Characteristics and Risk Factors in Onco-Hematological Patients Without Prior Hematopoietic Stem Cell Transplantation Requiring Intensive Care: A Cross-Sectional Study

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ABSTRACT

Background: Pediatric onco-hematological patients require intensive care due to the complexity of their conditions, aggressive disease progression, and the immunosuppressive effects of treatments like chemotherapy and immunotherapy, increasing their risk of life-threatening complications.

Objective: To detect the characteristics and investigate the different risk factors of mortality in onco-hematological patients without hematopoietic stem cell transplantation admitted to the PICU.

Patients and Methods: This Cross-sectional analytic study that was conducted on 150 pediatric onco-hematological patients without history of hematopoietic stem cell transplantation admitted to the PICU between September 2021 and September 2023. Sociodemographic data, Diagnosis, treatment, and Causes of PICU admission were recorded. Correlations between diagnosis, treatment, and Causes of PICU admission to mortality were analyzed.

Results: The average age of patients was 7.2±4.5 years. 55.3% were males. 40.7% of cases had ALL and 20.7 had AML. Induction phase treatment before PICU admission was reported in 79.3% of cases. Analyzing the outcome, (43.3%) of patients improved. AML patients had the highest mortality rate (74.2%, $p=0.027$). Mortality was higher (61.1%, $p=0.012$) in patients who received treatment before PICU admission than those who didn't. septic shock had the most striking association with mortality (100% of affected patients died, $p<0.001$), followed by respiratory failure (73.5% mortality, $p<0.001$) and metabolic disturbances (64.3% mortality, $p=0.001$).

Conclusion: This study highlights the high mortality risk in pediatric onco-hematological patients without prior HSCT in the PICU, primarily due to aggressive malignancies and treatment complications. Key mortality factors include AML, the induction phase of treatment, and critical conditions like respiratory failure, septic shock, and metabolic disturbances.

Keywords: Onco-hematologic; Children; HSCT; PICU; AML; ALL.

Introduction

Pediatric onco-hematological patients represent a vulnerable population requiring intensive medical management due to the complexities of their underlying conditions, including cancer and hematological disorders. These patients frequently have a higher risk of experiencing life-threatening consequences due to the aggressive nature of their disease, treatment regimens (such as chemotherapy and immunotherapy), and associated immunosuppressive effects [1].

Indeed, up to 40% of oncologic patients are hospitalized in the paediatric intensive care units (PICU) due to severe infections [2]. Despite constant improvement in the survival of these patients, their mortality rate is still higher than that of the general population [3].

Factors that were found to particularly affect the survival of children with onco-haematological diseases admitted to the PICU include the type of oncological disease, neutropenia duration, mechanical ventilation, and history of stem cell transplantation (SCT) [4,5].

While hematopoietic stem cell transplantation (HSCT) is a common therapeutic intervention for certain hematological conditions, a significant proportion of onco-hematological patients do not undergo this procedure, due to either the nature of their disease or it is contraindications. These patients may present with a range of complications, including but not limited to severe infections, multi-organ dysfunction, and treatment-related toxicity, all of which necessitate close monitoring and aggressive intervention in the PICU setting. Fewer studies have been conducted on the characteristics and outcomes of this subgroup of patients admitted to the PICU without a history of HSCT [6,7].

Interpreting these distinctive clinical profiles and outcomes can help identify risk factors, improve prognostication, and optimize PICU management strategies. This study aims to analyze the characteristics of onco-hematological patients without a history of hematopoietic stem cell transplantation admitted to the PICU and their risk of mortality.

Patients and Methods

This cross-sectional analytic study was carried out in an oncology center between September 2021 and September 2023. The Research Ethical Committee of the Faculty of Medicine, Cairo University approved the research protocol (code MD-34-2021), following the Helsinki Declaration of 1964, as revised in 2000. An informed written consent was obtained from the patient's guardian before enrollment.

Based on evidence from previous similar ***Pillon et al.*** [8] study and by considering the mortality rate at PICU discharge in onco-hematological patients as a primary outcome. Epi-calc 2000 was used to calculate the **sample size** of this cross-sectional analytical study. Assuming 80% power, 0.05 level of significance, 20% null hypothesis value and estimated proportion of 30%, **Sample size will be** 136 participants. Considering drop-outs rate of 10%, therefore the minimum required sample size will be 150 participants.

Ref: Predictors of mortality after admission to pediatric intensive care unit in nonhematologic patients without history of hematopoietic stem cell transplantation: A single-center experience.

Inclusion Criteria:

1. Age: all children less than 18-years old.
2. Gender: both males and females.
3. All patients known to have onco-hematological malignancies and requiring PICU admission without history of hematopoietic stem cell transplantation.

