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# A Systematic Review and Analysis of *Brucella* Endocarditis Cases


## ABSTRACT

Endocarditis is the most common cause of death from brucellosis. The information used to guide the management of cases with *Brucella* endocarditis has relied on case reports/series. Risk factors related to death and other adverse outcomes in patients with Brucella endocarditis were identified by an individual-patient data analysis of all reported Brucella endocarditis cases in the literature. The keywords "Bruce" and "endocard" were used to search articles published until July 2022 on PubMed and ULAKBIM databases. Case reports/series containing patients with endocarditis caused by *Brucella* spp., aged ≥17 years, and with data on antimicrobial or surgical treatment were included in the study. Epidemiological, clinical, laboratory, and treatment characteristics and outcomes of 273 cases from 86 eligible articles were recorded. It was found that male gender, a Wright serum tube agglutination (STA) titer of ≥1/1280 on admission, development of heart failure due to endocarditis were independent risk factors that increase mortality, while the usage of aminoglycoside and cardiac surgical intervention for endocarditis were factors reducing mortality. Including streptomycin or gentamicin in the treatment regimen may benefit patients with Brucella endocarditis. Valve surgery could be life-saving in patients with Brucella endocarditis. An STA titer of ≥1/1280, which probably reflects long-term and advanced disease, may be used as a marker for increased mortality. However, additional and more reliable studies are needed to define the most appropriate management approach in diagnosing and treating cases with Brucella endocarditis due to the low quality of the current evidence.


**Keywords:** Brucella, endocarditis, mortality

REVIEW


**Seniha Başaran**[1]
**Serap Şimşek-Yavuz**[1]
**Mukime Elif Sarıcaoğlu**[2]
**Mehtap Aydın**[3]
**Gökhan Aygün**[4]
**Alpay Azap**[2]
**Özlem Azap**[5]
**Aysun Benli**[1]
**Neşe Demirtürk**[6]
**Önder Ergönül**[7]
**Aysel Kocagül-Çelikbaş**[8]
**Ferit Kuşçu**[9]
**Selçuk Özger**[10]
**Selda Sayın Kutlu**[11]
**Nesrin Türker**[12]
**Emine Türkoğlu-Yılmaz**[13]

[1]*Department of Infectious Diseases and Clinical Microbiology, İstanbul University, İstanbul Faculty of Medicine, İstanbul, Türkiye*
[2]*Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Ankara University, Ankara, Türkiye*
[3]*Department of Infectious Diseases and Clinical Microbiology, Ümraniye Training and Research Hospital, İstanbul, Türkiye*
[4]*Department of Infectious Diseases and Clinical Microbiology, Cerrahpaşa Faculty of Medicine, İstanbul University Cerrahpaşa, İstanbul, Türkiye*
[5]*Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Başkent University, Ankara, Türkiye*
[6]*Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Afyon Kocatepe University, Afyon, Türkiye*
[7]*Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Koç University, İstanbul, Türkiye*
[8]*Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Hitit University, Çorum, Türkiye*
[9]*Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Çukurova University, Adana, Türkiye*
[10]*Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Gazi University, Ankara, Türkiye*
[11]*Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Pamukkale University, Denizli, Türkiye*


## INTRODUCTION

Brucellosis is caused by the Gram-negative coccobacillus *Brucella* spp., which are facultative intracellular microorganisms. Although human brucellosis has been eradicated in most high-income countries, localized human brucellosis cases are still seen in some European countries, including Albania, Bosnia-Herzegovina, North Macedonia, Serbia, Kosovo, Greece, Portugal, and Italy, and brucellosis is an endemic disease in many other countries in Asia, Africa, and Americas, including China, Russia, Türkiye, Saudi Arabia, Iran, Mexico, Palestine, Yemen, and Syria.[1]

Brucellosis can cause acute or chronic diseases affecting all organ systems in the body, including the osteoarticular, genitourinary, respiratory, and neurologic systems. Although only 1.3% of the patients with brucellosis present with infective endocarditis (IE), it is the deadliest form of the disease.[2] There are only case reports and case series published in the literature about the diagnosis and treatment of Brucella endocarditis, and published meta-analyses on the subject mostly focused on the effect of surgery on the mortality of cases with Brucella endocarditis.[3-5] Therefore, in this systematic analysis, the aim was to analyze all of the reported Brucella endocarditis cases in the literature and define the prognostic and measurable risk factors affecting mortality and other adverse outcomes of patients with IE due to *Brucella* spp.

