Evaluation of National Early Warning System for Mortality in Hematological Malignancy Patients Admitted to Intensive Care Unit: Prospective, Single Center, Observational Study

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ABSTRACT

Objective: Hematological malignancies (HM) are the cause of many deaths worldwide and the incidence is increasing day by day. New treatment models increase remission rates; but complications that require intensive care unit (ICU) are also increasing. The aim of this study was to investigate the effect of The National Early Warning System Score (NEWSS) on ICU mortality in HM patients.

Methods: This study was performed prospectively in the medical ICU. Patients transferred from hematology ward to the medical ICU were included in the study. NEWSS was calculated at the hematology ward before patients admitted to the ICU.

Results: A total of 91 patients were enrolled in the study with a median (IQR) age of 55 (29) years. The median (IQR) NEWSS was 8 (3). Independent risk factors for ICU mortality were requirement of renal replacement therapy (P= 0.008), high Sequential Organ Failure Assessment (SOFA) score (P=0.002), development of Acute Respiratory Distress Syndrome (ARDS) (P=0.005). ICU mortality rate was 62%.

Conclusion: Requirement of renal replacement therapy, high SOFA score and development of ARDS were important risk factors for ICU mortality in HM patients. The NEWSS was not found as a risk factor for ICU mortality in HM patients.

Keywords: hematological malignancy; mortality; risk factors; intensive care unit; early warning system

Introduction

Hematological malignancies (HM) are the cause of many deaths worldwide and the incidence is increasing day by day (1). Concentrated chemotherapy, stem cell transplants and biological treatment modalities increased remission rates; whereas complications such as leukopenia-related infection, drug toxicity and thrombocytopenia that require intensive care unit (ICU) are also increasing (2). The mortality and cost of intensive care for leukemia and lymphoma patients are higher than in any other patient group (3).

According to the literature, HM patients ICU survival rate varies between 2.5% and 46%. Advanced age, advanced stage disease, high Acute Physiology and Chronic Health Assessment (APACHE II) score, high Simplified Acute Physiology Score (SAPS II), multiorgan failure, invasive mechanical ventilation requirement, renal replacement therapy, neutropenia, allogeneic stem cell transplantation, hepatic dysfunction, Graft Versus Host Disease, sepsis and invasive fungal infection are among the factors increase the rate of mortality (4,5).

Our hypothesis is that; in this patient group, early detection of clinical deterioration in the hematology ward and early admission to ICU may reduce mortality.

Early warning system scores can help us to detect clinical deterioration early. For this reason we used The National Early Warning System Score (NEWSS). Some European and North American countries use NEWSS in the surgical clinics and emergency units for assessing the patient's condition at an early stage and admitting the patient without delay to ICU. NEWSS informs us whether the patient is critical by using the physiological data (systolic blood pressure, body temperature, pulse rate, respiratory rate, consciousness and oxygen saturation) of the

patient. According to the studies about NEWSS, this system reduced mortality and re-acceptance to ICU (6-9).

The aim of this study was to investigate the effect of NEWSS on ICU mortality in HM patients. The secondary aim was to examine other risk factors for ICU mortality in HM patients.

Material and methods

Research Setting

This prospective observational study was conducted in a university teaching hospital tertiary ICU service. HM patients who should be transferred to the ICU while in hematology ward were included in the study. Clinical data of all patients with an active HM admitted to the medical ICU was recorded for 6 months (between June 2015 and December 2015). During the study period 112 HM patients who were older than 18, was admitted to the medical ICU. We excluded patients from the study who were discharged or died within 24 hours. 91 patients were included in the study.

Data Collection and Definitions

In our study; we investigated the last 24 hours of HM patients before admission to the ICU. We recorded the time difference between the deterioration in the general condition of patients and the admission of patients to the ICU. NEWSS was used to detect deterioration in the general condition of the patient. As in previous study (6), patients NEWS score of 5 or above was considered critical and they transferred to ICU. Also, which form of nutrition was used in the ward (oral, parenteral, oral + parenteral), whether the patient received chemotherapy for hematological malignancy or not, whether the patient had a hematopoietic stem cell transplantation (HSCT) or not and whether the disease status of the patient has been in remission or not were also recorded. During the ICU follow-up period, basal cortisol and thyroid function test (TFT) levels, lactate level, Nutritional Risk Score 2002 (NRS 2002), APACHE II, Sequential Organ Failure Assessment (SOFA) and The Multinational Association for Supportive Care in Cancer (MASCC) scores, daily Glasgow Coma Score (GCS) were recorded. Requirements of vasopressor therapy, renal replacement therapy and invasive mechanical ventilation were also recorded. If acute respiratory distress syndrome (ARDS) developed in the ICU follow-up, it was examined how this effect on mortality. Finally, the duration of the patients' stay in ICU was recorded.

