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Brucella Prosthetic Valve Endocarditis: A Systematic Review

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Abstract

Objective: Brucella prosthetic valve endocarditis is a rare but a life-threatening complication of brucellosis. It remains a diagnostic challenge. Optimal treatment of Brucella prosthetic valve endocarditis is debated. Available data is limited to case reports or small case series. The purpose of this study was to systematically review all published cases of Brucella prosthetic valve endocarditis in the literature.

Method: A systematic review of PubMed database, Google, Google Scholar, and Scopus (From January 1974 to the present) for studies providing epidemiological, clinical and microbiological data as well as data on treatment and outcomes of Brucella prosthetic valve endocarditis was performed.

Results: A total of 51 reported cases were reviewed. Brucella melitensis (45%) and Brucella abortus (11.7%) were the most frequently isolated species. Most common type of prosthesis valve was mechanical prosthesis (84.3%) and ten patients had double valve prosthesis (19.6%). Fever and dyspnea were present in 100% and 37.2% of the cases, respectively. The diagnosis was set with echocardiographic finding in 30 cases (93.7%), which revealed vegetation in 27 cases (84.3%). Most used antibiotics were rifampicin, doxycycline and aminoglycoside or cotrimoxazole. No deaths were noted in patients treated by combined medical and surgical treatment, but mortality was noted in 27.7% of the cases treated by antibiotics alone (p = 0.006).

Conclusion: This systematic review highlights diagnostic challenges and demonstrates that surgery improved outcome by reducing mortality in patients treated with the combined surgical and medical treatment option. Brucellosis should be considered in the differential diagnosis of prosthetic valve endocarditis in patients residing in or traveling to areas of endemicity.

Keywords: Brucella, Endocarditis, Prosthetic valve, Antibiotics, Surgery

1. Introduction

Human brucellosis is a severe multisystemic disease that may affect any organ. Focal complications, therapeutic failure, and relapse might occur. Cardiovascular complications are rare, among which endocarditis is the most common cardiovascular involvement of the disease [1]. It accounts for 0.8%–5% of all cases of brucellosis and represents the main cause of death due to brucellosis [2]. Mortality is usually caused by cardiac failure especially in patients with late diagnosis [3].

Brucella prosthetic valve endocarditis (PVE) is extremely rare, as it remains a diagnostic and therapeutic challenge, due to the lack of controlled trials and treatment approach regarding the ideal treatment duration, combination of antibiotics, indication and timing of surgery. The purpose of this
study was to systematically review all published cases of Brucella PVE in the literature and describe the epidemiology, microbiology, clinical characteristics, treatment and outcomes of these infections.

2. Materials and methods

2.1. Data search

We reviewed all reported cases of Brucella PVE by searching PubMed, Google, Google Scholar and Scopus publications from January 1974 to the present. The used MeSH terms were: (Prosthetic valve OR valve prosthesis OR valve replacement OR bioprosthesis OR mechanical valve) and (brucella endocarditis or brucellosis and endocarditis). To find the old publications we used MeSH “Starr’s valve and brucella endocarditis”.

2.2. Study selection

We included the studies reporting data on patients’ clinical characteristics, microbiology, treatment and outcome. We included all the studies published in different languages. The majority of the articles were in the English language (n = 33), three articles were in French, two articles were in Spanish and two articles were in Turkish. We excluded from the analysis the studies which were secondary research papers (e.g., reviews) and studies not in humans. Brucella endocarditis on the native valve and cardiac device were excluded. Given the rarity of the pathology, all articles on Brucella PVE were included in this literature review regardless of the type of article (letter to the editor, case report, cases included in case series) to gather as much information as possible. The clinical data including demographic characteristics, clinical features, laboratory data, echocardiographic findings, treatment, and clinical outcome of these patients were collected and analyzed.

2.3. Outcomes of interest

The primary outcomes were to record on the (a) epidemiology of patients with Brucella PVE and (b) patients’ outcomes. Secondary outcomes were to record data on (a) the exact site of infection, (b) the patients’ clinical characteristics, (c) their laboratory and echocardiographic features and (d) their treatment. The identification of risk factors for mortality was another endpoint of this study.

2.4. Data extraction and definitions

The extracted data included patient demographic data (age and gender); patient’s relevant medical history (previous cardiac surgery or cardiac valve replacement, time after cardiac valve replacement); infection data and microbiology infection site, isolated strains, presence of complications, presence of embolic phenomena; treatment prescribed and outcomes (cure or death).

Diagnosis of infective endocarditis (IE) was confirmed by the investigators based on information provided by the authors and the modified Dukes’ criteria if the diagnosis was definite (2 major or 1 major and at least 3 minor criteria, or 5 minor criteria) or if pathological data established a diagnosis of IE. The complications recorded included any organ dysfunction or clinical deterioration that was considered by the authors to be related to the IE.

2.5. Statistical analysis

All of the continuous variables are expressed as mean ± standard deviation and the categorical variables as percentages. In univariate analysis, the Anova test or the Mann-Whitney test were used for the quantitative variables and the Chi-square test for the qualitative variables. A p-value < 0.05 was considered statistically significant. Due to the small number of patients, a multivariate analysis was not possible.

3. Results

3.1. Literature search

A total of 305 articles reporting Brucella endocarditis from PubMed, Google, Google Scholar and Scopus publications were screened. After reviewing the titles and abstracts, we identified a total of 41 articles of Brucella PVE. The full text of one article could not be found. We included a total of 40 articles reporting 51 cases (4–43) (Fig. 1). The first case of Brucella PVE has been published in 1974. Clinical,
biological, echocardiographic and therapeutic findings are summarized in Table 1.

3.2. Epidemiology

Most cases were from Turkey (21 patients, 42%), Spain (eight patients, 16%), and Iran (five patients, 10%) (Table 1). The mean age of patients was 42 ± 13 years [15–75 years], a male predominance was noted (34 males, sex ratio 2).

3.3. Microbiology

*Brucella melitensis* and *Brucella abortus* were the most frequently isolated species (n = 29, 56.8%). *B. melitensis* was isolated in 23 patients (45%), *B. abortus* in six patients (11.7%) and *B. suis* in one patient [35]. None patient had *Brucella* PVE caused by *B. canis*. Consumption of unpasteurized dairy product, raw milk, fresh goat’s cheese was reported in 22 cases (43%). Contact with infected animals and/or consumption of unpasteurized dairy milk has been reported in 26 patients (50.9%). Thirteen Patients (25.5%) were exposed by their profession or by their leisure activities: veterinarian in one patient [33], a stock- breeder in one patient [36], hunter in two patients [8,35], shepherd in five patients [8,27,30,31] and farmer in four patients [18,38,39,42] (Table 1).

