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CHARACTERISTICS AND OUTCOMES OF PEDIATRIC SEPTIC PATIENTS WITH CANCER: A RETROSPECTIVE COHORT STUDY

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☐ **Abstract—Background: Pediatric oncology patients may be at a higher risk of complications and mortality from sepsis compared with their nononcology counterpart. Objectives: The aim of this study is to compare characteristics, treatment, and sepsis-related mortality between oncology and nononcology patients presenting to the emergency department (ED). Methods: This is a retrospective single-center cohort study including patients <18 years old with a diagnosis of sepsis, severe sepsis, septic shock, or bacteremia presenting to an academic ED between January 2009 and January 2015. A total of 158 patients were included with 53.8% having an underlying malignancy. The primary outcome of the study was in-hospital mortality. Secondary outcomes included ED vital signs, resuscitation parameters, laboratory work, infection site, general practitioner unit, intensive care unit length of stay, and hospital length of stay. Results: Oncology patients had a higher in-hospital mortality (5.9% vs. 2.7%), however, it did not meet statistical significance ($p = 0.45$). On presentation, oncology patients had a lower respiratory rate (24.33 ± 9.48 vs. 27.45 ± 7.88; $p = 0.04$). There was a significant increase in the white blood count in oncology patients (4.011 ± 4.965 vs. 17.092 ± 12.806; $p < 0.001$) with this cohort receiving more intravenous fluids. In the first 6 hours (33.0 ± 27.7 mL/kg vs. 24.9 ± 16.1 mL/kg; $p = 0.029$) as well as having a higher percentage of vasopressor administration (15.3% vs. 1.4%; $p = 0.002$). Antibiotics were initiated at an earlier stage in the oncology cohort (1.25 ± 1.95 vs. 3.33 ± 1.97 hours; $p < 0.0001$). Cancer-free patients had a significantly higher rate of lung infections compared with cancer patients (68.5% vs. 32.9%; $p < 0.0001$). In terms of infection characteristics, cancer patients had a higher percentage of bacteremia (27.1% vs. 4.1%; $p < 0.001$). Conclusion: There was no statistical significance regarding mortality between the 2 cohorts. Pediatric cancer patients were found to have a higher incidence of bacteremia and received more aggressive treatment.**

☐ **Keywords—bone marrow transplant; emergency department; oncology; pediatric; sepsis; systemic inflammatory response syndrome**

INTRODUCTION

Around 75,000 children are hospitalized annually for severe sepsis in the United States (1). The incidence of severe sepsis in the pediatric age group has been gradually rising for the past 2 decades and is currently responsible for 4.4% of U.S. children's hospitals admissions and 7% of pediatrics intensive care unit admissions (1–3). In addition, U.S. data suggest that sepsis accounts for 9% of all pediatric cancer-related deaths (4). Pediatric cancer patients are susceptible

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to various infectious complications because of perturbations in their host defense mechanisms, and as such they constitute a unique cohort worth studying (5). Some studies have reported an in-hospital mortality rate ranging from 0–17% in the septic pediatric oncology population (6–8). However, to the best of our knowledge, there are no studies reviewing the emergency department (ED) management of pediatric oncology patients presenting with sepsis, severe sepsis, or septic shock, or the difference in treatment parameters and mortality when compared to nononcology pediatric patients. Some studies have examined the differences in adults, and have showed a higher hospital mortality in oncology patients presenting to a tertiary care medical center ED in comparison to their nononcology counterparts, despite aggressive management (9).

This study aims to explore the difference in demographics, presentation, treatment parameters, and mortality in pediatric oncology patients presenting to the ED with sepsis, severe sepsis, or septic shock, compared with their nononcologic counterparts. We aim to contribute to a better understanding of sepsis in this vulnerable population and to shed light on specific parameters that are helpful in treating septic oncology patients.

METHODS

Study Design, Patient Selection, and Information Collected

This was an institutional review board–approved (ER.GA.13), single-center, retrospective, chart review cohort study. All pediatric patients (<18 years of age) presenting to the ED of a tertiary care hospital between January 2009 and December 2015 were retrieved from the hospital's electronic health record. All clinical information, vital signs, laboratory results, and resuscitation parameters were extracted from the electronic health record by dedicated M.D. postdoctoral research fellows (KH, CEK, AS). Before data collection initiation, multiple meetings with the principal investigators were conducted to ensure standardization of the data extraction process. The first 10 charts were reviewed by all research fellows and principal investigators to standardize data entry and minimize possible variability. In addition, a quality check was conducted once 10% of the data entry was completed to further ensure coherence.

