

## RESEARCH ARTICLE

# Characteristics and Outcomes of Patients with Hematological Malignancies Admitted for Intensive Care - a Single Centre Experience

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### Abstract

**Background and Purpose:** Patients with hematological malignancies admitted to an intensive care unit (ICU) generally have a high mortality rate. The aim of our study was to assess the characteristics and outcomes of such patients and to identify factors predicting ICU mortality. **Material and Methods:** This retrospective chart review was conducted in the intensive care unit (ICU) of Shaukat Khanum Memorial Cancer Hospital and Research Centre over a period of 5 years, from January 2010 to January 2015. **Results:** Characteristics :A total of 213 patients were included in this study. There were 150 (70.4%) males and 63 (29.6%) females with the median age of 36 years (18-88 years). Main diagnosis was non-Hodgkin lymphoma in 127 (59.6%) followed by Hodgkin's disease in 27 (12.7%) and acute myeloid leukemia in 16 (7.5%). Most of the patients 154 (72.3%) were on active chemotherapy at the time of admission to ICU, while 28 patients (13.1%) had newly diagnosed disease and 22 (10.3%) featured either relapsed or progressive disease. The most common reason for admission to ICU was a combination of respiratory failure with septic shock (29.6%) followed by septic shock alone (19.7%) and acute respiratory failure (13.1%). Other causes included acute renal failure, alone (7.5%) or in combination with respiratory or circulatory collapse (10.8%) and central nervous system involvement (5.6%). The majority of admissions to ICU occurred between days one and five of admission to a ward (46.5%, n=99) whereas 49 (23%) were taken directly to the ICU. Mainstay of treatment in 38.5% of patients included both invasive ventilation and vasopressor support along with other supportive care like fluids and antibiotics. 23.5% received only supportive management. Duration of stay for 150 (70.4%) patients was between one to seven days. **Outcomes:** A total of 119 (55.9 %) patients expired while in ICU, while 14 (6.6%) died in hospital after being transferred out of ICU. ICU survival was 44.1% whereas hospital survival was 37.5%. After discharge from hospital in a stable condition, 18 (8.5%) patients were lost to follow up and 62 (29%) patients were alive after thirty days. A total of 33 (15.4 %) of patients survived for at least one year after ICU admission. Some 21 (9.8%) are still alive and healthy after a minimum median follow up of one and a half years. **Predictors of Mortality:** Overall, mechanical ventilation was required in 61% of patients. Out of the patients who expired, 92.4% required intubation, in contrast to 21.3% for those who survived the ICU stay. Involvement of three or more organs was apparent in 12.8% of improved patients and 70.6% of those who died during ICU stay. Neutropenia did not appear to be a major discriminatory factor, with 33% of improved and 42.9% of expired patients being neutropenic at the time of admission to ICU. The majority of patients from both the improved and expired group required intubation and vasopressors from day one onwards. **Conclusions:** Admission of patients with hematological malignancies to the intensive care unit is associated with poor outcome and high mortality. Identifying the patients who can benefit from aggressive care and prolonged ICU support is important especially when it comes to countries like ours with limited resources and major financial restraints. Multi-organ damage and requirement of invasive ventilation are two main predictors of increased mortality. Neutropenia is also associated with adverse outcome; however, the difference is not as significant as for the other two factors.

**Keywords:** Intensive care unit- hematological malignancy- mortality- multi-organ dysfunction

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### Introduction

Cancer is a leading cause of death, out of which hematological malignancy comprises of 20% of diagnosis (Azouley et al., 2013). While the advancements in therapy for hematological malignancy can lead to complete cure

(Subhash et al., 2003), around 70% of patients become critical while admitted in hospital (Hampshire et al., 2014). Treatment modalities like intensive chemotherapy and stem cell transplant have also increased the risk of complications (Evison et al., 2011). Patients with respiratory failure needing mechanical ventilation have

