Predictive Factors for Survival Outcomes of High-Risk Febrile Neutropenic Patients: a 3-Year Study at a Single Center in Thailand

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ABSTRACT

Objective: This study aimed to identify the risk factors associated with mortality in febrile neutropenic patients.

Materials and Methods: This 3-year, single center, retrospective, observational study was conducted at Chiangrai Prachanukroh Hospital, Chiangrai Province, Thailand. The inclusion criteria consisted of a patient age of over 15 years and a diagnosis of febrile neutropenia.

Results: Most of the 303 febrile neutropenic inpatients had a Multinational Association for Supportive Care in Cancer (MASCC) risk score < 21. The median length of stay was 6 days (interquartile range: 4-11 days). During 30 days of admission, 24.8% of the patients succumbed. In a univariate analysis, patients receiving G-CSF, the post-chemotherapy-related group, patients with MASCC score > 16, and patients admitted in private had significantly higher survival rate. In a multivariate analysis, a MASCC score ≤ 16 and non-chemotherapy-related groups were associated with an increased mortality risk.

Conclusion: The 30-day survival rate of febrile neutropenic patients in Thailand is seventy-five percent. Low MASCC score and non-chemotherapy-related neutropenia are associated with a higher risk of unfavorable outcomes.

Keywords: Febrile neutropenia; risk factors; mortality; Thailand; developing country (Siriraj Med J 2019; 71: 339-348)

INTRODUCTION

Febrile neutropenia is usually accompanied by other signs and symptoms of infection. The treatment outcomes of these patients, especially those in the high-risk group, are associated with high morbidity and mortality.[1] In cases with severe infections, previous guidelines recommend that patients should be admitted to hospital.[2,3] The hospital stays of febrile neutropenic patients with solid tumors and hematological malignancies have been reported to be approximately 1 to 2 weeks.[4] Most febrile neutropenia occurs during chemotherapy, especially in cases of hematologic malignancies and solid cancers.[5] Moreover, it could result from other neutropenia-causing diseases, for example, aplastic anemia, drug-induced agranulocytosis, HIV infections, and autoimmune diseases.[6-9] The treatment is costly due to both the length of the hospital stay and the associated complications. A retrospective study has reported the clinical and economic burden arising from the hospitalization of this patient group. The mean duration of hospitalization with febrile neutropenia in all cancer patients was 6 days and the median cost was $8,376 per episode of febrile neutropenia.[10]

These problems are present in all countries. From a previous study of patients with febrile neutropenia in a developed country, the mortality rate during admission was 10%, and the mean hospitalization duration was

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http://dx.doi.org/10.33192/Smj.2019.52

8.6 days.[11] The outcomes for developing countries still need to be documented. The present cohort study aimed to demonstrate data on the predictive factors and survival outcomes of patients with febrile neutropenia at a single center in a developing country.

MATERIALS AND METHODS

This 3-year, single center, retrospective, observational study was conducted at Chiangrai Prachanukroh Hospital, Chiangrai Province, Thailand. It focused on patients with febrile neutropenia who had been admitted to medical wards between January 1, 2014 and December 31, 2016. The inclusion criteria were (1) a patient age of over 15 years and (2) a diagnosis of febrile neutropenia. The patients were identified through the ICD-10-CM diagnosis code database using the codes for fever (R50) and agranulocytosis (D70). The primary outcome of the study was to identify the risk factors associated with mortality in febrile neutropenia. The clinical characteristics, clinical outcomes, laboratory findings, treatments and complications were recorded as secondary outcomes. This study was approved by the Ethical Committee for Research in Human Subject at Chiangrai Prachanukroh Hospital (0032.102/15693).

