

# Evaluating the Prognostic Role of Monocytopenia in Chemotherapy-Induced Febrile Neutropenia Patients Treated with Granulocyte Colony-Stimulating Factor

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**Objective:** Chemotherapy-induced febrile neutropenia is a common and serious oncological emergency which carries a substantial mortality and morbidity. The main objective of this study is to evaluate the usage of absolute monocyte count (AMC) at presentation as a prognostic factor for patients with chemotherapy-induced febrile neutropenia who were subsequently treated with granulocyte colony-stimulating factor (G-CSF).

**Study Design:** The electronic medical records of our center were used retrospectively to identify patients diagnosed with unprecedented chemotherapy-induced febrile neutropenia treated with G-CSF between January 2010 to December 2020 and diagnosed with solid and hematological malignancies. Patient's demographics, disease characteristics and laboratory investigations were extracted. Disease progression measures were statistically compared between the study groups in the short-term period of follow-up (six days) including absolute neutrophil count (ANC), ANC difference compared to the baseline readings, hospitalization period, and mortality.

**Results:** A total of 80 patients were identified and categorized into two groups namely monocytopenia (n = 34) and non-monocytopenia (n = 46) with an AMC cutoff point of  $0.1 \times 10^9$  cells/L. The monocytopenia group exhibited a worse prognosis with lower ANC values and slower improvement illustrated by the low ANC difference values at all follow up points ( $P$ -value  $\leq 0.05$ ) apart from day 5. A statistically significant lower hospitalization period was also observed in the non-monocytopenia group ( $P$ -value = 0.006). Linear regression analysis evaluated the association between AMC values at admission and ANC values at admission along with subsequent days of follow up which were found to be statistically significant ( $P$ -value  $\leq 0.05$ ). Receiver operating characteristic curves suggest a satisfactory predictability of ANC changes by AMC values at admission, days 1, 2, 3, 4 and 6.

**Conclusion:** Monocytopenia holds a worse prognosis in chemotherapy-induced febrile neutropenia patients treated with G-CSF. In addition, AMC values at presentation represents a potential risk factor that can predict short-term changes regarding ANC measures.

**Keywords:** febrile neutropenia, granulocyte colony-stimulating factor, G-CSF, chemotherapy, absolute monocyte count, monocytopenia, absolute neutrophil count

## Introduction

Febrile Neutropenia is a major and critical complication of chemotherapy provided for cancer patients, ensuring a tremendous impact on healthcare resources and patients' outcomes.<sup>1</sup> Neutropenia is defined by the American Society of Clinical Oncology (ASCO) and Infectious Diseases Society of America (IDSA) joint guideline as an absolute neutrophil count (ANC) of less than 1000 cells/ $\mu$ L. Moreover,

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fever in neutropenic patients has been defined as a single oral temperature of  $\geq 38.3^{\circ}\text{C}$  or a temperature of  $\geq 38.0^{\circ}\text{C}$  persisting over 1 hour.<sup>2</sup> A consistent definition is also provided by the European Society for Medical Oncology (ESMO) clinical practice guidelines, in which febrile neutropenia is defined as an oral temperature of more than  $38.3^{\circ}\text{C}$  or two consecutive readings of more than  $38.0^{\circ}\text{C}$  for two hours and an ANC of less than  $0.5 \times 10^9/\text{L}$  or expected to fall below it.<sup>3</sup>

Various pathophysiological pathways have been hypothesized previously to determine the probable cause of fever in neutropenic patients. To begin with, it has been regarded to the cytokines release by the immune cells and stromal cells in response to microorganisms and molecular motifs.<sup>4</sup> Furthermore, a reduction in anti-inflammatory molecules such as interleukin-10 (IL-10), antimicrobial peptides such as interleukin-1 (IL-1) receptor antagonists would prevent the physiological feedback inhibition of inflammation, intensifying the damage.<sup>4</sup> An elevation in uric acid levels may have a role as well, amplifying the response of innate immune cells to microbial stimulation by elevating the proinflammatory cytokines; tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin-1 alpha (IL-1 $\alpha$ ).<sup>5</sup> A vast amount of evidence regards fever to be a consequence of infection since patients are at a higher risk, albeit the lack of microbiological evidence in certain cases.<sup>6</sup> Fever of unidentified origin was observed in almost 40% of neutropenic patients.<sup>7</sup> A potential reason behind such phenomena can be justified by the release of danger-associated molecular patterns (DAMPs) because of mucosal barrier injury due to the cytotoxic effects of chemotherapeutic agents, which along with the pathogen-associated molecular patterns (PAMPs) eventually results in a substantial inflammatory response provoking fever.<sup>4</sup>

