Brucellosis in Patients with Neoplasm; A Research Article

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Abstract

Background: Brucellosis is an important zoonotic disease with numerous manifestations. The immune response induced by Brucella differs from those caused by other intracellular bacteria. To the best of our knowledge, the behavior of Brucella in patients with different cancers has not been reviewed. The present study aimed to evaluate brucellosis in this group of patients.

Methods: All cases of brucellosis in patients with neoplastic disorders were searched in PubMed, Google Scholar, Scopus, and Web of Science and retrieved from the relevant articles. The search was performed without time, language and age limitations and using keywords such as brucellosis, Brucella, cancer, neoplasm, malignancy, and chemotherapy. All clinical features, types of neoplasm, diagnoses, and treatment timings of neoplasms and brucellosis, as well as patient outcomes, were searched.

Results: Thirty-two eligible cases were extracted from 28 articles. The patients had a broad age range. Constitutional symptoms and febrile neutropenia were the most common clinical features. Hematological malignancies constituted the underlying disease in 16 patients. Brucellosis was detected in the majority of cases after diagnosis of cancers. *Brucella melitensis* was reported as the most frequent isolate. Moreover, positive blood culture was observed in 21 patients and 22 of whom were cured.

Conclusions: Patients with malignancies may present with atypical symptoms of brucellosis, which is a rare condition even in endemic countries, and clinicians should be aware of its potential effects in the cancer treatment. Brucellosis should be considered in the differential diagnosis of febrile neutropenia and patients with cancer, particularly in endemic countries.

Background

Brucellosis, the most common zoonotic infection worldwide [1], affects either healthy or immunocompromised hosts in endemic areas like Mediterranean countries, the Middle East, Eastern Europe, and continental America [2]. Although the occurrence of this infection is common in the world, only a small percentage of patients are diagnosed and reported annually [3]. The main transmission routes of brucellosis include direct contact with infected animals and ingesting unpasteurized dairy products such as milk, cheese, and ice cream. Despite the global decrease in the transmission through these routes, laboratory-acquired brucellosis came forward as a cause of concern in developed countries [4, 5].

Brucellosis can cause a broad spectrum of clinical manifestations associated with multi-organ involvement in the human body [6, 7]. Moreover, brucellosis can cause atypical manifestations in patients with neoplasms owing to their abnormal cellular and humoral immunity, neutrophil dysfunction, and neutrophilia or neutropenia [8].

This review was performed to analyze manifestations, duration of symptoms, transmission routes, and diagnostic tests of brucellosis as well as outcomes of patients with neoplasms.

Methods

Brucellosis patients with neoplastic disorders were searched in PubMed, Google Scholar, Scopus, and Web of Science databases and retrieved without time, language and age limitations. About 900 articles found until November 2019 with keywords that were relevant to aims of our study. The keywords included brucellosis, Brucella, cancer, neoplasm, malignancy, and chemotherapy. Two articles were about brucellosis as cause of cancer so was not eligible of our study. One review article was about molecular and genetic aspect of brucellosis in cancer patients. One review article has important information's about clinical aspects of brucellosis in 5 patients with hematological cancer.

All cases of this study checked about repetitive cases in other articles and duplicated cases deleted from study. In one study brucellosis was 10 years before cancer so in order to significant distance between brucellosis and cancer, deleted from our study. Finally twenty-eight articles founded eligible of our study. All of the clinical features, types of neoplasms, diagnoses, and treatment timing of patients with neoplasms and brucellosis along with patient outcomes were evaluated of each case in this review and classified.

Results

Flow chart of study selection for inclusion in this systematic review study summarized as Fig. 1.

Thirty-two cases with a mean age of 40.9 ± 22.5 years were retrieved from 28 articles. Fifteen patients were males, 14 females, and 3 patients undefined. Table 1 presents the origin of the patients.

