Outcome of patients with hematological malignancies admitted to the intensive care unit with life-threatening complications

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ABSTRACT

Objective: To assess the outcome of patients with hematological malignancies (HM) admitted to medical intensive care unit (MICU) and to identify prognostic factors that may affect patients' outcome.

Methods: Data were collected in 44 patients with HM admitted to the MICU at King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia within a 9-year period from 1993 to 2004. Demographic, physiological, clinical, laboratory and therapeutic data were collected on admission to MICU.

Results: Thirty-four percent of the patients had acute lymphocytic leukemia; 25% had acute myelocytic leukemia (AML) followed by non-Hodgkin's lymphoma in 20%, only 13.6% of these patients were in remission. The reasons for admission of these patients into MICU were shock (34.15%), respiratory failure (31.8%), cardiac arrest (20.4%), neurological causes (9.1%) and for other causes like small bowel perforation, hepatic failure, acute renal failure and metabolic disorders (4.5%). The overall in-hospital mortality was 72.7%, intensive care unit (ICU) mortality 61%, and the mean length of stay in the MICU was 5.4 ± 4.8 days. A statistically significant association was demonstrated between both remission status and aspartate aminotransferase values on one side and patient's outcome on the other side. Patients with AML had poorer prognosis with mortality rate of 90.9%.

Conclusion: Although mortality in patients with HM requiring ICU care is high, our results indicate that critical care support may be lifesaving. Apart from remission status and AML disease, no other prognostic factor could be identified.

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Despite improved treatment modalities, the aggressive treatment of hematological malignancies (HM) is frequently associated with complications, including infectious and non-infectious etiologies. Most of them land into life threatening complications needing intensive care admission.[1-5] Respiratory failure is the most common complication leading to intensive care unit (ICU) admission, and is also the leading cause of mortality following chemotherapy or bone marrow transplantation.[1,2] Other common reasons for transfer of this group of patients to the ICU include sepsis, pulmonary edema, electrolyte disturbances, alterations in mental status, acute airway obstruction and the need for postoperative observation.[1-5] The overall mortality for patients who require intensive care as a consequence of inpatient chemotherapy is approximately 50%.[3,5] Patients who do not require

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mechanical ventilation have a mortality rate of approximately 25%, which is similar to that of comparable ICU patients without cancer.[3,5-7] Those who require mechanical ventilation for acute respiratory failure experienced an ICU mortality of 78-100%.[1-3,5,8-18] Other factors reported to be associated with poor short-term outcome are hypotension necessitating inotropic, or vasopressor support, increasing number of organ failure, increasing age, and relapse.[1,9,12,19] However, different series reported different prognostic indicators. A humanitarian approach to the management of these patients as well as a more efficient use of limited resources mandates defining prognostic factors that can help identifying those who are likely to benefit from such therapy.

This study was conducted to assess the outcome of patients with HM admitted to the medical intensive care unit (MICU) in our institute and to identify the prognostic factors that affect the outcome of the disease.

Methods. Data were collected on 44 patients with HM admitted to King Khalid University Hospital, Medical Intensive Care Unit (MICU) between 1993 and 2004 (retrospectively for patients up to 1999, remaining patients were followed prospectively). This seven-bed unit admits critically ill patients who are above 12 years. Demographic, physiological and clinical data were collected on admission to MICU including age, gender, type of HM, treatment modalities (chemotherapy or radiotherapy), antimicrobial treatment (antibiotics, antifungal and antiviral) during hospitalization, disease status (relapse or remission), reasons for admission to MICU, vital signs including heart rate, systolic and diastolic blood pressures, laboratory data and therapeutic modalities within 24 hours of admission to MICU including white blood cell count (WBC), hematocrit, platelet count, blood urea, serum creatinine, bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, prothrombin time, activated partial thromboplastin time, fibrinogen, serum lactate, arterial blood gas values, arterial oxygen tension/inspiratory oxygen fraction(PaO_2/FiO_2) and the radiological findings on chest x-ray (type, distribution of radiological infiltrates, evidence of pleural effusion, cavities, nodules and any other findings). Pertinent contributory diagnoses on admission were noted such as shock, respiratory failure (pneumonia, pulmonary embolism, diffuse alveolar hemorrhage), neurological complications (convulsions, meningitis, central nervous system (CNS) infiltrates and others) cardiac arrest, and other reasons like hepatic or renal failure, disseminated intravascular coagulation (DIC). The type of malignancy was classified into one of 5 categories: Hodgkin's lymphomas (HL) or non-Hodgkin's lymphomas (NHL), acute lymphocytic leukemias (ALL) or acute myelocytic leukemias (AML) and others. If the patient is mechanically ventilated, the mode and settings of the ventilator were also included. Patient's Glasgow coma scale (GCS) at the time of admission to MICU, hemodynamic stability, the need and type of inotropic agents, and the ratio of heart rate to systolic blood pressure (HR/SBP) were recorded. Diagnostic and therapeutic procedures during MICU stay like bronchoscopic evaluation, open lung biopsy, radiological imaging techniques like ultrasonogram, computed tomography scan and magnetic resonance imaging were noted. The number of days since the last chemotherapy received, and the number of days the patient was in MICU was noted. Acute Physiology and Chronic Health Evaluation II (APACHE II) was calculated for each patient within first 24 hours of admission to MICU. The clinical outcome was evaluated in terms of death in the ICU or discharge from ICU and death in the hospital or discharge from the hospital. Patients were grouped as survivors versus non survivors, accordingly.