## METHODS

### Search Strategy and Selection Criteria

"Bruce" and "endocard," "Brus" and "endokard" keywords were used to search articles published until July 2022 on PubMed and ULAKBIM (Türkiye) databases. All

[12]*Department of Infectious Diseases and Clinical Microbiology, İzmir Atatürk Training and Research Hospital, İzmir, Türkiye*
[13]*Department of Infectious Diseases and Clinical Microbiology, Faculty of Medicine, Gaziosmanpaşa University, Tokat, Türkiye*

**Corresponding author:**
Seniha Başaran
✉ senihabasaran@yahoo.com

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published case reports and case series, including adult (>17 years) patients with a diagnosis of definite *Brucella* spp. IE according to modified Duke criteria,[6] written in English or Turkish with available full-text and detailed data of clinical findings, antimicrobial and surgical treatments, and outcomes were included in the analysis.

The following criteria were used for the diagnosis of *Brucella* spp. endocarditis:

- Growth of *Brucella* spp. in surgically removed heart valves or other cardiac tissues, or
- In a patient with a definite diagnosis of endocarditis according to modified Duke criteria, the presence of either growth of *Brucella* spp. in the blood cultures, positivity of Wright serum tube agglutination test (STA) at ≥1/160 dilution without definition of any other causative agent, or positivity of Brucella DNA by PCR (Polymerase Chain Reaction) in tissue or blood samples of the patient.

### Data Extraction

To make an analysis, age, gender, duration of symptoms, comorbidities including chronic renal failure, diabetes mellitus, hypertension, coronary artery disease, predisposing conditions for endocarditis (cardiac structural or functional valve diseases, presence of prosthetic valve, implantable cardiac devices (ICD), pacemaker (PACE), a previous history of brucellosis), previous anti-brucellosis treatments, involved heart valve, vegetation size [vegetation 1 (<10 mm), 2 (10-20 mm), 3 (>20 mm)], complications of endocarditis [abscess, fistula, aneurysm, valve dehiscence, central nervous system (CNS) embolism, peripheral embolism, congestive heart failure (CHF)], results of blood and valve cultures, Wright agglutination titer on admission, after 3 months and at the end of treatment, whether cardiac surgery was performed, complications after cardiac surgical intervention, antimicrobials used for the treatment of brucellosis [doxycycline/tetracycline (DOX), rifampicin (RIF), streptomycin, gentamicin, cotrimoxazole (SXT), ciprofloxacin (CIP), ceftriaxone (CRO)], duration and other details of treatment, mortality, and other adverse outcomes (relapse, readmission, adverse effects of used antimicrobials, and all other adverse outcomes) were recorded for all of the included patients.

### Statistical Analysis

We first evaluated risk factors affecting death and non-fatal adverse outcomes (relapse, readmission, adverse drug effects) with univariate analyses and then with multivariate logistic regression analyses.

### Quality Assessment

GRADE (Grading of Recommendations Assessment, Development and Evaluation) regards the quality of evidence from case reports and case series as low to very low.[7] The analysis was conducted to improve the quality of the evidence. To reduce the risk of bias, all reported definite Brucella endocarditis cases with sufficient data were selected, mortality was defined as an outcome, and a multivariate analysis was conducted.

Ethical approval was not obtained because this research included cases from the literature.

Artificial intelligence was not utilized in this research.

## RESULTS

After the literature search in PubMed and ULAKBIM, 408 articles were found, all the abstracts were read, and 86 [Supplementary Document] were considered eligible for

## HIGHLIGHTS

- Brucella endocarditis is affecting mainly younger male patients with predisposing conditions for endocarditis.
- The presence of a Wright serum tube agglutination titer higher than ≥1/1280 on admission, which could be an indicator of advanced endocarditis, was found to be a risk factor for mortality among cases of Brucella endocarditis.
- Including streptomycin or gentamicin in the treatment regimen may benefit patients with Brucella endocarditis.

