

Outcomes and prognostic factors for pediatric cancer patients admitted to an intensive care unit in a university hospital

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ABSTRACT

Background and objectives. The aim of this study was to investigate the factors predicting Pediatric Intensive Care Unit (PICU) mortality and the outcomes in cancer patients admitted to PICU.

Methods. We conducted a retrospective study in 48 consecutive cancer patients admitted to the PICU between January 1, 2015 and January 1, 2018. A total of 48 patients (21 males and 27 females) were enrolled in this study.

Results. The median age was 77 (33,5-149) months. The median duration of PICU stay was 5 (2-9) days. Patients were classified according to their stage of disease. Ten (20.8%) patients were in the remission group, 9 (18.8%) patients were in the induction period and 29 (60.5%) patients were in the progressive disease groups. Thirty-nine patients (81.2%) had hematological malignancies, 6 (12.5%) had extracranial solid tumors and 3 (6.3%) had intracranial solid tumors. Thirty-seven patients died and the mortality rate was found to be 77.1%. mortality rates were 11%, 88% and 93% for patients in remission, during induction period and in the progressive disease group, respectively ($p < 0.01$). The most frequent reasons of PICU admission were respiratory failure in 29 (60.4%), sepsis in 12 (25%), circulatory collapse in 2 (4.2%), and other reasons in 5 patients (10.4%). The median PRISM III among survivors was significantly lower than non-survivors (13.1 ± 6.4 ; vs. 20.7 ± 5.2 ; $p < 0.001$). At a cut-off value of 13, the sensitivity of the PRISM III was 94.4% and the specificity was 58.3% (AUC: 0.821). OSD was present in 41 (85%) patients, 82% of them died (34/41). The presence of MOF, the use of mechanical ventilation and inotrop support were significantly related with mortality. Univariate logistic regression analysis showed that male gender [odds ratio (OR)=5.588, $P=0.041$, 95% confidence interval (95%CI) 1.070-29.191], presence of organ system dysfunction [OR=12.143, $P=0.008$, 95%CI 1.947- 75.736], need for mechanical ventilation [OR=34.000, $P=0.001$, 95%CI 5.272-219.262], IS [OR=8.5, $P=0.001$, 95%CI 1.318-54.817] were the predictors of high mortality in pediatric cancer patients. PRISM III score ≥ 13 was a predictive criteria of PICU mortality.

Conclusion. We conclude that the key to improving survival rates is to pick up on this group of patients as soon as possible. We believe that cancer patients could be saved by earlier evaluation and intervention by the PICU team when they have a less severe disease.

Key words: cancer, pediatric, PICU.

Over the past few decades, development in current treatment protocols for cancer patients have resulted in a significant increase in survival rates. Thereby, an increased number of patients with cancer are requiring admission to pediatric intensive care units (PICU). Disease-related

complications or treatment-associated side effects may lead to severe and life threatening complications such as tumor lysis syndrome, sepsis, and respiratory and cardiovascular insufficiency. These complications may require prompt initiation of intensive care treatment. Therefore, identification of children whose admission to PICU will improve their survival are so very crucial.

Although there have been improvements in supportive care, previous published studies

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reported poor outcomes of children with cancer who required PICU admission specifically when invasive ventilation, inotropic support and continuous renal replacement therapy are needed.¹ Outcomes and risk factors associated with mortality in PICU are needed to establish the optimal clinical management of cancer patients.

The aim of our study was to investigate incidence, causes, outcomes and prognostic factors associated with mortality in cancer patients transferred to PICU.

Material and Methods

This retrospective, observational study was carried out in the 12- bed medical PICU of the Erciyes University Child Hospital in Kayseri, Turkey. We reviewed the clinical records of all cancer patients (<18 years old) who required PICU admission between January 1, 2015 and January 1, 2018. Only the first admission was recorded in patients with multiple PICU admissions. Patients who stayed in the PICU for shorter than 24 hours were also excluded.