The consequences of febrile neutropenia remain a source of concern that cannot be disregarded with major complications effecting the patient's treatment outcomes, cost, morbidity, and mortality, yet, variations exist due to the cancer type and stage, its treatment, and patient's demographics.<sup>20</sup> The economic burden is considerable with the costs going from \$16,000 to \$19,000 for the extraordinary greater part of patients being hospitalized, in which they require a prolonged hospitalization care period, which might end with the patient's death.<sup>8,9</sup> Additionally, febrile neutropenia patients are 50% more likely to have an infection with 20% of the patients having bacteremia. The most common sights infected being the lungs, the gastrointestinal tract, and the skin.<sup>22</sup> The most

common pathogens isolated were gram negative organisms *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. However, the trend is changing with the predominance of gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* (MRSA), as well as a rise of fungal infections, in particular *Candida*.<sup>10</sup> Therefore, the cornerstone of treatment for febrile neutropenic patients are antibiotics. Low risk patients are indicated oral antibiotics with fluoroquinolone as a primary treatment, which can be given in an outpatient setting even though patients should be cautiously chosen with attentive monitoring for any emergency if one occurs. In comparison, high risk patients are admitted with an intravenous (IV) antibiotics treatment plan including antipseudomonal beta-lactam agents.<sup>1</sup> It is recommended that all patients are continued on antibiotics until the patient is afebrile for at least 48 hours with an ANC exceeding 500 cells/mm<sup>3</sup>.<sup>1,11</sup> Nonetheless, if the patient does not improve, antimicrobial coverage ought to be expanded to cover resistant gram negative, gram positive, anaerobic microorganisms, and fungi.<sup>11</sup>

Notwithstanding anti-microbials, colony stimulating factors might be an essential part of a treatment plan. Evidence from existing literature has proven the favorable effects of colony stimulating factors in reducing the hospitalization and IV antibiotics administration periods.<sup>12</sup> Even though G-CSF does not reduce mortality in chemotherapy induced febrile neutropenia, it has been found that G-CSF added to antibiotics reduces the hospitalization period, antibiotic use, fever, neutropenia, and recovery of the neutrophils number duration.<sup>13,14</sup> Since a growing body of research suggests that the clinical course of neutropenic patients could be predicted by the usage of monocyte measures as monocyte percentage (MP) and absolute monocyte count (AMC). In this work, we hypothesized and tested the idea suggesting that the AMC could predict the clinical responsiveness of G-CSF therapy in febrile neutropenia patients without any age, gender, chemotherapy regimen or malignancy restrictions.

## Patients and Methods

### Patients and Data Collection

The aim of this study is to evaluate the utilization of AMC at presentation as a prognostic factor for patients with chemotherapy-induced febrile neutropenia and subsequently treated with G-CSF. Data was collected from King Abdullah University Hospital (KAUH), a tertiary

care center located in Ar Ramtha, Jordan. We retrospectively identified patients diagnosed with chemotherapy-induced febrile neutropenia for the first time and treated with G-CSF according to the current hospital guidelines between January 2010 to December 2020. The hospital electronic medical records were used to extract the following data including demographics, type of malignancy (solid tumors versus hematological malignancies), distant metastasis, bone marrow involvement, chemotherapeutic regimens and its current cycle, temperature at admission, clinical presentation, comorbidities, blood culture results, number of febrile neutropenia attacks, hospitalization period and mortality. Complete blood count (CBC) and the white blood cells (WBC) differential were also extracted at different time intervals representing the short-term progression or improvement after admission and treatment with G-CSF including day 1 to 6. After day 6, a minority of patients possessed a laboratory follow up results impairing the statistical judgment due to low statistical power, hence they were excluded from the analysis.

A total of 80 patients were enrolled. Exclusion criteria included patients missing key data such as CBC and WBC differential at presentation with no follow up laboratory results, patients did not get G-CSF therapy, non-malignant cases which developed febrile neutropenia including Chediak-Higashi syndrome, aplastic anemia, acquired immunodeficiency syndrome (AIDS), neutropenia, cyclical neutropenia, alcoholic liver cirrhosis and a severe malnutrition case. The first attack was only included in the analysis for patients who developed multiple febrile neutropenia attacks, to eliminate the personalized response bias. Patients were then categorized based on AMC values into two groups namely monocytopenia group ( $n = 34$ ) and a non-monocytopenia group ( $n = 46$ ) with a cutoff point of  $0.1 \times 10^9$  cells/L as previously described.<sup>15–19</sup> ANC and ANC differences at each follow up interval compared to ANC at admission were calculated. This study was conducted in accordance with the declaration of Helsinki, applying all the current regulations for retrospective studies in KAUH. Patient's consent was waived as data was used in aggregate anonymously.

## Statistical Analysis

Statistical analysis was performed using the IBM SPSS statistical package for Windows v.26 (Armonk, NY, USA). Data was expressed as frequency (percentage) for nominal data, mean  $\pm$  standard deviation of the mean (SD) for normally distributed continuous variables or median

(Interquartile range) for non-normally distributed continuous variables. Normality was tested using Shapiro–Wilk test. Statistical significance between the study groups regarding the previously mentioned parameters was determined using Chi-square test or Fisher's exact test, likelihood ratio accordingly, for categorical variables and Mann–Whitney *U*-test for non-normally distributed continuous variables and independent *t*-test for normally distributed continuous variables.  $P \leq 0.05$  was considered statistically significant.

