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Outcome of sepsis in pediatric oncology patients admitted in pediatric intensive care unit: A developing country perspective

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ABSTRACT

Objective: To determine the outcome of sepsis i.e. severe sepsis and septic shock in pediatric oncology patients admitted in pediatric intensive care unit (PICU).
Methods: Retrospective review of medical records of all children (1 month–16 years) having primary oncological diagnosis admitted in PICU with sepsis from January 2008 to June 2017 was done after ethical review committee approval. Data was collected on a structured proforma and included demographic details, clinical and laboratory/microbiological data and stage of chemotherapy, outcome (survived/expired).
Results: Total 63 patients were identified, 42 (66.7%) were males, and median age was 93 months. Primary oncological diagnosis included Leukemia (n = 45, 71.4%), lymphoma (n = 12, 19.0%), solid tumor (n = 3, 4.2%), central nervous system tumor (n = 2, 3.2%) Out of the 63 admissions, 34.9% (n = 22) went into septic shock and 52.4% (n = 33) survived after admission to PICU. The most commonly found microbial organisms were gram positive cocci, followed by gram negative rods. Organ dysfunction, use of mechanical ventilation and septic shock were associated with mortality ($p < 0.05$).
Conclusion: Sepsis in patients with primary oncological diagnosis carries very high mortality. Gram positive cocci were the most common etiological organisms.

1. Introduction

Every year around 8000 children are diagnosed with cancer in Pakistan. Majority of these are hematological cancers [1]. The overall survival and outcome of pediatric oncology patients has improved with the help of current chemotherapy protocols, radiation and surgery [2]. This is also true for Pakistan, where the overall outcome of children with cancer is also improving through multipronged approach which includes establishing specialized centers, capacity building, research, use of multidisciplinary teams and aggressive chemotherapeutic drugs [1]. The improvement in outcome has also been observed for the pediatric oncology patients admitted to the Pediatric Intensive Care Unit (PICU) [3,4]. In fact, one retrospective cohort study by Shannon et al. showed that amongst the children admitted in PICU with acute myeloid leukemia between 1999 and 2010, the overall mortality rate decreased from 23.7% in 1999–2003 to 16.4% in 2004–2010 [5]. This was attributed to advances in oncological treatment regimens as well as standardization of treatment, along with improved monitoring and treatment strategies from an infectious standpoint. The latter included hospitalization during ANC recovery and use of prophylactic antibiotics during periods of myelosuppression.

However, additional speculations have shown that despite these improvements, the aggressive therapy protocols also tend to cause immunosuppression, leading to life threatening complications, such as febrile neutropenia, invasive infections and infection-associated mortality [6]. Amongst these, bacterial infections pose the greatest risk for morbidity and mortality, with gram positive bacteria being the most common [6]. One such study done in 2012 by Siddiqui et al. showed a mortality rate of 12.5% amongst

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Abbreviation

PICU	Pediatric Intensive Care Unit
SPSS	Statistical Package for the Social Science
DNR	Do Not Resuscitate
PRISM score	Pediatric Risk of Mortality score
IQR	Interquartile Range
Echo	Echocardiogram
PALS	Pediatric Advanced Life Support
MODS	Multiple Organ Dysfunction Syndrome
HSCT	Hematopoietic Stem Cell Transplant
ANC	Absolute Neutrophil Count
APACHE	Acute Physiology And Chronic Health Evaluation

pediatric oncology patients in Pakistan due to health care associated infections [7].

Additionally, amongst these complications due to treatment protocol, community and hospital acquired sepsis remains a leading cause of death in these children especially in developing countries like Pakistan [2,8,9]. As per international pediatric sepsis consensus conference, sepsis is defined as systemic inflammatory response syndrome (SIRS) in the presence of or as a result of suspected or proven infection. Severe sepsis is sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions. Septic shock is sepsis and cardiovascular organ dysfunction [9].

Early identification and timely intervention in sepsis has been shown to be associated with better outcomes in terms of decreased mortality and less pediatric intensive care unit stay [8,10]. The aim of our study was to determine the outcome of pediatric oncology patients with sepsis admitted to our PICU.