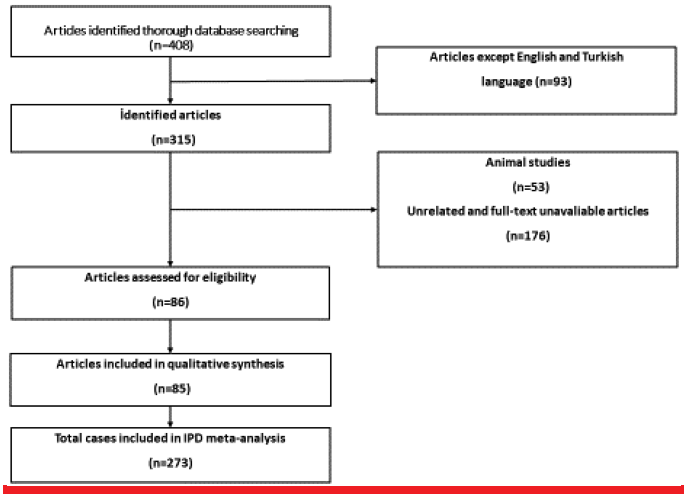


**Figure 1. PRISMA (The Preferred Reporting Items for Systematic reviews and Meta-Analyses) flowchart for review.**

analysis (Figure 1). Epidemiological features and comorbidities, clinical and laboratory findings, and treatment characteristics of 273 cases with *Brucella* IE were given in Tables 1-3, respectively.

Of the 273 patients, 209 (76.6%) were male, and the mean age was 43 ± 14 (range 18-82). Additionally, 167/182 (91.8%) had previously known heart disease predisposing them to IE (prosthetic heart valve in 63/273 patients, acute rheumatic fever sequelae in 60/182, ICD/PACE wire in 5/182). The aortic valve was the most commonly involved (69.2%), followed by the mitral valve (34.1%). *Brucella* spp. growth was reported in blood cultures and surgically removed heart valves in 65.2% and 34.8% (45/129) of the cases, respectively. The Wright STA test was found to be positive at a titer of 1/160 and above in 96.2% (254/264) of the patients whose Wright titer was measured on admission. The mean and median on admission Wright STA titers were 1/1255 ± 1/2178 (range 80-20.480) and 1/640, respectively, among 228 cases with a defined on-admission Wright STA titer. The 25th, 50th, 75th percentiles of on-admission Wright STA titers were 1/320, 1/640, and 1/1280, respectively. Vegetation was determined in 232/255 (90.9%) cases (vegetation size <10 mm 29.2%, 11-20 mm 55.8%, >20 mm 15%), abscess in 35/257 (13.6%), and fistula/aneurysm in 18/260 (6.9%). Complications of endocarditis developed in 46% (122/265) of the patients, including CHF, CNS embolism, and peripheral artery embolism. Doxycycline was used in 96.3% of the patients, RIF in 87.5%, streptomycin in 30.1%, gentamicin in 16.6%, SXT in 33.1%, CIP in 14.4%, and CRO in 24.7% of the patients. While a double antimicrobial combination was given in 19.3% of the cases, 81.5% of the cases were treated with a triple antimicrobial combination. Treatment duration was longer than 3 months in 51.6% of the cases. Valve surgery was performed in 68% of the patients.

Follow-up Wright STA titers during treatment were available for 26 patients; median and mean pretreatment titers were 1/640 and 1/1252 ± 1/2178, respectively; end-of-treatment titer decreased to a median of 1/160 and a mean of 1/574 ± 1/1351. A median of 0.125-fold reduction in antibody titer was observed at the end of treatment in 92% of those 26 patients, and ≤0.125-fold reduction was observed in 18/26 (69%) of the cases. Wright STA titer (2 and 4-fold) increases were observed in only 2 cases; in one of them, a 0.25-fold decrease was observed at the end of treatment, and a 2-fold increase was observed in the other one (Table 4).

Wright STA titers on admission and at the 3rd month of treatment were available for 18 patients; the median antibody titer was 1/640 at the 3rd month of treatment, 16/18 (89%) of the patients had a median 0.25-fold antibody titer decrease at the 3rd month of treatment, while 9/18 of them (50%) showed a reduction of ≤0.25 fold. Only 2 patients had an increasing (2 fold and 8 fold) Wright STA titer at the 3rd month of treatment; 1 of them had a 0.25-fold decrease at the end of treatment (Figure 2).

