Characteristics and Outcomes of Patients Admitted to a Pediatric Intensive Care Unit in Southwest of Iran

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Received: 18 Jan. 2022; Accepted: 20 Aug. 2022

Abstract- Data on pediatric critical care in Iran are insufficient. This study was performed to determine the outcomes and characteristics of critically ill children admitted to a pediatric intensive care unit (PICU) in Ahvaz, Iran. A retrospective study was conducted among all patients in the PICU of Abuzar Hospital for one year. Their medical documents were reviewed. A total of 400 patients were identified. The average age of patients was 29.94±39.55 months, and 53.8% of them were males. Nearly half of the cases were under age one. The most prevalent causes of PICU admission were respiratory (36.5%), neurological (18.5%), and infection-related diseases (15%). Besides, 55.7% of patients (n=223) had no history of underlying health problems. Admissions were more frequent in winter (n=125; 31.3%) and spring (n=101; 25.3%). The mortality rate and the mean hospital length of stay (LOS) were 15.5% and 10.79±6.39 days, respectively. In addition, 231 patients had an abnormal respiratory rate and a quarter of them (n=97) required ventilation support. Moreover, 377 and 82 patients were malnourished and severely underweight, respectively. A significant association was found between the mortality of patients and malnutrition, as well as having consanguineous parents (P<0.001). The death rate was significantly higher in patients with infectious disease than non-infectious, as well as in long-stay PICU patients than in short-stay patients (P<0.05). Additional studies are required to find factors contributing to the disease burden among PICU patients in Iran to develop appropriate therapeutic strategies and improve the outcomes of pediatric patients.

Acta Med Iran 2022;60(10):646-654.

Keywords: Pediatric intensive care unit (PICU); Epidemiological profile; Children; Infants; Ahvaz; Iran

Introduction

Intensive care is considered essential in the management of critically ill pediatric patients (1). The pediatric intensive care unit (PICU) is a section of the hospital where critically ill children who need advanced airway, hemodynamic, and respiratory help are commonly hospitalized to get a better outcome (2). The main goal in PICU is the management of resuscitation, stabilization, reversal of organ failure, and the critical disease process (3). The care of critically ill pediatric patients is one of the most challenging and demanding parts of the pediatrics field (1). Every year, a minimum of 200 children per 100,000 need admission to PICUs due to severe disease (4). However, pediatric patients in developing countries typically hospitalized more critically ill patients instead of surgical, lower age and socioeconomic levels compared with PICUs in developed countries (5). The main causes of death in children below the age of five in developing countries, as indicated by the World Health Organization (WHO), are curable and preventable disorders through care enhancement (6).

One of the main PICU objectives is to promote a high quality of care to obtain the greatest outcomes and enhance progress for critically ill pediatric patients (7). Over the past three decades, the clinical practice in PICU has improved dramatically (7). Insight into the pathology of fatal disorders and the technological ability to manage and cure pediatric patients has developed rapidly during this duration (7). Therefore, the goal of PICU, which is declining the death rate and morbidity, can be reached (8). Nevertheless, the availability of technology has not

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constantly succeeded in extending life expectancy and enhancing the quality of patient care (9).

In modern intensive care units (ICUs), mortality is the most prevalent evaluated outcome and an important criterion for the assessment of medical services (10). The factors affecting the mortality of patients are poor ICU performance, clinical and demographic characteristics of the patients, admission practice, nonmedical factors (organization and management), and infrastructure (7). A length of stay (LOS) longer than 13 and 30 days is considered long-stay and very long-stay hospitalization (9). Mortality and morbidity possibly are more common in patients with longer LOS and more severe disorders than those with less severe conditions and short LOS (11).

Ideal care in PICU relies on the level of proficiency and training of the health care staff, evidence-based management protocols, and the availability of resources (12). In higher-income countries, pediatric intensive care has developed, but the vast majority of developing countries do not have sufficient staff and financial resources to conduct better development in critical care (13). Prediction of disease severity and the likelihood of death is a significant component in identifying the medical prognosis of pediatric patients in PICU. In addition, a more precise prognostic evaluation can lead to more proper management, monitoring, and family counselling (7).

Understanding the epidemiological characteristics and outcomes of critically ill pediatric patients has a major role in the preparation of health policies to modify numerous factors associated with the progression of prevalent illnesses in children (12). Observational data is a good source for designing new clinical trials and protocols for disease management and reduction of mortality (12). The quality of services in PICU has the main role related to the outcome of critically ill children (13). This data enables prospective comparisons between similar healthcare units, including international and regional units, for the constant providing of necessary healthcare and enhancing the quality of patient care (12). The most frequently evaluated PICU outcomes are LOS, mortality, organ dysfunction, and functional outcome (7).