Table 1

Country	Number of patients
Turkey	18
Saudi Arabia	4
France	2
Spain	1
China	1
Jordan	1
Portugal	1
Greece	1
Japan	1
The Caucasus	1
Kuwait	1

• Geographic distribution of the patients

Blood culture was performed as the main diagnostic modality in the patients. Nine patients died of conditions such as septic shock and progressive neoplasms, 22 survived and one excluded from follow-ups. The most prevalent neoplasms with coexistent Brucellosis were hematological malignancies (50%). Table 2 summarizes the details of cancer types in patients. *Brucella melitensis* was recovered as the most prevalent species in 23 cases as it causes the most invasive and severe brucellosis infection in the world [9].

Table 2

Organ	Number of patients
Hematologic	16
Gastrointestinal	4
Lymphoproliferative	3
Urogenital	2
Musculoskeletal	1
Salivary gland	1
Lung	1
Thyroid	1
Brain	1
Breast	1
Ovary	1

• Organs affected by neoplasms in the patients

An obvious history of consuming unpasteurized dairy products was reported in only 25% of the patients. Moreover, 18% of the patients were farmers or those who lived in rural areas, two were working as a technician in laboratories that two outbreak of brucellosis were recently reported in one of these laboratories [6, 9]. One patient had a 15-year history of chronic and recurrent brucellosis [10]. The transmission routes of brucellosis were therefore identified and reported in only a few patients. Although assessing the history of the transmission routes of brucellosis is necessary, it may be unreliable [11]. Thus, diagnostic tests should be performed to rule out brucellosis in patients with clinically-suspected brucellosis even without a history of the condition, particularly in the endemic areas.

According to Fig. 2, the patients presented with different complaints. Broad-range symptoms and multi-organ involvement mimicking many diseases make the diagnosis of brucellosis difficult [12–14]. The most prevalent complaints of the patients included constitutional symptoms such as fever and neutropenia, which were associated with the highest mortality. Interestingly, a completely-asymptomatic patient was diagnosed through the follow-up computed tomography (CT) scan after cancer treatment [15].

Febrile Neutropenia

Although febrile neutropenia has rarely been reported in brucellosis patients so far, presentation of brucellosis in 31.25% of patients was febrile neutropenia in this study. Three patients had acute

lymphoblastic leukemia, two had acute myeloblastic leukemia, and two had gastric cancer and the others had breast cancer, non-Hodgkin Lymphoma and B cell lymphoma. Brucellosis developed after a cancer diagnosis in 90% of the patients and caused a challenging treatment of their neoplasms. Brucellosis and malignancy were concurrently diagnosed in one patient [16]. All the patients presenting with febrile neutropenia came from Turkey as an endemic area with proper diagnostic infrastructure. Brucellosis was diagnosed within 14 days after the emergence of its symptoms in patients with febrile neutropenia. Diagnosis was performed based on positive blood cultures in about 90% of patients and based on bone marrow cultures and the tube agglutination test in one patient. About 40% of patients were treated with doxycycline and rifampin, 30% with streptomycin, doxycycline and TMP-SMZ, 10% with TMP-SMZ and rifampin and 10% with ciprofloxacin, doxycycline, and rifampin. A delayed diagnosis possibly coupled with pulmonary embolism caused the death of one patient before initiating Brucellosis treatment [12]. one patient died due to septic shock despite receiving anti-Brucella medications [17] and two died probably of progressive neoplasms [1, 12].

Blood culture as the commonly-used standard diagnostic test was reported positive in about 65.6% of the patients. Highly-available serological tests, including the serum tube agglutination test, were preferred in clinical practice since the recovery of the pathogen in the cultures takes time. Researchers claimed that given the low sensitivity of agglutination tests in endemic areas, these tests might be insufficient in screening brucellosis patients with febrile neutropenia. They suggested applying the PCR as an alternative for diagnosis [18]. However, data are lacking regarding the standardization of PCR.

Brucellosis was detected after cancer diagnosis in the majority of the patients and of those who died when cancer and brucellosis were concurrently diagnosed in 37.5%. In patients with neoplasms, infections were major causes of morbidity and mortality and the risk of infection is related to the intensity and duration of immunosuppressive or cytotoxic treatments [10]. Brucellosis detected after the diagnosis of malignancies reveals high mortality in these patients, either due to brucellosis or underlying diseases, which confirms the need for more meticulous care in managing infections in these patients. The manifestation time of brucellosis compared to the time of receiving chemotherapeutics in the patients is a prominent finding (Table 3).

