionally, younger individuals and females tend to exhibit higher peak body temperatures during acute phases. Importantly, delays in response management correlate strongly with an increased likelihood of long-term complications, while general supportive actions—even without specific identification of the underlying cause—can help mitigate chronic progression. These insights contribute to more effective planning, resource prioritization, and decision-making for better strategic management of complex symptom-based conditions.

Keywords: chronic condition, data mining, diagnosis delay, long-term management strategies, treatment delay

1. Introduction

Appropriate and timely response to infectious exposure plays a vital role in minimizing long-term impacts and ensuring effective resource allocation. In many contexts, the progression from acute symptoms to long-term complications is influenced not only by the nature of the exposure but also by how quickly and strategically actions are taken. Understanding how symptom patterns emerge and vary across different populations can offer valuable insights for designing more effective response protocols and intervention strategies. Timely recognition of symptom severity, combined with an understanding of demographic and occupational risk factors, can inform policies that reduce the likelihood of chronic outcomes. In this study, we examine data from northern China related to a common disease, Brucellosis, to analyze symptom variation and assess the risk of long-term complications associated with delays in response.

Brucellosis, a zoonotic disease caused by various Brucella species, typically transmits from infected livestock to humans via inhalation, ingestion, or skin abrasions (Franco et al., 2007; Buchanan et al., 1974). The inaugural case in humans was recorded in 1886 by a British army surgeon. Over time, the disease has been known by several names, including Malta fever, Mediterranean fever, gastric remittent fever, and undulant fever. Today, Brucellosis remains a prevalent health issue in developing countries with inadequate sanitation and limited availability of personal protective equipment and is among the numerous infectious diseases that have been the subject of extensive research (Dietrich et al., 2018)

The Brucella that can lead to human infections has been reported with four species: B. abortus, B. canis, B. melitensis, and B. suis (Young, 1983). Each species has a preferred animal host and exhibits varying levels of virulence. B. abortus infects cattle, B. melitensis targets goats and sheep, B. suis is common in swine and B. canis affects dogs [3]. Notably, B. melitensis is reported to be the most virulent and invasive of these species (Glowacka et al., 2018).

Numerous factors have been identified as increasing the risk of Brucella infection. The World Health Organization (WHO) reported in 1997 that Brucellosis in sheep and goats is the leading cause of human infection (WHO, 1997), findings echoed by studies in China (Ying-wei et al., 2017). Infection is typically associated with direct contact with livestock. Consuming unpasteurized milk and dairy products from infected animals is a known risk factor for the general population (de Figueiredo et al., 2015; John et al., 2010; Majzobi et al., 2010) while occupational exposure poses a specific risk to those working in livestock-related fields (de Figueiredo et al., 2015; Jamil et al., 2021; Dadar et al., 2023). This includes rearing, slaughtering, processing, shipping, trading, and breeding of livestock. Symptom variation is considerable among different groups. A Burundi serological survey highlighted a higher positive serology in occupational at-risk individuals compared to those exposed through contaminated food (Laroche et al., 1987). Occupational exposure can occur through skin cuts, mucous membrane contact, or blood contact from infected animals (Andriopoulos et al., 2007). Studies in Northern Ireland (Andriopoulos et al., 2007) and India (Shome et al., 2017) have identified cattle breeding and veterinary professions, respectively, as high-risk occupations, while a Spanish survey pointed to risks for microbiological laboratory workers (Bouza et al., 2005). However, human-to-human transmission is extremely rare, and patients become non-infectious once treatment begins (Andriopoulos et al., 2007).

Common symptoms of Brucella include fever, fatigue, and excessive sweating, with potential arthralgia and myalgia due to bacterial migration to joints and muscles. However, symptom manifestation and severity vary widely among patients. Fever is a prevalent symptom, with some patients experiencing severe fevers up to 41℃, while others may not have a fever at all. Cases have been reported that the severeness of Brucellosis may be associated with gender, age groups, and the type of organ that gets infected (Khan & Zahoor, 2018; Assafi et al., 2019). However, the factors contributing to the severeness of various symptoms remain unclear.

