

Evaluation of Seropositive Brucellosis Cases in Nevşehir, Türkiye: An 11-Year Analysis

Nevşehir, Türkiye’de Görülen Seropozitif Bruselloz Olgularının Değerlendirilmesi: 11 Yıllık Bir Analiz

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ABSTRACT

Epidemiological and clinical analyses of brucellosis are vital for strengthening disease surveillance and case management strategies. This study aimed to evaluate the epidemiological characteristics of human brucellosis by seasonal distribution and year, and to determine brucellosis seropositivity in the region. A retrospective analysis was conducted of 4,510 suspected cases presented to Nevşehir State Hospital between 2013 and 2023. The Rose Bengal test (RBT) was used for screening, and RBT-positive sera were evaluated with a standard tube agglutination test. Titers $\geq 1/160$ were considered diagnostic. Of the 4510 patients, 405 (8.98%) were RBT positive, and 143 (35.3%) were confirmed with STA titers $\geq 1/160$, for an overall seropositivity rate of 3.18% (95% CI: 2.7-3.7). The majority were male (72.7%), and the mean age was 35.4 years. Most cases were linked to animal contact, with the incidence peaking in the summer months. A sharp increase was observed in 2022. Our findings demonstrate the prevalence of human brucellosis among patients with a pre-diagnosis of brucellosis in Nevşehir, influenced by occupational and seasonal factors. Strengthening animal vaccination, public awareness, and diagnostic capacity are essential to reduce the disease burden and improve surveillance. This study provides important regional data to guide control strategies.

Keywords: Brucellosis, Epidemiology, Laboratory diagnosis, Zoonosis

ÖZET

Brusellozun epidemiyolojik ve klinik analizleri, hastalık gözetimi ve vaka yönetimi stratejilerini güçlendirmeleri için hayati öneme sahiptir. Bu çalışmada, insan brusellozunun mevsimsel dağılıma ve yıllara göre epidemiyolojik özelliklerinin değerlendirilmesi ve bölgedeki bruselloz seropozitifliğinin belirlenmesi amaçlanmıştır. 2013-2023 yılları arasında Nevşehir Devlet Hastanesi'ne başvuran 4510 şüpheli vaka retrospektif olarak analiz edildi. Tarama için Rose Bengal testi (RBT) kullanıldı ve RBT pozitif serumlar standart tüp aglütinasyon testi ile değerlendirildi. $\geq 1/160$ titreleri tanısal kabul edildi. 4510 hastanın 405'i (%8.98) RBT pozitif ve 143'ü (%35.3) STA titreleri $\geq 1/160$ ile doğrulandı ve genel seropozitiflik oranı %3.18'di (%95 GA: 2.7-3.7). Çoğunluğu erkekti (%72.7) ve ortalama yaş 35.4 idi. Vakaların çoğu hayvan teması ile bağlantılıydı ve insidans yaz aylarında en yüksek seviyeye ulaşıyordu. 2022 yılında keskin bir artış gözlemlendi. Bulgularımız, mesleki ve mevsimsel faktörlerin etkisiyle Nevşehir'de bruselloz ön tanısı almış hastalar arasında insan brusellozunun yaygınlığını göstermektedir. Hastalık yükünü azaltmak ve sürveyansı iyileştirmek için hayvan aşılamasının, kamuoyu farkındalığının ve teşhis kapasitesinin güçlendirilmesi şarttır. Bu çalışma, kontrol stratejilerine rehberlik edecek önemli bölgesel veriler sunmaktadır.