2. Materials and methods

A retrospective review of medical records of all patients (aged 1 month–16 years) with primary diagnosis of cancer admitted in PICU with sepsis/septic shock, between January 2008 to June 2017 was done, after approval from ethical review committee (4541-PED-ERC-16). Pediatric oncology at Aga Khan University Hospital is a 12 bedded unit staffed by three pediatric oncologists and here, we use the chemotherapeutic protocol practiced at St Jude Children's Research Hospital. On the other hand, PICU is an 8 bedded unit staffed with three trained pediatric intensivists and a round-the-clock senior pediatric resident and fellow coverage.

For our study, patients were identified from the health information management system of the hospital with specific ICD codes that were rechecked from PICU log. Data was collected on a structured proforma. The data collection included demographics, admission source (ward or the emergency room), length of stay in the ward/emergency room before admission to the PICU and length of stay at the PICU. The pharmacy records were used to check antibiotics prescription and delivery timings. Type of cancer, stage of disease, echocardiography report, need for PICU therapies (inotropes, need for renal replacement therapy, mechanical ventilation) were recorded, along with relevant laboratory parameters (complete blood count, renal and liver function tests, coagulation parameters, and blood culture and sensitivity report). Absolute neutrophil count on admission to PICU and survival upon PICU discharge were also noted.

Fluid resuscitation at our center is done with crystalloids primarily and we follow American college of critical care medicine protocol for septic shock and hemodynamic support. Mechanical ventilation was used in case there were signs of respiratory failure as per PALS definitions. We do not have the facility of extracorporeal membranous oxygenation at our center. Neutropenic patients were prescribed granulocyte colony stimulating factor to achieve an absolute neutrophil count of 1500/mm3. A hemoglobin target of 10 gm/dl was achieved in all the patients.

The data was entered and analyzed using SPSS version 20. The results are presented as mean with standard deviation and frequency with percentage. Chi square test/student T test was used to determine the factors significantly associated with mortality. Odds ratio along with 95% confidence interval is reported.

3. Results

A total 63 children were identified and included in the study. These patients were admitted to PICU because they were either hemodynamically unstable (requiring inotropic support) OR had severe sepsis OR were patients with sepsis requiring mechanical ventilation or renal replacement therapy. Males were 42 (66.7%), and median age was 93 months with an interquartile range (IQR) of 96 months. Primary oncological diagnosis included Leukemia (n = 45, 71.4%), lymphoma (n = 12, 19.0%), solid tumor (n = 3, 4.2%), and central nervous system tumor (n = 2, 3.2%) (Table 1). There were 42 children (66.7%) in induction phase, 10 (16%) in consolidation/intensification phase, and 7 (11.1%) in maintenance phase. Thirty-nine patients (61.9%) were admitted from ward and 24 (32%) from the Emergency Room.

Twenty-two patients (35%) had septic shock, while MODS developed in 32(50.8%) patients. Fifty-four patients (82%) required mechanical ventilation due to respiratory failure while 25 (40%) required inotropic support. Eleven of these patients (17.5%) developed both renal and hepatic failure and no patient required renal replacement therapy. This is because, as per pediatric risk injury failure loss and end stage renal disease (pRIFLE) criteria for renal failure, all of these patients fell into risk and injury so there was no indication for renal replacement therapy. Median PRISM III score was 11 with IQR of 11. The total duration of stay before admission to the PICU was a mean of 24 h with an IQR of 66 h. PICU length of stay was 3 days with IQR of 10 days. 57.1% were Full Code (n = 36), while 42.9% (27) had a DNR code status at the time of death.

The absolute neutrophil count was <500/mm3 in 32 (50.8%) patients, between 500 and 1000/mm3 in 3 (4.8%) patients and >1000/mm3 in 25 (39.7%) of patients. Additionally, 26 (41.3%) patients had positive blood cultures, with the predominant organisms being gram positive cocci (n = 6, 23.1%), primarily Staphylococcus epidermidis (n = 2, 7.7%). The second most common organisms found were *Escherichia coli* species (n = 3, 11.5%). Other organisms that were found, albeit at a decreased frequency than the ones mentioned above, were inclusive of Klebsiella species, Pseudomonas species, Acinetobacter species, Bacillus species and yeast infections. Out of the 63 patients, 30 expired from which 22 were due to septic shock and the rest due to multiorgan dysfunction.