Terminology

Febrile neutropenia is a condition of fever > 38.3°C or > 38°C for 1 hour, with an absolute neutrophil count (ANC) of ≤ 500 cells/cu mm, or an ANC of ≤ 1,000 cells/cu mm with an expected nadir of ≤ 500 cells/cu mm.[12]

The Multinational Association for Supportive Care in Cancer (MASCC) risk index is a scoring method for identifying low-risk of complications in cancer patients with febrile neutropenia. This score comprises the following factors: burden of febrile neutropenia, hypotension, chronic obstructive pulmonary disease, previous fungal infection, dehydration, and age. Scores ≥ 21 signify a low-risk group of complications, while scores < 21 indicate a high-risk group of complications in patients with febrile neutropenia.[13]

Multi-drug resistant (MDR) organism is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories.[14] Severe infection is determined as severe sepsis by clinical of systemic inflammatory response syndrome with evidence of infection and end-organ dysfunction such as altered mental status, hypotension, oliguria (urine output < 0.5 ml/kg/hr) or hypoxia.[2]

Statistical analysis

PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the data. The sample size (330 cases) was calculated by the proportion of mortality rate between two groups from the previous study.[15] The critical value was 1.96 with 90% power. Continuous variables were represented as mean ± standard deviation, or median and interquartile range (IQR). For the continuous variables comparison consisting of age, complete blood counts and blood chemistry investigations, the results were calculated by the Mann–Whitney U test or student's t-test. Categorical variables including gender, diseases, MASCC risk index, infections and clinical outcomes were presented as frequency and percentage, and they were compared using Fisher's exact or chi-square test. The survival analysis and predictive factors associated with survival were compared using the log-rank test and presented as a Kaplan–Meier survival curve. A Cox proportional hazards analysis (enter method) was used for the univariate and multivariate factors associated with survival outcome, and they were exhibited as hazard ratio (HR) and 95% CI. A p-value < 0.05 was defined as statistically significant.

RESULTS

Baseline characteristics of febrile neutropenic patients

This study enrolled 303 cases of febrile neutropenic patients. In all, 328 cases were admitted to medical wards during the 3-year study period. Of the included cases, twenty-five were excluded: twenty-two were incompatible with the diagnostic criteria of febrile neutropenia, and the remaining three had inadequate documentation. The mean age was 53±2 years, and females predominated (51.4%). A large number of patients had hematologic diseases and solid cancers, which included acute leukemia (27.7%), solid tumors (21.1%), aplastic anemia (18.8%), and lymphoma (18.2%). The clinical severity of the patients was determined by their MASCC risk score. The median was 16 (IQR: 13-18), with 91.4% (277 cases) having a score below 21, indicating that they had a high-risk of febrile neutropenia.

According to the initial laboratory findings, the complete blood counts showed a median hemoglobin of 8.0 g/dl (IQR: 6.0–9.0 g/dl); a median ANC of 150 cells/cu mm (IQR: 13–385 cells/cu mm); a median platelet count of 28,000 cells/cu mm (IQR: 10,000-80,000 cells/cu mm). All initial laboratory results are summarized in Table 1.

Infectious etiologies, treatments, and survival outcomes

Organ-specific symptoms of infection were seen in 57.8% of patients. Respiratory tract infections were the most common (22.8%); they were followed by gastrointestinal

TABLE 1. The demographic and clinical characteristics and laboratory findings of febrile neutropenic patients.

	Febrile neutropenic patients (n = 303) Positive results (%)
Age (years), mean ± SD	53 ± 17
Gender	
Female	166 (54.8%)
Diseases	
Solid cancers	64 (21.1%)
Acute leukemia	84 (27.7%)
Aplastic anemia	57 (18.8%)
Lymphoma	55 (18.2%)
Myelodysplastic syndrome	10 (3.3%)
Multiple myeloma	3 (1.0%)
Infections	23 (9.6%)
Autoimmune disease	1 (0.3%)
Median MASCC score	16 (13–18)
0-10	63 (20.8%)
11-20	214 (70.6%)
21-23	26 (8.6%)
Laboratory findings	
Complete blood count	
Median Hb level (g/dl)	8.0 (6.0–9.0)
Median WBC count (cells/cu mm)	1,100 (600–1,800)
Median ANC count (cells/cu mm)	150 (13–385)
Median platelet count (cells/cu mm)	28,000 (10,000–80,000)
Blood chemistry	
Median creatinine (mg/dl)	1 (0.7–1.0)
Median albumin (g/dL)	3.0 (2.6–3.6)
Median total bilirubin (mg/dl)	1 (0.6–1.6)
Median direct bilirubin (mg/dl)	0.2 (0–0.7)
Median aspartate aminotransferase (U/L)	30 (20–52)
Median alanine aminotransferase (U/L)	22 (14–42)

