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ORIGINAL RESEARCH / *ÖZGÜN ARAŞTIRMA*

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Evaluation of Patients with Hematological Malignancies Admitted to the General Intensive Care Unit - Should There be Dedicated Hematological ICUs?

Genel Yoğun Bakım Ünitesine Kabul Edilen Hematolojik Maligniteli Hastaların Değerlendirilmesi - Özelleşmiş Hematolojik YBÜ Olmalı mı?

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ABSTRACT *Objective:* With new treatment modalities, the overall survival of patients with hematological malignancies (HM) has increased over the years. However, intensive care unit (ICU) mortality is still high. This study aimed to evaluate the clinical characteristics, treatment methods, and results of HM patients admitted to the ICU at a center in Turkey.
Materials and Methods: Patients with HM admitted to the ICU between January 2013 and 2020 were retrospectively evaluated. A total of 172 adult patients with HM were included in the study.
Results: The median (interquartile range) age of patients was 60 (47-67) years, admission Acute Physiology Assessment and Chronic Health Evaluation-II score was 30 (26-32), Sequential Organ Failure Assessment score was 10 (7-12). Results of the 172 patients, 60 (34.9%) had newly diagnosed malignancies, 16 (9.3%) were in remission, and 96 (55.8%) had relapsed/refractory disease. The ICU admission was mostly required for acute respiratory failure (62.5%) and/or shock (42.3%). Forty-seven (27.3%) patients had stem cell transplantation, and 59 (34.3%) were neutropenic. Of them, 143 (83.2%) patients were admitted to intensive care after intubation and 159 (92.4%) patients needed vasopressors during intensive care stay. Thirteen (7.5%) patients were diagnosed with fiberoptic bronchoscopy-bronchoalveolar lavage sampling only, and treatment was changed in 85% according to the results. We observed that the patients were admitted to the ICU at the 28th hour (11-55) after determining the need for ICU follow-up. Intensive care mortality was 94.3% (163).
Conclusion: Early detection of critical illness and rapid admission to the ICU are important for the patients with HM. Collaborative studies determining early admission criteria to ICUs should be performed by the intensivists and hematologists to improve survival. This may be achieved by allocating special ICUs for these patients within the hematology clinics.
Keywords: Hematological malignancies, intensive care, mortality, admission time

ÖZ *Amaç:* Yeni tedavi modaliteleri ile birlikte, hematolojik maligniteli (HM) hastaların genel sağkalımı yıllar içinde artmıştır. Ancak yoğun bakım ünitesi (YBÜ) mortalitesi hala yüksektir. Bu çalışmanın amacı, Türkiye'de bir merkezde YBÜ'ye yatırılan HM hastalarının klinik özelliklerini, tedavi yöntemlerini ve sonuçlarını değerlendirmektir.
Gereç ve Yöntem: Ocak 2013 ve 2020 tarihleri arasında YBÜ'ye yatırılan HM'li hastalar geriye dönük olarak değerlendirildi. HM'li toplam 172 erişkin hasta çalışmaya dahil edildi.
Bulgular: Hastaların ortanca yaşı 60 (47-67), başvuru Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-II skoru 30 (26-32), Sıralı Organ Yetmezliği Değerlendirmesi skoru 10 (7-12) idi. Yüz yetmiş iki hastanın 60'ı (%34,9) yeni tanı, 16'sı (%9,3) remisyon ve 96'sı (%55,8) relaps/refrakter hastalık olarak değerlendirildi. YBÜ'ye yatış nedeni çoğunlukla akut solunum yetmezliği (%62,5) ve/veya şok (%42,3) nedeniyleydi. Kırk yedi (%27,3) hastaya kök hücre nakli yapıldığı ve 59 (%34,3) hastanın nötropenik olduğu saptandı. Bunların 143'ünün (%83,2) yoğun bakıma entübe olarak kabul edildiği ve 159'unun (%92,4) yoğun bakımdayken vazopressör ihtiyacının olduğu saptandı. On üç (%7,5) hastaya sadece fiberoptik bronkoskopi-bronkoalveolar lavaj örneklemesi ile tanı konuldu ve sonuçlara göre %85 oranında tedavinin değiştiği saptandı. Hastaların yoğun bakım ihtiyacı belirlendikten sonra 28. saatte (11-55) yoğun bakıma alındıkları görüldü. Yoğun bakım mortalitesi %94,3 (163) idi.