Exclusion Criteria:

1. Patients who received at least one HSCT before PICU admission.
2. Patients who were already declared "do not resuscitate" by three attending consultants before PICU admission.
3. Patients staying for less than 24 hours.
4. Brain stem death.

Study procedure:

Data collection was performed within the first 24 hours of PICU admission. Each case underwent a comprehensive assessment, including detailed history-taking, clinical examination, laboratory investigations, and imaging studies.

1. History:

A thorough history was obtained, documenting demographic data, family history, underlying disease, and causes of PICU admission. The treatment phase before PICU admission was categorized as untreated, newly diagnosed, or undergoing specific treatment phases such as induction, consolidation, maintenance, or reinduction in relapsed cases.

2. Clinical Assessment:

Clinical examination included vital signs (blood pressure, heart rate, respiratory rate, capillary refill time, oxygen saturation, temperature, and random blood glucose levels). The Glasgow Coma Scale [4] was applied to assess neurological status. Signs of cardiac dysfunction, such as tachypnea, sinus tachycardia, hepatomegaly, and poor feeding in infants, were documented. Fluid overload was

monitored using pulmonary edema, liver enlargement, congested neck veins, and changes in body weight. It was quantitatively assessed using the formula:

[Total fluid input in 24 hours (mL) – total fluid output in 24 hours (mL)/weight at admission (g)] × 100 **[5].**

Additional assessments included the presence of complications such as neutropenic enterocolitis (typhlitis), disseminated intravascular coagulation (DIC), hepatic failure, and acute kidney injury (AKI) were evaluated according to KDIGO guidelines **[6].**

3. Laboratory Investigations:

Blood and urine samples were collected at admission and subsequently as required. Laboratory tests included :

a) complete blood count which is done by automated hematology analyzer**,**
b) blood gases which is done by blood gases analyzer**,** and
c) electrolyte levels including (sodium, potassium ,calcium, phosphorus**,** and magnesium
d) Kidney function including (urea, creatinine) and
e) liver function (ALT , AST, albumin) were assessed, along with coagulation parameters (PT, PTT., INR).
f) Additional tests such as serum lactate, cardiac enzymes troponin, lactate dehydrogenase, D-dimer**,** and serum ferritin were performed when clinically indicated.
g) Blood, urine, and sputum cultures were obtained to identify infectious agents.

4. Imaging Studies:

Routine imaging included chest X-rays and CT scans of the chest. Echocardiography was performed before initiating chemotherapy and repeated if signs of heart failure or fluid overload were present. Pelvi-abdominal ultrasound was utilized to assess the bowel wall thickening in cases of typhlitis and evaluate organomegaly and ascites.

Statistical analysis:

All data were collected, organized, and statistically analyzed using SPSS 26.0 for Windows (SPSS Inc., Chicago, IL, USA).

The Shapiro-Wilk test was applied to assess data distribution normality. Qualitative variables were presented as frequencies and percentages, with differences analyzed using the Chi-square (χ^2) test or Fisher's exact test when appropriate. Quantitative data were expressed as mean ± standard deviation (SD) for normally

distributed variables and as median with range for non-parametric data.

A significance level of $\mathbf{P \leq 0.05}$ is considered significant, $\mathbf{P < 0.001}$ indicates a highly significant difference, and $\mathbf{P > 0.05}$ is considered non-significant.

RESULTS

Table (1): Sociodemographic data of the participants

Characteristics	**n=150 (100%)**
Age (years)	
Mean ±SD	7.2±4.5
Median (range)	7 (0.2-17)
Gender	
Male	83 (55.3%)
Female	67 (44.7%)
Nationality	
Not Egyptian	24 (16%)
Egyptian	126 (84%)
Residence if Egyptian (n=126)	
Urban	62 (41.3%)
Rural	64 (42.7%)
Family history of onco-hematological diseases	
Negative	125 (83.3%)
Positive	25 (16.7%)

SD: standard deviation

Table 1 shows the sociodemographic data of the 150 participants included in the study. The mean age of the participants was 7.2 years, majority (84%) were Egyptians. Only 16.7% of patients had a positive family disease history of onco-hematological diseases.

