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Comparison between early and late mortalities due to severe sepsis in a pediatric intensive care unit: five-years-experience

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Abstract

Background: The majority of children who die of sepsis suffer from refractory shock and/or multiple organ dysfunction syndrome, with many deaths occurring within the initial 48–72 h of treatment.

Methods: A retrospective observational study of deceased patients due to severe sepsis over 5 years, from the 1st of August 2015 to the end of July 2020, that were admitted in a pediatric intensive care unit.

Results: Over 5-year duration of the study, the trend of cases with severe sepsis increased from 26.4% in 2015 to 40.7% in 2020. Meanwhile, the trend of mortality among this category of patients dropped from 66.7% in 2015 to 33.9% in 2020. From the studied 163 deceased patients, results showed predominance of *Klebsiella pneumoniae* of the extended resistance pattern in bronchoalveolar lavage and blood cultures, and it came second to *Candida* in urine cultures. Pandrug-resistant organism was recorded in 8.59% ($n = 14$ patients). Patients with bacteremia, acidosis, high pediatric index of mortality (PIM-2), and pediatric logistic organ dysfunction (PELOD) scores were statistically related to early fatality fate.

Conclusion: High mortality was associated with the increasing spread of resistant organisms especially *Klebsiella pneumoniae*. Patients with bacteremia, acidosis, and high PIM-2 and PELOD scores probably will need immediate, vigorous, and intense care in order to save their lives.

Keywords: Severe sepsis, Septic shock, Resistant organisms, Risk of early fatality

Background

Sepsis and septic shock are leading causes of death worldwide in pediatric population resulting in an estimated 7.5 million deaths annually [1]. The majority of children who die of sepsis suffer from refractory shock and/or multiple organ dysfunction syndrome, with many deaths occurring within the initial 48–72 h of treatment [2].

Predisposing factors associated with mortality due to sepsis include age, gender, associated comorbidities, bacteremia, focus of infection, the type of microorganism or drug resistance, multiorgan failure as heart failure and renal failure, and premature birth [3]. Defining the risk factors for mortality and morbidity can help to establish which patients might benefit from a more appropriate goal-oriented therapy according to the severity of the process and which patients might benefit from invasive monitoring and/or treatment [4].

Highlighting sepsis and the few simple emergency therapeutic interventions needed will focus on the actual problems that confront clinicians in regions with limited resources [5]. The Surviving Sepsis Campaign identified, "What are the predictors of sepsis long-term morbidity and mortality?" as one of the top six clinical sepsis research priorities [6].

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Aim of the study

So, the current research was designed to explore the most alarming factors associated with rapid mortality detected among fatal cases of sepsis in pediatric intensive care unit (PICU) in a resource-limited country.

Methods

Study design

This retrospective observational study was conducted where all files of admitted patients in PICU from first of August 2015 until the end of July 2020, 5 years, were assessed. Discharged patients were excluded, and files of the deceased one were examined for the cause of death. Cultures from different sites (blood, urine, BAL, etc.) are routinely collected from patients on admission to PICU. Cases whose death was directly related to sepsis or septic shock according to criteria derived from Surviving Sepsis Guidelines 2020 [6] were included in the study. Recruited cases were classified into two subgroups: early and late deceased as deaths occurred within or after 4 days from admission respectively

Study setting

A university-affiliated medical, nonsurgical PICU equipped with nine beds, with yearly admission rate of 250–300 cases is considered a tertiary center of referral serving four governorates of almost 20 million population. The high level of patient care provided in this PICU depended by 24 h 2 residents: one on duty in PICU and the other on call to ensure rapid rescue of cases in the emergency room or other wards. The high nurse-to-patient ratio is 1:1 for close monitoring of critically ill patients. All procedures were performed under the supervision of intensive care consultant. Patient's data were registered accurately on a computerized database filling system. Patients whose age is less than 30 days or more than 16 years were not admitted in this PICU.

Collection of data

Demographic and clinical data from medical records were collected. Data included patients' age, gender, underlying diagnoses, pediatric index of mortality score (PIM-2), pediatric logistic organ dysfunction (PELOD) score on the day of admission, routine laboratory investigations, all tests performed to isolate the causative organism of sepsis, different types of initial and supportive treatment given, mechanical ventilation, invasive devices, inotropes, PICU length of stay, and mortality.

