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BRUCELLOSIS CO-INFECTION IN A COVID-19 PATIENTS; A CROSS SECTIONAL DESCRIPTIVE ANALYTICAL STUDY

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Abstract

Objective. *Brucellosis is a global zoonotic infection with multisystem involvement. It typically presents with fever, chills, anorexia, malaise, musculoskeletal pain, and arthralgias - symptoms which are also associated with Coronavirus Disease 2019 (COVID-19). This study aimed to investigate the relative frequency of brucellosis in COVID-19 patients and its association with the severity of COVID-19.*

Method and materials. *In this cross-sectional, descriptive-analytical study, 180 COVID-19 patients referred to the Mofatteh Clininc of Yasuj during 2021-2022 were enrolled. The patients were divided into two groups: brucellosis positive (n=40) and brucellosis negative (n=140). The distribution of demographic characteristics and clinical symptoms among COVID-19 patients was compared based on their brucellosis test results. The association between the severity of COVID-19 and brucellosis status was evaluated.*

Results. *Among the 180 COVID-19 patients, 22.2% (n =40) were brucellosis positive based on the 2-Mercaptoethanol test, and the frequency of brucellosis in COVID-19 patients was significantly higher (P = 0.009). Clinical manifestations such as musculoskeletal pain, fever and sweating were associated with Malta fever (P<0.05), while anorexia and chills were not significantly different between brucellosis-positive and brucellosis-negative COVID-19 patients (P>0.05). There was a significant difference in the dairy consumption between brucellosis-negative and brucellosis-positive COVID-19 patients (P< 0.001). COVID-19 was more severe in brucellosis positive patients (P= 0.009).*

Conclusion. *Brucellosis is an endemic disease in Iran. It is important to examine the patient's history for possible exposure to Brucella. This etiology should be considered in the differential diagnosis of patients presenting with persistent fever, musculoskeletal pain, and chills in endemic areas during the COVID-19 pandemic. Moreover, the COVID-19 pandemic has negatively affected the diagnosis and treatment of brucellosis.*

Keywords: *Brucellosis, COVID-19, Dairy consumption*

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Introduction

In late 2019, a new virus emerged in Wuhan, Hubei, China, which eventually led to an international pandemic [*Huang C, et al., 2020*]. In February 2020, the World Health Organization named the virus as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the related disease Coronavirus Disease-2019 (COVID-19) [*Güven M, 2021*]. COVID-19 infection may involve several body systems, including the respiratory, nervous, digestive, skeletal and muscular systems. Due to the involvement of multiple body systems, there is controversy regarding the clinical manifestations of the COVID-19 [*Chen N, et al., 2020; Kucuk G, Gorgun S, 2021*]. Brucellosis is a prevalent zoonotic infection caused by bacterial genus Brucella [*Hasanjani Roushan M, Ebrahimpour S, 2015*]. Livestock is the main reservoirs, and humans are accidental hosts and play no role in maintaining the disease in nature [*Gwida M, et al.2010*]. Inhalation, contact with animals, and consumption of unpasteurized dairy products are the main routes of transmission to humans [*Tuon F, et al., 2017*]. Malta fever is relatively prevalent in Iran, and some studies have estimated the annual incidence of brucellosis at 1.100,000. The highest rates are reported in the western and northwestern regions [*Mirnejad R et al, 2017, Zeinali M et al, 2022*].

The manifestations of brucellosis vary from severe and generalized to limited symptoms affecting a single organ. The clinical complaints of brucellosis in humans are variable and nonspecific, including fever, anorexia, weight loss, malaise, back pain, and joint pain. These symptoms can resemble those of acute rheumatic fever; therefore, laboratory confirmation of the diagnosis is essential for the proper treatment [*Yagupsky P, et al., 2019; Güven M, 2021*]. On the other hand, typical manifestations of brucellosis such as fever, malaise, and arthralgia can be similar to those of COVID-19 [*Gemcioglu E, 2020; Tuon F, 2017*]. To the best of our knowledge, there are limited reports describing co-infections with SARS-CoV-2 and brucellosis. Considering the worldwide COVID-19 epidemic and its high mortality, as well as the overlap in musculoskeletal symptoms, fever, chills, and myalgia in patients with COVID-19 and brucellosis, this study aimed to investigate the frequency of brucellosis among COVID-19 patients and its association with the severity of COVID-19. An additional aim was to compare the distribution of demographic characteristics and clinical symptoms of COVID-19 patients based on their brucellosis test results.

