# Association of Clinical and Para-clinical Factors With the Occurrence of Febrile Neutropenia Following Autologous Bone Marrow Transplantation in Patients With Lymphoma

**Babak Nejati**
Tabriz University of Medical Sciences
**Zohreh Kourehpaz** ( rezasadat46@yahoo.com )
Tabriz University of Medical Sciences
**Roya Dolatkhah**
Tabriz University of Medical Sciences
**mojtaba Varshochi**
Tabriz University of Medical Sciences
**Maryam Farmani**
Tabriz University of Medical Sciences

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# Abstract

**Purpose**: Promising results have been achieved by the administration of autologous bone marrow transplantation (BMT) in patients with lymphoma. However, infectious complications limit its positive outcomes. Therefore, better identification of related factors to the occurrence of febrile neutropenia may lead to improved management of these patients. This study aimed to evaluate the incidence and associated factors with the occurrence of febrile neutropenia in following BMT in patients with lymphoma

**Method**: In this prospective study, 45 patients with a definite diagnosis of lymphoma who were candidates for BMT were consecutively included. Demographic characteristics, lymphoma type, and medical history, as well as the results of selected laboratory tests, were recorded. After BMT, neutrophil count and body temperature were evaluated.

**Results**: Febrile neutropenia occurred in 28 patients (62.5 %). No statistically significant difference was seen between those with febrile neutropenia and those without, in terms of age, gender, BMI, type of lymphoma, blood group, and the number of radiotherapy or chemotherapy courses ($p>0.05$ for all). Multivariable logistic regression analysis demonstrated a significant positive relationship between the number of administered units of platelet and serum uric acid and development of febrile neutropenia.

**Conclusion**: The results of our study showed that the incidence of febrile neutropenia is significantly high in lymphoma patients who receive BMT. Moreover, the number of administered units of platelet and uric acid before BMT are significantly associated with febrile neutropenia.


# Introduction:

Lymphomas are classified into two major categories of non-Hodgkin (90%, NH) and Hodgkin (10%, HL) lymphomas [1]. The global incidence of HL has increased by 38.66% - from 72,937 in 1990 to 101,133 in 2017 - however, due to improved treatment modalities, the age-standardized death rate and the annual age-standardized disability-adjusted life year (DALY) have decreased during these years [2, 3]. Bone marrow transplantation (BMT) or autologous hematopoietic stem cell transplantation (AHSCT) after high-dose chemotherapy are established as the standard treatment modality for refractory or relapsed lymphomas [4]. Patients with high-risk aggressive lymphoma who are unresponsive to the conventional regimens alone show better prognosis by receiving early consolidative transplantation. Moreover, it can significantly diminish the bone marrow tumor load and consequently bring about a higher rate of complete remission [4]. Despite substantial positive advances by these therapeutic modalities, transplant-related infectious complications are still causing considerable morbidity and mortality in lymphoma patients [5]. These complications occur in a varying range of 12 up to 51 percent of transplanted patients [6, 7]. Higher incidences are documented in the neutropenic phase or pre-engraftment [8, 9]. Moreover, the incidence of severe sepsis in AHSCT patients was reported to be five times higher than non–AHSCT cohort, and it was associated with a mortality rate of 32.9 percent in AHSCT patients [10]. The development of fever in BMT patients is characterized as the clinical hallmark of bacteremia which is usually associated with neutropenia (febrile neutropenia) [11]. Several associated factors have been suggested for the higher incidence of infectious complications, including > 18 years age, use of unrelated graft source and myeloablative conditioning regimen, transplant-associated thrombotic microangiopathy, acute graft versus host disease, high-risk malignant disease, mucositis, and steroid administration [12, 13]. However, unsuccessful results of attempts for preventing these complications necessities further investigations for other previously underappreciated associated factors. Furthermore, detecting these factors could help limit the use of antibacterial prophylaxis to high-risk patients to prevent multi-drug resistant microorganisms [14, 15]. In this study, the incidence and associated factors of occurrence of febrile neutropenia were evaluated in patients with lymphoma who receive BMT after high dose chemotherapy.

# Methods

# Study design and patients' inclusion

In this prospective study, 45 adult patients (aged between 18 and 65 years) with a definite diagnosis of lymphoma (HL or NHL) who were candidates for BMT due to relapse following standard chemotherapy and admitted in the Ghazi Hospital in Tabriz (the only tertiary referral hospital for hemato-oncological diseases in north-west Iran) were consecutively included between April 1, 2016, and March 31, 2018. Patients were excluded if they had co-morbidities and those who heavily treated (received more than three chemotherapy protocols). The study was conducted in accordance with the declaration of Helsinki, and informed consent was obtained from each patient.