Statistical Analysis

Statistical analyses were performed using IBM SPSS (Statistical Package for Social Sciences) statistical program version 21.0. Continuous variables were reported as means ± standard deviations or medians [interquartile ranges]. Frequency and percentage values were used for the presentation of categorical variables. Then, patients included in the study were separated into groups as survivors or non-survivors. Mann-Whitney U test or Student –t test was used to compare continuous variables, while χ2 (chi-squared) and Fisher exact test were used to compare categorical variables. Logistic regression analysis was used to determine independent risk factors for ICU mortality. P values lower than 0.05 were considered as statistically significant.

Ethics

The study was conducted according to the guidelines in the Declaration of Helsinki. The study was approved by the local ethics committee of Erciyes University School of Medicine (decision no: 2015/267 dated: 22.05.2015). Informed consent was provided by patient or caregiver after providing verbal and written information about the study.

Results

91 patients included in the study. 55 (60%) of them were male and 36 (40%) of them were female. The median (IQR) age of all patients was 55 (29) years. The most common hematological malignancy subtype was AML (33%) and the most common diagnoses for ICU admission were acute respiratory failure (49%) and septic shock (20%). The median (IQR) APACHE II score of all patients was 26 (13). The median (IQR) APACHE II score of died patients was 29.5 (13.5) and the median (IQR) APACHE II score of survived patients was 21 (11). There was a statistically significant difference between two groups according to APACHE II scores (p < 0.001). The median (IQR) SOFA score of all patients was 8 (7). The median (IQR) SOFA score of died patients was 11 (5.5) and the median (IQR) SOFA score of survived patients was 6 (4). There was a statistically significant difference between two groups according to SOFA scores (p <0.001). The median (IQR) GCS of all patients was 9 (10). GCS was lower in died patients compared to survived patients and this was statistically significant (p < 0.001).

The median (IQR) time difference between the deterioration in the general condition of patients and the admission of patients to the ICU was 7 (7) hours. In survived patients this time difference was 6 (8) hours and in died patients this time difference was 7.5 (7) hours. There was no statistically significant difference between two groups according to the transfer time (p = 0.36). In all patients, the median (IQR) NEWS score was 8 (3) whereas the median (IQR) NEWS score was 7 (3) for the survivors and 8 (3) for those patients that died. There was no statistically significant difference between two groups according to the NEWS scores (p = 0.3).

The median (IQR) cortisol level of all patients was 32 (27.6) μg/dL. The median (IQR) cortisol level of survived patients was 24 (20.5) μg/dL and the median (IQR) cortisol level of died patients was 43 (24.5) μg/dL. There was a statistically significant difference between two groups according to cortisol level (p = 0.005).

63 patients (69%) required vasopressor therapy. 7 (11%) of the survived patients required vasopressor therapy and 56 (89%) of the died patients required vasopressor therapy. There was a statistically significant difference between two groups according to requirement of vasopressor therapy (p < 0.001). 63 patients (69%) required invasive mechanical ventilation. 7 (11%) of the survived patients required invasive mechanical ventilation and 56 (89%) of the died patients required invasive mechanical ventilation. There was a statistically significant difference between two groups according to requirement of invasive mechanical ventilation (p < 0.001). 35 patients (38%) required renal replacement therapy. 4 (11%) of the survived patients required renal replacement therapy

and 31 (89%) of the died patients required renal replacement therapy. There was a statistically significant difference between two groups according to the requirement of renal replacement therapy (p < 0.001).

During the ICU follow-up, ARDS developed in 23 patients (25%). ARDS developed in 1 (4%) of the patients who survived and in 22 (96%) of the patients that died. There was a statistically significant difference between two groups according to the development of ARDS (p < 0.001). Characteristics of the whole study group were shown in Table 1.