Anahtar kelimeler: Bruselloz, Epidemiyoloji, Laboratuvar tanısı, Zoonoz

INTRODUCTION

Human brucellosis, a disease caused by *Brucella* species (spp.), is a global public health problem.¹ The causative agent of the disease is a small, aerobic, Gram-negative bacilli belonging to the *Brucella* genus, with an incubation period ranging from 1 week to 2 months.² It is a zoonotic infection transmitted to humans primarily through contaminated milk and secretions from infected small and large livestock.³ The primary routes of human infection are as follows: contact with contaminated animals and the consumption of unpasteurised dairy products.⁴ Brucellosis can be transmitted through laboratory infection, and rare cases of human-to-human transmission via blood transfusion and bone marrow transplantation have been reported.⁵

The *Brucella* genus comprises 12 species; six of which are classified as classical and the remaining six as atypical.⁶ The most pathogenic species causing disease in humans is *Brucella melitensis*, followed by *Brucella suis*. It is widely accepted that *Brucella abortus* is associated with a milder clinical course.⁷ The clinical symptoms of brucellosis in humans include fever, sweating and fatigue. In the animal kingdom, this condition has been observed to result in economic losses due to factors such as miscarriages and diminished milk production.^{4,8}

Human brucellosis is categorised as an acute systemic disease.⁹ In some patients, relapses may occur after treatment, or chronic osteoarticular (peripheral arthritis, sacroiliitis, and spondylitis), genitourinary (epididymo-orchitis), neurological (meningoencephalitis, meningovascular disease, brain abscesses, and demyelinating syndromes), or endocarditis may develop.^{5,10,11}

Recent studies have revealed a higher global incidence than was previously estimated, with 1.6–2.1 million new human cases each year.^{12,13} The Mediterranean region, the Middle East and African countries are high endemic areas for Brucellosis.¹⁴ Although human brucellosis has been generally eradicated in Europe, the disease remains endemic in Albania, Bosnia and Herzegovina, North Macedonia, Serbia, Kosovo, Greece, Portugal and Italy. However, a significant decrease in the number of cases has been observed since 2016.^{15,16} Within the Asian continent, brucellosis remains endemic in numerous nations, most notably Yemen, Syria, Iran, Palestine, and Saudi Arabia. Despite the dearth of data concerning the African

context, a substantial number of cases have been documented in Kenya, Eritrea, and Algeria. The incidence of cases in North America is relatively low; in South America, although not as high as in Asia, it is more frequently identified in Argentina, Brazil, Venezuela, and Ecuador than in other regions.¹⁷ Although its prevalence is low in Australia, the disease is known.¹⁷ The prevalence of this condition in our country is most pronounced in the Southeastern and Eastern Anatolia regions. It is noteworthy that the distribution of cases by province indicates that the disease is widespread throughout the country, with a higher prevalence recorded in the Eastern and Southeastern Anatolia regions.¹⁸

Brucellosis, known to be endemic in Türkiye, has only been studied to a limited extent in Nevşehir to date. The aim of this study is to determine the prevalence of brucellosis in our region and to illuminate the course of brucellosis infection by examining the distribution of cases by year, season, age and gender.

METHODS

Ethical approval

The study protocol was conducted in accordance with the Declaration of Helsinki, and the research was approved by the Kapadokya University Research Ethics Committee (approval date: October 16, 2024; approval code: G.O. 24/2024).

Data source

The data source for this study consisted of brucellosis cases followed at Nevşehir State Hospital between January 1, 2013, and December 31, 2023, and the data were evaluated retrospectively.

Specimen collection and initial testing

Specimens suspected of brucellosis were sent to our hospital's microbiology laboratory for analysis. All samples were evaluated using the Rose Bengal test (Seromed, Türkiye) and the standard tube agglutination test (Seromed, Türkiye).

Rose bengal test (RBT)

The Rose Bengal test (RBT) involves mixing the Rose Bengal test antigen (*B. abortus* S99 strain) with patient serum for four minutes. The test result was considered positive when a visible clump formed and negative when a homogeneous appearance was observed.

Standard tube agglutination test (STA)

The standard tube agglutination test (STA) was applied to the sera of patients found positive by RBT. Patient sera were prepared with the relevant antigen in serial

dilutions ranging from 1:20 to 1:1280 in glass tubes, and the tubes were incubated at 37°C for 24 hours. Button-shaped sediments were considered negative, while lace-shaped agglutinations were considered positive at dilutions of 1:160 and above. Because STA titers of 1:160 or above were considered positive, only demographic data from the year of diagnosis for these patients were evaluated in the study.

