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Factors Affecting Short-Term Outcome of Critically Ill Children with Malignancies Admitted in Pediatric Intensive Care Unit: A Retrospective Observational Study

Priyanka Aggarwal[1] Ishan Kumar[2] Sunil Kumar Rao[3] Pradhap K[3] Vineeta Gupta[1]

[1]Department of Pediatrics, Division of Pediatric Hematology Oncology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India
[2]Department of Radiodiagnosis, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India
[3]Department of Pediatrics, Division of Pediatric Intensive Care and Pulmonology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India

Address for correspondence Priyanka Aggarwal, MBBS, MD (Pediatrics) Department of Pediatrics, Division of Pediatric Hematology Oncology, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, Uttar Pradesh, India (e-mail: tamanna.horizon@gmail.com).

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Abstract

Introduction Pediatric cancer contributes <1% of all malignancies. Childhood cancer survival has improved dramatically with the use of more intensive chemotherapy regimens, better stratification, and improvement in supportive care with enhanced facilities in pediatric intensive care unit (PICU).

Objective The aim of this study was to identify the risk factors responsible for poor outcome in critically ill children with malignancies admitted in PICU.

Materials and Methods Sixty-four children with a primary diagnosis of malignancy admitted in PICU with disease or treatment related complications were enrolled retrospectively. The short-term outcome, that is, shifting from PICU to ward, was assessed in relation to the presence of febrile neutropenia, organ failure, hepatitis, acute renal failure as well as requirement of inotropes and mechanical ventilation. Death was considered as an adverse outcome in this study.

Results The mean age of study population was 6.25 ± 3.91 and M:F ratio 2.4:1. The majority of children had hematological malignancies (81.25%), that is, pre-B acute lymphoblastic leukemia (ALL) (45.3%), non-Hodgkin lymphoma (21.3%), acute myeloid leukemia (12.5%), T ALL (10.9%), and Hodgkin lymphoma (3.1%). Few children also had retinoblastoma (4.7%) and Langerhans cell histiocytosis (1.6%). The mean duration of PICU stay was 3.16 ± 2.31 days. Sepsis (37.5%) was the most common indication for PICU admission, followed by metabolic disturbance (26.6%), respiratory failure (17.2%), neurological complaints (15.6%), and anaphylactic shock (3.1%). Children requiring mechanical ventilation ($p < 0.001$), inotrope support ($p < 0.001$), having acute renal failure ($p = 0.001$), and >1 organ failure ($p < 0.001$) were associated with adverse outcome. The overall survival at the time of discharge from PICU was 64%.

Conclusion In the context of low- and middle-income countries, optimal resource utilization by early identification of risk factors for clinical deterioration is required to allow timely admission to PICU and delivery of life-saving therapy to salvageable patients.

Keywords
- pediatric cancer
- outcome
- PICU

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Introduction

Pediatric cancer contributes <1% of all malignancies.[1] The survival of children with cancer has improved dramatically over the past few decades with 5-year survival rates approaching to ~80% from 40% in developed countries[1,2] due to use of more intensive chemotherapy regimens, better stratification, and substantial advances in supportive care. Unfortunately, survival data from low- and middle-income countries is scarce.[2]

Pediatric intensive care unit (PICU) is an important aspect of supportive care. Children with cancer are admitted to PICU for varied reasons, that is, tumor-related problems like superior vena cava (SVC) syndrome and tumor lysis syndrome (TLS), or therapy-related toxicity and/or immunosuppression resulting into infectious complications.[3,4] Most of the data regarding PICU outcomes is available from developed countries. There are studies that look at outcome of children admitted in PICU where adverse outcome was reported if children required inotrope support or ventilation in context of sepsis after bone marrow transplantation.[5,6] Few other studies conducted to identify prognostic factors at the time of PICU admission stressed on age (varied cut off levels), type as well as stage of malignancy, remission status, and response to chemotherapy. However, results of these studies were not uniform among other reports.[7,8]

In developing countries, as most centers lack PICU facilities for critically ill children with malignancy, similar data regarding PICU outcomes is limited. However, there are few studies to suggest requirement of mechanical ventilation, inotrope usage, and multiorgan dysfunction syndrome following sepsis as predictors of adverse outcome.[9,10] Due to limited infrastructure, there is a need for identifying children in whom survival chances may improve if PICU facility is provided to them. Therefore, to improve survival in these children, it is prudent to identify risk factors responsible for poor outcome in critically ill children with malignancies admitted in PICU and thus the study was planned accordingly.

