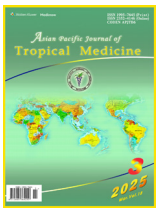

Systematic Review

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# Brucellosis in patients with malignancies: A systematic review

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## ABSTRACT

**Objective:** To explore the epidemiological trends and clinical presentations of brucellosis in patients diagnosed with different types of cancer.

**Methods:** A systematic review was performed utilizing PubMed, Embase, Scopus, Web of Science, and Google Scholar following PRISMA guidelines until September 2022. An update in December 2023 was conducted to ensure thorough coverage of the literature.

**Results:** A total of 28 articles met the eligibility criteria, reporting 38 cases of brucellosis in patients with cancer. Among these cases, hematological cancers were the most common, comprising 66% of the cases, and *B. melitensis* was identified as the predominant species. The primary clinical manifestations of brucellosis infection included constitutional symptoms in a notable 60.5% of cases and febrile neutropenia in 21%. Additionally, six cases (15.8%) experienced relapse or recurrence of brucellosis, all of which were managed using a combination therapy of rifampin and doxycycline. While 28 patients successfully achieved remission from both brucellosis and their underlying neoplastic conditions, unfortunately, nine cases resulted in mortality attributed to septic shock, progressive liver failure, and massive embolism; no deaths directly related to brucellosis were reported. Among the non-surviving cases, hematologic malignancies were the most prevalent neoplastic conditions (77.7%).

**Conclusions:** Brucellosis-cancer co-occurrence is rare but is not related to increasing mortality. The risk of relapse is higher in cancer patients, especially with hematologic malignancies. Screening, monitoring, and judicious antibiotic use can mitigate brucellosis risks in neoplastic patients.

**KEYWORDS:** Brucellosis; Immunocompromised; Cancer; Malignancy; Opportunistic infection

**Summary**

**Question:** What are the epidemiological patterns and clinical manifestations of brucellosis in patients with malignancies?

**Findings:** This systematic review revealing that hematological cancers accounted for 66% of cases. The predominant species was *Brucella* melitensis, with significant clinical manifestations including constitutional symptoms (60.5%) and febrile neutropenia (21%).

**Meaning:** Co-occurrence of brucellosis and cancer is rare and does not significantly increase mortality; however, cancer patients, especially those with hematologic malignancies, have a higher risk of relapse, emphasizing the need for vigilant screening and treatment strategies.

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## 1. Introduction

Brucellosis, is a zoonotic that can transmitted from animals to humans, caused by pathogenic bacteria belonging to the *Brucella* genus[1]. Noteworthy species within this group include *Brucella* (*B.*) *melitensis*, *B. abortus*, *B. suis*, and *B. canis*, with *B. melitensis* being the prevalent strain worldwide[2]. The disease is particularly common in certain areas including Middle East, Mediterranean territories, parts of Africa, and South America[3,4]. Symptoms of brucellosis can vary widely and may involve multiple organ systems presenting as fever, arthralgia, headache, back pain, and orchitis, along with severe complications such as endocarditis and meningoencephalitis, thereby posing considerable health risks[5-7]. Additionally, insufficient antibiotic treatment can lead to latent infections, increasing the chances of recurrent episodes and flare-ups[8].

In a previous study, we investigated the occurrence of brucellosis in immunocompromised patients who had undergone organ transplants. The findings indicated that brucellosis is relatively rare in transplant recipients occuring in 42.8% of cases in the early post-transplantation period and 57.1% in the later stages[9]. To our knowledge, by searching in databases, no comprehensive research study investigated brucellosis in patients with cancer extensively. It is well established that individuals with malignanies, especially those with hematological cancers, are at an increased risk for opportunistic infections due to immune suppression caused by chemotherapy and/or the underlying disease[10,11]. Since the concurrence of brucellosis and neoplasms is poorly understood according to evidence, this systematic review aims to explore this issue, focusing on clinical manifestations, diagnosis challenges, treatment difficulties, and the potential effect of their co-occurrence on disease progression. The study offers a comprehensive academic perspective on this unexplored medical topic through a detailed analysis of the existing literature.

## 2. Materials and methods

### 2.1. Search strategy

The present study was conducted according to the guidelines of "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA)[12]. A thorough literature search was performed utilizing various web-based search engines, including PubMed, Embase, Scopus, and Web of Science. On the search imposed no restrictions regarding time, age, language, or other filters, and was conducted up to September 2022. Furthurmore, searched manual search of the Google Scholar database was undertaken to ensure that no relevant articles were missed. The Mesh-indexed keywords were searched in the mentioned databases, using a combination of the key terms and Boolean operators such as "OR" and "AND". The detailed search strategies used in the databases are mentioned in supplementary file 1. To ensure that no newly published articles were overlooked, an additional search was conducted from 2022 to December 2023. However, no additional articles were identified for inclusion during this timeframe.