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a reported mortality of around 75-85% which increases further with organ failure or if the patient has undergone allogeneic bone marrow transplant (Benoit et al., 2003) Admission to the ICU itself comes with a high risk potential with studies showing only 40% of such patients making it to discharge from the hospital (Hampshire et al., 2014). This grim prognosis has led to a general reluctance on behalf of intensivists to admit these patients in intensive care units (Benoit et al., 2003). However, refusing ICU admission based on the type of hematological malignancy or the diagnosis in general is not justifiable (Torres and Soares, 2015). Reason being that in some patients advanced intensive and supportive care can be lifesaving and has improved the overall survival of critically ill patients with hematological malignancy (Subhash et al., 2013; Sylvio and Namendys-Silva, 2014), and also an improvement in the prognosis of such patients over the past years (Thiery et al., 2007). This requires a lot of interaction between the intensivist and hematologist/oncologist for appropriately selecting patients who can benefit from intensive care (Torres and Soares, 2015)

This study aims to look at the identification of predicting factors which determine the ICU and hospital mortality and the outcome of patients admitted in ICU with hematological malignancy. We also looked at the secondary outcomes after patients were discharged from the hospital in the form of survival at 30 days, 90 days and 1 year. The goal is to identify that group of patients who are unlikely to benefit from advanced or prolonged ICU support so as to decrease the chances of compromise to the potential survivors.

## Materials and Methods

This was a retrospective study of all patients with hematological malignancy admitted to Intensive care unit of Shaikat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan over a period of 5 years from January 2010 to January 2015. A standard proforma was used for data collection. This study was approved by ethical committee of the hospital.

### Inclusion criteria

- Patients with the established diagnosis of hematological malignancy newly diagnosed/relapsed or on active treatment.
- Both genders
- 18 years and above.

### Exclusion Criteria

Patients admitted to ICU without a diagnosis of hematological malignancy.

### Study Protocol

Patients with hematological malignancy were identified by review of database and those who got admitted to intensive care unit were included. Detailed data pertaining to demographics, clinical characteristics, management during ICU stay and outcomes were extracted.

Descriptive statistics were obtained both for the

continuous and categorical variables. These included age, gender, diagnosis, disease status, reasons for ICU admission, time from presentation to ICU admission, management during ICU stay, duration of ICU stay, and patient outcome in terms of mortality/survival, association with mechanical ventilation, vasopressor requirement, neutropenia, and multi-organ failure were analyzed to generate the results. Chi-square tests were conducted to determine the association between the outcome of interest (improved/expired) and need of mechanical ventilation, multi-organ dysfunction, neutropenia, time from admission to ICU to need of mechanical ventilation, time from admission to ICU to vasopressors, and time from admission to ICU to hemodialysis/renal replacement therapy. The tests were considered significant at an alpha-level of 0.05.

Primary outcome was the ICU mortality whereas secondary outcome was further subdivided as hospital mortality, and survival at 30 days, 90 day, 1 year and to date. Median follow up was 1.5 years. Tertiary outcome was determination of factors associated with ICU mortality.

Diagnosis included Hodgkins Lymphoma (HL), Non Hodgkin Lymphoma (NHL), Acute Myeloid Leukemia (AML), acute Lymphoblastic leukemia (ALL), Multiple Myeloma, Chronic Myeloid Leukemia and Chronic Lymphocytic Leukemia. Status of the disease was specified as newly diagnosed, on active chemotherapy, in complete remission, in partial remission, or relapsed/refractory/progressive disease. Date of admission to the ICU was taken as day 0 if it was a direct ICU admission, between D1 to day 5 and more than 5 days after admission to hospital. Reason for ICU admission was categorized as respiratory failure, septic shock, circulatory collapse, CNS complication, renal failure and combinations of various causes. Management during ICU stay was broadly divided into invasive ventilation, vasopressors, renal replacement therapy (RRT) or various modalities together.