Each patient's ED presentations were filtered by an experienced data user using extensive structured keyword search and *International Classification of Diseases, Ninth Revision* codes, including diagnoses codes for sepsis (995.91), severe sepsis (995.92), septic shock (785.52), and bacteremia (790.7). The medical records department at our tertiary care center assigns *International Classification of Diseases, Ninth Revision* codes based on all diagnoses made throughout the patient's hospital stay. This includes the diagnosis made by the emergency physician, the hospitalist, and the intensivist. Sepsis, severe sepsis, and septic shock were defined according to the International Consensus Conference on Pediatric Sepsis (8).

Inclusion criteria for our study were suspicion of infection in addition to the presence of 2 of the following 4 criteria (with at least 1 being abnormal temperature or leukocyte count): abnormal temperature, abnormal heart rate, elevated respiratory rate, and abnormal leukocyte count.

Abnormal temperature, measured by rectal, bladder, oral, or central probe, was defined as >38.5°C or <36°C. Abnormal heart rate was either tachycardia, defined as a mean heart rate of >2 standard deviations above normal for age, or bradycardia defined as a mean heart rate <10th percentile for age. Bradycardia was only considered in the inclusion criteria of children ≤1 year of age. Abnormal respiratory rate was defined as >2 standard deviations above normal for age. In addition, patients on mechanical ventilation for an acute pulmonary process were considered to have an abnormal respiratory rate.

Abnormal leukocyte count was defined according to age. Furthermore, patients with >10% immature neutrophils were also considered to have an abnormal leukocyte count. Table 1 summarizes the age-specific cutoff criteria regarding heart rate, respiratory rate, and leukocyte count (8).

Severe sepsis was defined as ≥2 organ system dysfunctions. Septic shock was defined as sepsis with cardiovascular dysfunction (hypotension, need for vasoactive drug administration to maintain a normal blood pressure, or 2 of the following: prolonged capillary refill, metabolic acidosis, oliguria, or elevated arterial lactate) that persists despite administering ≥40 mL/kg of isotonic saline in an hour. Bacteremia was defined as 2 positive blood culture sets with skin flora pathogens or 1 positive blood culture set with non–skin flora pathogens. The exclusion criteria were incomplete charts, patients >18 years of age, patients who were pregnant, or patients who presented because of trauma.

Exposure Status

During the selected study period, 411 patients were identified using the *International Classification of Diseases, Ninth Revision* codes previously specified. Of those, 158 patients fulfilled our inclusion criteria (Figure 1). All patients who met the inclusion criteria were stratified according to the presence of an underlying active solid or hematologic malignancy, which was considered our risk factor. The information regarding malignancies was extracted from the medical records charts. Eighty-five patients (53.8%) had an active solid or hematologic

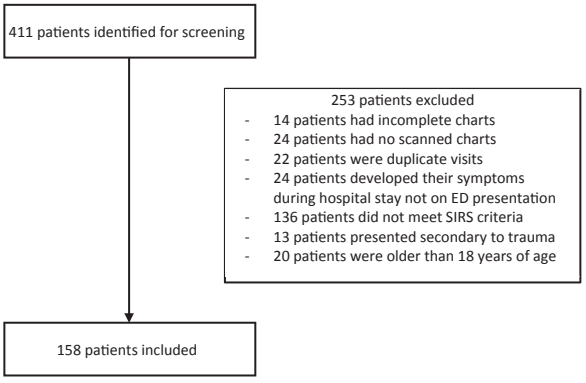

Figure 1. CONSORT flow, study attrition diagram. ED = emergency department; SIRS = systemic inflammatory response syndrome.

malignancy and were considered as the positive risk factor group in the cohort study. All other patients (n = 73) were included in the non–risk factor cohort. The medical records of both cohorts were searched and information regarding the patient's age, gender, and comorbidities were retrieved. For the risk factor cohort, the type of cancer, history of bone marrow transplantation (BMT), and types of treatments received were also retrieved.

Outcome Measures

The primary outcome of the study was in-hospital mortality. Secondary outcomes included ED vital signs, resuscitation parameters, laboratory work, infection site, general practitioner unit (GPU), intensive care unit (ICU) length of stay, and hospital length of stay. Length of stay was calculated for the patients who survived to discharge.

Vital signs were collected from the scanned ED triage sheet and the results of the laboratory work drawn in the ED were obtained from the hospital's electronic health record. Information that was collected from the scanned physician order sheets included the type of antibiotics used and the time to starting them, fluid resuscitation given within the first 6 and 24 h, the duration and type of vasopressor if used, and whether steroids were administered or not. Culprit micro-organisms were retrieved through blood, sputum, urine, or other fluid culture results.

