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Lower uric acid and adequate hydration are associated with lower risk of febrile neutropenia following autologous bone marrow transplantation in patients with lymphoma

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ABSTRACT

Background. Despite the promising results of autologous bone marrow transplantation (BMT) in patients with lymphoma, infectious complications limit its positive outcomes. This study evaluated the incidence and associated factors of febrile neutropenia (FN) following BMT in patients with lymphoma.

Materials and methods. The study consecutively included 147 patients with lymphoma who were candidates for BMT. Clinical and laboratory results were recorded, and after BMT, the occurrence of FN was investigated through the daily evaluation of neutrophil count and body temperature.

Results. On average, FN occurred in 91 patients (61.9%) after 12.77 ± 2.45 days after BMT. Lower fluid balance was associated with a higher risk of FN (lowest adjusted odds ratio [OR] at day -2 = 0.602, 95% confidence interval [CI] = 0.299 – 0.870, p-value = 0.007). The higher uric acid level was associated with a higher risk of FN (highest adjusted OR at day -10 = 1.617, 95% CI = 1.328 – 1.963, p-value = 0.035). LDH was also positively correlated with FN (highest adjusted OR at day 0 = 1.501, 95% CI = 1.198 – 2.104, p-value = 0.004).

Conclusions. Adequate hydration of the patients is of paramount importance for preventing FN in patients who receive BMT. Furthermore, uric acid and LDH could be considered in future studies for the risk stratification of FN.

Introduction

Lymphomas are classified into two major categories: non-Hodgkin (90%, NHL) 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]. After high-dose chemotherapy, bone marrow transplantation (BMT) or autologous hematopoietic stem cell transplantation (AHSCT) is the standard way to treat lymphomas that do not respond to treatment or have come back [4]. Patients with high-risk aggressive lymphoma who are unresponsive to conventional regimens alone show a better prognosis by receiving early consolidative transplantation. Moreover, it can significantly diminish the bone marrow tumour load and consequently bring about a higher complete remission rate [4]. Despite substantial positive advances due to 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% 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 in the non–AHSCT cohort, and it was associated with a mortality rate of 32.9 percent in AHSCT patients [10]. A fever in people with a bone marrow transplant is a sign of bacteremia, often linked to low white blood cells (febrile neutropenia, or FN) [11]. Several associated factors have been suggested for the higher incidence of infectious complications, including > 18 years of 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]. Nevertheless, the failure to prevent these complications necessitates further investigations into other previously overlooked factors associated with them. 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 FN were evaluated in patients with lymphoma who receive BMT after high-dose chemotherapy.

Methods

Study design and patients' inclusion

In this prospective study, 147 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 to the Ghazi Hospital in Tabriz (the only tertiary referral hospital for haemato-oncological diseases in north-west Iran) were consecutively included between December 1, 2016, and July 30, 2022. Patients were excluded if they had co-morbidities and those who were heavily treated (received more than three chemotherapy protocols). The study was conducted following the declaration of Helsinki, and each patient gave informed consent. We obtained ethical clearance from the medical ethics committee at Tabriz University of Medical Sciences in Iran.

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. The hospital staff employed strict handwashing procedures using disinfectant agents before entering patients' rooms. BMT and standard medical care were performed following established guidelines [16]. After admission, patients received a 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 a 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) from the day of BMT until three months later [16].

Study variables

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 fluid balance measurements (Intake–Output) were conducted three, two and one day before transplantation and on the transplantation day. After transplantation, the neutrophil count was measured daily, and body temperature was evaluated meticulously in the armpit (axillary). A neutrophil count less than 1.5×10^9/L was considered 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 it lasted more than one hour. As elucidated above, FN was defined as a simultaneous presence of fever and neutropenia.

Profound neutropenia was defined as a neutrophil count < 500 cells/μL or a neutrophil count < 1000 cells/μL when a further decrease to < 500 cells/μL over the next 48 hours was expected [18].