3.4. Underlying cardiopathy and comorbidities

Most common type of prosthesis valve was mechanical prothesis (n = 43; 84.3%), eight (15.7%) patients had bioprosthesis valve [6–9,20,21,28,32], And ten patients (19.6%) had double valve prosthesis [5,18,19,23,29,31,32,36,39]. Prosthetic aortic valve involvement was reported in 27 patients (52.9%), prosthetic mitral valve involvement was reported in 18 patients (35.3%) and in two cases (3.9%) both the aortic and mitral prosthesis were affected [23,36]. No endocarditis in the tricuspid prosthesis valve was reported (Table 2).

The etiology of the valvulopathy for which the patient had a valvular replacement with valve prosthesis has been specified in 27 patients. It was rheumatic valvular heart disease in 15 of these patients (55.5%) [4,8,11,12,15,17,18,20,21,23,24,26,30,39] (Table 1). The average duration between implantation of the prosthesis and the episode of *Brucella* PVE was 8 ± 7 years (extremes: 4 months-
| Authors | Year | Country | Age/sex | Risk factors: | Underlying cardiopathy | Symptoms and physical findings | Laboratory findings | Serological test/blood culture | TTE/TEE findings | Complication | Antibiotics combination | Surgical surgery: | Follow up |
|---------|------|---------|---------|---------------|------------------------|-----------------------------|-------------------|-----------------------------|-----------------|-------------|--------------------------|----------------|----------|
| O’Meary J B 1974 | London/Italian patient | 38f | Yes/AntiHLA | Mitrail mechanical RHEUMATIC | Fever, rigour, cough, dyspepsia, abdominal pain | - | ++ B.melitensis, B.abortus | HF | Mitrail prosthesis sternia in cardiac catheterization | T/12 months | Cephalaxin, + Tetracyclines | 2 years Ischemic stroke | - |
| Lestand H 1980 | Spain | 45M | Yes/none | Aortic/prosthesis - Mitral | Fever, dyspepsia, petechial Diastolic aortic murmur 1 month | ++ | B.melitensis Initial negative blood culture | HF | Severe paravalvular leak on aortic prosthesis in cardiac catheterization | T/3 weeks | Rectal sulfadiazine | 1 year negative Replacement of aortic and mitral prosthesis | - |
| Iglesias A 1981 | Spain | 25F | - | Aortic Bioprosthesis x Ven enroll | Fever, pruritus, Signs of aortic regurgitation SMG | 14 months | ++ B.melitensis | HF | T=8 weeks | Yes/AntiBF, B.melitensis | 6 months uneventful | - |
| Rubio Abarca 1983 | Spain | 28f | bioprosthesi | - | Fever | No | - | HF | Uneventful | Cured by antimicrobial therapy | - |
| Fernández alGuerrero 1987 | Spain | 45M | No/AntiHLA | Aortic mechanical prosthesis Calcified AS | Fever, (NRA, dyspepsia, general malaise Diastolic aortic murmur | Anemia ESR=64/113 | ++ | B.melitensis | HF | Pulmonary ometal and retro zebra trunk | T/1 weeks | T/1 weeks HS | Year/AntiB.melitensis | 4 years Uneventful |
| Fernández alGuerrero 1987 | Spain | 62M | Yes/none | Aortic mechanical prosthesis Rheumatic valve | Fever, chills back pain, Diastolic aortic murmur 3 weeks | Anemia ESR=80/100 | ++ | B.melitensis | HF | Sulfadiazine | 3/1 weeks T/3 weeks D/7 weeks H/2 weeks | Year/Antibi B.melitensis | 3 years uneventful |
| Fernández alGuerrero 1987 | Spain | 62M | Year/Hunter | Aortic bioprosthesis IE on Bicuspid valve | Fever, chills SMG, SMG Diastolic murmur | Anemia ESR=28/56 | ++ | B.melitensis | HF | T/1 weeks | Yes/AntiB.melitensis | 2 years Uneventful |
| Al-Kasab 1988 | Saudi Arabia | 25f | - | Mitrail prosthesi 5 years | Fever, dyspepsia SMG, 2 heart sound, the new systolic murmur of MR | ESR/10=15/15 | ++ | B.melitensis | HF | T/14-2 weeks D/4 weeks | Year/Antibi B.melitensis | 2 years Uneventful |
| D’Agrosa 1988 | France | 38M | Yes/AntiHLA | Aortic mechanical prosthesis IE (bruella highly probable) | Fever | ++ | B.melitensis | AV Block | Year/Antibi, B.melitensis | Post-operative Ischemic stroke | Sudden death 1 year after the operation, of an unknown cause | - |
| Flugima n Mt 1990 | Israel | 25M | Yes/AntiHLA | Aortic mechanical prosthesis Rheumatic valve | Fever, weakness, anemia, infected aortic murmur 2 months | ESR/25 | ++ | B.melitensis SAT initially Positive | Normal | T/15 R/4 weeks | No Aptemia Decrease SAT, Risk of infection | Blood group |
| Kamoun S 1991 | Tunisia | 22M | - | Aortic mechanical prosthesis 5 years | Fever | ++ | B.bior In | HF | R/1 Then R/O Cephalaxin | Yes/AntiB.melitensis | 1 year Uneventful |
| A Antela 1992 | Spain | 15b | - | Mitral valve prothesis 2 months | Fever | Valvular failure | Ischemic stroke | Antibiotic therapy | Yes | Medical treatment Not sufficient | - |
| A.M. saadeh 1996 | Jordan | - | - | Aortic mechanical prosthesis | Failure after 6 months of recovery from brucella end occult splenic abscess | Prolonged ATB | Yes | Recovery | - | - |