Adverse outcomes were seen in a total of 68/271 (25%) patients (death in 32/271 (11.8%) and non-fatal adverse

**Table 1. Characteristics of 273 Patients with Infective the Endocarditis Caused By *Brucella* spp.**

| Features | All Cohort (n = 273) | Patients Without Mortality (n = 239) | Patients With Mortality (n = 32) | *P* |
|---|---|---|---|---|
| **Age, mean ± SD (n = 272)** | **43.86 ± 14.26** | **44.63 ± 14.46** | **38.00 ± 11.50** | **.015** |
| **Gender, male, n (%) (n = 273)** | **209 (76.6)** | **177 (74.1)** | **30 (93.8) (17.4)** | **.013** |
| Previous history of brucellosis, n (%) (n = 246) | 43 (17.5) | 37 | 6 (18.8) | .848 |
| Duration of complaints, week, mean ± SD, (n = 175) | 3.84 ± 4.08 | 3.76 ± 4.11 | 4.66 ± 3.73 | .168 |
| Comorbidity, n (%) (n = 265) | 160 (60.4) | 137 (58.8) | 21 (70) | .238 |
| Diabetes mellitus, n (%) (n = 252) | 4 (1.6) | 4 (1.8) | 0 (0) | 1.000 |
| Hypertension, n (%) (n = 252) | 10 (3.9) | 8 (3.6) | 2 (6.7) | .342 |
| Coronary artery disease, n (%) (n = 242) | 1 (0.4)1 | 0 (0) | 1 (3.3) | .125 |
| **Chronic renal failure, n (%), (n = 252)** | **7 (2.8)** | **2 (0.9)** | **5 (16.7)** | **<.001** |
| Predisposing conditions for infective endocarditis, n (%) (n = 182) | 167 (91.8) | 148 (92.5) | 17 (85) | .223 |
| Presence of chronic rheumatic heart valve disease, n (%) (n = 182) | 60 (33) | 52 (32.5) | 7 (35) | .822 |
| Precense of ICD/PACE, n (%) (n = 273) | 5 (1.8) | 5 (2.1) | 0 (0) | 1.000 |
| Presence of prosthetic valve, n (%) (n = 273) | 63 (23.1) | 56 (23.4) | 7 (21.9) | .845 |

ICD/PACE, implantable cardioverter-defibrillator/pacemaker; STA, standard agglutination; TMP-SXT, trimethoprim/sulfamethoxazole.

**Table 2. Clinical and Laboratory Characteristics of Patients with Brucella Endocarditis**

| Findings | All Cohort (n = 273) | Patients Without Mortality (n = 239) | Patients With Mortality (n = 32) | *P* |
|---|---|---|---|---|
| Mitral valve involvement, n (%) (n = 273) | 93 (34.1) | 84 (35.1) | 9 (28.1) | .432 |
| Aortic valve involvement, n (%) (n = 273) | 189 (69.2) | 163 (68.2) | 24 (75) | .435 |
| Tricuspid valve involvement, n (%) (n = 273) | 12 (4.4) | 11 (4.6) | 1 (3.1) | 1.000 |
| Presence of paravalvular abscess, n (%) (n = 257) | 35 (13.6) | 31 (13.6) | 3 (11.1) | 1.000 |
| Aneurysm, fistula, valvulary dehiscence, n (%) (n = 260) | 18 (6.9) | 14 (6.1) | 3 (11.1) | .400 |
| Presence of CNS emboli, n (%) (n = 264) | 18 (6.9) | 16 (6.9) | 2 (6.9) | 1.000 |
| Presence of periphery emboli, n (%) (n = 264) | 11 (4.2) | 9 (3.9) | 2 (6.9) | .349 |
| **Presence of congestive heart failure due to endocarditis, n (%) (n = 264)** | **72 (27.3)** | **57 (24.5)** | **15 (51.7)** | **.002** |
| Wright STA titer on admission, mean ± SD, (n = 228) | 1255 ± 12178 | 1213 ± 2213 | 1566 ± 2033 | .108 |
| Wright STA positivity on admission, n (%) (n = 263) | 253 (96.2) | 224 (96.6) | 29 (93.5) | .334 |
| Wright STA titer ≥1/640 on admission, n (%) (n = 227) | 152 (67) | 132 (66) | 20 (74.1) | .402 |
| Wright STA titer ≥1/1280 on admission, n (%) (n = 227) | 90 (39.6) | 75 (37.5) | 15 (55.6) | .072 |
| Wright STA titer at the 3rd month of treatment, mean ± SD, (n = 18) | 1093 ± 1270 | 1093 ± 1270 | – | |
| Wright STA titer at the end of treatment, mean ± SD, (n = 27) | 574 ± 1351 | 574 ± 1351 | – | |
| Vegetation detected, n (%), (n = 253) | 231 (91.3) | 208 (91.6) | 23 (88.5) | .481 |
| Vegetation length, mm, mean ± SD, (n = 60) | 12.46 ± 6.59 | 11.98 ± 6.60 | 16.14 ± 5.63 | .092 |
| Vegetation length, n (%), (n = 113) <10 mm | 33 (29.2) | 30 (30.3) | 3 (21.4) | .681 |
| 10-20 mm | 63 (55.8) | 55 (55.6) | 8 (57.1) | |
| >20 mm | 17 (15) | 14 (14.1) | 3 (21.4) | |
| *Brucella* spp. growth in blood and/or valve culture, n (%), (n = 272) | 183 (67.3) | 164 (68.6) | 17 (54.8) | .125 |
| *Brucella* spp. growth in blood, n (%) (n = 272) | 178 (65.4) | 159 (66.5) | 17 (54.8) | .199 |
| *Brucella* spp. growth in valve culture, n (%) (n = 129) | 45 (34.9) | 44 (36.1) | 1 (16.7) | .665 |