### 2.2. Study selection

All identified studies were imported into the Endnote software version X.8 and then duplicated. Two authors screened the remaining articles based on their title and abstract and then by full-text. In case of any conflicts, they were resolved during the interviews. The eligibility criteria for this review were all articles that reported on brucellosis patients concurrent with neoplastic disorders. All articles that were irrelevant or did not report cases of brucellosis co-occurred with neoplasm were excluded from study. The yielded articles were finally considered in this study.

### 2.3. Data extraction and analysis

Following the screening, the selected articles were incorporated in the study, and a quality assessment was undertaken supplementary Table 1. Two independent authors reviewed the full texts of the included articles, subsequently extracting and categorizing the necessary data which included sociodemographic information, types of the malignancies, the presentations due to brucellosis, diagnosis measurements, antibiotic regimens, relapse or recurrence, and outcomes. In the case of discrepancy, a discussion was held between the reviewers, and the conflicts were resolved by a third independent author.

### 2.4. Review registration

The study was registered in PROSPERO the international prospective register of systematic reviews. Registration No: CRD42025633963.

## 3. Results

### 3.1. Studies characteristics

The articles selection process is presented in Figure 1. According to the search results, we identified a total of 1 890 articles. After removing the duplicated and irrelevant studies, 28 articles were included in the present review which were published from 1956 to 2020. Table 1 represents the characteristics of the 28 eligible articles. The twenty-eight included studies enrolled 38 patients with an average age of (41.2±17.8) years. The number of female and male patients were 14 and 21, respectively and 3 cases did not have a reported sex.