Statistical analysis

Data are presented as mean ± standard deviation (SD) or frequency and percentage. The Kolmogorov-Smirnov test evaluated the normal distribution of the data. Chi-square or Fischer's exact test was conducted on categorical data, and the student T-test or Mann-Whitney U test was used to compare 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 (OR) with 95% confidence intervals (CI) were calculated. The analysis was performed using SPSS v 24. A p-value < 0.05 was considered statistically significant.

Results

A total of 147 lymphoma patients were included. **Table 1** describes the baseline characteristics of

Table 1. Baseline characteristics of lymphoma patients undergoing bone marrow transplantation with and without febrile neutropenia.

	Subtype	Total	Febrile neutropenia (n = 91)	Non-Febrile neutropenia (n = 56)	P value
Age $_{\text{mean ± SD}}$		35 (10)	37 (11)	31 (10)	0.113*
BMI $_{\text{mean ± SD}}$		30.05 (22.14)	32.18 (27.84)	26.55 (4.36)	0.512**
Gender $_{\text{n (%)}}$	Male	104 (70.7)	61 (67.0)	43 (76.7)	0.733#
	Female	43 (29.3)	30 (33.0)	13 (23.3)	
Type of lymphoma $_{\text{n (%)}}$	NHL	48 (32.7)	29 (31.9)	19 (33.9)	0.990#
	HD	99 (67.3)	62 (68.1)	37 (66.1)	
Blood group $_{\text{n (%)}}$	A+	37 (25.2)	17 (18.7)	20 (35.3)	0.595$
	A-	5 (3.4)	2 (2.2)	3 (5.9)	
	B+	30 (20.4)	20 (22.0)	10 (17.6)	
	B-	5 (3.4)	5 (5.4)	0 (0)	
	AB+	9 (6.1)	9 (9.9)	0 (0)	
	AB-	0 (0)	0 (0)	0 (0)	
	O+	52 (35.4)	32 (35.2)	20 (35.3)	
	O-	9 (6.1)	6 (6.6)	3 (5.9)	
Number of radiotherapy courses before BMT $_{\text{mean ± SD}}$		11 (12)	10 (12)	19 (5)	0.471**
Number of chemotherapy courses before BMT $_{\text{mean ± SD}}$		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.
BMI = Body mass index, BMT = Bone marrow transplantation, NHL = Non-Hodgkin lymphoma, HL = Hodgkin lymphoma, SD = Standard deviation, n = Number.

Table 2. Laboratory test results before bone marrow transplantation in lymphoma patients with and without febrile neutropenia.

	Days before BMT	Total	Febrile neutropenia	Non-Febrile neutropenia	P-value
ESR (mm/h)	0	21.41 (14.66)	26.00 (7.31)	14.38 (10.02)	0.002
	-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 (mg/L)	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)	4.70 (1.51)	3.74 (1.18)	0.048
	-5	6.38 (2.16)	7.96 (2.25)	5.74 (1.80)	0.012
	-10	4.91 (1.32)	5.58 (1.33)	4.60 (1.22)	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 (IU/L)	0	373 (351)	460 (127)	289 (89)	0.030
	-5	415 (170)	476 (216)	341 (113)	0.006
	-10	484 (184)	600 (180)	362 (104)	0.007
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)	0.129
Plt (cells $*10^3$/L)	0	129.5 (63.2)	126.9 (52.1)	133.6 (79.2)	0.791
	-5	143.2 (60.6)	135.2 (53.6)	156.4 (70.2)	0.367
	-10	104.9 (48.0)	98.85 (48.3)	114.9 (47.2)	0.246
MPXI (Index)	0	7.01 (13.74)	6.72 (15.84)	7.47 (9.94)	0.399
	-5	-2.45 (8.59)	-3.60 (8.50)	-0.56 (8.67)	0.178
	-10	-4.89 (9.39)	-4.89 (9.71)	-4.90 (9.13)	0.935
LUC (109/L)	0	0.31 (0.85)	0.41 (1.07)	0.14 (0.11)	0.276
	-5	0.52 (0.62)	0.56 (0.74)	0.44 (0.32)	0.990
	-10	0.12 (0.14)	0.14 (0.13)	0.10 (0.16)	0.225
Retic count (%)	0	1.07 (0.90)	1.06 (1.13)	1.08 (0.70)	0.720
	-5	1.50 (0.00)	1.50 (0.00)	-	-
	-10	0.35 (0.21)	0.35 (0.21)	-	-
Fluid balance (ml)	-1	771.05 (902.51)	300.00 (53.19)	892.73 (297.29)	0.004
	-2	879.47 (195.00)	563.75 (162.87)	1418.18 (165.1)	0.012
	-3	437.50 (960.99)	148.89 (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 ($\times 10^6$)		14.56 (49.34)	22.82 (65.11)	3.75 (2.45)	0.837
Number of administered packed cells		1 (1)	2 (1)	1 (1)	0.038**
Number of administered units of platelet		16 (11)	19 (12)	12 (3)	0.014**