CNS, central nervous system; STA, serum tube agglutination.

**Table 3. Treatment Characteristics and Outcomes of Patient with Brucella Endocarditis**

| Features | All Cohort (n = 273) | Patients Without Mortality (n = 239) | Patients With Mortality (n = 32) | *P* |
|---|---|---|---|---|
| **Valve surgery for endocarditis, n (%) (n = 272)** | **185 (68)** | **174 (73.1)** | **10 (31.3)** | **<.001** |
| Treatment including doxycycline/tetracycline, n (%), (n = 272) | 262 (96.3) | 229 (96.2) | 31 (96.9) | 1.000 |
| Treatment including rifampin, n (%), (n = 272) | 238 (87.5) | 208 (87.5) | 28 (87.4) | 1.000 |
| Treatment including an aminoglicoside, n (%), (n = 272) | 123 (45.2) | 113 (47.5) | 10 (31.3) | .084 |
| Treatment including streptomycin, n (%), (n = 272) | 82 (30.1) | 74 (31.1) | 8 (25) | .482 |
| Treatment including gentamicin, n (%), (n = 271) | 45 (16.6) | 43 (18.1) | 2 (6.3) | .128 |
| Treatment including TMP-SXT, n (%), (n = 272) | 90 (33.1) | 83 (34.9) | 6 (18.8) | .068 |
| Treatment including ciprofloxacin, n (%), (n = 271) | 39 (14.4) | 32 (13.5) | 7 (21.9) | .207 |
| Treatment including ceftriaxone, n (%), (n = 271) | 67 (24.7) | 57 (24.1) | 9 (28.1) | .615 |
| Dual antimicrobial therapy, n (%), (n = 270) | 52 (19.3) | 45 (19) | 7 (22.6) | .634 |
| Triple antimicrobial therapy, n (%), (n = 270) | 220 (81.5) | 193 (81.4) | 25 (80.6) | .916 |
| **Duration of treatment >3 months, n (%), (n = 258)** | **133 (51.6)** | **128 (55.9)** | **5 (17.9)** | **<.001** |
| Relapse, n (%), (n = 250) | 3 (1.2) | 2 (0.8) | 1 (9.1) | .127 |
| Readmission to the hospital, n (%), (n = 249) | 5 (2) | 4(1.7) | 1(9.1) | .254 |
| Drug adverse effects, n (%), (n = 255) | 10 (3.9) | 9 (3.8) | 1 (6.3) | .485 |
| Other adverse outcomes, n (%), (n = 250) | 17 (6.8) | 16 (6.7) | 1 (8.3) | .579 |
| Composite non-mortality adverse outcomes, n (%), (n = 258) | 36 (14) | | | |
| Mortality, n (%), (n = 271) | 32 (11.8) | | | |

TMP–SXT, trimethoprim/sulfamethoxazole.

outcomes in 36/258 (11.4%) patients (3 relapses, 5 rehospitalizations, 10 adverse drug effects, and 18 patients had other adverse outcomes).