The appropriate use of antibiotics was defined as a broad-spectrum antibiotic regimen covering Gram-positive and Gram-negative bacteria, including anaerobic bacteria and *Pseudomonas aeruginosa*. As for the infection site, it was determined based on documentation in the medical record, culture results, or radiology reports (e.g., chest radiography). The infection source was deemed to be blood if the patients were bacteremic and no other source of infection was identified.

In addition, length of stay in the ED, length of stay in the ICU or GPU, and disposition status were also noted by reviewing the patients' admission and discharge documents. The hospital 72-h mortality and 28-day mortality were documented.

Sample Size Calculation

Before to institutional review board submission, sample size calculation was based on literature that showed a mortality rate difference of 23% between the 2 cohorts (11–14). Therefore, based on this difference and assuming a study power of 80% and a confidence level of 95% (0.05 á significance), the sample size needed was 146 patients (73 patients per cohort).

Statistical Analysis

Statistical analyses were performed using SPSS Statistics for Windows (v. 21.0; IBM Corp., Armonk, NY). The distributions of the continuous and categorical variables were presented as mean ± standard deviation and frequency (percentages) respectively, with all our data being normally distributed. The different parameters were then stratified by the risk factor defined as active malignancy (oncology or nononcology). In the bivariate analysis, the Student's *t*-test and Pearson $\div^2$ test were used to assess the significance of the statistical association between the independent variables (continuous and categorical) and hospital mortality (the dependent variable). The Pearson $\div^2$ test was used to assess for statistical significance for

Table 1. Age-Specific Vital Signs Cutoff Values (Heart Rate, Respiratory Rate, Leukocyte Count, and Systolic Blood Pressure)*

Age Group	Heart Rate, Beats/Min		Respiratory Rate, Breaths/Min	Leukocyte Count, 3 × 10/mm	Systolic Blood Pressure, mm Hg
	Tachycardia	Bradycardia			
0 days to 1 week	>180	<100	>50	>34	<59
1 week to 1 month	>180	<100	>40	>19.5 or <5	<79
1 month to 1 y	>180	<90	>34	>17.5 or <5	<75
2–5 y	>140	N/A	>22	>15.5 or <6	<74
6–12 y	>130	N/A	>18	>13.5 or <4.5	<83
13–<18 y	>110	N/A	>14	>11.5 or <4.5	<90

* Data from Goldstein et al. (10).

the categorical variables while a 2-tailed sample *t* test was used for the continuous variables. Tests were interpreted at a significance level of á = 0.05. The mortality rate difference, not risk ratio, was calculated because we are interested in calculating the absolute difference between the 2 cohorts. We also opted to use the difference because one of our main study objectives is to compare to similar studies reported in the literature which summarized the rates as a percentage of difference (2,6).

RESULTS

Patient Characteristics

One hundred eighty-five patients were included in this study, and 53.8% had a malignancy (Table 2). The mean ± standard deviation age at presentation was 7.97 ± 4.89 years, and 3.75 ± 3.83 years for patients with and without a malignancy respectively ($p < 0.0001$). Concordantly, the weight for oncologic patients was significantly higher than that of the control group. Moreover, there were more male patients among the oncology group compared with the nononcology group (52.6% vs. 49.3%). The oncology cohort had a higher percentage of Down syndrome (5.9% vs. 0%; $p = 0.06$) and a lower percentage of congenital heart disease (0% vs. 8.2%; $p = 0.01$).

Among the oncology group, the most prevalent tumors were hematologic (70.6%), with the most common type being leukemias (61.2%). Among leukemias (n = 52), acute lymphoblastic leukemia was the most common (78.8%). In terms of therapy, 8.3% of the hematologic patients had undergone BMT and 81.2% had received chemotherapy within a month of presentation to the ED (Table 3). When comparing 72-h, 28-day, and in-hospital mortality between patients with hematologic malignancies and patients with solid tumors, no significant mortality difference was noted. Regarding our primary outcome, patients with a malignancy had an in-hospital mortality rate of 5.9% compared with 2.7% in the nononcology group; however, there was no statistically significant difference ($p = 0.45$). A multivariate analysis was performed using logistic regression to evaluate the association between in-hospital mortality and the 2 groups, adjusting for age and weight. There was no statistically significant difference between the 2 groups. Other variables were not included in a multivariate analysis because the number of patients that died in the hospital, which is our primary outcome, was small.