# Medical procedure

All patients received standard medical care during hospitalization. Patients were isolated in positive pressure reverse isolation rooms and were indicated to avoid raw fruits and vegetables. No medication was administered by rectal, vaginal or intramuscular routes. Strict handwashing procedures using the disinfectant agents were employed by the hospital staff before entering patients' rooms. The procedure of BMT and standard medical care were performed following established guidelines [16]. After admission, patients received conditioning regimen including lomustine (CCNU) 200 $mg/m^2$ (one dose), cytarabine 400 $mg/m^2$ (two times daily for two days), VP16 400 $mg/m^2$ (two times daily) and melphalan 140 $mg/m^2$ (Once). Later, stem cell collection was conducted using apheresis. The following day, BMT was performed using intravenous infusion of the obtained stem cells. Moreover, all patients received prophylaxis regimen since the day of admission and also after BMT, including acyclovir 800 mg (two times daily), fluconazole 150 mg (two times daily), and ciprofloxacin 500 mg (two times daily during the neutropenic days). They also received trimethoprim / Sulfamethoxazole 800 mg/160 mg (two times daily for two days per week) since the day of BMT until three months later [16].

# Study variables

A series of clinical and paraclinical variables were selected based on our clinical experiences and a preliminary literature review. Demographic characteristics, lymphoma type, and medical history of included patients were recorded in a pre-prepared questionnaire. Laboratory blood tests and liquid balance measurement (Intake – Output) were conducted 10 and 5 days before transplantation and at the transplantation day. After transplantation, the neutrophil count was measured daily, and body temperature was evaluated every four hours. A neutrophil count less than $1.5 \times 10^9/L$ was considered as neutropenia [17]. Body temperature (BT) was measured at 8–9 AM each day after transplantation, and the patient was considered febrile if they had BT > 38.3° C or BT > 38 if lasts more than one hour. Febrile neutropenia was defined as a simultaneous presence of fever and neutropenia, as elucidated above.

# Statistical analysis

Data are presented as mean ± standard deviation (SD) or frequency and percentage. The normal distribution of the data was evaluated by the Kolmogorov-Smirnov test. Chi-square or Fischer's exact test was conducted on categorical data and student T-test or Mann-Whitney U test for comparison between groups in parametric and non-parametric data, respectively. Simple and multiple logistic regression analyses were conducted in the context of univariate and multivariate analyses, and unadjusted and adjusted odds ratios (with 95% confidence intervals [CI]) were calculated. The analysis was performed by SPSS v 24. A p-value < 0.05 was considered as statistically significant.

## Result

An overall 45 lymphoma patients were included. The baseline characteristics of the patients are described in Table 1. Patients had a mean age of 34.79 +/- 10.49, and 28.9 percent of the patients were female. Febrile neutropenia occurred in 28 patients (62.5%) on average after 12.77 +/- 2.45 days after BMT. No statistically significant difference was seen between two groups (those with febrile neutropenia and those without) in terms of age, gender, BMI, type of lymphoma, blood group, and the number of radiotherapy or chemotherapy courses ($p > 0.05$ for all, Table 2). Patients with febrile neutropenia had received packed cells more frequently than control group (median [min-max] = 2 [0–7] in febrile neutropenia group vs 0 [0–4]

in control group, p = 0.021). Also, higher number of units of platelet had been administered in febrile neutropenia group (median [min-max] = 18.5 [5–53] in febrile neutropenia group vs 12 [0–26] in control group, p = 0.043).

Table 1
Baseline characteristics of included patients

| | | Total | Febrile neutropenia | Control | P value |
|---|---|---|---|---|---|
| Age<br>mean +/- SD | | 35 (10) | 37 (11) | 31 (10) | 0.113* |
| BMI<br>mean +/- SD | | 30.05 (22.14) | 32.18 (27.84) | 26.55 (4.36) | 0.512** |
| Gender | Male | 32 (71.1) | 19 (67.9) | 13 (76.5) | 0.733# |
| n (%) | Female | 13 (28.9) | 9 (32.1) | 4 (23.5) | |
| Type of lymphoma | NHL | 15 (33.3) | 9 (32.1) | 6 (35.3) | 1.000# |
| n (%) | HD | 30 (66.7) | 19 (67.9) | 11 (64.7) | |
| Blood group | A+ | 11 (24.4) | 5 (17.9) | 6 (35.3) | 0.595$ |
| n (%) | A- | 2 (4.4) | 1 (3.6) | 1 (5.9) | |
| | B+ | 9 (20.0) | 6 (21.4) | 3 (17.6) | |
| | B- | 2 (4.4) | 2 (7.1) | 0 (0.0) | |
| | AB+ | 3 (6.7) | 3 (10.7) | 0 (0.0) | |
| | AB- | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| | O+ | 15 (33.3) | 9 (32.1) | 6 (35.3) | |
| | O- | 3 (6.7) | 2 (7.1) | 1 (5.9) | |
| Number of radiotherapy courses mean +/- SD | | 11 (12) | 10 (12) | 19 (5) | 0.471** |
| Number of chemotherapy courses mean +/- SD | | 14 (5) | 15 (6) | 12 (4) | 0.244** |
| * Student T-test was used (two-sided significance). | | | | | |
| ** Mann-Whitney U test was used (two-sided significance). | | | | | |
| # Fisher's exact test was used (two-sided significance). | | | | | |
| $ Pearson chi-square test was used. | | | | | |