A simple linear regression was used to assess the direction and strength of the relationship between the AMC at admission and the ANC at admission and different time intervals of follow up (day 1–6). The data was transformed using the natural logarithm (ln) since the data was skewed to the right. The sensitivity and specificity of AMC values as a predictor variable for the ANC change at different time intervals was assessed using the receiver operating characteristic (ROC) curves. The ANC change at different time intervals was dichotomized into a binary system (1 for an increase and 0 for a decrease or no-change compared to reported admission ANC value) as previously described.<sup>20</sup> ROC parameters were calculated including the area under the curve (AUC) and the cut-off point which indicates the point of the maximum sensitivity and specificity. The Kaplan–Meier analysis was used to calculate the probability of a second attack and the probability of survival as a function of time. Second attack and death were coded a value of 1. While patients who lived or did not develop a second attack during the period of data collection were assigned as 0. Statistical significance between Kaplan–Meier curves were tested using the Log rank test. Graphs were generated using GraphPad Prism 8 (San Diego, CA, USA).

## Results

A total of 80 patients were enrolled in the analysis, ranging in age from 1 to 78 years-old, who were admitted to the hospital for a febrile neutropenia attack (47.5% males and 52.5% females). According to the AMC values at admission, patients were divided into two subgroups; 34 patients (42.5%) were included in the monocytopenia group, while the non-monocytopenia group included 46 patients (57.5%). According to the type of malignancy 36 patients (45%) had a hematological malignancy in which Hodgkin's lymphoma, non-Hodgkin's lymphoma and diffuse large B-cell lymphoma were the highest three occurring malignancies, on the other hand, breast cancer, neuroblastoma and Ewing's sarcoma were the most

occurring solid malignancies (55%,  $n = 44$ ). Of the 80 patients included, 12 had a bone marrow involvement, in addition to 17 patients (21.3%) who had a distant metastasis. Patient's chemotherapy regimens varied, with R-CHOP (15%), ABVD (6.3%), AC (6.3%), VCD (5%), and ICE (5%) being the most used protocols ([Supplementary data, Table S1](#)), with a median of 3.00 (3.00) prior cycles of treatment. Additionally, most patients presented with fever solely in both monocytopenia (61.8%,  $n = 21$ ) and non-monocytopenia (54.3%,  $n = 25$ ) groups, succeeded by fever with cough (12.5%,  $n = 10$ ) and fever with general weakness (7.5%,  $n = 6$ ) respectively. At the time of admission, the patients's temperatures ranged between 38°C and 41°C. Principally, patients were free of any co-morbidity, apart from 21 patients who had one or more co-morbidities, with diabetes mellitus and hypertension being the dominant observations. In 10 patients, there was an obvious indication of a microbiologically defined infection, with five having a positive blood culture, four having a positive urine culture, and only one having a positive sputum culture ([Supplementary data, Table S2](#)). No statistically significant difference was observed amidst demographics and baseline characteristics, apart from gender ( $P$ -value = 0.049) when comparing the mentioned subgroups ([Table 1](#)).

The CBC parameters alongside the WBC differential values were obtained at admission and at different follow up time intervals up to 6 days following the attack. Statistical significance was calculated between the study groups regarding the previously mentioned parameters ([Supplementary data, Table S3–S9](#)). At admission, no significance was highlighted between both groups except for baseline WBCs count ( $P$ -value < 0.001), red cell distribution width (RDW) ( $P$ -value = 0.026), platelets count ( $P$ -value = 0.016), lymphocytes ( $P$ -value < 0.001) and basophils ( $P$ -value = 0.041). WBCs count illustrated a significant difference at all the observational readings apart from day five, in which the non-monocytopenia group exhibited a better prognosis presented by a higher WBCs count at follow ups. The same trend was also seen in the neutrophil's percentage and ANC values, emphasizing the importance of monocytopenia in determining the improvement degree of febrile neutropenia patients after G-CSF therapy. The statistically significant difference observed regarding other CBC parameters and WBC differential values at different follow ups will not be discussed since they are totally not germane. But such analysis was performed to explore the possible concurrent

significant variables that could be optimized and utilized as predictive measures for future work as in the case of lymphocyte percentage. Additional measures including liver and kidney function tests were also shown for both groups ([Supplementary data, Table S10 and S11](#)).

The main prognostic outcomes included in the analysis were WBCs count, neutrophils percentage, ANC, ANC difference at different follow up time intervals, and the hospitalization period. ANC difference represent the degree of improvement calculated by the mathematical difference in ANC at a specific follow up point compared to the baseline reading. Albeit the lack of significance identified in neutrophils percentage and ANC at admission, they have showed to be significant at all the follow up intervals as illustrated in [Table 2](#). [Figure 1](#) illustrates a visual representation of the ANC values at admission and different follow up intervals regarding the monocytopenia and non-monocytopenia groups, which shows a preferred prognostic path displayed by the non-monocytopenia group with a curve up shift to a higher ANC values, thus a better response to G-CSF treatment. ANC difference was also significant at all the follow up observations. Initially, on day one ( $P$ -value = 0.006) and subsequently progressing through the consecutive days, day two ( $P$ -value < 0.001), day three ( $P$ -value < 0.001), day four ( $P$ -value = 0.001), and day six ( $P$ -value = 0.019), except day five with  $P$ -value of 0.056. The hospitalization period of patients within the monocytopenia group was 6.0 (2.25) which was higher compared to the non-monocytopenia group which was 5.0 (3.00) ( $P$ -value = 0.006).