Table 1. Clinical, biological, echocardiographic and therapeutic data of the reviewed cases of Brucella prosthetic valve endocarditis.
| Case 1 | 2001 | Turkey | 27/F | YES | Autitic, mechanical prosthesis Rheumatic, 4 months | Fever, weight loss, cough, chest pain, dyspnea, HMO, hemoptysis, arthralgia, Systolic thrill 1 month | Anemia ESR=90 | B.Melitensis | L'hariti aortic-left ventricular HF | SH+TV+3 months | Yes | 3 months | Uneventful |
| Case 2 | 2001 | Turkey | 27/F | YES | Autitic, mechanical prosthesis Rheumatic, 4 months | Fever, dyspnea III-IV | +/- | Yes | Prosthetic valve culture+ | R+D+G | Yes | Prosthetic valve culture- | Uneventful |
| Case 3 | 2001 | Turkey | 53/F | Yes | Mitral, mechanical prosthesis Rheumatic, 15 years | Fever, general malaise, arthralgia | -/+ | Initial SAT normal | VL | Brachial, anaemia | R+D+T, O by ciprofloxacin (side effects) | 12 months | No | 4 years | Uneventful |
| Case 4 | 2001 | Turkey | 42/F | YES | Double mechanical prosthesis Rheumatic, 8 months | Fever, chills, night sweats, arthralgia, skin rash, weight loss, dyspnea 9 SMG, HMG, Mitral murmur palpable | ESR=145 | Anemia pannicytopenia | B abortus | Involved prosthesis: Mitral VI, Normal aortic prosthetic: Native insufficiency related to native failure | R+D/G | Yes | Positive Interval time diagnosis-surgery: 95 days | Uneventful |
| Case 5 | 2001 | Qatar | 29/F | YES | Double mechanical prosthesis Rheumatic | Fever, cough, sweating, anemia, Hemorrhages 9 months | Anemia ESR=33 | B.melitensis | Involved prosthesis: Aortic VALA | Ischemic stroke | R+D/15/20weeks | Yes/ | Positive Interval time diagnosis-surgery: 46days | 10 months | Uneventful |
| Case 6 | 2001 | Qatar | 39/M | Yes | Aortic, mechanical prosthesis | Fever, sweat, anemia, Cough 3 Weeks | -/+ | V | Brucella species | V+D Than D+R Than D+H+T1/3 WEEKS | Yes/-negative | Interval time diagnosis-surgery: 10days | 1 year | Uneventful |
| Case 7 | 2001 | Qatar | 35/M | Yes | Mitral, mechanical prosthesis | Fever, cough, sweating, 3 months | -/+ | V | R+D+T | Yes/-negative | Interval time diagnosis-surgery: 11 Weeks | 10 months | Uneventful |
| Case 8 | 2001 | Turkey | 43/F | Yes | Mitral bioprosthesis Rheumatic, 6 years | Fever, weight loss, Sweating, dyspnea 2 months | High ESR Normal WBC | B.melitensis | V large Left atrium thrombus | R+D+T | Yes/ | Negative Interval time diagnosis-surgery: 6 weeks | 6 months | Unilative decreased serology tiers |
| Case 9 | 2001 | Turkey | 58/F | YES | Aortic Mechanical prosthesis | Fever Fatigue 15 days | - | B.melitensis/ Negative initial SAT Infecion S. aureus | V (native mitral valve) | Acute myocardial infarction | Antibiotic therapy against S. aureus | No | Died |
| Case 10 | 2001 | Turkey | 40/F | YES | Hinchical Mechanical prosthesis Mitral, Then Bioprosthetic mitral struk | Fever, cough, Weakness, dyspnea | PCR positive | V+H+H stroke Ischemic stroke | CHF 3 months | No | 3 years | Uneventful |
| Case 11 | 2006 | Germany | 55 F | YES | Aortic/mitral prosthesis Rheumatic, 18 years/2 years | Fever, anemia, fatigue, chest pain, 4 weeks | Anemia CRP 1-14 ESR 70 | B.melitensis | Involved prosthesis: aortic, mitral V 15-11mm A L | HF Pulmonary Edema | R+D/G months (taken only two months) | Yes/-/ | Initially refused | 2 years | Uneventful |
| Case 12 | 2006 | Turkey | 58/F | YES | Mitral, Mechanical prosthesis Rheumatic | Fever, fatigue, dyspnea, HMO, generalized pain Systolic murmur 2 months | CRP 143 ESR 47 | +/+ | 2V 1.23 mm 95 mm Normal TTE | Toranade de Poinnes, Ventricular fibrillation | D+RH/I/12 months | Yes/negative | D+RH/I/2 months | 12 months | Uneventful |
| Case 13 | 2006 | Turkey | 52/F | - YES | Aortic, Mechanical prosthesis ASceding aorta dilation 4 years | Fever, Cough, dyspnea, chest pain sweating, weight loss, arthralgia, aortic, diastolic murmur 2 months | Anemia ESR 58 | B.melitensis | Vegetal regurgilation | HF O+R+M months | Year/spoiz h Internal diagnosis-surgery: 5days | 24 months | Normalization SAT |
| Case 14 | 2006 | Italy | 45/F | YES | Farmer | Mitral, mechanical prosthesis Rheumatic, 10 years | Fever, 3 weeks | Leukopenia ESR 70 CRP 180 | -/+ | Brucella Spp | V (TEE) | R+D/H/G weeks | No | Negative侵入 blood culture Disappearance of vegetation |
| Case 15 | 2006 | Tunisia | 50/M | YES | Sheepherd Consumption of raw milk | Mitral Starr Bioprosthesis 16 years ago | Fever Night sweating Fatigue 5 days | ESR=40 leukocopenia | VI/H/TEE 6 mm Glomereulure nephritis | R+D+diagnosis+ | Yes | Sweroski test became negative within 3 month: 6 months: Unfavorable |
| Name                     | Country | Age | Sex | Breed | Disease/Condition | Duration | Site | Type | Prosthesis | Antibiotic Therapy | Outcome |
|-------------------------|---------|-----|-----|-------|------------------|----------|------|------|------------|--------------------|---------|
| Botta L                  | Tunisia | 56+ | M   | -     | Aortic bioprosthesi | 7 months | A    | 46/16/F | -          | -/+/B.mellitae  | Died     |
| Gunes Y                  | Turkey  | 53- | M   | -     | Double prosthesis  | 2 weeks   | 61/75/A | 46/F   | DIED       | 36 Days            | DIED    |
| Karadag Lan              | Turkey  | 42F | Consumpt roe | Double prosthesis | Mechanical Mitral/Aortic | 1 year  | HF  | 42/F   | GMS +/+/B.mellitae | R+D+/-/S+/-T+/-/S/6 weeks | Rejected |
| Karadag Lan              | Turkey  | 27M | sheep herder | Mitral prosthesis | Rheumatic fever | 1 month  | TEE | 27/M   | Vegetation on aortic valve/TEE | R+D+/-/S+/-T+/-/S/6 weeks | Rejected |
| Karadag Lan              | Turkey  | 56/2 | Unspecified milk | Mechanical prosthesis | Rheumatic fever | 2 weeks  | ESR/80 | 56/2  | Vegetation on aortic valve/TEE | R+D+/-/S+/-T+/-/S/6 weeks | Rejected |
| Kashkarian Jahromi       | Iran    | 34M | Yes  | Shepherd | Double prosthesis | Mechanical Mitral/Aortic | 100 days | High ESR | Involved prosthesis: A/L | R+D+/-/S+/-T+/-/S/6 weeks | Year/-/ 18 years |
| Kashkarian Jahromi       | Iran    | 31M | Yes  | Shepherd | Double prosthesis | Mechanical Mitral/tricuspid | 2 months | HMG | Involved prosthesis: Mitral V 8/10 mm | Shack | Died before antibiotics |
| Samasz A                 | Turkey  | 43M | -    | -     | Mitral bioprosthesi | 4 months  | Fever | 43/M   | V/v/5 mm Aortic atheroma | UHR/95/60 | Year/-/ 18 years |
| Samasz A                 | Turkey  | 45M | -    | -     | Double prosthesis  | Mechanical Mitral/Aortic | 30 days | Fever | Involved prosthesis: Mitral V 4/5 mm | R+D+/-/S+/-T+/-/S/6 weeks | Died after surgery (stroke) |
| Amolighian AA            | Turkey  | 38M | -/+ | Veterinarian | Mechanical Mitral/Aortic | 30 days | Fever | 38/M   | Massive aortic root infected pseudovenous aneurysm, normal prosthesis valve leaks | UHR/95/60 | Year/-/ 18 years |
| Kekic Boshnak            | Serbia  | 75M | -    | -     | Mechanical Valve prosthesis | Aortic insufficiency | 4 months | 75/M   | Night sweating | B.mellitae | Vegetation | Died after surgery |
| Carrington M             | USA     | 46F | -/len | -/len | Aortic prosthesis | Mechanical Four separate aortic graft Marfan's syndrome | 15 months | 46/F   | Aorta biotype I PCR positive | Shock | Multiple Spicul-infant | Died after surgery |
| Mekic N                  | Bosnia  | 46M | -    | -/len | Double prosthesis | Mechanical Mitral/Aortic | 9 months | 46/M   | Subclinical | B.mellitae | - | No |
|                           |         |     |      |       |                  |           |      |       |            |                  |         |             |