The parameters that had a significant P-value ($P < 0.05$) in determining patient survival outcome during data analysis were code status (with patients on DNR having lower survival rate than those on Full code), hepatic failure, renal failure, use of mechanical ventilation and septic shock (Table 2).

4. Discussion

Our study reveals depressingly a very high mortality rate in pediatric oncology patients admitted in PICU with septic shock and severe sepsis. There could be many explanations of this findings. PICU was only 3–4 bedded till mid of 2016 so there was limited space available to cater many of these patients early and only the

Table 1
Clinical & demographic characteristics of oncology patients admitted with sepsis in PICU.

Variable		Frequency n = 63 (Percentage)
Age in months (median with IQR)		93 (median)
		96 (IQR)
Gender (male)		42 (66.7)
Primary oncological Diagnosis	Leukemia	45 (71.4)
	Lymphoma	12 (19.0)
	Solid Tumor	3 (4.8)
	Brain Tumor	2 (3.2)
	Others	1 (1.6)
Length of stay before admission to PICU (hrs)		24 (median)
		66 (IQR)
Length of stay at PICU (days)		3 (median)
		10 (IQR)
PRISM III Median		11 (IQR)
Positive Blood Cultures		26 (41.3)
Phase of therapy	Induction	42 (66.7)
	Maintenance	7 (11.1)
	Consolidation	2 (3.2)
	Intensification	8 (12.7)
	Just completed treatment	4 (6.3)
Admission Source	ER	24 (38.1)
	Ward	39 (61.9)
Code Status	Full code	36 (57.1)
	DNR	27 (42.9)
Cardiac function on ECHO (%) n = 48		65 (median)
		14.75 (IQR)
Multiorgan dysfunction		35 (55.5)
Fungal Sepsis		11 (17.5)
Central Line		56 (88.9)
Septic Shock		22 (34.9)
Mechanical ventilation		53 (84.1)
Outcome: survivor		33 (52.4)

Table 2
Comparison of variables between survivors and non-survivors.

Variable			Over All	Survivors	Non-Survivors	P value	OR (95% CI)
Admission source		ER	24	12	12	0.77	0.86 (0.31–2.37)
		Ward	39	21	18		
Diagnosis: leukemia		Leukemia	45	23	22	0.82	
		Lymphoma	12	7	5		
		Solid Tumor	3	2	1		
		Brain Tumor	2	1	1		
		Others	1	0	1		
Phase of therapy		Induction	42	19	23	0.495	
		Maintenance	7	4	3		
		Consolidation	2	1	1		
		Intensification	8	6	2		
		Just completed treatment	4	3	1		
Code Status		Full code	36	25	11	0.002	5.18 (1.74–15.44)
		DNR	27	8	19		
Multiorgan dysfunction			35	9	26	0.005	5.45 (2.13–13.9)
Fungal sepsis	Yes		11	4	7	0.242	0.45 (0.12–1.74)
	No		52	29	23		
Central line	Yes		56	31	25	0.181	3.10 (0.55–17.35)
	No						
Blood culture	Positive		26	10	16	0.064	0.38 (0.14–1.07)
	Negative		37	23	14		
Septic shock	Yes		22	7	15	0.017	0.27 (0.09–0.81)
	No		41	26	15		
Mechanical ventilation	Yes		53	23	30	0.001	043 (0.32–0.59)
	No		10	10	0		
Age in months			63	82.70 +- 48.52	113.37 +- 62.96	0.036	(-59.89 – -2.09)
Length of stay before admission to PICU (hrs)			63	63.61 +- 79.70	41.18 +- 42.58	0.789	(-4.74 – 6.16)
Length of stay at PICU (days)			63	9.11 ± 9.07	8.76 ± 9.45	0.619	(-3.71 – 4.96)
PRISM III			63	7.58 +- 5.65	15.50 +- 5.94	−8.000	(-10.97 – -5.04)
Cardiac function on ECHO (%)			48	60.43 +- 15.07	58.79 +- 16.87	0.730	(-7.92 – 11.21)