Table 2
Pre-bone marrow transplantation laboratory tests results

| | Day | Total | Febrile neutropenia | Control | P-value |
|---|---|---|---|---|---|
| ESR (mm/h) | **0** | 21.41 (14.66) | 24.00 (15.31) | 17.38 (13.02) | 0.162 |
| | **-5** | 23.37 (15.89) | 27.48 (16.35) | 17.07 (13.32) | **0.048** |
| | **-10** | 17.49 (13.32) | 21.27 (15.21) | 11.71 (6.71) | **0.050** |
| CRP (U) | **0** | 1 (1) | 1 (1) | 1 (1) | 0.649 |
| | **-5** | 1 (1) | 2 (1) | 1 (1) | 0.326 |
| | **-10** | 0 (1) | 0 (1) | 0 (0) | 0.506 |
| Uric acid (mg/dL) | **0** | 4.08 (1.36) | 3.74 (1.18) | 4.70 (1.51) | **0.048** |
| | **-5** | 6.38 (2.16) | 5.74 (1.80) | 7.96 (2.25) | **0.012** |
| | **-10** | 4.91 (1.32) | 4.60 (1.22) | 5.58 (1.33) | **0.021** |
| Fibrinogen (mg/dL) | **0** | 336.87 (119.83) | 347.41 (137.68) | 317.29 (82.87) | 0.311 |
| | **-5** | 351.23 (74.98) | 365.37 (81.45) | 328.60 (64.91) | 0.435 |
| | **-10** | 323.91 (109.81) | 343.46 (110.55) | 298.50 (109.13) | 0.446 |
| LDH (U/L) | **0** | 373 (351) | 399 (427) | 326 (139) | 0.730 |
| | **-5** | 715 (370) | 776 (416) | 641 (313) | 0.456 |
| | **-10** | 484 (184) | 500 (180) | 462 (194) | 0.347 |
| WBC (cells/L) | **0** | 6031 (6328) | 4674 (4683) | 8187 (7995) | 0.094 |
| | **-5** | 29731 (15948) | 31702 (15907) | 26485 (15952) | 0.349 |
| | **-10** | 8490 (7732) | 8065 (5593) | 9190 (10525) | 0.598 |
| N (cells/L) | **0** | 4580 (5795) | 3276 (4198) | 6652 (7361) | 0.151 |
| | **-5** | 25868 (13970) | 26474 (14559) | 24871 (13315) | 0.797 |
| | **-10** | 7689 (7060) | 7423 (5249) | 8128 (9500) | 0.607 |
| Hb (g/dL) | **0** | 11.3 (1.5) | 11.0 (1.5) | 11.7 (1.6) | 0.223 |
| | **-5** | 11.3 (1.3) | 11.1 (1.3) | 11.7 (1.3) | 0.150 |
| | **-10** | 10.8 (1.9) | 10.6 (1.2) | 11.2 (2.8) | **0.029** |
| Plt (cells/L) | **0** | 129559 (63205) | 126963 (52169) | 133682 (79273) | 0.791 |
| | **-5** | 143244 (60613) | 135250 (53696) | 156412 (70299) | 0.367 |
| | **-10** | 104933 (48018) | 98857 (48328) | 114941 (47206) | 0.246 |

Data are presented as mean +/- SD

All analysis is performed using the Mann-Whitney U test.

Days are reported in relation to BMT (0 = the day of BMT, -5 = five days before BMT, -10 = ten days before BMT), ESR = erythrocyte sedimentation rate, LDH = Lactate dehydrogenase, WBC = White blood cells, N = neutrophil count, Hb = Hemoglobin, Plt = platelet, MPXI = Myeloperoxidase index, LUC = Large unstained cells, CMV = cytomegalovirus

| | Day | Total | Febrile neutropenia | Control | P-value |
|---|---|---|---|---|---|
| MPXI | **0** | 7.01 (13.74) | 6.72 (15.84) | 7.47 (9.94) | 0.399 |
| | **-5** | -2.45 (8.59) | -3.60 (8.50) | − .56 (8.67) | 0.178 |
| | **-10** | -4.89 (9.39) | -4.89 (9.71) | -4.90 (9.13) | 0.935 |
| LUC | **0** | .31 (.85) | .41 ()1.07 | .14 (.11) | 0.276 |
| | **-5** | .52 (.62) | .56 (.74) | .44 (.32) | 0.990 |
| | **-10** | .12 (.14) | .14 (.13) | .10 (.16) | 0.225 |
| Retic count | **0** | 1.07 (.90) | 1.06 (1.13) | 1.08 (.70) | 0.720 |
| | **-5** | 1.50 (00) | 1.50 (.00) | . | - |
| | **-10** | .35 (.21) | .35 (.21) | . | - |
| Liquid balance (ml) | **0** | 771.05 (902.51) | 700.00 (953.19) | 822.73 (907.29) | 0.840 |
| | **-5** | 1479.47 (1095.00) | 1563.75 (1062.87) | 1418.18 (1165.1) | 0.904 |
| | **-10** | 437.50 (960.99) | -48.89 (693.28) | 835.45 (991.48) | **0.038** |
| Ferritin (ug/L) | | 518.17 (403.20) | 468.38 (462.61) | 558.00 (369.68) | 0.360 |
| CD34 (*10^6) | | 14.56 (49.34) | 22.82 (65.11) | 3.75 (2.45) | 0.837 |
| Data are presented as mean +/- SD | | | | | |
| All analysis is performed using the Mann-Whitney U test. | | | | | |
| Days are reported in relation to BMT (0 = the day of BMT, -5 = five days before BMT, -10 = ten days before BMT), ESR = erythrocyte sedimentation rate, LDH = Lactate dehydrogenase, WBC = White blood cells, N = neutrophil count, Hb = Hemoglobin, Plt = platelet, MPXI = Myeloperoxidase index, LUC = Large unstained cells, CMV = cytomegalovirus | | | | | |