Data are presented as mean ± SD; the analysis is performed using the Mann-Whitney U test.
Days are reported concerning the date of bone marrow transplantation (BMT): 0 = the day of BMT, -5 = five days before BMT, -10 = ten days before BMT; Hb = Hemoglobin, Plt = platelet, MPXI = Myeloperoxidase index, LUC = Large unstained cells.

Table 3. Relationship between study variables and febrile neutropenia in lymphoma patients undergoing bone marrow transplantation.

	Subtype/ day	Unadjusted Odds ratio	95% CI		P-value	Adjusted Odds ratio*	95% CI		P-value
			Lower	Upper			Lower	Upper	
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-	-	0.000	-	0.999	-	-	-	-
	AB+	-	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	2.118	1.010	2.937	0.031
ESR	0	1.034	0.987	1.084	0.061				
	-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	0	1.091	0.636	1.87	0.752	-	-	-	-
	-5	1.343	0.774	2.327	0.294	-	-	-	-
	-10	2.263	0.557	9.189	0.253	-	-	-	-
Uric acid	0	1.572	1.318	1.827	0.061	1.601	1.124	2.101	0.007
	-5	1.578	1.368	1.909	0.018	1.525	1.288	1.958	0.036
	-10	1.535	1.300	1.953	0.034	1.617	1.328	1.963	0.035
Fibrinogen	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	0	1.401	1.098	1.904	0.007	1.501	1.198	2.104	0.004
	-5	1.411	1.099	1.941	0.007	1.471	1.118	1.933	0.006
	-10	1.421	1.097	1.955	0.006	1.462	1.107	1.915	0.007
WBC	0	1	1	1	0.087	-	-	-	-
	-5	1	1	1	0.288	-	-	-	-
	-10	1	1	1	0.637	-	-	-	-
N	0	1	1	1	0.072	-	-	-	-
	-5	1	1	1	0.706	-	-	-	-
	-10	1	1	1	0.744	-	-	-	-
Hb	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	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	-	-	-	-
	-5	1.446	0.415	5.036	0.562	-	-	-	-
	-10	7.005	0.057	868.347	0.429	-	-	-	-
Fluid balance	-1	0.680	0.331	0.841	0.004	0.670	0.312	0.801	0.004
	-2	0.638	0.399	0.801	0.009	0.602	0.299	0.870	0.007
	-3	0.799	0.398	0.890	0.007	0.637	0.304	0.708	0.006
Ferritin		0.999	0.997	1.002	0.632	-	-	-	-

* Adjusted for age, gender, Body mass index (BMI), and type of lymphoma. Only those significant variables in unadjusted simple regression were considered in multiple regression analysis.
Days are reported in relation to date of BMT (0 = the day of BMT, -5 = five days before BMT, -10 = ten days before BMT), N = neutrophil count, Hb = Hemoglobin, Plt = platelet, MPXI = Myeloperoxidase index, LUC = Large unstained cells.

Table 4. Relationship between study variables and febrile neutropenia with profound neutropenia in lymphoma patients undergoing bone marrow transplantation.