Male gender (OR 6.002, 95% CI 1.021-35.276, *P* = .047), a Wright STA titer of ≥1/1280 on admission (OR 7.009, 95% CI 1.965-24.997, *P* = .003), and the development of congestive

**Table 4. Wright STA Titer Changes Under Treatment Among 27 Cases with Brucella Endocarditis**

| Case No. | STA Titer on Admission | STA Titer at the 3rd Month of Treatment | STA Titer at the End of Treatment | Coefficient of Decrease at the 3rd Month of Therapy | Coefficient of Decrease at the End of Therapy |
|---|---|---|---|---|---|
| 1 | 20 480 | 640 | | 0.031 | |
| 2 | 20 450 | 5120 | 5120 | 0.25 | 0.25 |
| 3 | 5120 | 2560 | 640 | 0.5 | 0.125 |
| 4 | 4000 | 800 | 800 | 0.20 | 0.20 |
| 5 | 2560 | 640 | 320 | 0.25 | 0.125 |
| 6 | 2560 | 640 | 320 | 0.25 | 0.125 |
| 7 | 2560 | | 80 | | 0.031 |
| 8 | 2560 | | 80 | | 0.031 |
| 9 | 2560 | | 160 | | 0.063 |
| 10 | 2400 | 2000 | 40 | 0.83 | 0.020 |
| 11 | 2400 | 540 | 160 | 0.225 | 0.067 |
| 12 | 2000 | 400 | 160 | 0.20 | 0.08 |
| 13 | 1400 | 1120 | 80 | 0.80 | 0.057 |
| 14 | 1280 | | 80 | | 0.0625 |
| 15 | 1280 | 2560 | 5120 | 2 | 4 |
| 16 | 1000 | 320 | 80 | 0.32 | 0.08 |
| 17 | 640 | 320 | 80 | 0.50 | 0.125 |
| 18 | 640 | | 160 | | 0.25 |
| 19 | 640 | | 80 | | 0.125 |
| 20 | 640 | | 320 | | 0.5 |
| 21 | 640 | | 80 | | 0.125 |
| 22 | 640 | 160 | 160 | 0.25 | 0.25 |
| 23 | 600 | 400 | 400 | 0.67 | 0.67 |
| 24 | 480 | 20 | 40 | 0.042 | 0.083 |
| 25 | 320 | 160 | 40 | 0.5 | 0.125 |
| 26 | 160 | 1280 | 320 | 8 | 2 |
| 27 | 160 | | 20 | | 0.125 |

STA, serum tube agglutination.

heart failure due to endocarditis (OR 15.400, 95% CI 3.991-59.431, $P \leq .001$) were found to be independent risk factors increasing mortality, while the usage of aminoglycoside-containing regimens (OR 0.250, 95% CI 0.075-0.831, $P = .024$) and cardiac surgical intervention for endocarditis (OR 0.068, 95% CI 0.019-0.237, $P < .001$) were found to be factors reducing mortality. Of the 32 patients who died, only 5 could receive treatment for >3 months, while the others died within the first 3 months of treatment. It was not possible to define the effect of treatment duration on death, as patients who could receive treatment for >3 months were usually survivors.

The factors increasing the risk for non-mortality composite outcome were found to be the presence of perivalvular abscess ($P = .014$), pre-treatment Wright STA titer of ≥1/1280 ($P = .016$), treatment schedules not containing DOX, RIF, or CRO ($P = .013$, $P \leq .001$ and $P = .012$, respectively), treatments containing aminoglycosides ($P < .001$), double combination antimicrobial therapy ($P = .038$), and the absence of triple combination antimicrobial therapy ($P = .026$), in univariate analyses.

In multivariate analysis, the presence of perivalvular abscess ($P = .014$) and aminoglycoside use (OR 2.84, 95% CI 1.06-7.58, $P = .036$) were independent risk factors for non-mortality composite outcome. In contrast, DOX ($P = .041$) usage was associated with fewer composite outcomes (Table 5). There was no difference in the incidence of non-mortality composite outcome between patients who received and did not receive treatment for >3 months (16/113, 14.15% vs. 16/132, 12.12%, $P = .949$).