## Results

### Patient Characteristics

A total of 213 patients with hematological malignancy were admitted to the intensive care unit over a period of 5 years from January 2010 to January 2015. There were 150 (70.4%) males and 63 (29.6%) females with the median age of 36 years (18-88 years). Main diagnosis was Non- Hodgkin Lymphoma in 127 (59.6%) patients followed by Hodgkin's Disease 27 (12.7%) and 16 Acute Myeloid Leukemia (7.5%). Most of the patients 154 (72.3%) were on active chemotherapy at the time of admission to ICU, while 28 patients (13.1%) had newly diagnosed disease and 22 (10.3%) were with either relapsed or had progressive disease. Most common reason for admission to ICU was a combination of respiratory failure with septic shock (29.6%) followed by septic shock alone (19.7%) and acute respiratory failure (13.1%). Other causes included acute renal failure alone (7.5%) or in combination with respiratory or circulatory collapse (10.8%) and central nervous system involvement (5.6%). Majority of admissions to ICU occurred between day one

Table 1. Patient Characteristics

Patient Characteristics	Number	Percentage
Total Patients and Gender distribution	213	
Males (N, %)	150	70.40%
Females	63	29.60%
Median age, Range(years)	36 (18-88)	
Median Follow-up (Months)	18	
Diagnosis		
Non Hodgkins Lymphoma	127	59.6
Hodgkins Lymphoma	27	12.7
Acute Myeloid Leukemia	16	7.5
Acute Lymphoblastic Leukemia	14	6.6
Multiple Myeloma	9	4.2
Chronic Myeloid Leukemia	7	3.3
Chronic Lymphocytic Leukemia	13	6.1
Disease Status		
Newly Diagnosed	28	13.1
Undergoing Chemotherapy	154	72.3
Complete or Partial Remission	9	4.2
Relapsed/refractory/Progressive disease	22	10.3
Reason for ICU admission		
Acute Respiratory Failure	28	13.1
Septic Shock	42	19.7
Acute Renal Failure	16	7.5
Circulatory Collapse	4	1.9
CNS complications	12	5.6
Respiratory Failure with septic shock	63	29.6
Respiratory Failure with circulatory collapse	3	1.4
Renal Failure with either respiratory failure or septic shock	23	10.8
Others	22	10.3
Time from presentation to admission to ICU		
D0	49	23
D1-D5	99	46.5
More than D5	65	30.5
Management During ICU stay		
Invasive Ventilation	18	8.5
Vasopressors	17	8
Both Vasopressors and Invasive Ventilation	82	38.5
Hemodialysis	13	6.1
Hemodialysis with either Vasopressors or invasive ventilation or both	30	14.1
Only Supportive management	50	23.5
Made DNR and given symptomatic care	3	1.4
Duration of ICU stay		
Less than 7 days	150	70.4
7 to 14 days	31	14.6
More than 14 days	31	15

Table 2. Primary and Secondary Outcomes of Patients Admitted to Intensive Care Unit

Primary Outcome	N	%
ICU mortality	119	55.9
ICU survival	94	44.1
Secondary Outcome		
Hospital Mortality	14	6.6
Lost to follow up after discharge from the hospital	18	8.5
30 day survival	62	29.1
90 day survival	47	22
1 year survival	33	15.4
Alive and healthy to date (Minimum median follow up 18months)	21	9.8

Table 3. Predictors of Mortality Need for Mechanical Ventilation; p value: 0.0001

		Outcome		Total
		Improved	Expired	
Need of Mechanical ventilation	yes	20	110	130
	No	74	9	83
Total		94	119	213

and five of admission to floor (46.5%, n=99) whereas 49 (23%) patients were taken directly to the ICU. Mainstay of treatment in 38.5% of patients included both invasive ventilation and vasopressor support along with other supportive care like fluids and antibiotics. 23.5% received only supportive management. Duration of stay for 150 (70.4%) patients was between one to seven days (Table 1).

