Mortality Correlation Factors in Patients with Lymphoma and Acute Myeloid Leukemia Admitted into the Intensive Care Unit at a Referral Center in the South of Thailand

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Background: *Recent treatments in hematological malignancies have substantially improved. Unfortunately, once a patient with a hematological malignancy has complications, the prognosis is poor and the in hospital and ICU mortality rates are high. Debates concerning the reluctance to admit patients into ICUs with poor prognoses often emerge. The aim of the present study is to identify the patients who are more likely to benefit from ICU admissions.*

Objectives: *To assess the outcomes and to identify early mortality risk factors in patients with lymphoma and acute myeloid leukemia admitted to the Intensive Care Unit (ICU) at Songklanagarind Hospital in the south of Thailand.*

Material and Method: *This is a retrospective study of patients diagnosed with lymphoma and acute myeloid leukemia admitted to the ICU during the period of January 2004 through May 2008. Demographic factors, acute physiology, Acute Physiology and Chronic Health Evaluation (APACHE) II scores and variables noted in the first 24-hours were collected. The risk factors for deaths in the ICU were studied by univariate and multivariate analysis. The risk factors taken from the best multivariate analysis model were calculated to predict the probability of ICU mortality.*

Results: *A total of 145 patients were studied. The ICU mortality rate was 55.2%. The major cause of death was septic shock. Using univariate analysis, the significant mortality risk factors were neutropenia, mechanical ventilation, the use of vasopressors, abnormal serum creatinine (Cr) and APACHE II scores ($p<0.05$). Using multivariate analysis, ICU mortality was best predicted on admission by mechanical ventilation, the use of vasopressors and the APACHE II scores. The presence of neutropenia, mechanical ventilation, vasopressors and an APACHE II score of greater than 27 predicts 80% sensitivity and a 75% specificity for an 82% ICU mortality.*

Conclusion: *Patients with lymphoma and acute myeloid leukemia admitted into the ICU referral center in the south of Thailand who had mechanical ventilation, use of vasopressors and APACHE II scores greater than 27 were associated with a higher ICU mortality rate. The authors suggest that early identification of the subgroup of patients whose probability of survival is so low that advanced ICU support should not be continued would be a more reasonable goal. This will allow more efficient care to potential survivors not in this group.*

Keywords: *Mortality, Acute leukemia, Lymphoma, Intensive care unit*

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Currently, treatment modalities in hematological malignancies are well developed and more advanced. However, post chemotherapy complications such as acute respiratory failure, circulatory collapse neurological impairment, acute renal failure and multi-organ failure remain high and result in requiring transfer to an intensive care unit (ICU) for monitoring and/or advanced support[1-7]. In hospital and in ICU mortality rates continue to be high and vary from 47% to 61%[2,5,8] and 26% to 62%, respectively[1-7,9,10]. This results in a reluctance to transfer patients with hematological malignancies to the ICU, especially, in conditions of limited resources. Prognostic factors in these patients from previous studies had shown conflicting results[1-10]. The different outcomes may have occurred from heterogeneity and the limited number of patients

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in those studies. The objective of the present study is to assess the outcomes and to identify early mortality risk factors in patients with lymphoma and AML admitted into the intensive care unit at Songklanagarind Hospital. Songklanagarind Hospital is a referral center in the south of Thailand and is discriminate to the patients who are more or less likely to benefit from an advanced, or prolonged ICU admission.

Material and Method

This is a retrospective study of 145 consecutive patients with lymphoma and AML who were at least 15 years of age and admitted into the medical intensive care unit at Songklanagarind Hospital during the period from January 2004 through May 2008. The medical records, computerized hospital laboratory results and the admission databases were reviewed. Demographic data include age, sex, the primary reason for ICU-admission, diagnosis and length of ICU stay. Variables collected within the first 24 hours of admission included the use of mechanical ventilation, the use of vasopressors, Blood Urea Nitrogen (BUN) (mg/dl), Cr (mg/dl), serum glutamic oxaloacetic transaminase (SGOT) (IU/L), serum glutamic-pyruvic transaminase (SGPT) (IU/L), total white blood cell count (total WBC), absolute neutrophil count (ANC), the presence of neutropenia, recent assays with resulting bacteremia, Acute Physiology and Chronic Health Evaluation (APACHE) II scores and hematological disease status. If a patient had more than one hospital admission due to complications from critical illness, only the first admission was included in the data collection.

