Original Article

Outcomes of Patients with Hematological Malignancies Admitted to the Intensive Care Unit at a Tertiary Care Center in Saudi Arabia

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Abstract

Background: Patients with hematological malignancies (HM) are at risk for complications, including neutropenia and admission to the intensive care unit (ICU). Granulocyte colony-stimulating factors (GCSF) can accelerate progenitor cells' proliferation and differentiation, and thus compensate for neutropenia. In patients with HM admitted to ICUs in Saudi Arabia, the outcome and impact of GCSF use on neutropenia duration and severity is understudied.

Objective: To evaluate the outcome and impact of GCSF on neutropenia in patients with HM admitted to the ICU of a tertiary care center in Saudi Arabia.

Methods: This retrospective study included all consecutive patients diagnosed with an HM admitted to the ICU at King Saud University Medical City, Riyadh, Saudi Arabia, from 2018 to 2022. Data on demographics, clinical information, ICU admission, and outcomes were collected.

Results: A total of 44 patients with HM admitted to the ICU were included, of which 43.2% were females and the mean age was 50.2 ± 21.1 years. The mean length of ICU stay was 12.3 ± 14.7 (range: 0–62) days. ICU mortality was 61.4%, with no further mortality within 90 days after discharge. There was no significant association between survival and age ($P = 0.205$), gender ($P = 0.7$), and neutropenia ($P = 0.566$) or the use of GCSF prior to ICU admission ($P = 0.882$). There was a significant association between the category of ICU intervention and survival ($P = 0.007$).

Conclusion: Patients with hematological malignancies who were admitted to an ICU in Saudi Arabia had a high mortality, regardless of neutropenia or the use of granulocyte colony-stimulating factor.

Keywords: Granulocyte colony-stimulating factor, hematological malignancies, intensive care unit, neutropenia, mortality, Saudi Arabia, survival

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Submitted: 04-May-2024 **Revised:** 29-Oct-2024 **Accepted:** 06-Nov-2024 **Published:** 11-Jan-2025

Access this article online	
Quick Response Code:	Website: https://journals.lww.com/sjmm
	DOI: 10.4103/sjmms.sjmms_257_24

How to cite this article: Alotaibi GS, Alekrish Y, Aldokhayel F, Alassaf A, Alzahrani M, Aljabry M, *et al*. Outcomes of patients with hematological malignancies admitted to the intensive care unit at a tertiary care center in Saudi Arabia. Saudi J Med Med Sci 2025;13:47-52.

INTRODUCTION

Globally, over the past two decades, the incidence of leukemia and non-Hodgkin lymphoma (NHL) has increased by 26% and 45%, respectively.[1] Both conditions, although heterogeneous, have high mortality rates.[2] In 2020, worldwide, the estimated incidence rate of hematological malignancies (HM) was 1.3 million, with mortality peaking at 700,000 deaths.[1]

Patients with HM admitted non-electively to hospitals are at a higher risk of fatal disease outcomes due to several factors. The underlying pathogenic mechanisms and the chemotherapeutic regimens being administered to the patients influence the risk of clinical complications that can lead to more severe or fatal disease outcomes.[3] The most common complications that can lead to intensive care unit (ICU) admission, clinical deterioration, and/or death include chemotherapy-related organ-specific toxicities, infections, and the sequelae of malignancy itself, including bleeding, leukostasis, and tumor lysis syndrome.[3,4] Community-acquired and nosocomial infections are common causes of morbidity and mortality among the patients with HM.[5]

The prognostic indicators for overall ICU survival are typically unique to the underlying disease and its severity. These factors frequently influence the necessity for ICU admission, the anticipated course of the admission, and the interventions offered. Multiorgan failure at admission is the strongest risk factor, with correlation between the number of failing organ systems and a progressive rise in mortality rates.[6] Patients with lower long-term survival rates are less likely to benefit from ICU treatment and risk stratification. However, some malignancy groups, such as acute myeloid leukemia (AML) subtypes and diffuse large B-cell lymphoma, can show optimal long-term prognosis following ICU survival.[6-8] The course of the disease, such as relapse or newly diagnosed, can also influence the ICU survival rates.[6] The well-established prognostic markers, including cytogenetic markers and disease-specific risk scores, are not known to predict the survival rates in ICU-admitted patients with HM.[4]

The bone marrow reserves of the granulocytes significantly decrease in chemotherapy-induced neutropenia. Exogenous granulocyte colony-stimulating factor (GCSF) can assist in accelerating the proliferation and differentiation of progenitor cells, thereby rapidly compensating for the neutrophil replenishment and reducing the length of neutropenia phase.[9] However, the impact of exogenous GCSF on survival has not been well-established in the Saudi population. Furthermore, the literature on the outcomes of patients with HM admitted to the ICU is scarce from this region. These gaps necessitate the exploration of the disease outcomes for these patients and determining factors that increase the risk of mortality. This study aimed to evaluate the outcomes in HM patients admitted to the ICU of a tertiary care center in Saudi Arabia and identify the relationship between neutropenia, GCSF use, and overall survival.

