

# Incidence of Febrile Neutropenia in Neutropenic Cancer Patients Admitted to Oncology Ward of Shahid Ghazi Tabatabai Hospital in Tabriz, Iran, During 2018 - 2020

Loghman Ghaderi<sup>1</sup>, Ali Reza Naseri<sup>2,\*</sup>

<sup>1</sup>Surgery Group, Kordestan University of Medical Sciences, Kordestan, Iran (ORCID: 0000-0002-0823-830X)

<sup>2</sup>Tuberculosis and Lung Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran (ORCID: 0000-0001-9714-2379)

\*Corresponding Author: Ali Reza Naseri, Tuberculosis and Lung Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran. Email: dr\_dr\_tabriz@yahoo.com

Received 2020 November 01; Accepted 2020 December 20.

## Abstract

**Background:** Chemotherapy-induced neutropenia is one of the risk factors for infection in patients undergoing chemotherapy (due to the weakened immune system). Febrile neutropenia (FN) may be the sole indicator of an underlying infection in these patients.

**Objectives:** Since infection is associated with an increased risk of mortality in patients undergoing chemotherapy, the present study aimed to assess the incidence of FN in neutropenic cancer patients admitted to an oncology ward.

**Methods:** This retrospective, descriptive, and cross-sectional study was conducted on 52 patients (selected using the census method) with signs of infection (i.e., FN) hospitalized in Ghazi Tabatabai Hospital in Tabriz, Iran, within 2018 - 2020. The data were collected by a researcher-made form and analyzed using descriptive statistics (e.g., frequency, percentage, and mean) and chi-square in SPSS software (version 20). The significance level was considered less than 0.05.

**Results:** The absolute neutrophil count was less than 500 cells/ml in 15.38% of the patients (n = 8). Infection was the cause of FN in 69.23% of the subjects (n = 36). An unknown factor was the cause of infection in 30.77% of the cases. The incidence of all types of infections (i.e., perianal abscess, sepsis, oral infection, cutaneous infection, gastrointestinal infection, pharyngitis, pneumonia, and urinary tract infection) was higher in patients undergoing chemotherapy than that reported for those not receiving chemotherapy.

**Conclusions:** The results of this study suggested that cancer patients undergoing chemotherapy should be aware of infection signs; accordingly, they can visit treatment centers in case of the first symptoms of infection to prevent progression of infection and reduce mortality rates.

**Keywords:** Fever; Chemotherapy; Cancer; Neutropenia; Infection

## 1. Background

Infection is one of the leading causes of death in neutropenic patients. The statistics have shown an increased risk of mortality in patients with severe neutropenia by 40% if not efficiently treated. However, timely treatment reduces both complications and mortality rates (1, 2). Febrile neutropenia (FN) is one of the most common complications and important causes of hospitalization in patients with immunodeficiency and those receiving immunosuppressive therapy. Studies have shown the incidence of FN in 10% - 50% of patients with solid tumors and 80% of patients with leukemia. The FN is associated with a 7-12-day duration of therapy, 1,500\$ cost of treatment, and increased mortality rate (3).

Malignancies and connective tissue diseases might also cause fever, although fever is the sole indicator of infec-

tion, especially in neutropenic patients. The FN is defined as a single axillary temperature equal to or greater than 38.5°C for more than 1 h or three measurements of axillary temperature equal to or greater than 38°C for 24 h. A fever of unknown origin (FUO) in neutropenic patients is defined as a temperature greater than 38.3°C for more than 3 weeks with an unknown cause even after three-day hospitalization or three outpatient visits (4).

Peripheral blood absolute neutrophil counts (ANC) in different societies and black people residing in the Middle East were  $5.2 \times 10^9/L$  and  $5.1 \times 10^9/L$ , respectively. Neutropenia is defined as the ANC of 500 cells/mL or less than 1,000 cells/mL with an anticipated decline to less than 500 cells/mL. Patients with an ANC of less than  $5.0 \times 10^9/L$  or 500 cells/ $\mu L$  might be susceptible to recurrent in-



fections. The risk of infections might be higher in case of ANC of less than  $2.0 \times 10^9/L$ . The risk of acquired infection progressively increases with half-life and low numbers of circulating neutrophils (5).