Definition

The diagnosis of AML and lymphoma was categorized as acute myeloid leukemia (acute non-lymphoblastic leukemia, acute myeloid leukemia, acute myelomonoblastic leukemia, acute monoblastic leukemia and acute promyelocytic leukemia), non-Hodgkin lymphoma (diffuse large B cell, peripheral T-cell and others) and Hodgkin's disease. Hematological disease status was categorized as active or stable. Patients with disease progression, who were in relapse or who had to receive chemotherapy within the 4-week period prior to admission were categorized as with active disease and patients who did not meet the criteria of an active disease were categorized as with stable disease. Mechanical ventilation is defined as an intubated patient who requires a mechanical ventilator. Vasopressor use was defined as any vasopressor or inotropic drug (5 μg/min of adrenalin or noradrenalin, 5 μg/kg/min of dopamine or dobutamine) that was started for the patient with hypotension not responding to a fluid challenge or, patients with verified cardiac failure by echocardiography or pulmonary artery catheterization within 24 hours of admission[2]. Neutropenia was defined as a total neutrophil count of less than 500/mm^3. Recent bacteremia was defined as at least two positive hemocultures for coagulase negative staphylococcus or Corynebacterium spp or at least one positive hemoculture for other bacteria 48 hours prior to admission or found on the day of admission[2].

Statistical analysis

Continuous variables were expressed as mean $\pm$ standard deviation (SD) or mean with a minimum and a maximum dependent on the distribution of data and discrete variables that were expressed in percentages. The dependent variable used in the analyses was the patients' status (alive or deceased) in the ICU. Both groups were compared by the Student's t-test or Wilcoxon rank sum test, depending on the distribution of continuous variables, by the Chi-square test and the Fisher-exact test for categorical variables. Univariate and multivariate analysis (logistic regression) were used to assess the relationships between multiple patient characteristics and ICU-mortality. All statistical analyses were carried out using the R program.

Results

Of the 145 patients with an AML and lymphoma admitted to the medical ICU, 76 (52.4%) were males and 69 (47.6%) were females. The mean age was 47$\pm$16 years of age. The mean length of ICU stay was at 4.52 (1, 40) days. ICU-mortality was at 55.2% and the most common cause of death was septic shock. Excluding 58 patients who died within 24 hours of their ICU admission, the mean APACHE II score was 28.7$\pm$9.96. The principle diagnosis of non-Hodgkin lymphoma, Hodgkin's disease and AML was at 59.3%, 6.9% and 33.8%, respectively. Approximately 94.5% was in active disease as defined previously. Two-thirds of the cases were admitted to the ICU after the development of multiple organ failure and/or cardiovascular failure.

Compared to those who failed to survive, the survivors had significantly longer lengths of ICU stays and lower APACHE II scores. Non-survivors have shown a more significant number of patients with neutropenia, mechanical ventilation and the use of vasopressors in comparison to the survivors. In

reference to the laboratory investigations done within 24 hours of admission, the survivors had shown a significantly higher total white blood cell count and absolute neutrophil count when compared to the assays from the non-survivors. However, the non-survivors had higher mean BUN and Cr values than the survivors (Table 1).

By univariate logistic regression analysis using survival status as the dependent variable; neutropenia, mechanical ventilation, the use of vasopressors, Cr values and APACHE II scores were statistically significant at predicting ICU mortality ($p<0.05$). In addition, when APACHE II scores were stratified at 27 or less or greater than 27; the patients who had APACHE II scores greater than 27 were more likely to be associated with the risk of death as compared to those with APACHE II scores of 27 or less. There were 58 patients who did not have APACHE II scores; however, by regression analysis, when compared to the patients with APACHE II scores less than 27, these patients were at a similar risk of death to those with APACHE II scores greater than 27.

By multivariate linear regression analysis (Table 2), using survival status as the dependent variable and with the significant parameters taken from the univariate analysis as independent variables, the final model is shown in Table 2. The use of a vasopressor, the use of a mechanical ventilator and the APACHE II scores were the significant parameters in predicting the risk of death.