In the treatment of acute Brucella infections, appropriate therapeutic interventions typically shorten the disease's course to a few weeks. Antibiotic therapy, particularly the combination of rifampicin and doxycycline, is endorsed by the World Health Organization (WHO) and is also the standard treatment protocol for Brucellosis in the focal aera of this paper. The selection of specific drug regimens is contingent upon various patient-specific factors, including age, overall health status, and the severity of the infection. Early and timely treatment is imperative for symptom mitigation and the prevention of further complications, as underscored by existing literature (Castano & Solera, 2009). Despite adherence to prescribed antibiotic regimens, patients remain at risk for relapse or progression to a chronic form of Brucellosis. A notable study conducted in Iran revealed that approximately 3.7% of patients evolved into a chronic state of Brucellosis, characterized by symptoms persisting beyond one year (Castano & Solera, 2009; Roushan et al., 2016). This chronic manifestation of Brucellosis can lead to complications in multiple organ systems, including the testis, liver, spleen, heart, and central nervous system, thereby significantly impairing the functional capacity of affected individuals (Atluri et al., 2011). Moreover, chronic Brucellosis exerts a substantial socioeconomic impact due to the prolonged medical care required (Svetic et al., 1993; Kydyshov et al., 2022). The chronicity of Brucellosis is frequently attributed to an inadequate initial immune response, resulting in a persistent intracellular infection of macrophages (Byndloss & Tsolis, 2016; Tolomeo et al., 2003; Skedrios & Doura, 2013). Consequently, immediate diagnosis and effective antibiotic therapy are crucial for the effective management of Brucellosis (Khan & Zahoor, 2018; Castano & Solera, 2009). Accurate diagnosis of Brucellosis relies on understanding and interpreting complex clinical contexts and interrelated evidence (Cahan & Cimino, 2017). Data-driven methods have been reported that utilizing modern data tools like the Baidu index can enhance the surveillance and outbreak management of infectious diseases such as Brucellosis (Wang et al., 2023). ARIMA models can also be constructed by incorporating real-tome data such as the BSI to enhance the prediction and monitoring of Brucellosis outbreaks (Luo et al., 2023). However, in certain underdeveloped areas, the lack of objective diagnostic methods for Brucellosis often results in delays in both diagnosis and treatment, which can exacerbate the risk of the disease becoming chronic (Castano & Solera, 2009). Therefore, it is essential to investigate the correlation between diagnostic and treatment delays and the likelihood of Brucellosis progressing to a chronic condition.

In view of the considerable variation in Brucellosis symptoms and the necessity to understand the progression into chronic conditions, this research aims to elucidate two primary objectives: (1) identifying key determinants influencing the spectrum and severity of symptoms in Brucellosis, and (2) examining the relationship between the delays in treatment and diagnosis and the progression to chronic Brucellosis. To investigate the first research question, logistic regression analyses were employed to discern factors associated with the manifestation of symptoms during infection. Specifically, the study concentrated on fever symptoms, employing ordinary least square regression analyses to determine principal factors influencing body temperature variations during fever episodes. Various control variables were incorporated into the models and fixed effect models were tested to ensure the consistency and robustness of the results. Regarding the second research question, logistic regression analyses were conducted to explore the association between chronic Brucellosis and delays in treatment and diagnosis. The findings indicate a significant correlation between treatment delays and the subsequent development of chronic Brucellosis. However, this association appears to be less pronounced between diagnostic delays and the chronicity of the disease. In essence, the results suggest that while timely diagnosis is crucial for optimal treatment of Brucellosis, the medical treatment administered, even with some delay in diagnosis, may still play a pivotal role in averting the progression to chronic conditions.

The rest of the paper is organized as follows. In section 2, we introduce the study area, the data collection process, and statistic summary. In section 3, we first study the likelihood of developing fever symptoms in Brucellosis by conducting a set of logistic regression analyses. We then discuss the likelihood of developing other symptoms besides having fever. We also conduct a set of ordinary least square regression analyses to identify the key factors affecting body temperatures when patients are experiencing fever symptoms. In particular, we study the association between chronic Brucellosis and treatment delay and diagnosis delay. In section 4, we discuss valuable insights which provide guidelines for health workers in the prevention of chronic Brucellosis development. We then conclude the paper and present limitations of the study and potential future research directions.

2. Methods

2.1 Study Area

The study was conducted in the city of Dalian and the surrounding area in the Liaoning Province, which is in the northeastern area on China. Dalian is the 16th most populated city in China. According to the 2020 census, the metro area of Dalian and the surrounding area has a population close to 8 million (Macrotrends, 2023). The major ethnic group in the region is Han.

Liaoning is a province adjacent to Inner Mongolia Autonomous Region, which is a highly endemic province for brucellosis due to the development of nomadism (Cui & Shang, 2004; Zhao et al., 2008; Wang et al., 2008). A Surveillance for brucellosis in 2017 shows that livestock trade with Inner Mongolia contributes to its high incidence in Liaoning Province (Su et al., 2017). However, Dalian is located in southern part of Liaoning, i.e., the further end from Inner Mongolia Autonomous Region, about 600 km away, thus the severeness of effect from Inner Mongolia is greatly attenuated. The area we focus on in this study covers population from urban, suburban, and rural areas, thus the results obtained in this study are not restricted to certain groups of people but have a wide application.

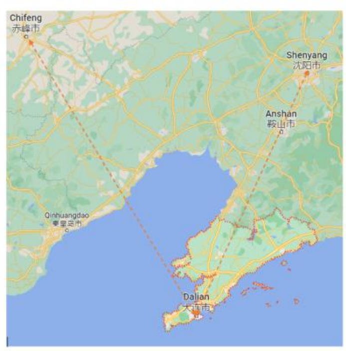

Figure 1. The Focal City Dalian, 400km south to Shenyang, the capital city of the Liaoning Province, and 600km southeast to Chifeng, the most populated city of the Inner Mongolia Province, where stock breeding is its backbone industry

2.*2 Data Collection*

All Brucellosis patients who were presented to hospitals in Dalian and the surrounding area from January 2021 to December 2022 were reported to Dalian Center for Disease Control and Prevention (CDC) and were included in this study. Questionnaire data were collected by CDC staff by visiting patients' homestead. Questions on the questionnaires are divided into three groups. The first group consists of basic demographic information of the patients which includes gender, age, ethnic group, occupation. The second group of questions asks for patients' infection history and livestock contact history, including the date of onset, date of diagnosis and treatment, and the time and manner they contact with livestock such as cattle and sheep. The third group of questions collect information on whether personal protection equipment, including medical masks, gloves, protective clothing, and disinfectant, are used during their contact with livestock. Diagnosis of Brucellosis relies on Rose Bengal Plate Test and Serum Agglutination Test, combining with patients' livestock contact history and clinical symptoms.