Table (2): Diagnosis, treatment, and Causes of PICU admission

Characteristics	n=150 (100%)
Diagnosis	
ALL	61 (40.7%)
AML	31 (20.7%)
HLH	29 (19.3%)
Lymphoma	14 (9.3%)
Others	15 (10%)
Received treatment before PICU admission	
No	24 (16%)
Yes	126 (84%)
Type of treatment (n=126)	
Induction	100 (79.3%)
Consolidation	5 (3.9%)
Re-induction in relapsed cases	20 (15.9%)
Maintenance	1 (0.8%)
Causes of PICU admission	
Metabolic and electrolyte disturbance	112 (74.7%)
Respiratory failure	102 (68%)
Septic shock	59 (39.3%)
Gastrointestinal and hepatic	47 (31.3%)
Haematological	47 (31.3%)
Central nervous	46 (30.7%)
Cardiovascular	37 (24.7%)
Acute kidney injury	11 (7.3%)
Time from onset of underlying disease to PICU admission (days)	
Mean ±SD	144.6± 253.2
Median (range)	60 (6-1600)

This table shows that most of the cases had ALL and AML (61.3%). 84% of patients had received treatment before PICU admission, where induction phase treatment was the most common (79.3%). Metabolic and electrolyte disturbance represent 74.7% of the causes of PICU admission followed by respiratory failure and septic shock. (Table 2)

Table (3): Culture results among the studied sample

Characteristics	n=150 (100%)
Blood culture	
Negative	88 (58.7%)
Positive	62 (41.3%)
Results of blood culture (n=62)	
Klebsiella	33 (53.2%)
Candida	8 (12.9%)
Pseudomonas	8 (12.9%)
Acinetobacter	4 (6.5%)
Rhizopus oryzae	3 (4.8%)
Staph epidermidis	2 (3.2%)
Streptococcus	2 (3.2%)
Enterobacter	1 (1.6%)
E-coli	1 (1.6%)
Urine culture	
Negative	148 (98.7%)
Candida	2 (1.3%)
ETA culture	
Negative	131 (87.3%)
Positive	19 (12.7%)
Results of ETA culture (n=19)	
Klebsiella	8 (42.1%)
Pseudomonas	5 (26.3 %)
Acinetobacter	2 (10.5%)
Candida	2 (10.5%)
Staph epidermidis	1 (5.3%)
Streptococcus	1 (5.3%)

Table 3 shows that blood cultures were positive in 41.3% of cases, with Klebsiella being the most common pathogen (53.2%), followed by Candida and Pseudomonas (12.9% each). Acinetobacter (6.5%) and Rhizopus oryzae (4.8%) were also identified. 98.7% had negative urine cultures. Endotracheal aspirate cultures were positive in 12.7%, with Klebsiella (42.1%) and Pseudomonas (26.3%) being the most prevalent.

Table (4): Relation between diagnosis, treatment, and Causes of PICU admission to outcome.

Characteristics	n=150	Dead n=85(56.7%)	Improved n=65(43.3%)	p-value
Diagnosis				
ALL	61	34 (55.7%)	27 (44.3%)	0.850
AML	31	23 (74.2%)	8 (25.8%)	**0.027**
HLH	29	17 (58.6%)	12 (41.4%)	0.813
Lymphoma	14	8 (57.1%)	6 (42.9%)	0.975
Others e.g.: Aplastic anaemia, HLH	15	3 (20%)	12 (80%)	0.003
Treatment phase at the moment of PICU admission				
Yes	126	77(61.1%)	49 (38.9%)	**0.012**
Causes of PICU admission				
Metabolic causes and electrolyte disturbance				
Yes	112	72 (64.3%)	40 (35.7%)	**0.001**
Septic shock				
Yes	59	59 (100%)	0 (0%)	**<0.001**
Haematological (anemic heart failure, neutropenia, thrombocytopenia, and coagulopathy)				
Yes	47	33 (70.2%)	14 (29.8%)	**0.024**
Respiratory failure				
Yes	102	75 (73.5%)	27 (26.5%)	**<0.001**
Gastrointestinal and hepatic				
Yes	47	34 (72.3%)	13 (27.7%)	**0.009**
Central nervous				
Yes	46	25 (54.3%)	21 (45.7%)	0.703
Cardiovascular				
Yes	37	21 (56.8%)	16 (43.2%)	0.990
Acute kidney failure				
Yes	11	7 (63.6%)	4 (36.4%)	0.628

The mortality rate in this cohort was high 85(56.7%). And the survival rate was 65(43.3%). Mortality varied significantly across different diagnoses and clinical conditions. AML patients had the highest mortality rate (74.2%, p=0.027). Mortality was higher (61.1%, p=0.012) in patients who received treatment before PICU admission than those who didn't. Among causes of PICU admission, septic shock had the most striking association with mortality (100% of affected patients died, p<0.001), followed by respiratory failure (73.5% mortality, p<0.001) and metabolic disturbances (64.3% mortality, p=0.001). (Table 4)

DISCUSSION

Due to the implementation of rigorous, combined treatment procedures that include chemotherapy, immunotherapy, radiation, and surgery, the prognosis for children with onco-hematological illnesses has improved dramatically over time. However, these intensive therapies can result in life-threatening complications. Severe infections are responsible for the hospitalization of up to 40% of oncology patients in the PICU [2]. Despite ongoing advancements in survival rates for these patients, their mortality remains higher compared to the general population [3]. This study presents a comprehensive analysis of 150 PICU patients, primarily focusing on their demographic characteristics, diagnoses, treatment phases, causes of admission, microbiological culture results, and clinical outcomes.