Table 3

Number	Timing of Brucellosis diagnosis (in patients brucellosis detected after cancer diagnosis)
1	Before initiating remission-induction chemotherapy
2	Five months after the treatment completion
3	On the 56th day of chemotherapy
4	During the second course of remission-induction chemotherapy
5	Not mentioned
6	Not mentioned
7	Four months after receiving two chemotherapy regimens
8	Five days after receiving two chemotherapy regimens
9	Eight days after receiving two chemotherapy regimens
10	Before initiating chemotherapy
11	After achieving the third complete remission (5 years after diagnosing acute lymphoblastic leukemia)
12	After chemotherapy
13	After the first course of chemotherapy
14	After the first course of chemotherapy
15	After the first course of chemotherapy

• Time of diagnosing brucellosis (in all the patients with brucellosis emerging after cancer diagnosis)

Doxycycline, rifampin, and Trimethoprim-Sulfamethoxazole were the most commonly used antibiotics (used for the treatment of 65.6%, 59.3%, and 21.8% of the patients, respectively). Streptomycin, ciprofloxacin, and tetracycline were also used in 25%, 15.6%, and 15.6% of patients, respectively. Doxycycline and rifampin were, however, the most commonly used medication regimens in both treated patients and those who died.

Despite extensive studies, the best antibiotic treatment for brucellosis needs to be clarified [3]. But the current evolving data stresses the importance of aminoglycoside based regimens. The course of antimicrobial treatment of Brucellosis can be problematic, owing to its high recurrence rates [19]. Although there are controversies in the treatment of Brucellosis, early diagnosis and treatment significantly affect the prognosis. Neoplastic diseases were treated using various chemotherapy regimens and surgical methods. Comparing treatments between different patients is difficult due to variations in the type and stage of their underlying diseases.

Any interfering factors such as complications related to cancer medications and infections impose serious risks on these patients for improving prognosis. Paying special attention to opportunistic infections and endemic diseases in patients receiving chemotherapy regimens may reduce mortality [8].

Mortality

Death was reported in 9 patients. The crude mortality rate does not necessarily reveal the virulence of the disease and it could be due to underestimation of confirmed cases in other countries. Figure 3 shows the clinical presentation of the patients who died. Hematologic malignancies were the most prevalent neoplastic disease in these patients (66.6%). Lymphoproliferative malignancies were observed in two of these patients and Ewing's sarcoma in one. Given *Brucella melitensis* as the most prevalent Brucella species in most of the patients died (55.5%) and the type of Brucella appears useless in the prognosis of cancer in all studied patients [6]. The patients' manifestations were also different.

The detection of brucellosis after cancer diagnosis in five (55.5%) patients suggests that brucellosis in the presence of neoplastic diseases or during the course of chemotherapy can play a key role in patients' outcomes. Delayed Brucellosis diagnosis and treatment in patients with neoplasms may result in poor outcomes. Contracting brucellosis before the initiation of any neoplastic treatment deemed not significantly affect cancer prognosis.

Exploring the main cause of death in these patients showed that not only the type of neoplasm but also diagnostic methods, the timings of diagnosis, treatment, and complication management significantly affected the outcome; for instance, an 11-year-old female patient presenting with fever, sweating, and low back pain was diagnosed with and treated for brucellosis. She underwent more investigations given her lack of improvement and development of neurological symptoms. On the 22nd day of the treatment, she was ultimately diagnosed with Ewing's sarcoma. Despite undergoing pharmacological treatments and surgery, her paraplegia persisted and the patient died owing to peri-sacral decubitus ulcers. MRI of the thoracolumbar spine on the 22nd day of treatment showed Ewing's sarcoma. Although the patient ultimately underwent surgery, paraplegia persisted, peri-sacral decubitus ulcers developed and she died of the infection [20]. Further studies are recommended to be conducted on diagnosing comorbid diseases.