This project was initiated by CDC Dalian. The data collection method and project plan were approved by the government, indicating that all the regulations related to human subject research were followed in the project design. All patients participating in the study have signed a written informed consent. Participation in the study is voluntary and no financial incentive is provided. The data is obtained for research analysis in August 2022 and patients' personal information is removed so that no individual patient can be identified from the data in order to protect patients' privacy. The research data is organized, stored and owned by CDC Dalian. The access to dataset is restricted to protect patient privacy and approvals are required to access the dataset.

2.3 Statistic Summary

After cleaning the original data, 274 records remain and are included in our analysis. The summary statistics of all the variables is presented in Table 1. We divide the variables into outcome variables and independent variables. For independent variables, we further categorize them into five groups, as illustrated below.

Table 1. Summary Statistics

	Variable	Mean	Standard Deviation	Min	Max
Outcome					
	Fever	0.631	0.483	0	1
	Sweating	0.482	0.501	0	1
	Fatigue	0.726	0.447	0	1
	Temperature	37.7	1.14	36.5	41
	Chronic	0.018	0.134	0	1
Demographic					
	Gender	0.719	0.450	0	1
	Age	52.26	13.83	3	80
	Occupation	0.682	0.466	0	1
Infection History					
	Diagnosis_Delay	33.23	46.32	0	338
	Treatment_Delay	32.48	47.44	0	390
	Hospitalized	0.529	0.500	0	1
Contact Species					
	Sheep	0.839	0.368	0	1
	Cow	0.066	0.248	0	1
Contact Activity					
	Rearing	0.661	0.474	0	1
	Slaughtering	0.022	0.147	0	1
	Processing	0.095	0.294	0	1
	Shipping and Trade	0.018	0.134	0	1
	Vet	0.033	0.179	0	1
	Breeding	0.018	0.134	0	1
	Neighbor	0.073	0.261	0	1
	Consumption	0.230	0.422	0	1

PPE					
	Mask	0.237	0.426	0	1
	Gloves	0.215	0.412	0	1
	Clothing	0.018	0.134	0	1
	Disinfectant	0.011	0.104	0	1
Fixed Effect					
	Hospital	11	5.25	1	24
	Year	1.36	0.481	1	2

Outcome Variables: Fever is the major symptoms in Brucellosis. In our dataset, over 63% of patients experienced fever symptoms during their infection. A binary variable Fever is defined which takes value 1 if the patients ever experience fever during the infection, and 0 if no fever is observed. Besides fever, many patients experienced fatigue and night sweating during their infection even without the presence of fever symptoms. To understand the pattern among different symptoms, we also define binary variables for fatigue and sweat, respectively, and they take value one if such symptom presents. A continuous variable Temperature is used to document the highest ever temperature recorded since the patient gets infected and is used to analyze the key factors contributing to high body temperature during infection. A binary variable Chronic is used to denote the type of Brucellosis. Chronic takes value 0 if the infection is acute and 1 if the infection is chronic.

Demographic Information: The first group consists of basic descriptive information of the patient, which includes gender, age, and occupation. Variable Gender equals 1 if the patient is male and 0 if the patient is female. Variable Age documents the patient's age when he is infected, which takes value between 3 and 80. Variable Occupation describes the job occupation of the patient. We further categorize patients' job occupation into two groups. Patients who work in agriculture, farming, and stock breeding related jobs are categorized in the "1" group since they have higher possibilities to have contact with livestock in their working environment. Other patients working in jobs such as educational, industrial, craft related or trading related areas that have lower exposure to livestock, are grouped into the "0" group.

Infection History: The second group of variables describes the patient's infection history. Specifically, we pay attention to diagnosis and treatment delays. Variable Diagnosis_Delay, or simply referred to as D_Delay hereafter, is calculated as the days between the time the patient ever had any symptoms and the time the patient was diagnosed. Variable Treatment_Delay, or simply referred to as T_Delay hereafter, is calculated as the days between the time the patient ever had any symptoms and the time the patient ever received any treatment. The two variables are included in the logistic regression to study the factors contributing to the development of chronic Brucellosis. Since the diagnosis delay and treatment delay may be correlated, we only included one of these two variables in all the following analysis. We also define binary variable Hospitalized for all the inpatients who have a record of being hospitalized during their infection.

Livestock Species: The third group of variables describes the type of livestock that the patient has been in contact with. According to our data, sheep and cow are the two types of livestock, and we introduced two binary variables for each of them, indicating the existence of contact.

Livestock Contact Activities: The fourth group of variables covers various types of livestock contact activities, including slaughtering, processing, shipping, etc. We created one binary variable for each of these activities and included it in our models. It has been reported that people with certain occupations may develop antibodies against certain diseases due to their long-term exposure and infection histories in the past. The binary control variables we added in this group may help us better depict the full picture of key factors contributing to Brucellosis symptoms.