**Table 1. (Continued).**
28 years). Early *Brucella* PVE was noted in eight patients [4,8,11,15,18,21,28,34]. Only three patients had comorbidities, two patients had diabetes [21,28] and one patient had cardiac liver cirrhosis [39].

### 3.5. Clinical presentation

The commonest symptoms were fever, chills, night sweating, dyspnea, fatigue, weight loss, osteoarticular and muscular symptoms. The mean duration of the symptoms before diagnosis was 3 ± 3 months (with extremes ranging from one week to 15 months). This duration was between two months and one year in ten patients [8,19,31,37,38,41–43], less or equal to two months in 24 patients [5,8,9,11,13,17–20,22–28,30,31,35,39,40] and above one year in four patients [6,15,35,36]. It was not specified for the rest of the patients.

In 11 patients (21.5%), one or more hospitalizations because of fever preceded by a few weeks the diagnosis of *Brucella* PVE [5,6,19,21,23,28,35,36]. In three patients among them, the diagnosis of *Brucella* PVE was made 1 year, 14 years and 6 months, the disease. In the patient reported by Botta et al. [23], Mehanic et al. [36]. In patients reported by Al Dhahouk et al. [23], Mehanic et al. [36], Carrington et al. [35], and Hamieh et al. [43], echocardiography was not performed at the time of diagnosis of brucellosis. We can't precise whether they had endocarditis from the beginning or endocarditis developed later during the course of the disease. In the patient reported by Botta et al. [28], transthoracic and transesophageal echocardiography were normal.

A history of IE was found in six patients [8,10,14,36,41] among them three patients [13,15,19] had a history of *Brucella* endocarditis, reinfection has occurred one year, 14 years and 6 months,

### Table 1. (Continued).

| Author, Year | Country | Sex/Farm er | Age | Year | Pathology | Symptoms | Signs | Initial Treatment | Outcome | Complications |
|--------------|---------|-------------|-----|------|-----------|----------|------|-------------------|---------|---------------|
| Al-Obeid et al. 2015 [37] | Turkey | 55M | 35 | 1 year | Mitral Mechanical prosthesis 7 years | Fever, fatigue, anorexia, joint, back pain, sweats, cough, weight loss, HRG, SMG. | SMG | R+D+G/3 weeks | Died | Refused |
| Al-Dhahouk et al. 2015 [23] | Iran | 55M | 20 | 2 years | Mechanical prosthesis | Fever, loss of weight, low mEq/leukopenia CRP 46 mg/l | No | R+D+TS | Died | No |
| Al-Khanshali et al. 2018 [41] | Portugal | 65F | Yes/Farm er | 4 years | Aortic Mechanical prosthesis 4 years | Fever, loss of weight, low back pain, chest pain New onset of symptoms | No | R+D/9 months | Judged non-necessary | Shrinkage of vegetation 2 years |
| Hamieh et al. 2020 | Lebanon | 35M | Yes | 3 months | Aortic Mechanical prosthesis 20 years | Fever, night sweating, generalized fatigue 3 months | No, mEq/Leucopenia | R+D+V3 weeks | Surgery planned but not performed due to hemodynamic instability Died 24H after admission |

*P: Positive; -: Negative; ns: not specified

**A:** Abscesses; **AR:** Aortic regurgitation; **AS:** Aortic stenosis; **AV:** Atrioventricular; **CRP:** C reactive protein; **D:** Prothrombin valve disinsertion [mg/l]; **ESR:** Erythrocyte sedimentation rate mm/h; **IF:** Heart failure; **HMID:** Hepatomegaly; **IE:** Infective endocarditis; **L:** Leak; **M:** Mitral stenosis; **MI:** Mitral insufficiency; **MS:** Mitral stenosis; **PCR:** Polymerase chain reaction; **SAT:** Serum agglutinin test; **SMG:** Splenomegaly; **V:** Vegetation; **WBC:** White blood cells.