Patients with febrile neutropenia had significantly higher ESR than control groups at the days − 5 and − 10 (p value = 0.048 and 0.050, respectively). Moreover, uric acid was significantly lower in patients with febrile neutropenia in all three days of 0, -5, and − 10 (p value = 0.048, 0.012, and 0.021, respectively). Hemoglobin of patients with febrile neutropenia was significantly lower at day − 10 (p = 0.029). Also, we found a significantly lower liquid balance at 10 days before BMT (median [min – max] = -350 [-1050–1000] in febrile neutropenia and 1120 [-1150–1850] in control, p = 0.038).

Logistic regression analysis demonstrated a significant positive relationship between the number of administered packed cells (unadjusted OR = 1.766, 95%CI = 1.01–3.089), the number of administered units of platelet (unadjusted OR = 1.082, 95%CI = 1.000 -1.173), and ESR (at day − 10) (unadjusted OR = 1.078, 95%CI = 1.007–1.155) and development of febrile neutropenia (Table 3). Moreover, we detected a negative relationship between uric acid levels at days − 5 and − 10 and the development of febrile neutropenia (unadjusted OR = 0.578, 95%CI = 0.368–0.909 for − 5 day, and unadjusted OR = 0.535, 95%CI = 0.3–0.953 for day − 10).

Table 3
relationship between study variables and febrile neutropenia

| | Subtype/day | Unadjusted Odds ratio | 95% CI | | P-value | Adjusted Odds ratio* | 95% CI | | P-value |
|---|---|---|---|---|---|---|---|---|---|
| | | | lower | Upper | | | min | max | |
| Age | | 1.056 | 0.986 | 1.13 | 0.117 | - | - | - | - |
| Gender | Male | 0.650 | 0.165 | 2.564 | 0.538 | - | - | - | - |
| | Female | Ref | - | - | - | - | - | - | - |
| BMI | | 1.028 | 0.938 | 1.128 | 0.553 | - | - | - | - |
| Type of lymphoma | NHL | 0.868 | 0.243 | 3.099 | 0.828 | - | - | - | - |
| | HL | Ref | - | - | - | - | - | - | - |
| Number of radiotherapy courses | | 0.928 | 0.797 | 1.081 | 0.337 | - | - | - | - |
| Number of chemotherapy courses | | 1.12 | 0.973 | 1.29 | 0.115 | - | - | - | - |
| Number of administered packed cells | | 1.766 | 1.01 | 3.089 | **0.046** | 2.022 | .917 | 4.462 | 0.081 |
| Blood type | A+ | Ref | - | - | - | - | - | - | - |
| | A- | 0.500 | 0.013 | 19.562 | 0.711 | - | - | - | - |
| | B+ | 1.000 | 0.063 | 15.988 | 1.000 | - | - | - | - |
| | B- | 807737432.147 | 0.000 | . | 0.999 | - | - | - | - |
| | AB+ | 807737432.147 | 0.000 | . | 0.999 | - | - | - | - |
| | AB- | 0.750 | 0.055 | 10.233 | 0.829 | - | - | - | - |
| | O+ | 0.417 | 0.013 | 6.064 | 0.522 | - | - | - | - |
| | O- | 0.500 | 0.063 | 19.562 | 0.711 | | | | |
| Number of administered units of platelet | | 1.082 | 1.000 | 1.173 | **0.050** | 1.118 | 1.010 | 1.237 | **0.031** |
| ESR (mm/h) | **0** | 1.034 | 0.987 | 1.084 | 0.161 | | | | |
| | **-5** | 1.057 | 0.998 | 1.118 | 0.057 | | | | |
| | **-10** | 1.078 | 1.007 | 1.155 | **0.032** | 1.084 | .998 | 1.176 | 0.056 |
| CRP (U) | **0** | 1.091 | 0.636 | 1.87 | 0.752 | - | - | - | - |

* Adjusted for age, gender, BMI, type of lymphoma. Only those variables which were significant in unadjusted simple regression were considered in multiple regression analysis.