The following information was abstracted from the medical charts of the patients: sex and age, underlying primary disease, reason for admission, thrombocytopenia, neutropenia, therapeutic interventions (positive inotropic support, mechanical ventilation, and dialysis), PRISM III score, length of PICU stay, number of organ failures, and outcome (survivors vs. nonsurvivors at the time of leaving the PICU). For organ system dysfunctions (OSD) and sepsis, International Pediatric Sepsis Consensus Conference Report of "Definitions for sepsis and organ dysfunction in pediatrics" on January 2005 was used in this study.²

Patients admitted to PICU were evaluated from the medical charts of the patients with a pediatric hematology-oncology fellow and they were classified according to stage of disease in 3 treatment groups as remission, induction period and progressive disease groups.

Infection was defined as a suspected or proven infection. Pathogenic organisms were proved by positive culture or polymerase chain reaction test. The definition also included clinical syndromes associated with a high probability of infection, such as petechiae and purpura in a child with hemodynamic instability, or fever, cough, and hypoxemia in a patient with leukocytosis and pulmonary infiltrates on chest radiograph. Additionally, an elevation of C-reactive protein and procalcitonin were also presumed to be an infection. Invasive fungal infections were defined according to "Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group". Thrombocytopenia was defined as a platelet count below the lower limit of normal (<150,000/microL) and neutropenia was defined as absolute neutrophil count less than 1500/mL. The patients who had arterial blood pressure less than 2 standard deviations of normal value for age and whom received any vasopressor or inotropic drug within 24 hours of admission were defined as positive inotropic support. The patients who were unable to maintain adequate oxygenation or ventilation (PaO₂<70 mm Hg PaCO₂>65 mm Hg when FiO₂>0.60), received mechanical ventilation.

Patients were discharged from the PICU after documented hemodynamic/respiratory and neurological stability lasting >48 and 24 hours, respectively. Hemodynamic stability was defined as no need for inotropic drugs for continuous volume expansion; diuresis >1 mL/kg/h, and no need for renal replacement therapy. Respiratory stability was defined as off MV for >48 hours, no need for noninvasive ventilatory support, and oxygen saturation (SpO₂) >95% with FiO₂.

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0 (IBM, Armonk, NY). The normality

of parametric data was analyzed by the Shapiro Wilk test. Numerical variables were expressed as mean \pm SD or median (25-75p). Comparisons between groups for data with a normal distribution were performed using Student's t-test, and the comparisons between groups for data that did not show a normal distribution were performed using the Mann-Whitney U test. Categorical variables were compared using the χ^2 test. The bivariate correlation tests were used to analyze the correlations. Whether PRISM III value was a significant marker that differentiated survivors from non-survivors was explored using 95% confidence intervals and the area under ROC curve. When a significant area under the curve was obtained, the maximum possible sum of the sensitivity and specificity levels was considered the best cut-off point. The statistically significant risk factors were analyzed by univariate logistic regression analysis. A p value less than 0.05 was considered statistically significant

Results

During the study period, a total of 48 patients (21 males and 27 females) were enrolled in this study. Forty-three patients were transferred from the Haematology Department and 5 patients were admitted from the emergency department. The median age at the time of admission was 77 (33,5-149) months. The median duration of PICU stay was 5 (2-9) days. Table I shows the clinical characteristics of all patients included in the study. Thirty-nine patients (81.2%) had hematological malignancies, 6 (12.5%) had extracranial solid tumors and 3 (6.3%) had intracranial solid tumors.

Thirty-seven patients died and the mortality rate was found to be 77.1%, higher than the yearly overall PICU mortality rate (16%) ($p < 0.001$). In estimation of overall PICU mortality rate, patients were excluded who died of cancer. Fourteen of the study cohort were followed because of hematopoietic stem cell transplantation. Among these patients, 6 received allogeneic, 5 haploidentical and 3 autologous and 11 of them (78%) died.

The most frequent reasons of PICU admission were respiratory failure in 29 (60.4%), sepsis in 12 (25%), circulatory collapse in 2 (4.2%), and other in 5 patients (10.4%). For the 2 patients who were admitted to PICU due to circulatory collapse, mortality rate was found to be 100%, and it was 96.6% for respiratory failure, 58.3% for sepsis and 40% for other diagnoses.