	Subtype/ day	Unadjusted Odds ratio	95% CI		P-value	Adjusted Odds ratio*	95% CI		P-value
			Lower	Upper			Lower	Upper	
Age		1.864	0.613	3.115	0.606	-	-	-	-
Gender	Male	1.729	0.212	3.245	0.539	-	-	-	-
	Female	0.886	0.505	1.267	0.532	-	-	-	-
BMI		1.384	0.030	2.738	0.570	-	-	-	-
Type of lymphoma	NHL	2.938	0.589	5.286	0.593	-	-	-	-
	HL	0.811	0.426	1.196	0.817	-	-	-	-
Number of radiotherapy courses		2.171	0.182	4.160	0.800	-	-	-	-
Number of chemotherapy courses		1.036	0.400	1.671	0.523	-	-	-	-
Number of administered packed cells		1.800	1.735	1.865	0.035	1.913	-1.615	5.441	0.629
Blood type	A+	2.426	0.789	4.062	0.741	-	-	-	-
	A-	1.431	0.711	2.150	0.826	-	-	-	-
	B+	0.690	0.071	1.310	0.600	-	-	-	-
	B-	2.600	0.173	5.027	0.636	-	-	-	-
	AB+	1.045	0.063	2.027	0.834	-	-	-	-
	AB-	1.184	0.817	1.550	0.600	-	-	-	-
	O+	2.765	0.303	5.228	0.957	-	-	-	-
	O-	1.984	0.022	3.946	0.752	-	-	-	-
Number of administered units of platelet		1.600	1.543	1.656	0.025	1.924	1.867	1.981	0.014
ESR	0	2.045	0.876	3.214	0.846	-	-	-	-
	-5	1.602	0.884	2.321	0.197	-	-	-	-
	-10	2.781	0.869	4.693	0.737	-	-	-	-
CRP	0	2.846	0.733	4.960	0.542	-	-	-	-
	-5	2.102	0.608	3.596	0.853	-	-	-	-
	-10	2.486	0.525	4.447	0.987	-	-	-	-
Uric acid	0	1.356	1.224	1.488	0.008	1.748	1.615	1.880	0.010
	-5	1.167	1.121	1.212	0.030	1.606	1.341	1.871	0.034
	-10	1.326	1.060	1.591	0.027	1.654	1.522	1.786	0.031
Fibrinogen	0	0.939	0.645	1.233	0.379	-	-	-	-
	-5	2.843	0.659	5.027	0.796	-	-	-	-
	-10	0.627	0.153	1.101	0.239	-	-	-	-
LDH	0	1.942	1.885	1.998	0.005	1.952	1.687	2.217	0.015
	-5	1.739	1.683	1.796	0.006	1.416	1.370	1.462	0.021
	-10	1.468	1.202	1.733	0.045	1.043	0.987	1.100	0.035
WBC	0	2.926	0.853	4.999	0.846	-	-	-	-
	-5	1.777	0.178	3.376	0.521	-	-	-	-
	-10	1.190	0.462	1.917	0.225	-	-	-	-
N	0	0.510	0.445	0.575	0.124	-	-	-	-
	-5	1.944	0.336	3.551	0.071	-	-	-	-
	-10	2.937	0.530	5.343	0.630	-	-	-	-
Hb	0	0.671	0.646	0.696	0.041	-	-	-	-
	-5	0.668	0.501	0.835	0.038	-	-	-	-
	-10	0.599	0.364	0.833	0.039	-	-	-	-
Plt	0	2.496	0.172	4.819	0.883	-	-	-	-
	-5	2.247	0.383	4.110	0.381	-	-	-	-
	-10	1.213	0.266	2.160	0.720	-	-	-	-
MPXI	0	2.868	0.484	5.252	0.681	-	-	-	-
	-5	1.954	0.351	3.557	0.410	-	-	-	-
	-10	2.169	0.616	3.722	0.963	-	-	-	-
LUC	0	1.467	0.749	2.185	0.110	-	-	-	-
	-5	0.925	0.031	1.819	0.309	-	-	-	-
	-10	0.913	0.573	1.253	0.939	-	-	-	-
Fluid balance	-1	0.344	0.144	0.544	0.015	0.424	0.206	0.643	0.004
	-2	0.531	0.516	0.546	0.024	0.769	0.640	0.898	0.033
	-3	0.639	0.603	0.674	0.038	0.827	0.755	0.899	0.024
Ferritin		1.349	0.606	2.093	0.813	-	-	-	-