Materials and Methods

A retrospective observational study including children with a primary diagnosis of malignancy who were admitted from 1 December 2015 to 30 October 2019 in the PICU at a tertiary hospital from North India was planned.

Inclusion criteria:

1. Children with hematological or nonhematological malignancy who qualified PICU admission criteria and got admitted in PICU.

Exclusion criteria:

1. Children with hematological or nonhematological malignancy who required PICU admission but could not be admitted due to nonavailability of beds in PICU.
2. Data incomplete or missing.

Data was collected from hospital records including age, sex, initial diagnosis, indication of admission, comorbidities, need of vasopressors, requirement for ventilation, presence of organ failure, duration of stay, and the short-term outcome.

Criteria for PICU Admission

I. All newly diagnosed children with malignancy (hematological or nonhematological) were admitted, if they had tumor-related complications, that is,
   1. Life-threatening respiratory compromise, that is, high supplemental O_2 requirement (fraction of inspired oxygen ≥ 0.5) and/or potential need for emergency endotracheal intubation and mechanical ventilation, as a consequence to
      i. SVC syndrome.
      ii. Pulmonary/pleural metastasis.
      iii. Peritoneal metastasis/large intraabdominal tumor.
   2. Clinical/laboratory TLS[11] (as per Cairo Bishop Classification).
   3. Circulatory failure.

II. Children receiving chemotherapy were admitted, as a consequence of therapy-related complications, that is,
   1. Anaphylactic shock.
   2. Severe sepsis with/without respiratory and/or hemodynamic instability.
   3. Neurological complaints, that is, status epilepticus and neurological weakness (if there was associated respiratory compromise/autonomic instability).
   4. Metabolic disturbance (hypoglycemia, hypo/hypercalcemia, hypo/hyperkalemia, hypernatremia).
   5. Progressive disease with respiratory and/or circulatory failure.

Blood and urine cultures were sent for all patients admitted with a baseline diagnosis of neutropenic sepsis. Those children who developed neutropenic sepsis during PICU stay were subjected to cultures from blood, urine, and/or bronchoalveolar lavage as per PICU protocol. Sepsis and organ dysfunction was diagnosed according to International Pediatric Sepsis Consensus Conference: definition for sepsis and organ dysfunction in pediatrics.[12]

Children were admitted to PICU from outpatient department or ward depending on the availability of beds in PICU. Outcome from PICU was assessed as discharge from PICU or death of the child.

Statistical Analysis

SPSS (SPSS Inc., Chicago, Illinois, United States) for windows was used for data entry and analysis. All numerical variables are expressed as median with range. For comparison of categorical data, chi-squared test was used. For categorical variables with cell values <5, Fisher's exact test was used. A p-value < 0.05 was taken as significant. Receiver operating characteristic (ROC) curve was plotted for number of inotropes to predict mortality and cutoff value was derived using coordinates of the curve. Binary logistic regression analysis

with hierarchical entry of categorical variables were used to predict mortality in our cohort.

Ethics

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional) and with the Helsinki Declaration of 1964, as revised in 2013. Ethical clearance from Institute Ethical Committee of Institute of Medical Sciences, Banaras Hindu University, was obtained (dated 24.09.2020, No Dean/2020/EC/2132). A waiver of informed consent was obtained from the Ethics Committee.

Results

Sixty-four children (2.5%) were admitted to PICU with a primary diagnosis of malignancy. The mean age of these children was 6.25 ± 3.91 years and male:female ratio was 2.4:1. Hematological malignancies accounted for 81.25% of the total admissions, that is, pre-B acute lymphoblastic leukemia (ALL) (29; 45.3%), non-Hodgkin lymphoma (14; 21.3%), acute myeloid leukemia (8; 12.5%), T ALL (7; 10.9%), and Hodgkin lymphoma (2; 3.1%). Few children had retinoblastoma (3; 4.7%) and Langerhans cell histiocytosis (1; 1.6%).