As a result of the different hospitalization periods, 67 patients were tested on the first day of follow up, 78 in the second, 64 on the third, 46 on the fourth, 32 on the fifth, and only 20 on the sixth day out of the 80 patients included in the present study which subsequently conducted a CBC test on the day of admission. To evaluate the relationship between AMC values at admission and ANC at different time intervals, linear regression analysis was utilized to further examine this relationship, since ANC difference at different time intervals exhibited a significant difference between monocytopenia and non-monocytopenia groups. The AMC values at admission were found to have a significantly positive relationship with ANC levels at various time intervals ([Figure 2](#)). A significant linear equation was found for day one ( $F(1,65) = 43.943$ ,  $P$ -value < 0.001,  $R^2 = 0.403$ ) ( $\beta = 0.736$ ,  $P$ -value < 0.001), day two ( $F(1,76) = 112.744$ ,  $P$ -value < 0.001,  $R^2 = 0.597$ ) ( $\beta = 1.049$ ,  $P$ -value < 0.001), day three

**Table I** Patient's Demographics, Malignancy Characteristics and Chemotherapy Regimens of the Selected Population

Variable	Total (n = 80)	Monocytopenia (n = 34)	Non-Monocytopenia (n = 46)	P-value
<b>Age (Years)</b>	36.5 (42.5)	26.5 (45.5)	41.0 (36.0)	0.355
<b>Sex</b>				0.049
Male	38.0 (47.5)	21.0 (61.8)	17.0 (37.0)	
Female	42.0 (52.5)	13.0 (38.2)	29.0 (63.0)	
<b>Malignancy</b>				0.317
Hematological	36.0 (45.0)	18.0 (52.9)	18.0 (38.3)	
Solid	44.0 (55.0)	16.0 (47.1)	28.0 (60.9)	
<b>Distant metastasis</b>				0.587
Yes	17.0 (21.3)	6.00 (17.6)	11.0 (23.9)	
No	63.0 (78.8)	28.0 (82.4)	35.0 (76.1)	
<b>Chemotherapy cycles</b>	3.00 (3.00)	2.00 (3.00)	3.00 (3.00)	0.374
<b>Co-morbidities<sup>a</sup></b>				0.196
None	59.0 (73.8)	23.0 (67.6)	36.0 (78.3)	
One Co-morbidity	13.0 (16.3)	5.00 (14.7)	8.00 (17.4)	
Two Co-morbidities	6.00 (7.50)	5.00 (14.7)	1.00 (2.20)	
Three Co-morbidities	2.00 (2.50)	1.00 (2.90)	1.00 (2.20)	
<b>Bone marrow involvement</b>				0.111
Yes	12.0 (15.0)	8.00 (23.5)	4.00 (8.7)	
No	68.0 (85.0)	26.0 (76.5)	42.0 (91.3)	
<b>Temperature at admission</b>	38.5 (0.950)	38.4 (0.875)	38.5 (1.00)	0.579
<b>Presentation</b>				0.780
Fever only	46.0 (57.5)	21.0 (61.8)	25.0 (54.3)	
Fever with cough	10.0 (12.5)	3.00 (8.80)	7.00 (15.2)	
Fever with General weakness	6.00 (7.50)	2.00 (5.90)	4.00 (8.70)	
Others <sup>b</sup>	18.0 (22.5)	8.00 (23.5)	10.0 (21.7)	
<b>Chemotherapy regimens</b>				0.218
ABVD	5.00 (6.30)	-	5.00 (10.9)	
AC	5.00 (6.30)	1.00 (2.90)	4.00 (8.70)	
Hyper-CVAD	3.00 (3.80)	2.00 (5.90)	1.00 (2.20)	
ICE	4.00 (5.00)	1.00 (2.90)	3.00 (6.50)	
PACLITAXEL	3.00 (3.80)	1.00 (2.90)	2.00 (4.30)	
R-CHOP	12.0 (15.0)	5.00 (14.7)	7.00 (15.2)	
R-ICE	3.00 (3.80)	1.00 (2.90)	2.00 (4.30)	
VCD	4.00 (5.00)	1.00 (2.90)	3.00 (6.50)	
Others <sup>c</sup>	41.0 (51.3)	22.0 (64.7)	19.0 (41.3)	

**Notes:** Data are presented as n (%) or median (interquartile range (IQR)). <sup>a</sup>Co-morbidities include diabetes mellitus, hypertension, asthma, hyperlipidemia, systemic lupus erythematosus, hypothyroidism, and hyperthyroidism. <sup>b</sup>Other presentations include irritability, hypoactivity, abdominal pain, menorrhagia, bone pain, night sweats, skin rash, diarrhea, and headache. <sup>c</sup>Other chemotherapeutic regimens are discussed in the supplementary material (Table S1).

**Abbreviations:** ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; AC, adriamycin, and cyclophosphamide; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; ICE, ifosfamide, carboplatin, and etoposide; R-CHOP, rituximab, cyclophosphamide, daunorubicin, vincristine, and prednisone; R-ICE, rituximab, ifosfamide, carboplatin, and etoposide; VCD, bortezomib, cyclophosphamide, and dexamethasone.