Septic shock was the cause of death in (6.25%) two patients that differential diagnostic tests for microorganisms other than Brucella were negative. But in this articles did not mentioned obviously weather the septic shock caused by brucellosis. One of them was a 46-year-old male with hepatosplenomegaly and pancytopenia from a village in Algeria. Hairy cell leukemia was diagnosed and Brucella grew on bone marrow culture. Doxycycline and rifampin were prescribed and mechanical ventilation was initiated for progressive pneumonia. Splenectomy was performed and the patient died of septic shock 10 days later [17, 21].

In conclusion, accurate managing of complications for underlying diseases and treatments is essential in improving patient prognosis. Researches were done on anti-tumor effects of the Brucella species and

Brucella vaccines, but have not resulted in compelling evidence for their effects [20]. Clarifying the potential interactions between cytotoxic and antimicrobial drugs used in brucellosis is crucial for determining the need for delaying the initiation of chemotherapy in patients with brucellosis [22].

Discussion

The surprisingly-low prevalence of brucellosis observed in cancer patients, even in endemic countries, can be explained by the lack of diagnostic facilities, misdiagnosis, failure to report the cases and early death caused by underling diseases before performing diagnostic tests for brucellosis. Given non-specific manifestations of brucellosis in non-endemic countries, practitioners may be unfamiliar with and misdiagnose the disease [23]. In endemic regions, patients with atypical manifestations such as neurological symptoms should be assessed for brucellosis [24].

In non-endemic areas where brucellosis is uncommon, almost all cases are reported; in endemic areas with a high prevalence of brucellosis, it is possible that the clinicians under-report their cases even in immunocompromised patients [3].

The low prevalence of brucellosis in patients with malignancies can be explained by globally providing these patients with special care and paying special attention to their nutrition, occupation and other health factors.

In many patients with neoplasms, medications such as aminoglycosides, anti-pseudomonal beta-lactam prescribed following the onset of fever can partially affect Brucella spp. or disrupt diagnostic tests for brucellosis [25]. Although hematologic malignancies are not a common cancer worldwide, brucellosis was most commonly observed in patients with this type of neoplasms. The incidence of brucellosis is also low in lung and breast cancers as the most common neoplasms worldwide. The occurrence of brucellosis, therefore, appears not to definitely relate to the prevalence of neoplasms. Different causes such as the stage of neoplasm, severity of disease, treatment modalities, and medication type can affect patient prognosis, and brucellosis appears to be related to increased mortality in patients with hematologic cancer.

Given its broad spectrum of clinical manifestation, brucellosis can be considered in the differential diagnosis of many diseases, including neoplasms. In endemic countries, attention should be paid to life-threatening diseases, mimicking brucellosis. In case of persistent symptoms of brucellosis after antimicrobial treatment, other comorbidities that mimic the symptoms should be evaluated [26–28], including other endemic infections e.g., tuberculosis or non-infectious conditions e.g., lymphoproliferative diseases.

Taking history about the transmission routes of brucellosis appears necessary though unreliable, as only a few study patients had a history of consuming non-pasteurized dairy products or other transmission routes of the disease. Therefore, diagnostic tests should be performed to rule out brucellosis in patients with clinically-suspected brucellosis even without a history of the condition, particularly in endemic areas.

Brucellosis is a rare cause of febrile neutropenia as a serious problem in patients with neoplastic disorders [3, 12]. As the etiology of febrile neutropenia, infections are mainly bacterial in cancer patients. Febrile neutropenia was reported to disappear after treating the brucellosis patient [29]. The slow growth of Brucella in blood cultures and the late-emerging manifestations of Brucellosis prevent the disease from being diagnosed at the early stages of febrile neutropenia and may cause the treatment failure of empiric antibiotics [3]. Therefore, Brucellosis is considered in the differential diagnosis of febrile neutropenia, especially in endemic countries [8, 18]

Blood culture is a standard diagnostic test for Brucellosis [30], and no cases were found with a positive blood culture and negative serological test. No evidence was also found for the effect of malignancies and antineoplastic agents on specific antibody levels and specific serological test results.

Conclusions

Despite being uncommon in patients with neoplastic disorders, brucellosis can cause challenges in their treatment. Timely diagnosis of infections and selecting the best antibiotics for treatment are major concerns in these patients. Brucellosis can have different manifestations and early diagnosis and treatment can reduce its mortality and morbidity. Given its potential atypical symptoms in patients with neoplasms, brucellosis should be discriminated from many other complaints in these patients, especially in endemic areas.