Although the physical signs and symptoms of infection are no longer decipherable in patients with a weakened immune system (neutropenia), vital signs (especially body temperature) still play a crucial role in the diagnosis of infection. Researchers claimed that a blood culture is the most widely diagnostic tool for the assessment of fever in microbiology (6). A blood culture specifies the causes of fever in 10% - 40% of the cases. Since neutropenic patients are abnormally susceptible to bacterial infection, antibiotics should be administered in case of suspected infection to combat the pathogen.

Therefore, early treatment regimens are used to fight the pathogens that are the most possible causes of bacterial infection in these patients (7). This issue triggered several studies for the determination of the causes of fever in these patients to identify the common sites and causes of infection in neutropenic patients to adopt preventive and prophylactic measures for the timely treatment of infection as well as reduction of risk factors, complications, and mortality rates in these patients. Therefore, the present study aimed to assess the incidence of FN in neutropenic patients with breast cancer admitted to the Oncology Ward of Shahid Ghazi Tabatabai Hospital in Tabriz, Iran, within 2018-2020.

## 2. Objectives

Since the epidemiology of diseases allows making practical clinical decisions, the epidemiological model varies in different regions, and no study has addressed this issue in the aforementioned region.

## 3. Methods

### 3.1. Study Design

This retrospective, descriptive, and cross-sectional study was conducted on 52 neutropenic patients who developed FN admitted to Shahid Ghazi Tabatabai Hospital (affiliated to Tabriz University of Medical Sciences) from early 2018 to late 2020. The inclusion criteria were the development of FN ( $ANC < 0.5 \times 10^9/L$  or  $ANC < 500$  cells/ $\mu L$ ). The exclusion criteria were incomplete medical records and a history of infectious diseases in the past 3 months. The census method was used for the selection of the samples, and all the patients were included in the study in this period.

In this study, the records of all hospitalized patients with FN were examined to extract the necessary information, including age, gender, type of malignant disease (i.e., hematological or non-hematological), history of chemotherapy, history of splenectomy, presence

of a central venous catheter, site of infection based on physical examination (e.g., oral lesions, cutaneous lesions, gastrointestinal infections, urinary tract infections, and pneumonia), positive cultures (i.e., urinary, blood, and esophageal), type of isolated microorganism (i.e., fungus, Gram-negative bacteria, and Gram-positive bacteria), and ANC. The data were recorded in a checklist. Culture results were not included in some medical records, which were excluded from the study. The limitations of the study consisted of the technical issues, such as culture medium and impossibility of determination of other possible causes of infection (e.g., anaerobes and viruses). The data were collected through field notes and a checklist (i.e., an instrument designed by the researcher with respect to objectives of the study, with approved content validity).

### 3.2. Ethical Considerations

The researcher tried to respect all ethical considerations. The project was authorized by the Ethics Committee of Tabriz University of Medical Sciences (code: IR.TBZMED.REC.1397.598). Data confidentiality was respected in this study, and the collected data were not misused. Necessary arrangements were made with the authorities of Shahid Ghazi Tabatabai Hospital.

### 3.3. Data Analysis

The data were analyzed using SPSS software (version 20) following data collection and coding. Descriptive (i.e., frequency, percentage, mean, and range) and inferential statistics (i.e., chi-square) were used to analyze the data. The significance level was considered less than 0.05.