Sonuç: HM hastaları için, kritik hastalığın erken tespiti ve YBÜ'ye hızlı kabulü önemlidir. Yoğun bakım uzmanları ve hematologlar tarafından sağkalımı artırma açısından YBÜ'ye erken kabul kriterlerini değerlendirmek için ortak çalışmalara ihtiyaç vardır. Hematoloji kliniklerinde bu hastalara özel YBÜ'leri tahsis edilerek sağkalım artabilir.
Anahtar Kelimeler: Hematolojik maligniteler, yoğun bakım, mortalite, kabul süresi

Introduction

Although there are new treatment regimens and supportive treatments, overall survival in patients with hematological malignancies (HM) is still high. In previous studies, mortality in patients with HM admitted to the intensive care unit (ICU) ranged from 37.6% to 90% (1-3).

High Acute Physiology Assessment and Chronic Health Evaluation-II (APACHE-II) (4,5) and Sequential Organ Failure Assessment (SOFA) (6) scores, invasive mechanical ventilation (IMV) (7), neutropenia (8), prior history of stem cell transplantation (SCT) (3) and sepsis (5) are several factors associated with poor prognosis in critical patients with HM during ICU stay. The presence of positive blood culture with neutropenia has also been shown to be associated with an increase in mortality over 28 days (9).

The possible short- and long-term poor prognosis in patients with HM, as well as the necessity of time and costly treatments, has also led to the reluctance of intensive care professionals to accept and treat patients with HM (4). In addition, patients with advanced and refractory hematologic malignancies were found to be referred to palliative care services less frequently and received more aggressive treatments than patients with end-stage treatment-resistant solid tumors (10,11). Therefore, given high ICU and in-hospital mortality and limited ICU resources, identifying factors affecting mortality will help hematologists and intensivists to identify patients who may benefit from ICU treatment and to decide on treatment options. However, careful monitoring and early detection of these patients in terms of the critical disease process and rapid ICU transfer are important for survival (12).

The aim of this study is to evaluate the clinical characteristics, treatment methods and outcomes of critical patients with HM admitted to the general ICU.

Materials and Methods

Study Population and Design

Patients over 18 years with HM who were admitted to ICU from January 2013 to January 2020 were included in this study. Patients under the age of 18, patients who were followed up with HM but in complete remission and were admitted to ICU for another reason, and whom length of ICU stay less than 24 hours were excluded. The study was approved by the Non-Interventional Research Ethics Committee of Dokuz Eylül University (decision no: 2019/19-36, date: 31.07.2019).

The decision to admit the patient to the ICU was made by the intensive care specialist. In all consultations, the hematologist's opinion on the course and condition of the disease was asked and the ICU admission decision process were finalized accordingly. Treatment of HM was planned by the attending hematologist for each patient.

Definitions

The diagnoses of HM were classified as acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma (NHL), multiple myeloma and myelodysplastic syndrome. The type of SCT was identified as autologous or allogenic.

Disease status was determined by hematologists before ICU admission and categorized as "new diagnosis", "in remission" and "relapsed/refractory" according to each HM's specific criteria. Patients were categorized based on ICU admission reason as; disease-related, septic shock, graft-versus-host disease, acute respiratory failure (ARF), neurologic, gastrointestinal, and post cardiopulmonary resuscitation.

ARF was defined as less than 90% of oxygen saturation in room air or below 60 mmHg of arterial partial oxygen pressure (PaO_2) and severe shortness of breath during resting, as well as symptoms of inability to speak of a full sentence or respiratory rate or clinical respiratory distress of more than 30 breaths per minute (13). Sepsis and septic shock are defined according to the 2016 Third International Definition of Sepsis and Septic Shock Consensus (14). Neutropenia was defined as absolute neutrophil count $<0.5x10^3/\mu L$ and thrombocytopenia as platelet count $<50x10^3/\mu L$. The diagnosis of systemic fungal infection was clinically determined according to the revised definition

of invasive fungal disease (15). The use of inotropes and vasopressors was defined as the use of dobutamine, noradrenaline, adrenaline, and vasopressin in any dose.