Days are reported in relation to BMT (0 = the day of BMT, -5 = five days before BMT, -10 = ten days before BMT), ESR = erythrocyte sedimentation rate, LDH = Lactate dehydrogenase, WBC = White blood cells, N = neutrophil count, Hb = Hemoglobin, Plt = platelet, MPXI = Myeloperoxidase index, LUC = Large unstained cells, CMV = cytomegalovirus

| | Subtype/day | Unadjusted Odds ratio | 95% CI | | P-value | Adjusted Odds ratio* | 95% CI | | P-value |
|---|---|---|---|---|---|---|---|---|---|
| | **-5** | 1.343 | 0.774 | 2.327 | 0.294 | - | - | - | - |
| | **-10** | 2.263 | 0.557 | 9.189 | 0.253 | - | - | - | - |
| Uric acid (mg/dL) | **0** | 0.572 | 0.318 | 1.027 | 0.061 | - | - | - | - |
| | **-5** | 0.578 | 0.368 | 0.909 | **0.018** | .525 | .288 | .958 | **0.036** |
| | **-10** | 0.535 | 0.3 | 0.953 | **0.034** | .617 | .328 | 1.163 | 0.135 |
| Fibrinogen (mg/dL) | **0** | 1.002 | 0.994 | 1.01 | 0.587 | - | - | - | - |
| | **-5** | 1.008 | 0.99 | 1.026 | 0.385 | - | - | - | - |
| | **-10** | 1.004 | 0.996 | 1.013 | 0.329 | - | - | - | - |
| LDH (U/L) | **0** | 1.001 | 0.998 | 1.004 | 0.597 | - | - | - | - |
| | **-5** | 1.001 | 0.999 | 1.004 | 0.397 | - | - | - | - |
| | **-10** | 1.001 | 0.997 | 1.005 | 0.586 | - | - | - | - |
| WBC (cells/L) | **0** | 1 | 1 | 1 | 0.087 | - | - | - | - |
| | **-5** | 1 | 1 | 1 | 0.288 | - | - | - | - |
| | **-10** | 1 | 1 | 1 | 0.637 | - | - | - | - |
| N (cells/L) | **0** | 1 | 1 | 1 | 0.072 | - | - | - | - |
| | **-5** | 1 | 1 | 1 | 0.706 | - | - | - | - |
| | **-10** | 1 | 1 | 1 | 0.744 | - | - | - | - |
| Hb (g/dL) | **0** | 0.748 | 0.493 | 1.135 | 0.172 | - | - | - | - |
| | **-5** | 0.69 | 0.415 | 1.148 | 0.153 | - | - | - | - |
| | **-10** | 0.838 | 0.576 | 1.221 | 0.359 | - | - | - | - |
| Plt (cells/L) | **0** | 1 | 1 | 1 | 0.729 | - | - | - | - |
| | **-5** | 1 | 1 | 1 | 0.264 | - | - | - | - |
| | **-10** | 1 | 1 | 1 | 0.276 | - | - | - | - |
| MPXI | **0** | 0.996 | 0.953 | 1.041 | 0.858 | - | - | - | - |
| | **-5** | 0.955 | 0.882 | 1.034 | 0.254 | - | - | - | - |
| | **-10** | 1 | 0.937 | 1.067 | 0.996 | - | - | - | - |
| LUC | **0** | 22.895 | 0.12 | 4373.027 | 0.243 | - | - | - | - |

* Adjusted for age, gender, BMI, type of lymphoma. Only those variables which were significant in unadjusted simple regression were considered in multiple regression analysis.

Days are reported in relation to BMT (0 = the day of BMT, -5 = five days before BMT, -10 = ten days before BMT), ESR = erythrocyte sedimentation rate, LDH = Lactate dehydrogenase, WBC = White blood cells, N = neutrophil count, Hb = Hemoglobin, Plt = platelet, MPXI = Myeloperoxidase index, LUC = Large unstained cells, CMV = cytomegalovirus

| | Subtype/day | Unadjusted Odds ratio | 95% CI | | P-value | Adjusted Odds ratio* | 95% CI | | P-value |
|---|---|---|---|---|---|---|---|---|---|
| | -5 | 1.446 | 0.415 | 5.036 | 0.562 | - | - | - | - |
| | -10 | 7.005 | 0.057 | 868.347 | 0.429 | - | - | - | - |
| Liquid balance (ml) | -1 | 1 | 0.999 | 1.001 | 0.764 | - | - | - | - |
| | -2 | 1 | 0.999 | 1.001 | 0.769 | - | - | - | - |
| | -3 | 0.999 | 0.998 | 1 | 0.051 | - | - | - | - |
| Ferritin | | 0.999 | 0.997 | 1.002 | 0.632 | - | - | - | - |

* Adjusted for age, gender, BMI, type of lymphoma. Only those variables which were significant in unadjusted simple regression were considered in multiple regression analysis.

Days are reported in relation to BMT (0 = the day of BMT, -5 = five days before BMT, -10 = ten days before BMT), ESR = erythrocyte sedimentation rate, LDH = Lactate dehydrogenase, WBC = White blood cells, N = neutrophil count, Hb = Hemoglobin, Plt = platelet, MPXI = Myeloperoxidase index, LUC = Large unstained cells, CMV = cytomegalovirus

However, when we adjusted these variables with baseline characteristics including age, gender, BMI, and type of lymphoma, only the number of administered units of platelet and uric acid remained significant. The number of administered units of platelet had a weakly positive relationship with febrile neutropenia, suggesting that the higher number of units of platelet can lead to a higher risk of febrile neutropenia (odds ratio = 1.118, 95% CI = 1.010–1.0237, p = 0.031). Uric acid at day − 5 had a negative relationship with febrile neutropenia, suggesting that the higher uric acid level was associated with a lower risk of febrile neutropenia (odds ratio = 0.525, 95% CI = 0.288–0.958, p = 0.036).