**Antibiotics:** **R:** Rifampicin; **D:** Doxycyclin; **S:** Streptomycin; **G:** Gentamicin; **T:** Tetracyclin; **TS:** Sulfamethoxazole and Trimethoprim.
respectively. Relapse of brucellosis after an appropriate treatment was recorded in five patients [8,10,14,33,42]. Mean duration of symptoms before the diagnosis of PVE was also prolonged in patients with a history of brucellosis (brucellosis with failure of treatment, relapse, history of brucella endocarditis) [8,10,14,23,28,33,42] ranging between 2 and 4 months. Heart failure was noted in 16 patients (31.3%).

3.6. Biological findings

Diagnosis of brucellosis was made by serology and/or culture in all except one patient [21]. Blood culture was positive in 31 patients (60.7%). It was negative in 20 patients (39.3%), in these patients the diagnosis of brucellosis was done by the serologic tests. Both positive blood culture and serologic tests were observed in only 23 patients (4%). Two patients with positive blood culture were seronegative [19,26]. Results of serologic tests were not mentioned in six patients [12,28,35,36,38,40]. PCR test was performed in only three patients [22,35,43]. It was positive in two patients among them [22,35]. It allowed the diagnosis of brucellosis in one patient [5]. The effect of antibiotics on mortality cannot be assessed owing to the small number of patients.

3.7. Echocardiographic findings

Echocardiographic data were available in 32 patients (62.7%) (not performed in eight patients, this technique of imaging was not developed at the time [2–4,4–8]). Echocardiographic data of the rest of patients were not available. It was abnormal in 30 of them (93.7%). Twenty-seven (84.3%) patients had vegetation, in eight patients among them a large vegetation (size equal or above 10 mm) was noted (29.6%) [9,20,23,24,30,31,36,41].

In three patients vegetations was detected in transesophageal Echocardiogram, it was not shown in transthoracic echocardiogram [24,37,42]. Six patients had abscess [1,10,23,30,31] and 11 patients had paravalvular leak and regurgitation [15,17–19,23,25,28,31,32,41,43].

An Aorta-left ventricle fistula was seen in the patient reported by Arslan et al. [15], a massive aortic root infected pseudoaneurysm was reported by Amirghofrane et al. [33] and an aortic aneurysm was reported by Keshtkar et al. [31]. In old reports, cardiac catheterization has shown a mitral prosthetic valve obstruction in one patient [4] and a severe leak in the aortic prosthetic valve in another patient [5].

3.8. Treatment

Mean duration of treatment was 6 ± 3 months [1–14 months]. There was no standard antibiotic regimen used. Most used antibiotics are Rifampicin, Doxycycline (or Tetracycline) and Aminoglycoside (Streptomycin or Gentamycin), or Co-trimoxazole. Co-trimoxazole (Trimethoprim-Sulfamethoxazole) was prescribed in 16 patients (31.3%). Quinolones (ciprofloxacin or ofloxacin) were used in six patients (11.7%) and cephalosporin antibiotics were used in seven patients (13.7%). Sulfadiazine was prescribed in one patient (2%) [5] (Table 1). The effect of antibiotics on mortality cannot be assessed owing to the small number of patients.

3.9. Comparison of medical treatment alone versus combined surgical and medical treatment

We identified 29 patients (56.8%) who had combination of medical and surgical treatment (group 1) [4–6,8–10,12–16,18–20,23–25,27,28,31–33] and 18 patients (35.2%) who had medical treatment alone (group 2) [7,11,17,21,26,29,30,32,34,36–39,41–43]. Three patients (5.8%) have died before treatment [22,31,35] (Table 3).

No difference was noted between the two groups concerning age and sex, with p-value at 0.18 and 0.77, respectively. The mean duration of symptoms before diagnosis was 3 ± 3 months in group 1 and 4 ± 3 months in group 2 (p = 0.51). The incidence of heart failure was similar in the two groups (p = 0.22) (Table 2). No difference was noted between the two groups concerning positivity of blood culture (p = 0.49). The mean duration of treatment in group 1 was 6 ± 3 months [3 weeks-13 months] and in group 2 was 7 ± 5 months [6 weeks-12 months] (p = 0.52). In patients who underwent surgery (group 1): The median duration of antibiotics until surgery was 10 days [5–66 days].

The most frequent indications for surgery were: Failure of medical treatment with uncontrolled infection and enlarging or persistence of vegetation despite antibiotics [9,13,18,24,27,33], valvular regurgitation, and congestive heart failure in 12 patients [4–6,8,10,12,15,23,25,28], preventing embolic complications [20], relapse after recovery by antibiotics alone [14] and severe hemodynamic instability which developed during antibiotic therapy [16]. Intracardiac complications with abscess in five patients [10,19,23,31] and an aortic root infective pseudoaneurysm in one case [33] were indication
for surgery. In two patients, surgery was initially refused and performed later when antibiotic therapy alone was inefficient [18,23].

The echocardiographic findings were confirmed during surgery in all the patients except the patient reported by Amirghofrane et al. [33], prosthetic valve disinsertion was noted intraoperatively but not shown in echocardiography. In five patients in whom echocardiography was not performed (the technique was not developed at the time), surgical examination revealed abscesses in five patients [6,8,12] and dehisced prosthetic valve in six patients [6,8,12].

Culture of vegetation, excised tissues, or prosthesis valve was positive in ten patients [6,8,16,18,19,25,28]. All of them had positive blood culture except two patients [8], among whom the diagnosis of brucellosis was determined by serologic tests. In three patients [18,23,28], culture of the prosthesis was positive despite appropriate and prolonged antibiotics, with treatment duration respectively at 95 days, 2 months, and 8 weeks.

All patients who underwent surgery were cured by combination surgery and antimicrobial therapy (Fig. 2). Few postoperative complications have been reported, including a regressive ischemic stroke in two patients [4], atrioventricular block treated by a pacemaker in one patient [6], and reoperation in two patients for disinsertion of the valve prosthesis without signs of endocarditis [8].