Data Collection and Medical Records

Hospital records and laboratory data were examined in each patient and the following data were collected: Age, gender, Charlson comorbidity index (CCI), HM type, SCT and related complications, disease status, causes of admission, APACHE-II and SOFA scores, treatment types and supportive measures used during ICU stay including the use of [high-flow nasal oxygen therapy (HFNOT), non-invasive mechanical ventilation (NIMV), IMV, renal replacement therapy (RRT), vasoactive therapy, plasmapheresis, leukapheresis, blood product replacements, chemotherapy, fiberoptic bronchoscopy (FOB)]; laboratory parameters on the first day of ICU admission including arterial blood gas results PaO_2, $PaCO_2$; arterial partial carbon dioxide pressure, FiO_2; fraction of inspired oxygen, PO_2/FiO_2, HCO_3; bicarbonate, SO_2; oxygen saturation, lactate, complete blood count, C-reactive protein (CRP), procalcitonin, serum creatine, and fibrinogen. Length of ICU and hospital stay and ICU mortality were recorded. All microbiological results of the included patients were obtained from the hospital database. For each patient, all cultures sampled 24 hours before and after admission to the ICU were screened. Bronchoalveolar lavage (BAL) sampling was performed by experienced experts with fiberoptic bronchoscope (FOB, Olympus, Japan) in patients with >20,000/μL platelet count. The diagnosis of *pneumocystis jirovecii* pneumonia (PcP) was detected in tracheal secretion or BAL sampling, while cytomegalovirus (CMV) DNA was detected in BAL and peripheral blood by studying real-time polymerase chain reaction (PCR).

Statistical Analysis

Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as the median and interquartile range (IQR). Statistical analysis was performed with SPSS (Statistical Package for the Social Sciences Version 26.0; IBM Corporation, Armonk, NY, USA) program.

Results

Patient Characteristics

Between January 2013 to January 2020, 172 patients [median age 60 (47-67), 60.5% male] with HM who were admitted to ICU were included in the study. The median APACHE-II score was 30 (26-32), SOFA score on the day of admission was 10 (7-12) and CCI was 7 (5-8). NHL was the most common HM (30.2%). It was determined that 47 (27.3%) patients had a history of SCT. Of them, 26 (15.1%) were autologous and 21 (12.2%) were allogeneic transplants. Sixty (34.9%) patients had novel diagnosis of HM (Table 1).

The most common reason of ICU admission was ARF (36.0%), the most common reasons of ARF were pneumonia (23.2%) and alveolar hemorrhage (4.6%). It was followed by septic shock (28.4%) and disease-related causes (13.3%). The most common reasons of septic shock were respiratory tract infection (16.9%) and catheter-related infection (4.75%). Thirteen patients (7.6%) were admitted after cardiac arrest and resuscitation (Table 2).

Table 1. Baseline clinical characteristics patients with haematological malignancy (n=172)

Clinical characteristics	All patients (n=172)
Age (years)	60 (47-67)
Male sex	104 (60.5)
APACHE-II score	28 (24-32)
SOFA score	10 (7-12)
CCI	7 (5-8)
ICU admission from	
Emergency department	12 (7)
Hematology clinic	160 (93)
Haematological malignancy	
Non-Hodgkin's lymphoma	52 (30.2)
Acute myeloid leukaemia	44 (25.6)
Multiple myeloma	33 (19.2)
Acute lymphoblastic leukaemia	16 (9.3)
Chronic lymphocytic leukaemia	12 (7.0)
Hodgkin's lymphoma	11 (6.4)
Chronic myelogenous leukaemia	3 (1.7)
Myelodysplastic syndromes	1 (0.6)
Previous stem cell transplantation	
Autologous stem cell transplant	26 (15.1)
Allogeneic stem cell transplant	21 (12.2)
Disease status	
Newly diagnosed	60 (34.9)
Relapsed/refractory	96 (55.8)
In remission	16 (9.3)

All values are expressed as numbers (percentages) or median (interquartile range). APACHE-II: Acute Physiology Assessment and Chronic Health Evaluation-II, CCI: Charlson comorbidity index, SOFA: Sequential Organ Failure Assessment, ICU: intensive care unit

Laboratory Results

The median hemoglobin level on the day of admission was 8.4 (7.5-9.6) gr/dL, platelet count was 37.5 (18.0-84.0) x10^3/μL, and neutrophil count was 2.4 (0.2-8.2)x10^3/μL. Neutropenia and thrombocytopenia were detected in 59 (34.3%) and 108 (62.8%) patients, respectively. Median (IQR) CRP and procalcitonin levels were 178 (92-271) mg/L, 2.82 (0.9-12) ng/mL, respectively. In arterial blood gas analysis, median PaO_2 and $PaCO_2$ were 69 (44-98) and 35 (28-40) mmHg, respectively. Additionally, The median SaO_2 and PO_2/FiO_2 were 92% (89-94) and 122 (108-172), respectively. The median lactate level was detected as 2.3 (1.3-4.2) mmol/L (Table 3).