(F (1,62) = 60.157,  $P$ -value < 0.001,  $R^2$  = 0.492) ( $\beta$  = 0.964,  $P$ -value < 0.001), day four (F (1,44) = 21.441,  $P$ -value < 0.001,  $R^2$  = 0.328) ( $\beta$  = 0.786,  $P$ -value < 0.001), day five (F (1,30) = 7.909,  $P$ -value = 0.009,  $R^2$  = 0.209) ( $\beta$  = 0.511,  $P$ -value = 0.009) and finally, day six (F

(1,18) = 12.969,  $P$ -value = 0.002,  $R^2$  = 0.647) ( $\beta$  = 0.799,  $P$ -value = 0.002).

ROC analysis was used to evaluate the predictive role of AMC at admission regarding the ANC improvement after G-CSF therapy at different time intervals (Figure 3). A cutoff



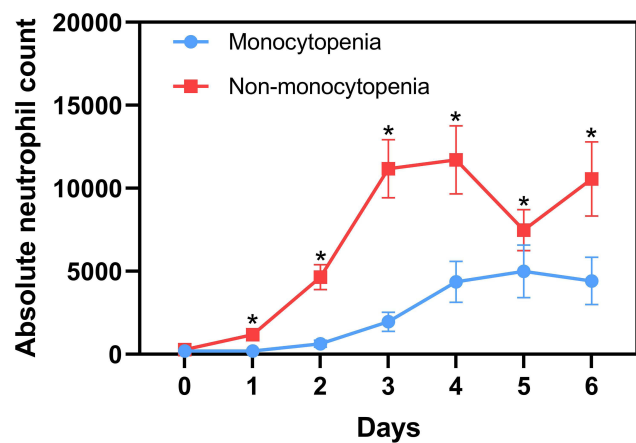
**Table 2** Neutrophil Percentage, Absolute Neutrophil Count, and Absolute Neutrophil Count Difference at Several Days Following the Febrile Neutropenia Attack Treated with G-CSF

Variable	Total (n = 80)	Monocytopenia (n = 34)	Non-Monocytopenia (n = 46)	P-value
<b>Admission</b>				
Neutrophils (%)	18.2 ± 15.1	17.7 ± 17.5	18.5 ± 13.4	0.819
ANC	234 ± 296	186 ± 333	269 ± 264	0.215
ANC difference	-	-	-	-
<b>Day one</b>				
Neutrophils (%)	23.1 ± 20.7	16.0 ± 15.0	28.9 ± 23.0	0.011
ANC	731.0 ± 1438.0	190.0 ± 312.0	1168.0 ± 1810.0	0.003
ANC difference	61.2 (290)	3.3 (106)	145 (613)	0.006
<b>Day two</b>				
Neutrophils (%)	40.2 ± 26.0	25.7 ± 22.0	51.4 ± 23.3	< 0.001
ANC	2892.0 ± 4288.0	630.0 ± 1237.0	4640.0 ± 4958.0	< 0.001
ANC difference	785 (3461)	34.8 (412)	2971 (5333)	< 0.001
<b>Day three</b>				
Neutrophils (%)	49.7 ± 28.8	35.5 ± 27.5	63.9 ± 22.5	< 0.001
ANC	2881 (9717)	446 (2308)	8973 (12,257)	< 0.001
ANC difference	2779 (9676)	221 (2242)	8412 (12,129)	< 0.001
<b>Day four</b>				
Neutrophils (%)	55.0 ± 29.1	47.4 ± 30.1	68.0 ± 22.5	0.012
ANC	7078.0 ± 8103.0	4364.0 ± 6633.0	11,708.0 ± 8459.0	0.002
ANC difference	3858 (11,433)	984 (5376)	10,883 (12,091)	0.001
<b>Day five</b>				
Neutrophils (%)	53.8 ± 28.1	47.3 ± 29.9	68.1 ± 17.6	0.021
ANC	2887 (9105)	1605 (5325)	8916 (7100)	0.035
ANC difference	2875 (9058)	1441 (5359)	8755 (6819)	0.056
<b>Day six</b>				
Neutrophils (%)	59.4 ± 27.6	51.3 ± 30.6	74.3 ± 11.4	0.028
ANC	6565.0 ± 6070.0	4415.0 ± 5158.0	10,559.0 ± 5901.0	0.026
ANC difference	3802.0 (9931)	1390 (7856)	11,010 (12,073)	0.019
<b>Hospitalization period</b>	5.0 (3.00)	6.0 (2.25)	5.0 (3.00)	0.006

**Notes:** Data is presented as mean ± standard deviation (SD) or median (interquartile range (IQR)). ANC difference represents the difference between ANC at day (1–6) compared to the ANC at the onset of the febrile neutropenia attack.

value of 107 for ANC difference at day one yielded a sensitivity of 63.6% and a specificity of 65.2%, with an AUC of 0.625. At the second day, a cutoff value of 103 for ANC difference yielded a sensitivity of 61.9% and a specificity of 73.3%, with an AUC of 0.705. At the third day, a cutoff value of 67.0 yielded a sensitivity of 64.3% and a specificity of 87.5%, with an AUC of 0.752. At the fourth day, a cutoff value of 17.4 yielded a sensitivity of 80.5% and a specificity of 60.0%, with an AUC of 0.634. At the fifth day, a cutoff value of 17.4 yielded a sensitivity of 67.9% and a specificity of 50.0%, with an AUC of 0.518. Finally, at the sixth day, a cutoff value of 3.2 yielded a sensitivity of 89.5% and a specificity of 100%, with an AUC of 0.895.