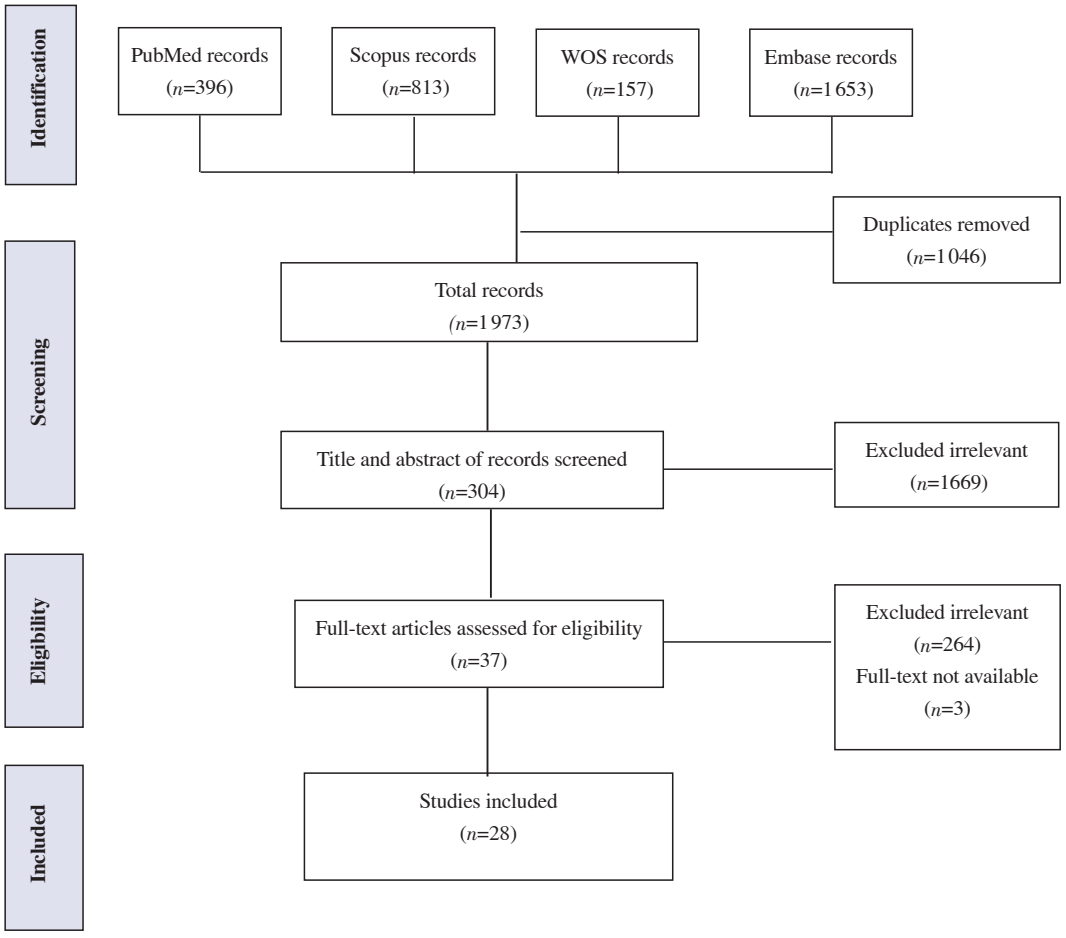


**Figure 1.** PRISMA folw chart.

### *3.2. Symptoms*

Constitutional symptoms including fatigue, malaise, fever, weight loss, and chronic pain were the most complaints. These symptoms were present in 23 out of 38 cases (60.5%). Additionally, approximately 21% of patients (8 out of 38 cases) presented with febrile neutropenia. A notable incidental case involved a woman with ovarian cancer who was asymptomatic. However her brucellosis was diagnosed later, a follow-up CT scan of lumbar vertebrae revealed some degenerative changes.

### *3.3. Patient assessment*

Among the cases, the most neoplasms associated with brucellosis were hematological malignancies, present in 25 out of 38 cases (65.78%). Among these, acute lymphocytic leukemia was the most reported, occurring in 11 out of 38 cases (28.94%). Each of the following conditions was present in 3 patients: acute myeloid leukemia, multiple myeloma, myelodysplastic syndrome, and lymphoma (1 B-cell lymphoma and 2 non-Hodgkin lymphoma). Additionally, one patient had myelofibrosis and one another had hairy cell leukemia co-occurring with brucellosis.

The investigation included an additional cohort of 13 patients with various forms of cancer. Two patients were identified with hepatocellular carcinoma, two with thyroid malignancies, two with breast cancer, one with lung squamous cell carcinoma, one with stomach cancer, one with Warthin tumor, and one with astrocytoma. Furthurmore, one patient diagnosed with each of ovarian cancer, sertoli cell tumor, and seminoma.

A significant history of consumption unpasteurized dairy products was reported in 16 cases (16/38, 42.1%). Our review indicated that blood culture and serological assessments were the primary methods employed for diagnosing *Brucella* infection. Notably, blood cultures, recognized as the gold standard for brucellosis diagnosis, yielded positive results in 25 cases (25/38, 65.68%). The predominant species identified in the cultures was *B. melitensis* (21/25, 84%). Serum tube agglutination assay for antibodies against the bacteria was performed for all the studied cases due to the high availability of

**Table 1.** Baseline characteristics of the cancer patients afflicted with brucellosis.

| Author/Study reference | Year of publication | Region/Country | Case number | Sex of cases | Study type | Signs/Symptoms- related brucellosis | Type of neoplasm |
|---|---|---|---|---|---|---|---|
| Akkoyunlu ME *et al.*[13] | 2013 | Turkey | 1 | Male | CR | Constitutional symptoms | Lung, SCC |
| Al-Anazi KA *et al.*[14] | 2007 | Saudi Arabia | 2 | 2 Males | CR | Constitutional symptoms & pancytopenia | MDS and ALL |
| Alduraibi AK *et al.*[15] | 2019 | Saudi Arabia | 1 | Male | CR | chronic and progressive low back pain | Seminoma |
| Arda B *et al.*[16] | 2007 | Turkey | 1 | Male | CR | Febrile neutropenia | Non-Hodgkin lymphoma |
| Bakri FG *et al.*[17] | 2010 | Jordan | 1 | Female | CR | Pancytopenia | Myelofibrosis |
| Barutca S *et al.*[18] | 1998 | Turkey | 1 | Male | CR | Constitutional symptoms | HCC |
| Bay A *et al.*[19] | 2007 | Turkey | 2 | 1 Male 1 Female | CR | Constitutional symptoms & pancytopenia | ALL |
| Charoniti I *et al.*[20] | 2006 | Greece | 1 | Male | CR | Constitutional symptoms | Sertoli cell tumor |
| Citak EC *et al.*[21] | 2011 | Turkey | 1 | Male | CR | Constitutional symptoms | ALL |
| Cokca F *et al.*[22] | 2006 | Turkey | 1 | Male | CR | Constitutional symptoms & pancytopenia | MDS |
| Eser B *et al.*[23] | 2006 | Turkey | 2 | 2 Females | CR | Constitutional symptoms & pancytopenia | ALL |
| Horasan ES *et al.*[24] | 2011 | Turkey | 1 | Male | CR | chronic and progressive low back pain | Warthin tumor |
| Li JJ *et al.*[25] | 2012 | China | 1 | Female | CR | Constitutional symptoms & pancytopenia | Myelodysplastic syndrome |
| Metan G *et al.*[26] | 2006 | Turkey | 1 | Female | CR | Febrile neutropenia | ALL |
| Oksenhendler E *et al.*[27] | 1988 | France | 1 | Male | CR | Constitutional symptoms & others | HCL |
| Ozbalci D *et al.*[28] | 2011 | Turkey | 1 | Female | CR | Febrile neutropenia | AML |
| Kasap T *et al.*[29] | 2016 | Turkey | 1 | Male | CR | Constitutional symptoms | B-cell Lymphoma |
| Özçay F *et al.*[30] | 2000 | Turkey | 1 | Female | CR | Febrile Neutropenia | ALL |
| Sari R *et al.*[31] | 2002 | Turkey | 3 | Unidentified | CR | Febrile Neutropenia | 2 Breast & 1 Stomach cancer |
| Solmaz S *et al.*[32] | 2014 | Turkey | 1 | Male | CR | Febrile Neutropenia | AML |
| von Graevenitz A *et al.*[33] | 1990 | Switzerland | 2 | 1 Female 1 Male | CR | acute non-suppurative thyroiditis and constitutional symptoms | Thyroid malignancy |
| Montes J *et al.*[34] | 1986 | United State | 1 | Female | CR | Constitutional symptoms and a miscarriage | Astrocytoma |
| Meneses A *et al.*[35] | 2010 | France | 1 | Female | CR | Asymptomatic | Lymphoma |
| Dogu M *et al.*[36] | 2016 | Turkey | 1 | Male | CR | Constitutional symptoms | MM |
| Emara M *et al.*[37] | 2007 | Kuwait | 1 | Female | CR | Asymptomatic | Ovarian cancer |
| Cocchi S *et al.*[38] | 2010 | Italy | 1 | Male | CR | Constitutional symptoms & others | HCC |
| Sari I *et al.*[39] | 2008 | Turkey | 5 | 3 Males 2 Females | CR | Constitutional symptoms | 1 AML, 3 ALL & 1 MM |
| Rahdar HA *et al.*[40] | 2020 | Iran | 1 | Male | CR | Constitutional symptoms | MM |