Diagnostic criteria. Shock was defined as systolic blood pressure <90 mm Hg, unresponsive to fluids or requiring vasopressors and associated with hypoperfusion, which is assessed by mentation, urine output, skin perfusion ± oxygen consumption and lactic acid. The severity of sepsis induced hemodynamic compromise was assessed by the ratio of HR/SBP, which is a sensitive indicator for hemodynamic instability.[20] A threshold of >1 is generally thought to reflect severe volume depletion. Neutropenia was defined as neutrophil count of <500/µL. Respiratory failure was defined as PaO_2 < 60 mm Hg on room air or $PaCO_2$>55 mm Hg. Mechanical ventilation was initiated if the patient developed respiratory failure or needed airway protection. Acute renal failure was defined as an abrupt decline in renal function, as reflected by sudden and sustained decline in glomerular filtration rate. Serum creatinine of ≥177 U/L was taken as a marker of acute renal failure in our study. Hepatic failure was defined as a progressive rise in total serum bilirubin associated with an inability to maintain normal coagulation in the absence of documented DIC or other factor consumption. A probable infection was defined as a suspected infection based on clinical signs and symptoms or a documented infection from blood, urine, sputum, bronchial brushing, broncho-alveolar lavage or other specimen sent for culture or positive serology of influenza, para-influenza, chlamydia, mycoplasma and legionella.

Prognostic analysis. In the whole population, the parameters: PaO_2/FiO_2 at admission to MICU, requirement of vasopressor agents, number of organ failure, disease status (relapse versus remission), shock, APACHE II within first 24 hours of

admission to MICU and the disease type: AML, ALL, NHL and HL were tested for an association with death.

Statistical Analysis. The data was entered in Micro Soft Excel and analyzed using the Statistical Package for Social Sciences for personal computer version 10 software. Data was expressed in text and tables as mean ± standard deviation (SD). Univariate analysis was performed using Student's t-test for 2 independent groups and Fisher's exact test to observe significant differences of continuous/categorical variables in relation to the outcome.

Results. Forty-four patients with HM were included in the study. Mean age was 35.8 ± 20.5 years. Males constitute 61.4% of the studied group (**Table 1**). Their mean APACHE II score at the time of admission was 28.7 ± 8.75. Thirty-four percent of the patients had ALL; 25% had AML followed by NHL of 20%. Only 13.6% of these patients were in remission. The reasons for admission of these patients into MICU were, shock (34.15%), respiratory failure (31.8%), cardiac arrest (20.4%), neurological causes (9.1%) and for other causes like small bowel perforation, hepatic failure, acute renal failure and metabolic disorders (4.5%). The overall ICU mortality was 61% and in-hospital mortality was 72.7%. The mean length of MICU stay was 5.4 ± 4.8 days. Analyzing the observed mortality in relation to the reason for admission revealed the following; neurological diseases (4 patients, 100% mortality), post cardiopulmonary resuscitation (9 patients, 89% mortality), shock (15 patients, 66% mortality), respiratory failure (14 patients, 64% mortality) and other causes (2 patients, 100%). Comparison of clinical characteristics (HR/SBP, GCS, pH, and WBC) of these patients in relation to their in-hospital outcome has shown non-significant association, (**Table 2**). Twenty-seven (61%) patients showed evidence of severe hemodynamic compromise as reflected by a ratio of HR/SBP > 1 and all of these patients needed vasopressor agents. Mean GCS was 8.5 ± 5.84 in patients who were alive and 7.9 ± 5.1 in those who died. Patients who died in the MICU were severely acidemic (pH ≤ 7.1) compared with those who survived (pH within normal). **Table 3** summarizes the results of the univariate analysis correlating different categorical variables in relation to outcome. Seventy-nine percent of patients who were in relapse died, whereas only 33.3% of patients in remission died (p=0.042). Patients with high AST values (≥74 U/L) had higher mortality rate, compared with those who had low AST values (<74 U/L) (92.9% vs. 62.1%) (p=0.035). No statistically significant associations were found between other categorical study variables and outcome. Of the 32 patients (72%) who needed mechanical ventilation, 23 (72%) died. Twenty-nine (66%) patients had multi-organ dysfunction among whom 22 (76%) died. Twenty-six (59%) patients had neutropenia with a mortality rate of 80%. Patients with renal impairment had higher mortality, whereas 86% of the patients who had high serum creatinine (≥177 µmol/L) died, none of the patients who required renal replacement therapy survived. Recent bacteremia was associated with high mortality of 79%.