## 4. Results

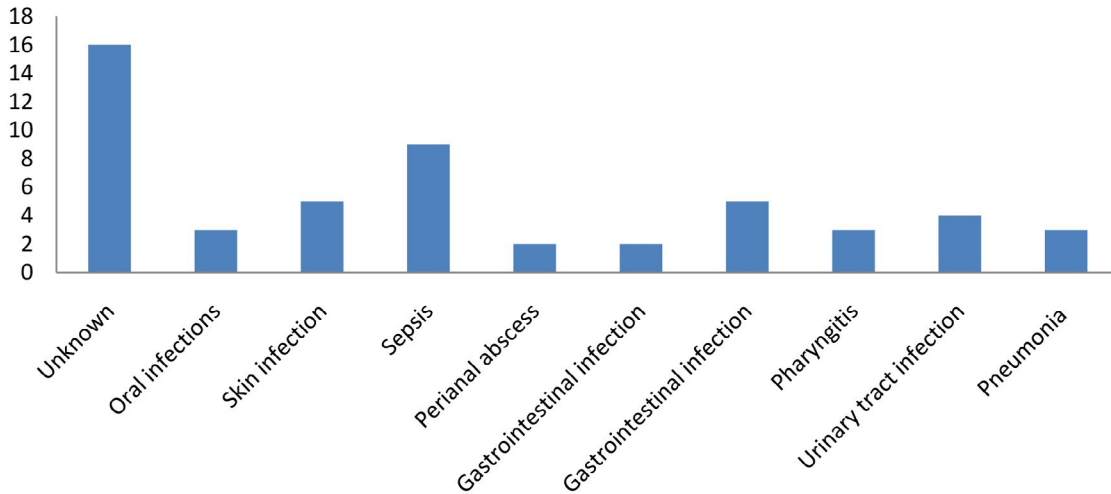
In this study, 21 patients (40.38%) were male, and the rest were female. The mean age of the participants was  $51.83 \pm 17.06$  years. The mean age values of male and female patients were  $63.36 \pm 15.86$  and  $44.24 \pm 13.26$  years, respectively. Most of the subjects were within the age ranges of 51 - 60 ( $n = 14$ ; 26.92%) and 41 - 50 ( $n = 12$ ; 23.07%). Hematologic malignancies (e.g., acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, and chronic myeloid leukemia) accounted for 61.53% of the patients ( $n = 32$ ). Furthermore, non-hematologic malignancies (e.g., gastric, colon, lung, breast, ovarian, esophageal, pancreatic, and rectal cancers in addition to lymphoma and multiple myeloma) accounted for 38.47% of the patients ( $n = 20$ ).

In this study, 17 women (54.38%) and 15 men (71.42%) developed hematological malignancies. Additionally, 6 women (28.57%) and 11 men (35.48%) developed non-hematological malignancies. The mean age values of the patients with hematologic and non-hematologic

malignancies were  $35.5 \pm 13.6$  and  $45.5 \pm 11.26$  years, respectively. In the present study, 78.84% of the patients (n = 41) had a history of chemotherapy, and 21.15% of the patients (n = 11) underwent chemotherapy for the first time. In addition, 9 cases (17.30%) had a history of splenectomy. Only 2 participants (2.84%) had a central

venous catheter. The ANC was less than 500 cells/mL in 15.38% of the subjects (n = 8).

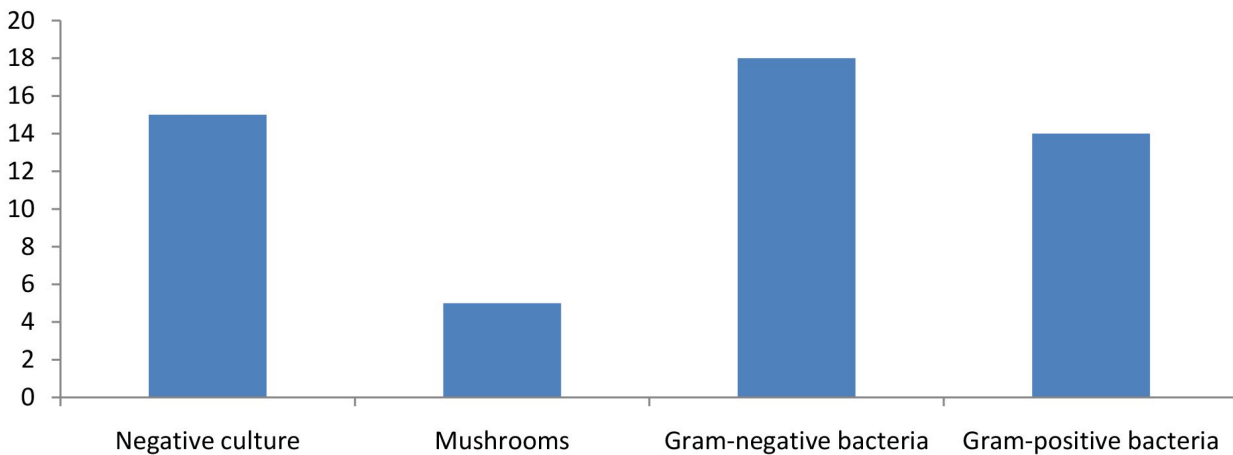
Paraclinical findings and physical examinations revealed that infection was the cause of fever in 69.23% of the cases (n = 36); however, FUO was the cause of fever in 30.77% of the patients (Figure 1).