Cross-tabulation of the outcome (improved/expired) with other variables showed a statistically significant association with 1) need of mechanical ventilation (Chi-square=111.8, df=1, p-value<0.001); 2) multi-organ failure (Chi-square=109.1, df=6, p-value<0.001); 3) , time from ICU admission to need of mechanical ventilation (Chi-square=116.1, df=3, p-value<0.001); and 4) time from ICU admission to vasopressors (Chi-square=60.35, df=3, p-value<0.001). There was no statistically significant association between the endpoint of interest and neutropenia or time from ICU admission to start of

Table 4. Multi Organ Involvement; p value: 0.0001

		Outcome		Total
		Improved	Expired	
Multi organ Dysfunction	Respiratory	11	7	18
	Cardiac/Circulatory	11	1	12
	Renal	16	0	16
	CNS	4	1	5
	2 system involvement including respiratory	14	26	40
	3 or more organ involvement including respiratory	12	84	96
Total	None	26	0	26
		94	119	213

HD ( $p>0.05$ ).

#### *Outcome of ICU admission*

ICU mortality and survival were 55.9% and 44.1%, respectively. Secondary outcome was hospital survival, and survival at 30 day, 90 day and 1 year which was 37.5%, 29%, 22% and 15.4%, respectively. At a minimum follow up period 18 months, 9.8 patients were still alive (Table 2).

#### *Predictors of Mortality*

Tables 3 and 4 report the factors that are significantly associated with ICU mortality. Need of mechanical ventilation (Table 3) and multi organ dysfunction (Table 4) with involvement of three or more organs was significantly associated with ICU mortality  $p=0.0001$ , whereas neutropenia though less prominent in surviving patients was not significant  $p=0.14$ .

## **Discussion**

ICU admission for cancer patients especially those with hematological malignancy is a highly debated topic and for a long time intensive care has been considered futile for this subset of patients. The trend has changed recently owing to studies and reports which have challenged this generalized perception.

This study is a retrospective analysis of ICU and post ICU outcomes in patients with hematological malignancies. It is of importance to note that the data has been collected from a dedicated and specialized cancer ICU.

Our ICU mortality was 55.9% which is higher when compared to the similar studies conducted in the European part of the world where the ICU mortality has been reported to as less as 30% to 40% (Bird et al., 2012; Azouley et al., 2013). However, when compared to a regional study (Subhash et al., 2003), the ICU mortality in our unit was significantly lower. A Brazilian study (Barreto et al., 2015) showed comparable results with an ICU mortality of 47.8%. In another similar study (Medic et al., 2015) ICU mortality rate was 53.5% which too was close to the results generated from our study. These studies, including ours, highlight that patients with hematological malignancies carry high risk of mortality when admitted to ICU.

Literature review shows that ICU mortality of patients with hematological malignancies often exceeds 50% (Barreto et al., 2015). Because of increased mortality associated with hematological malignancies, a question is raised if the transfer to intensive care unit is justifiable. There have been recent studies, which suggest that the ICU mortality does not only depend on the diagnosis or the stage of disease but also on the nature and extent of complications responsible for transfer to the ICU and hence denying ICU admission only based on the diagnosis itself is not appropriate (Barreto et al., 2015; Cornish et al., 2016).

It is beneficial to know the predictors of ICU outcome in patients with hematological malignancy as it will help to take appropriate medical decisions regarding ICU

transfers. The course of ICU stay too helps determine the outcome and requirement of mechanical ventilation and vasopressors together with multi organ dysfunction are broadly considered to be associated with a poorer outcome (Cornish et al., 2016).

Acute respiratory failure in isolation or in combination with other causes remains as one of the most common reason for admission to the ICU in patients with hematological malignancy. Our study also showed that acute respiratory compromise either alone or in combination with septic shock or renal involvement was the main reason of ICU transfer in more than 50% of the patients. Studies have shown that in patients requiring mechanical ventilation, the mortality is high and this has plateaued to around 50 to 60% over the last ten years (Lemiale et al., 2015).