* Adjusted for age, gender, Body mass index (BMI), and type of lymphoma. Only those significant variables in unadjusted simple regression were considered in multiple regression analysis.
Days are reported concerning the date of BMT (0 = the day of BMT, -5 = five days before BMT, -10 = ten days before BMT), N = neutrophil count, Hb = Hemoglobin, Plt = platelet, MPXI = Myeloperoxidase index, LUC = Large unstained cells.

the patients. Patients' age was 34.79 ± 10.49, and 29.3% of the patients were female. On average, FN occurred in 91 patients (61.9%) after 12.77 ± 2.45 days after BMT.. No statistically significant difference was seen between the two groups (those with FN 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 FN had received packed cells more frequently than the non-FN group (2 ± 1 in the FN group vs 1 ± 1 in the non-FN group, $p = 0.038$, **Table 3**). Also, more platelet units were administered in the FN group (19 ± 12 in the FN group vs 12 ± 3 in the non-FN group, $p = 0.012$).

Patients with FN had significantly higher erythrocyte sedimentation rates (ESR) than non-FN groups on days 0, -5, and -10 (p values = 0.002, 0.048, and 0.050, respectively). Moreover, uric acid was significantly higher in patients with FN on all three days of 0, -5, and -10 (p values = 0.048, 0.012, and 0.021, respectively). Accordingly, we found a significantly lower fluid balance at days -1, -2, and -3 before BMT in the FN group (p values = 0.004, 0.012, and 0.038). Furthermore, lactate dehydrogenase (LDH) was significantly higher in patients with FN on all three days of 0, -5, and -10 (p values = 0.030, 0.006, and 0.007, respectively).

Logistic regression analysis demonstrated a significant positive relationship between the development of FN and the number of administered packed cells, the number of administered units of platelet, ESR (at day -10), uric acid, and LDH (**Table 3**). Moreover, we detected an inverse relationship between fluid balance and the development of FN. When the analysis for these variables was adjusted with baseline characteristics including age, gender, BMI, and type of lymphoma, the results of multivariate regression analysis revealed that the number of administered units of platelet, uric acid, LDH, and fluid balance were independent predictors of FN (**Table 3**). Uric acid had a positive relationship with FN, suggesting that the higher uric acid level was associated with a higher risk of FN (highest adjusted OR at day -10 = 1.617, 95% CI = 1.328 – 1.963, p value = 0.035). LDH also positively correlated with FN (highest adjusted OR at day 0 = 1.501, 95% CI = 1.198 – 2.104, p-value = 0.004). The fluid balance inversely correlated with FN, suggesting that the lower fluid balance was associated with a higher risk of FN (lowest adjusted OR at day -2 = 0.602, 95% CI = 0.299 – 0.870, p-value = 0.007). The number of administered platelet units positively correlated with FN, suggesting that the higher number of units of platelet could lead to a higher risk of FN (adjusted OR = 2.118, 95% CI = 1.010 – 2.937, p value = 0.031).

FN with profound neutropenia was detected in 41 patients (27.8%). A significant positive relationship was identified between the occurrence of FN with profound neutropenia and various factors, including the administration of packed cells, platelet units, haemoglobin (Hb), uric acid levels, and LDH (**Table 4**). An inverse correlation was also observed between fluid balance and the development of FN with profound neutropenia. After adjusting for baseline characteristics such as age, gender, BMI, and lymphoma type, the results of the multivariate regression analysis demonstrated similarly that the number of administered platelet units, uric acid levels, LDH, and fluid balance independently served as predictors for the occurrence of FN with profound neutropenia (**Table 4**).