The burden of critical disease in low-and middle-income countries (LMICs) is high, and there is a lack of data to describe the outcomes of pediatric critical care in these areas (14). Epidemiological data regarding disease burden, outcomes, and practice variability are necessary to design clinical trials, recognize research priorities, develop guidelines for diagnosis and treatment, track disease-specific metrics, and allocate healthcare resources (15). Insight into the determinants and outcomes in critically ill patients enhances prognostic assessment of patients and provides attention to proper treatment and research for improvement in the long-term and short-term outcomes (16). Awareness of diverse diseases, their etiology, and their mortality rate of them could be more useful in tertiary, secondary, and primary prevention. Numerous medical centers have an objective to decrease the mortality rate in PICUs. In the absence of proper data from PICUs, some researchers tried to reliably and systematically collect this kind of information, but very few related studies were conducted in Iran. We explored the possible outcomes and characteristics of PICU patients who were admitted to a hospital in southwest Iran. This would help to determine the magnitude of each disease that requires redistribution of resources and intensive care.

Materials and Methods

This retrospective study was conducted among all patients (children and infants) who were hospitalized in the PICU of Abuzar Hospital (Ahvaz, Iran) between 2018 and 2019. The hospital is a medical training center with a well-equipped, 20 bedded PICU (with an isolation room) that admits pediatric patients under 16 years of age who require intensive care and are critically ill but recoverable, as well as postsurgical patients. The protocol of this study was approved by the medical Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (AJUMS) (IR.AJUMS.REC.1397.299).

The age range of patients was between two months to 16 years. The documents of 500 infants and children were assessed. The medical records of 100 patients were excluded. A total of 400 children (215 boys and 185 girls) with complete medical records and accurate information were included in the present study. The exclusion criteria were medical records of children who were treated in the PICU for less than 48 hours and infants younger than 2 months of age, as well as patients with incomplete documents.

A data extraction form was prepared for patients' data, including demographics (age, gender, etc.), admission time, clinical symptoms, preclinical findings, diagnosis at admission, vital signs, underlying disease (neurological, cardiovascular, metabolic diseases, etc.), nutritional status (using standard Z-scores), height, weight, mortality rate, length of stay (LOS) at the PICU, parental consanguinity, final diagnosis, mechanical ventilator use, admission outcome (death, discharge, transfer), condition at discharge, and any associated comorbidity. Parental consanguinity was categorized into

three groups: first-cousin marriages (parents were cousins), second-cousin marriages (grandparents were cousins), and not related. We classified the principal diagnoses for each hospital admission as diseases of the respiratory system (acute lower or upper respiratory tract infections and asthma, etc.), endocrine and metabolic diseases, congenital malformations, diseases of the circulatory, nervous, and digestive systems, infectious and parasitic diseases, complications of medical care, musculoskeletal disorders, injury and external causes of morbidity and mortality. Moreover, patients were divided into three categories of hypothermia ($\leq 36^0$ C), normal body temperature (36.5^0 C-37.9^0 C), and hyperthermia ($\geq 38^0$ C). The completeness and consistency of all records were crosschecked (100%) by two independent researchers and then extracted in an Excel file.

Statistical analysis

The data were analyzed using the SPSS software, version 25. The normality of the data was checked by applying the Kolmogorov-Smirnov test. The descriptive data were summarized as median (interquartile range), percentage, and mean (standard deviation). The Mann–Whitney and t-test tests were applied to analyze continuous nonparametric and parametric data, respectively. In addition, the chi-square (χ 2) test was used to analyze categorical variables. The level of significance was $P<0.05$.

Results

Medical records of 400 PICU patients were evaluated. More than half of them were males (53.8%, *n*=215), and 46.2% were females (*n*=185). Their average age was 29.94±39.55 months (ranging from two months to 16 years). The highest rate of PICU admissions (49.7%, *n*=199) and mortality (56.5 %, *n*=35) were in children under age one (Table 1).

Table 1. Association between characteristics of PICU patients and survival status (n=400)