Coombs test

The Coombs test was applied to samples with titers strongly suggesting brucellosis in the preliminary diagnosis but with STA results below 1:160. Accordingly, tubes that did not show agglutination were subjected to a series of washes followed by three centrifugation cycles. They were then reincubated with Coombs antiserum (Dialab, Austria) for 24 hours. Button-shaped sediments were considered negative, and lace-shaped agglutinations were considered positive at dilutions of 1:160 and above.

Culture and additional tests

Culture (blood, bone marrow, tissue culture) is the gold standard for diagnosing brucellosis. However, due to the biosafety risks inherent in the growth of the microorganism, culture is not preferred for routine clinical diagnosis in hospitals. Furthermore, due to the additional reagent and processing requirements, as well as the difficulty and complexity of its use, no 2-mercaptoethanol test has been performed on any patient samples.

Statistical analysis

Descriptive statistical analyses were performed using frequency (n), percentage (%), mean ($\bar{x}$), median, standard deviation (SD), minimum, and maximum values. Because the study data consisted of categorical variables (sero-positivity status and antibody titer levels), parametric tests such as the independent samples t-test or non-parametric alternatives such as the Mann-Whitney U test could not be applied. Instead, the Chi-square test (Pearson Chi-square) with a significance level of $p < 0.05$ was used to compare the distribution of antibody titers between genders. The seropositivity rate was calculated using the Wilson method with a 95% confidence interval (CI). Post-hoc power analysis for the Chi-square test comparing titer distributions was performed with G*Power 3.1.

Handling of missing data

Some epidemiological variables (occupation, exposure history, place of residence) contained high proportions of “Not reported” values. Therefore, missing data were

handled through listwise deletion, and variables with missing values were excluded from the relevant analyses. The high level of missingness, particularly in exposure-related variables, was considered a potential source of information bias and was addressed in the Limitations section.

RESULTS

Serum samples from 4510 patients with suspected brucellosis were included in the study. RBT positivity was detected in 8.98% ($n=405$) of the 4510 patients with suspected brucellosis. The STA method was applied to the sera of RBT-positive patients. Agglutination was detected in 143 (35.31%) of the STA-positive sera at a titer of $\geq 1/160$, and in 262 (64.69%) at a titer of $< 1/160$. According to the data, all samples with a STA test positivity below 1/160 but clinically suspected brucellosis ($n=262$) had negative Coombs test results. The mean age of patients with STA titers above 1/160 was 35.4 ± 13.7 years, and 72.73% of the patients were male ($n=104$). When examined by place of residence, it was seen that approximately half of the cases, both female (53.85%) and male (49.04%), resided in the city center, while the remainder resided in districts. When occupational distribution was examined, it was determined that female (46.15%) and male (47.12%) were engaged in farming or animal husbandry. When exposure history was evaluated, animal contact was reported in 46.15% of females and 47.12% of males, while the exposure history was unknown in the other cases (Table 1).

Table 1. Demographic characteristics of positive patients ($n=143$)

			Seropositive patients	
Age average ($\bar{x} \pm SD$)			35.4 $\pm$ 13.7	
			n (%)	
Sex			Female	Male
			39 (27.27)	104 (72.73)
Place of residence	of	Provincial center	21 (53.85)	51 (49.04)
		Districts	18 (46.15)	53 (50.96)
Occupation		Farmer/Livestock	18 (46.15)	49 (47.12)
		Not reported	21 (53.85)	55 (52.88)
Exposure history		Animal contact	18 (46.15)	49 (47.12)
		Not reported	21 (53.85)	55 (52.88)
STA Titer		1/160	26 (66.66)	81 (77.88)
		1/320	11 (28.21)	22 (21.16)
		1/640	2 (5.13)	1 (0.96)
		1/1280	0	0

When the cases were evaluated seasonally, it was seen that the highest number of positive diagnoses was in the summer, with 32.16% ($n=46$) (Figure 1).