Table 1 - Patients characteristics at the time of admission to Medical Intensive Care Unit.

Variables	Patients n=44	(%)
Age (years)	35.8 ± 20.5	
Gender, male	27	(61.4)
APACHE II score	28.7 ± 8.75	
GCS	7.9 ± 5.8	
Type of hematological malignancy		
NHL	9	(20.4)
HL	3	(6.8)
ALL	15	(34.1)
AML	10	(25)
Others	6	(13.6)
Disease status		
Remission	6	(13.64)
Relapse	38	(86.36)
Reason for admission		
Shock	15	(34.1)
Respiratory failure	14	(31.8)
Cardiac arrest	9	(20.4)
Neurological consequences	4	(9.1)
Other causes	2	(4)

APACHE-II - Acute Physiology and Chronic Health Evaluation II, GCS - Glasgow coma scale, NHL - non-Hodgkin's lymphomas, HL - Hodgkin's lymphomas, ALL - acute lymphocytic leukemias, AML - acute myelocytic leukemias.

Table 2 - Comparison of patient's clinical characteristics in relation to their outcome.

Clinical Characteristics	Alive (n=12)	Dead (n=32)	t-value	p-value
HR/SBP	1.28 ± 0.49	1.34 ± 0.47	-0.388	NS
GCS	8.5 ± 5.84	7.9 ± 5.1	0.331	NS
pH	7.4 ± 0.17	7.1 ± 1.3	0.80	NS
WBC	4 ± 7.3	6.2 ± 11.4	-0.59	NS

HR/SBP - ratio of heart rate to systolic blood pressure, GCS - Glasgow coma scale, WBC - white blood cell count, NS - not significant, pH - hydrogen-ion concentration.

Table 3 - Comparison of distribution of categorical study variables across the patients who survived and died after admission to Medical Intensive Care Unit.

Variables	Alive (n=12)		Dead (n=32)		*p*-value
	n	(%)	n	(%)	
Remission status					
Yes	4	(66.7)	2	(33.3)	0.042
No	8	(21)	30	(79)	
No. of organ failure					
≤2	5	(33.3)	10	(66.7)	NS
≥3	7	(24.1)	22	(75.9)	
APACHE-II Score					
≤28	6	(26.1)	17	(73.9)	NS
>28	5	(26.3)	14	(73.7)	
HR/SBP					
<1	5	(33)	10	(67)	NS
≥1	7	(24)	22	(76)	
Mechanical ventilation					
Yes	9	(28.1)	23	(71.9)	NS
No	3	(27.3)	8	(72.7)	
PaO_2/FiO_2					
≥200	4	(25)	12	(75)	NS
<200	8	(29.6)	19	(70.4)	
Vasopressors					
Used	7	(25.9)	20	(74.1)	NS
Not Used	5	(31.2)	11	(68.8)	
Neutropenia					
Yes	4	(19)	17	(81)	NS
No	8	(35)	15	(65)	
Serum creatinine					
≥177	1	(14.3)	6	(85.7)	NS
<177	11	(30.5)	25	(69.5)	
RRT					
Yes	0	0	5	(100)	NS
No	12	(31)	27	(69)	
Total bilirubin					
≥68	2	(16.7)	12	(83.3)	NS
<68	10	(34.5)	19	(65.5)	
ALT					
≥74	1	(7.1)	13	(92.90	0.035
<74	11	(37.9)	18	(62.1)	
AST					
≥130	1	(11.1)	8	(88.9)	NS
<130	11	(32.3)	23	(67.7)	
Albumin					
<25	1	(12.5)	7	(87.5)	NS
>25	11	(31.4)	24	(68.6)	
PT					
≥19.5	4	(26.7)	11	(73.3)	NS
<19.5	8	(28.6)	20	(71.4)	
APTT					
≥44	2	(16.7)	10	(83.3)	NS
<44	10	(32.2)	21	(67.8)	

