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Predictors of Outcome in an Egyptian Pediatric Intensive Care Unit

Ramadan A. Mahmoud, Rania G. Abdelatif, Mohamed A. M. Bakheet, Montaser M. Mohamed
Department of Pediatrics, Faculty of Medicine, Sohag University, Sohag, Egypt
***Corresponding author**: Rania G. Abdelatif, **Mobile:** (+20)1102227494, **Email:** d.rania.gamal@gmail.com

ABSTRACT

Background: Pediatric intensive care unit (PICU) has improved the outcome of children in developed countries. However, little is known about the PICU outcomes in resource-limited settings.

Objective: This study was aimed to investigate outcomes predictors at an Egyptian PICU.

Patients and Methods: This prospective study was conducted at PICU of Sohag University Hospital from March 2018 to June 2020. Collected data included patients' demographics, clinical, laboratory parameters, severity of illness scores, management, and length of stay in days. Main outcomes were PICU mortality and functional status deterioration (assessed by functional status scale) on discharge and after 6 months. Outcome predictors were evaluated by multivariable logistic regression analysis.

Results: This study included 451 patients. The median (IQR) age was 7 (3 – 24) months. Sepsis was the major diagnosis (60.1%). The PICU mortality rate was 37.9%. Of survivors, 18.9% developed new disability at PICU discharge. At 6 months only 7.5% had a residual new disability. Multivariable analysis showed that presence of multiorgan dysfunction (AOR=44.9, 95%CI (15-134.3), p <0.001), acute kidney injury (AOR = 11.6, 95%CI (1.82-74.2), p = 0.009), need for prolonged intravenous fluid administration (AOR = 1.2, 95%CI (1.1-1.3), p = 0.005), vasoactive inotropic support on first day of admission(AOR = 1, 95%CI (1-1.1), p = 0.038) and antibiotic escalation (AOR = 4.6, 95%CI (1.5-14.1), p =0.007) contributed to higher mortality outcome.

Conclusion: It could be concluded that the PICU mortality was high while the rate of developing functional deterioration was relatively low. Factors related to sepsis-induced organ dysfunction and its treatment were associated with the poor outcomes.

Keywords: Pediatric intensive care unit, Mortality, Morbidity, Resource-limited settings.

INTRODUCTION

Children with a range of life-threatening diseases and those needing advanced medical and surgical care are treated in the pediatric intensive care unit (PICU) [1].

Its establishment in 1950s in the developed world was reflected in a significant reduction in child mortality**.** Pediatric intensive care services have been significantly increased in the poor countries since the start of the new century [2]**.** Nevertheless, many PICUs in the low-middle income countries (LMICs) lack organizational details [3]. Many units are still deficient in properly-trained medical staff, adequate nurse-to-patients ratios, proper tools, monitoring capacity or ancillary assistance [4]**.** The lack of published data on pediatric critical care in LMICs, notably in Egypt, makes it challenging to change practices and improve outcomes.

Additionally, the majority of research focusing on predicting mortality and morbidity outcomes in PICUs are carried out in resource-rich settings and are dependent on clinical and laboratory indicators, which are not easily accessible in resource-poor ones. Moreover, health needs in these settings frequently exceed available resources [4, 5]. According to a recent WHO report, that if treatment is improved, the leading causes of fatalities in children under the age of five in underdeveloped countries might be avoided and treated [4].

This study was aimed to delineate the baseline patient characteristics, admission pattern, major treatment protocols and the outcomes of patients admitted to the PICU at Sohag University Hospital in terms of mortality and short term morbidity. The second objective was to determine the most important predictors of these outcomes. Therefore, the study's findings would aid in creating preventative and treatment plans for the main avoidable causes of unfavorable outcomes. Furthermore, our study helps us gain insight into the current performance of our unit that can be used for future assessment. It can also serve as a benchmark to compare the current performance against the results of other PICUs, both within and outside Egypt.

PATIENTS AND METHODS

This single-center prospective observational study included a total of 451 patients who needed admission to PICU, attending at Sohag University Hospital, Sohag, Egypt. This study was conducted over a period of 28 months from March 2018 to June 2020.

Sohag University Hospital is a tertiary care hospital that serves Sohag Governorate with about 5 million populations. Our PICU was relaunched in 2014. It provides qualified health services for a large proportion of the population in Southern Egypt as it also receives referral from other Egyptian governorates, particularly Qena, Luxor, and Aswan Governorates.

Our PICU has two rooms with 10 fully-equipped beds, including hemodynamic monitors and mechanical ventilations. There are portable X-ray and ultrasound machines. An infection control policy is available.

The PICU team consists of residents, fellows, general pediatric specialists; pediatric consultants, and a handful of senior-level nurses, but there are no

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pediatric intensivists, respiratory therapists, pharmacists, physiotherapists and dieticians. Twenty-four-hour shifts are covered by two residents and one specialist. The consultants lead daily morning rounds and are on call 24 hours. The nurse-to-patient ratio ranges from 1:2 to 1:4. There are 2 nurse shifts, day and night, each lasts 12 hours. The number of patients admitted averages 350 -500 patients annually.

Inclusion Criteria and Exclusion Criteria: Patients who stayed more than 6 hours in the PICU were included in the study. We excluded children who were readmitted, those with incomplete data and those who refused to be enrolled in the study.

Data collection procedure:

The clinical and laboratory data were collected daily by the treating physicians and prospectively recorded on a standardized case report form. The collected data were double-checked by the data collector and the principal investigator. The principal investigator supervised the overall process and checked the completeness of case record forms every day.