CR: Case report; MDS: Myelodysplastic syndrome; ALL: Acute lymphoblastic leukemia; HCC: Hepatocellular carcinoma; AML: Acute myeloid leukemia; MM; Multiple myeloma; HCL: Hairy cell leukemia.

such tests and the time-consuming results of blood culture. However, the definitive diagnosis based solely on a positive serological test was established in 2 cases where blood cultures returned negative despite the presence of clinical symptoms and increase in antibody titer.

### *3.4. Patient treatment*

Table 2 outlines the antibiotics and final clinical outcomes among patients. The most frequently utilized antibiotics included doxycycline (31/38, 81.6%), rifampin (23/38, 60.5%), and streptomycin (12/38, 31.5%). Ciprofloxacin and co-trimoxazole (trimethoprim/sulfamethoxazole) were also used in 5 cases. Combination of rifampin and doxycycline emerged as the predominant regimen administered to 18 patients (47.4%). Additionally, 11 patients received a combination of streptomycin and doxycycline. Among 8 patients of experiencing neutropenic fever, 6 patients received dual therapy: doxycycline/rifampin ($n$=1), rifampin/tetracycline ($n$=3), doxycycline/streptomycin ($n$=1), and doxycycline/ciprofloxacin ($n$=1). Additionally, two patients were treated with co-trimoxazole along with dual therapy.