Treatments and Outcomes

One hundred forty three (83.2%) patients were transferred to ICU after intubation. Amongst the others 26 (15.1%) patients were treated with NIMV, 3 patients (1.7%) were treated with HFNOT. Of them, 22 (84.6%) patients needed escalation of respiratory support and were intubated during ICU follow-up. Sixty four (37.2%) patients were started on vasopressors in ICU, while 159 (92.4%) patients needed vasopressors at any time during ICU stay.

FOB was planned for 55 (32.0%) patients for microbiological sampling, but it has only been performed on 28 (16.2%) patients (due to resistant thrombocytopenia and hemodynamic instability FOB could not be performed). Tracheostomy was performed in 9 (5.2%) patients on the median 14th day (IQR 6-23) of ICU stay.

Fourteen (8.1%) patients received chemotherapy for a median of 2 days (2-4). Six (3.5%) patients received 5 days (4-6) of plasmapheresis, five (2.9%) patients received 2 days (1-4%) of leukapheresis, and one (0.5%) patient received 5 days of photopheresis during ICU stay.

Table 2. Reason for ICU admission of patients with haematological malignancy

Reason for ICU admission	All patients (n=172)
ARF	**62 (36.0)**
Pneumonia	40 (23.2)
Alveolar hemorrhage	8 (4.6)
Tumor progression causing pleural effusion	7 (4.0)
Pulmonary edema	5 (2.9)
Superior vena cava syndrome	1 (0.5)
Pulmonary embolism	1 (0.5)
Septic shock	**49 (28.4)**
Respiratory tract infection	29 (16.9)
Catheter-related infection	8 (4.7)
Unknown source of infection	7 (4.1)
Urinary tract infection	5 (3.6)
Malignancy related	**23 (13.3)**
Hyperviscosity syndrome	10 (5.8)
Graft-versus-host disease	9 (5.2)
Tumor lysis syndrome	4 (2.3)
Disturbed consciousness	**19 (11)**
Intracranial bleeding	12 (7.0)
Malignant central nervous system infiltration	4 (2.4)
Seizure	3 (1.7)
Post-CPR	13 (7.6)
Gastrointestinal bleeding	6 (3.6)

All values are expressed as numbers (percentages). ARF: Acute respiratory failure, CPR: cardiopulmonary resuscitation, ICU: intensive care unit

Table 3. Laboratory findings of patients with haematological malignancy on ICU admission

Variables	
Hemoglobin, gr/dL	8.4 (7.5-9.6)
Neutrophil, 10^3/μL	2.4 (0.2-8.2)
Neutropenia (<500/μL)	59 (34.3%)
Platelet, x10^3/μL	37.5 (18.0-84.0)
Thrombocytopenia (<50x10^3/μL)	108 (62.8)
CRP, mg/L	178 (92-271)
Procalcitonin, ng/mL	2.82 (0.9-12)
INR	1.4 (1.2-1.7)
Fibrinogen, g/L	4.5 (2.81-6.07)
Creatinine, mg/dL	1.28 (0.77-2.18)
Arterial blood gas analysis	
pH	7.38 (7.30-7.43)
PaO_2, mmHg	69 (44-98)
$PaCO_2$, mmHg	35 (28-40)
FiO_2, %	0.50 (0.45-0.60)
PO_2/FiO_2	122 (108-172)
SaO_2, %	92 (89-94)
HCO_3, mmol/L	21 (18-24)
Lactate, mmol/L	2.3 (1.3-4.2)

All values are expressed as numbers (percentages) or median (interquartile range). INR: International normalized ratio, PaO_2: arterial partial oxygen pressure, $PaCO_2$: arterial partial carbon dioxide pressure, CRP: C-reactive protein, FiO_2: fraction of inspired oxygen, HCO_3: bicarbonate, SO_2: oxygen saturation, Scr: serum creatinine, ICU: intensive care unit

Patients were admitted to ICU median 28 (11-55) hours after the first consultation. Median ICU stay was 5 (2-12) days and median length of hospital stay was 26 (12-44) days. ICU mortality was 94.3% (n=163), hospital mortality was 98.3% (n=169), overall (Table 4).