We recorded the following data during admission:

- Demographic data, referring place, arrival method, clinical, laboratory parameters and admission diagnosis.
- Severity of illness (SOI) assessment scores (Pediatric index of mortality-2 and 3(PIM-2 and PIM-3) and Pediatric risk of mortality IV(PRISM IV):

PIM-2 and PIM-3scores were calculated from the information collected within in the first hour of admission [6]. The calculator of PIM-2 and PIM-3 and the predicted mortality is available on the website of the French Society of Anesthesia and Intensive Care http:// www.sfar.org. PRISM IV was recorded from the information collected within the first 4 hours of PICU admission [7]. The calculator of PRISM IV and the predicted mortality is available at https://www.cpccrn.org/calculators/prismiicalculator/

- The major outlines of treatment approaches utilized in respiratory support including mechanical ventilation (MV), circulatory support, antibiotics, blood products, sedation and nutrition.
- Pre- PICU, PICU and total hospital length of stay (LOS) in days.

Outcome measurement:

The outcomes were mortality and deterioration in the functional status (assessed by the functional status scale (FSS) [8]**)** at PICU discharge. All survivors were reevaluated by FSS 6 months after hospital discharge. The evaluation was performed either physically as the patients had to come for a checkup at 6 months or telephonically for those who could not come to the hospital.

Variables of the study and operational definitions:

- **Worse outcome** refers to PICU mortality or surviving with a new disability at PICU discharge.
- **New disability** is defined as there is a change "from the baseline scale" by greater than or equal to 1 category in the FSS excluding the changes to category 6, i.e., brain death [5].
- **The patient's nutritional status** is classified according to the Egyptian growth charts. The weight-for-age curve was used. Children were categorized into having good nutritional status (−2 ≤ Z score < 2 standard deviation (SD)), being under-weight (Z score <−2 SD), severely underweight (Z score <-3 SD), or overweight (Z score >2 SD) [9].
- **Comorbidity** is defined as any chronic illness that was identified before the patient was brought to the PICU, such as cerebral palsy, diabetes, renal disease, autoimmune disease, congenital abnormality, and congenital heart disease [10].
- **Sepsis, severe sepsis, and septic shock** are defined using the Goldstein 2005 criteria [11].
- **Fluid balance data:** Fluid overload percentage (FO%) is calculated as follows: FO% = (Total fluid intake in liters – Total fluid output in liters ÷ Admission weight in kilograms) ×100. FO% was calculated from the first 24h after PICU admission until discharge or until the seventh day at PICU if the length of stay exceeded 7 days [12]. In results, the cumulative fluid balance percentage that is more than 10% is referred to as a FO% >10%.
- **Multiorgan dysfunction syndrome (MODS):** refers to a physiologic disorder that might be reversed in two or more organ systems. The definition of specific organ dysfunction was based on Goldstein 2005 criteria [11].
- **Acute kidney injury (AKI)**: is characterized as a sudden (within 48 hours) decline in kidney function according to the Acute Kidney Injury Network (AKIN) categorization. The decrease is indicated by either a drop in urine production (confirmed oliguria of less than 0.5 ml/kg per hour for more than six hours) or a percentage rise in serum creatinine of greater than or equal to 50% (1.5-fold from baseline) [13].
- **The pattern of antimicrobial resistance:** The multidrug-resistant organisms **(**MDROs) are defined as non-susceptibility to at least one agent in three or more antimicrobial categories. This definition is based on the Center for disease control and prevention (CDC) definition in 2011[14].
- **Vasoactive inotropic score (VIS)** was calculated at 24 hours from admission using the following formula, [VIS=Dobutamine dose (μg/kg/min) + Dopamine dose (μg/kg/min) + 100×Epinephrine dose (μg/kg/min) +10×Milrinone dose (μg/kg/min)+10,000 Vasopressin dose

(units/kg/min) + 100 × Norepinephrine dose (μg/kg/min)] [15].

- **Antibiotic escalation:** means the escalation of antimicrobial agents from the first line to the second and/or third lines. First-line agents included ampicillin/sulbactam and third-generation cephalosporins. Second-line agents included vancomycin. Third-line agents included meropenem, linezolid, and fluoroquinolones. Escalation was performed when there was a failure of response to the first-line antimicrobial agents within 48 hours of initial use. This protocol is based on Infectious Disease Society of America (IDSA) guidelines for antimicrobial use available at https://www.idsociety.org/practice-guideline/amr-guidance/

Ethical approval:

Sohag Faculty of Medicine Research Ethics Committee approved the study. Written informed consent was obtained from guardians for inclusion in the study. The data were collected with respect to all aspects of confidentiality. The Declaration of Helsinki for human beings, which is the international medical association's code of ethics, was followed during the conduct of this study.

Statistical analysis

The IBM Statistical Package for the Social Sciences (SPSS version 26.0, IBM Crop., Armonk, NY, USA, 2019) software was used to import the data for statistical analysis. Shapiro-Wilk and Kolmogorov-Smirnov tests were applied to determine whether the distribution was normal. For continuous numerical data, medians and interquartile ranges (IQR) were utilized; for categorical data, frequencies and percentages were employed. Univariate followed by multivariate logistic regression analysis of important variables were carried out to determine the risk factors of "poor outcomes," such as mortality or new disability after PICU discharge. The factors that were clinically pertinent, statistically significant, and did not cause multicollinearity were incorporated in the multivariate model via logistic regression.

Age, baseline FSS, nutritional z score, PRISM IV pre-PICU cardiac arrest, diagnosis, pre-PICU LOS, MODS, AKI, MV, length of intravenous fluids, VIS on the first day of admission, escalation of antibiotics, sedation, blood products, and enteral feedings were among these factors. The threshold of significance was set at 0.05 as a probability level (*p*-value).

RESULTS

A total of 451 patients out of 506 admitted during the 28-month study period were included in the final analysis. Fifty-five patients were excluded due to prespecified exclusion criteria. The study flow is provided in **(Fig. 1)**.