Table 2. Clinical presentation and complications of the reviewed cases.

| Clinical presentation            | Number | Percentage (%) | References                                      |
|--------------------------------|--------|----------------|------------------------------------------------|
| Fever                          | 51     | 100            | [4-43]                                          |
| Dyspnea                        | 19     | 37.2           | [4,5,8,9,15,16,20,21,23,24,25,28,30,33,35,36,39]*Case 1, **Case 1.2, ***Case 1.2 |
| Night sweating                 | 15     | 29             | [8,18-20,23,25,27,28,34,36,37,39,43]            |
| Fatigue, asthenia, weakness     | 14     | 27             | [11,18,21-25,27,28,35-37,42,43]                 |
| Chills                          | 12     | 23.5           | [8,15,28,29,31,33,34,36]                        |
| Osteoarticular symptoms        | 10     | 19.6           | [8,15,17,18,24,25,33,35,37,40,41,42]            |
| Splenomegaly                   | 9      | 17.6           | [6,8,9,18,31,35,37]                             |
| Hepatomegaly                   | 9      | 17.6           | [8,15,18,24,31,36,37]                           |
| Weight loss                    | 7      | 13.7           | [15,18,20,25,28,37,42]                          |
| Associated sites               |        |                |                                                 |
| Sacroilitis                    | 2      | 3.9            | [8,21]                                          |
| Spondyloarthritic              | 2      | 3.9            | [41,42]                                         |
| Underlying cardiopathy         |        |                |                                                 |
| DVP: Mitral and aortic prosthesis | 8    | 15.6           | [5,18,19,23,29,31,32,33,36]                     |
| DVP: Mitral and tricuspid prosthesis | 2   | 3.9           | [31] Case 2, [39]                              |
| Aortic prosthesis              | 21     | 41             | [6,8,10-12,14,15,19,22,25,28,30,31,34,40,42,34]|
| Mitral prosthesis              | 14     | 27.4           | [4,9,13,17,19-21,24,25,27,30,32,33,37,38]       |
| Bentall intervention           | 2      | 3.9            | [33,41]                                         |
| Aortic graft and mechanical aortic prosthesis | 1 | 1.9     | [35]                                            |
| Complications                  |        |                |                                                 |
| Heart failure                  | 16     | 31.3           | [4-6,8,10,12,15,22,23,25,28,36,38,41,43]        |
| Septic shock                   | 1      | 1.9            | [43]                                            |
| Myocarditis                    | 2      | 3.9            | [10,35]                                         |
| Myocardial infarction          | 2      | 3.9            | [22,40]                                         |
| Rhythm disturbance             | 1      | 1.9            | [24]                                            |
| Atrioventricular block         | 1      | 1.9            | [10]                                            |
| Artery mycotic aneurysm        | 1      | 1.9            | [17]                                            |
| Ischemic stroke                | 4      | 7.8            | [13,19,21,30]                                   |
| Glomerulonephritis             | 3      | 5.8            | [27,36,37]                                      |
| Renal failure                  | 1      | 1.9            | [18]                                            |
| Meningitis                     | 1      | 1.9            | [41]                                            |
| Multiple splenic infarct       | 2      | 3.9            | [14,35]                                         |

DVP: Double valve prosthesis.
Seventeen patients had antibiotic therapy alone (group 2), among them 13 patients have been cured [7,11,17,21,26,30,32,34,37,39,42] and four patients have deceased [29,36,38,41] (Fig. 2). In patients cured by antibiotic therapy alone, surgery was planned but refused by the patients in three cases [30,32,39]. In the other patients [7,11,17,21,26,30,34,37,42], surgery was not performed because there were no heart failure and prosthetic dysfunction with good evolution and disappearance of vegetation. In group 2, therapeutic choice (medical treatment alone) was consistent with current guidelines [48] in all these patients except in the patient reported by karaoğlan et al. [30] in which cardiac abscess was treated by antibiotics alone, and the patient reported by Mehani et al. who had heart failure [36].

The average follow-up was 1 year [0,5–18 years], no significant difference was noted between the two groups (p = 0.56). Neither relapses nor late death related to Brucella PVE was noted in the two groups. Sudden death of unknown cause has occurred in one patient one year after surgery [9].

3.10. Early mortality

Early mortality was noted in 16% of the cases (8/50 patients). There was no information about treatment in one patient. Five patients were treated with antibiotics alone, and three patients with PVE died before the diagnosis of Brucella PVE [22,31,35]. No deaths were noted in patients treated by combined medical and surgical treatment, but mortality was noted in 27.7% of the cases treated by antibiotics alone (5/18). Table 4 summarize clinical and paraclinical data in deceased patients compared to cured patients.

4. Discussion

Human Brucellosis is the most frequently encountered world-wide zoonotic disease, it affects both adult and child and remains a major human health problem in many developing regions, especially in the Mediterranean basin, North and East Africa, the Middle East, the Arabian Peninsula, the Indian subcontinent and parts of South America and Central Asia [44,45]. According to the World Health Organization, 500,000 new Brucella cases are reported each year with a prevalence of more than 10/100,000 population is noted in endemic countries [46].

4.1. Clinical presentation and risk factors of brucellosis

As noted in this review, the disease affects mostly the young population. The infection is usually associated with contact with infected animals or through the consumption of unpasteurized dairy milk [44]. A careful assessment of epidemiological risk factors is crucial for the diagnosis of brucellosis. In reported cases, these risk factors were not sought in nearly half of the patients. Clinicians should obtain information about patient activities including travel, food consumption, occupation, and outdoor recreation. Brucella species should be considered in the differential diagnosis of PVE in patients leaving or returning from a region of endemicity. This review emphasizes the importance of performing a detailed patient interview, as it can provide useful information regarding potential exposure to infectious agents.

Human brucellosis is a multisystemic disease with a large spectrum of symptoms [2]. In the cases

| Table 3. Clinical, biological, echocardiographic data among patients treated with combined treatment (group 1) and patients treated by antibiotic therapy alone (group 2). |
|-----------------|-----------------|---------------|
|                 | Group 1 (n = 29) | Group 2 (n = 18) | P-value |
| Age (years)     | 40 ± 14         | 45 ± 13        | 0.18     |
| Gender (male)   | 18              | 15             | 0.77     |
| Duration of symptoms before diagnosis (months) | 3 ± 3 | 4 ± 3 | 0.51 |
| Heart failure   | 10              | 5              | 0.22     |
| Double prosthesis | 4               | 5              | 0.45     |
| Mechanical prosthesis | 19             | 17             | 0.09     |
| Prosthetic disinsertion | 15           | 2*             | 0.002    |
| Cardiac abscess | 10              | 1**            | 0.04     |
| Negative blood culture | 12          | 5              | 0.49     |
| Follow up duration (years) | 2 ± 4 | 4 ± 3 | 0.56 |
| Mean duration of antibiotherapy (months) | 6 ± 3 | 7 ± 5 | 0.52 |

Group 1: patients treated with medical and surgical treatment, group 2: patients treated by medical treatment alone. Bold value indicates the difference between the groups was significant (p < 0.05).