Abbreviations: MASCC = the Multinational Association for Supportive Care in Cancer; SD = standard deviation; WBC = white blood cell; ANC = absolute neutrophil count

infections (16.8%). Nearly 20% of the patients had positive blood culture. The most common infectious organisms were gram negative bacteria: *Acinetobacter* spp. (9.2%), *Escherichia coli* (8.3%), *Pseudomonas* spp. (5.3%), and *Klebsiella* spp. (5%). Furthermore, multidrug-resistant bacterial infections were recorded at 14.5%, while fungal infections were present in a small number of patients. These results are illustrated in Table 2.

The median length of hospital stay was 6 days (IQR: 4-11 days). The median duration of an ANC below 500 cells/cu mm was 3 days (IQR: 2-7 days). Approximately 85% of cases were admitted to a common ward. Eighty-three percent of the patients received an antibiotic within 4 hours. Sixty percent of the patients had post-chemotherapy associated neutropenia, and nearly half received granulocyte colony stimulating factor (G-CSF) after developing febrile neutropenia. As to the complications, acute respiratory failure developed in 64 cases (21.1%), while another 60 (19.8%) had clinical of shock.

Of the 303 febrile neutropenic patients, 228 (75.2%) survived and were discharged from the hospital. By the 30th day of febrile neutropenia, Fifty-three patients (70% of dead cases) died during neutropenic time, before their neutrophil recovering. The common causes of death were severe infections (83.5%) and bleeding associated with thrombocytopenia (12.7%). In the mortality group, the median survival during admission was 6 days (IQR: 2–9 days), as shown in Table 2.

Risk factors associated with mortality outcome

We classified the patients into 2 groups to determine predictive factors that might impact on the survival outcomes during 30 days of admission. In a univariate analysis, a patient age ≤ 60 years had a 30-day survival rate of 77.3%, while the corresponding figure for those aged > 60 years was 69.6% (p = .175; Fig 1A). The 30-day survival rate in patients with ANC ≤ 100 cells/cu mm was not significantly different from those with ANC > 100 cells/cu mm (71.9% versus 76.2%, p = .421). The 30-day survival rate for patients receiving G-CSF was 84.9%, compared with 65.6% for those who did not receive G-CSF (p = < .001; Fig 1B). Furthermore, the post-chemotherapy-associated neutropenia group had 30-day survival rate of 83.2%, which was superior to the non-chemotherapy-related group (60.5%; p = < .001; Fig 2A). For MASCC score, the lower score is associated with higher risk of complications of febrile neutropenia. A MASCC score ≤ 16 yielded a 30-day survival rate of 58.2% whereas a MASCC score > 16 had a 30-day survival rate of 96.7% (p = < .001; Fig 2B). Patients who were admitted to a private room must be clinically stable and needed to copay for their stay. These group was found to have a 30-day survival rate of 88.4%, which was moderately higher than the 72.0% for those admitted to a general ward (p = .034; Fig 3A). In addition, patients who received antibiotics < 4 hours and ≥ 4 hours after arrived at ward had 30-day survival rate of 73.7% and 78%, respectively (p = .481; Fig 3B). Focusing on the duration of neutropenia in each group, the groups with aged > 60 years, ANC > 100 cells/cu mm, receiving G-CSF and receiving antibiotics < 4 hours had significantly shorter neutropenic duration (Table 3).

In a multivariate analysis, the results showed that an MASCC score ≤ 16 and the non-chemotherapy-related group were associated with an increased risk of mortality (HR = 16.88, 95% CI = 6.15–46.32, p = < .001; and HR = 2.37, 95% CI = 1.19-4.72, p = .014, respectively). Table 3 exhibits the univariate and multivariate analyses of the risk factors impacting on the survival outcomes of febrile neutropenic patients during 30 days of admission.