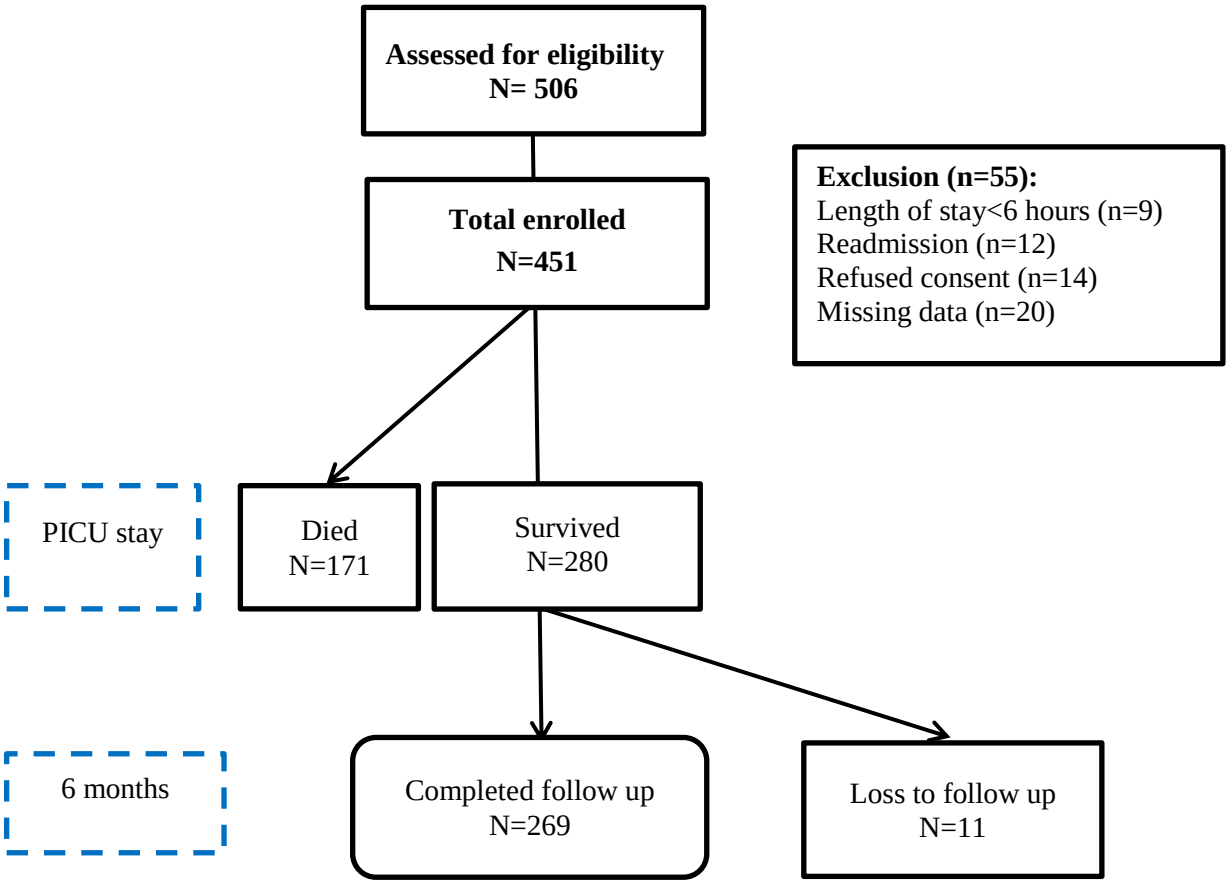

Figure (1): Flow chart describing numbers enrolled, discharged, and followed up until 6 months. PICU pediatric intensive care unit

The median age at admission was 7 months with IQR (3 – 24) months, with a male-to-female ratio of 1.2:1. The other basic characteristics of patients are outlined in **Table 1**.

Table (1): Baseline characteristics of the patients admitted to the pediatric intensive care unit in Sohag University hospital.

Variables	N = 451	(%)
Age		
< 1 year	268	66.1
1 – 5 years	95	21.1
> 5 years	58	12.8
Gender		
Male	250	55.4
Female	201	44.6
Address		
Rural	269	59.7
Urban	182	40.3
Referring place		
Private clinic/hospital	189	41.9
None	134	29.7
Other places inside the hospital	73	16.2
Governmental hospital	55	12.2
Arrival method		
Without ambulance	391	86.7
Private ambulance	39	8.6
Public ambulance	21	4.7
Nutritional Z score (weight for age)		
Normal	250	55.4
Under weight	69	15.3
Severely underweight	125	27.7
Overweight	7	1.6
Comorbidity (n=257)	257	57
Cardiac disease	66	25.7
Neurological disease	51	19.8
Endocrine disease	29	11.3
Respiratory disease	20	7.9
Renal disease	20	7.9
Genetic syndrome	19	7.4
Neonatal complications	12	2.9
Nutritional disorders	12	2.9
Hematological/immune disease	9	3.5
Disorders requiring plastic surgery	9	3.5
Others	12	2.9

Table 2 illustrates the major clinical information and basic treatment lines utilized in our PICU. In all models used to assess illness severity, predicted mortality was lower than observed mortality, as reflected by an SMR of 2.2, 4.75, and 4.5 for the PIM-2, PIM-3, and PRISM IV predictions, respectively.

The current study demonstrated that the most common disease needing PICU admission was sepsis and its severe forms either severe sepsis or septic shock as it occurred in 271 (60.1%) patients. The most common sources of infection were pneumonia in 105 (38.8%) patients, CNS infection in 93 (34.2%) patients and complicated gastroenteritis in 63 (23.2%) patients. Culture-proven sepsis was detected in only 103 (22.8%) of total patients. We observed that all the isolated bacteria were MDROs.

Table (2): Clinical information and basic treatment lines for patients admitted to the pediatric intensive care unit in Sohag University hospital.