*Two patients with disinsertion of the prosthesis were not received surgery, in the patient reported by Cakalagooglu C, medical treatment was chosen as the adequate treatment option, and in the second patient, surgery was planned but the patient is deceased before.

** Brucella prosthetic valve endocarditis complicated with periannular abscess treated with antibiotic therapy alone.
analyzed here, the spectrum of symptoms is closer to that of brucellosis than that of PVE. In patients with a prosthetic valve, brucellosis must be evoked when fever is associated with night sweating, muscular pain, arthralgia, back pain, and spondylodiscitis, especially in patients with risk factors. Relapse of brucellosis was noted in five patients. Relapsing bacteriemia after appropriate treatment for acute brucellosis is an important clue for the diagnosis of brucella endocarditis in patients who have prosthetic valves [8,10,14,33,42].

In this current review, heart failure was frequent and represented a risk factor of mortality. It remains the most common cause of death due to IE and the most frequent reason for surgery in these patients [3,28].

4.2. Diagnosis work-up and challenges

Brucella PVE remains a diagnostic challenge. Meticulous history taking, clinical examinations, and detailed laboratory tests such as serologic tests and blood culture, and echocardiography are required through the diagnosis process. In the reviewed cases, prolonged interval time between the onset of symptoms and diagnosis of Brucella PVE was noted. This interval time was prolonged even in patients with a known history of brucellosis. The delayed diagnosis can be explained by the difficulty in the culture of Brucella species and the lack of specificity of symptoms. Brucellosis is often misdiagnosed. By screening for Brucella antibodies of all sera from febrile patients, Purwar et al. reported almost two new cases per month of brucellosis, most of which are not suspected by clinicians [47]. According to some authors, serious damage is likely to be caused not so much by the supposed poisonousness of the bacteria as by a late diagnosis due to the difficulty in the culture of this agent [48]. Special attention is then necessary for patients with prosthetic heart valves.

In cases reviewed here, a high rate of negative blood culture was noted (39.3%). Brucella endocarditis is often culture-negative endocarditis. In many series, it forms part of the pool of cases of pathogen-induced endocarditis with negative blood cultures. A negative culture could potentially lead to a delay in diagnosis and treatment [31]. Blood cultures, although highly specific, present a low sensitivity (15–70%) due to the low growth rate of Brucella spp., the necessity of proper culture medium, and their fastidiousness. In patients with PVE and negative blood culture, a high degree of suspicion of brucella PVE is needed especially in young male patients with a history of exposure to farm animals.

Due to the lack of sensitivity of blood cultures, serology is being used increasingly to allow an early diagnosis and is a major criterion in Duke’s criteria [49]. However, serologic tests are not wholly specific, may be difficult to interpret in endemic areas, and maybe negative during the early stages of the

| Table 4. Clinical and paraclinical data in deceased and cured patients. |
|---------------------------------------------------------------|
| **Deceased patients** (n = 8) | **Cured patients** (n = 43) | **P-value** |
| Heart failure* | 5 | 10 | 0.04 |
| Age (Years) | 45 ± 13 | 41 ± 14 | 0.50 |
| Gender (male) | 8 | 25 | 0.06 |
| Negative blood culture | 5 | 25 | 0.6 |
| Large vegetation | 3 | 4 | 0.04 |
| Antibiotherapy alone/combined treatment** | 8/0 | 10/29 | 0.006 |
| Desinsertion of the valve prosthesis | 0 | 16 | 0.01 |
| Intracardiac abscess | 0 | 11 | 0.26 |

OR: Odds ratio, CI: Confidence interval.
*Heart failure at admission, **Combined treatment: Surgery combined with medical treatment (antibiotherapy).
disease. They are considerably more reliable in the diagnosis of brucellosis when evaluated together with a consistent clinical presentation. In the majority of the cases reviewed here, the diagnosis was made initially by the serologic tests.

In this review, two seronegative patients with positive blood culture were reported. In literature about *Brucella* endocarditis, 6% of the patients with acute brucellosis present with an initial titer ≤1/160, but it becomes at least four-fold higher on subsequent testing [50]. According to some authors, serologic tests are not suitable for the follow up of patients since titers can remain high for a prolonged period [51]. The high sensitivity and specificity of the PCR assays may provide a valuable tool for the diagnosis of brucellosis which is the case of the patient reported by Kalaycioglu et al. [22].

In cases reviewed here, echocardiography played a crucial role in the diagnosis of *Brucella* PVE and its complications. When available, echocardiography has been used as the first-line diagnostic approach and it allowed the diagnosis of endocarditis in the majority of cases. Some authors [52] recommended echocardiography in all patients with *Staphylococcus aureus* bacteremia because of the high frequency of endocarditis in such cases and because of the high morbidity and mortality of *S. aureus* endocarditis. In the same vein, can we suggest the systematic practice of echocardiography in all patients with cardiac valve prosthesis and brucellosis. This suggestion is supported by analyzing the echocardiographic findings in reviewed cases. *Brucella* PVE was misdiagnosed in some febrile patients or patients with a confirmed diagnosis of brucellosis because repeated echocardiography has not been done [19,23,33,35,36,42,43].

*Brucella* spp. can cause destruction and ulceration in tissues slowly, explaining the frequency of paravalvular leakage reported in 19 cases (37.2%) (revealed by echocardiography, cardiac catheterization, and surgical examination) and abscesses reported in 11 cases (21.5%) (revealed by echocardiography and surgical examination). These intra-cardiac complications reflect the severity of the disease. When compared with other bacterial pathogens, *Brucella* endocarditis is characterized by a greater tendency toward fibrosis, hyalinization, and calcification involving the cardiac valves. Therefore, due to its rapid and wide tissue destruction, higher mortality rates were observed during this disease [1,38,39,49] and has been noted in this review. Nearly the third of reviewed cases have large vegetation, which could be explained by the diagnostic delay and the prolonged evolution before the echocardiography is performed.