Personal Protective Equipment (PPE): The last group of variables describes protection through livestock contact. Four types of PPEs are included in the empirical model, including masks, gloves, clothing, and disinfectant. We introduced a binary variable for each type of the above-mentioned PPE type to describe whether the patient is having proper protection during livestock contact.

3. Results

3.1 Various Symptoms During Infection

To answer the first research question and identify the contributing factors to different symptoms, we conducted a set of logistic regression analyses. We first focus on the fever symptom since it is the most commonly observed among Brucellosis patients. The outcome of the logistic regression is whether the diagnosed patient has experienced fever symptoms or not, denoted by a binary variable Fever. Variable Fever equals 1 if the patient experienced fever and 0 if not. Fever can be modeled as

$$p(Fever = j|\boldsymbol{X}) = \frac{e^{\beta_0 + X\beta}}{1+e^{\beta_0 + X\beta}} \quad (1)$$

Where $j \in \{0,1\}$, and X is the vector of independent variables as described below.

We developed four different models. In the first model, we only included basic regressors, including patients' demographic information and infection history. We use treatment delay in the analysis since we believe the time of receiving treatment has a greater impact on fever and other symptoms than the time of Brucellosis diagnosis. In the second model, we include more control variables besides the basic regressors, including the stock contact species, stock contact activities, and the PPE situation. All the patients included in this study were diagnosed and treated in several different hospitals in Dalian and the surrounding areas, thus in the third model, we considered hospital fixed effect. All the patients were treated in several hospitals in the city of Dalian and surrounding areas over two years. We capture the hospital and year fixed effect in the third and fourth model, respectively. Table 2 shows the result on the likelihood of a patient experiencing fever symptoms during infection under all the four models.

Table 2. Likelihood of Developing Fever Symptom

	Fever	Model 1	P value	Model 2	P value	Model 3	P value	Model 4	P value
Demographic	Gender	0.652 (0.192)	0.146	0.675 (0.209)	0.205	0.632 (0.218)	0.183	0.635 (0.203)	0.156
	Age	0.995 (0.010)	0.649	0.988 (0.011)	0.294	0.979 (0.013)	0.108	0.986 (0.011)	0.240
	Occupation	0.423 (0.128)	0.004	0.375 (0.136)	0.007	0.300 (0.123)	0.003	0.385 (0.142)	0.010
Infection History	T_Delay	0.999 (0.003)	0.731	0.999 (0.003)	0.790	1.000 (0.003)	0.952	1.001 (0.003)	0.712
Contact Species	Sheep	-		0.414 (0.254)	0.151	0.451 (0.317)	0.258	0.393 (0.254)	0.149
	Cow	-		0.581 (0.433)	0.466	0.614 (0.484)	0.536	0.682 (0.541)	0.629
Activity	Feeding	-		1.207 (0.661)	0.732	1.056 (0.651)	0.930	1.122 (0.636)	0.839
	Slaughtering	-		0.083 (0.099)	0.036	0.049 (0.063)	0.020	0.061 (0.073)	0.020
	Processing	-		0.817 (0.451)	0.714	0.864 (0.516)	0.806	0.827 (0.477)	0.742
	Shipping and Trade	-		1.352 (1.416)	0.773	1.244 (1.462)	0.853	1.465 (1.562)	0.720

	Vet	-	0.397 (0.465)	0.430	0.355 (0.434)	0.396	0.640 (0.770)	0.711
	Breeding	-	0.896 (0.885)	0.912	0.787 (0.852)	0.825	0.922 (0.989)	0.940
	Neighbor	-	1.450 (1.039)	0.604	1.538 (1.212)	0.585	1.708 (1.268)	0.471
	Consumption	-	0.975 (0.430)	0.954	0.607 (0.311)	0.330	0.831 (0.385)	0.688
PPE	Mask	-	0.814 (0.380)	0.659	0.846 (0.467)	0.761	0.638 (0.306)	0.348
	Gloves	-	0.980 (0.473)	0.966	0.775 (0.435)	0.650	0.958 (0.466)	0.929
	Clothing	-	1.670 (2.622)	0.744	1.542 (2.658)	0.802	0.805 (1.294)	0.893
	Disinfectant	-	1.242 (1.698)	0.874	1.790 (2.604)	0.689	2.145 (3.167)	0.605

In all four models, the odds ratio of Occupation is positive and significant among all the independent variables. In model 1, the odds ratio of Occupation is 0.423, in order words, patients who are working in agriculture, farming, and stock breeding related areas are associated with about 60% reduction in the relative risk of having fever compared with patients who are not working in these areas. The odds ratio of occupation in the other models shows similar results, indicating a 60-70% reduction in relative risk of having fever for people working in agriculture, farming, and stock breeding related jobs compared with other patients. The control variable Slaughtering is also statistically significant, with a positive odds ratio of less than 0.1 for all the models.

The results indicate that patients in our study who are working as butchers or in slaughterhouses have over 90% reduction in the relative risk of experiencing fever symptoms during Brucellosis when compared with other types of stock contact activities. The result is consistent with a study in Cameroon which found the seroprevalence of abattoir personnel to be significantly higher than the general public and the percent of abattoir personnel reporting Brucellosis symptoms to be significantly lower than average (Awah- Ndukum et al., 2018). A possible explanation for the observed result is that more antibodies exist in the blood of people who have slaughtering-related jobs, and these antibodies can help relief the symptoms during infection.