Subgroup analysis

We selected 277 patients who were categorized as a high-risk group by MASCC score to analyze the survival outcome. The patients who received G-CSF, or developed febrile neutropenia after chemotherapy, or had MASCC score > 16 were more likely to have significantly better survival outcome in a univariate analysis. In a multivariate analysis, the patients with MASCC score > 16 and those who developed febrile neutropenia after chemotherapy were correlated with better outcome (Supplementary Table S1).

Furthermore, subgroup analysis of the patients who developed febrile neutropenia after chemotherapy revealed that MASCC score ≤ 16 leaded to an increased risk of mortality when compared to those with MASCC score > 16 (HR = 58.14, 95% CI = 3.05–1,108.10, p = .007).

DISCUSSION

This study aimed to identify the risk factors associated with a fatality outcome for febrile neutropenic patients during a 30-day admission period. Approximately 70% of the patients were cancer cases. Almost all cases had a clinical severity by MASCC risk score below 21, which is considered to signify a high risk.[16] In a univariate analysis, favorable factors of survival outcome consist of chemotherapy-associated neutropenia, G-CSF exposure, admitted to private room, and MASCC score > 16. Post-chemotherapy-associated neutropenia patients had more favorable outcomes. This would be because these patients

TABLE 2. The infections, complications and outcomes of febrile neutropenic patients.

	Febrile neutropenic patients (n = 303) Positive results (%)
Infections	
Site of infection	57.8%
Respiratory	22.8%
Gastrointestinal	16.8%
Genitourinary	11.2%
Bacteremia	19.1%
Skin and soft tissue	8.9%
Head and neck	3%
Central nervous system	0.7%
Infectious organisms	37.3%
Bacteria	
Acinetobacter spp.	9.2%
Escherichia coli	8.3%
Pseudomonas spp.	5.3%
Klebsiella spp.	5.0%
Streptococcus spp.	4.6%
Staphylococcus spp.	3.3%
Enterococcus spp.	2.3%
Multidrug-resistant bacteria	14.5%
Fungus	
Penicillium spp.	2.3%
Aspergillus spp.	1.7%
Candida spp.	1.0%
Complications	
Respiratory failure	21.1%
Shock	19.8%
Median duration of ANC < 500 cells/cu mm (days)	3 (2-7)
Median length of hospital stays (days)	6 (4-11)
Outcomes on 30th day	
Death	75 (25.6%)
Median time to death (days)	6 (2-9)
Cause of death	
Infection	83.5%
Bleeding	12.7%

Abbreviation: ANC = absolute neutrophil count

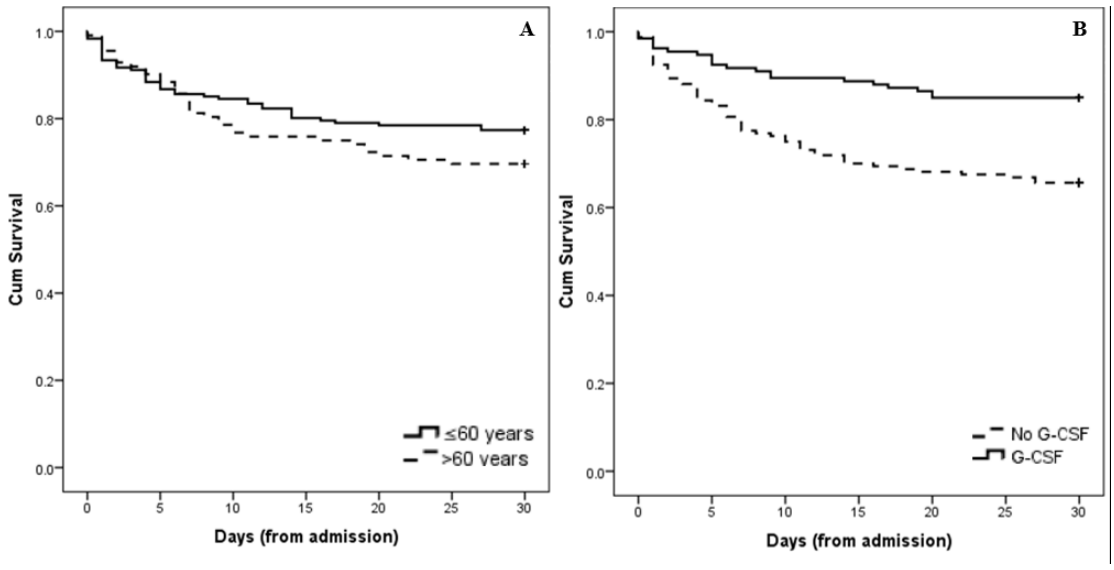

Fig 1. Overall survival curves according to (A) age groups (p-value = .175); (B) receiving G-CSF groups (p-value < .001).