Kaplan–Meier estimator was used to assess the role of monocytopenia at the first attack in the recurrence probability of a second febrile neutropenia incidence. A total of 32 patients developed a second attack during the retrospective study period with 16 patients in each group. The Log rank test revealed no statistically significant difference between the monocytopenia and non-monocytopenia groups with *P*-value of 0.297 (Figure 4A). The same analysis was also applied to patients's mortality rates. In which 19 deaths in both groups, 8 in the non-monocytopenia group and 11 in the monocytopenia group with no statistically significant difference (*P*-value = 0.198) as presented in Figure 4B.



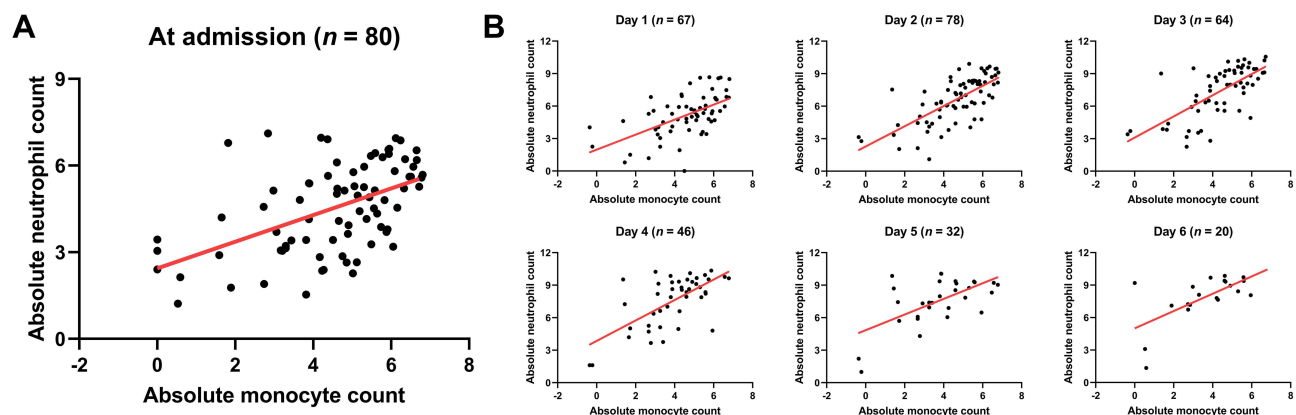
**Figure 1** The short-term progression of patients with chemotherapy-induced febrile neutropenia (n=80) and subsequently treated with G-CSF illustrated by the daily change in ANC values. Patients were categorized into two groups namely monocytopenia (n=34) and non-monocytopenia (n=46) groups with a cutoff point of  $0.1 \times 10^9$  cells/L. Data points are presented as mean  $\pm$  standard error of the mean (SEM). \*P-value  $\leq 0.05$ .

## Discussion

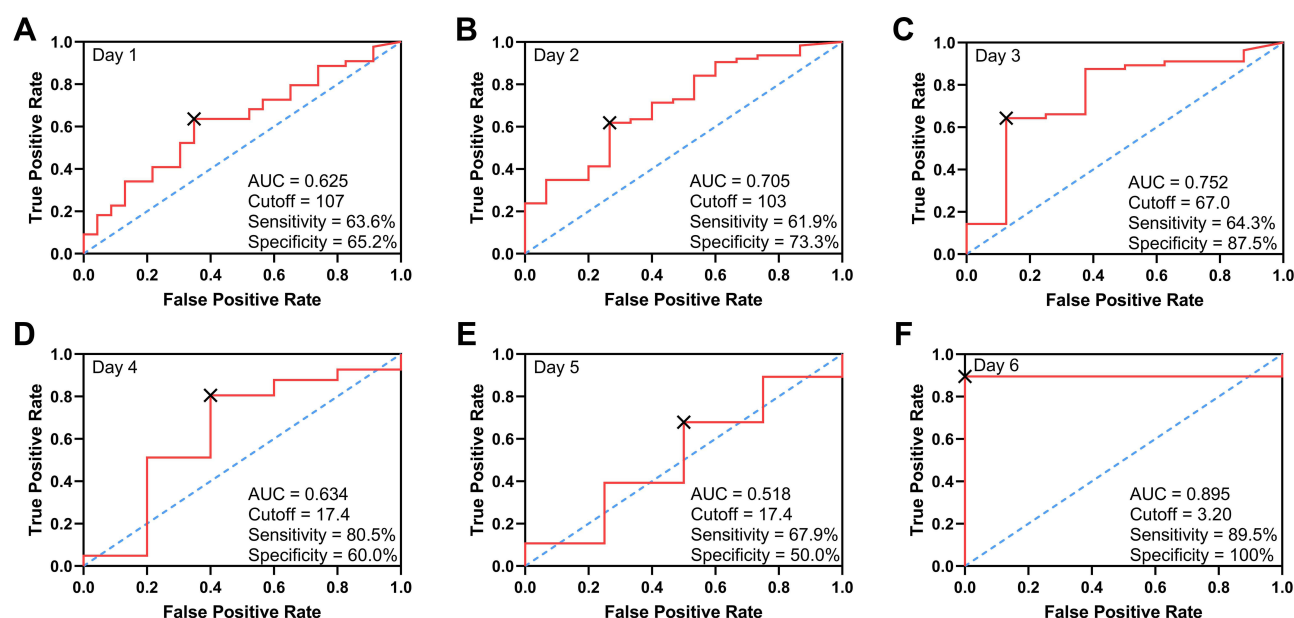
Chemotherapy-induced febrile neutropenia is a common and serious oncological emergency which develops in about 1% of patients undergoing a chemotherapeutic regimen and can reach up to 18% in the case of myelosuppressive agents' usage.<sup>21–23</sup> Certain patients have been identified to have a greater risk of developing febrile neutropenia, the components effecting such probability are treatment protocols, type of malignancy, and patient's demographics and characteristics.<sup>24</sup> Age has been identified as one of the risk factors for patients with non-Hodgkin lymphoma, in which it was noteworthy in patients older than 65 years.<sup>25–27</sup> Female sex has been perceived as a potential risk factor in small-cell lung cancer patients who were more likely to be hospitalized,