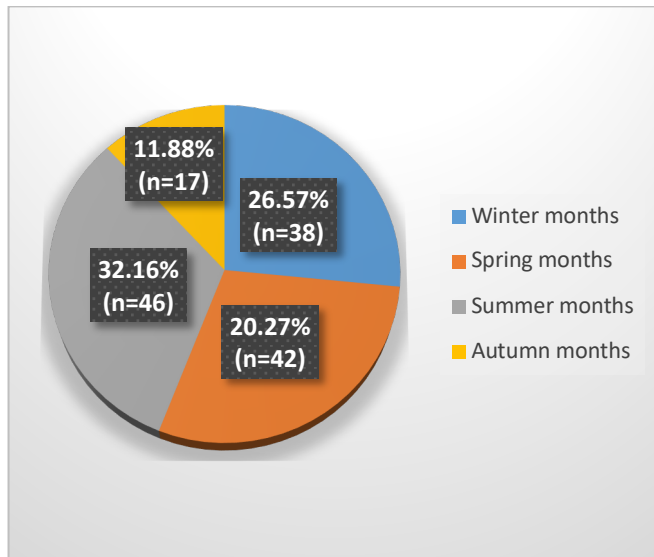


Figure 1. Evaluation of brucellosis cases according to seasons (n=143)

A more detailed analysis of RBT and STA seropositivity by year revealed that the highest number of patients was detected in 2022, with a rate of 21.6% (n=31) (Figure 2). The standard tube agglutination test results of the patients included in the study ranged from 1/160 to 1/640.

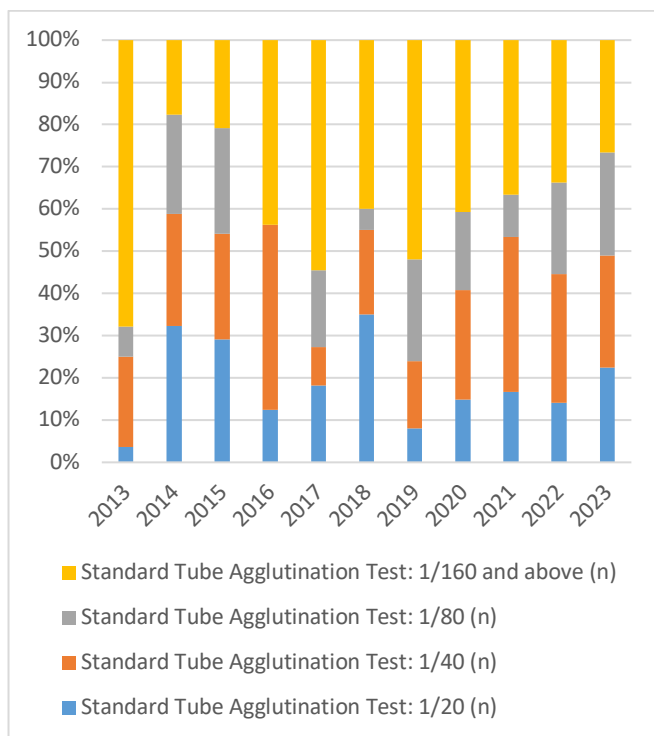


Figure 2. Standard tube agglutination test positivity rates (%) of the patient serums according to years (n=405)

The standard tube agglutination test positivity rates of patient sera by year are shown in Figure 2. According to our findings, the rates of seropositive patients at 1/160, 1/320, and 1/640 titers are shown in Table 1. The

difference in titer distributions between genders was assessed using the Chi-square test; no statistically significant difference was found ($\chi^2=3.43$; $SD=2$; $p=0.179$). In addition, the post-hoc power analysis of the Chi-square test comparing titer levels between genders was found to be 0.68. According to the study findings, the seropositivity rate for brucellosis in Nevşehir over an 11-year period was 3.18% (95% CI: 2.7%-3.7%).