Many patients often experience other symptoms besides fever during Brucellosis, among which fatigue and night sweating are very commonly observed. In our study, close to half of the patients experienced night sweating and 70% of the patients experienced fatigue. The sweating and fatigue discussed here are different from the “tired feeling” and the sweating that people commonly experience as a side effect during fever but are referring to the Brucellosis symptoms that are more long-lasting, often occur after the fever or without experiencing a fever.

3.2 Key Factors Affecting Body Temperature During Fever

To understand the key factors contributing to the development of sweat and fatigue symptoms, we conducted another set of logistic regression analyses, in which we use binary variables Sweat and Fatigue as the outcome variables. Since these symptoms are often observed after fever, and fever is commonly used as a criterion to evaluate the severeness of infection and the necessity of hospitalization, we are interested in evaluating the potential association between hospitalization and the development of sweat and fatigue symptoms, and we incorporated a binary control variable Hospitalized to differentiate inpatients and outpatients. Variable Hospitalized equals 1 for inpatients and 0 for outpatients. For each symptom, we conduct two regression analyses, one for the base model with only demographic information and infection history and one for the full model with all the control variables incorporated. The odds ratios are presented in Table 3.

Table 3. Likelihood of Developing Other Symptoms

		Sweat				Fatigue			
		Base Model	P value	Full Model	P value	Base Model	P value	Full Model	P value
Demographic	Gender	1.028 (0.285)	0.921	1.135 (0.327)	0.661	1.207 (0.377)	0.547	1.131 (0.373)	0.709
	Age	1.002 (0.009)	0.860	1.000 (0.010)	0.992	1.022 (0.011)	0.041	1.024 (0.012)	0.033
	Occupation	1.192 (0.329)	0.526	1.093 (0.342)	0.776	1.409 (0.437)	0.268	1.392 (0.493)	0.351
Infection History	Hospitalized	1.833 (0.463)	0.016	1.985 (0.545)	0.012	1.309 (0.375)	0.346	1.245 (0.392)	0.486
	T_Delay	1.000 (0.003)	0.862	1.000 (0.003)	0.998	1.009 (0.005)	0.060	1.008 (0.005)	0.068
Contact Species	Sheep	-		0.679 (0.364)	0.470	-		1.547 (0.884)	0.445
	Cow	-		1.729 (1.248)	0.448	-		1.029 (0.790)	0.970
Activity	Rearing	-		0.871 (0.451)	0.789	-		0.589 (0.325)	0.337
	Slaughtering	-		0.216 (0.253)	0.190	-		0.655 (0.636)	0.663
	Processing	-		0.710 (0.383)	0.525	-		0.497 (0.273)	0.204
	Shipping and Trade	-		0.199 (0.245)	0.191	-		0.487 (0.533)	0.551
	Vet	-		0.175 (0.226)	0.178	-		1.218 (1.618)	0.882
	Breeding	-		0.740 (0.737)	0.763	-		2.448 (3.031)	0.470
	Neighbor	-		0.492 (0.325)	0.283	-		0.486 (0.357)	0.326
	Consumption	-		0.689 (0.289)	0.374	-		0.402 (0.181)	0.043
PPE	Mask	-		1.245 (0.579)	0.637	-		0.666 (0.339)	0.424
	Gloves	-		0.875 (0.414)	0.778	-		0.624 (0.321)	0.359
	Clothing	-		0.596 (1.024)	0.763	-		0.519 (0.845)	0.687
	Disinfectant	-		0.417 (0.574)	0.525	-		0.985 (1.352)	0.991

The previous section sheds light on the likelihood of experiencing fever symptoms during Brucellosis. However, among patients who experience fever, there also exists significant variance in the fever symptoms. Some patients experienced high fever with highest body temperatures reaching 41℃ while others may only have a mild fever. To understand the key variables affecting body temperature during fever symptoms, we conducted a set of ordinary least square regression analyses on the data. The model allows us to unveil some of the interesting patterns in body temperatures among patients who have fever symptoms.

In our analysis, the dependent variable Temperature is defined as the highest recorded temperature for the patient since infection. The variable is numerical and takes value between 36.5℃ and 41.0℃. The independent variables are similar to the five groups of predictors described in section II. The OLS full model with all the control variables included (Model 2 in Table 4) can be expressed as follows:

$$Temperature = \beta_0 + \beta_1 Gender + \beta_2 Age + \beta_3 Occupation + \beta_4 T_{Delay} + \beta_5 Sheep + \beta_6 Cow + \beta_7 Rearing + \beta_8 Slaughtering + \beta_9 Processing + \beta_{10} Shipping\ and\ Trade + \beta_{11} Vet + \beta_{12} Breeding + \beta_{13} Neighbor + \beta_{14} Consumption + \beta_{15} Mask + \beta_{16} Gloves + \beta_{17} Clothing + \beta_{18} Disinfectant \quad (2)$$

Table 4 reports how the patients highest recorded body temperature changes for each increase in the corresponding predictors. As reported in the table, gender is negative and statistically significant, which indicates that in average, female patients experience higher fever than the male counterpart by about 0.5℃. The result is consistent with the results in many published studies that females have higher average body temperature than males (Kim et al., 1998; Waalen & Buxbaum, 2011). The results also show that the highest recorded body temperature is lower among senior patients than among younger patients. Take model 2 for example, for each 1 year of age increase, the highest recorded body temperature reduces by 0.011℃. This is also consistent with the fact that senior people in general have lower body temperature when compared with younger people (Waslen & Buxbaum, 2011; Geneva et al., 2019).