4.3. Treatment approach

Owing to the lack of large series, the optimal association, and duration of antibiotics is unknown. The intracellular location of the microorganism makes it inaccessible to the action of many antibiotics [53]. Ideally, the antimicrobial agent should be bactericidal to prevent relapse in brucellosis [54]. According to some authors, the addition of a third-generation cephalosporin (ceftriaxone), to the combination of a tetracycline group and rifampicin was more effective than aminoglycosides [55]. Quinolones such as ofloxacin and ciprofloxacin are the alternative drugs in combination therapy of brucellosis. They can be included due to their great tissue distribution and a great capacity to penetrate in vegetations in patients with IE and PVE [48].

Long-term treatment is necessary for *Brucella* infection since it is an intracellular and antibiotic-resistant infection [49,56]. By analyzing data of reviewed cases, it seems to be unanimous agreement on the need to prolong the *Brucella* PVE therapy, but there is no fixed duration in all patients. The mean duration of antibiotics varied from 1 month to 14 months. Prolonged therapy is necessary, before and after surgery, mostly in patients with prosthesis valve culture positive. In current guidelines, a duration of over 3–4 months was recommended in patients with *Brucella* endocarditis [49]. We believe that a longer duration of antibiotics may be necessary in cases of *Brucella* PVE.

Combined treatment associating surgery and medical treatment versus medical treatment alone was debated. Although recovery has been reported with antibiotics alone, surgery after medical treatment has been adopted as the most common therapeutic approach. In articles reviewed here [4–6,8–10,12–16,18–20,23–25,27,28,30–33,39] and in the literature about *Brucella* endocarditis (on the native valve and prosthetic valve) [22,56,57], authors suggest an early surgical approach with preoperative antibiotic therapy and immediate surgery after clinical stabilization due to the degree of tissue ulceration and destruction caused by *Brucella*. The high rate of recurrence and resistance of *Brucella* to medical treatment and development of large vegetations carrying a significant risk of embolization [25]. Other studies reported cases of *Brucella* endocarditis cured by antibiotics alone [7,11,17,21,26,30,32,34,37,39,42,58–60]. They stress the need for prognostic stratification of each case and support conservative treatment in low-risk cases without cardiac failure and with a short disease interval medical treatment. According to
them, careful monitoring is necessary because recurrence risk is high. All cases of Brucella endocarditis cured by medical therapy alone were reviewed by Mert et al. [58], who thought that the probable success of medical therapy was attributable to the absence of the compelling indications for surgery, such as heart failure, valve destruction, abscess formation or prosthetic valves dysfunction.

The results of this literature review support the opinion of the authors that believe that surgery is the most efficient approach for the treatment of Brucella PVE by showing a significant decrease in mortality in the group of patients treated with surgical treatment compared to the group of patients treated with antibiotics alone. Moreover, this superiority of surgical treatment was observed despite the lack of difference between the two groups in terms of clinical presentations. Given the slowly destructive character of Brucella Spp., relapses, the multiple antibiotics needed to control this infection, her prolonged duration and the improved outcome with surgery, the question that arises is “Can we add Brucella species to the microorganisms listed in the guidelines related to the management of IE (Staphylococci or non-HACEK gram-negative bacteria and fungi) [49] to be considered as an indication for surgery?”. However, the number of patients reviewed here is limited which does not allow a recommendation.

4.4. Limitations

Although this review is the only and the largest one evaluating the diagnosis and therapeutic approach in Brucella PVE, it relies entirely on retrospectively published data, in some cases, crucial information is missing. Another important limitation is the small number of patients resulting in restricted statistical analysis. Therefore, the results of the survival analysis could not be extended by multivariate analysis. Moreover, because the review spanned many decades, during them the diagnosis, definition, surgical indication, and antibiotic treatment of endocarditis changed, this must be considered a limitation in interpreting the data.

5. Conclusion

This review points out the main reported characteristics of Brucella PVE, highlights the difficulties in its diagnosis. Brucella spp. should be considered as one of the etiologic agents of PVE in patients living or returning from endemic region, with a history of ingestion of unpasteurized dairy products and/or exposure to animals with prolonged and unexplained fever especially in patients with negative blood culture and clinical signs suggestive of brucellosis that must be carefully researched. Earlier diagnosis and treatment lead to decreasing morbidity and mortality related to this infection.

Optimal treatment of Brucella PVE is a subject of great controversy. We suggest that successful management of Brucella PVE requires a combination of medical and early surgical therapy to achieve the sterilization of infected cardiac tissue and to replace the infected prosthesis valve, but given the limited number of patients, a formal therapeutic approach cannot be validated.

Summary section

Brucella prosthetic valve endocarditis affects mostly the young population with risk factors. Brucella prosthetic valve endocarditis is usually culture-negative endocarditis. High rate of negative blood culture was reported, in almost 40% of the cases.

Echocardiography has a crucial role in the diagnosis of Brucella prosthetic valve endocarditis and its complications.

Although recovery was reported with antibiotics alone, combined medical and surgical therapy is the most efficient therapeutic approach as a significant decrease in mortality was reported.

Author contribution

Karima Taamallah: Conception and design of Study; Literature review; Acquisition of data; Analysis and interpretation of data; Research investigation and analysis; Data collection; Drafting of manuscript; Data preparation and presentation; Supervision of the research. Fatma Hammami: Conception and design of Study; Literature review; Acquisition of data; Analysis and interpretation of data; Research investigation and analysis; Data collection; Drafting of manuscript; Revising and editing the manuscript critically for important intellectual contents; Data preparation and presentation; Supervision of the research; Research coordination and management. Hédi Gharsallah: Acquisition of data; Research investigation and analysis; Data collection; Drafting of manuscript; Revising and editing the manuscript critically for important intellectual contents. Makram Koubaa: Conception and design of Study; Literature review; Acquisition of data; Analysis and interpretation of data; Research investigation and analysis; Drafting of manuscript; Revising and editing the manuscript critically for important intellectual contents; Data preparation and presentation; Supervision of the research; Research coordination and management.
Mounir Ben Jemaa: Conception and design of Study; Data collection; Revising and editing the manuscript critically for important intellectual contents; Supervision of the research; Research coordination and management. Wafa Fehri: Conception and design of Study; Revising and editing the manuscript critically for important intellectual contents; Supervision of the research; Research coordination and management.

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