Ethical consideration

All procedures performed in the current study were in accordance with the 1964 Helsinki Declaration and its amendments. Alexandria University ethical committee approved the study design on October 2020 (IRB: 00012098—FWA: 00018669, serial number: 0106561). Since the study was retrospectively observational, the informed consent was waived with complete security of the confidentiality of personnel patients' data.

Statistical consideration

Statistical analysis used SPSS (Statistical Package for Social Science) program (version 21). Since Kolmogorov-Smirnov test of normality revealed significance in the distribution of some variables, so the nonparametric statistics was adopted. Comparisons were carried out between two studied independent not-normally distributed subgroups using Mann-Whitney *U*-test. Chi-square test was used to test association between qualitative variables. Fisher exact corrections were carried out when indicated. The binary logistic model was used to estimate the probability of a binary response based on independent variables. The calibration was assessed by directly comparing the observed and customized predicted mortality across subcategories of risk. An alpha level was set to 5% with a significance level of 95%, and a beta error accepted up to 20% with a power of study of 80%.

Results

Figure 1 shows the strategy of recruitment of the studied cases according to the reporting of studies conducted using observational routinely collected data (RECORD) system. The demographic data of these 163 finally recruited cases were presented in Table 1. It was noticed that studied cases had high PIM-2 and PELOD scores. The majority of them (62%) were below 1 year of age, 60% were male, and their mean body mass index was less than 18.5 and classified as underweight. Figure 2 shows the trend of cases admitted to the PICU with the diagnosis of severe sepsis or septic shock that increased from 26.4% in 2015 to 40.7% in 2020. Meanwhile, the trend of mortality among this category of patients dropped from 66.7% in 2015 to 33.9% in 2020. Table 2 presents the retrieved pathogens from the studied cases stratified according to their resistance pattern. Results showed predominance of *Klebsiella pneumoniae* of the extended resistance pattern in bronchoalveolar lavage (BAL) and blood cultures which were resistant to all antimicrobial agents except to polymyxin group. From the studied 163 deceased patients due to sepsis, 14 patients (8.59%) had been infected with a pandrug-resistant (PDR) organism. The most common PDR organism was *Klebsiella pneumoniae*. The second organism was *Acinetobacter*. *Candida* resistant to all available antifungal agents was reported in 3/14 cases. The last PDR organism was *Streptococcus*