APACHE II - Acute Physiology and Chronic Health Evaluation II, HR/SBP - ratio of heart rate/blood pressure, PaO2/FiO2 - arterial oxygen tension/inspiratory oxygen fraction, RRT - renal replacement therapy, ALT - alanine aminotransferase, AST - aspartate aminotransferase, NS - not significant, PT - prothrombin time, PTT - activated partial thromboplastin time

Analyzing the outcome of different types of malignancies showed that patients with AML had poor prognosis with mortality rate of 90.9%. Only one patient was discharged from MICU in a state of hypoxic encephalopathy. The mortality for NHL was 45%, 100% for HL, 67% for ALL, and 100% for other HM.

Discussion. In this study, the data of 44 patients with HM who were admitted to MICU for a life threatening complication was analyzed. In hospital mortality rate in our group was 72%, which is relatively high compared with the mortality rates reported in recently published studies.[21-23] However, it is difficult to compare the outcome between different series. Our patient group was more ill compared to the population of patients with HM in the studies by Massion et al[21] and Benoit et al[22] as suggested by the higher number of patients who needed mechanical ventilation (73% in our study, compared to 47-57% in the previous studies, higher APACHE-II score; 28 in our study compared to 24), higher prevalence of relapse, 86% in our study compared to 27% and increased need for vasopressors support (61% versus 46%).[22] Survival was better in patients who were in remission at the time of ICU admission. Mortality rate in the remission group was 33% compared to 79% in patients with active disease. Our findings concur with the findings of Massion et al[21] who reported lower mortality rate in patients in remission. Patients with lower AST had better survival, which probably reflect less involvement of the liver. Different studies reported different predictors of survival in patients with HM. The need for mechanical ventilation was reported as a poor prognostic factor in patients with HM.[1-3,5,12] We could not elicit any significant difference in prognosis between ventilated versus non-ventilated patients, and patients requiring vasopressors versus those who did not. The importance of neutropenia as a risk factor for mortality in patients with HM is controversial; few studies have reported high mortality in patients with neutropenia.[1,2,14,24,25] However, other studies did not confirm this.[13,26-28] Renal impairment has been reported to be an indicator of poor prognosis.[20,22] In our series, none of the patients needing renal replacement therapy survived the ICU course. Variables like HR/SBP, which is an indicator of hemodynamic compromise, had been reported to correlate with outcome in patients with HM.[20] Staudinger et al[20] found a HR/SBP > 1.2 is significantly associated with death. We found no such correlation in our patients. Survival among patients with AML requiring ICU admission was poor. The ICU mortality was 90.9%. One patient was discharged to the ward in a state of hypoxic encephalopathy. High mortality among AML patients admitted to ICU has been reported before.[21] In fact, better prognosis has been reported in the literature with HM other than AML.[1,12,29]

The absence of correlation between some of the studied variables and the outcome in our series may be due to few factors. First, our sample size is relatively small as we only included patients with HM to get a homogeneous group. Some of the previous reports included patients with solid organ malignancy, a group of patients that have different prognosis compared to HM. Second, we do not know the karyotype of HM in our patients. It is quite possible that the karyotype of HM in our patients is different from that in Western population. This calls for the need for a national multicenter study to be able to recruit enough number of patients to have adequate study power to detect predictors of poor outcome in our local patients with HM.

Although mortality in patients with HM requiring ICU care is high, our results indicate that critical care support may be lifesaving. Apart from remission status and AML disease, no other prognostic factor could be identified. In our view (excluding AML patients), patients with HM who are not in relapse should be offered critical care support in case they develop life-threatening complications until there is no prospect of recovery from the acute illness or the underlying malignancy cannot be controlled. Further local studies addressing this issue are needed.

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