## Discussion

There is a growing concern for the widespread emergence of multidrug-resistant microorganisms in medical centers, especially in hematology-oncology wards [18, 19]. These microorganisms diminish the effectiveness of routine antibacterial prophylaxis with oral fluoroquinolones in patients undergoing BMT or AHSCT [20, 21, 18]. In one study, discontinuing the administration of antibacterial prophylaxis in AHSCT recipients did not have a significant adverse effect on the early mortality of the patients after transplantation [22]. Therefore, it is suggested that bacterial prophylaxis be considered for only high-risk patients [14]. However, no risk stratification system has been established so far for such cases. One of the reasons can be that the related and predictive factors are not fully recognized yet. Considering the close association of febrile neutropenia with infection in lymphoma patients receiving BMT [11], in this prospective study, we evaluated the incidence and associated clinical and paraclinical factors of post-transplantation development of febrile neutropenia. A considerably high incidence of febrile neutropenia occurred in these patients in our study, which was similar to the reports of previous studies [23–25]. No significant differences were detected in baseline characteristics between those patients who developed febrile neutropenia and those who did not (control); however, some of the other related factors were significantly different between groups including the number of administered packed cells, erythrocyte sedimentation rate (ESR) at the − 5 and − 10 days, uric acid at all three days of 0, -5, and − 10, and hemoglobin at -10 day. We also found a significantly lower liquid balance at 10 days before BMT in patients with febrile neutropenia which highlights the importance of adequate hydration of the patients over the days before BMT. Our further analysis by controlling for baseline characteristics revealed that only uric acid and the number of administered units of platelet were significant predictors of febrile neutropenia. The prognostic value of serum uric acid for both short and long term outcome of admitted medical patients has been emphasized in previous studies [26]. However, in contrast with our results, serum uric acid is demonstrated to have a positive correlation with poor outcome and mortality [27–29]. The lower uric acid level in those patients who would develop febrile neutropenia may be related to malnutrition which leads to lower production of uric acid. Also, the presence of a higher

background inflammatory state (before BMT) may lead to impaired renal uric acid reabsorption [30]. Accordingly, in a study on 43 Taiwanese patients with SARS, 16 patients develop marked renal hypouricemia due to inflammation [31]. Over-hydration could be another reason for lower uric acid levels in patients who develop febrile neutropenia. However, this hypothesis contrast with our findings of the negative correlation of liquid balance at -10 day with the development of febrile neutropenia. Furthermore, low Na intake may result in hypouricemia in these patients who are at higher risk of febrile neutropenia [30].

In a similar attempt to identify the related factors of infection in patients receiving AHSCT, C-reactive protein and ferritin were proposed as predictive factors [14]. However, this study evaluated these factors only on the day of transplantation. Nevertheless, we believe it can be more helpful if these factors get evaluated a few days before transplantation so that the clinicians have more time for making proper modifications to the treatment strategies, for instance, on bacterial prophylaxis. Furthermore, we observed some dissimilarities in the results of laboratory tests on different days (-10, -5, 0) which also had an impact on the extent of relationship of the results of these tests with the development of febrile neutropenia. This finding can highlight the time-dependent feature of the laboratory tests for the prediction of febrile neutropenia.

Other studies have identified several other related factors including the time to platelet engraftment [32], the number of stem cells infused [33], duration of neutropenia [34, 35], contamination of stem cells, presence of an indwelling central venous catheter, therapy-related mucosal damage, etc. [36, 37]. However, these factors are mostly related to the post-transplantation period or during the procedure of transplantation; therefore, it may not be useful for risk stratification and modification of pre-transplantation treatment.

We would like to address some limitations of our study. Due to the relatively small sample size, the results may not be generalized for the whole population, and further studies are needed to confirm our findings. The strategy for administration of bacterial prophylaxis was patient-dependent in some cases (for example ciprofloxacin was administered only during the neutropenic days), and this issue could affect our results; however, due to the established protocol of patients' treatment and ethical issues, we were not allowed to equalize the treatment in both groups.

## Conclusion

The results of our study showed that the incidence of febrile neutropenia is significantly high in lymphoma patients who receive BMT. Moreover, some associated factors for febrile neutropenia were also investigated, and despite the limitations of our study, the results showed that the number of administered units of platelet and uric acid at five days before BMT are significantly associated with febrile neutropenia.

## Abbreviations

BMT
autologous bone marrow transplantation
DALY
annual age-standardized disability-adjusted life year
AHSCT
autologous hematopoietic stem cell transplantation
NH
non-Hodgkin lymphomas
HL
Hodgkin lymphomas
BT
Body temperature
SD

standard deviation

## Declarations

**Compliance with Ethics Guidelines:**

Ethics approval and consent to participate: Ethical clearance was sought from medical ethics committee of Tabriz University of Medical Sciences, Tabriz, Iran. Written informed consent was obtained from the participants.

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**Availability of data and materials:**All Data and material collected during this study are available from the corresponding author upon reasonable request.