Materials and methods

In this cross-sectional, descriptive-analytical study, 180 COVID-19 patients who presented to Mofatteh Clininc of Yasuj during 2021-2022, and the 180 COVID-19-negative individuals who visited the same center for routine check-ups, were included. Three inclusion criteria were applied for Covid-19 patients: 1) COVID-19 was confirmed by real-time Polymerase Chain Reaction (PCR) test using oropharyngeal swab samples; 2) despite receiving necessary supportive treatment in the follow-up, the patients continued complaining of the respiratory symptoms, digestive symptoms, myalgia, headache and musculoskeletal pain, after 3-4 weeks; 3) they had a history of contact with animals or consumption of non-pasteurized dairy products. The 180 COVID-19 negative individuals who referred to this center for checking up were included as control group. All subjects were tested for brucellosis using laboratory serological diagnostic tests, including the Wright, Coombs-Wright and 2-Mercaptoethanol test (2-ME tests), to assess the possible association between Covid-19 and brucellosis. Serological results of Wright > 1/80 and 2-ME ≥ 1/40 were considered positive for brucellosis.

For the Covid-19 patients, demographic and clinical data were recorded using a questionnaire, and these variables were compared based on the brucellosis results. COVID-19 patients were also categorized into three groups: mild, moderate, and severe, and the association between COVID-19 severity and brucellosis status was investigated.

Patients with positive brucellosis were treated with doxycycline and rifampin. Two weeks after the start of treatment, the patients were followed up, and their clinical symptoms were re-evaluated. The study was approved by the Ethical Committee of Yasuj University of Medical Sciences (Ethics code IR.YUMS.REC.1400.21).

Statistical analysis: Categorical variables are presented as numbers (percent) and continuous variables are presented as mean ± standard devia-

TABLE 1.

Distribution of brucellosis among COVID-19-positive and COVID-19-negative individuals

Variables	Brucellosis-positive		Brucellosis-negative		P value
	Frequency	Percent	Frequency	Percent	0.009
COVID-19-positive	40	22.2	140	77.8	
COVID-19 -negative	22	12.2	158	87.8	

tion or median (P25-P75). Categorical variables were compared using the Pearson's chi-square test. For 2×2 tables with low expected frequencies (any cell <5), Fisher's exact test was applied. When expected frequencies were close to 5, Yates' continuity correction was used to adjust the chi-square test. For larger contingency tables (r×c) with small expected values in more than 20% of cells, Monte Carlo simulation was conducted to obtain exact p-values. For continuous variables, we assessed normality using the Kolmogorov-Smirnov test. Based on normality, group comparisons were conducted using the Student's t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables.

All statistical analyses were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA). A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS

The current findings showed an association between COVID-19 and brucellosis; accordingly, the frequency of brucellosis was significantly higher among COVID-19 patients (P = 0.009) (Table 1).

Among the 180 COVID-19 patients, 22.2% (n =40) were brucellosis-positive based on the 2-ME, and Wright tests, while the Coombs-Wright test showed a positivity rate of 22.4%. The results of 2-ME and Wright test were considered for differential diagnosis of brucellosis.

Demographic characteristics of COVID-19 patients, including sex (P= 0.71), weight (P = 0.74), age (P= 0.52), height (P= 0.33), marital status (P= 0.72), occupation (P=0.74), urban/rural residence (P=0.41) and contact with livestock (0.311) did not differ significantly based on brucellosis status. However, consumption of unpasteurized dairy products was associated with brucellosis in Covid-19 patients (< 0.001) (Tables 2). Clinical manifestations, such as musculoskeletal pain (P= 0.03), fever (P< 0.001), and sweating (P<0.001), were associated with brucellosis, while anorexia (P= 0.15) and chills (P=0.24) were not significantly different between positive and negative brucellosis-COVID-19 patients.

Table 3 presents the association between COVID-19 severity and brucellosis status. The data indicate a statistically significant relationship (p < 0.001) between brucellosis and the severity of COVID-19. Among individuals with mild COVID-19,

TABLE 2.

Distribution of demographic and clinical qualitative variables of COVID-19 patients based on the brucellosis test results

Variables		Brucellosis		p - value
		positive	negative	
Age, mean (SD)		40.15 (9.97)	40.83 (10.71)	0.526
Weight, mean (SD)		40.15 (9.97)	40.83 (10.71)	0.741
Height, median (P25-P75)		168.9 (161.5-174.9)	169.4 (162.8-175.1)	0.333
Sex, n (%)	Male	24 (21.1%)	90 (78.9%)	0.375
	Female	16 (24.2%)	50 (75.8%)	
Marital status, n (%)	Single	7 (24.1%)	22 (75.9%)	0.729
	Married	33 (22.1%)	116 (77.9%)	
	Divorced	0 (0%)	2 (1.4%)	
Residence, n (%)	Urban	29 (21.5%)	106 (78.5%)	0.682
	Rural	11 (24.4%)	34 (75.6%)	
Contact with Livestock, n (%)	No	35 (21.1%)	131 (78.9%)	0.311
	Yes	5 (35.7%)	9 (64.3%)	
Occupation, n (%)	Unemployed	15 (20.3%)	59 (79.7%)	0.74
	Employed	25 (23.8%)	80 (76.2%)	
	Farmer?	0 (0%)	1 (100%)	
Dairy consumption, n (%)	No	10 (10.9%)	82 (89.1%)	< 0.001
	Yes	30 (34.1%)	58 (66.9%)	
Musculoskeletal pain, n (%)	No	1 (4.5%)	21 (95.5%)	0.031
	Yes	39 (24.7%)	119 (75.3%)	
Fever, n (%)	No	16 (12.7%)	110 (87.3%)	< 0.001
	Yes	24 (44.4%)	30 (55.6%)	
Sweating, n (%)	No	6 (4.2%)	138 (95.8%)	< 0.001
	Yes	34 (94.4%)	2 (5.6%)	
Anorexia, n (%)	No	17 (17.9%)	78 (82.1%)	0.154
	Yes	23 (27.1%)	62 (72.9%)	
Chills, n (%)	No	9 (16.1%)	47 (83.9%)	0.245
	Yes	31 (25%)	93 (75%)	