Abbreviations

PCR
polymerase chain reaction, TMP-SMZ:Trimethoprim/sulfamethoxazole

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data generated or analyzed during this study are included in published articles are mentioned in references

Competing interests

All the authors declare that they have no competing interests

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Authors' contributions

F.I: analysis, interpretation of data, drafted the work

M.R: analysis, interpretation of data

Sh.Sh: design of the work, acquisition

H.E: have drafted the work or substantively revised it

I.A: design of the work, conception, the acquisition, drafted the work,

All authors have read and approved the manuscript

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Figures

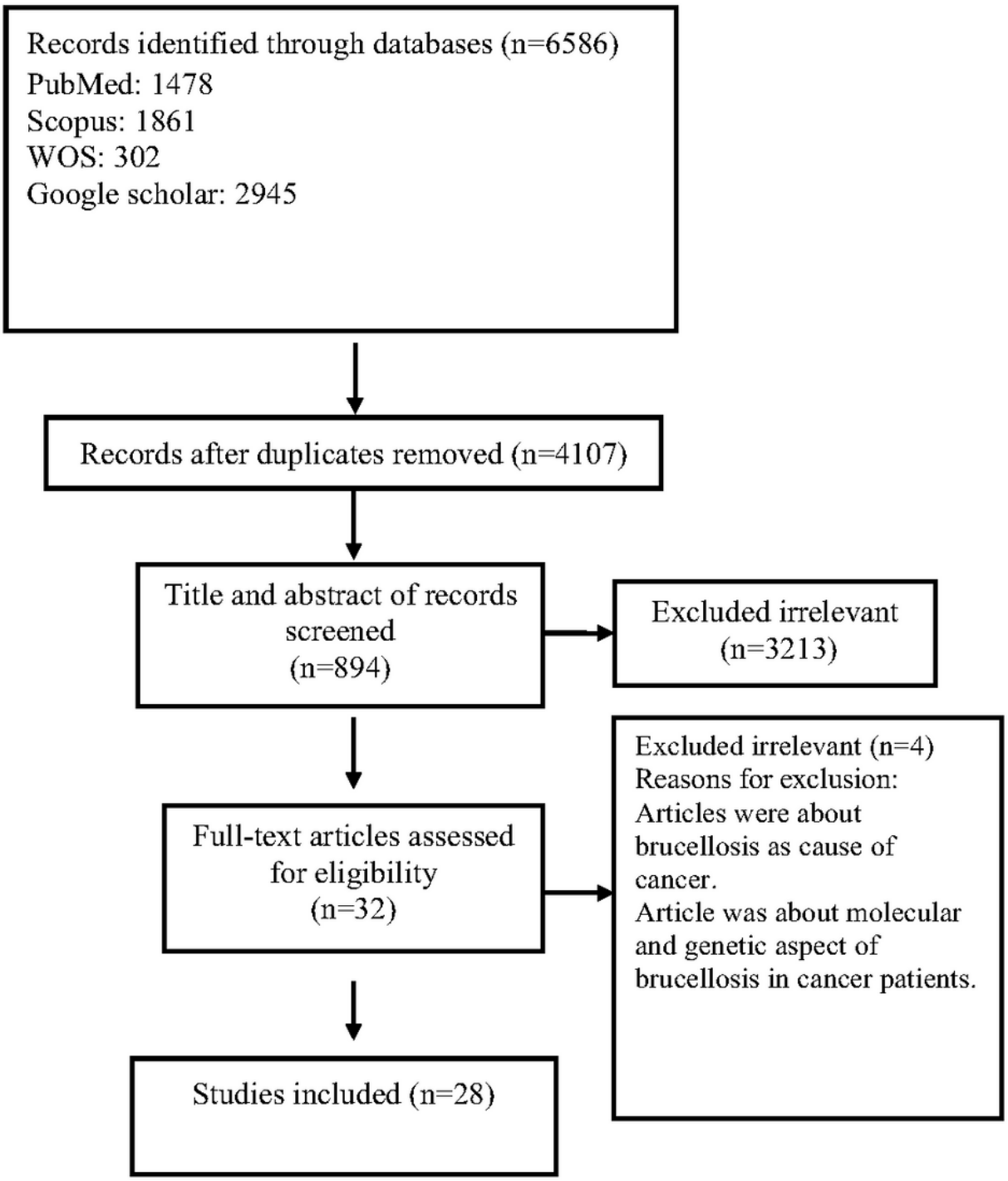

Figure 1

Flow chart of study selection for inclusion in this systematic review study summarized as