DISCUSSION

The World Health Organization considers brucellosis to be one of the seven most neglected diseases. The disease continues to be a problem in developing countries due to its spread through increased animal movements and human migration.¹⁸⁻²⁰ In this study, the seropositivity of brucellosis in Nevşehir province was determined to be 3.18% over an 11-year follow-up period.

Brucellosis is a zoonotic infection that can be endemic in Türkiye. Our country's geopolitical location creates a favorable environment for the spread of infectious diseases, particularly from our eastern and southeastern neighbors. Brucellosis is also endemic in Türkiye's neighboring countries.^{21,22} According to data from the Ministry of Health, an increase in the number of brucellosis cases has been observed since 2015, with an incidence rate of over 10 per 100,000 in 2019.²² The 2024 report on the current status of brucellosis in Türkiye stated that cases were observed in all provinces, with a higher concentration in the Eastern and Southeastern Anatolia regions. The same report highlighted the increase in cases in the Central Anatolia Region in recent years.²² For this reason, we aimed to evaluate brucellosis cases in Nevşehir, a province in the Central Anatolia Region.

In our study, as a result of an 11-year evaluation, 405 (8.98%) of 4510 cases with a preliminary diagnosis of brucellosis tested positive in the Rose Bengal test, and 143 (35.3%) cases were definitively diagnosed with brucellosis based on clinical findings, positive Rose Bengal test, and positive standard tube agglutination test. In a study conducted in Istanbul in 2019, 107 (1.8%) of 6045 cases suspected of brucellosis were reported as seropositive. Of the 107 seropositive cases of brucellosis, 73 (68.2%) were found to be positive in both the Rose Bengal and serum agglutination tests.²³ In this study, all patients with clinically suspected brucellosis but with STA titers below 1/160 had negative Coombs test results. It is theoretically possible that there would be no difference between STA and Coombs, but Coombs is generally more sensitive when

there is clinical suspicion or a chronic condition. The lack of a difference in the study suggests that the samples included were truly low-titer and lacked blocking antibodies.

Culture is widely regarded as the gold standard for laboratory diagnosis of brucellosis; however, it is not always a viable option. Consequently, RBT and STA tests, which are low-cost, simple, and rapid serological methods, are the most widely preferred methods worldwide for diagnosis. However, both tests have the potential to yield false-negative results.²⁴ While RBT is particularly successful in diagnosing acute brucellosis, it may yield a high rate of false-negative results in chronic and complicated cases. In the STA test, the presence of false-negative or low-titer positive results may be attributable to the Prozone phenomenon and the existence of blocking antibodies in the early and late stages of brucellosis.²⁵

Consequently, it is advised that STA results be validated through the implementation of tests such as Brucellacapt or ELISA, which possess high sensitivity and specificity, particularly within endemic regions.^{24,25} It is evident that the Bruselloz test demonstrates a high degree of sensitivity and specificity when conducted using a polymerase chain reaction (PCR) approach. Notwithstanding their expense, the necessity for experienced personnel and advanced technical equipment means that they are not recommended for use as a preliminary diagnostic test at this stage. Notwithstanding the negative STA test result, the continuation of the clinical investigation is recommended in cases where the culture result is awaited, as this may result in a delay in diagnosis and treatment, potentially leading to adverse outcomes. In such instances, the utilisation of PCR-based tests for the diagnosis of brucellosis is advised.¹⁶ However, it should be noted that these tests were not available at the centres where this study was conducted.

In the present study, it was established that the STA test titer was 1/160 or higher in approximately 35.31% of RBT-positive patients, and these patients were designated as seropositive. Among the seropositive female patients, 26 (66.66%) had a titer of 1/160, 11 (28.21%) had a titer of 1/320, and 2 (5.13%) had a titer of 1/640. Among male patients, 81 (77.88%) patients were positive at a titer of 1/160, 22 (21.16%) patients were positive at a titer of 1/320, and 1 (0.96%) patient was positive at a titer of 1/640. In a study conducted in Ağrı, Türkiye, the titer distribution was examined

according to the standard tube agglutination test and it was reported that the titer was positive at 9.3% at 1/20, 15.6% at 1/40, 18.4% at 1/80, 17.2% at 1/160, 16.4% at 1/320, 12.6% at 1/640, and 10.1% at 1/1280.²⁶ In our study, most seropositive patients were clustered at the 1/160 titer level, with only a small proportion reaching 1/320 or 1/640. In contrast, higher titers were more frequently reported in a study from Ağrı, an area with higher endemicity. The relatively lower titer distribution in Nevşehir suggests either earlier detection or lower exposure intensity, highlighting the importance of strengthening surveillance systems and ensuring region-specific diagnostic strategies in endemic areas.