Relapse was observed in five patients all these received rifampin

**Table 2.** Summary of antibiotics and final clinical outcomes among the patients.

| No. | Author/Study reference | R | D | S | T | Ci | Co | Brucellosis Final status | Ultimate status due to concurrent cancer and brucellosis |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Akkoyunlu ME *et al.*[13] | | | Yes | Yes | | | Cured | Alive |
| 2 | Al-Anazi KA *et al.*[14] | Yes | Yes | | | | | Relapsed | Alive |
| 3 | Al-Anazi KA *et al.*[14] | Yes | Yes | | | | | Relapsed | Alive |
| 4 | Alduraibi AK *et al.*[15] | | Yes | Yes | | | | Cured | Alive |
| 5 | Arda B *et al.*[16] | | Yes | | | Yes | | Cured | Dead |
| 6 | Bakri FG *et al.*[17] | Yes | Yes | Yes | | | | Not mentioned | Alive |
| 7 | Barutca S *et al.*[18] | | Yes | Yes | | | | Cured | Alive |
| 8 | Bay A *et al.*[19] | Yes | Yes | | | | | Cured/ Recurrence | Alive |
| 9 | Bay A *et al.*[19] | Yes | | | Yes | Yes | | Cured | Dead |
| 10 | Charoniti I *et al.*[20] | | | | Yes | Yes | Yes | Cured | Alive |
| 11 | Citak EC *et al.*[21] | Yes | Yes | | | | | Cured | Dead |
| 12 | Cokca F *et al.*[22] | Yes | Yes | | | | | Cured | Alive |
| 13 | Eser B *et al.*[23] | Yes | Yes | | | | | Cured | Alive |
| 14 | Eser B *et al.*[23] | | Yes | | | Yes | | Cured | Dead |
| 15 | Horasan ES *et al.*[24] | Yes | Yes | | | | | Relapsed | Alive |
| 16 | Li JJ *et al.*[25] | Yes | Yes | | | | | Relapsed | Alive |
| 17 | Metan G *et al.*[26] | | Yes | Yes | | | | Not mentioned | Alive |
| 18 | Oksenhendler E *et al.*[27] | Yes | | | Yes | | | Not mentioned | Alive |
| 19 | Ozbalci D *et al.*[28] | Yes | | | Yes | | | Cured | Alive |
| 20 | Kasap T *et al.*[29] | | Yes | Yes | | | | Cured | Alive |
| 21 | Özçay F *et al.*[30] | | Yes | Yes | | | | Cured | Alive |
| 22 | Sari R *et al.*[31] | Yes | | | Yes | | | Cured | Dead |
| 23 | Sari R *et al.*[31] | Yes | | | Yes | | Yes | Cured | Alive |
| 24 | Sari R *et al.*[31] | | Yes | Yes | | | | Cured | Alive |
| 25 | Sari R *et al.*[32] | Yes | Yes | | | | | Cured | Dead |
| 26 | von Graevenitz A *et al.*[33] | | Yes | Yes | | | | Cured | Alive |
| 27 | von Graevenitz A *et al.*[33] | Yes | Yes | | | | | Not mentioned | Alive |
| 28 | Montes J *et al.*[34] | Yes | Yes | | | | Yes | Not mentioned | Not mentioned |
| 29 | Meneses A *et al.*[35] | | Yes | Yes | | | Yes | Cured | Alive |
| 30 | Dogu M *et al.*[36] | | Yes | Yes | | | | Cured | Alive |
| 31 | Emara M *et al.*[37] | Yes | Yes | | | | | Cured | Alive |
| 32 | Cocchi S *et al.*[38] | Yes | Yes | | | | | Cured | Dead |
| 33 | Sari I *et al.*[39] | Yes | Yes | | | | | Relapsed | Alive |
| 34 | Sari I *et al.*[39] | Yes | Yes | | | Yes | | Cured | Alive |
| 35 | Sari I *et al.*[39] | | Yes | | | Yes | | Cured | Alive |
| 36 | Sari I *et al.*[39] | Yes | Yes | | | | | Cured | Dead |
| 37 | Sari I *et al.*[39] | Yes | Yes | | | | | Cured | Dead |
| 38 | Rahdar HA *et al.*[40] | | Yes | Yes | | | | Not mentioned | Alive |

and doxycycline combination. Furthermore, a recurrence of infection was reported in a patient diagnosed with acute lymphoblastic leukemia and brucellosis two years after a complete treatment regimen by rifampin and doxycycline. 28 Patients (28/38, 73.7%) Alive after receiving antibiotics.

### *3.5. Mortality*

Among all identified patients, nine patients did not survive. Of these, three patients experienced septic shock, two died from progressive liver failure due to neoplasm metastasis, two cases were attributed to massive pulmonary embolism, and one case was reported as expired following end-stage cancer without further details. One patient did not follow up, while the remaining twenty-eight were reported as surviving from both cancer and brucellosis. Consequently, brucellosis was not determined to be the cause of mortality in any of the cases. Hematologic cancers were the most prevalent among those who did not survive, accounting for seven cases (7/9, 77.8%). Specifically, four of these pateints suffered from acute lymphoblastic leukemia, while one patient suffered from each of acute myeloid leukemia, multiple myeloma, and non-Hodgkin lymphoma.

## 4. Discussion

Immunosuppression has been shown to elevate the risk of brucellosis in patients, and may lead to new infections and relapses[41]. Our systematic review uncovered an unexpectedly low prevalence of brucellosis among cancer patients, even in areas where the disease is endemic. This discrepancy may be attributed to the possibility that brucellosis goes undiagnosed in certain cases, particularly in cancer patients who present with multiple complications, where the significance of brucellosis may not be adequately acknowledged[21].

As expected, *B. melitensis* was the most reported causative species among cancer patients, with no notable difference in sex as 14 patients were females, 21 were males, and 3 were undefined. The occurence of brucellosis in this population may be attributed to two primary factors: the reactivation of latent infections or the revelation of previously undiagnosed infections due to immunosuppression, alongside the acquisition of new infections through conventional *Brucella* transmission pathways[42].