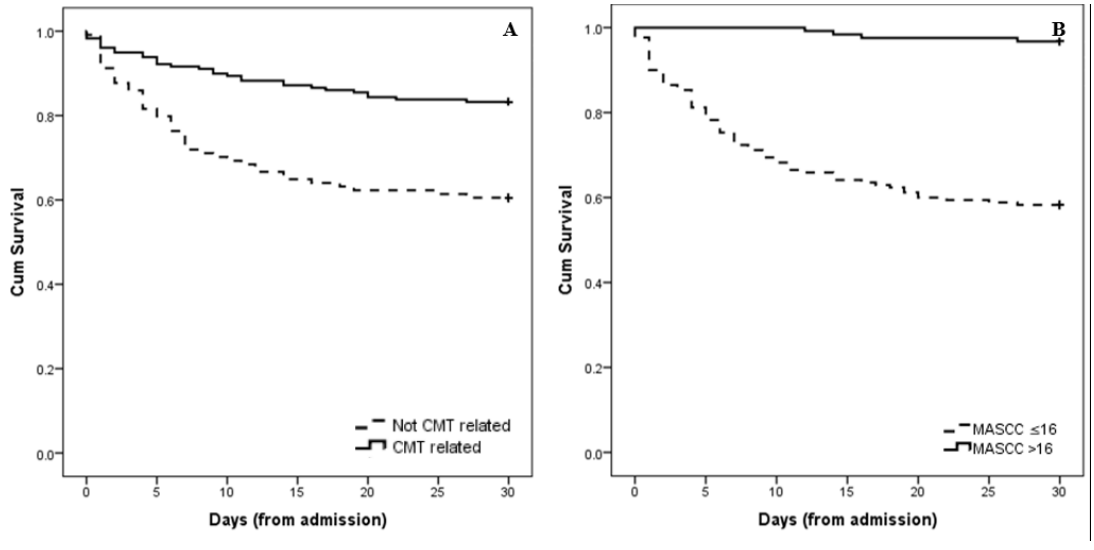

Fig 2. Overall survival curves according to (A) chemotherapy related groups (p-value <.001); (B) MASCC score groups (p-value < .001).

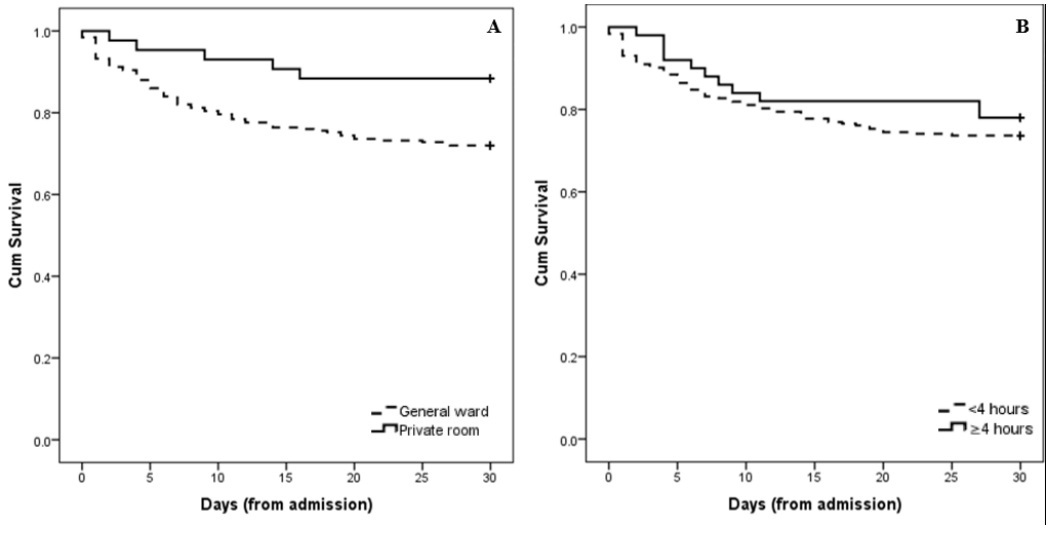

Fig 3. Overall survival curves according to (A) admitted ward-type groups (p-value = .034); (B) time to receive antibiotics (p-value =.481).