sickest of patients were admitted, which is evident by how so many of our patients had organ failure on admission to PICU. Secondly, we follow St. Jude's chemotherapeutic protocols and do not have local pharmacokinetic and pharmacodynamics data of these drugs which may be more toxic in our population. Thirdly, many of these patients belong to remote areas with no emergency transport

services. Hence, there is a potential of delayed presentation/admission in PICU. Two thirds of our patients who had septic shock expired, which again shows that probably these patients were very sick at presentation, had progressed to multi-organ failure and did not receive resuscitation on time. We also do not have extracorporeal life support at our center.

The outcome of sepsis in oncology patients has been found to be worse compared to patients with sepsis without underlying malignancy [11,12]. This can be extrapolated to the pediatric population as well. Fiser et al. showed a mortality rate of 17% for children admitted to the PICU with severe sepsis. Along with that significant number of patients were alive at 6 months despite aggressive interventional measures used during the PICU stay. This encourages the admission of such children with sepsis to the PICU in order to improve their survival rate. A study on outcome of pediatric oncology patients admitted in PICU for various underlying reasons showed an overall mortality of 32.4% (24/74) which again shows sepsis in pediatric oncology is associated with greater mortality [13].

Organ failure was significantly associated with mortality in our patients. Out of the 35 patients who went in to multiorgan dysfunction 26 did not survive. A similar finding was also narrated by Pillon et al., in 2017 which showed hepatic failure at admission to PICU to be significantly associated with mortality in patients undergoing hematopoietic stem cell transplantation (HSCT) [14]. Another study by An et al., in 2016 also showed that the patients who died had multi-organ damage in comparison to survivors [15]. Also, out of the 53 patients who required mechanical ventilation, 23 survived and 30 died ($P = 0.001$). This finding has also been proven by Rowan CM in 2018, where he concluded that impaired oxygenation and use of elevated ventilator pressures were associated with a higher rate of mortality in HSCT patients admitted to PICU with respiratory failure [16].

Furthermore, out of the 63 patients included in our study, the overall mortality was 48.6% (30/63). This was an increase in comparison to a previous study from our center in 2011, which looked at all the patients with oncological diagnosis admitted in PICU irrespective of underlying cause. In this study, the overall mortality was 32.4% [13]. Such results show that in our population, sepsis with underlying oncological disease has higher rates of mortality.

The length of ICU stays in patients with hematological malignancies pointed out to be significant in another study, by Bird et al., in 2012, however, it was not a factor significant in our study [17]. The same study also concluded how 'traditional' factors such as neutropenia, transplantation status, and APACHE II score had no predictive values in determining patients' in-hospital mortality. In our study, the variables that were also not considered significant in determining outcome were positive blood cultures, use of central lines, fungal sepsis, admission source, primary oncological diagnosis and phase of therapy.

Having said that, our results must be looked at while considering the unavoidable limitations of this study, with one being its retrospective nature and limited sample size. Another important prognostic factor in prior studies was ANC. In a study by Green et al. on the prognostic factors of outcome of invasive fungal infection in the pediatric population, ANC seemed to be the single most important factor responsible for increase in survival rate [18]. However, in our study, ANC count did not prove to be statistically significant. We also did not have a control group of pediatric oncology patients who were not admitted to the PICU and managed in the ward or another setting.

However, this is one of the very few studies on determining predictive factors of sepsis in children with malignancies who were admitted to the PICU in a developing country.

We think that there is a dire need to evaluate our practice of care of these patients and also look into the time lag from symptoms to presentation, along with other risk factors for mortality, such as malnutrition. The way forward with this approach can be conducting prospective-multicenter studies, especially done in local settings, with a much larger sample size and investigation of more possible predictive factors. This can further contribute to determining a more accurate outcome of mortality in these children.

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