## DISCUSSION

Our data revealed that the presence of a Wright STA titer higher than ≥1/1280 on admission, development of CHF due to endocarditis, treatment with antimicrobial combinations not including an aminoglycoside, and lack of cardiac surgical intervention for endocarditis were significant risk factors for mortality in cases with Brucella endocarditis. A Wright STA test titer of ≥1/1280 on admission could be an indicator of chronic, advanced IE, which was shown to be associated with mortality in cases with endocarditis caused by other microorganisms.[8] No other study reporting an association between on-admission Wright STA test titer and mortality was found. It was also found that the Wright STA test titer decreased significantly at the 3rd month and the end of treatment by nearly eightfold in patients under treatment. There is some limited indirect evidence suggesting that Wright STA test titers could be used as a marker to monitor treatment

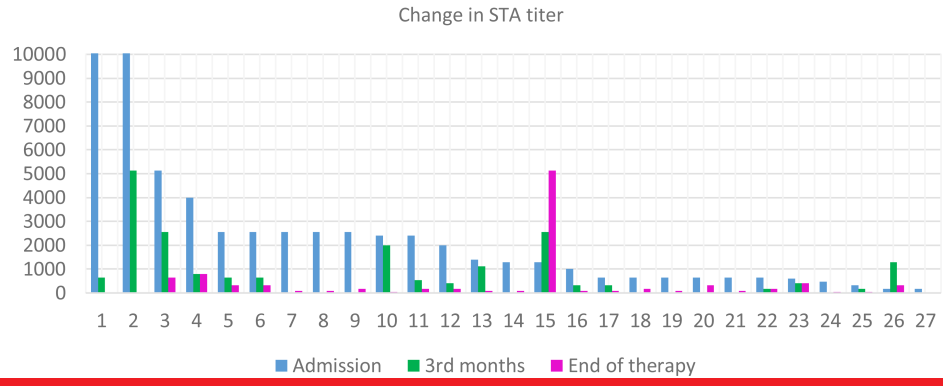


**Figure 2. Course of Wright STA titer under treatment among 27 cases with *Brucella* endocarditis.**

response: in 1 report of 7 Brucella endocarditis cases, continuing treatment until the normalization of the Wright STA test (<1/160) was reported to be successful in all of the 7 cases.[9] In another report of 4 cases of Brucella endocarditis, despite having higher titers of the Wright STA test on diagnosis (ranging from 1/2560 to 1/16 000), titers were decreased significantly in a very short time (about 1 month) after the cardiac valvular surgical interventions.[10] Finally in the study of Al Kasab et al,[11] Wright STA test titers were decreased significantly after successful surgical and medical therapy. On-admission Wright STA test titer may be used as a prognostic factor and as a factor to forecast the total duration of illness and advanced disease, and Wright STA test titers may be monitored to assess the response to the treatment among patients with *Brucella* IE. However, the number of patients with available data was only 27 in this study; additional studies are needed to make a stronger recommendation.

Consistent with previous reports, including cases of endocarditis caused by pathogens other than *Brucella* spp.[12,13] or *Brucella* spp,[4] it was found that valve surgery is a protective factor against mortality in cases with *Brucella* spp. endocarditis. Surgery was the most critical factor for reducing mortality, with an OR of 0.068. As a result, it is essential to carefully evaluate the indications for emergency or elective heart valve surgery by the "infective endocarditis team" in patients with endocarditis due to *Brucella* spp. and to perform the surgery without delay when there are indications for valve surgery in these patients to reduce mortality. Also, in accordance with previous studies looking for mortality risk factors among cases with endocarditis[14] it was also found that the development of heart failure due to endocarditis increases mortality in patients with Brucella endocarditis by about 15-fold. This finding also indicates the importance of performing valve surgery before heart failure complications occur.

**Table 5. Independent Risk Factors for Composite Non-Mortality Adverse Outcomes Among 273 Patients with Infective Endocarditis Caused By *Brucella* spp.**

| Variables | *P* | OR | 95% CI |
|---|---|---|---|
| Presence of paravalvular abscess | .014 | 3.634 | 1.298-10.176 |
| Wright STA titer ≥ 1/1280 on admission | .093 | 2.244 | 0.875-5.756 |
| Treatment including doxycycline/tetracycline | .041 | 0.192 | 0.039-0.938 |
| Treatment including aminoglicosides | .036 | 2.848 | 1.069-7.583 |

STA, serum tube agglutination.