On admission, the mean PRISM III score was 18.8 (\pm 6.4). The mean PRISM III among survivors was significantly lower than among non-survivors (13.1 ± 6.4 ; vs. 20.7 ± 5.2 ; $p < 0.001$). At a cut-off value of 13, the sensitivity of PRISM III was 94.4% and the specificity was 58.3% (AUC: 0.821). ROC curve of the PRISM III differentiating survivors from non-survivors is presented in Figure 1.

According to their stage of disease we classified the patients into 3 treatment groups: remission ($n=10$, 20.8%), induction period ($n=9$, 18.8%) and progressive disease ($n=29$, 60.4%). Patients admitted to the PICU in the remission

Table I. Characteristics of pediatric cancer patients admitted to the Pediatric Intensive Care Unit.

Variables	N (%)
Sex	
Male	21 (43.8)
Female	27 (56.2)
Diagnosis of Patients	
Hematological malignancy	39 (81.3)
Intracranial solid tumors	3 (6.3)
Extracranial solid tumors	6 (12.5)
Reason for admission	
Sepsis	12 (25)
Respiratory failure	29 (60.4)
Circulatory Collaps	2 (4.2)
Other	5 (10.4)
Stage of Disease	
Remission	10 (20.8)
Progressive disease	29 (60.5)
Induction period	9 (18.8)
Outcome	
Survival	11 (22.9)
Non-Survival	37 (77.1)

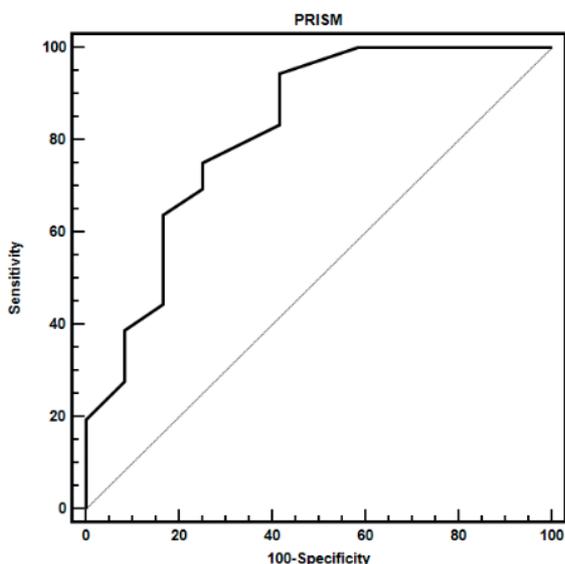


Fig. 1. ROC curve of the PRISM III differentiating survivors from non- survivors.

group had the highest survival rate (89%) compared to patients in the induction period and progressive disease groups (12% and 7%, respectively; $p < 0.01$). In the remission group the mean PRISM III score was 11.4 (± 6.5), 20.8 (± 5.3) in the progressive disease group and 19.4 (± 5.2) in the induction period group ($p < 0.01$).

Three therapeutic modalities used in the ICU were mechanical ventilation, inotropic support and renal replacement therapy (RRT). Mechanical ventilation (invasive or noninvasive) was applied to 39 patients (3 patients in the remission group, 27 patients in the progressive disease group and 8 patients in the induction period group) and the median day of mechanical ventilation was 3 days (2-6). Thirty-four of these were both mechanically ventilated and received positive inotropic

support. RRT was used in 5 patients (3 patients in the induction period group and 2 patients in the progressive disease group). Among these, 4 needed inotropic support (IS) and mechanical ventilation (MV). Five patients were applied only IS and 3 patients were performed neither MV, IS, nor RRT. Among mortality rates in therapeutic interventions, it was highest in the patients where all the 3 interventions were performed together (100%), followed by patients who required both mechanical ventilation and positive inotropic support (Table II).

OSD was present in 41 (85%) of patients, 82% of them died (34/41). Mortality was significantly correlated to the number of organ failure (p -value < 0.001). The presence of OSD was detected in 4 (40%) patients in remission group, 8 (88%) patients in progressive disease group and 29 (100%) patients in induction period. In the remission group the presence of OSD rate was significantly lower when compared with patients in the induction period and progressive disease group ($p < 0.01$).