Table 1 Characteristics of the study population

Characteristic	Result
Age (y)	
Mean± SD	6.25 ± 3.91
Gender	
Male, *n* (%)	45 (70.3)
Female, *n* (%)	19 (29.7)
Diagnosis	
Pre-B ALL, *n* (%)	29 (45.3)
NHL, *n* (%)	14 (21.9)
AML, *n* (%)	8 (12.5)
T ALL, *n* (%)	7 (10.9)
RB, *n* (%)	3 (4.7)
HL, *n* (%)	2 (3.1)
LCH, *n* (%)	1 (1.6)
Indication for PICU admission	
Sepsis, *n* (%)	24 (37.5)
Metabolic disturbances, *n* (%)	17 (26.6)
Respiratory failure, *n* (%)	11 (17.2)
Neurological complaints, *n* (%)	10 (15.6)
Anaphylactic shock, *n* (%)	2 (3.1)
Duration of stay (d)	
Median	3
Range	1–13
Mechanical ventilation, *n* (%)	24 (37.5)
Days of ventilation (d)	
Median	1
Range	1–6

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; LCH, Langerhans cell histiocytosis; NHL, non-Hodgkin lymphoma; PICU, pediatric intensive care unit; RB, retinoblastoma; SD, standard deviation.

Sepsis

Sepsis (24; 37.5%) was the most common indication for admission, followed by metabolic disturbance (17; 26.6%), respiratory failure (11; 17.2%), neurological complaints (10; 15.6%), and anaphylactic shock (2; 3.1%) (►**Table 1**). Children admitted for sepsis included those with septic shock (8; 33.3%), pneumonia (not requiring oxygen supplementation) (7; 29%), neutropenic enterocolitis (7; 29%), severe malaria (1; 4%), and severe dengue (1; 4%).

As per PICU protocol, 102 specimens including cultures from blood, urine, pleural fluid, bronchoalveolar fluid, and/or stool of children admitted with a baseline diagnosis of neutropenic sepsis ($n = 24$) or those who developed neutropenic sepsis during PICU stay ($n = 14$) were sent. Fifteen organisms were isolated from 102 specimens. Among these, nine (60%) isolates were Gram-negative organisms, that is, *Klebsiella pneumonia* (3; 20%) followed by *Escherichia coli* (2; 13.3%), *Acinetobacter baumannii* (2; 13.3%), and *Citrobacter spp.* (2; 13.3%). *Staphylococcus aureus* was reported as a causative organism in four (26.6%) cases and *Candida* spp. in two (13.3%) cases. Five organisms were isolated from cultures that were sent from children who developed neutropenic sepsis during hospital stay. Majority of the isolates were Gram-negative, that is., *Acinetobacter baumannii* ($n = 2$) and *Citrobacter sp.* ($n = 1$) followed by *Candida* spp. ($n = 2$). In our patient cohort, febrile neutropenia was recognized as an independent risk factor for mortality ($p = 0.003$).

Metabolic Disturbances

Another important cause of PICU admission in our cohort was electrolyte abnormalities. This was encountered as a component of TLS or in isolation. Twenty-six children experienced either hypocalcemia (8; 12.5%), hypokalemia (7; 10.9%), both hypocalcemia and hypokalemia (6; 9.4%), or hypercalcemia (5; 7.8%).

Respiratory Failure

Children were also admitted for respiratory failure. This group comprised of children who presented with respiratory distress due to presence of SVC syndrome, disease-related pulmonary metastasis, pleural effusion and/or ascites, and pneumonia required oxygen supplementation.

Neurological Complaints

Among those admitted for neurological complaints, status epilepticus was the most common indication. In these children, the cause of seizures was posterior reversible encephalopathy during induction chemotherapy ($n = 4$), infective meningitis ($n = 2$), intracranial bleed ($n = 2$), and malignant cell infiltration in the central nervous system owing to progressive disease ($n = 1$). One child was admitted as he had Guillain-Barré syndrome with respiratory involvement.