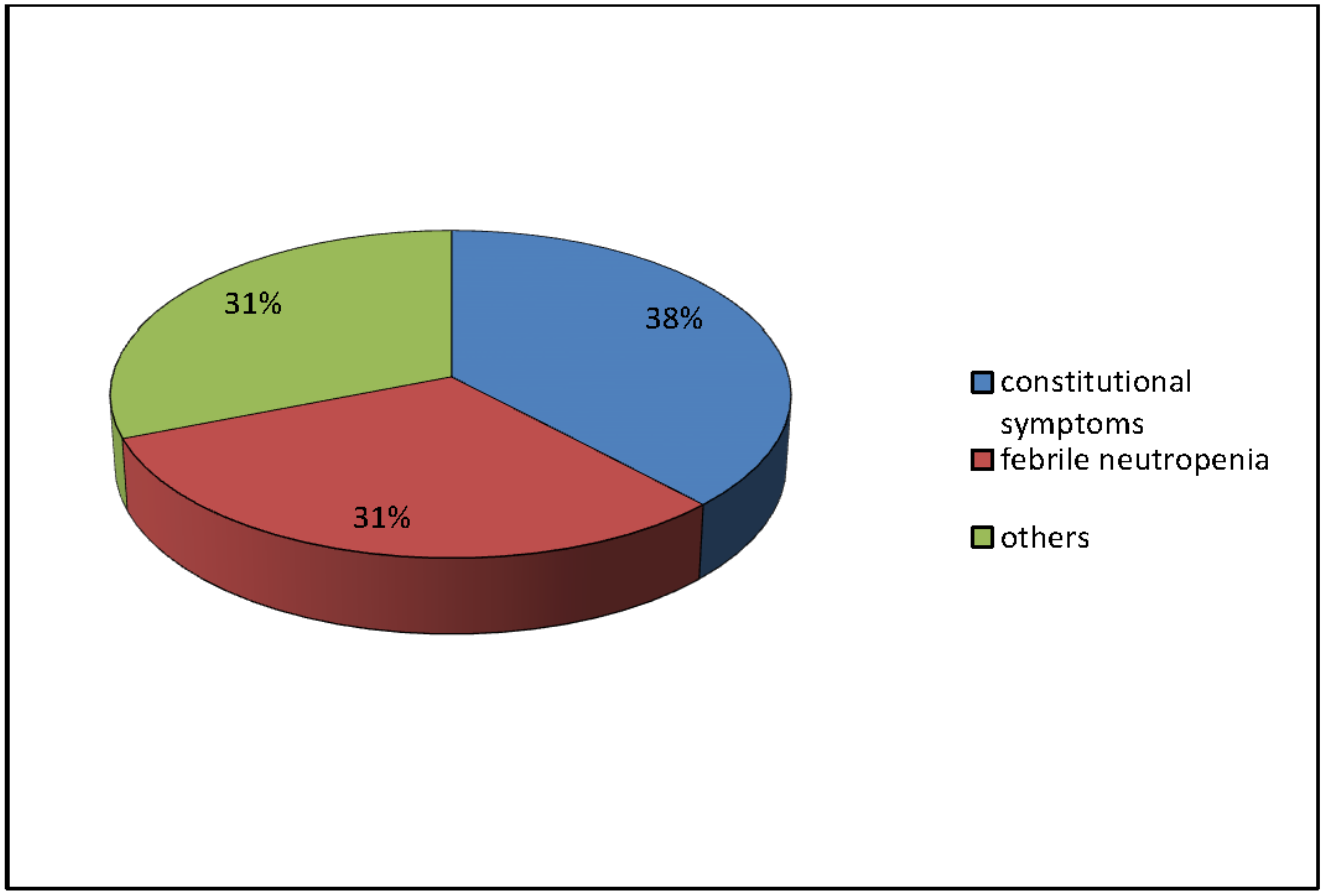

Figure 2

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