Table 4. Effects on Highest Temperature among All Patients

	Temperature	Model1	P value	Model2	P value	Model3	P value	Model4	P value
Demographic	Gender	-0.502 (0.150)	0.001	-0.465 (0.153)	0.003	-0.396 (0.156)	0.012	-0.466 (0.152)	0.002
	Age	-0.008 (0.005)	0.122	-0.011 (0.005)	0.044	-0.013 (0.006)	0.021	-0.011 (0.005)	0.037
	Occupation	-0.462 (0.149)	0.002	-0.429 (0.167)	0.011	-0.401 (0.175)	0.023	-0.405 (0.167)	0.016
Infection History	T_Delay	0.001 (0.001)	0.662	0.0005 (0.001)	0.733	0.001 (0.001)	0.716	0.001 (0.001)	0.473
Contact Species	Sheep	-		-0.215 (0.279)	0.441	-0.087 (0.290)	0.765	-0.207 (0.277)	0.455
	Cow	-		-0.100 (0.373)	0.788	0.009 (0.370)	0.981	-0.045 (0.371)	0.904
Activity	Rearing	-		0.011 (0.262)	0.966	-0.149 (0.271)	0.582	-0.011 (0.260)	0.966
	Slaughtering	-		-0.843 (0.481)	0.081	-1.020 (0.474)	0.032	-0.920 (0.479)	0.056
	Processing	-		-0.164 (0.275)	0.551	-0.242 (0.276)	0.381	-0.163 (0.273)	0.552
	Shipping and Trade	-		0.202	0.713	0.077	0.892	0.218	0.690

				(0.549)		(0.567)		(0.545)	
	Vet	-		-0.610 (0.622)	0.327	-0.726 (0.618)	0.241	-0.459 (0.622)	0.461
	Breeding	-		0.381 (0.514)	0.459	0.255 (0.508)	0.617	0.389 (0.511)	0.447
	Neighbor	-		0.538 (0.342)	0.117	0.428 (0.347)	0.219	0.576 (0.340)	0.091
	Consumption	-		0.272 (0.221)	0.221	0.055 (0.240)	0.818	0.231 (0.221)	0.297
PPE	Mask	-		0.079 (0.241)	0.744	-0.029 (0.258)	0.909	0.014 (0.241)	0.955
	Gloves	-		-0.109 (0.249)	0.662	-0.055 (0.258)	0.832	-0.110 (0.248)	0.657
	Clothing	-		0.156 (0.802)	0.846	-0.095 (0.790)	0.904	-0.080 (0.805)	0.921
	Disinfectant	-		0.028 (0.676)	0.967	0.390 (0.665)	0.558	0.161 (0.674)	0.812
Year Fixed Effect		-	-	-	-	-	-	-0.307 (0.145)	0.035

Variable Occupation is also significant in our analyses across the four models, indicating a lower body temperature in clinical record for people working in agriculture, farming, or stock breeding related areas. These people in general, have more opportunities to have close contact with livestock and poultry, thus it is possible for them to have antibodies developed against Brucellosis already, which may suppress the fever symptoms. We also observed the significance of control variable Slaughtering with a negative coefficient, and the potential explanation is similar to variable occupation. However, the effect is marginal across different models.

To check the robustness of our results, we further conducted the same set of analysis only among the patients who experienced fever symptoms during infection. The remaining dataset has 173 records. The regression results are shown in Table 5. The results are consistent with what we obtained in the previous set of analyses presented in Table 4.

Table 5. Effects on Highest Temperature among Patients with Fever Symptoms

	Temperature	Model1	P value	Model2	P value	Model3	P value	Model4	P value
Demographic	Gender	-0.473 (0.130)	<0.001	-0.461 (0.132)	0.001	-0.320 (0.131)	0.016	-0.456 (0.132)	0.001
	Age	-0.009 (0.004)	0.030	-0.009 (0.005)	0.043	-0.011 (0.005)	0.022	-0.009 (0.005)	0.052
	Occupation	-0.136 (0.126)	0.282	-0.084 (0.140)	0.551	0.020 (0.146)	0.890	-0.087 (0.140)	0.533
Infection History	T_Delay	0.002 (0.001)	0.263	0.001 (0.001)	0.428	-0.001 (0.002)	0.576	0.001 (0.001)	0.484
Contact	Sheep	-		0.053	0.822	0.201	0.405	0.040	0.865