METHODS

Study design, setting, and participants

This retrospective study included patients with HM who were initially admitted to the hematology unit and then shifted to the ICU of King Saud University Medical City (KSUMC) between January 2018 and December 2022. KSUMC is a major tertiary care hospital in Riyadh, Saudi Arabia. The patients admitted to the ICU with HM and transferred to a different setting during the treatment were excluded from this study.

The Institutional Review Board and Ethical Committee at King Saud University, Riyadh, approved the study. The collected data were stored with assigned codes that blinded any link to the patients.

Data collection

The data were retrieved from the electronic medical records and recorded in a confidential database. The selected variables were obtained directly from the electronic medical records or calculated using standardized tools. Any observed discrepancies were resolved by repeated record verification.

Demographic information, hematological diagnosis, admission characteristics before the ICU admission (performance status, neutropenia, and comorbidities), and outcomes were collected. The time course of ICU admission, the reason for the ICU admission, treatment prior to ICU admission, and the ICU intervention (intubation and/or use of vasopressors) were also recorded.

Statistical analysis

Descriptive statistics were computed for continuous variables, including means, standard deviations (SD), minimum and maximum values, and 95% confidence interval (CI), where appropriate, and frequencies for categorical variables. Cross-tabulation was done for categorical variables, and Fisher's exact test was used, as the data set was small. Student's *t*-test was used for continuous variables to determine significant differences in the mean values. Kaplan–Meier survival curves were used

to illustrate the overall survival rate (defined as the time from treatment to death, regardless of disease recurrence) and survival analysis or time-to-event analysis (defined as analyzing the length of time until a well-defined endpoint of interest). A univariate log-rank (Mantel–Cox) test was used to compare the survival distribution of patients based on age (<50 years and ≥50 years) and gender. STATA software package (version 17) was used for the analysis. A statistical significance threshold of $P = 0.05$ was adopted. No attempt at imputation was made for missing data.

RESULTS

The study included 44 patients with HM. The mean age at admission was 50.2 ± 21.1 (range: 15.0–90.6) years. The age distribution is shown in Figure 1. The average time from hospital admission to ICU transfer was 22.8 ± 31.0 (range: 0–135) days. Data regarding the ICU stay was available for 35 patients, with the mean length of ICU stay being 12.3 ± 14.7 (range: 0–62) days. Regarding gender distribution, there was a slight male predominance, with 25 males (56.8%) and 19 females (43.2%). In terms of mortality, 27 patients (61.4%) died during the hospital stay. Prior to ICU admission, neutropenia was present in 17 patients (38.6%) and GCSF was administered in 25 patients (56.8%).

The most common diagnoses were non-Hodgkin's lymphoma (n = 21; 48.8%) and Hodgkin lymphoma (n = 11; 25.6%), collectively accounting for 74.4% of the cases. The remaining cases included acute leukemias (acute lymphoid leukemia [ALL], AML, and acute promyelocytic leukemia [APL]; 16.3%), chronic leukemias (chronic lymphocytic leukemia [CLL] and chronic myeloid leukemia [CML]; 4.7%), and plasma cell disorders (multiple myeloma [MM] and plasma-plastic lymphoma/myeloma; 4.7%). One patient's diagnosis was not recorded in the provided data [Table 1].