In addition, the representation below the receiver operating characteristic (ROC) curve (Fig. 1) between the 4 predictive variables in Table 2 shows the probability of death is at 0.82. It also gave 80% sensitivity and 75% specificity in the prediction for ICU mortality.

Discussion

Previous studies had indicated that ICU mortality was high and varies from 26% to 62%. ICU mortality in this study is at 55.2% and the mean APACHE II score was 28.7. However, an ICU mortality comparison made directly between these studies is difficult because of unadjusted, patient severity measurements.

By univariate analysis, the factors associated

Table 1. Number and percentage of patients who were alive or dead by level of categorical variables

Variable	No. of patients	Alive	Dead	p-value
Age (years)	145	45 (16-89)	46 (19-75)	0.590*
Sex (% of male)	145	35 (24.13%)	41 (14.48%)	0.880^{+}
Length of ICU stay (days)	145	4 (1-40)	2 (1-29)	0.009*
Disease status: active	145	60 (41.38%)	77 (53.10%)	0.467^{++}
Reasons for admission	145			0.217^{++}
cardiovascular	54	25	29	
multiorgan failure	53	19	34	
pulmonary	25	12	13	
neurology	2	2	0	
others	11	7	4	
APACHE II scores	87	25 (8-41)	32 (15-52)	<0.001*
Mechanical ventilator use	145	46 (31.72%)	77 (53.10%)	<0.001^{+}
Vasopressor use	145	37 (25.52%)	68 (46.89%)	<0.001^{+}
Neutropenia (%)	145	17 (11.74%)	45 (31.03%)	<0.001^{+}
ANC (/mm^3)$^{\#}$	139	3,168 (0-37,740)	0 (0-40,330)	0.0068*
Total WBC (/mm^3)$^{\#}$	139	5,100 (50-89,100)	1,300 (0-66,400)	0.0256*
Recent bacteremia	111	10 (9%)	19 (17.12%)	0.221^{+}
BUN (mg/dl)$^{\#}$	137	22.90 (3.7-96.8)	33.40 (4.4-96)	0.016*
Cr (mg/dl)$^{\#}$	138	1.21 (0.46-4.3)	1.59 (0.38-4.7)	0.006*
SGOT(IU/L)$^{\#}$	106	45.50 (7-1,551)	54.50 (5-1,908)	0.718*
SGPT (IU/L)$^{\#}$	108	36.00 (5-1,031)	30.50 (3-1,100)	0.826*

*Wilcoxon rank sum test

$^{+}$Chi-square test, $^{++}$Fisher exact test

$^{\#}$excluding WBC > 100,000/mm^3, BUN >100 mg/dl, Cr >6 mg/dl, SGOT >2,000 IU/L and SGPT >1,500 IU

Table 2. Multivariate analysis between probability of death and predictive variables

Variables	Adjusted odds ratio	95% CI	p-value
Neutropenia	2.21	0.95-5.11	0.064
Mechanical ventilator use	5.31	1.32-21.33	0.010
Vasopressor use	2.75	1.09-6.97	0.032
APACHE II scores			
Scores >27/unknown*	6.13	2.56-14.66	<0.001

* Compared to APACHE II scores ≤27

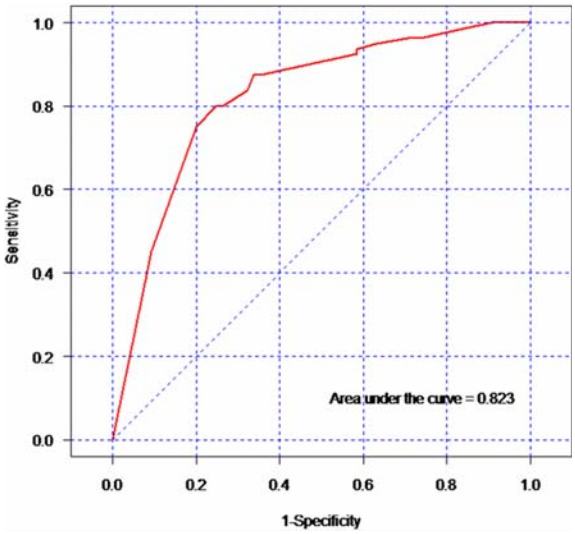

Fig. 1 ROC curve between risk of death and predictive variables (neutropenia, mechanical ventilator use, vasopressor use and APACHE II scores).