nevertheless sex was not identified as a significant risk factor in most studies.<sup>27,28</sup> Multiple comorbidities have also been recognized as risk factors of developing febrile neutropenia including cardiovascular and renal diseases. All things considered, the number of comorbidities present concurrently with a malignancy type contribute to the hospitalization and mortality in neutropenic hospitalized patients.<sup>24</sup> Certain chemotherapeutic agents are more present in inducing neutropenia including anthracyclines, vinorelbine, alkylators, taxanes, gemcitabine and topoisomerase inhibitors. In addition to the history of previous chemotherapy cycles and admission of three or more agents, notwithstanding the tumor type and stage.<sup>24</sup> Genetic related risk factors including TP53 R72P and MDM2 SNP309, GSTM1 and UGT1A1 genotypes in patients treated by the FEC (fluorouracil + epirubicin + cyclophosphamide), FOLFOX (fluorouracil + oxaliplatin) and IROX (irinotecan + oxaliplatin) chemotherapy protocols respectively.<sup>29,30</sup>

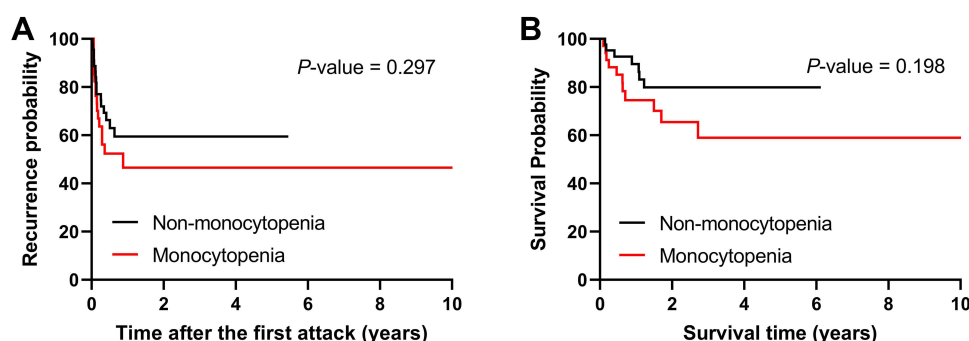
As a result of the wide variation of risk factors, multiple risk indices have been developed including the Multinational Association for Supportive Care in Cancer (MASCC) and the Clinical Index of Stable Febrile Neutropenia (CISNE) guiding the clinical decision process. The MASCC index, which is now being widely used, was developed to identify patients with a lower risk of developing serious complications having a score of more than or equal to 21.<sup>1,31</sup> Those patients are eligible for oral antibiotics treatment in the outpatient setting if being stable after 24 hours of monitoring.<sup>16</sup> On the other hand, the CISNE index is a promising prognostic tool which divides patients into three categories depending on six variables including low (0 points), intermediate (1–2



**Figure 2** Linear regression analysis evaluated the association between AMC values at admission and ANC values at admission (A) and subsequent follow up days (B). AMC and ANC values were transformed using the natural logarithm (ln).



**Figure 3** Receiver operating characteristic (ROC) curves of the AMC values at admission for prediction of ANC changes at day 1 to 6 (A-F).



**Figure 4** Kaplan-Meier curves to assess the role of monocytopenia in determining the recurrence (A) and survival (B) probability.

points), and high risk (3 points or more) patients for predicting critical complications in patients with solid tumors and stable episodes of febrile neutropenia.<sup>32</sup> More recent evidence reveals that CISNE index can be more accurate and predictive than the MASCC score.<sup>33,34</sup>