Vital Signs and Laboratory Parameters on ED Presentation

The 2 cohorts had similar vital signs at presentation, with a statistically significant difference only detected for the respiratory rate (24 ± 9 breaths/min in patients with cancer vs. 27 ± 8 breaths/min in patients who were cancer-free, $p = 0.04$). With regard to laboratory studies, the oncology cohort had significantly lower levels of all complete blood cell count parameters. They also had significant differences in potassium, phosphate, calcium, bicarbonate, chloride, and magnesium. No significant difference could be reported with respect to bilirubin levels, coagulation assays, C-reactive protein levels, and arterial blood gas analysis between the 2 cohorts (Table 4).

Sepsis Diagnosis, Resuscitation Parameters, Infection Site, and Patients' Length of Stay

The diagnosis of septic shock was more common in patients with cancer (18.8% vs. 2.7%; $p = 0.002$). In terms of infection characteristics, cancer patients had a higher percentage of bacteremia (27.1% vs. 4.1%; $p < 0.001$). The oncology cohort had significantly higher percentages of skin (9.4% vs. 0%; $p = 0.01$) and unknown (9.4% vs. 0%; $p = 0.01$) site of infections. However, the nononcology group had a higher percentage of lung infections (68.5% vs. 32.9%; $p < 0.0001$). A complete list of infection sites is shown in Table 1.

There were multiple differences regarding resuscitation parameters between the 2 cohorts. Patients with cancer received significantly more fluids at 6 h, with an average of 32.95 mL/Kg compared with 24.87 mL/Kg in the cancer-free group ($p = 0.029$). A total of 15.3% of patients with cancer required vasopressors compared with 1.4% of patients without cancer. Moreover, steroid use was more significant in the oncology cohort (16.5% vs. 5.5%; $p = 0.03$). All patients received antibiotics except 1 control patient who was diagnosed with a viral pneumonia. Patients with cancer were more likely to receive their antibiotics in the ED (95.3%) compared with patients without cancer (75%). As for the door-to-antibiotics time, there was a statistically significant difference between the 2 groups where the oncology patients' time was an average of 1.3 h compared with the nononcology group, which had an average of 3.33 h. There was no significant difference between the 2 cohorts regarding ED, ICU, or GPU length of stays.

Table 5 summarizes the differences in the ED management between the 2 study arms.

DISCUSSION

Our study aimed at assessing whether pediatric oncology patients presenting to the ED with sepsis, severe sepsis, or septic shock had any differences in demographics, ED management, and mortality when compared with pediatric nononcology patients. A total of 158 septic pediatric patients were enrolled in our study, with 85 (53.8%)

Table 2. Demographic Characteristics of Patients Presenting to the Emergency Department with Sepsis

	Oncology (N = 85)	Nononcology (N = 73)	*p* Value
Age, years (mean ± SD)	7.97 ± 4.9	3.75 ± 3.8	<0.0001
Weight, kg (mean ± SD)	29.05 ± 19.5	15.4 ± 11.5	<0.0001
Gender, n (%)			
Male	45 (52.9)	36 (49.3)	0.65
Female	40 (47.1)	37 (50.7)	
Diagnosis, n (%)			
Sepsis	69 (81.2)	71 (97.3)	0.002
Severe sepsis/septic shock	16 (18.8)	2 (2.7)	
Medical history, n (%)			
Down syndrome	5 (5.9)	0 (0.0)	0.06
Metabolic disease	0 (0.0)	2 (2.7)	0.21
Congenital heart disease	0 (0.0)	6 (8.2)	0.01
Asthma	1 (1.2)	5 (6.8)	0.10
Blood dyscrasias	0 (0.0)	2 (2.7)	0.21
End stage renal disease	0 (0.0)	2 (2.7)	0.21
Site of infection, n (%)			
Middle ear	4 (4.7)	3 (4.1)	1
Catheter	5 (5.9)	0 (0.0)	0.06
Oral cavity	2 (2.4)	4 (5.5)	0.42
Skin	8 (9.4)	0 (0.0)	0.01
Urine	13 (15.3)	15 (20.5)	0.39
Blood	8 (9.4)	2 (2.7)	0.11
Gastrointestinal	12 (14.1)	7 (9.6)	0.38
Lung	28 (32.9)	50 (68.5)	<0.0001
Other (mastoid/perianal/tonsils)	5 (5.9)	5 (6.8)	1.00
Unknown	8 (9.4)	0 (0.0)	0.01
Bacteremia	23 (27.1)	3 (4.1)	<0.0001
Organism, n (%)			
Klebsiella pneumonia	5 (21.7)	0 (0.0)	0.37
Escherichia coli	5 (21.7)	1 (33.3)	1.00
Streptococcus species	2 (8.7)	0 (0.0)	1.00
Enterococcus species	2 (8.7)	0 (0.0)	1.00
Pseudomonas aeruginosa	1 (4.3)	0 (0.0)	1.00
Staphylococcus coagulase– negative	6 (26.1)	2 (66.7)	0.22
Staphylococcus aureus	1 (4.3)	0 (0.0)	1.00
Other (*Campylobacter jejuni*, *Hemophilus influenza*, *Ralstonia picketti*)	3 (13.0)	0 (0.0)	1.00