with ICU mortality were neutropenia, mechanical ventilation, the use of vasopressors, Cr values and the APACHE II scores which were similar to previous studies[2-5,9,10]. The most common cause of death in our study was septic shock. It is possible that these findings were associated with the septic shock or multi-organ failure, so these variables were likely to predict ICU mortality. However, in contrast with previous studies (Table 3), bacteremia[2], hepatic failure or hepatic damage was not associated with ICU mortality[1,8]. Due to retrospective data collection, there were 35 patients who had no documented liver function tests and/or bacteremia data. This may possibly result in a lower number of patients with these parameters who had revealed significant results in previous studies. In addition, the status of the hematological disease which was a predictive mortality risk factor in a previous study[6] was not considered a risk factor in the present study. The explanation is that in our study, 94% of the patients are categorized as in active disease. When using multivariate analysis, only the use of a vasopressor, the use of a mechanical ventilator and APACHE II scores were significant parameters in predicting the risks of death. Furthermore, we analyzed the levels of APACHE II scores to discriminate who were at risk of death. The patients who have APACHE II scores greater than 27 or those whose scores were not known (i.e. patients without scores because they died within 24 hours of ICU admission or the recorded data were incomplete), are statistically at a higher risk of death than those with APACHE II scores of 27 or less (Table 2). In addition, the total risk factors from the best multivariate analysis model were given an 82% probability with 80% sensitivity and 75% specificity in predicting ICU mortality.

The strength of the present study is that we have included only patients with acute myeloid leukemia and lymphoma which are the most common types of hematological malignancies admitted into our ICU, whereas other studies included patients with solid organ tumors or any other types of hematological malignancies[1-9,11-13] that have higher variations of the baseline characteristics in the population. Furthermore, other studies had shown longer periods of data collection, approximately 7-10 years[1,5,7,9,10]. This is a period longer than done in the present study. This probably created a treatment bias because longer periods of study might have produced changes or new developments in treatment protocols which can result in different outcomes. However, there are still some limitations in the present study. First, this is a retrospective data collection which may have incomplete data. Second, because we did not have a protocol for the selection of patients admitted to the ICU, there is some bias resulting from a reluctance to admit patients with a very poor prognosis or patients' refusals for invasive treatments or accepted "Do Not Attempt Resuscitation" orders. Both limitations should be addressed with the conduction of a prospective

Table 3. Summarized predictive mortality risk factors from previous studies in hematologic patients admitted into ICU

Author	Period	Design	Patients	ICU mortality (%)	Hospital mortality (%)	Predictive factors
Massion[5]	1988-1997	Observation	84	38	61	Respiratory failure, fungal infection
Benoit[2]	1997-2000	Retrospective	124	42	54	Leucopenia, using vasopressor, urea >0.75 g/l
Moran[9]	1989-1999	Retrospective	89	39	NA	APACHE II, using ventilator, time to ICU admission
Evison[1]	1990-1997	Retrospective	78	26	NA	Organ failure, liver damage
Silfvast[6]	1994-1998	Retrospective	30	43	NA	SOFA, disease status
Kroschinsky[4]	1995-2004	Retrospective	104	44	NA	Using ventilator, SAP II, CRP
Cornet[7]	1995-2004	Retrospective/ Prospective (only last 2 years)	58	62	NA	SOFA
Gordon[8]	2001	Prospective	101	NA	47	Liver and CNS failure
Rabbat[10]	9 years	Retrospective	83	34	NA	SAP II, using ventilator
Staudinger[3]	66 months	Retrospective	414	47	NA	Septic shock, using ventilator

study determining risk factors that may discriminate these patients. In addition, we should develop advances in the treatments of septic shock as this is shown to be the common cause of death in these patients.

The authors conclude that patients with lymphoma and acute myeloid leukemia admitted into the ICU at Songklanagarind Hospital who had mechanical ventilator use, the use of vasopressors and APACHE II scores greater than 27 showed an association with a higher ICU mortality rate. Early identification of the subgroup of patients whose probability of survival is so low that advanced ICU support should not be continued would be a more reasonable goal. This will allow more efficient care to potential survivors not in this group.

Potential conflicts of interest

None.