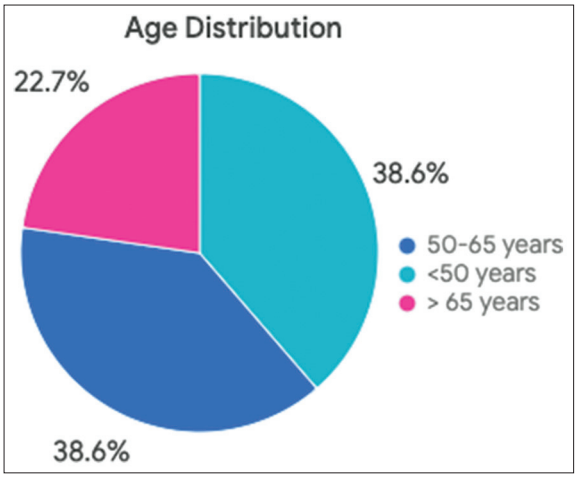

Figure 1: Age distribution of the cohort

Sepsis and shock-related complications were the predominant indications (29.5%), followed by respiratory complications (18.2%) and hemodynamic issues (15.9%) [Table 2]. Analysis of critical care interventions revealed that most patients required advanced organ support. Combined vasopressor support and mechanical ventilation were the most common interventions (31.8%), followed by isolated vasopressor/inotropic support (15.9%) and antimicrobial therapy and other supportive care measures without advanced organ support (15.9%). Special interventions were required in 4 (9.1%) patients, including one case each of ECMO support and cardiopulmonary resuscitation with central line placement. Five patients (11.4%) were admitted for monitoring and required no major interventions. Overall, 26 (59.1%) patients required some form of circulatory support (vasopressors/inotropes), while 21 (47.7%) patients needed either invasive or non-invasive ventilatory support [Table 3].

Table 1: Demographic and clinical characteristics of the patients

Characteristic	*n* (%)
Demographics	
Age (years), mean (range)	50.2±21.1 (15.0–90.6)
Gender: Female	19 (43.2)
Clinical parameters	
Days to ICU admission, mean (range)	22.8±31.0 (0–135)
ICU length of stay (days), mean (range)	12.3±14.7 (0–62)
Outcomes	
Discharge status: Dead	27 (61.4)
Pre-ICU characteristics	
Neutropenia; yes	17 (38.6)
GCSF use; yes	25 (56.8)
Primary diagnosis	
NHL	21 (48.8)
HL	11 (25.6)
Acute leukemias (ALL, AML, APL)	7 (16.3)
Chronic leukemias (CLL, CML)	2 (4.7)
Plasma cell disorders	2 (4.7)

ICU – Intensive care unit; ALL – Acute lymphoid leukemia; AML – Acute myeloid leukemia; APL – Acute promyelocytic leukemia; CLL – Chronic lymphoid leukemia; CML – Chronic myeloid leukemia; NHL – Non-Hodgkin's lymphoma; HL – Hodgkin lymphoma; GCSF – Granulocyte-colony stimulating factor

Table 2: Indication for intensive care unit admission

Indication	*n* (%)
Sepsis and shock-related	13 (29.5)
Respiratory complications	8 (18.2)
Hemodynamic issues	7 (15.9)
Bleeding and coagulation issues	6 (13.6)
Neurological events	4 (9.1)
Cardiac events	2 (4.5)
Monitoring/observation	4 (9.1)

ICU mortality was 61.4% (n = 27), while early mortality, defined as death within 30 days of ICU admission, was 54.5% (n = 24). The 90-day mortality rate was 61.4% (n = 27), identical to the ICU mortality rate, and thus there were no deaths between ICU discharge and the following 90 days. This pattern suggests that the critical illness period during ICU stay represents the highest risk period for mortality in these patients. However, the ICU stay was not significantly related to ICU mortality using the Student's t-test (P = 0.67) or the Fisher information test using ICU stays less than or greater than 30 days as binary variables (P = 0.198).

The Fisher's exact test showed no significant association between age and survival status (P = 0.205). The survival rate was 38.6%. Kaplan–Meier estimates for survival according to the patient's age and gender are provided in Figure 2, with survival time given in days. The graph shows that patients aged ≥50 years had lower survival rates than those aged <50 years. However, the log-rank test for equality of survivor functions for the two age groups showed no significant difference (P = 0.59). The survival graph for gender did not indicate a gender-based difference in survival. The log-rank test for equality of survivor functions for the two gender groups showed no significant difference (P = 0.7).

The distribution of diagnosis is illustrated in Figure 3, which shows that the most frequent diagnosis were NHL (48.8%) and Hodgkin lymphoma (HL) (25.6%). The remaining diagnoses were ALL in 3 (7.0%), AML and APL in 2 (4.6%), and CLL, CML, and MM in 1 (2.3%) each. Among all diagnoses, HL and NHL comprised 32 (75%) patients.

Table 3: Summary of interventions during the intensive care unit stay

Intervention	*n* (%)
Vasopressors/inotropic support only	7 (15.9)
Intubation only	5 (11.4)
Combined vasopressors + intubation	14 (31.8)
Noninvasive ventilation (BiPAP)	2 (4.5)
Antimicrobial/supportive care only	7 (15.9)
No major interventions	5 (11.4)
Special interventions	4 (9.1)

The Fisher's exact test between neutropenia before ICU admission and survival status (dead or alive) showed no significant association (P = 0.566). Similarly, GCSF use prior to ICU admission did not improve survival status (P = 0.882) [Table 4]. There is a statistically significant association between the category of ICU intervention and survival (P = 0.007). Patients requiring advanced organ support had the highest survival rate (62.96%), while those not requiring any significant intervention had the lowest (0%) [Table 5].