Microbiological Examinations

Positive cultures were detected in tracheal secretions of 58 patients (33.7%) and the most common bacterial pathogens were *Acinetobacter* spp. (17.4%) and *Klebsiella* spp. (5.2%). Positive BAL cultures were detected in 21 patients, of which 5 (2.9%) were *Aspergillus* spp., 5 (2.9%) were *Candida* spp., 4 (2.3%) were *Acinetobacter* spp. compared to tracheal cultures, *Aspergillus* spp. in 3 patients and *Candida* spp. in 2 patients was detected only with BAL culture and not with tracheal culture. PcP PCR tested on BAL sampling was positive in 8 (4.6%) patients. Positive results were detected in the blood culture of 48 (27.9%) patients and the most common factors were *Acinetobacter* spp. (10.5%) and *Klebsiella* spp. (4.1%). CMV DNA was found to be significantly higher in the blood of 22 (12.8%) patients and in BAL of 3 (1.7%) patients in the samples examined with clinical and radiological suspicion (Table 5).

Discussion

In this study, clinical characteristics, supportive and hematologic treatments, and outcomes of HM patients admitted to ICU were examined in detail and important results were deduced. The median duration of delay in ICU admission was 28 hours. ICU mortality of patients with HM was 94.3% and hospital mortality was 98.3%, which is significantly higher than the date presented in the literature.

Many studies examined the factors affecting the prognosis and outcomes of patients with HM after ICU admission and although the results varied over the years with developing treatment regimens and significant improvement in ICU mortality (3), the high mortality rates in our study were notable.

First of all, in our study, the most common reasons for ICU admission of patients with HM were ARF and septic shock and this is compatible with the literature (3,6,16). The high APACHE-II and SOFA scores, which are significantly associated with ICU mortality, are consistent with other studies in the literature but our hospital and ICU mortality rates are higher than the data presented in the literature. In a study by Demandt et al. (6), the mean APACHE-II score was 29.5±7.4 and the mean SOFA score at admission was 10.9±3.4 while ICU mortality was 52% and hospital mortality was 60%. In another study, which showed an ICU mortality rate of 33.7%, the non-survivors group's median APACHE-II score was 27, and SOFA score was 11 (17).

Table 4. Types of pathogens isolated from various sites

Tracheal secretion sample culture	**58 (33.7)**
Acinetobacter spp.	30 (17.4)
Klebsiella spp.	9 (5.2)
Stenotrophomonas spp.	7 (4.1)
Pseudomonas spp.	4 (2.3)
Candida spp.	3 (1.7)
Staphylococcus spp.	3 (1.7)
Aspergillus spp.	2 (1.2)
Blood culture*	**48 (27.9)**
Acinetobacter spp.	18 (10.5)
Klebsiella spp.	14 (4.1)
Enterobacter spp.	6 (3.5)
Pseudomonas spp.	5 (2.0)
Stenotrophomonas spp.	2 (1.2)
Candida spp.	1 (0.6)
Urine culture	**10 (5.8)**
Candida spp.	5 (2.0)
Escherichia coli	3 (1.7)
Klebsiella spp.	2 (1.2)
Central catheter culture	**7 (4.1)**
Acinetobacter spp.	2 (1.2)
Klebsiella spp.	2 (1.2)
Pseudomonas spp.	2 (1.2)
Candida spp.	1 (0.6)
BAL sample	21 (12.2)
Aspergillus spp.	5 (2.9)
Candida spp.	5 (2.9)
Acinetobacter spp.	4 (2.3)
Klebsiella spp.	3 (1.7)
Stenotrophomonas spp.	2 (1.2)
Pseudomonas spp.	2 (1.2)
Bronchoalveolar lavage sample	
BAL PcP PCR	8 (4.6)
BAL CMV PCR	3 (1.7)
Blood CMV PCR	22 (12.8)

*Collected percutaneously or via a central vein. All values are expressed as numbers (percentages). PcP: *Pneumocystis carinii* pneumonia, BAL: bronchoalveolar lavage, CMV: cytomegalovirus, PCR: polymerase chain reaction

The high ICU and hospital mortality can be explained by the delayed admission of patients to the ICU and the high rates of need for IMV and vasopressor support in the first 24 hours.