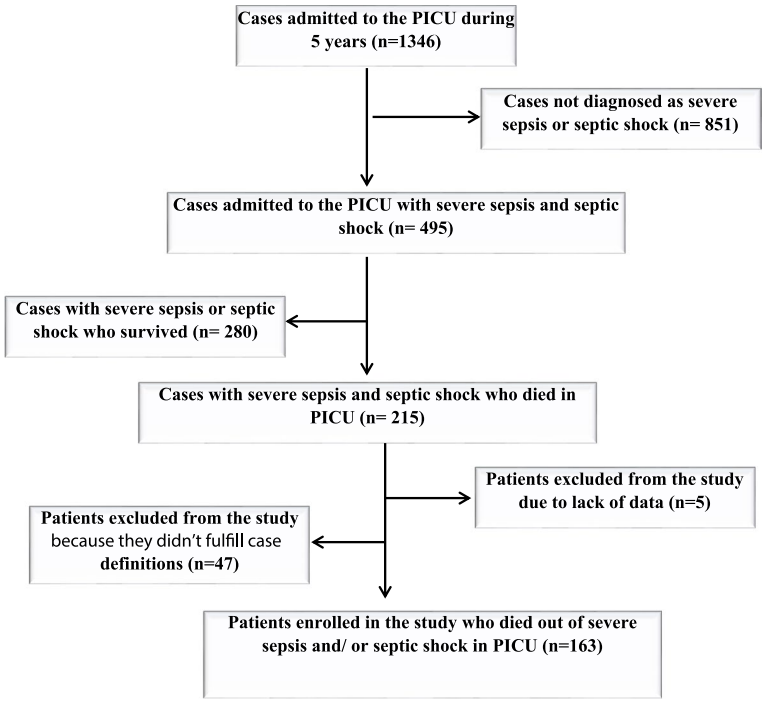

Fig. 1 RECORD flow diagram of strategy of recruitment of the studied population

pneumoniae isolated from blood culture. In Fig. 3, the bar chart represents days from severe sepsis recognition to death showing two important peaks: the first occurred within the first day of admission, and the second peak occurred during the period from 4th to the 9th day from admission. Hence, authors divided the studied population into two subgroups: early and late deceased as deaths occurred within or after 4 days from admission respectively. Table 3 shows that early deceased patients had higher PIM-2 and PELOD scores. The late deceased group had chest or urinary infections as portal of entry to sepsis, while bacteremia was more linked to early mortality. Early deaths were related to a state of acidosis on admission as evidenced by low blood pH and bicarbonate (Table 4). The multiple logistic regression model revealed that acidosis especially low bicarbonate was an independent factor associated with early mortality (Table 5).

Discussion

The current study showed that the trend of cases of severe sepsis assumed an upward curve increased from 26.4% of admitted cases in 2015 to 40.7% in 2020, while the case fatality rate due to sepsis decreased from 66.7% in 2015 to 33.9% in 2020. Even after this decrease in mortality, yet, this mortality rate is considered very high compared to worldwide mortality of sepsis around 25% as stated by Weiss et al. [7] The intensive care team working in this PICU is highly committed to adhere to the latest surviving sepsis campaign guidelines and provides optimum care to their patients. And that is why it was essential to study mortality cases due to sepsis and assess the risk factors and possible explanation for this high incidence.

The most common organism retrieved from all cultures was *Klebsiella pneumoniae* predominantly of extended drug-resistant strains. The most alarming finding of this study was the appearance of a large number of pandrug-resistant organisms (8.59%) from all positive cultures. These organisms represented a real challenge in their treatment; infectious disease specialist tried to defeat them using combinations of last resort antimicrobials such as colistin or tigecycline. Still, the general prognosis of infection with a PDR organism was very poor. The WHO latest report stated that antibiotics are becoming increasingly ineffective and warned that drug resistance is spreading globally leading to more difficult to treat infections and deaths. The WHO added that these resistant infections have been observed worldwide, indicating that we are running out of effective antibiotics [8].

Many studies in literature considered *Klebsiella* as one of the most virulent pathogen often associated with high morbidity and mortality. The carbapenemase producing

Table 1 Demographic and clinical characteristics of the studied population ($n = 163$)

	***n* (%)**
Sex	
Male	98 (60.1%)
Female	65 (39.9%)
Age (months)	
Min.–max.	1.0–180.0
Mean ± SD.	25.54 ± 36.94
Median (IQR)	9.0 (4.0–33.50)
Weight (kg)	
Min.–max.	1.70–77.0
Mean ± SD.	10.52 ± 10.57
Median (IQR)	7.30 (4.40–11.0)
Previous hospital admission	74 (45.4%)
Comorbid conditions	62 (38.0%)
Comorbid	
Chest	3 (1.8%)
Cardiac	19 (11.7%)
Hematology	14 (8.6%)
Renal	11 (6.7%)
Gastroenterology	10 (6.1%)
Genetic	7 (4.3%)
Immunity	3 (1.8%)
Failure to thrive	3 (1.8%)
Neurology	2 (1.2%)
Endocrine	2 (1.2%)
Bone	1 (0.6%)
PICU stay (days)	
Min.–max.	1.0–60.0
Mean ± SD.	9.06 ± 10.63
Median (IQR)	5.0 (2.0–12.0)
PIM2	
Min.–max.	3.40–100.0
Mean ± SD	52.04 ± 30.26
Median (IQR)	53.0 (24.50–79.50)
PELOD	
Min.–max.	3.0–33.0
Mean ± SD	15.93 ± 7.44
Median (IQR)	14.0 (10.0–20.0)
Mechanical ventilation	
Invasive devices	163 (99.4%)
CVC	163 (99.4%)
Urine catheter	163 (99.4%)
Chest tube	7 (4.3%)
Dialysis	13 (8.0%)

PICU pediatric intensive care unit, *PIM-2* pediatric index of mortality, *PELOD* pediatric logistic organ dysfunction, *CVC* central venous catheter

Klebsiella has been recognized as an emerging challenge worldwide usually exhibiting extensive resistance. Capone et al. [9] also warned from colistin-resistant *Klebsiella* which evolute to pandrug resistance. The fears of the beginning of a post-antibiotic era appear to be justified specifically gram-negative bacteria, and *Klebsiella* comes on top of these highly dangerous pathogens.