Species				(0.237)		(0.241)		(0.237)	
	Cow	-		0.069	0.834	0.255	0.432	0.035	0.917
				(0.331)		(0.323)		(0.333)	
Activity	Rearing	-		-0.007	0.976	-0.215	0.367	0.005	0.983
				(0.229)		(0.238)		(0.229)	
	Slaughtering	-		0.610	0.460	0.297	0.712	0.657	0.427
				(0.824)		(0.803)		(0.824)	
	Processing	-		0.008	0.977	-0.176	0.498	0.026	0.921
				(0.263)		(0.259)		(0.264)	
	Shipping and Trade	-		0.172	0.739	-0.091	0.876	0.169	0.744
				(0.517)		(0.582)		(0.516)	
	Vet	-		-0.360	0.557	-0.541	0.361	-0.405	0.509
				(0.611)		(0.591)		(0.612)	
	Breeding	-		0.768	0.099	0.547	0.223	0.821	0.079
				(0.463)		(0.447)		(0.465)	
	Neighbor	-		0.650	0.024	0.468	0.099	0.630	0.028
				(0.284)		(0.282)		(0.285)	
	Consumption	-		0.401	0.056	0.333	0.151	0.406	0.048
				(0.209)		(0.230)		(0.209)	
PPE	Mask	-		0.293	0.202	0.089	0.702	0.311	0.176
				(0.229)		(0.232)		(0.229)	
	Gloves	-		-0.109	0.645	0.039	0.870	-0.101	0.669
				(0.236)		(0.240)		(0.236)	
	Clothing	-		-0.372	0.676	-0.629	0.466	-0.329	0.712
				(0.889)		(0.860)		(0.889)	
	Disinfectant	-		0.240	0.713	0.477	0.442	0.219	0.736
				(0.649)		(0.619)		(0.649)	
Year Fixed Effect		-	-	-	-	-	-	0.149	0.270
								(0.134)	

3.3 Treatment Delay and Chronic Condition

A certain portion of Brucellosis can develop into chronic conditions and could last over a year or longer. People who suffer from chronic Brucellosis often experience symptoms such as long-term fatigue, recurrent fevers, joint inflammation, arthritis of spinal bones, inflammation of inner lining of heart chambers, etc. Chronic Brucellosis can seriously affect patients' normal life, however, the relationship between chronic condition and treatment and diagnosis schedule remains not clear. In this section, we explore the association between developing into chronic Brucellosis condition and treatment and diagnosis delay.

We define the treatment delay to be the span between the time that a patient first has any Brucellosis symptoms developed and the time that any medical treatment is given to the patients, even if the treatment is not specifically targeting Brucellosis. We define the diagnosis delay to be the span between the time that a patient first has any Brucellosis symptoms developed and the time that the patient is first diagnosed as Brucellosis infection. In our dataset, most patients are diagnosed within a week or two and receive treatment in a similar time frame. However, not all patients with Brucellosis can get diagnosis and treatment in a timely manner.

The delay in diagnosis and treatment can have various causes. On patients' side, some of them may choose not to see doctors if the symptoms are mild. Some patients may not have health insurance and may suffer from financial burdens that they are unwilling to go to hospital unless absolutely necessary. On the healthcare givers' side, due to the variation in patient symptoms, doctors sometimes may not be able to give the Brucellosis diagnosis in a timely manner and may initially treat it as normal cold or flu. Some areas covered in this study lack the medical equipment needed to reach a diagnosis and the medical treatment levels are very low. All the above-mentioned reasons could lead to diagnosis and treatment delay, although the specific reason for each delay is beyond the scope of this study. Though a lot of times patients receive treatment after getting the diagnosis, treatment can actually start prior Brucellosis diagnosis due to the delay in diagnosis or misdiagnosis. In our study, we frequently observe cases in which treatment starts before the Brucellosis diagnosis. The medians of diagnosis and treatment delay are 18 and 17, respectively, and the means of diagnosis and treatment delay are 33.23 and 32.48, respectively.

According to CDC definition, Brucellosis with symptom clinical presentation time less than two months are defined as acute type, while the infection with clinical presentation time more than two months are defined as chronic type. A binary variable Chronic is thus introduced accordingly, and it takes value 0 for acute type and 1 for chronic type. A logistic regression model for studying the likelihood of developing chronic Brucellosis can thus be developed as follows, with variable Chronic to be the outcome variable.

$$p(Chronic = k|\boldsymbol{X}') = \frac{e^{\gamma_0 + X'\gamma}}{1+e^{\gamma_0 + X'\gamma}} \quad (3)$$

Where $k \in \{0,1\}$, and X' is a set of predictors.

We developed two models to study the association between the delay in diagnosis and treatment and the likelihood of developing into chronic conditions. We only use the base model for this analysis, i.e., the predictors only include the basic demographic information and infection history. In the first model, we use diagnosis delay in the infection history, while in the second model, we use treatment delay instead.

Table 6 reports the likelihood of developing chronic Brucellosis. It can be seen from the table that variable treatment delay is statistically significant, with an odds ratio of 1.011. In other words, for each 1 day of treatment delay, the risk of developing chronic Brucellosis increases by 1.1%. Interestingly, we do not observe diagnosis to be statistically significant, though it is marginal (p-value = 0.082). The results show that getting treatment for Brucellosis patients in time plays a key role in preventing Brucellosis developing into chronic conditions. The treatment, however, may not be the medicine specifically target treating Brucellosis, such Rifampicin and Doxycycline suggested by WHO for Brucellosis treatment. Taking some medicines such as fever reducer or general antibiotics for alleviating symptoms, though not ideal in Brucellosis treatment, may be helpful in preventing the development of chronic Brucellosis when compared with leaving it untreated. Though diagnosis delay is correlated with treatment delay and may also contribute to the development of chronic Brucellosis, its effect is significantly attenuated.