Table 5. Treatments and outcomes of patients with haematological malignancy

Variables	All patients (n=172)
Treatments	
Respiratory support within 24 h of ICU admission	
MV	143 (83.2%)
NIMV	26 (15.1%)
HFNO	3 (1.7%)
Vasopressors on ICU admission day	64 (37.2%)
Vasopressors during ICU admission	159 (92.4%)
RRT	39 (22.7%)
RRT, days	4 (2-6)
Bronchoscopy for microbiological sampling	22 (12.8%)
Chemotherapy before ICU admission*	35 (20.3%)
Chemotherapy in ICU	14 (8.1%)
Chemotherapy in ICU, days	2 (2-4)
Plasmapheresis	6 (3.5%)
Plasmapheresis, days	5 (4-6)
Leukapheresis	5 (2.9%)
Leukapheresis, days	2 (1-4)
Photopheresis	1 (0.5)
Photopheresis, days	5 (5-5)
Tracheostomy	9 (5.2)
Tracheostomy day from admission	14 (6-23)
Total erythrocyte transfusion, unit	4 (2-8)
Apheresis platelets transfusion, unit	2 (1-5)
Pooled platelets transfusion, unit	12 (8-21)
Cryoprecipitate transfusion, unit	12 (8-14)
Fresh frozen plasma, unit	5 (2-8)
Outcomes	
Duration of IMV, days	4 (2-9)
Time from consultation to ICU admission, hours	28 (11-55)
Length of hospital stay, days	26 (12-44)
Length of ICU stay, days	5 (2-12)
Hospital mortality	169 (98.3%)
ICU mortality	163 (94.3%)

*Chemotherapy within 15 days of ICU hospitalization, all values are expressed as numbers (percentages) or median (interquartile range). HFNO: High flow nasal oxygen, ICU: intensive care unit, MV: mechanical ventilation, IMV: invasive mechanical ventilation, NIMV: non-invasive mechanical ventilation, RRT: renal replacement therapy

As shown in other studies (3,7,16,18) IMV is the most important factor affecting mortality in patients with HM. Irie et al. (17) emphasized that mortality is high in patients who need IMV within the first 24 hours of ICU admittance. Depuydt et al. (19) found that 48.9% of patients with HM needed IMV within the first 24 hours, and this group had ICU mortality rate of 63% and hospital mortality rate of 80%. In another study, hospital mortality was 75% in patients who needed IMV, 21.6% in patients who didn't receive IMV, compared to 90.6% in patients receiving IMV support with a history of SCT (20).

In our study, 108 patients (62.7%) were intubated on ICU admission. It was determined that 143 (83.7%) patients received IMV support within 24 hours of ICU acceptance and this group had 100% mortality. The most common reason for admission is ARF and median PaO_2/FiO_2 on the day of hospitalization is consistent with moderate acute respiratory distress syndrome. Considering the time passed between acceptance to ICU and admittance, we determined that admittance was delayed, especially for patients who required IMV within the first 24 of ICU admittance. In cancer patients, 84% of whom had HM, who was admitted to ICU with ARF the time between the onset of respiratory failure symptoms and transfer to the ICU has been shown to directly affect mortality (12). In previous studies, prolonged NIMV administration and delayed intubation have been associated with increased mortality and early management and treatment of ARF in ICU have been shown to reduce the risk of intubation (1,13).

The need for vasopressors during ICU hospitalization is another risk factor for mortality in patients with HM (2,20). In our study, it was determined that 49 (28.4%) patients needed vasopressors during ICU admittance and 159 (92.4%) patients needed vasopressors during ICU stay and vasopressor use is associated with increased mortality. In our study, it can be said that the incidence of sepsis and septic shock was high in this patient group when we consider median lactate, CRP, and procalcitonin values. This can also be explained by a delay in the transfer of ICU patients with HM. In a study, which examined critical neutropenic cancer patients, 83.6% of whom had HM, septic shock was detected in 59% of patients at ICU admission, and ARF was the most common cause of sepsis-related ICU admission indications. In the same study, it was emphasized that early ICU acceptance reduced the incidence of septic shock in

neutropenic patients (21). In our study, ARF and septic shock were the most common reasons of ICU admission.