When survivors are compared with nonsurvivors, no significant differences were found in primary underlying disease, presence of neutropenia, presence of thrombocytopenia, presence of fungal infection and RRT. Mortality rate was significantly related to gender, presence of OSD, MV and IS. (Table III. Univariate logistic regression analysis showed that it was higher in males [OR=5.588, $p = 0.041$, 95%CI 1.070-29.191], with a presence of OSD [OR=12.143, $P = 0.008$, 95%CI 1.947-75.736], mechanical ventilation [OR=34.000, $P = 0.001$, 95%CI 5.272-219.262], and IS [OR=8.5, $P = 0.001$, 95%CI 1.318-54.817].

Table II. Mortality rates according to therapeutic interventions.

Therapeutic interventions	N(%)	Mortality	
		N (%)	Overall Mortality (%)
MV	1 (2)	0 (0)	0
MV+IS	34 (70)	2 (94)	86
MV+IS+RRT	4 (8)	4 (100)	11

Five patients were applied IS and 1 patient was applied RRT. Three patients were performed neither MV, IS, nor RRT
IS: indicates inotropic support, MV: mechanical ventilation, RRT: renal replacement therapy.

Table III. Risk factors related to survival for pediatric hematology/oncology patients admitted to the Pediatric Intensive Care Unit.

Risk Factors	No. Patients (%)	No. Mortality (%)	p
Gender			0.03
Male	21 (43.8)	19 (90)	
Female	27 (56.3)	17 (62)	
Primary diagnosis			ns
Hematologic malignancy	39 (81)	29 (74)	
Solid tumors	9 (19)	7 (78)	
Presence of neutropenia			ns
Yes	37 (77)	28 (75)	
No	11 (23)	8 (72)	
Presence of Thrombocytopenia			ns
Yes	42 (88)	33 (79)	
No	6 (12)	3 (50)	
Presence of OSD			0.007
Yes	41 (85)	34 (83)	
No	7 (15)	2 (29)	
Presence of fungal infection			ns
Yes	17 (36)	14 (82)	
No	31 (64)	22 (64)	
Mechanical ventilation			0.001
Yes	38 (80)	34 (89)	
No	10 (20)	2 (20)	
Positive inotropic support			0.028
Yes	42 (88)	34 (81)	
No	6 (12)	2 (33)	
Renal replacement therapy			ns
Yes	5 (10)	4 (80)	
No	43 (90)	32 (74)	
PRISM score			0.03
<13	4 (8)	0	
>13	44 (92)	36 (81)	

No. Patients: Number of patients, No. Mortality: Number of mortality, ns: non spesifik, OSD : organ system dysfunction, PRISM: Pediatric Risk of Mortality

Discussion

The present study is one of the small number of retrospective studies on pediatric cancer patient populations who need PICU admission. In this study, we evaluated the data of 48 cancer patients to identify the prognostic factors that affect the outcome of PICU admission. Despite improvement of intensive care support, our results indicated that the mortality rate of advanced stage cancer patients is still high. In our study cohort, while the overall PICU mortality

rate in pediatric cancer patients was found to be much higher than non cancer patients, it was similar to overall PICU mortality rates in the remission group. The observed mortality rate is relatively high compared with the rates reported in recently published studies.^{3,4} However, it is important to emphasize a fundamental difference between patient groups. Compared to the population of patients in the study of Akhtar et al.⁴ most of our patients presented with advanced disease (Higher PRISM III score; 18.8 versus 7). Additionally children admitted

postoperatively are far less immunosuppressed compared with those with hematological malignancies. Our cohort did not include the patients who needed PICU admission for routine postsurgical management and majority of the patients were in the progressive disease group in which survival is expected to be low. These factors may explain this discrepancy.