Table 6. Likelihood of Developing Chronic Condition

	Chronic	Chronic Condition with Diagnosis Delay		Chronic Condition with Treatment Delay	
		Coefficient	P value	Coefficient	P value
Demographic	Gender	omitted	-	omitted	-
	Age	0.981 (0.033)	0.565	0.981 (0.034)	0.579
	Occupation	0.990 (1.049)	0.992	0.968 (1.067)	0.975
Infection History	Diagnosis Delay	1.010 (0.006)	0.082	-	-
	Treatment Delay	-	-	1.011* (0.005)	0.037
	Hospitalized	0.179 (1.261)	0.173	0.150 (1.340)	0.157

4. Discussion

In this research, we conducted a comprehensive analysis of Brucellosis cases in Dalian China and surrounding area from 2021 to 2022, utilizing data mining techniques to identify factors influencing various Brucellosis symptoms and their severeness. The study revealed a diminished likelihood of fever symptoms among individuals employed in agriculture, farming, and livestock breeding. People working in slaughtering business are also likely to experience fevers during Brucellosis infection, indicating a potential presence of antibody development among these patients. Additionally, we developed models to investigate the relationship between chronic Brucellosis and delays in treatment and diagnosis. Our findings indicate a significant association between treatment delay and the progression to chronic Brucellosis. However, the impact of diagnostic delays on chronic Brucellosis is less pronounced. This suggests that while receiving medical treatment without a confirmed Brucellosis diagnosis is not the ideal approach, it can still mitigate the risk of developing a chronic form of the disease to a certain degree.

This research presents invaluable insights and actionable strategies for the effective management of Brucellosis. It emphasizes tailored approaches that are especially relevant for underdeveloped areas, where medical resources are scarce and access to advanced healthcare is limited. The study meticulously addresses the unique challenges faced in these regions, proposing cost-effective, feasible treatment methods that can be implemented even in settings with basic healthcare infrastructure. Additionally, it underscores the importance of community awareness and local health worker training to enhance the overall effectiveness of Brucellosis treatment in these environments.

Our study, while contributing valuable insights into Brucellosis treatment, is subject to several limitations that could be addressed in future research endeavors:

Sample Size and Population Scope: The research is based on data from approximately 200 Brucellosis cases in Dalian, a city with nearly 8 million residents. This sample size and patient population may not be sufficiently representative. Future studies could benefit from encompassing a broader population, enhancing the generalizability of the findings.

Longitudinal Data: The current study is limited to data from 2021 and 2022, restricting our ability to comprehensively analyze the progression to chronic Brucellosis. A longitudinal study spanning multiple years could provide a more in-depth understanding of the chronic development of the disease.

Data Collection Methodology: The reliance on patient-completed questionnaires, based on personal records and memory, introduces potential inaccuracies due to memory bias. Additionally, misinterpretations of questionnaire items could lead to further data inaccuracies. Enhancing data verification processes and possibly incorporating post-survey data collection could improve data quality.

Treatment Adherence: The study records treatments based on doctor prescriptions, but it is challenging to monitor the exact adherence of patients to these prescriptions. Understanding patient compliance with treatment regimens is crucial, as deviations from prescribed therapies could significantly impact the study's outcomes and interpretations.

Brucellosis, as a prevalent epidemic, exerts a substantial impact on public health. The importance of our research lies in its contribution to enhancing healthcare professionals' understanding of the diverse symptomatology associated with Brucellosis. Challenges in achieving a timely diagnosis of Brucellosis often stem from symptom variability, patient cooperation levels, and varying standards of medical practice. Notwithstanding these challenges, our findings underscore the paramount importance of prompt treatment over immediate diagnosis in preventing the progression to chronic Brucellosis. This insight offers valuable guidance for the management and treatment of potential Brucellosis cases, especially in the underdeveloped areas with insufficient medical resources, highlighting the critical role of early therapeutic intervention in the prevention of chronic Brucellosis.

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Authors’ contributions

Mrs. Fan, Dr. Han, Dr. Zhang, and Dr. Wu were responsible for study design and revising. Mrs. Chen and Mrs. Yang was responsible for data collection. Mrs. Fan drafted the manuscript and Dr. Han, Dr. Zhang, and Dr. Wu revised it. All authors read and approved the final manuscript.

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Institutional Review Board statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by Dalian Center for Disease Control and Prevention Medical Ethics Expert Committee (date of approval July 28 2021). The data used in this study is secondary data with no human direct contact involved.

Conflicts of interest

The authors declare no conflicts of interest.

Informed consent

Informed consent was obtained from all subjects involved in the study.

Ethics approval

The Publication Ethics Committee of Sciedu Press.

The journal and publisher adhere to the Core Practices established by the Committee on Publication Ethics (COPE).

Provenance and peer review

Not commissioned; externally double-blind peer reviewed.

Data availability statement

This project was initiated by CDC Dalian. The data collection method and project plan were approved by the government, indicating that all the regulations related to human subject research were followed in the project design. All patients participating in the study have signed a written informed consent. Participation in the study is voluntary and no financial incentive is provided. The data is obtained for research analysis in August 2022 and patients' personal information is removed so that no individual patient can be identified from the data in order to protect patients' privacy. The research data is organized, stored and owned by CDC Dalian. The access to dataset is restricted to protect patient privacy and approvals are required to access the dataset.

Data sharing statement

No additional data are available.

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