Table 2 Prognostic factors affecting outcome of children admitted in pediatric intensive care unit

	Discharged, *n*	Expired, *n*	*p*-Value
Age	5.59 ± 3.54	7.43 ± 4.31	0.069
Gender			
Male, *n* (%)	32 (71)	13 (29)	0.160
Female, *n* (%)	9 (47)	10 (53)	
Febrile neutropenia	11	15	0.003
>1 organ failure	1	12	<0.001
Hepatitis	3	4	0.215
Acute renal failure	1	7	0.001
Inotrope support	10	21	<0.001
Mechanical Ventilation	5	19	<0.001

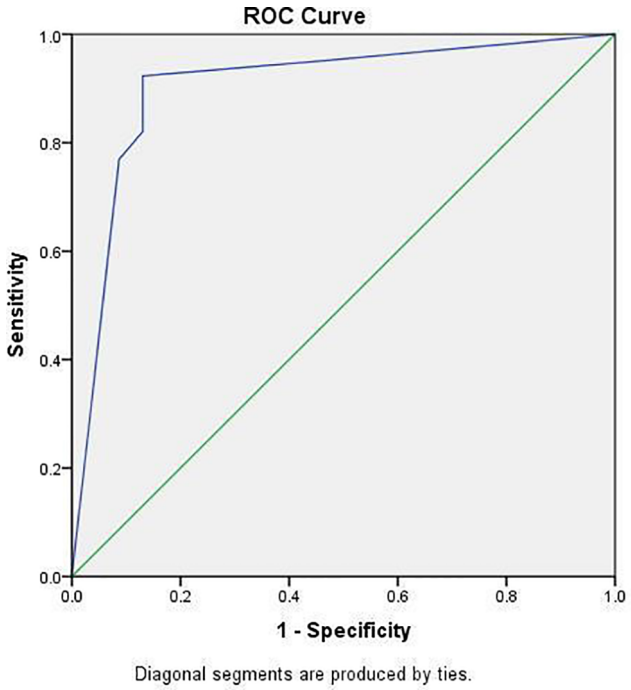

Fig. 1 Receiver operating characteristic (ROC) curve to predict mortality for number of inotropes used.

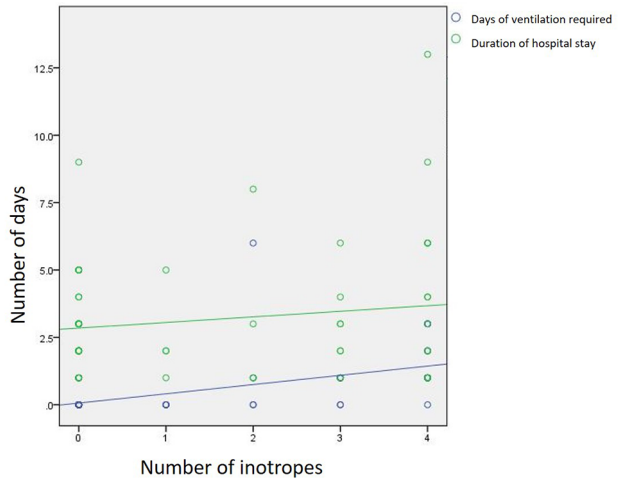

Fig. 2 Scatter plot between the number of inotropes (X-axis) and duration of mechanical ventilation (purple) as well as the duration of pediatric intensive care unit stay (green) on Y-axis showing linear relation.

The median duration for PICU stay was 3 days (1–13 days). Twenty-four children required mechanical ventilation for a median duration of 1 day (1–6 days).

The overall survival at the time of discharge from PICU was 64% and did not correlate with age and gender. Organ failure occurred on 35 occasions. Circulatory failure was the most prominent (31 occasions) followed by respiratory failure (24 occasions), renal failure (8 occasions), and hepatic failure (7 occasions). Thirteen children developed more than one organ failure that was associated with statistically significant adverse outcome (i.e., $p < 0.001$). Requirement of mechanical ventilation due to respiratory failure ($p < 0.001$), presence of acute kidney injury ($p = 0.001$), and circulatory failure as evidenced by use of inotropes ($p < 0.001$) was associated with poor outcome. Seven children also developed acute hepatitis, but it was not associated with poor outcome ($p = 0.215$; ►**Table 2**).

ROC curve was plotted to predict mortality for number of inotropes used that revealed an area under curve 0.905. Coordinates of the curve yielded a cutoff value of more than 2 for number of inotropes predicting mortality with 92.3% sensitivity and 87% specificity (►**Fig. 1**). A scatter plot suggested that number of inotropes showed linear relation with the duration of mechanical ventilation as well as the duration of PICU stay (►**Fig. 2**). Binary logistic regression model (►**Table 3**) could explain 73.6% mortality. History of more than two inotrope administrations was the only significant predictor of mortality.