Variables		Total (n=400) [n (%)]	Survived (n=338) [n (%)]	Died (n=62) [n (%)]	*P*
Gender	**Male**	215 (53.8)	188 (55.6)	27 (43.5)	0.53
	Female	185 (46.2)	150 (44.4)	35 (56.5)	
Age	**< 1-year-old (2-11 months)**	199 (49.8)	164(48.5)	35(56.5)	0.287
	1-5 (12- 60 months)	137 (34.2)	116 (34.3)	21 (33.8)	
	>5 (above 60 months)	64 (16)	58(17.2)	6(9.7)	
Type of Disease	**Respiratory**	146 (36.5)	128 (37.9)	18 (29)	0.184
	Non-respiratory	254 (63.5)	210 (62.1)	44 (71)	
Nutritional status (weight/age)	**Normal**	23 (5.8)	17(5)	6(9.7)	<0.001**
	Malnourished	377 (94.2)	321(95)	56 (90.3)	
Parental consanguinity	**Yes**	276 (69)	226 (66.9)	50 (80.6)	<0.001**
	No	124 (31)	112(33.1)	12 (19.4)	
Underlying disease	**Yes**	177 (44.2)	146 (43.2)	31 (50)	0.321
	No	223 (55.8)	192 (56.8)	31 (50)	
Body temperature status	**Normal**	282 (70.5)	235 (69.5)	47 (75.8)	0.321
	Hypothermia	13 (3.3)	10(3)	3 (4.8)	
	Hyperthermia	105 (26.3)	93 (27.5)	12(19.4)	

Analysis method: Chi-square test; **significant at < 0.001

Admission was more frequent in winter (n=125; 31.3%) and spring (n=101; 25.3%) in comparison with fall (n=88; 22%) and summer (n=86; 21.5%). The mean PICU stay was 10.79±6.39 days (range 2-57 days). The mean delay from the onset of symptoms before accessing referral care was 5.94 days.

The most prevalent causes of PICU admission were respiratory (bronchiolitis and pneumonia, etc.) (n=146; 36.5%), neurological (meningitis, status epilepticus (SE) and encephalopathy, etc.) (n=74; 18.5%), and infection-related diseases (*n*=60; 15.0%). Moreover, 57.75% of patients (*n*=231) had an abnormal respiratory rate, 25.25% (*n*=97) required ventilation support, and no significant association was found between underlying diseases and the mortality of patients (Table 1).

Furthermore, 94.2 of patients (*n*=377) were malnourished, and there was a significant association between malnutrition and mortality of the patients ($P<0.001$). More than half of the patients (*n*=282) had normal body temperature at the time of accessing referral care, and no significant association was observed between body temperature and survival of patients

(*P*>0.05) (Table 1).

Sixty-two patients died, and the death rate was 15.5%. The mortality rate was significantly higher in patients with infectious disease than non-infectious, as well as long-stay PICU patients than short-stay patients (*P*<0.05). The death rate was higher in infants younger than one year of age. There were no significant differences between survivors and non-survivors regarding age and gender. In addition, 55.7% of patients (*n*=223) had no history of underlying health problems, and there was no significant association between having an underlying disease and the death of patients (Table 1). The most frequent underlying medical disorders were neurological (n=46; 11.5%) and metabolic (n=37; 9.25%) diseases. Moreover, 69 % of patients (*n*=276) had consanguineous parents, and there was a significant association between parental consanguinity and the mortality of patients (*P*<0.001) (Table 1).

The anthropometric profile of the patients based on survival status and gender is summarized in Table 2. Nearly 20.5% (n=82) and 15.8 % (*n*=63) of patients were severely and moderately underweight, respectively. While 38 patients did not survive. In addition, 71 (17.8%) and 51 (12.8 %) patients were severely and moderately stunted, respectively, while 26 patients did not survive.

Table 3 shows a comparison of the median value of laboratory and clinical data between non-survivors and survivors. The median values of platelets were significantly lower in the non-survivors group compared with the survivors.

Table 2. Anthropometric profile of PICU patients based on survival status and gender (n=400)