Multi organ failure is another important predictor of ICU mortality. Involvement of three or more organs has been associated with higher mortality of upto 70.1% as compared to 20% in case of two or lesser organ dysfunction (Herrera-Gomez, 2013).

There have been studies (Cornish et al., 2016) which also identified neutropenia as the predictor of poor outcome, however, in our study there was no significant association between neutropenia and ICU mortality.

It is well known that in patients with hematological malignancy, admission to the intensive care unit is a major decision not only because of prolonged stay and treatment costs but also due to the fact that in many regions of the world, meticulous ICU care and resources are limited. We also know from recent studies (Cornish et al., 2016) that patients with hematological malignancies who survive ICU admission have a comparable quality of life with those of other malignancies. Therefore, this decision should be an interdisciplinary approach involving a hematologist and an intensivist. The aim should be neither to deprive patients of ICU care based on the underlying malignancy alone nor to extend advanced care to patients with minimal chances of recovery due to any or multiple reasons. Identification of potential survivors is complex but identifying the predictors of ICU mortality can guide physician in this crucial decision (Benoit and Depuydt, 2008).

The results of our study highlight that though the ICU mortality was high at 55.9% but those who did survive ICU had a meaningful survival with 15.4% alive at 1 year. Need for mechanical ventilation and multi-organ dysfunction were the two major predictors of ICU mortality which is consistent with established evidence; while neutropenia was not significantly associated with mortality. Another important factor in our study was that a significant number of patients (23%) were admitted directly to ICU from emergency department. It means these patients were very sick at the outset, which may be a contributory factor for the poor outcome in this group of patients. Because of poor community services in this part of the world, patients present with advanced stage and have already developed many complications before presenting to a tertiary centre. In addition, a significant proportion admitted to ICU had relapsed, refractory disease, and these patients have poor bone marrow reserves and immunity to combat infection



and other complications. After discharge from ICU and then from ward, patient must have good community/rehab services. Unfortunately, we lack these supportive measures and hence that is one of the major factors responsible for poor outcome of our patients.

While collecting data, we made sure to look at all the patient details pertinent to our study objectives including age, gender, primary diagnosis, disease status at the time of presentation, reason for ICU admission, duration of ICU stay, management, outcomes and need of mechanical ventilation, vasopressors or hemodialysis with their role as predictors of outcome. It would have been ideal if we could have recorded and analyzed the baseline functional, nutritional, socioeconomic status along with mental well-being since all these factors have a profound impact in determining morbidity and mortality that is associated with the disease and/or treatment. Needless to say, cancer patients presenting to our centre are already nutritionally compromised owing to a number of factors as mentioned earlier as well, and from a low income population group which has a contributory role in the relatively high mortality rates depicted in our study.

The role of high dose therapy followed by stem cell transplant though an important predictor of ICU mortality was not significant in our study as only three patients had undergone the treatment; therefore this predictor was not included in the analysis.

APACHE 11 Scoring at the time of admission to ICU is one of the important tools in assessment of severity of disease and also helps in predicting ICU course and outcomes. Unfortunately, they were not documented for every patient in our data and hence were not taken as a variable.

In conclusion, admission to the intensive care unit in a patient with hematological malignancy is associated with poor outcome and high mortality. Identifying the patients who can benefit from aggressive care and prolonged ICU support is important particularly in areas like ours, where there are limited resources and financial restraints. Multi organ damage and requirement of invasive ventilation are two main predictors of high mortality. Neutropenia is also associated with adverse outcome, however, the difference is not as significant as the other two factors mentioned. There is a need to develop community rehab services, which may be of help in improving outcomes and quality of life of these patients once they survive ICU. Decision for transferring a patient with hematological malignancy to the ICU and then identifying potential survivors requires collaborative efforts amongst the hematologist-oncologist, intensivist and ancillaries. This kind of multidisciplinary approach will help to provide an optimal care to these patients.

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