In our study, hematological malignancies were the most prominent diagnosis among patients admitted to our PICU with solid tumors accounting for only 19% of the cases. Hematologic malignancy was not found as a risk factor in survival and this was consistent with previous studies.⁵

Mortality is influenced by the reason for admission. Respiratory failure is a major cause of PICU admission and patients admitted because of respiratory failure and circulatory collapse had the worst outcomes (96.5%, 100%, respectively). Our findings concur with the findings of Dursun et al.³ who reported higher mortality rate in patients with circulatory collapse and respiratory failure. Additionally, the present study investigated that the mortality was significantly influenced by the patients' stage of disease. Children in remission group had a lower mortality rate when compared with those in induction period and progressive disease groups. High Mortality rate is expected in progressive disease groups. However, in our study, mortality rate was found to be high (88%) also in the induction group. The low survival rates in the induction group can be explained by the severity of patients on admission (the mean PRISM III score on admission was 19.4 (± 5.2)). This indicates a delayed presentation to the PICU in the induction period. Due to sepsis, respiratory failure and need for IS, these patients may require intensive care. Therefore patients should be consulted with PICU immediately.

A variety of prognostic factors has been described in patients requiring PICU. In our study we found a high incidence of OSD (85%) and the presence of OSD was found to be a risk for mortality, with a mortality rate of 83% in patients with two or more organ failures

against a 29% mortality rate, similar to the findings of others.⁵ Furthermore, in univariate analysis, our results showed that the presence of OSD increases the mortality with an odds ratio of 12.143. Similar to the present results, previous studies have also demonstrated a significant correlation between the number of organ failure and mortality in pediatric cancer patients admitted to the PICU.^{1,6,7}

The PRISM III score evaluates the mortality risk based on data collected during the first 24 hours in the PICU.⁸ Thus creating the Oncological-PRISM score, some authors have proposed to add important prognostic factors for children posthematopoietic stem cell transplantation and a score > 10 points is accepted as high. However, it has not yet been validated.⁹ Akhtar et al.⁴ demonstrated the mortality rates 51.6% and 18.6% in patients with high (>10 points) and low (<10 points) PRISM III, respectively. This concept is supported by the finding of Dursun et al.³ who reported the sensitivity and specificity of estimating outcome using PRISM III score (cut-off value for poor survival >10 points) were 90% and 50%, respectively. Our analysis confirmed the reported relationship between survival and PRISM III scores in cancer patients. However, the present study found that patients with PRISM III score ≥ 13 had very poor outcome and it was a good indicator for death in PICU with a sensitivity of 94.4% and specificity of 58.3%. Our results could be used to better analyze cohorts of cancer patients admitted to PICU and in the evaluation of new treatment strategies.

For a better understanding of which cancer patients were at higher risk for mortality, we described three therapeutic modalities and analyzed the risk factors separately. The use of mechanical ventilation, inotropic support and renal replacement therapy were found to be associated with poor prognosis. Their combination was associated with a worse prognosis with the mortality rate reaching from 94% to 100%. In univariate analysis, the use of mechanical ventilation showed the strongest association with unfavorable

prognosis after PICU admission, with an almost 34-fold increase in mortality risk and we also found that inotropic support increased 8.5 folds. These data are supported by previous findings.^{10,11} We also reported that no significant differences were seen in presence of leukopenia, thrombocytopenia, fungal infection and RRT when survivors were compared with nonsurvivors.

The limitations of our study are its retrospective nature and its single-center design. Furthermore, the relatively small sample size leads us to refrain from drawing solid conclusions. Nevertheless, our study investigated the significant conclusions about risk factors. Because of variations in the underlying disease composition, ICU admission, and discharge criteria it is rather difficult to compare the mortality in different studies.

In conclusion, the mortality rate of cancer patients in the induction period and progressive disease groups was high. However, it was similar to non cancer patients' mortality rate in the remission group. Factors associated with mortality after PICU admission may prove particularly useful for clinicians to inform patients and families. PRISM III score ≥ 13 was predictive criteria of PICU mortality. As we mentioned before, most of our patients were referred late to PICU. From these data, we conclude that the key to improve survival rates is to pick upon this group of patients as soon as possible. We believe that cancer patients could be saved by earlier evaluation and intervention by the PICU team when they have a less severe disease.

The study was approved by the "Medical Research Local Ethics Committee" of the Erciyes University with a number of 2018/51. All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. We obtained informed consent from the parents.

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