This study also revealed that antimicrobial treatment combinations including aminoglycoside were more efficient than combinations not including aminoglycoside in the treatment of cases with Brucella IE. In the meta-analysis of observational and randomized controlled studies comparing the treatment of cases with uncomplicated brucellosis, it was also observed that treatment success was higher in regimens containing an aminoglycoside.[15,16] However, it was also found that these agents were related to more adverse drug effects, especially renal toxicity ($P = .036$). Therefore, while closely monitoring well-defined adverse effects of aminoglycosides including nephro/ototoxicity, one may prefer an aminoglycoside-containing treatment regimen for the treatment of cases with Brucella endocarditis.[17] To prevent nephro/ototoxic effects of aminoglycosides among those patients who already additional risk factors for nephrotoxicity such as using multiple drugs, presence of heart failure and low cardiac output stages, concomitant use of drugs such as diuretics, or other nephrotoxic antimicrobials including vancomycin should be avoided as much as possible in those patients.

The analysis revealed that patients with Brucella endocarditis are mainly younger males (77% of cases were male with a mean age of 44 years). The reason for this seems to be related to the fact that mainly young men are engaged in animal husbandry, which is a well-defined risk factor for brucellosis in endemic settings. Interestingly, younger age and male gender were found to be risk factors increasing mortality, and 17% of cases had a history of previous brucellosis before the diagnosis of endocarditis. Although the exact reason for these findings could be multifactorial, it could be hypothesized that the higher tolerance capability of younger people without another comorbidity to the insidious symptoms of chronic brucellosis, along with lower compliance with medical treatments among younger persons, could lead to both advanced disease and late admission to the hospital. Some of the other findings also support the late admission of these patients to the hospital, such as the detection

of vegetation size larger than 10 mm in 70% of patients, and nearly 50% of complication rate due to endocarditis, including heart failure, embolic events, and other intracardiac complications such as abscess, aneurysm, and fistula. This hypothesis could be analyzed in future studies. However, as endocarditis is the most deadly complication of brucellosis and 91.8% of the patients in this analysis had a predisposing cardiac valve disease, all patients diagnosed with brucellosis should always be evaluated for the presence of an underlying heart condition predisposing to IE by at least anamnesis, history, and physical examination.

This study has some limitations. The evidence obtained is relatively weak, as all of the included studies were case reports or case series, which inherently limits the generalizability of the findings. While efforts were made to include studies with complete data, some information was unavailable in some of the included studies. Additionally, the optimal duration of medical treatment could not be suggested, as all of the deaths due to Brucella endocarditis occurred before the completion of the 3-month treatment duration. Therefore, the treatment duration could not be compared between patients who survived and those who did not. Finally, patients with more complicated courses are generally published, leading to a publication bias which could also limit the generalizability of the results.

This study also has several strengths. All Brucella endocarditis cases with sufficient data reported in both English and Turkish literature were included. A comprehensive analysis was also conducted, including both univariate and multivariate risk factor analyses, to ensure a greater reliance on the findings.

In conclusion, it was found that Brucella endocarditis primarily affects younger male patients with predisposing conditions for endocarditis. The findings also suggest that the inclusion of either streptomycin or gentamicin in the treatment regimen may be beneficial for patients with Brucella endocarditis. A Wright STA test titer of ≥1/1280 may serve as a marker for increased mortality, likely indicating long-term and advanced disease. However, the low quality of evidence underscores the urgent need for additional and more reliable studies to define the most effective strategies for diagnosing and treating cases with Brucella endocarditis.

**Ethics Committee Approval:** We did not receive ethical approval because this research included the cases in the literature.

**Informed Consent:** We did not obtained informed consent because this research included the cases in the literature.

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**Author Contributions:** The project was conceived by S.B., S.Ş.Y., and ÖE. The data were collected by S.B., E.A.B., and A.B. Bioistatistics analysis was conducted by S.Ş.Y. and S.Ö. The draft paper was critically edited by G.A., A.A., Ö.A., N.D., A.K.Ç., M.A., F.K., S.S.K., E.T.Y., N.T., and Ö.E. S.B. and S.Ş.Y. wrote the paper.

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**[SUPPLEMENTARY DOCUMENT]**

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