A growing body of literature has been devoted to study the correlation between monocytes measures and neutropenia in several clinical settings. In a retrospective clinical study conducted by Moriyama et al, the utilization of monocyte nadir has been investigated as a clinical indicator for neutrophil nadir in patients with lung cancer who developed chemotherapy induced neutropenia. A strong correlation between ANC nadir and AMC nadir has been observed, which potentiates the role of AMC nadir in the prediction of ANC nadir and its timing.<sup>35</sup> In another similar study, Shimanuki et al have investigated the use of pre-

treatment hematological laboratory parameters to construct a prediction model for chemotherapy induced febrile neutropenia in patients with head and neck squamous cell carcinoma. The model has revealed that AMC values less than 370cells/mm<sup>3</sup> are a good predictor for TPF (Docetaxel, cisplatin, and fluorouracil) regimen induced febrile neutropenia.<sup>36</sup> Sato et al have studied the use of pre-treatment monocytes percentage in the prediction of docetaxel monotherapy induced neutropenia in patients suffering from several types of malignancies. The study has demonstrated an inverse correlation between monocytes percentage and neutrophil count decrease in G-CSF administration and non-treated groups.<sup>37</sup> Adding to this, Ouyang et al have demonstrated that monocytes and neutrophils count change possess the same time-wise trend in patients who developed chemotherapy induced neutropenia. In the same study,



monocytes nadir occurred before neutrophil nadir with an inverse correlation between neutrophil decrease value and monocyte baseline percentage.<sup>38</sup> Furthermore, a baseline monocyte count less than 150 cells per  $\mu\text{L}$  has been established as a bad prognostic variable in chemotherapy induced febrile neutropenia patients along with chemotherapeutic protocol, underlying malignancy, body surface area of less than or equal to  $2\text{ m}^2$  and bone marrow involvement.<sup>39</sup> In a retrospective study conducted among 62 patients with chemotherapy-induced febrile neutropenia, AMC and MP were evaluated for their short-term prognostic role regarding ANC changes, which revealed that MP can predict ANC changes with a cutoff point of 6.5% elucidating a sensitivity and specificity of 80 and 88.6% respectively and an AUC value of 0.908.<sup>20</sup> Finally, multiple reports suggests that monocyte measures could have a predictive role in the clinical prognostic parameters of chemotherapy-induced febrile neutropenia.<sup>40,41</sup>

The exact pathophysiological mechanism that links AMC to ANC in the case of febrile neutropenia is not well understood or studied, which indicates the need to explore the cellular and molecular interactions in such clinical setting. The counter effects neutrophils and monocytes exhibit could be explained by hematopoiesis since they share a common progenitor namely “granulocyte-monocyte progenitor”. The differentiation route of neutrophils depends on the expression of C/EBP- $\epsilon$  and Gfi-1 followed GATA-1 down expression, while C/EBP- $\alpha$  and PU.1 induce monocyte and macrophage generation.<sup>42</sup> In addition, human adherent monocytes have experimentally illustrated a synthetic capability of hematopoiesis modulators such as G-CSF and GM-CSF.<sup>43</sup> G-CSF is the main granulopoietic cytokine involved in neutrophil production and mobilization, it increases the survival of neutrophils, influences its function in infection sites and sensitize them to chemotactic factors.<sup>44,45</sup> On the other hand, GM-CSF mediates neutrophil progenitor’s proliferation and growth, other functionalities include its effect on mature neutrophils and the synergistic role with growth factors it exhibits.<sup>46,47</sup> Monocytes even cause G-CSF driven mobilization of hematopoietic stem cells.<sup>44</sup> So clinically speaking, a high monocyte count could result in partially higher concentration of these mediators leading to neutrophil production which could prevent neutropenia. G-CSF affects a variety of cellular pathways and modulates the secretory cytokine profile.<sup>48</sup> These actions could influence monocytes to mediate granulopoiesis since they express the G-CSF receptor.<sup>49</sup> Adding to this, G-CSF has been

proven experimentally to modulate monocyte cytokine secretion.<sup>50,51</sup> The exact mechanism of action should be subjected to further studies since such clinical observation has the potential to furnish a new insight in the fields of immunology and molecular biology along with its clinical applications.

## Conclusion

In the current work, we represent a comprehensive analysis evaluating AMC values as a prognostic variable in determining ANC changes following G-CSF therapy in febrile neutropenia patients. A retrospective search throughout the electronic system of KAUH was performed representing a 10-year single center data of febrile neutropenia cases. Based on the current analysis, AMC values hold a prognostic entity regarding ANC changes in chemotherapy-induced febrile neutropenia without any restriction to patients’ demographics and characteristics following G-CSF treatment. The findings emphasize the role of AMC in notifying emergency doctors and oncology specialist toward high-risk febrile neutropenia patients and can predict the responsiveness of G-CSF therapy. The main limitation in this study is its retrospective nature with moderate sample size. The first attack of each patient was included, and the rest were omitted to eliminate the factor of response bias, which necessitate the need for additional analysis of recurrent attacks with their compatibility to the first one. Although AMC values could predict ANC changes to a certain degree, it did not exhibit any statistically significant difference in determining the morality and recurrence probability paths according to Kaplan-Meier analysis. Further studies are needed to increase the sample size and to specify the target population regarding the type of malignancy and chemotherapy protocol utilized. Future work should be also directed toward a more specific and sensitive risk prediction indices for chemotherapy-induced febrile neutropenia following G-CSF therapy.

## Ethical Approval

The study was approved by the institutional review board committee in King Abdullah University Hospital (KAUH). This study was conducted in accordance with the declaration of Helsinki, applying all the current regulations for retrospective studies in KAUH. Patient consents were waived as data was used in aggregate anonymously.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design,

execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no conflicts of interest for this work.

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