**Authors' contributions:** Conceived the idea: BN, ZK. Designed the study methodology: BN, ZK, MV, RD. Conducted the study: MF, ZK. Analyzed the data: ZK, MF. Interpreted the results: RD, BN. Wrote the draft manuscript: ZK, MF, MV. Revised and edited the final manuscript: BN, RD. Approved the manuscript: BN, ZK,RD,MV,MF

**Competing interests:**The authors declare that they have no competing interests.

## References

1. Mugnaini EN, Ghosh N. Lymphoma. Primary Care: Clinics in Office Practice. 2016;43(4):661 – 75.
2. Zhou L, Deng Y, Li N, Zheng Y, Tian T, Zhai Z, et al. Global, regional, and national burden of hodgkin lymphoma from 1990 to 2017: estimates from the 2017 Global Burden of Disease Study. J Hematol Oncol. 2019;12(1):107.
3. Somi MH, Dolatkhah R, Sepahi S, Belalzadeh M, Sharbafi J, Abdollahi L, et al. Cancer incidence in the East Azerbaijan province of Iran in 2015–2016: results of a population-based cancer registry. BMC Public Health. 2018;18(1):1266.
4. Jiang Y, Zhen Y, Xu Q, He D, Chen G, Chen Y. Bone Marrow Versus Peripheral Blood Stem Cell Transplant in Lymphoma: A Systematic Review and Meta-Analysis. Experimental and clinical transplantation: official journal of the Middle East Society for Organ Transplantation. 2018;16(5):596–607. doi:10.6002/ect.2017.0073.
5. Sarashina T, Yoshida M, Iguchi A, Okubo H, Toriumi N, Suzuki D, et al. Risk factor analysis of bloodstream infection in pediatric patients after hematopoietic stem cell transplantation. J Pediatr Hematol Oncol. 2013;35(1):76–80.
6. Blennow O, Ljungman P, Sparrelid E, Mattsson J, Remberger M. Incidence, risk factors, and outcome of bloodstream infections during the pre-engraftment phase in 521 allogeneic hematopoietic stem cell transplantations. Transplant Infectious Disease. 2014;16(1):106–14.
7. Dandoy CE, Ardura MI, Papanicolaou GA, Auletta JJ. Bacterial bloodstream infections in the allogeneic hematopoietic cell transplant patient: new considerations for a persistent nemesis. Bone marrow transplantation. 2017;52(8):1091–106.
8. Mikulska M, Del Bono V, Raiola AM, Bruno B, Gualandi F, Occhini D, et al. Blood stream infections in allogeneic hematopoietic stem cell transplant recipients: reemergence of Gram-negative rods and increasing antibiotic resistance. Biol Blood Marrow Transplant. 2009;15(1):47–53.
9. Kikuchi M, Akahoshi Y, Nakano H, Ugai T, Wada H, Yamasaki R, et al. Risk factors for pre-and post-engraftment bloodstream infections after allogeneic hematopoietic stem cell transplantation. Transplant Infectious Disease. 2015;17(1):56–65.
10. Kumar G, Ahmad S, Taneja A, Patel J, Guddati AK, Nanchal R, et al. Severe Sepsis in Hematopoietic Stem Cell Transplant Recipients*. Critical Care Medicine. 2015;43(2).