SD = standard deviation.

patients suffering from oncologic illnesses. Oncology patients had a higher mortality rate (5.9%) compared with nononcology patients (2.7%) with a 3.2% difference; however, it was not statistically significant ($p = 0.45$). Despite the non–statistically significant difference in mortality, the rate difference we detected was similar to that found in recent literature, where Fiser et al. described a 17% mortality rate in pediatric oncology patients and Ruth et al. described a 14.4% mortality rate in pediatric nononcology patients, the difference being 2.6% (2,6). This difference was found to be distinctive from that reported in the literature at the time of study initiation, which was 23% (11–15). Similarly, oncology patients had a significantly higher rate of bacteremia. These findings may be explained by the increased immunodeficiency in cancer patients, making them prone to a higher risk of bacterial and fungal infections (16). Increased immunodeficiency in oncology patients may be related to multiple causes, including cytotoxic chemotherapy, malignant infiltration resulting in myelosuppression and neutropenia, and functional defects in neutrophils. Neutrophils' functional defects may include defects in chemotaxis, phagocytosis, bactericidal capacity, and respiratory rates (16).

On the other hand, the study yielded many notable differences between the 2 cohorts concerning our a priori selected secondary outcomes. The 2 cohorts differed greatly in their demographics and ED management. On presentation, both cohorts had similar vital signs except for a significantly higher respiratory rate among the control group. A possible explanation for the increased respiratory rate could be that 68.5% of the cancer-free patients had a lung infection compared with 32.9% in cancer patients. Furthermore, the respiratory, genitourinary, and abdominal infections were found to be the most common sites of infection in both cohorts. This is in accordance

Table 3. Types of Malignancy and Treatment of Oncology Patients Presenting to the Emergency Department with Sepsis

	Oncology Patients (N = 85)
Total hematologic tumors, n (%)	59 (70.6)
Underwent BMT	3 (51)
Leukemia	52 (88.1)
ALL	41 (78.8)
AML	10 (19.2)
JML	1 (1.9)
Lymphoma	7 (11.9)
Hodgkin	4 (57.1)
Non-Hodgkin	3 (42.9)
Langerhans cell histiocytosis	1 (1.7)
Total solid tumors, n (%)	25 (29.4)
Bone	5 (20)
Liver	1 (4)
Ovarian	1 (4)
Brain	13 (52)
Neuroblastoma	1 (4)
Rhabdomyosarcoma	2 (8)
Retinoblastoma	2 (8)
Radiation therapy within the past 3 months, n (%)	2 (2.4)
Chemotherapy within the past month, n (%)	69 (81.4)

ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; BMT = bone marrow transplant; JML = juvenile myelomonocytic leukemia.

with the published literature, as a retrospective study by Ruth et al. on 49,153 pediatric patients with severe sepsis found the respiratory and genitourinary systems to be the most common foci of infection (2). Moreover, oncology patients were found to have a higher incidence of infection with an unknown focus. Among our study's 8 oncologic patients with no documented focus of infection, 5 were patients with febrile neutropenia. This coincides with several studies that have noted no microbiologic evidence of infection in ≤60% of patients presenting with fever and therapy-induced neutropenia (17–22). Patients with cancer were also found to have a higher rate of dermatologic infections. This may be explained by the underlying malignant processes or therapy in patients with cancer that may disrupt the skin (22). The skin is the most common site of complication of many anticancer therapies because it is the first line of defense against organisms, which increases the vulnerability to infections.

During their time in the ED, oncology patients received a significantly higher amount of intravenous fluids per weight at 6 h compared with the nononcology patients. They also received significantly more vasopressors, specifically dopamine. This suggests a more severe illness at presentation that required more aggressive treatment at the time. The time to antibiotic administration from presentation was also significantly shorter in the oncology group. Data concerning fluid requirements and antibiotic initiation time align with the current studies that focus on providing appropriate guidelines for managing septic pediatric oncology patients in the ED (3,23). There have been multiple efforts to improve sepsis care for children over the past 10 years (23). As a way to improve the recognition and understanding of pediatric septic patients, many institutions have worked on guidelines to appropriately manage pediatric patients presenting with sepsis (3,23). The Society for Critical Care Medicine introduced guidelines for pediatric sepsis patients in 2002, and these guidelines were revisited in 2007 (24). Since then, many institutions have developed specific sepsis clinical practice guidelines, which have resulted in improved time to key interventions and outcomes (25,26) These guidelines also aim to evaluate the influence of presenting symptoms on resuscitation, antibiotic treatment, morbidity, and mortality (27). A study done by Pakakasama et al. describes the impact of the new guidelines on patients (7). It aimed at decreasing door to antibiotic initiation time in the ED to a median of 75 min, which resulted in a decrease in the mortality rate (7).