TABLE 3. Univariate and multivariate analyses for overall mortality of febrile neutropenic patients (days).

Univariate	N	Median neutropenic duration (days, IQR)	Overall survival (days)	*P*-value	HR (95% CI)
Age				.175	
≤ 60 years	181	4 (2–10)	24.8		1
> 60 years	112	2 (1–4)	23.4		1.37 (0.87–2.16)
ANC					
≤ 100 cells/cu mm	121	4 (2–8)	23.9	.421	1
> 100 cells/cu mm	172	2 (1–6)	25.4		0.83 (0.52–1.31)
G-CSF				< .001	
Yes	133	2 (2–4)	26.7		1
No	160	5 (2–11)	22.2		2.56 (1.54–4.28)
Chemotherapy				< .001	
Yes	179	2 (2–7)	26.4		1
No	114	4 (2–7)	20.9		2.74 (1.72–4.35)
MASCC score				< .001	
> 16	123	3 (2–6)	29.6		1
≤ 16	170	3 (2–9)	20.4		16.42 (5.99–44.99)
Private room				.034	
Yes	43	4 (2–10)	27.6		1
No	250	3 (2–6)	23.7		2.67 (1.08–6.61)
Time to antibiotic (hours)				.481	
< 4	243	3 (2–6)	25.6		1
≥ 4	50	6 (2–15)	24.0		1.26 (0.66–2.39)

Multivariate	*P*-value	HR (95% CI)
No G-CSF	.501	1.30 (0 .61–2.78)
No chemotherapy	.014	2.37 (1.19–4.72)
MASCC ≤ 16	< .001	16.88 (6.15–46.32)
No private room	.210	1.80 (0.72–4.49)

A *p*-value < .05 indicates statistical significance

Abbreviations: ANC = absolute neutrophil count; CI = confidence interval; G-CSF = granulocyte colony stimulating factor; HR = Hazard ratio; IQR = interquartile range, MASCC = the Multinational Association for Supportive Care in Cancer

SUPPLEMENTARY TABLE S1. Univariate and multivariate analyses for overall mortality of high-risk febrile neutropenic patients (days).

Univariate	Overall survival (days)	*P*-value	HR (95% CI)
Age		.396	
≤ 60 years	24.2		1
> 60 years	23.3		1.22 (0.77–1.94)
ANC			
≤ 100 cells/cu mm	23.1	.531	1
> 100 cells/cu mm	24.3		0.86 (0.54–1.37)
G-CSF		< .001	
Yes	26.4		1
No	21.8		2.57 (1.53–4.31)
Chemotherapy		< .001	
Yes	26.1		1
No	20.1		2.86 (1.79–4.57)
MASCC score		< .001	
> 16	29.8		1
≤ 16	20.4		43.87 (6.09–315.96)
Private room		.086	
Yes	27.7		1
No	23.2		2.42 (0.88–6.65)
Time to antibiotic (hours)		.859	
< 4	23.6		1
≥ 4	24.9		1.06 (0.55–2.05)

Multivariate	*P*-value	HR (95% CI)
No G-CSF	.438	1.36 (0 .63–2.96)
No chemotherapy	.022	2.28 (1.13–4.62)
MASCC ≤ 16	< .001	44.07 (6.09–318.79)
No private room	.716	1.21 (0.43–3.41)