**Figure 1.** Prevalence of infection in studied patients

All types of infections (i.e., perianal abscess, sepsis, oral infection, cutaneous infection, gastrointestinal infection, pharyngitis, pneumonia, and urinary tract infection) were more prevalent in the group with a history of chemotherapy than those reported for the group undergoing chemotherapy for the first time or with no history of chemotherapy; in this regard, the difference was statistically significant. Negative cul-

ture results were observed in 15 patients (28.84%) and positive culture results in the rest (Figure 2). Culture results showed that *Escherichia coli* (n = 11; 29.72%), *Streptococcus* (n = 9; 24.32%), *Staphylococcus aureus* (n = 7; 18.91%), *Klebsiella* (n = 3; 18.91%), and *Candida albicans* (n = 3; 08.10%) were the most frequent causes of infection.



**Figure 2.** Assessment of culture results in studied patients

Table 1 shows the causes of fever according to gender, type of underlying disease, and history of chemotherapy in the studied patients. The urinary tract in-

fections were more prevalent in women than those in men, with a statistically significant difference.

**Table 1.** Distribution and Frequency of Febrile Neutropenia in Neutropenic Patients

Type of Infection	Gender		P-Value	Type of Malignancy		P-Value	Chemotherapy		P-Value
	Male, No. (%)	Female, No. (%)		Hematological, No. (%)	Non-Hematological, No. (%)		Yes, No. (%)	No, No. (%)s	
<b>Unknown</b>	6 (37.5)	10 (62.50)	0.054	12 (75)	4 (25)	0.003	10 (62.50)	6 (37.50)	0.112
<b>Perianal abscess</b>	1 (50)	1 (50)	0.999	2 (100)	0 (0)	0.001	2 (100)	0 (0)	0.001
<b>Oral infection</b>	1 (33.33)	2 (66.66)	0.032	2 (66.66)	1 (33.33)	0.018	3 (30.76)	0 (30.76)	0.001
<b>Sepsis</b>	3 (33.33)	6 (66.66)	0.999	7 (77.78)	2 (22.22)	0.039	7 (77.78)	2 (22.22)	0.039
<b>Skin infection</b>	2 (40)	3 (60)	0.0198	4 (80)	1 (20)	0.008	5 (100)	0 (0)	0.001
<b>Gastrointestinal infection</b>	1 (50)	1 (50)	0.999	1 (50)	1 (50)	0.999	1 (50)	1 (50)	0.999
<b>Pharyngitis</b>	1 (33.33)	2 (66.66)	0.042	2 (66.66)	1 (33.33)	0.114	3 (30.76)	3 (30.76)	0.001
<b>Pneumonia</b>	1 (33.33)	2 (66.66)	0.039	3 (100)	0 (30.76)	0.001	3 (100)	3 (30.76)	0.001
<b>Urinary tract infection</b>	1 (25)	3 (75)	0.015	3 (75)	1 (75)	0.014	3 (75)	3 (75)	0.014

## 5. Discussion

The current study aimed to assess the incidence of FN in neutropenic patients with breast cancer admitted to the Oncology Ward of Shahid Ghazi Tabatabai Hospital in Tabriz within 2018 - 2020. Infections and coagulations are currently the most common problems of cancer patients during treatment. The use of cytotoxic and immunosuppressive drugs reduces the number of white blood cells, mainly neutrophils, and makes the patients vulnerable to infections caused by infectious and opportunistic organisms. The microorganisms responsible for infection could be identified in one-third of FN cases (8).