A binary logistic regression analysis was performed to detect the possible parameters that affect ICU mortality. Age, sex, NEWSS, APACHE II score, SOFA score, requirement of renal replacement therapy, development of ARDS were included in the binary logistic regression analysis model to determine the independent risk factors for ICU mortality. Logistic regression analysis demonstrated that high SOFA score, requirement of renal replacement therapy and development of ARDS were associated with greater odds of ICU mortality. However, we showed that NEWS score was not related with ICU mortality. The results of logistic regression analysis were summarized in Table 2.

Table 1. Patient's demographics and clinical characteristics (n=91)

Variable	All patients (n=91)	Survivors (n=35)	Non-survivors (n=56)	p values
Age, (IQR) year	55 (29)	51 (33)	57.5 (26)	0.419
Sex, n(%)				
Male	55 (60)	20 (57)	35 (63)	0.66
Female	36 (40)	15 (43)	21 (37)	
Reasons for ICU admission, n(%)				
Respiratory failure	45 (49)	13 (37)	32 (57)	
Sepsis	10 (11)	7 (20)	3 (5)	0.058
Severe Sepsis	5 (5)	2 (6)	3 (5)	
Septic Shock	18 (20)	5 (14)	13 (23)	
Neurologic Disorders	7 (8)	5 (14)	2 (4)	
Others	6 (7)	3 (9)	3 (6)	
Hematological diagnosis of the patients, n (%)				
AML	30 (33)	15 (43)	15 (27)	
MM	21 (23)	6 (17)	15 (27)	
ALL	13 (15)	6 (17)	7 (12)	0.36
Hodgkin Lymphoma	3 (3)	1 (3)	2 (4)	
Non-Hodgkin Lymphoma	12 (13)	5 (14)	7 (12)	
Ohers	12 (13)	2 (6)	10 (18)	
APACHE II score (IQR)	26 (13)	21 (11)	29.5 (13.5)	< 0.001
SOFA score (IQR)	8 (7)	6 (4)	11 (5.5)	< 0.001
GCS (IQR)	9 (10)	15 (3)	6 (6)	< 0.001
NRS 2002 score (IQR)	4 (2)	4 (2)	4 (2)	0.189
The National Early Warning System Score (IQR)	8 (3)	7 (3)	8 (3)	0.30
The Time Difference Between the Deterioration in the General Condition of Patients and the Admission of Patients to the ICU, hours (IQR)	7 (7)	6 (8)	7.5 (7)	0.36
Total Cortisol Level; µg/dL (IQR)	32 (27.6)	24 (20.5)	43 (24.5)	0.005
Requirement of Vasopressor Therapy, n (%)	63(69)	7(11)	56(89)	< 0.001
Requiremen of Mechanical Ventilation, n (%)	63(69)	7(11)	56(89)	< 0.001
Requirement of Renal Replacement Therapy, n (%)	35 (38)	4 (11)	31 (89)	< 0.001
Development of ARDS, n (%)	23(25)	1(4)	22(96)	< 0.001

AML: Acute Myeloid Leukemia; MM: Multiple Myeloma; ALL: Acute Lymphoblastic Leukemia; APACHE II: Acute Physiology and Chronic Health Assessment; SOFA: Sequential Organ Failure Assessment; GCS: Glasgow Coma Score; NRS 2002: Nutritional Risk Score 2002; ICU: Intensive Care Unit; ARDS: Acute Respiratory Distress Syndrome; n: number; (IQR): interquartile ranges

Table 2. Logistic Regression Analysis for ICU Mortality*

Risk Factor	OR	%95 Confidence Interval	p
Requirement of Renal Replacement Therapy	6.37	1.63- 24.80	0.008
Development of ARDS	21.80	2.53-187.89	0.005
SOFA score	1.32	1.11- 1.57	0.002
Age	1.03	0.99-1.07	0.12
Sex	1.28	0.34- 4.78	0.7
APACHE II	1.02	0.92- 1.12	0.67
NEWSS	1.16	0.86- 1.56	0.32

*Age, Sex, APACHE II score, SOFA score, requirement of Renal Replacement Therapy, development of ARDS, NEWSS were included in the model.
OR: Odd's ratio, CI: Confidence interval

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Discussion

As a result of this study, it was determined that NEWS score was not related with ICU mortality in HM patients. The risk factors affecting ICU mortality of HM patients were high SOFA score, development of ARDS and requirement of renal replacement therapy. ICU mortality rate was 62%.