Comparison revealed that early deceased patients had higher PIM-2 and PELOD scores compared to the late deceased group. This finding emphasizes the importance of these scores to predict mortality, and higher values were significantly related to rapid fatal outcome.

Bacteremia as a primary site of infection was associated with early mortality. This might be owed to the widespread dissemination of infection into different organs with rapid deterioration of their functions leading to multiorgan dysfunction syndrome.

Comparison also highlighted the importance of metabolic acidosis and low blood bicarbonate level on admission. The multiple logistic regression model proved that low blood bicarbonate was an independent biomarker related to early mortality with the odds of 0.938. This finding was supported by many researchers like Javed et al. [10] and Ganesh et al. [11]

It is recommended to initiate goal-directed therapy to patients with severe sepsis as early as possible because every hour delay in treatment increases mortality by 8% [12]. Physicians are urged to take all possible and vigorous resuscitation measures with special attention to those at high risk of rapid mortality, considering starting combinations of antimicrobial agents for those infected with pandrug-resistant organisms.

To the best of our knowledge, this study is one of few studies in literature addressing the risk markers of early mortality in pediatric severe sepsis population. Nevertheless, this study is not without limitations. First is the retrospective nature of the study, although meticulous efforts were implemented to gather all relevant data. Yet, some important informations were lacking such as serum lactate on admission and its clearance over time, vaccination history, and resuscitation measures prior to PICU admission. Second, the study was conducted in a tertiary care level academic PICU, and its performance could not be generalized to all PICUs even within the same country. Third, the mortality was only considered when it occurred in PICU, and we could not assess post discharge mortality. All these limitations could not reduce the importance of the findings in this study.

Conclusion

Reducing mortality from sepsis in children is a worldwide challenge. This study suggests that high mortality was associated with the increasing spread of PDR

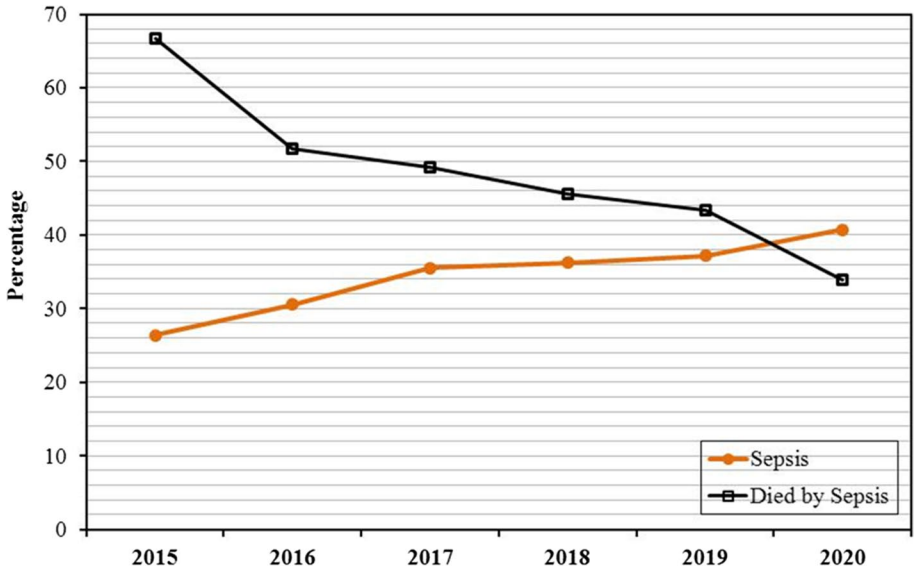

Fig. 2 Trend of severe sepsis and deaths due to sepsis over the 5 years

Table 2 Distribution of the retrieved causative organisms of sepsis in different cultures according to their resistance to antibiotics