Clinical data	**N = 451**	**(%)**
Severity of illness scores		
PIM-2 probability	6.8	1.8-18.7
PIM-3 probability	1.7	0.8-4
PRISM IV probability	3	2-7
Type of patient's case		
Medical	407	90.2
Surgical	44	9.8
Main medical diagnosis	**451**	**(%)**
Sepsis, severe sepsis, septic shock	271	60.1
Diabetic ketoacidosis	28	6.2
Dysrhythmia	19	4.2
Renal disease	19	4.2
Poisoning	11	2.4
Trauma	8	1.8
Main types of surgeries	44	
Cardiothoracic surgeries	16	36.4
Plastic surgeries	12	27.3
General pediatric surgeries	8	18.2
ENT surgeries	5	11.4
Multiorgan dysfunction syndrome	217	48.1
Fluid overload percentage > 10%	120	26.6
Acute kidney injury	107	23.7
Culture-proven sepsis	103	22.8
Therapeutic data		
Mechanical ventilation	156	34.6
CVL insertion	114	25.3
Number of fluid (NS) boluses before PICU entry		
1	82	18.2
2	52	11.5
3	137	30.4
Vasoinotropic agents	213	47.2
VIS on the first day	5	0-20
Antibiotics	445	98.7
Antibiotic escalation	271	60
Blood products	156	36.6
Sedation	72	16
Enteral nutrition	280	62.1
Length of stay, d		
Pre-PICU	0.2	0-2
PICU	4	2-8
Total hospital	8	4-14

CVL: central venous line, ENT: ear, nose and throat, d: days, NS: normal saline, PICU: pediatric intensive care unit, PIM: pediatric index of mortality, PRISM: pediatric risk of mortality, VIS: vasoactive-inotropic score.

The clinical outcomes of the PICU patients were evaluated in this study. Accordingly, among 451 patients admitted to the PICU; 280 (62.1%) patients survived, while 171 (37.9%) died at the end of the PICU stay.

FSS categories at baseline, at PICU discharge, and at 6 months follow-up are exposed in **Figure 2**. Of survivors, there were only 53 (18.9%) patients who developed a new disability at PICU discharge, categorized as mild new disability 17 (6.1%), moderate new disability 26 (9.3%), and severe new disability 10 (3.6%). At 6 months of follow-up, there was an improvement in FSS categories in 32 (11.4%) patients, while only 21(7.5%) patients had a residual new disability. Patients who had central nervous system (CNS) infection or intracranial hemorrhage during PICU admission continued to have a disability at 6 months follow-up.

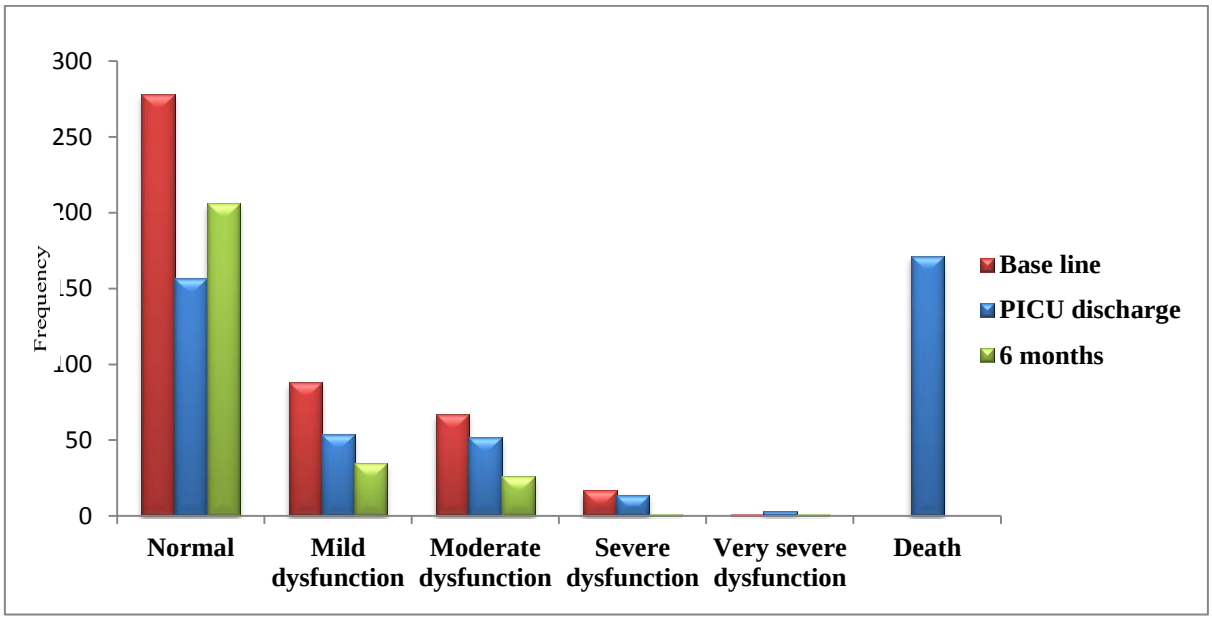

Figure (2): Functional status scale categories at baseline, pediatric intensive care unit discharge and 6 months follow up. *PICU*: pediatric intensive care unit.

Table 3 demonstrates the logistic regression analysis of factors associated with mortality in our unit. The findings of the multivariate analysis noted that the presence of MODS (AOR = 44.85, 95% CI (14.98-134.29), $p < 0.001$) and AKI (AOR = 11.6, 95%CI (1.82-74.2), $p = 0.009$) were significantly associated with increased PICU mortality. Additionally, prolonged intravenous fluid duration (AOR = 1.18, 95% CI (1.05-1.32)), VIS on the first day of admission (AOR = 1.03, 95%CI (1.00-1.06), $p = 0.038$), antibiotic escalation (AOR = 4.64, 95%CI (1.53-14.09), $p = 0.007$) were significantly linked with high mortality in our unit. In contrast, enteral feeding was significantly associated with low mortality outcomes (AOR = 0.02, 95%CI (0.01-0.06), $p < 0.001$).

Table (3): Logistic regression analysis of associated demographic, clinical, and therapeutic variables with pediatric intensive care unit mortality.