In this investigation, neutropenic fevere, fever, headache, myalgia, lower back pain, anorexia, and fatigue were the main clinical symptoms of patients who suffered from co-occurrence of brucellosis and malignany. Brucellosis affects multiple organs, results in various clinical presentations that make challenges in diagnosing[43]. In the research conducted, the predominant symptoms in conjunction with febrile neutropenia. Notably, while febrile neutropenia is generally rare among brucellosis patients who possess a functional immune system, it identified in roughly 21% of cases analyzed in our study (8 out of 38 cases). Among these cases, six patients experienced febrile neutropenia within a few days following chemotherapy, specifically occurring between the chemotherapy course and the eighth-day post-treatment. Notably, one patient did not undergo chemotherapy, while another received chemotherapy after the fever had been managed. Given the history of chemotherapy administration, it remains unclear whether the observed neutropenia is attributable to the chemotherapy itself or other factors, such as bone marrow infiltration by malignancies or infections like brucellosis. This uncertainty is particularly important to considering brucellosis in oncological patients who are at an elevated risk for complications, especially those who demonstrate resistance to standard treatments in regions where brucellosis is endemic.

In the patients of this investigation, while the positive blood culture was the most frequent method for diagnosing brucellosis, only 2 patients were detected merely by a positive serological test. Serological diagnosis based on the standard tube agglutination test uses anti-*Brucella* antibody concentrations in the plasma and/or tissue specimen to diagnose. Even though it is recommended that 1:160 and 1:80 agglutination titer is suggestive to diagnose brucellosis infection in endemic and non-endemic areas respectively, specific cut-off should not be determined. Eventually, considering the epidemiological prevalence, clinical suspicious, and trend of titer (four-fold rising titer between acute and convalescence sera) may suggest the ultimate diagnosis. Hence, plasma/tissue culture or polymerase chain reaction (PCR) techniques may assist in verifying suspicious antibody concentrations[44,45]. It can be inferred that, one of the factors contributing to the comparatively low incidence of brucellosis case reports in patients with neoplasms may be the reliance on negative serological tests rather than performing high-risk tests like blood culture in symptomatic individuals. In endemic areas, clinicians often limited laboratory evaluations to standard tube agglutination tests due to biosafety issues of specific culture methods, as well as the lengthy and potentially delaying processes. Thus, the high percentage of microbial culture results among reported cases in this systematic review indicate that these cases were deliberately organized for reporting purposes.

The world Health Organization (WHO) recommends a standard antibiotic regimen for the treatment of brucellosis without focal neurologic involvement. This regimen consists of doxycycline administered for 42 days, in conjunction with streptomycin for 15 days or gentamicin for 7-10 days. Alternative treatment options include a combination of doxycycline and rifampin at a dosage of 15 mg/kg/day for 42 days, or the use of an aminoglycoside or rifampin alongside co-trimoxazole in cases where the doxycycline is contraindicated[2]. Of note, using alternatives such as doxycycline, or rifampin, as well as compatibility of eradicating intracellular organisms such as *Brucella* spp. Similarly, cases evaluated in this investigation who experienced relapse or recurrence received a rifampin/doxycycline combination. Additionally, presence of bone marrow suppression due to malignancy, particularly in hematologic cancers, complicates the selecting of suitable antibiotics. For instance, co-trimoxazole is commonly associated with myelosuppression, leadingclinicians to hesitate in prescribing it in immunocompromised patients, despite its potential effectiveness. Likewise, co-trimoxazole was the least frequent used drug in the studied patients which added up to other drug combinations in all 5 cases. Furthuremore, specific conditions such as neurological or spinal involvement may necessitate adjustment to the optimum duration of treatment. It is important to note that the recurrence could be relapse (the same microorganism) or reinfection (new infection). In endemic regions and among high-risk patients, reinfection might be possible because socioeconomic, nutritional, and occupational factors often remain unchanged after the initial episode of the disease. Furthermore, it seems that brucellosis does not lead to persistent and effective immunologic resistance in humans. Consequently, it could be difficult to determine the exact nature of cases reported as relapses or reinfections, along with understanding the potential effects of malignancies and treatment issues in this context.

Mortality was reported in 9 cases out of total of 38 cases of brucellosis in cancer patients (23.7%). Among these 9 mortality cases, 7 patients were diagnosed with hematologic malignancies (77.8%). Additionally, hematologic cancers were the most frequent reported in brucellosis cases of this review while these malignancies are not the most prevalent in the general population. This might be due to the potential immunosuppressive state of these malignancies. These results seem to suggest a potential risk of brucellosis in patients with hematologic malignancies, especially those with acute lymphoblastic leukemia. However, it appears that brucellosis may not have been the main cause of death in these cases, as mortality could have largely been due to cancer progression and possibly septic shock associated with immunodeficiency. According to earlier studies, brucellosis appears to have no significant impact on the advancement and emergence of hematologic malignancies in humans[23]. In contrast, research conducted on mice suffering from both brucellosis and acute lymphoblastic leukemia revealed a greater infiltration of splenic tissue by neoplastic cells than that observed in mice with acute lymphoblastic leukemia only[46].