11. Serody JS, Berrey MM, Albritton K, O'Brien SM, Capel EP, Bigelow SH, et al. Utility of obtaining blood cultures in febrile neutropenic patients undergoing bone marrow transplantation. Bone marrow transplantation. 2000;26(5):533–8.
12. Mitchell AE, Derrington P, Turner P, Hunt LP, Oakhill A, Marks DI. Gram-negative bacteraemia (GNB) after 428 unrelated donor bone marrow transplants (UD-BMT): risk factors, prophylaxis, therapy and outcome. Bone marrow transplantation. 2004;33(3):303–10.
13. Dandoy CE, Haslam D, Lane A, Jodele S, Demmel K, El-Bietar J, et al. Healthcare burden, risk factors, and outcomes of mucosal barrier injury laboratory-confirmed bloodstream infections after stem cell transplantation. Biol Blood Marrow Transplant. 2016;22(9):1671–7.
14. Kanda J, Mizumoto C, Ichinohe T, Kawabata H, Saito T, Yamashita K, et al. Pretransplant serum ferritin and C-reactive protein as predictive factors for early bacterial infection after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2011;46(2):208–16. doi:10.1038/bmt.2010.108.
15. Trinkaus MA, Lapinsky SE, Crump M, Keating A, Reece DE, Chen C, et al. Predictors of mortality in patients undergoing autologous hematopoietic cell transplantation admitted to the intensive care unit. Bone Marrow Transplant. 2009;43(5):411–5. doi:10.1038/bmt.2008.336.
16. Handin RI, Lux SE, Stossel TP. principles and practice of hematology. Lippincott Williams & Wilkins; 2003.
17. Sahai T, Hauser N, Mukkamalla SKR, Menendez AG, Roberts TF, Tandon R. Outcomes of febrile neutropenia following hematopoietic stem cell transplantation. American Society of Clinical Oncology; 2016.
18. Gomez L, Garau J, Estrada C, Marquez M, Dalmau D, Xercavins M, et al. Ciprofloxacin prophylaxis in patients with acute leukemia and granulocytopenia in an area with a high prevalence of ciprofloxacin-resistant Escherichia coli. Cancer. 2003;97(2):419–24.
19. Cattaneo C, Quaresmini G, Casari S, Capucci MA, Micheletti M, Borlenghi E, et al. Recent changes in bacterial epidemiology and the emergence of fluoroquinolone-resistant Escherichia coli among patients with haematological malignancies: results of a prospective study on 823 patients at a single institution. Journal of antimicrobial chemotherapy. 2008;61(3):721–8.
20. Prabhu RM, Piper KE, Litzow MR, Steckelberg JM, Patel R. Emergence of quinolone resistance among viridans group streptococci isolated from the oropharynx of neutropenic peripheral blood stem cell transplant patients receiving quinolone antimicrobial prophylaxis. Eur J Clin Microbiol Infect Dis. 2005;24(12):832–8.
21. Saito T, Yoshioka S, Iinuma Y, Takakura S, Fujihara N, Ichinohe T, et al. Effects on spectrum and susceptibility patterns of isolates causing bloodstream infection by restriction of fluoroquinolone prophylaxis in a hematology–oncology unit. European Journal of Clinical Microbiology Infectious Diseases. 2008;27(3):209–16.
22. Kanda J, Ichinohe T, Saito T, Yamashita K, Kondo T, Ishikawa T, et al. Impact of discontinuing fluoroquinolone prophylaxis on early mortality after allogeneic marrow or peripheral blood SCT with myeloablative conditioning. Bone marrow transplantation. 2010;45(8):1369–71.
23. Celebi H, Akan H, Akçağlayan E, Üstün C, Arat M. Febrile neutropenia in allogeneic and autologous peripheral blood stem cell transplantation and conventional chemotherapy for malignancies. Bone marrow transplantation. 2000;26(2):211–4.
24. Akan H, Koç H, Arslan Ö, Beksaç M, İlhan O, Gürman G, et al. Febrile neutropenia in a bone marrow transplantation unit. Int J Antimicrob Agents. 1997;8(2):127–30. doi:https://doi.org/10.1016/S0924-8579(96)00364-0.
25. 10.1016/j.transproceed.2015.01.013
Zhang WX, Zhao QY, Huang HQ. Febrile Neutropenic Infection Occurred in Cancer Patients Undergoing Autologous Peripheral Blood Stem Cell Transplantation. Transplantation Proceedings. 2015;47(2):523-7. doi:https://doi.org/10.1016/j.transproceed.2015.01.013.
26. Abe O, Abe R, Enomoto K, Kikuchi K, Koyama H, Masuda H, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366(9503):2087–106.

27. El Din UAS, Salem MM, Abdulazim DO. Uric acid in the pathogenesis of metabolic, renal, and cardiovascular diseases: A review. Journal of advanced research. 2017;8(5):537–48.
28. Wasserman A, Shnell M, Boursi B, Guzner-Gur H. Prognostic significance of serum uric acid in patients admitted to the department of medicine. Am J Med Sci. 2010;339(1):15–21.
29. Habibollahi P, Garjani A, Vahdati SS, Sadat-Ebrahimi S-R, Parnianfard N. Severe complications of tramadol overdose in Iran. Epidemiology and health. 2019;41.
30. Mount DB. Hypouricemia. Causes and clinical significance. Up to date 2019. https://www.uptodate.com/contents/hypouricemia-causes-and-clinical-significance. Accessed 4/13/2020 2020.
31. Wu V-C, Huang J-W, Hsueh P-R, Yang Y-F, Tsai H-B, Kan W-C, et al. Renal hypouricemia is an ominous sign in patients with severe acute respiratory syndrome. American journal of kidney diseases. 2005;45(1):88–95.
32. Fujii K, Aoyama M, Shinagawa K, Matsuo K, Takenaka K, Ikeda K, et al. Risk of neutropenic fever and early infectious complications after autologous peripheral blood stem cell transplantation for malignant diseases. Int J Hematol. 2002;76(2):186–91.
33. Perez-Simon JA, Martin A, Caballero D, Corral M, Nieto MJ, Gonzalez M, et al. Clinical significance of CD34 + cell dose in long-term engraftment following autologous peripheral blood stem cell transplantation. Bone marrow transplantation. 1999;24(12):1279–83.
34. Nosanchuk JD, Sepkowitz KA, Pearse RN, White MH, Nimer SD, Armstrong D. Infectious complications of autologous bone marrow and peripheral stem cell transplantation for refractory leukemia and lymphoma. Bone marrow transplantation. 1996;18(2):355–9.
35. Engels EA, Ellis CA, Supran SE, Schmid CH, Barza M, Schenkein DP, et al. Early infection in bone marrow transplantation: quantitative study of clinical factors that affect risk. Clinical infectious diseases. 1999;28(2):256–66.
36. O'brien SN, Blijlevens NMA, Mahfouz TH, Anaissie EJ. Infections in patients with hematological cancer: recent developments. ASH Education Program Book. 2003;2003(1):438–72.
37. Cainelli F. Transplant infections. The Lancet. 2004;363(9409):666.