DISCUSSION

HM patients are at an increased risk of short-term deterioration and poor outcomes following ICU admission. The overall disease outcomes can vary depending on the underlying disease condition, the type of malignancy, and the chemotherapeutic regimes.[10] Identifying these prognostic determinants can help in the risk stratification of HM patients. This can, in turn, assist in reducing the overall mortality rates caused by the short-term deterioration in these patients.[11] This study aimed to evaluate the disease outcomes in a cohort of HM patients admitted to the ICU and determine the prognostic value of the patient characteristics. Forty-four patients with HM were admitted to the ICU during the study period, of which only 38.6% survived. No statistically significant association was noted between neutropenia or the use of GCSF prior to ICU admission and survival; however, these findings could also have been owing to the small sample size of the study.

The average length of hospital stay varies in the previous studies on HM patients admitted to the ICU. Rawson *et al*.[4] reported an average stay of 4.4 days for these

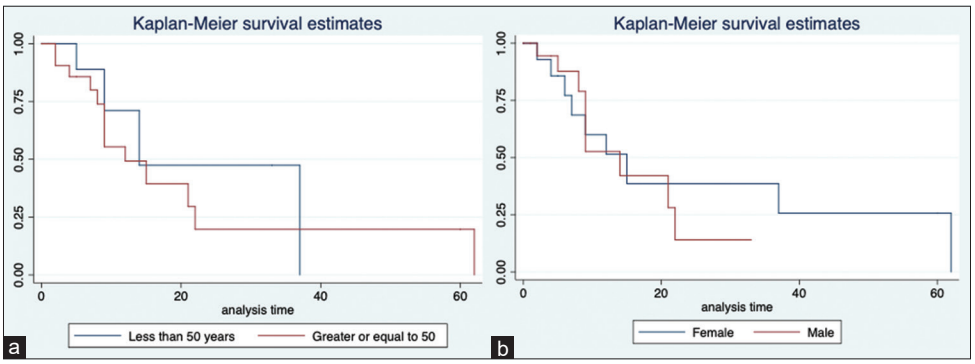

Figure 2: Kaplan–Meier survival estimates for (a) age groups and (b) gender

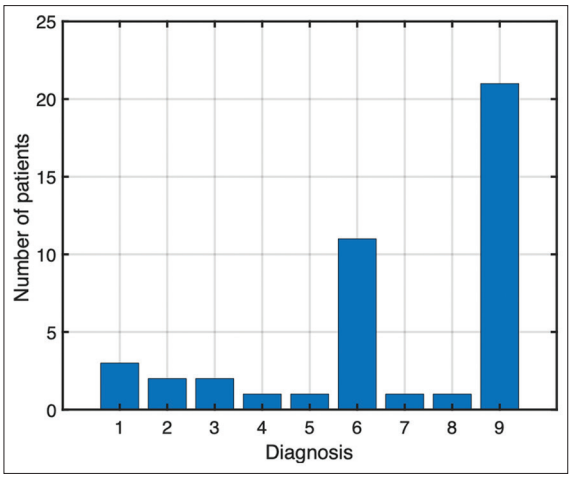

Figure 3: Distribution of diagnoses among intensive care unit admitted patients. The x-axis represents the following diagnoses: 1 – Acute Lymphoblastic Leukemia (ALL), 2 – Acute Myeloid Leukemia (AML), 3 – Acute Promyelocytic Leukemia (APL), 4 – Chronic Lymphocytic Leukemia (CLL), 5 – Chronic Myeloid Leukemia (CML), 6 – Hodgkin Lymphoma (HL), 7 – Multiple Myeloma (MM), and 9 – Non-Hodgkin Lymphoma (NHL). The y-axis shows the number of patients for each diagnosis

Table 4: Cross-tabulation of survival status compared with neutropenia and GCSF use before ICU admission

Status	Neutropenia prior to ICU admission	
	No, *n* (%)	Yes, *n* (%)
Alive	8 (33)	7 (39)
Dead	16 (66)	10 (61)
P	0.566	
Status	**GCSF use before ICU admission**	
	No, *n* (%)	**Yes, *n* (%)**
Alive	7 (42)	9 (32)
Dead	10 (58)	16 (68)
P	0.882	