In the immunosuppression condition associated with malignancies, particularly in hematologic malignancies, some opportunistic organisms flare up, causing higher mortality rates and patient care costs, as well as challenges in diagnosingand treating. *Mycobacterium tuberculosis* is an intracellular pathogen that shares similarities with *Brucella*. Research indicates that individuals with hematoligic malignancies face a relative risk of developing tuberculosis that is 2-40 times greater than that in the general population. This underscore the critical importance of early detection and preventive treatment for *Mycobacterium tuberculosis* in patients experiencing immunosuppression related to malignancies[47,48]. Cytomegalovirus is another intracellular pathogen that can remain dormant in the host for a lifetime. Cytomegalovirus can reactivate in the setting of immunodeficiency associated with cancers and is always considered by clinicians as a differential diagnosis in the setting of immunosuppression due to its propensity for reactivation[49,50].

Of note, tuberculosis and cytomegalovirus in contrast to brucellosis, have routine and active screening strategies that could detect cases even in the subclinical state of disease. A high prevalence of infection in a region leads to make it commonplace for clinicians. Therefore, it is expected that physicians, when confronted with that infection-even if it is unusual in a patient- will not report it. This may spotlight the underestimation of brucellosis by clinicians in cancerous individuals even in endemic regions. Further, initial wide-spread empirical antibiotic therapy or antibiotic monotherapy which is commonly administered as prophylaxis or in those with constitutional symptoms in cancerous cases, could potentially lead to resistant forms of *Brucella* species, more severe or unusual forms of organ involvement, subsequent flare-ups, relapse, and recurrence events. Therefore, it could be speculated that the role of brucellosis could be modest compared to other opportunistic agents in neoplasm patients even in endemic regions. Based on our findings, 18.8% (6 cases) of the total 38 patients who had reported status regarding brucellosis experienced relapse/reinfection which is relatively high compared to the average rate of relapse of 5%-15% in recent epidemiological studies[8]. The rarity of the condition and the inclusion of a limited number of cases resulted in a small sample size. Furthermore, as this review incorporated case reports, certain essential data, such as patient follow-up information, were incomplete. Consequently, there is insufficient information to generalize the findings to a broader population. Additional studies are necessary to gain a more comprehensive understanding of the concurrent occurrence of brucellosis and malignancies.

In conclusion, this systematic review study shows that the predominance of constitutional symptoms and the high rate of hematological malignancies among patients underscore the complexity of diagnosing brucellosis in oncological settings. Notably, the study highlights the effectiveness of combination antibiotic therapy, particularly with doxycycline and rifampin, which contributed to a survival rate of 73.6%. Despite the challenges posed by concurrent malignancies, brucellosis may did not emerge as a direct cause of mortality, suggesting that management strategies must prioritize infectious and oncological considerations. These findings emphasize the importance of thorough patient histories regarding dietary habits and prompt diagnostic testing for brucellosis in patients presenting with relevant symptoms, particularly in those with a background of hematologic cancers. Further research is warranted to explore optimal treatment protocols and long-term outcomes for this patients' population.

## Conflict of interest statment

The authors declare that they have no competing interests.

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## Authors' contributions

S.A. and I.A.D. contributed to the conception. M.G., K.M., S.A., and F.I. wrote the original draft. I.A.D., HAN, and H.E. contributed to the manuscript revision and editing. M.G. contributed to the figure conceptualization and designing.

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## Publisher's note



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**Supplementary Table 1.** Quality assessment of the selected articles.