A *p*-value < .05 indicates statistical significance

Abbreviations: ANC = absolute neutrophil count; CI = confidence interval; G-CSF = granulocyte colony stimulating factor; HR = Hazard ratio; MASCC = the Multinational Association for Supportive Care in Cancer

could spontaneously achieve neutrophil count recovery after their nadir period. Furthermore, a previous study has confirmed that the use of G-CSF is beneficial to short neutropenic duration in solid cancer patients with high-risk febrile neutropenia receiving chemotherapy.[17] Aplastic anemia and infection were common causes in non-chemotherapy related neutropenic group. A previous large cohort study of aplastic anemia in developing country represented the mortality rate of 9 percents.[7] In addition, increase severity of neutropenia had been reported in advanced HIV infection and leaded to fatal secondary infections.[6] G-CSF may be advantageous to temporary increase of neutrophil counts in patients with severe aplastic anemia with fever.[18] In addition, patients who admitted to private room had better outcomes because this group was possibly correlated with clinically stable, higher socioeconomic status and better nursing care. As to the factors associated with poor outcomes in the multivariate analysis, an MASCC score ≤ 16 and non-chemotherapy-related neutropenia were susceptible to a higher mortality risk. We decided to use MASCC score ≤ 16 and > 16 to divide patients into two groups because 16 is the median score of this cohort and this level was the beginning of the score that can discriminate the outcome between alive and dead. This result was correlated with a large observational study carried out by MASCC score at the beginning of febrile neutropenia in relation to bacteremia, the score <15 represented much higher mortality of 36% compared with 3% in patients with MASCC score ≥21.[19] Taking all into account, we encourage physicians to determine the MASCC score of febrile neutropenia patients early. For patients with lower MASCC scores, especially ≤ 16, or patients who have non-chemotherapy-related neutropenia, extensive investigations, intensive vital sign monitoring, and promptly antibiotics and specific treatments are needed to improve their survival outcomes.

More than 25% of the cases in this cohort died during admission, which is a higher rate than the previously reported results in a developed country.[11] We particularly focused on the survival outcomes on the 30th day of admission because the previous study had shown that the mortality rate ratios were highest within 1 month for patients treated with chemotherapy for malignant diseases.[20] Thrombocytopenic bleeding is listed as the second most common cause of death. Because there are some problems of platelet's availability and utilization of platelets depending on each physician's decision making.

The median duration of an ANC below 500 cells/cu mm was 3 days. This short duration for neutropenic recovery was probably related to the fact that 60.1% of the cases were post-chemotherapy-associated neutropenia, who typically would be able to restore neutrophils to normal levels within a few days.[21] However, many patients in this study died during neutropenic period so we cannot demonstrate the real neutrophil recovery time in this group.

The three most common sources of infection in our study were respiratory tract infections, bacteremia, and gastrointestinal tract infections. Similar to previous results, pneumonia and gastrointestinal infections were the important causes of morbidity and mortality for febrile neutropenic patients.[22] This study found that the most common infectious organisms were gram negative bacteria, with 14.5% being multidrug-resistant organisms. However, fungal infections were only present in a small number of the patients in our study. This is because of the limited availability of computerized tomography of the lungs and the long period for serum galactomannan results. These result in an under-detection of fungal infections, especially invasive pulmonary aspergillosis. The main limitation of our study is that it was a retrospective study; some data, therefore, are lacking or limited. For instance, the exact duration of febrile neutropenia could not be estimated because some patients had history of fever before admitted to the hospital. The complications of this study were mainly focused on acute respiratory failure and shock; nevertheless, other complications might be co-occurred but did not be recorded. Moreover, several primary physicians took care of the febrile neutropenic patients followed an old specific hospital protocol to prescribe antibiotics within 4 hours after making diagnosis. However, current guidelines recommend prescribing antibiotics within an hour. The indications of G-CSF for febrile neutropenia in our hospital during the study period were vary in each physicians. Fortunately, a policy for G-CSF usage in febrile neutropenia in our hospital is recently applied. Further investigation about the outcome after releasing the new policy is ongoing collected.

CONCLUSION

The 30-day survival rate of febrile neutropenic patients in Thailand is seventy-five percents. A low MASCC score and non-chemotherapy-related neutropenia are associated with a higher risk of unfavorable outcomes.

Declaration of conflicting interest: The authors have declared that no conflicts of interest exist.

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