only 6.8% were brucellosis-positive, while 93.2% were brucellosis-negative. In severe COVID-19 cases, 85.7% were brucellosis-positive, and only 14.3% were brucellosis-negative. These findings suggest that brucellosis positivity is associated with increased severity of COVID-19, highlighting a potential link that may warrant further investigation.

Table 3.

Association between COVID-19 severity and brucellosis status

COVID-19 Severity	Brucellosis positive		Brucellosis negative		P value
	Frequency	Percent	Frequency	Percent	
Mild	10	6.8	138	93.2	< 001
Moderate	18	100	0	0	
Severe	12	85.7	2	14.3	

Discussion

Very few epidemiological studies have been conducted on co-infection with brucellosis and COVID-19 [*Tsagkaris C, et al., 2022*]. Our result showed that frequency of brucellosis was significantly higher among COVID-19 patients compared to non COVID-19 individuals. However, due to the COVID-19 pandemic and the risk of virus transmission, obtaining a detailed medical history of brucellosis in patients has been delayed.

The most prevalent sign of brucellosis is fever, which is frequently accompanied by chills, myalgia, arthralgia, nausea, weight loss, and enlarged lymph nodes [*Calik S, Gokengin A, 2011*]. According to our findings, clinical manifestations of musculoskeletal pain, fever and sweating were significantly associated with brucellosis among Covid19-patents.

Given the similar clinical symptoms, physician working in hospitals focused on treating COVID-19 patients may easily miss the diagnosis of brucellosis. As a result, a considerable number of brucellosis patients received no or delayed diagnosis, or were mistakenly treated as potential COVID-19 cases [*Calik S, Gokengin A2011; Alkan S, et al. 2022, Tsagkaris C, et al. 2022*]. In the study by *Alkan et al*., the patient was hospitalized in a dedicated SARS-CoV-2 facility, and brucellosis was overlooked on the day of admission [*Alkan S, et al., 2022*].

Brucellosis remains an important public health problem in Iran and is usually transmitted through contact with unpasteurized animal products or infected livestock [*Mirnejad R, et al. 2017*]. According to our findings, a significant correlation was observed between dairy consumption and brucellosis.

A high rate of co-infection between SARS-CoV-2 and other respiratory pathogens has been described in many studies [*Richardson S, et al.2020; Saavedra-Velasco M, et al. 2020*]. It is important that the presence of other pathogens, especially respiratory viruses, should not be taken as evidence that a patient does not also have co-infection with SARS-CoV-2 [*Kim D, et al. 2020*]. COVID-19 can mimic other febrile illnesses or be unrecognized, so a positive test for SARS-CoV-2 is not indicative of the absence of other infections, especially when the presentation is unclear [*Christian H, Bingisser R, 2020; Nickel C, Bingisser R, 2020*]. Based on our findings, a significant association was observed with the severe form of COVID-19 and brucellosis.Inflammation is a hallmark of brucellosis and affected tissues usually exhibit inflammatory infiltrates. As Brucella lacks exotoxins, exoproteases or cytolysins, pathological findings in brucellosis probably arise from inflammation-driven processes [*Baldi P, Giambartolomei G, 2013*]. Co-infection notably increases the risk of disease severity [*Ramadan H et al.2020*]. For the possible justification of this association, common factors of immunopathogenesis of COVID-19 and brucellosis can be mentioned. Other clinical investigations reported that in patients with mild to moderate COVID-19 a shared variety of clinical and laboratory characteristics can be found in other diseases such as malt fever [*Mirnejad R, et al.2017; Gemcioglu E, et al.2020*].

During the COVID-19 pandemic, it is important to consider other diagnoses, especially brucellosis, in patients presenting with persistent fever and joint pain. Notably, other endemic diseases should not be overlooked in COVID-19 patients, as SARS-CoV-2 may be a bystander infection, and many individuals may remain asymptomatic. Physicians should be aware that delays in the treatment of brucellosis may lead to considerable patient suffering and may even result in permanent joint deformities.

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