At our institution, guidelines similar to that of the Infectious Diseases Society of America for pediatric oncology patients presenting with fever and neutropenia are applied for all oncology patients suspected of infection (28). Once a patient presents with any concern for infection, or recent myelosuppressive chemotherapy and fever, he/she is subcategorized further based on clinical assessment and hemodynamic status. Hemodynamically unstable patients receive appropriate fluid and vasopressors resuscitation as well as intravenous cefepime or meropenem empirically, after blood cultures were withdrawn (7). If the patient is considered stable, laboratory workup including neutrophil count, blood cultures (aerobic, anaerobic, and fungal from all lumens of central venous catheter), urine analysis and culture, rapid respiratory virus polymerase chain reaction, chest radiography, and other diagnostic tests as clinically indicated are collected. The choice of antibiotics is guided by their absolute neutrophil count and previous blood culture history (7,29).

First, appropriate resuscitation measures including intravenous fluids and vasopressors are provided as clinically indicated. Then a laboratory workup is taken, including a complete blood cell count with differential, absolute neutrophil count, serum levels of creatinine and blood urea nitrogen, serum electrolytes level, hepatic transaminase enzymes, total bilirubin, blood cultures (aerobic and anaerobic from each lumen of the central venous catheter), chest radiography in case of respiratory symptoms, and other diagnostic tests as clinically indicated. Our institution also collects urine analysis and culture on every patient, even though these are not included

Table 4. Vital Signs and Laboratory Workup of Patients Presenting to the Emergency Department with Sepsis

	Oncology (N = 85)	Nononcology (N = 73)	*p* Value
Temperature (°C), (mean ± SD)	38.29 ± 0.98	38.22 ± 1.16	0.67
Heart rate (beats/min), (mean ± SD)	141.42 ± 23.93	147.70 ± 32.37	0.17
Systolic blood pressure (mm Hg), (mean ± SD)	110.45 ± 21.00	111.84 ± 17.07	0.68
Diastolic blood pressure (mm Hg), (mean ± SD)	65.64 ± 13.51	66.53 ± 15.76	0.72
Respiratory rate (breaths/min), (mean ± SD)	24.33 ± 9.48	27.42 ± 7.88	0.04
Oxygen saturation (%), (mean ± SD)	98.35 ± 4.69	96.75 ± 5.34	0.06
SIRS criteria, n (%)			
0	3 (3.5)	5 (6.8)	0.414
1	22 (25.9)	23 (31.5)	
≥2	60 (70.6)	45 (61.6)	
WBC, $10^3/mm^3$ (mean ± SD)	4.011 ± 4.965	17.092 ± 12.806	<0.0001
ANC, $10^3/mm^3$ (mean ± SD)	2.522 ± 4.017	12.018 ± 11.513	<0.0001
Hemoglobin, g/dL (mean ± SD)	9.71 ± 1.99	11.43 ± 1.51	<0.0001
Platelet count, $10^3/mm^3$ (mean ± SD)	165434 ± 143369	349915 ± 151969	<0.0001
BUN, mg/dL (mean ± SD)	10.38 ± 8.83	11.85 ± 9.58	0.34
Creatinine, mg/dL (mean ± SD)	0.35 ± 0.17	0.52 ± 1.2	0.2
Sodium, mmol/L (mean ± SD)	137.35 ± 4.66	136.10 ± 3.12	0.06
Potassium, mmol/L (mean ± SD)	3.63 ± 0.54	4.58 ± 0.73	<0.0001
Bicarbonate, mmol/L (mean ± SD)	22.02 ± 3.61	20.39 ± 3.05	0.005
Chloride, mmol/L (mean ± SD)	101.91 ± 6.12	96.73 ± 12.85	0.002
Phosphate, mg/dL (mean ± SD)	3.75 ± 1.07	4.61 ± 1.08	<0.0001
Calcium, mg/dL (mean ± SD)	8.50 ± 0.79	9.63 ± 0.76	<0.0001
Magnesium, mg/dL (mean ± SD)	1.83 ± 0.28	2.12 ± 0.21	<0.0001
Total bilirubin, mg/dL (mean ± SD)	0.93 ± 1.31	1.88 ± 2.82	0.21
INR (mean ± SD)	1.66 ± 0.47	1.10 ± 0.20	0.08
PT, s (mean ± SD)	19.02 ± 5.55	12.70 ± 2.33	0.09
PTT, s (mean ± SD)	37.06 ± 8.18	29.33 ± 4.73	0.16
CRP, mg/dL (mean ± SD)	52.16 ± 51.37	69.80 ± 84.47	0.55