| Author | Year | Demographic characteristics? | History? | Current clinical condition? | Diagnostic tests and assessments? | Intervention and Tx? | Post-intervention? | Adverse events? | Takeaway Lessons? | Sum |
|---|---|---|---|---|---|---|---|---|---|---|
| Muhammed Emin Akkoyunlu | 2013 | No | No | Yes | Yes | Yes | Yes | No | Yes | 5 |
| Khalid Ahmed Al-Anazi (Case 1) | 2007 | No | No | Yes | Yes | Yes | Yes | No | Yes | 4 |
| Khalid Ahmed Al-Anazi (Case 2) | 2007 | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 6 |
| Alaa Khalid Alduraibi | 2019 | No | No | Yes | Yes | No | Yes | Yes | Yes | 5 |
| B. Arda (Case 1) | 2007 | No | No | Yes | No | No | Yes | Yes | Yes | 4 |
| B. Arda (Case 2) | 2007 | No | No | Yes | No | No | Yes | Yes | Yes | 4 |
| Faris G. Bakri | 2009 | No | No | Yes | Yes | No | Yes | No | Yes | 4 |
| Sabri Barutca | 1998 | No | No | Yes | Yes | No | Yes | No | Yes | 4 |
| Ali Bay (Case 1) | 2007 | No | No | Yes | Yes | No | Yes | Yes | Yes | 5 |
| Ali Bay (Case 2) | 2007 | No | No | Yes | Yes | No | Yes | Yes | Yes | 5 |
| Ioanna Charoniti | 2005 | No | No | Yes | Yes | No | Yes | No | Yes | 4 |
| Elvan Caglar Citak | 2010 | No | No | Yes | Yes | No | Yes | Yes | Yes | 5 |
| Fugen Cokca | 2006 | No | No | Yes | Yes | Yes | Yes | No | Yes | 5 |
| Bulent Eser (Case 1) | 2006 | No | No | Yes | Yes | Yes | Yes | No | Yes | 5 |
| Bulent Eser | 2006 | No | No | Yes | Yes | Yes | Yes | No | Yes | 5 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| (Case 2) | | | | | | | | | | |
| Tuba Kasap | 2016 | No | No | Yes | Yes | No | Yes | No | Yes | 4 |
| Jun-Jie Li | 2011 | No | No | Yes | Yes | No | Yes | No | Yes | 4 |
| Gokhan Metan | 2005 | No | No | Yes | Yes | No | Yes | No | Yes | 4 |
| Erik Oksenhendler | 1988 | No | No | Yes | Yes | No | Yes | No | Yes | 4 |
| Demircan Ozbalci | 2011 | No | No | Yes | Yes | Yes | Yes | Yes | Yes | 6 |
| Figen O¨zc¸ay | 2000 | Yes | No | Yes | Yes | No | Yes | No | Yes | 5 |
| R. SARI | 2002 | No | No | Yes | Yes | Yes | Yes | No | Yes | 5 |
| Soner Solmaz | 2014 | No | No | Yes | Yes | No | Yes | Yes | Yes | 5 |
| A. von Graevenitz (Case 1) | 1990 | No | No | Yes | Yes | Yes | No | No | Yes | 4 |
| A. von Graevenitz (Case 2s) | 1990 | No | No | Yes | Yes | Yes | No | No | Yes | 4 |
| J. MONTE | 1986 | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 7 |
| A. Meneses | 2009 | No | No | Yes | Yes | Yes | Yes | No | Yes | 5 |
| Mehmet Hilmi Dogu | 2016 | No | No | Yes | Yes | No | Yes | unclear | Yes | 4 |
| Yasser mohamed abdolreuf ibrahim | 2007 | Yes | No | Yes | Yes | Yes | Yes | No | Yes | 6 |
| Stefania Cocchi | 2010 | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 7 |

Search strategy in databases:

1. **Embase:** (results in 1653 articles)

(‘brucellosis:ti’:ti,ab,kw OR ‘brucella’:ti,ab,kw OR 'brucellosis'/exp OR 'brucella'/exp) AND (‘neoplasm*’:ti,ab,kw OR ‘cancer*’:ti,ab,kw OR ‘malignancy*’:ti,ab,kw OR ‘chemotherapy*’:ti,ab,kw OR 'neoplasm'/exp OR 'malignant neoplasm'/exp)

2. **WOS:** (results in 157 articles)

(((TI=(brucellosis)) OR TI=(brucella)) OR (AB=(brucellosis)) OR AB=(brucella)) AND (((((((TI=(malignancy)) OR TI=(neoplasm)) OR TI=(cancer)) OR TI=(chemotherapy)) OR (AB=(malignancy)) OR AB=(neoplasm)) OR AB=(cancer)) OR AB=(chemotherapy))

3. **Scopus:** (results in 813 articles)

(TITLE-ABS-KEY ( brucellosis ) OR TITLE-ABS-KEY ( brucella )) AND (TITLE-ABS-KEY ( neoplasm* ) OR TITLE-ABS-KEY ( cancer* ) OR TITLE-ABS-KEY ( malignancy ) OR TITLE-ABS-KEY ( chemotherapy ))

4. **Pubmed:** (results in 396 articles)

((((brucellosis[Title/Abstract]) OR (brucellosis[MeSH Terms])) OR (brucella[MeSH Terms])) OR (brucella[Title/Abstract])) AND (((((cancer[Title/Abstract]) OR (Neoplasms[Title/Abstract])) OR (Neoplasms[MeSH Terms])) OR (malignancy[Title/Abstract])) OR (chemotherapy[Title/Abstract]))