The slight male predominance (55.3%) is consistent with the known epidemiological trends in pediatric oncology, where certain malignancies such as leukemia show a higher incidence in boys [9], and the average age was 7.2 years, with a wide range of 0.2 to 17 years. This aligns with previous studies, which report that pediatric onco-hematological patients are often young, with a slightly higher prevalence of male patients [2]. A noteworthy observation was that 16.7% of the patients had a positive family history, which may suggest a genetic or environmental predisposition. However, this proportion is lower than that observed in some other pediatric cancer studies [3].

Regarding the underlying diseases, ALL and AML were the prevalent diagnoses, accounting for 61.3% of cases. This finding is in line with the epidemiology of childhood cancers, where leukemia is the most prevalent malignancy in this age group [9,10]. In terms of treatment, most patients were in the induction phase (79.3%) when admitted to the PICU, similar to a study that evaluated 3238 patients [8], which reflects the aggressive nature of the disease, and the intensity of the treatment protocols employed, including chemotherapy, that can predispose these patients to severe complications.

The leading causes of PICU admission were metabolic disturbances and electrolyte imbalances, which affected 74.7% of the patients. These are common complications in onco-hematological patients, particularly due to the effects of chemotherapy, tumor lysis syndrome, and altered renal function [11]. Respiratory failure, septic shock, and gastrointestinal issues like typhilitis also contributed significantly to the reasons for admission. These results are consistent with findings from other studies indicating that

infections and respiratory issues are common in critically ill pediatric oncology patients [2,8].

In terms of outcomes, 56.7% of patients in this study did not survive their PICU stay, which is a substantial mortality rate in comparison to other centers [12,13,14]. However, survival rates may differ based on underlying disease and severity of illness. The significant factors influencing mortality in this cohort included the diagnosis, treatment phase, and cause of PICU admission. Particularly, patients with AML had a higher mortality rate compared to other diagnoses (74.2% vs. 44.3% in ALL, p=0.027). This may be explained by the more aggressive nature of AML, which typically requires more intensive chemotherapy regimens and is associated with a higher incidence of complications [15,16]. In addition, **Pechlaner et al.,** attributed the improvement in the outcome of their patients to improvement in intensive care therapies, such as timely completion of the sepsis treatment bundle (antibiotic and fluid administration, blood cultures), lung protective ventilation strategies, and early use of invasive extracorporeal therapies such as CRRT and ECMO [17].

Notably, the death rate was higher in patients who were receiving treatment before PICU admission in contrast to those who were newly diagnosed or not yet treated (61.1% vs. 33.3%, p=0.012). This finding underscores the risks associated with induction chemotherapy, which can lead to severe immunosuppression and increased vulnerability to infections and other complications [18]. Respiratory failure and septic shock emerged as the most significant causes of mortality, with 100% of septic shock cases resulting in death (p<0.001), which is consistent with previous literature reporting the high mortality associated with sepsis in pediatric cancer patients [13,19].

Metabolic and electrolyte disturbances also contributed to mortality, with a significantly higher mortality rate in patients with these complications (p=0.001). This highlights the importance of early detection and management of such imbalances, as they can be life-threatening if not addressed promptly. Similarly, gastrointestinal and hepatic issues were associated with a higher mortality rate (p=0.009), reflecting the critical nature of these conditions in the context of onco-hematological diseases [20].

Conclusion:

this study highlights the high mortality risk among pediatric onco-hematological patients without a history of HSCT in the PICU, primarily due to aggressive malignancies and treatment-related complications. Key factors influencing mortality include AML diagnosis, treatment phase before PICU admission, and critical conditions such as respiratory failure, septic shock, and metabolic disturbances.

Recommendations:

The findings emphasize close collaboration between intensivist, haemato-oncologist, and infectious disease teams for early identification of sepsis in cancer patients who might profit from early aggressive medical intervention before irreversible organ damage occurs. Future research should focus on predictive models for PICU admission and optimizing supportive care protocols to mitigate treatment-associated risks.

Limitations:

The high prevalence of multidrug-resistant organisms further underscores the importance of stringent infection control.

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