Discussion

Children with malignancy contribute <10% of total PICU admissions worldwide.[13,14] They remain the most complex and challenging group with significantly worse outcome as compared with children admitted to PICU for other illnesses.[15,16] The mortality of pediatric cancer patients admitted to PICU worldwide is high (28%)[17] as it was in this study (36%). This is partly because these children become

Table 3 Summary of logistic analysis for variables predicting mortality in our patients

Predictor	Odds ratio	SE	95% CI	*p*-Value
Febrile neutropenia	0.942	1.19	0.091–9.79	0.96
>1 organ failure	6.19	1.58	0.27–137.9	0.249
Acute renal failure	2.79	2.02	0.05–148.3	0.61
Inotrope support (>2 inotropes)	19.5	1.19	1.4–260.8	0.025
Mechanical ventilation	4.0	1.0	0.48–33.8	0.195

Abbreviations: CI, confidence interval; SE, standard error.

immunocompromised during treatment and develop life-threatening infectious complications that need aggressive antibiotic policy. Also, children presenting with advanced malignancy with various malignancy-related complications require intensive care along with aggressive blood product support.

In accordance with previous studies, sepsis (37.5%) and respiratory failure (17.2%) were the most common indications for PICU admissions.[6,18,19] However, in the present study metabolic disturbances also contributed to 26.6% of the PICU admissions. Metabolic disturbance as an indication for PICU admission has not been considered separately in previous studies.[9,19,20]

Although boys were admitted more as compared with girls, mortality was higher among girls (i.e., 53 vs. 29%) with no statistical significance. This may be because girls presented with very severe symptoms as compared with boys at the time of diagnosis. Ali et al. in a similar study conducted in Egyptian children found the cause of male preponderance is poor socioeconomic status and special preference of parents for male children in seeking treatment.[21]

The majority of children experiencing metabolic disturbances were those who developed hypocalcemia due to TLS or developed hypocalcemia and/or hypokalemia due to coexistence of malnutrition during intensive chemotherapy. Although the presence of metabolic disturbance was an important indication for PICU admission, it was not associated with statistically significant adverse outcome. However, as metabolic disturbances can be corrected with appropriate and timely intervention, we want to emphasize their early identification and appropriate management for improving outcome.

Children in this study had a survival rate of 64%, which is comparable with previous reports. In retrospective studies by van Veen et al,[22] among 51 patients over 10 years, and Heney et al,[18] among 70 patients over 6 years, a survival rate of 70 and 51% has been reported, respectively.

The single most important predictor of death in our study was multiorgan failure. Among 13 children who developed multiorgan failure, 12 children died in this study. As with general population, mortality exceeding 70% has been reported by various researchers if ≥ 3 organs are involved.[19,23,24] Most of the children who developed acute renal failure during PICU stay had a statistically significant adverse outcome that is in accordance with studies performed in children[25] and adults[26] with cancer. Although mortality was more if the child developed hepatitis in isolation, it was not significant statistically.

Also, as observed across other studies,[9,10,19,21,24] cohort of children requiring inotropic support and mechanical ventilation had a high mortality, that is, 79 and 64% respectively. Thus, presence of multiorgan dysfunction, acute renal failure, requirement of multiple inotropes, and mechanical ventilation can be taken as predictors of adverse outcome. However, use of more than 2 inotropes was recognized as the most important predictor of adverse outcome among all these parameters.

The limitations in our study were small sample size, nonquantification of various metabolic disturbances, nonavailability of data regarding patients who were denied admission to PICU due to nonavailability of beds, as it was a retrospective analysis.

Conclusion

PICU outcomes and resource utilization have not been studied rigorously. Most of the information available is by means of single-center retrospective studies. Thus, there is a need of large multicentric prospective interventional studies that compare PICU outcomes for pediatric cancer population, which would improve understanding about underlying mechanisms for organ dysfunction, early identification of risk factors for clinical deterioration, and prioritization of patients that are salvageable, thereby allowing timely admission to PICU and delivery of life-saving therapy.

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None

Conflict of Interest
None

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