Although physicians have always tried to reduce symptoms and complications since the onset of the first symptoms or even before the onset of symptoms, most patients develop severe infection despite receiving potent and efficacious antibiotics (9). The risk of infection increases in patients with leukemia due to chemotherapy drugs (dramatically declining the number of neutrophils), vascular catheters, and inefficient use of antibiotics. Infections are still the most important causes of death, although the timely injection of coagulators and blood components has largely prevented bleeding and infection (10). Infections, injections of blood components, and chemotherapy drugs are the most important causes of fever in oncology patients.

The site of infection was detected in only one-third of the patients with FN in the initial assessment of recent studies. The cause of infection was detected in 69.23% of the patients with FN in a recent study. The most common cause of infection was sepsis in the aforementioned study with regard to gender, history of chemotherapy, and type of malignancy (11).

Hatamabadi et al. (12) examined 95 patients with FN over

a decade. In the aforementioned study, 44.2% and 60% of the cases were observed to develop an infection in microbiological assessment and clinical examination, respectively. The most common causes of infection in these patients were pulmonary (17.9%) and urinary tract (10.5%) infections (12). However, positive culture results were reported in 71% of patients, and the most common causes of infection were sepsis and then cutaneous infection in the present study. Although urinary tract and lung infections were more prevalent, the prevalence of these infections varied in both of these studies. The aforementioned results are not consistent with the results of the current study. Lung infection was the most prevalent infection in the study by Hatamabadi et al. (12); however, urinary tract infection was the most prevalent infection in the present study. These confounding results might be due to the type of underlying disease, treatment regimens, and environmental factors (12).

Positive culture results were observed in 71% of the patients in this study. The pathogens responsible for infection were fungi (13.50%), Gram-negative bacteria (48%), and Gram-positive bacteria (37%). The bacteria causing infection in this study were *E. coli* (n = 11; 29.72%), *Streptococcus* (n = 9; 24.32%), *Staphylococcus aureus* (n = 7; 18.91%), *Klebsiella* (n = 7; 18.91%), and *Candida albicans* (n = 3; 10.08%). Nomura et al. (13) detected FN in 45 patients (52.9%) among 85 patients undergoing chemotherapy and hospitalized due to fever in Japan. Michels et al. (14) demonstrated that the causes of fever in 29 neutropenic patients admitted to the Oncology Ward of the University of Pennsylvania Medical Center in the United States were bacterial infection (17%), viral infection (21%), fungal infection (21%; *Aspergillus* [n = 4] and *Candida* [n = 2]), and unknown causes (41%) in the United States.

The causes of infection were mostly bacteria, and viruses were not detected in this study at all. This might be due to limited diagnostic methods, environmental factors, type of underlying diseases, and dose, duration, and type of drugs.

Rasoul Hassan et al. examined 117 patients admitted to the Oncology Ward of General Hospital in Penang, Malaysia, and reported 83 cases with FN (70.9%). Culture specimens were prepared for only 34 patients (29.1%) out of whom only 14 patients (41.2%) had positive culture results. Out of these 14 cases, 9 cases (64.2%) were positive for Gram-negative bacteria (i.e., the most important bacteria reported as *E. coli* in 5 cases), and 5 cases (35.7%) were positive for Gram-positive bacteria (8). These results are not consistent with the results of the present study since Gram-positive bacteria were the most common causes of infection in this study. However, the most prevalent Gram-negative bacterium was *E. coli*, which is consistent with the results of this study.

Ahmadinejad (15) examined 95 patients with FN 40% of whom developed fever due to FUO. Positive blood (13.7%), urinary (13.7%), and esophageal (7.4%) culture results were observed in the aforementioned study. Fungi were regarded as the cause of infection in 6.3% of patients (*Candida* as the most prevalent fungi in the cultures). Among Gram-negative bacteria, *E. coli* (78.6%), *Klebsiella* (10.7%), and *Pseudomonas* (3.6%) were isolated from the cultures. Among Gram-positive bacteria, *Staphylococci* (42.9%) and *Streptococci* (42.9%) were isolated from the cultures (15). These results are consistent with the results of the present study since *Staphylococci* and *Streptococci* among Gram-positive bacteria, and *E. coli* among Gram-negative bacteria were the most prevalent causes of infection in both studies.