ANC = absolute neutrophil count; BUN = blood urea nitrogen; CRP = C-reactive protein; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; SIRS = systemic inflammatory response syndrome; WBC = white blood cell.

in the Infectious Diseases Society of America guidelines. After laboratory values are obtained, antibiotics, usually ceftriaxone, are initiated within 2 h of presentation. This is in accordance with the applied guidelines where pediatric oncology patients receive antibiotics regardless of final diagnosis or laboratory results. On the other hand, the decision to administer antibiotics in the nononcology group is dependent on the clinical assessment, laboratory values, and radiologic results. In addition, pediatric oncology patients presenting with fever or concern for sepsis are more likely to be roomed faster and seen in a timelier fashion. These factors explain the shorter time to antibiotic initiation in the oncology cohort of our study, with a time to antibiotic of 78 min in the oncology group compared with 198 min in the nononcology group.

It is also important to highlight that our pediatric oncology mortality rate (5.9%) was different from a study by Fiser et al. that showed a total mortality rate of 17% in pediatric oncology patients with sepsis in the ICU (6). The difference in percentage can be justified by the fact that antibiotic initiation in the oncology patients presented by Fiser et al. was dependent on the discretion of the intensivist, oncologist, and infectious disease consultant. The study did not mention any strict clinical practice guidelines or a specific time window for antibiotic initiation and empiric treatment (6). Moreover, their study had a higher number of patients who underwent a BMT compared with our study (132 vs. 3). This may have affected the mortality rate because BMT patients are at higher risk of infections, occurrence of resistant bacterial strains, and worse outcomes when compared with non-BMT patients (30).

Another study by Pakakasama et al. reported a mortality rate decrease from 6.5% to 0% once the new guidelines were applied (7). The guidelines, as previously mentioned, mainly focused on decreasing time to antibiotic initiation in the ED (7).

The difference between our institutional guidelines and those applied by Pakakasama et al. is mainly related to antibiotic administration. Pakakasama et al. describe more accurate guidelines by subcategorizing patients and further individualizing antibiotic plans. Moreover, they administer broader spectrum antibiotics with more Gram-positive and Gram-negative coverage. These differences might attribute to the difference in mortality between the mentioned study and our results (0% vs. 5.9%)

Table 5. Sepsis Treatment Variables, Length of Stay, and Outcomes of Patients Presenting to the Emergency Department with Sepsis

	Oncology (N = 85)	Nononcology (N = 73)	*p* Value
IV fluid requirement, mL/kg (mean ± SD)			
First 6 h	33.0 ± 27.7	24.9 ± 16.1	0.029
First 24 h	77.7 ± 59.5	82.0 ± 31.0	0.577
Vasopressor use, n (%)	13 (15.3)	1 (1.4)	0.002
Norepinephrine	1 (1.2)	1 (1.4)	1.00
Dopamine	13 (15.3)	0 (0)	<0.001
Time to vasopressor use			
First 24 h (mean ± SD)	6.2 ± 3.9	2.3 ± 0	0.35
Duration of vasopressor use			
First 24 h (mean ± SD)	42.9 ± 50	3.0 ± 0	0.46
Steroid use, n (%)	14 (16.5)	4 (5.5)	0.03
Antibiotic use, n (%)	85 (100)	72 (98.6)	0.279
Appropriate antibiotic use, n (%)	85 (100)	71 (100)	NA
Antibiotics initiation location, n (%)			0.001
ED	81 (95.3)	54 (75.0)	
GPU	4 (4.7)	14 (19.4)	
ICU	0 (0.0)	4 (5.6)	
Time to initiation of antibiotics, h (mean ± SD)	1.3 ± 2.0	3.3 ± 2.0	<0.001
Intubation in the ED	1 (1.2)	1 (1.4)	0.91
Intubation within the first 48 h	3 (3.5)	3 (4.1)	1.00
ED LOS, h (Mean ± SD)	6.9 ± 6.6	8.0 ± 9.9	0.38
ED disposition: admitted to hospital, n (%)	85 (100)	73 (100)	
Admission disposition, n (%)			0.20
GPU	71 (83.5)	66 (90.4)	
ICU	14 (16.5)	7 (9.6)	
ICU LOS, h (mean ± SD)	62.2 ± 51.7	115.5 ± 95.4	0.13
GPU LOS, h (mean ± SD)	202.6 ± 221.3	154.1 ± 295.6	0.26
72-h mortality	2 (2.4)	0 (0.0)	0.50
Hospital mortality	5 (5.9)	2 (2.7)	0.45
Disposition			0.45
Hospital mortality, n (%)	5 (5.9)	2 (2.7)	
Discharged home, n (%)	80 (94.1)	71 (97.3)	

ED = emergency department; GPU = general practice unit; ICU = intensive care unit; IV = intravenous; LOS = length of stay.