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ปัจจัยที่สัมพันธ์กับอัตราตายในผู้ป่วยมะเร็งต่อมน้ำเหลืองและมะเร็งเม็ดเลือดขาวชนิดมัยอีลอยด์ ในผู้ป่วยที่ได้รับการรักษาในหออภิบาลผู้ป่วยในโรงพยาบาลระดับตติยภูมิในภาคใต้ในประเทศไทย

จีรทีปต์ ขวัญแก้ว, รังสรรค์ ภูรยานนทชัย

ภูมิหลังและวัตถุประสงค์: *ผลการรักษาโรคมะเร็งทางโลหิตวิทยาในปัจจุบันมีผลที่ดี แต่อย่างไรก็ตามในผู้ป่วยที่มีภาวะแทรกซ้อนจากการรักษาจะมีพยากรณ์โรคที่ไม่ดี ซึ่งทำให้อัตราตายสูงในโรงพยาบาล และในหออภิบาลผู้ป่วยทำให้เกิดความลังเลของแพทย์ในการที่จะรับผู้ป่วยเข้ารักษาในหออภิบาล การศึกษานี้จึงมีเป้าหมายในการบ่งชี้ และคัดแยกผู้ป่วยที่จะได้ประโยชน์มากที่สุดในการรับเข้ารักษาในหออภิบาลของโรงพยาบาลสงขลานครินทร์*

วัสดุและวิธีการ: *เป็นการศึกษาทบทวนย้อนหลังของผู้ป่วยที่เป็นมะเร็งต่อมน้ำเหลือง และมะเร็งเม็ดเลือดขาว ชนิดมัยอีลอยด์ที่ได้รับการรักษาในหออภิบาลตั้งแต่ เดือนมกราคม พ.ศ. 2547 ถึง เดือนพฤษภาคม พ.ศ. 2551 โดยมีการบันทึกถึงข้อมูลประชากรพื้นฐาน คะแนน APACHE-II และข้อมูลต่างๆ ใน 24 ชั่วโมงแรก และนำข้อมูลต่างๆ มาหาปัจจัยต่ออัตราตายด้วยการวิเคราะห์แบบ univariate และ multivariate*

ผลการศึกษา: *ผู้ป่วยจำนวน 145 ราย ได้เข้าร่วมการศึกษานี้ มีอัตราตายโดยรวมประมาณร้อยละ 55.2 โดยสาเหตุการเสียชีวิตส่วนใหญ่เกิดจากภาวะช็อกจากการติดเชื้อ จากการวิเคราะห์แบบ univariate พบว่าภาวะเม็ดเลือดขาวนิวโตรฟิลต่ำ, การใช้เครื่องช่วยหายใจ, การใช้ยาตีบหลอดเลือด, ครีอะตินินและคะแนน APACHE-II เป็นปัจจัยที่มีผลต่ออัตราตาย ($p<0.05$) แต่การวิเคราะห์แบบ multivariate พบว่าการใช้เครื่องช่วยหายใจ, การใช้ยาตีบหลอดเลือด และ APACHE-II เป็นปัจจัยที่สัมพันธ์กับอัตราตาย ภาวะเม็ดเลือดขาวนิวโตรฟิลต่ำ, การใช้เครื่องช่วยหายใจ, การใช้ยาตีบหลอดเลือด และ APACHE-II ที่มากกว่า 27 จะมีความไวประมาณร้อยละ 80 และความจำเพาะประมาณ ร้อยละ 75 ในการทำนายอัตราตายในหออภิบาลประมาณ ร้อยละ 82*

สรุป: *ผู้ป่วยมะเร็งต่อมน้ำเหลือง และมะเร็งเม็ดเลือดขาวชนิดมัยอีลอยด์ ที่ได้รับการรักษาในหออภิบาลที่ได้รับการใส่เครื่องช่วยหายใจ มีการใช้ยาตีบหลอดเลือดและมีคะแนน APACHE-II มากกว่า 27 จะสัมพันธ์กับอัตราตายที่สูงที่สุด การศึกษานี้อาจช่วยบ่งชี้ผู้ป่วยที่มีอัตรารอดชีวิตน้อยในหออภิบาล จะช่วยทำให้การจัดการรักษาผู้ป่วยที่มีอัตราการรอดชีวิตสูงได้รับการรักษาที่สมเหตุสมผลมากขึ้น*