FOB and BAL sampling are frequently used in ICU and are important diagnostic tools for patients with HM who have ARF. Azoulay et al. (13), who investigated the strategies of ARF diagnosis in patients with HM, sampled FOB-BAL in 32.7% of patients and changed treatment according to the results in all patients. In addition, 18% of patients were only diagnosed with FOB-BAL (13). For this purpose, it is recommended that this procedure, which is performed safely in critical patients with ARF, be added to non-invasive tests immediately after ICU hospitalization (13). In our study, it was determined that 16.2% of patients were diagnosed with FOB-BAL, 85% had treatment changes according to the results and only 13 (7.5%) patients were diagnosed with FOB-BAL. Therefore, early ICU admission and early treatment modification, especially antimicrobials are very important. Especially invasive aspergillosis is associated with increased mortality in patients presenting with ARF (1). In our study, *Aspergillus* spp. was detected in tracheal secretion culture in 2 (1.2%) patients and FOB-BAL culture in 5 patients (2.9%), and treatment was started. *Aspergillus* was identified as the most common pathogen in the study evaluating the BAL results of patients with HM and is consistent with our study. Other opportunistic infections such as PcP and CMV are especially common in patients with SCT and are associated with increased mortality (22,23). In our study, 8 (4.6%) patients were diagnosed with PcP, and 3 (1.7%) patients were diagnosed with CMV by FOB-BAL, and treatment was started.

Each hour of delay for ICU admission is associated with increased mortality in critically ill patients (24). Early ICU transfer of patients reduces mortality after diagnosis of critical illness (25).

In a multicenter study involving general ICU patients, the time from triage to admission was 2.1±3.9 hours (26). In our study, the median time between the evaluation of patients with HM and the admission to the ICU was 28 (11-55) hours. Lack of a separate ICU for HM patients may be an important reason for the delay in ICU admission. In a multicenter study, ICU mortality in all patients was 70.4%, compared to 66% in hematology centers with their ICU (27). Another reason for the delayed admission of the patients with HM to ICUs is the attiribution lower chance of benefit of the ICU treatment in patients with advanced or relapsed/refractory HM by intensivist. Hence, these patients might have been positioned last in triage due to the limited ICU sources.

Communication and cooperation between the hematologist and the intensivist are very effective in determining which patient will benefit from ICU. Costly treatments of HM patients continue at ICU and primary disease treatments are continuing with leukapheresis, plasmapheresis, chemotherapy protocols, blood product replacements ordered by hematologists. In our study, it was seen that these treatments are applied to a significant number of ICU patients and when possible, it is very important to determine beforehand which patients would benefit from these treatments (in ICU) and use them accordingly, in terms of both cost and using the limited ICU resources efficiently. A study showed that aggressive treatments continued in the last months of the lives of patients with HM, highlighting the need for better and earlier integration of palliative care approaches in standard hematology practice (28).

There are some limitations in our study. First of all, this is a retrospective single-center study and our results are not generalizable. Second, due to high mortality, the causes affecting mortality could not be evaluated statistically. However, there are some strengths: Our study is the first to comprehensively examine the characteristics and treatments of patients with HM admitted to the general ICU.

Conclusion

Patients with HM still have high ICU and hospital mortality. The HM disease and current treatment regimens are risk factors for critical illness. Delayed ICU admission time may increase mortality in patients with critical HM. Considering the high treatment costs and limited ICU bed capacity, the establishment of specialized ICUs for hematological patients in hematology clinics and early recognition of critical illness, and rapid intervention and transfer to intensive care may improve outcomes.

Ethics

Ethics Committee Approval: The study was approved by the Non-Interventional Research Ethics Committee of Dokuz Eylül University (decision no: 2019/19-36, date: 31.07.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.K., M.C.Ö., M.N.Y., B.C., A.N.G., İ.A., B.E., Design: M.K., M.C.Ö., B.Y., Bi.E., M.N.Y., B.C., A.N.G., İ.A., B.E., Data Collection and Process: M.K., M.C.Ö., B.Y., Bi.E., M.N.Y., A.N.G., İ.A., Analysis or Interpretation: M.K., M.C.Ö., B.Y., Bi.E., B.C., İ.A., B.E., Literature Search: M.K., M.C.Ö., B.Y., Bi.E., M.N.Y., B.C., A.N.G., İ.A., B.E., Writing: M.K., Bi.E., M.N.Y., B.E.

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