Culture	Organism retrieved	Total		Susceptible		MDR		XDR		PDR	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%
BAL culture (*n* = 53) Retrieved organisms (*n* = 64)[a]	*Klebsiella*	24	45.3	0	0.0	5	9.4	15	28.3	4	7.5
	Candida	12	22.6	10	18.9	1	1.9	1	1.9	0	0
	Acinetobacter	9	17.0	1	1.9	2	3.8	2	3.8	4	7.5
	Pseudomonas	6	11.3	4	7.5	2	3.8	0	0.0	0	0.0
	E. coli	4	7.5	0	0.0	3	5.7	1	1.9	0	0.0
	Staphylococcus aureus	3	5.7	1	1.9	2	3.8	0	0.0	0	0.0
	Citrobacter	2	3.8	2	3.8	0	0.0	0	0.0	0	0.0
	Proteus	2	3.8	0	0.0	2	3.8	0	0.0	0	0.0
	Aspergillus	1	1.9	1	1.9	0	0.0	0	0.0	0	0.0
	Enterobacter	1	1.9	0	0.0	0	0.0	1	1.9	0	0.0
Blood culture (*n* = 31)	*Klebsiella*	11	35.5	1	3.2	3	9.7	7	22.6	0	0.0
	S. aureus	5	16.1	1	3.2	4	12.9	0	0.0	0	0.0
	Candida	4	12.9	4	12.9	0	0.0	0	0.0	0	0.0
	Citrobacter	3	9.7	0	0.0	1	3.2	2	6.5	0	0.0
	Pseudomonas	2	6.5	2	6.5	0	0.0	0	0.0	0	0.0
	E. coli	1	3.2	0	0.0	1	3.2	0	0.0	0	0.0
	Enterobacter	1	3.2	0	0.0	0	0.0	1	3.2	0	0.0
	Acinetobacter	1	3.2	0	0.0	1	3.2	0	0.0	0	0.0
	Enterococcus	1	3.2	1	3.2	0	0.0	0	0.0	0	0.0
	Streptococcus pneumoniae	1	3.2	0	0.0	0	0.0	0	0.0	1	3.2
	Burkholderia	1	3.2	1	3.2	0	0.0	0	0.0	0	0.0
Urine culture (*n* = 26)	*Candida*	17	65.4	14	53.8	1	3.8	0	0.0	2	7.7
	Klebsiella	4	15.4	0	0.0	2	7.7	2	7.7	0	0.0
	Enterococcus	3	11.5	0	0.0	3	11.5	0	0.0	0	0.0
	Acinetobacter	1	3.8	0	0.0	0	0.0	1	3.8	0	0.0
	Stenotrophomonas	1	3.8	1	3.8	0	0.0	0	0.0	0	0.0

MDR multidrug resistant, *XDR* extended drug resistance, *PDR* pandrug resistant, *BAL* bronchoalveolar lavage

[a] One BAL culture could yield more than one organism

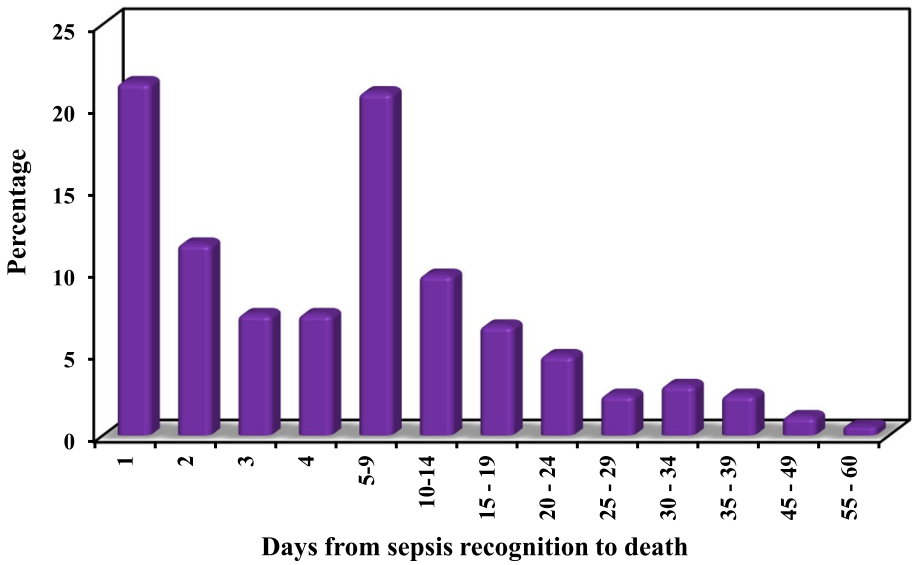

Fig. 3 Incidence of deaths stratified according to days from recognition of sepsis to death