Gram-negative bacteria were the most prevalent pathogens up to the 1980s. Later, Gram-positive organisms were reported to be more prevalent than Gram-negative bacteria. Gram-positive organisms accounted for 62% - 76% of blood infections in the United States; nevertheless, the prevalence of Gram-negative organisms was estimated within the range of 14% - 22% during 1995 - 2000 (16). Gram-negative bacteria were more prevalent than Gram-positive bacteria in this study; nonetheless, it is not noticeable in comparison to those of studies carried out in other countries. This might be due to the specific characteristics of patients, environmental factors, technical and diagnostic limitations, and failure to receive prophylactic treatment in this study. However, Gram-negative bacteria were more prevalent than Gram-positive bacteria in the only study conducted in Iran (17).

### 5.1. Limitations

The examination of only 1 center, no assessment of the effects of drug regimen, and risk factors for infections were the limitations of this study in addition to the limitations previously mentioned in the discussion section.

### 5.2. Recommendations

It is recommended to transcend the limitations of this

study, select a larger sample size, and examine more than 1 center in future studies.

### 5.3. Conclusions

The results of this study suggested that cancer patients undergoing chemotherapy should be aware of infection signs; accordingly, they can visit treatment centers in case of the first symptoms of infection to prevent the progression of infection and reduce mortality rates. Neutrophil levels and risk factors should also be determined in patients with malignant diseases undergoing chemotherapy to take effective measures for the prevention of infection.

### 5.4. Study Highlights

What is current knowledge?

1) Neutropenia is the most common cause of infection in patients receiving chemotherapy drugs.

2) The most important symptom of infection is fever.

What is new here?

Infection is a major cause of fever and neutropenia in cancer patients with a history of chemotherapy.

### Acknowledgments

**The authors would like to express their gratitude to the team of Tuberculosis and Lung Diseases Research Center of Tabriz University of Medical Sciences.**

Authors' Contribution:

All the authors contributed to the conception and design of the study, literature review, data collection, data interpretation, and drafting the manuscript.

Conflict of Interests:

The authors declare that there is no conflict of interest in this study.

Ethical Approval:

This study was approved by the Regional Ethics Committee of Tabriz University of Medical Sciences (code: IR.TBZMED.REC.1397.598).

Funding/Support:

This study was funded by the Tuberculosis and Lung Diseases Research Center of Tabriz University of Medical Sciences.

### References

1. Decker MR, Greenblatt DY, Havlena J, Wilke IG, Greenberg CC, Neuman HB. Impact of neoadjuvant chemotherapy on wound complications after breast surgery. *Surgery*. 2012;**152**(3):382-8. doi:10.1016/j.surg.2012.05.001. [PubMed:22739071]. [PMC3432709:PMC3432709].
2. Aghamohammadi D, Mehdinavaz Aghdam A, Khanbabayi Gol M. Prevalence of Infections Associated with Port and Predisposing Factors in Women with Common Cancers Under Chemotherapy Referred to Hospitals in Tabriz in 2015. *The Iranian Journal of Obstetrics, Gynecology and Infertility*. 2019;**21**(11):7-13.
3. Fontanella C, Bolzonello S, Lederer B, Aprile G. Management of breast cancer patients with chemotherapy-induced neutropenia or febrile neutropenia. *Breast Care (Basel)*. 2014;**9**(4):239-45. doi:10.1159/000366466. [PubMed:25404882].