In a prospective study of 1354 patients by Kivipuro et al., the relationship of NEWSS with 30-day mortality was evaluated. In this study, patients were divided into three groups; first group those who came directly from the emergency room to the ICU, second group those who came from the emergency room to any service and then to the ICU within 72 hours and third group who came from the emergency services to other services. As a result, high NEWS scores in the emergency department were independently associated with in- hospital and 30-day mortality (7).

In another retrospective study by Lee et al., the relationship of NEWSS with hospital mortality was evaluated on 1300 heterogeneous patients. As a result, it was observed that patients with a moderate to high NEWS score had a low chance for survival (8).

In another study that took place in Turkey consisted of 104 patients. The aim of the study was to determine the NEWSS of the patients in the internal medicine clinic, the relationship between the NEWSS and hospital stay, the need for ICU, the first 24-hour and 28-day survival rate as well as the frequency of cardiac attacks. In the study, 46% of the patients had HM. The 28-day mortality rate of the patients with high NEWS scores was higher compared to patients with low NEWS scores. No secondary analysis was performed in patients with malignancy (9).

85,322 patients were evaluated in a retrospective cohort study of Bedoya et al. In this study, the NEWS score was found to be a bad predictor for predicting hospital mortality (10).

In our study, no relationship between NEWS and ICU mortality was found. In died patients NEWSS were higher but between survivors and non-survivors there was no statistically significant difference. In a large-scale research, the relationship between NEWSS and ICU mortality in HM patients may be found. Also the common feature of the studies discussed above is that they studied on heterogeneous patient groups. This was the first study searching relationship between NEWSS and ICU mortality only

in HM patients. In our study, median time difference between the deterioration in the general condition of patients and the admission of patients to the ICU was 7 hours. For survivors this time difference was 6 hours and for non-survivors this time difference was 7.5 hours. These times are very late for critically ill patients. Of course there are reasons for this; but if we can shorten these times NEWSS might work then.

In many previous study, the relationship between ICU scoring systems and ICU mortality of HM patients investigated and found that we can rely on the ICU scoring systems to monitor these patient (3, 11, 12). In our study, logistic regression analysis demonstrated that, high SOFA score increased the ICU mortality 1.3 fold in HM patients. Previous studies and our study showed that ICU scoring systems are the scoring systems that we can rely on to monitor HM patients.

Requirement of renal replacement therapy in ICU is one of the most important risk factors for mortality (11, 12). In our study, 35 patients received renal replacement therapy and 31 (%89) of them died. There was a statistically significant difference between two groups according to requirement of renal replacement therapy. Also logistic regression analysis demonstrated that, requirement of renal replacement therapy increased the ICU mortality 6.3 fold in HM patients. Based on previous studies and our study, this experience leads us to conclude that requirement of renal replacement therapy in the ICU may guide us for the prognosis of HM patients.

ARDS is a common and devastating complication after acute illness or injury, and it results in high morbidity, mortality, and healthcare costs (13-15). In our study, ARDS developed in 23 patients (25%). 1 (4%) of them survived and in 22 (96%) of them died. Logistic regression analysis demonstrated that, development of ARDS increased the ICU mortality 21.8 fold in HM patients. Development of ARDS in the ICU may guide us for the prognosis of HM patients

Conclusion

In conclusion, the NEWS score was not found as a predictor for ICU mortality in HM patients. Development of ARDS, requirement of renal replacement therapy and high SOFA score are reliable for predicting the ICU mortality of HM patients.

AUTHOR CONTRIBUTIONS:

Concept: II, RC; **Design:** II, RC; **Materials:** II, RC; **Data Collection and/or Processing:** II, RC, KG, ST, MS; **Analysis and/or Interpretation**: II, RC, ST, KG, MS; **Literature Search:** II, RC, ST; **Writing Manuscript**: II, RC, ST, KG, MS; **Critical Review:** II, RC, ST, KG, MS.

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