Table 3 Comparison between subgroups (early deceased) and (late deceased)

	(Early deceased) ($n = 78$) *n* (%)	(Late deceased) ($n = 85$) *n* (%)	Test of sig.	*P*
Sex				
Male	44 (56.4%)	54 (63.5%)	$\chi^2 = 0.860$	0.354
Female	34 (43.6%)	31 (36.5%)		
Age category				
1 month–1 year	41 (52.6%)	60 (70.6%)	$\chi^2 = 5.669$	0.059
1 year–5years	21 (26.9%)	15 (17.6%)		
5 years–15 years	16 (20.5%)	10 (11.8%)		
Weight for age (Z-score)				
Under	25 (32.1%)	32 (37.6%)	$\chi^2 = 2.228$	$^{MC}p = 0.325$
Normal (−3 to +3)	53 (67.9%)	51 (60.0%)		
Over	0 (0.0%)	2 (2.4%)		
Previous hospital admission				
No	42 (53.8%)	47 (55.3%)	$\chi^2 = 0.034$	0.853
Yes	36 (46.2%)	38 (44.7%)		
Comorbid conditions				
No	52 (66.7%)	49 (57.6%)	$\chi^2 = 1.404$	0.236
Yes	26 (33.3%)	36 (42.4%)		
PIM-2 median	66.50	39.0	$U = 2194.5$*	< 0.001*
PELOD median	16.0	12.0	$U = 2414.5$*	0.003*
Primary site				
Chest	28 (35.9%)	47 (55.3%)	$\chi^2 = 6.160$*	0.013*
Cardiac	1 (1.3%)	1 (1.2%)	$\chi^2 = 0.004$	$^{FE}p = 1.000$
Urinary system	2 (2.6%)	9 (10.6%)	$\chi^2 = 4.162$*	0.041*
Gastroenterology	11 (14.1%)	12 (14.1%)	$\chi^2 = 0.0$	0.998
Blood	27 (34.6%)	14 (16.5%)	$\chi^2 = 7.113$*	0.008*
Neurology	8 (10.3%)	7 (8.2%)	$\chi^2 = 0.199$	0.656
Skin	1 (1.3%)	2 (2.4%)	$\chi^2 = 0.258$	$^{FE}p = 1.000$
Peritoneum	1 (1.3%)	2 (2.4%)	$\chi^2 = 0.258$	$^{FE}p = 1.000$
Peritoneal dialysis	1 (1.3%)	12 (14.1%)	9.131*	0.003*

PIM-2 pediatric index of mortality, *PELOD* pediatric logistic organ dysfunction

* p value statistically significant

Table 4 Comparison of laboratory findings between subgroups (early deceased) and (late deceased)