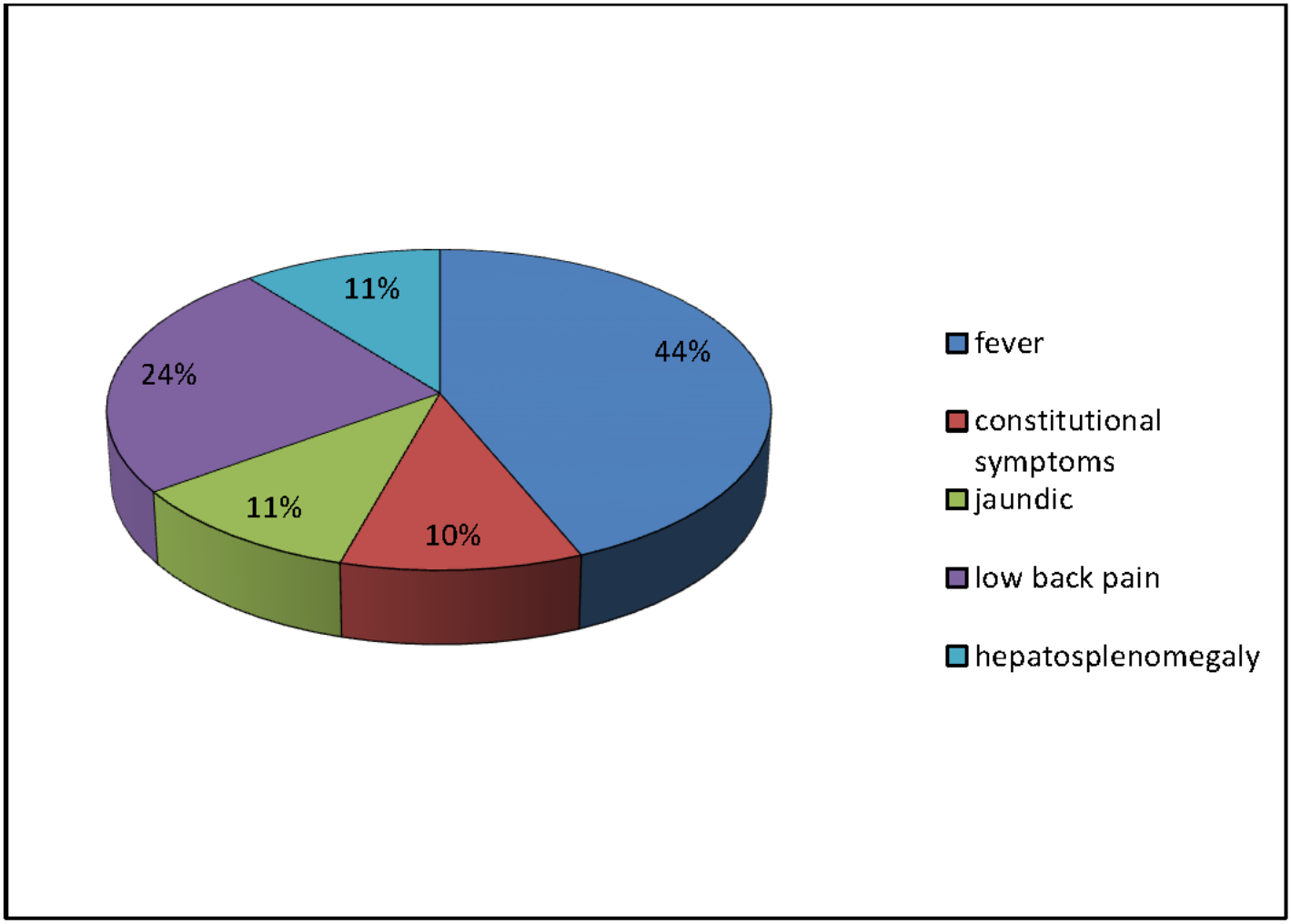

Figure 3

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