- [PMC4209284:PMC4209284].
4. Cameron D. Management of chemotherapy-associated febrile neutropenia. *Br J Cancer*. 2009;**101** Suppl 1:S18-22. doi:10.1038/sj.bjc.6605272. [PubMed:19756002]. [PMC2752227:PMC2752227].
  5. Cho BJ, Kim KM, Bilegsaikhan SE, Suh YJ. Machine learning improves the prediction of febrile neutropenia in Korean inpatients undergoing chemotherapy for breast cancer. *Sci Rep*. 2020;**10**(1):14803. doi:10.1038/s41598-020-71927-6. [PubMed:32908182]. [PMC7481240:PMC7481240].
  6. Chan A, Chen C, Chiang J, Tan SH, Ng R. Incidence of febrile neutropenia among early-stage breast cancer patients receiving anthracycline-based chemotherapy. *Support Care Cancer*. 2012;**20**(7):1525-32. doi:10.1007/s00520-011-1241-6. [PubMed:21818641].
  7. Lyman GH, Abella E, Pettengell R. Risk factors for febrile neutropenia among patients with cancer receiving chemotherapy: A systematic review. *Crit Rev Oncol Hematol*. 2014;**90**(3):190-9. doi:10.1016/j.critrevonc.2013.12.006. [PubMed:24434034].
  8. Lyman GH, Michels SL, Reynolds MW, Barron R, Tomic KS, Yu J. Risk of mortality in patients with cancer who experience febrile neutropenia. *Cancer*. 2010;**116**(23):5555-63. doi:10.1002/cncr.25332. [PubMed:20715160].
  9. Whyte S, Cooper KL, Stevenson MD, Madan J, Akehurst R. Cost-effectiveness of granulocyte colony-stimulating factor prophylaxis for febrile neutropenia in breast cancer in the United Kingdom. *Value Health*. 2011;**14**(4):465-74. doi:10.1016/j.jval.2010.10.037. [PubMed:21669371].
  10. Lyman GH, Kuderer NM. Epidemiology of febrile neutropenia. *Support Cancer Ther*. 2003;**1**(1):23-35. doi:10.3816/SCT.2003.n.002. [PubMed:18628128].
  11. Engert A, del Giglio A, Bias P, Lubenau H, Gatzemeier U, Heigener D. Incidence of febrile neutropenia and myelotoxicity of chemotherapy: a meta-analysis of biosimilar G-CSF studies in breast cancer, lung cancer, and non-Hodgkin's lymphoma. *Onkologie*. 2009;**32**(10):599-604. doi:10.1159/000232580. [PubMed:19816079].
  12. Hatamabadi H, Arhami Dolatabadi A, Akhavan A, Safari S. Clinical Characteristics and Associated Factors of Mortality in Febrile Neutropenia Patients; a Cross Sectional Study. *Arch Acad Emerg Med*. 2019;**7**(1):39. [PubMed:31555769]. [PMC6732199:PMC6732199].
  13. Nomura M, Morita Y, Kakiuchi A, Ishida K, Iizuka M, Yagi Y, et al. The association between chemotherapy-induced febrile neutropenia and breast cancer subtype in Japanese patients. *Int J Clin Pharm*. 2020;**42**(1):7-10. doi:10.1007/s11096-019-00952-x. [PubMed:31865592].
  14. Michels SL, Barron RL, Reynolds MW, Smoyer Tomic K, Yu J, Lyman GH. Costs associated with febrile neutropenia in the US. *Pharmacoeconomics*. 2012;**30**(9):809-23. doi:10.2165/11592980-000000000-00000. [PubMed:22804805].
  15. Ahmadinejad Z. Fever and neutropenia due to cytomegalovirus infection in a breast cancer patient under chemotherapy: a case report. *Tehran Univ Med J*. 2010;**68**(3).
  16. Farzanfar F, Parvaresh S, Farahmandinia Z, Sarafinejad A, Gharaei N. The Diagnostic Value of IL8 Compared with CRP , ESR in the Detection of Bacterial Infections in Pediatric Oncology Patients with Febrile Neutropenia. *J Ilam Univ |Med Sci*. 2017;**25**(3):160-8. doi:10.29252/sjimu.25.3.160.
  17. Keyhanian S, Alipoor ZJ, Moghaddam HZ, Fotoukian Z, Nava MO, Saravi M. A study of fever causes in neutropenic patients hospitalized in oncology ward of Imam-Sajjad Hospital in Ramsar. *Sci J Iran Blood Transfusion Organ*. 2014;**11**(3).