GCSF – Granulocyte-colony stimulating factor; ICU – Intensive care unit

Table 5: Cross-tabulation between intervention categories and status

Intervention category	Deceased, *n* (%)	Discharged alive, *n* (%)
Advanced organ support	6 (26.1)	17 (73.9)
Invasive	2 (22.2)	7 (77.8)
Medication	4 (57.1)	3 (42.8)
No intervention	5 (100)	0
P	0.007	

patients, while Yerzhan *et al*.[5] reported an average length of 14.9 days, which is similar to our study findings of 12.3 days. Discrepancies in length of stay can be attributed to the admission of intermediate-care patients with relatively reduced need for intensive care. The survival rate of our cohort was significantly lower compared with the survival rates reported by Rawson *et al*.[4] but similar to that reported by Yerzhan *et al*.[5] These findings suggest that the underlying cause for ICU admission can be an important factor in determining the overall mortality risk among patients. Hospital-acquired infections can increase the risk of more severe disease outcomes and mortality among patients suffering from malignancies. Unfortunately, even patients with HM who are discharged from the ICU continue to suffer high mortality in the short term.[12]

Neutropenia is a common complication of the chemotherapeutic agents used to treat HM[13] and can be a life-threatening complication for patients suffering from malignancies. However, we did not find any statistically significant correlation between neutropenia and outcomes in ICU-admitted patients. GCSF can reduce the overall duration of neutropenia during the hospital stay and can help in chemotherapy administration at closer intervals.[14] This study did not find a significant correlation between GCSF and the overall survival rates among ICU-admitted patients. Data regarding outcomes of ICU-admitted Saudi patients with HM are scarce in the literature.[12,15] The duration and severity of neutropenia are also important factors in hematological malignancy. Bahammam *et al*.[15] reported the outcome of a similar number of HM patients admitted to the ICU over a 12-year period, and found that mortality rates were very similar to our cohort, indicating little improvement in the survival of these patients. Al-Dorzi *et al*.[12] studied the outcome of HM patients who required mechanical ventilation in the ICU and reported a mortality rate of 71.5%, while most of the deaths occurred in the ICU.

The present study shows that patients with HM admitted to ICU continue to have high mortality. This study also explored the association of the key risk factors and found patients requiring advanced organ support had the highest survival rate (62.96%), while those who did not require any significant intervention had the lowest (0%); however, it was not found to be statistically significant and could be attributed to a relatively small sample size. Therefore, there is a need for further studies with larger sample sizes to identify and devise mitigation and management plans for key risk factors in patients suffering from HM.

The incidence of leukemia is higher than Hodgkin lymphoma and NHL in Saudi Arabia.[16] However, in this study cohort, the percentage of leukemia patients was much lower than lymphoma. Therefore, future studies must be designed with a sampling ratio representative of the actual prevalence rates of the HM in the country.

Limitations

Although this study investigates an important aspect of the outcomes of patients with HM admitted to the intensive

care unit, it does not come without its limitations; such as, the small sample size, and the fact that it is a single-center study, which makes it difficult to generalize the results to the whole population of patients with HM admitted to the intensive care unit. It is also worth noting that the retrospective nature of this study could lead to certain biases that might lead to inaccurate results. However, this serves as an initial step for further studies that can build upon the findings presented in this study.

CONCLUSION

The mortality rate in patients with hematological malignancies admitted to an ICU in Saudi Arabia was 61.4%; there was no additional mortality within 90 days after discharge, suggesting that the critical illness period during ICU stay represents the highest risk period for mortality in these patients. No significant association was found between survival and neutropenia or the use of GCSF prior to ICU admission. There was a significant association between the category of ICU intervention and survival. However, the small sample size limits generalizability, and large-scale studies are needed to validate these findings.

Ethical considerations

The study was approved by the Institutional Review Board of King Saud University, Riyadh, Saudi Arabia (approval no.: E-22-7384; date: December 05, 2022). Requirement for patient consent was waived owing to the study design. The study adhered to the principles of the Declaration of Helsinki, 2013.

Peer review

This article was peer-reviewed by two independent and anonymous reviewers.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

Conceptualization: G.S.A., Y.A.; Methodology: G.S.A., Y.A., F.A., A.A.; Data analysis: G.S.A., Y.A., F.A., A.A.; Writing–original draft preparation: G.S.A., Y.A., F.A., A.A., M.A., M.A., B.A., F.A., S.S., F.A., K.A., A.J., A.A.; Writing – review and editing: G.S.A., Y.A., F.A., A.A., M.A., M.A., B.A., F.A., S.S., F.A., K.A., A.J., A.A.; Supervision: G.S.A.

All authors have read and agreed to the published version of the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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