Discussion

There is a growing concern about the widespread emergence of multidrug-resistant microorganisms in medical centres, especially in haematology-oncology wards [19,20]. These microorganisms diminish the effectiveness of routine antibacterial prophylaxis with oral fluoroquinolones in patients undergoing BMT or AHSCT [19,21,22]. In one study, discontinuing the administration of antibacterial prophylaxis in AHSCT recipients did not significantly affect the early mortality of the patients after transplantation [23]. Therefore, bacterial prophylaxis should be considered for only high-risk patients [14]. However, a risk stratification system is yet to be established for such cases. One of the reasons can be that the related and predictive factors still need to be fully recognized. Considering the close association of FN with infection in lymphoma patients receiving BMT [11], we evaluated the incidence and associated clinical and paraclinical factors of post-transplantation development of FN in this prospective study. A considerably high incidence of FN

occurred in these patients in our study, similar to previous studies' reports [24-26]. No significant differences were detected in baseline characteristics between those patients who developed FN and those who did not (non-FN); however, some other related factors were significantly different between groups, including the number of administered packed cells, the number of administered platelet units, ESR, uric acid, and LDH. We also found a significantly lower fluid balance before BMT in patients with FN. Our further analysis by controlling for baseline characteristics revealed that uric acid, LDH, fluid balance, and the number of administered units of platelet were significant predictors of FN. The prognostic value of serum uric acid for both short and long-term outcomes of admitted medical patients has been emphasized in previous studies [27]. Likewise, serum uric acid positively correlates with poor outcomes and mortality [28-30]. On the other side, a study on 112 lymphoma patients undergoing BMT revealed that LDH > 330 U/l was a significant adverse predictor of survival in these patients [31]. Reduced survival of the lymphoma patients undergoing BMT with higher LDH can be due to the higher rates of FN following BMT, which supports our findings [31]. Therefore, uric acid and LDH could be considered in future studies for risk stratification of patients undergoing BMT for the possibility of developing FN.

Another significant aspect of our findings was that higher uric acid and lower fluid balance can both suggest suboptimal hydration in FN patients before BMT. Adequate hydration is essential and can increase antimicrobial therapy results [32]. Furthermore, it can diminish the risk of urinary tract infections [32]. These findings highlight the importance of adequate hydration of the patients over the days before BMT for reducing the risk of FN.

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, it can be more helpful if these factors are evaluated a few days before transplantation so that the clinicians have more time to modify the treatment strategies, such as bacterial prophylaxis. Furthermore, we observed some dissimilarity in the results of laboratory tests on different days (-10, -5, 0), which also impacted the extent of the relationship of these tests' results with the development of FN. This finding can highlight the time-dependent feature of the laboratory tests for predicting FN.

Other studies have identified several other related factors, including the time to platelet engraftment [33], the number of stem cells infused [34], duration of neutropenia [35,36], contamination of stem cells, presence of an indwelling central venous catheter, therapy-related mucosal damage [37,38]. However, these factors are mostly related to the post-transplantation period or during the procedure of transplantation; therefore, they may not be valuable for risk stratification and modification of pre-transplantation treatment.

We want to address some limitations of our study. 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 FN is significantly high in lymphoma patients who receive BMT. A higher number of administered platelet units, higher LDH, higher uric acid, and lower fluid balance before BMT are significantly associated with FN and even FN with profound neutropenia. Accordingly, controlling the fluid balance by measuring daily input and output and adequate hydration of the patients is paramount for preventing FN in patients who receive BMT. Furthermore, uric acid and LDH could be considered in future studies for risk stratification of patients undergoing BMT for the possibility of developing FN.

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

Authors' contributions: BN and ZK Conceived the idea.. BN, ZK, MV, and RD designed the study methodology. MF, AP, and ZK conducted the study. ZK and MF analyzed the data.. RD, AP, and BN interpreted the results.. ZK, MF, AP, and MV wrote the draft manuscript..BN and RD revised and edited the final manuscript. BN, ZK,RD,MV, and MF approved the manuscript.

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