(7). This potentially highlights the necessity of advancing our protocol similarly by further subcategorizing our patients and individualizing treatment in guidelines to further decrease mortality rates.

Limitations

This was a retrospective chart review cohort study; as such, the authors are aware of the inherent limitations of such a type of study. To minimize biases that this may cause, frequent meetings were held between the principal investigator and data collectors to standardize the way in which data were collected and entered.

Our study is also limited by its small sample size, which explains the low prevalence of the primary outcome. Our small sample size is related to the fact that this was a single-center study, as well as the fact that more than half of the patients identified for screening were excluded from the data cohort. In addition, the small sample size could have affected our capability to adjust for confounders and carry out a stratified analysis taking into account factors such as major medical problems as well as factors relating to sepsis, such as the presence of indwelling lines and history of recent hospitalization. Associations were therefore reported at the bivariate level, and our inability to adjust for these factors led to unequally matched cohorts. Moreover, the sample size calculation was based on the mortality rate difference found in the literature (23%) at the time of study initiation; however, the difference decreased greatly in newly published literature found at the time that this article was written. This might have affected our power in detecting significance in mortality—making us unable to make conclusions in that regard. There also might be a difference in population characteristics and demographics included in our study in comparison to those previously studied. The lack of a high number of pediatric oncology patients who underwent BMT, and the differences in the institutionalized guidelines applied, may have also played a role. Moreover, the study was conducted at a tertiary care referral center ED that receives regional complicated cases, which can affect the

generalizability of the results to the whole oncologic subpopulation. Lastly, it is important to note that cross-sectional studies are only able to discover associations and it is difficult to establish causal relationships, creating a risk of possible spurious associations (31).

CONCLUSION

In this study, we compared the characteristics of pediatric septic patients stratified by the presence of malignancy. There were notable differences in presentation, management, and infection rates. Oncology patients received higher rates of IV fluid in the first 6 h, vasopressors, and steroids. The time to antibiotic initiation was much lower in the oncology group as well. Higher rates of bacteremia, skin infections, and infections of unknown foci were reported in the oncology group. Regarding in-hospital mortality and length of stay, we were unable to detect statistical significance between the 2 cohorts. Although pediatric oncology patients presenting with sepsis, severe sepsis, or septic shock remain at high risk, our findings suggest that their outcomes and mortality have improved from previously reported data, possibly because of the institutionalized clinical practice guidelines. With the appropriate guidelines in the ED, patients are treated more aggressively and in a timelier manner, ensuring a lower risk of complications.

Pediatric oncology patients are a vulnerable group at high risk of infection; however, with appropriate attention by physicians and practice protocols, improved outcomes may be achieved. We hope our study leads to further research on sepsis in the pediatric oncology population in order to establish guidelines that may result in clinical improvement.

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ARTICLE SUMMARY

1. Why is this topic important?

Sepsis accounts for 9% of all pediatric cancer-related deaths, making them a vulnerable population. No studies have explored the differences in demographics, presentation, and treatment parameters in pediatric oncology patients presenting to the ED with sepsis, severe sepsis, or septic shock compared with their nononcologic counterparts.

2. What does this study attempt to show?

This study aims to contribute to a better understanding of sepsis in this vulnerable population, and to shed light on specific parameters that are helpful in treating pediatric oncologic patients presenting with sepsis.

3. What are the key findings?

Although pediatric oncology patients presenting with sepsis, severe sepsis, or septic shock remain at high risk, our findings suggest that their outcomes and mortality have improved from previously reported data. Oncology patients received more intravenous fluids and were more likely to be started on vasopressors and steroids than their nononcology counterparts.

4. How is patient care impacted?

This study highlights the importance of institutionalized guidelines for treating pediatric oncology patients presenting with sepsis. Providing them with the appropriate treatment in a timely manner treatment results in improved outcomes for these patients. Moreover, it also highlights the importance of aggressive intravenous fluid requirements, vasopressors, and steroids use, as well as antibiotic administration, which may result in enhanced patient care.