Variables	**Survivors** N= 280	**Deaths** N= 171	**COR (95% CI)**	**AOR(95%CI)**
Demographic data				
Age				0.59 (0.30-1.15)
< 1 year	156(55.7)	120(70.2)	0.34 (0.17-0.66)*	
1-5 years	73(26.1)	42(24.6)	0.86 (0.58-1.27)	
> 5 years	51(18.2)	9(5.3)	Ref.	
Gender				
Male	155(55.4)	95(55.6)	0.99 (0.68-1.46)	
Female	125(44.6)	76(44.4)		
Residence				
Rural	159(56.8)	110(64.3)	1.37 (0.93-2.03)	
Urban	121(43.2)	61(35.7)		
Admission data				
Referring place				
None	78(27.9)	56(32.7)	Ref.	
Governmental hospital	37(13.2)	18(10.5)	0.83 (0.49-1.14)	
Private clinic/hospital	105(37.5)	84(49.1)	1.08 (0.77-1.52)	
Any place in the hospital	60(21.4)	13(7.6)	0.44 (0.25-0.80)*	
Baseline FSS				1.67(0.98-2.82)
Normal	195(69.6)	83(48.5)	Ref.	
Mild dysfunction	49(17.5)	39(22.8)	1.22 (0.83-1.78)	
Moderate dysfunction	30(10.7)	37(21.6)	1.41 (0.95-2.08)*	
Severe dysfunction	6(2.1)	11(6.4)	1.88 (1-3.53)*	
Very severe dysfunction	0	1(0.6)	1.3 (0.18-9.43)	

Variables	Survivors N= 280	Deaths N= 171	COR (95% CI)	AOR(95%CI)
Nutritional z score				
Good	160(57.1)	90(52.6)	Ref.	
Underweight	44(15.7)	25(14.6)	1 (0.59-1.71)	
Severely underweight	71(23.4)	54(13.6)	1.02 (0.66-1.56)	
Overweight	5(1.8)	2(1.2)	2.56 (0.49-13.56)	
Comorbidity	158(56.4)	99(57.9)	1.07 (0.72-1.56)	
Clinical data				
Severity of illness scores				
PIM-2 probability	2.8 (1.4-8.3)	20.3 (8.6-48.6)	1.07 (1.05-1.09)	
PIM-3 probability	1.3(0.4-1.2)	4(2-12.2)	1.17 (1.1-1.24)*	
PRISM IV probability	2 (1-3)	8(4-19)	1.18 (1.13-1.23)*	1.05(0.99-1.11)
Diagnosis				1(0.82-1.22)
Sepsis, severe sepsis, septic shock.	125(44.6)	146(85.4)	42.7 (19.2-94.8)*	
Surgical operation.	40(14.3)	4(1.8)	0.17(0.07-0.38)*	
Diabetic ketoacidosis.	27(9.6)	1(0.6)	0.03 (0.01-0.25)*	
Renal disease	13(4.6)	6(3.5)	0.58 (0.22-1.5)	
Dysrhythmias.	19(6.8)	0	0.05 (0.01-0.39)*	
Poisoning	11(3.9)	0	1	
Trauma	6(2.5)	2(1.2)	1.01(0.25-4.1)	
MODS	57(20.4)	160(93.6)	56.9(28.9-111.95)*	44.85(14.98-134.29)*
FO > 10%	13(4.6)	107(62.6)	1 (5.74-14.02)*	
Acute kidney injury	12(4.3)	95(55.6)	2.73(2.02-3.71)*	11.6(1.82-74.2)*
Culture proven sepsis	60(21.4)	44(25.7)	1.23(0.48-3.17)	
Therapeutic data				
MV	46(16.4)	110(64.3)	11.9(7.51-18.98)*	1.17(0.4-3.46)
MV duration d	0(0-0)	1(0-3)	1.55(1.33-1.80)*	
CVL duration d	0 (0-0)	0 (0-3)	1.04 (0.99-1.1)	
Pre-PICU fluid resuscitation	94(33.6)	100(58.5)	2.79 (1.88-4.13)*	
Intravenous fluid duration d	2 (0.9-3)	3 (1-7)	1.19(1.12-1.27)*	1.18 (1.05-1.32)*
VIS on d1	0 (0-5)	20(20-40)	1.12 (1.1-1.14)*	1.03(1-1.06)*
Antibiotic escalation	132(47.1)	139(81.3)	4.87(3.11-7.64)*	4.64(1.53-14.09)*
Sedation	41(14.6)	94(55)	7.12(4.55-11.14)*	
Blood products	63(22.5)	102(59.6)	5.09(3.36-7.71)*	
Specific therapy	95(33.9)	20(11.7)	0.26(0.15-0.44)*	
Enteral feeding	243(86.8)	38(22.2)	0.04(0.03-0.07)*	0.02 (0.01-0.06)*
Length of stay, d				
Pre-PICU	0.2 (0-1)	0.3 (0-2)	1.10 (1.03-1.18)*	1.04(0.89-1.22)
PICU	4 (2-8)	4 (1-8)	0.98(0.95-1.01)	
Total hospital	9.3 (6-15)	5 (2-10)	0.92(0.98-0.95)*	

Data are presented as n (%) or median (interquartile range).

*Shows statistical significance at a *p*-value of < 0.05.

AOR: adjusted odds ratio, *COR*: crude odds ratio, 95%CI: 95% confidence interval, *CVL*: central venous line, *d*: days, *FO>10%:* fluid overload percentage> 10%. *MV*: mechanical ventilation, *MODS:* multiorgan dysfunction syndrome, *PICU*: pediatric intensive care unit, *PIM:* pediatric index of mortality, *PRISM*: pediatric risk of mortality, *Ref*: reference, *VIS*: vasoactive inotropic score.