	(Early deceased) ($n = 78$)	(Late deceased) ($n = 85$)	Test of sig.	*P*
CBC				
Hemoglobin (gm/dl)	9.30	9.0	$t = 0.710$	0.479
WBCS ($\times 10^3$)	11.65	12.0	$U = 3262.5$	0.862
Platelet ($\times 10^3$)	135.0	180.0	$U = 2864.5$	0.134
Renal functions				
BUN	23.0	21.0	$U = 3193.5$	0.686
Creatinine	0.78	0.65	$U = 2828.0$	0.106
Liver functions				
ALT	44.0	53.0	$U = 3213.0$	0.735
AST	79.5	94.0	$U = 3126.5$	0.531
Albumin	2.25	2.60	$U = 2834.0$	0.110
Electrolytes				
Na	138.50	140.0	$U = 2931.5$	0.202
K	3.70	3.80	$U = 3231.5$	0.781
Ca	7.65	7.90	$U = 2972.0$	0.254
ABG				
Ph	7.24	7.30	$t = 2.800$*	0.006*
PCO2	35.50	38.0	$U = 2821.5$	0.101
PaO2	43.0	36.0	$U = 3047.0$	0.373
HCO2	14.50	20.0	$U = 2113.5$*	< 0.001*
CRP	34.0	30.0	$U = 3137.5$	0.555
Positive cultures				
Blood	13 (16.7%)	18 (21.2%)	0.537	0.464
CSF	1 (1.3%)	2 (2.4%)	0.258	$^{FE}p = 1.000$
Urine	3 (3.8%)	23 (27.1%)	16.348*	< 0.001*
Skin	2 (2.6%)	6 (7.1%)	1.761	$^{FE}p = 0.280$
BAL	14 (17.9%)	39 (45.9%)	14.464*	< 0.001*
Ascitic	0 (0.0%)	2 (2.4%)	1.858	$^{FE}p = 0.498$
Susceptibility				
Susceptible	14 (38.9%)	34 (34.0%)	0.277	0.599
Resistant	22 (61.1%)	66 (66.0%)		

CBC complete blood count,*WBCs* white blood cells, *BUN* blood urea nitrogen, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *Na* sodium, *K* potassium, *Ca* calcium, *ABG* arterial blood gases, *CRP* C-reactive protein, *CSF* cerebrospinal fluid, *BAL* bronchoalveolar lavage

* p value statistically significant

Table 5 Univariate and multivariate logistic regression analysis for the significant differences between early and late deceased cases ($n = 78$ vs. 85)

	Univariate		Multivariate	
	p	***OR* (95% *CI*)**	***p***	***OR* (95% *CI*)**
Urine positive culture	**< 0.001***	0.108 (0.031–0.376)	0.004*	0.133 (0.034–0.517)
BAL positive culture	**< 0.001***	0.258 (0.126–0.529)	0.003*	0.274 (0.115–0.653)
PIM2 score	**< 0.001***	1.020 (1.009–1.031)	0.044*	1.013 (1.000–1.027)
Primary site chest	**0.014***	0.453 (0.241–0.850)	0.715	1.173 (0.498–2.764)
Primary site urinary system	**0.060**	0.222 (0.046–1.063)		
Primary site blood	**0.009***	2.685 (1.282–5.622)	0.084	2.325 (0.892–6.063)
PH	**0.007***	0.104 (0.020–0.540)	0.528	0.431 (0.032–5.897)
HCO_3	**< 0.001***	0.926 (0.888–0.965)	0.035*	0.938 (0.884–0.995)

BAL bronchoalveolar lavage, *PIM-2* pediatric index of mortality, *HCO3* bicarbonate, *OR* odds ratio

* p value statistically significant

organisms. The study also warned that patients with bacteremia, acidosis, and high PIM-2 and PELOD scores probably will need immediate, vigorous, and intense care to save their lives. Further similar studies on wider scale including comparisons with surviving sepsis patients would be recommended to enforce these findings.

Abbreviations
PIM-2: Pediatric index of mortality-2; PELOD: Pediatric logistic organ dysfunction; PICU: Pediatric intensive care unit; RECORD: The reporting of studies conducted using observational routinely collected data; BAL: Bronchoalveolar lavage; PDR: Pandrug resistant.

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Authors' contributions
SRZ was responsible for data analysis and revision of the manuscript. DAE was responsible for protocol development and data collection. MAMA was responsible for the idea of the research, protocol development, data analysis, and writing of the manuscript. The corresponding author has full access to data and has the right to publish such data. The author(s) read and approved the final manuscript.

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Availability of data and materials
All raw data and materials are available upon request from the corresponding author via an email.

Declarations

Ethics approval and consent to participate
All procedures performed in the current study were in accordance with the 1964 Helsinki Declaration and its amendments. The university ethical committee approved the study design on October 2020 (IRB: 00012098—FWA: 00018669, serial number: 0106561).

Consent for publication
Since the study was retrospectively observational, the informed consent was waived with complete security of the confidentiality of personnel patients' data.

Competing interests
The authors declare that they have no competing interests.

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