In developed countries, the majority of brucellosis cases occur in men, and this is largely attributed to increased occupational risk factors.²⁷ A 2022 study by the European Centre for Disease Prevention and Control (ECDC) revealed that the incidence of brucellosis is significantly higher among men over the age of 45.²⁸ Similarly, a recent study reported in our country found the proportion of seropositive male patients to be 69.84%.²⁹ Our analysis showed that 72.73% (n=104) of the seropositive population were male patients, and 46.85% (n=67) of the cases had a history of contact with animals. As evidenced by the findings of this study, the predominance of males in the workforce can be attributed to the region's economic dependence on agriculture and farming. Transmission of brucellosis usually begins through direct or indirect contact with animals such as cattle, sheep, and goats.³⁰ Direct or indirect household contact, including activities such as assisting animals in giving birth, shearing wool, and contact with aborted fetuses and secretions, has been identified as a significant risk of infection.³¹ The data presented here suggest that farmers are at high risk of infection, which is not unexpected given the nature of their work, which is conducive to disease transmission. The European Centre for Disease Prevention and Control (ECDC) noted in its 2022 report that the highest incidence of brucellosis occurs in July and September.²⁸ Although the disease can be observed throughout the year in our country, its prevalence increases in the spring and summer months, which coincide with the breeding season of sheep and cheese production.^{23,32,33} Our findings were consistent with the literature and were found to be detected in 61.5% (n=88) of the cases in the spring and summer months (Figure 2). This may be due to the intensive production of dairy products

during the spring and summer months, as well as the excessive population of domestic animals in the spring. In our study, we also evaluated the distribution of cases in Nevşehir according to the provincial center and districts and found that the highest incidence rate was in the provincial center (Table 1). This is because people in the provincial center can seek medical attention more quickly when they notice symptoms, making detection easier; in rural areas, the disease is often confused with infections such as influenza and may not be diagnosed; there may be unreported cases in rural areas; unpasteurized products such as raw milk and cheese from rural areas may be consumed in the more densely populated provincial center, leading to higher exposure rates and, consequently, higher case rates in the provincial center.

In a study conducted in our country analyzing 1,028 patients aged 3-81, the average age of cases was reported as 33.7 years.³⁴ In another study, 268 cases of brucellosis were investigated, and the average age was determined to be 38.7 years.³⁵ In our study, the average age was found to be 35.4 years, which is consistent with the findings in the aforementioned literature. The finding that the disease mostly affects young and middle-aged people may be related to its representativeness of people in the workforce.

Türkiye is a country where brucellosis has not yet been eradicated. Brucellosis infection causes significant economic losses and negatively impacts sustainable livestock farming, threatening both animal and community characteristics.^{21,22} Early diagnosis and treatment of brucellosis are crucial for reducing the overall morbidity of brucellosis. In our study, we evaluated the positivity rates in standard tube agglutination tests of patient sera over the years (Figure 2). While *Brucella* seropositivity in Nevşehir has fluctuated over the years, a significant increase has been observed, particularly in recent years (2022-2023). The most important reasons for this increase are the intensity of animal husbandry, consumption of raw milk/dairy products, inadequate control measures, and increased patient access to diagnostic laboratories based on recommendations from family physicians. Restrictions on access to healthcare services, particularly due to the COVID-19 pandemic, may have led to delays in transportation and reporting. Accordingly, mandatory reporting in the United States has been declining during the pandemic.³⁶ Similarly, in the southeastern United States, there are delays in diagnosis and treatment for

tick-borne illnesses after COVID-19, exceeding the delay by a factor of 1.8.³⁷ These models suggest that the pandemic not only suppressed diagnosis but also promoted clinical responses, leading to historically underestimated brucellosis incidence. Despite this significant increase in seropositivity, animal-borne transmission appears to have continued. A sharp increase in all titers (especially at 1/160 and above) was observed in 2022 and 2023. Consequently, the increase in seropositivity in these years reflects the increased implementation of control measures for both human and animal health.