Table 4 presents the univariate and multivariate logistic regression analysis of factors associated with "new disability" at PICU discharge. Intravenous fluid duration (AOR=1.3, 95%CI (1.03-1.63), $p = 0.026$) and the need for blood products transfusion (AOR=2.47, 95%CI (1.13-5.37), $p = 0.023$) remained statistically significant in multivariate analysis. However, admission due to postoperative care was independently associated with better functional outcomes (AOR =0.08, 95%CI (0.01-0.69), $p = 0.022$).

Table (4): Logistic regression analysis of associated demographic, clinical, and therapeutic variables with functional deterioration at pediatric intensive care unit discharge.

	Variables	No new disabilty(N= 227)	New disability(N=53)	COR(95% CI)	AOR(95% CI)
Demographic data	**Age**				
	< 1 year	116(51.1)	40(75.5)	2.94(1.5-5.8)*	3.02(0.71-12.92)
	1-5 years	63(27.8)	10(18.9)	0.61(0.29-1.28)	2.37(0.50-11.36)
	> 5 years	48(21.1)	3(5.7)	0.22(0.07-0.75)*	
	Gender Male	126(55.5)	29(54.7)	1.03(0.57-1.88)	
	Female	101(44.5)	24(45.3)		
	Residence Rural	128(56.4)	31(58.5)	1.09(0.59-2)	
	Urban	99(43.6)	22(41.5)		
Admission data	**Referring place**				
	None	64(28.2)	14(26.4)	Ref.	
	Governmental hospital	30(13.2)	7(13.2)	1.07(0.39-2.92)	
	Private clinic/hospital	83(36.6)	22(41.5)	1.21(0.58-2.55)	
	Any place in the hospital	50(22)	10(18.9)	0.91(0.37-2.23)	
	Baseline FSS				
	Normal	155(68.3)	40(75.5)	Ref.	
	Mild dysfunction	38(16.7)	11(20.8)	1.12(0.53-2.39)	
	Moderate dysfunction	28(12.3)	2(3.8)	0.28(0.06-1.21)	
	Severe dysfunction	6(2.6)	0	1	
	Very severe dysfunction	0	0	0	
	Nutritional z score				
	Good	127(55.9)	33(73.3)	Ref.	
	Underweight	35(15.4)	9(17)	0.99(0.43-2.26)	
	Severely underweight	63(27.8)	8(15.1)	0.49(0.21-1.12)	
	Overweight	2(0.9)	3(5.7)	5.77(0.92-35.98)	
	Comorbidity	134(59)	24(45.3)	0.57(0.31-1.05)	
	Pre-PICU fluid resuscitation	71(31.3)	23(43.4)	1.68(0.91-3.10)	
Clinical data	**Severity of illness scores**				
	PIM-2 probability	2.6(1.3-7.2)	3.8 (1.8-13)	1.02(1-1.05)*	0.98(0.95-1.02)
	PIM-3 probability	1.1(0.4-2)	1.6(0.8-2.6)	1.05(0.98-1.12)	
	PRISM IV probability	2 (1-3)	3(2-4)	1.05(1-1.1)	
	Diagnosis				
	Sepsis, severe sepsis, septic shock	87(38.3)	38(71.7)	4.08(2.12-7.85)*	1.28(0.55-2.95)
	Surgical operation.	38(16.7)	2(3.8)	0.1(0.01-0.71)*	0.08(0.01-0.69)*
	Diabetic ketoacidosis.	27(11.9)	0	1	
	Renal disease	12(5.3)	1(1.9)	0.35(0.04-2.71)	
	Dysrhythmias.	18(7.9)	1(1.9)	0.22(0.03-1.71)	
	Poisoning	11(4.8)	0	1	
	Trauma	5(2.2)	2(3.8)	1.74(0.33-9.23)	
	Others	29(12.8)	10(18.9)	1.59(0.72-2.50)	
	MODS	41(18.1)	16(30.2)	1.96(1-3.86)	
	FO > 10%	10(4.4)	3(5.7)	1.32(0.61-2.88)	
	Acute kidney injury	9(4)	3(5.7)	1.31(0.60-2.87)	
	Culture proven sepsis	43(18.9)	17(32.1)	2.02(1.04-3.93)*	0.77(0.32-1.88)
Therapeutic data	MV	31(13.7)	15(28.3)	1.55(0.68-3.53)	
	MV duration, d	0(0-0)	0(0-0)	1.03(0.68-3.53)	
	CVL duration, d	0 (0-0)	0 (0-5)	1.1(1.01-1.19)*	0.97(0.87-1.07)
	Intravenous fluid duration d	0 (0-0)	3 (2-6)	1.35(1.19-1.53)*	1.3(1.03-1.63)*
	VIS on d1	0 (0-0)	5 (0-15)	1.04(1.01-1.07)*	1.0(0.96-1.04)
	Antibiotic escalation	98(43.2)	34(64.2)	2.36(1.27-4.38)*	
	Sedation	28(12.3)	13(24.5)	2.31(1.1-4.84)*	1.91(0.75-4.88)
	Blood products	40(17.6)	23(43.4)	3.58(1.89-6.81)*	2.47(1.13-5.37)*
	Specific therapy	82(36.1)	13(24.5)	0.579(0.29-1.14)	
	Enteral feeding	195(85.9)	48(90.6)	1.58(0.58-4.28)	
Length of stay, d	Pre-PICU length of stay d	0.2 (0-1)	0.2 (0.1-2)	1.06(0.93-1.21)	
	PICU length of stay d	4 (2-7)	8(4-13)	1.09(1.04-1.14)*	0.99(0.91-1.07)
	Total hospital length of stay d	9(5-14)	15 (11-18)	1.06(1.03-1.09)*	1.01(0.96-1.07)

Data are presented as n (%) or median (interquartile range). *Shows statistical significance at a *p*-value of < 0.05. *AOR*: adjusted odds ratio, *COR*: crude odds ratio, 95%CI: 95% confidence interval, *CVL*: central venous line, *d*: days, *FO>10%:* fluid overload percentage> 10%. *MV*: mechanical ventilation, *MODS:* multiorgan dysfunction syndrome, *PICU*: pediatric intensive care unit, *PIM:* pediatric index of mortality, *PRISM*: pediatric risk of mortality, *Ref*: reference, *VIS*: vasoactive inotropic score.

DISCUSSION

Our study is one of the few prospective studies in PICUs in Egypt that reports patient characteristics, mortality, and short-term morbidity outcome. Moreover, it highlighted the most important factors associated with mortality and short-term morbidity in our unit. The mortality rate at our unit was high (37.9%). Sepsis was the major diagnosis on admission. The presence of MODS, AKI, the need for prolonged intravenous fluid administration, the need for vasoactive inotropic support and escalating antibiotics were significant and independent predictors of mortality. The results of the study can help physicians practice evidence-based medicine in a resource-limited setting. More importantly, our findings may direct healthcare planners toward more efficient resource utilization.

In this study, children under the age of five years were the major age group representing about 87% of all admissions and infants in particular represented 66%. This is in line with studies conducted in Egypt and other developing countries. An Egyptian study reported that children younger than 5 years represented about 94% of all admissions [16]. A recent study in Sri Lanka revealed that children younger than one year were the most vulnerable age group constituting about 37% [17]**.** This suggests that greater funding should be devoted to lower the in-hospital mortality of this susceptible age group.

Our study revealed that admission due to medical disorders constituted the vast majority of cases (90.2%) while a minority of admissions was due to surgical causes (9.8%). This was consistent with similar studies in resource-poor settings [18]**.** This is opposite to studies performed in resource-rich settings, in which the proportion of surgical patients ranged from 16 to 60% [7]. Sepsis was the primary diagnosis in about 60% of all admissions in our unit. Sepsis is prevalent all over the world, particularly in developing countries. In many LMICs, where a combination of environmental and socioeconomic variables plays the primary role in the spread of illnesses, the significantly greater proportion of sepsis among the pediatric population is well established [19].

The proportion of mortality in this study was 37.9%. Mortality rates varied markedly in the recent studies conducted in developing countries. It largely depends on the availability of resources and severity of illness of the admitted patients. In resource-rich settings, the mortality was as low as 6.54 % in a Saudi Arabian PICU [20]. In resource-poor settings, the mortality was as high as 54.3% in a mixed adult/adult-PICU in Malawi [4].Our mortality is comparable with mortality rate found in Egyptian units as it was 36% recorded in 2 large Egyptian PICUs [21].

In our study, 48% of patients had MODS and its presence significantly contributed to increased risk of mortality. Severe sepsis and septic shock were the presumed antecedents of MODS in our cohort. This was in harmony with several studies all over the world; particularly in LMICs were sepsis is the major PICU diagnosis. An Egyptian study reported that the incidence of MODS in patients with severe sepsis and septic shock reached up to 68.9% [22]. The MODS was reported to be the most common cause of deaths in an Ethiopian PICU [3].

In our study cohort, 107 (23.7%) patients had AKI on admission. The presence of AKI was an independent risk factor of mortality. Our results are in line with a major, international research on the epidemiology of AKI in children and young adults in ICUs, which discovered that around one-fourth of patients developed the condition during the first week of their hospitalization [23]. They stated that severe AKI was an independent risk factor of death by day28 of PICU admission after adjustment of covariates.

On the other hand, our incidence is much lower than what was reported in an Egyptian study as (56%) of the patients developed AKI in PICU [24]. However, the total number of patients in the mentioned study was 60 patients which was much fewer than ours. In addition, the disparity of the reported results might result from differences in disease severity and coexisting conditions.

The multivariate model suggested that intravenous fluid duration was significantly linked with mortality. Every one-day increase in the intravenous fluid administration was associated with an 18% increase in the odds of mortality (AOR = 1.18, 95% CI (1.05-1.32)). Multiple studies supported our findings [10, 12].

The pathogenesis of FO associated with increased mortality is not clearly understood. However, the integration of the renal hemodynamic and physiological systems might help to partially explain it. The danger of endothelial glycocalyx injury may be raised in the presence of FO and other insults, such as sepsis [10]. This results in capillary leak leading to organ hypoperfusion and might end in AKI. According to a comprehensive study, FO was linked to an increased risk of AKI and death [12].

However, a recent study found that in critically sick infants, cumulative fluid balance up to 3% in the first 7 days was not significantly related with death and morbidity [25]. The authors carefully monitored fluid balance while employing a limited fluid approach. This might explain why there is no discernible difference in mortality and morbidity and the mean cumulative fluid balance is lower.

As an indicator of shock, the quantity of vasoactive inotropic treatment required to establish and sustain organ perfusion can be utilized to forecast clinical outcomes [26]. This is what we found as there was a strong association between the VIS on the first day of admission and mortality, even after adjustment of the other variables. Each unit increase in the score was associated with a 3% increase in the odds of mortality by 3% (AOR = 1.03, 95%CI (1.00-1.06)). It

reflects the high proportion of hemodynamic instability in septic shock which was the main diagnosis in our unit. Our results were in line with a recent study revealing that VIS is independently linked to unfavorable outcomes such the risk for intubation, cardiac arrest, and hospital mortality [27].

Nearly 99% of patients received antibiotics during their stay in our unit. Most antibiotics were prescribed empirically or as prophylaxis on admission without having microbiological evidence of infection. Culture-proven sepsis was detected in only 103 (22.8%) of total patients. All the isolated bacteria were MDROs. Moreover, antibiotics were escalated in 271 (60%) patients. The critical conditions of our patients, the higher incidence of MDROs together with the limited microbiological diagnostic tools, and the delayed results were the reasons for the empirical use or escalating strategy. Antibiotic consumption in PICUs is very high especially in resource-limited settings where the use is usually empirical in most cases [28].