According to the 2019 report of the Nevşehir Provincial Directorate of Agriculture and Forestry, animal husbandry in our province is ripe for development. Similarly, meat and milk production accounts for approximately 3-4% of Türkiye's total production.³⁸ However, Nevşehir has experienced migration in recent years due to socioeconomic and sociocultural factors. Agricultural and livestock activities, in particular, have increased the demand for information. The increasing expansion from rural areas to cities has led to increased travel, occupational exposure, and seasonal improvements in personal seropositivity. Considering this impact, brucellosis remains a significant public health problem in this region.

This study has several limitations. First, culture, the gold standard for diagnosis, was not performed due to biosafety risks. Second, the study was conducted at a single center, which may limit the generalizability of the results. Third, advanced diagnostic methods such as ELISA or PCR were not available during the study period. Additionally, some epidemiological variables had high proportions of missing data ('Not reported'), which may have introduced information bias, particularly in the interpretation of occupational and exposure-related risk factors. The post hoc power analysis indicated moderate statistical power for comparisons involving titer distribution, which may have limited the detection of small effect sizes.

Finally, the serological approach used does not fully distinguish between acute infection and long-term seropositivity. In distinguishing between active infection and long-term seropositivity, we relied on a combination of clinical findings, epidemiological history, and Rose Bengal and STA titers as part of the diagnostic evaluation, in accordance with national diagnostic algorithms. Differentiating between active

and past infection based solely on serology is difficult, and clinical correlation is important.

CONCLUSION

This study provides valuable epidemiological information on human brucellosis in Central Anatolia over an 11-year period. Despite some limitations, the findings highlight the continuing endemicity of the disease and the need for sustainable public health interventions. Future studies should aim to overcome these limitations by incorporating culture-based confirmation, expanding to multicenter cohorts, and adopting advanced diagnostic tools such as ELISA and PCR. Furthermore, closer integration of serological data with clinical and epidemiological findings is important to distinguish active infection from long-term seropositivity. Addressing these issues will increase diagnostic accuracy, improve surveillance, and support more effective control strategies against brucellosis in endemic areas. Finally, this study provides the first long-term analysis of brucellosis in Nevşehir, filling a significant gap in regional epidemiological data and providing actionable information for local public health strategies. The findings highlight that brucellosis remains an endemic and underrecognized public health problem influenced by demographic, occupational, and seasonal factors. Urgent and coordinated action is needed to reduce the burden of brucellosis. Public health strategies should focus on raising public awareness of the risks of consuming unpasteurized dairy products, improving surveillance and reporting systems, supporting routine animal vaccination programs, and expanding access to advanced diagnostic methods in clinical laboratories. Addressing these gaps will reduce the human and economic impact of brucellosis and bring it one step closer to control in endemic regions like Central Anatolia.

Authorship contribution statement

Concept and design: NA.

Acquisition of data: EK.

Analysis and interpretation of data: NA, EK.

Drafting of the manuscript: NA.

Critical revision of the manuscript for important intellectual content: NA, EK.

Statistical analysis: NA.

Declaration of competing interest

None of the authors have potential conflicts of interest to be disclosed.

Ethical approval

The study protocol was approved by the Kapadokya University Research Ethics Committee (16.10.2024; 24.18 G.O.).

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Funding

No financial support was received for this research.

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To Cite: Akman N, Karat E. Evaluation of Seropositive Brucellosis Cases in Nevşehir, Türkiye: An 11-Year Analysis. *Farabi Med J.* 2025;4(4):124-131.