The most striking point is that antibiotic escalation contributed significantly to higher mortality observed in our unit as shown in the multivariate analysis (AOR= 4.64, 95% CI(1.53-14.09)). Antibiotic escalation was independently associated with 4.6 times increase in the risk of mortality. We had to escalate antibiotics in very critically ill patients with suspected life-threatening infections such as pneumonia or CNS infection with septic shock in whom the mortality was very high. However, prolonged empirical antibiotic therapy may induce abnormal colonization of the gastrointestinal tract (dysbiosis) by inhibiting or eradicating protective bacteria and favoring the proliferation of potentially pathogenic and resistant microorganisms. This is particularly evident in young infants who had the highest mortality in our unit. Previous studies described that the initial and prolonged empirical use of antibiotics in the neonatal population was a possible risk factor in the development of late sepsis, necrotizing enterocolitis, and death [29].

The current study showed that enteral feeding was significantly associated with low mortality (AOR =0.02, 95% CI (0.01-0.06)). Our results were comparable with those of a large multicenter study about the association between early enteral nutrition (in the first 4 days of admission) and mortality outcome. They concluded that early enteral nutrition was strongly associated with lower mortality rates in PICUs even after adjusting for other factors associated with mortality [30].

We found that patients with baseline functional morbidity were more likely to die in our study. Patients with functional disabilities are more liable to acute infection as a result of associated malnutrition and impaired immunity. Likewise, **Blair and colleagues** [31] detected that infections were to blame for 49% of deaths in people with cerebral palsy. In contrast to our study, **Rusmawatiningtyas and co-authors** [10] found that patients with cerebral palsy had better survival than other patients. They explained the better outcome by the fact that their patients with cerebral palsy hag good nutritional status. Moreover, they were treated aggressively with intracranial doses of antibiotics when infection was suspected.

At PICU discharge, there were 53 (11.8 %) patients developed a new disability. Our finding is slightly higher than what was observed in the TOPPIC study, a large multicenter study assessing both short and long-term outcomes of PICU patients [32]. The authors in this study reported that 9% of the admitted patients developed new disabilities at hospital discharge. On the contrary, the new overall disability in our study was much lower than reported by **Sanker *et al.*** [5] as it approached 50% of patients at PICU discharge. The mortality rate in our unit (37.9%) was higher than in the **Sanker's** study (26%) This might explain why there were fewer patients with new disabilities in our cohort.

Although children at PICU discharge had varying functional impairments, the majority improved with time. At 6 months follow-up, we detected that only 21(4.7%) patients had residual new disabilities acquired during PICU stay. Various studies have demonstrated this phenomenon as the improvement is expected during the recovery from critical illness [5, 32].

We found that the risk factors for functional deterioration at PICU discharge, after adjusting for other covariates, were the duration of intravenous fluid and the need for blood products. These factors reflected the magnitude and duration of organ dysfunction and rescue therapy associated with functional impairment at hospital discharge.

Our findings were in alignment with a recent large multicenter study conducted to evaluate the critical illness factors associated with adverse outcomes (long-term mortality and/or significant disability) among children encountering septic shock [33]. The authors noticed that among children with septic shock at month three of follow-up, physiologically plausible characteristics related to organ dysfunction from sepsis-associated critical illness and its treatment were associated with poor outcomes [30-33].

Of note, our study indicated that postoperative patients had a significantly favorable functional outcome. Surgical intervention was associated with a decline in the odds of functional deterioration at PICU discharge by 92% in the multivariate regression analysis (AOR = 0.08, 95%CI (0.01-0.69)). It is expected as most surgical patients were previously healthy. Moreover, some interventions were scheduled and performed electively without acute illness. Consistently, **Volakli *et al.*** [34] showed that postoperative and respiratory diagnoses had better functional outcomes compared to the other diagnostic categories. **Namachivayam *et al.*** [35] had opposing

results as they mentioned that about one-third of their patients requiring prolonged intensive care stay after cardiac surgery had long-term moderate to severe disabilities. However, the type of surgeries and patient characteristics are completely different. Major cardiac surgeries for complex congenital heart diseases like hypoplastic left heart syndrome were performed in their center while these surgeries were not be performed in our center.

Our study is one of the few prospective studies in PICUs in Egypt that assessed the disease pattern and different treatment modalities utilized in our unit. It also reported mortality, and short-term morbidity outcomes. Moreover, it highlighted the most important factors associated with mortality and short-term morbidity in our unit.

However, this study has some limitations. First, it is a single center study; hence, the results could not be generalized to other settings in Egypt or other countries. Another limitation is the relatively small number of the study participants. This might have reduced the power of the study to detect statistically significant associations between possible risk factors and outcomes. Furthermore, our PICU included mainly medical cases without a sufficient number of surgical cases. Thus, the outcome of surgical patients based on our study could not be compared to other studies in which surgical patients constituted the greatest proportion of the study cohort. Moreover, our PICU lacks some of the technologically-advanced equipment utilized in monitoring (e.g. invasive arterial blood pressure monitoring) or life support modalities (e.g. continuous renal replacement therapy). Therefore, our PICU outcome may change dramatically after the use of such equipment. Finally, the period of follow up of our PICU survivors were relatively shorter than in other relevant studies that evaluated morbidity outcome of PICU survivors for at least 1 year after PICU discharge. However, we chose 6 months as a sufficient period for follow up because we feared that many cases would not continue the regular follow up and would be dropped out from the study.

CONCLUSION

The mortality rate at our unit was high as in similar resource-limited units. Sepsis was the major diagnosis. The presence of MODS, AKI, the need for prolonged intravenous fluid administration, the need for vasoactive inotropic support and escalating antibiotics were significant and independent predictors of mortality. In contrast to the high mortality, the rate of developing functional deterioration at PICU discharge was relatively low and generally improved with time. This study may direct healthcare stakeholders toward better resource utilization.

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