Anthropometric profile	Survival Status				Total (n=400)	
	Survived (n=338)		Died (n=62)			
	Boys (n=188) Mean±SD	Girls (n=150) Mean±SD	Boys (n=27) Mean±SD	Girls(n=35) Mean±SD	Boys(n=215) Mean±SD (range)	Girls (n=185) Mean±SD (range)
Weight (kg)	11.18±7.64	11.52±8.54	9.01±9.20	9.56±8.61	10.90±7.86 (2.5 - 41)	11.15± 8.56 (2.5-45)
Height(cm)	81.02±25.29	82.24±27.21	73.30±23.55	75.77±25.06	80.05±25.16 (38-148)	81.02±26.87 (47-157)
WAZ among infants <2 years of age	-1.61±2.37	-1.00±2.24	-2.81±2.24	-2.22±2.07	-1.76±2.38 (-7.00-8.90)	-1.25±2.25 (-5.70-14.80)
WAZ among children ≥2 years of age	-0.84±2.63	-1.28±1.89	-1.90±4.99	-0.93±1.91	-0.99±3.03 (-11.87-9.57)	-1.23±1.88 (-6.32-2.04)
HAZ among infants <2 years of age	-1.28±3.36	-0.80±2.28	-1.91±1.81	-1.68±2.25	-1.35±3.22 (-15.90-18.80)	-0.99±2.29 (-8.40-8.80)
HAZ among children ≥2 years of age	-0.81±1.84	-0.40±1.62	0.67±4.88	-0.27±2.47	-0.61±2.48 (-6.10-13.28)	-0.38±1.74 (-5.30-4.10)
Cut off Values (17)	[n (%)]	[n (%)]	[n (%)]	[n (%)]	[n (%)]	[n (%)]
Weigh-for-age Z-Score						
Severe underweight (< –3.00 WAZ)	42(22.3)	19(12.7)	11(40.7)	10(28.6)	53(24.7)	29(15.7)
Moderate underweight (–3 to −2.01 WAZ)	23(12.2)	23(15.3)	5(18.5)	12(34.3)	28 (13)	35(18.9)
Mild underweight (−2 WAZ to -1.01 WAZ	112(59.6)	102(68)	9(33.3)	9(25.7)	121(56.3)	111(60)
Normal (±1.00 WAZ)	11(5.9)	6(4)	2(7.4)	4(11.4)	13(6)	10 (5.4)
Height for Age Z-score						
Severe stunting (<–3.00 HAZ)	38(20.2)	17(11.3)	8(29.6)	8(22.9)	46(21.4)	25 (13.5)
Moderate stunting (–3 to −2.01 HAZ)	26(13.8)	15(10)	6(22.2)	4(11.4)	32(14.9)	19(10.3)
Mild stunting (−2 HAZ to -1.01 HAZ	96(51.1)	89(59.3)	12(44.4)	18(51.4)	108 (50.2)	107 (57.8)
Normal (±1.00 HAZ)	28(14.9)	29(19.3)	1(3.7)	5(14.3)	29(13.5)	34(18.4)

HAZ: Height-for-age Z-score; WAZ: Weight-for-age Z-score; The weight was measured in kilograms

Table 3. Comparison of clinical parameters of PICU patients based on survival status (n=400)

Parameters		Total (n=400) [Median (IQR)]	Survived (n=338) [Median (IQR)]	Died (n=62) [Median (IQR)]	*P*
Laboratory Values	Hemoglobin (Hb)	10.90 (9.72-12.10)	11 (9.90-12)	10.65 (9.30-12.55)	0.608
	White Blood Cells (WBCs)	12.75 (8.62-17.27)	12.60(8.67-17.10)	13.1 (8.17-19.17)	0.588
	Red Blood Cells (RBCs)	3.80 (3.30-4.26)	3.80(3.30-4.29)	3.50 (3.10-4.22)	0.157
	Platelets	334.40 (247-448)	341.50 (256-453)	287 (169-396)	<0.001**
Vital Signs	Heart Rate (HR)	120 (105.25-133.75)	120 (105-135)	120 (109-130)	0.494
	Respiratory rate (RR)	38 (27.25-50)	37.50 (28-50)	38(25-45.25)	0.676
	Systolic Blood Pressure (SBP)	90 (85-100)	90(85-100)	90(83.75-100)	0.548
	Diastolic Blood Pressure (DBP)	60 (50-60)	60 (50-60)	55(45-60)	0.055

IQR: Interquartile range; Analysis method: Mann Whitney U test; **significant at < 0.001

Discussion

In this study, the mean age of patients in the PICU was 2.6 years, and half of them were under age one, which was similar to a study that was performed at the same PICU unit (18). The majority of the patients had no history of underlying health problems. In other studies which were conducted in Nepal (19) and China (20), patients with a comorbid disorder were at greater risk of death than those without the comorbid disorder.

The highest PICU admission was in winter and spring, reflecting the possibility of droplet infection predominance (respiratory manifestations) or can be attributed to viral lower respiratory tract infections (LRTIs). Moreover, in a study that was conducted in a similar center in Ahvaz, the admissions related to LRTIs were more frequent in winter and spring (21). However, complicated pneumonia was more prevalent in winter and autumn (22). A significant factor is the seasonal climate, which can have an impact on the transmission of the pathogen. The difference in seasonal detection possibly was associated with demographic factors and a region's climate (21).

In this study, respiratory disorders were the major causes of PICU admission, similar to other previous studies (14,18,23,24). However, the common causes of under-five PICU admission in the present study were infectious diseases, commonly pneumonia and meningitis, which were similar to those in studies carried out in Malawi, Iran, and Tanzania (14,18,25). It has been suggested that early therapy of pneumonia in the community can reduce medical costs in comparison with late treatment in the hospital (26). In recent years, it has been emphasized on pediatric neurocritical care, early disease diagnosis, and timely proper interventions to enhance the outcome (27,28). Even though the incidence of meningitis in children is declined as a result of preventive strategies and vaccination, community-acquired bacterial meningitis is related to high neurological mortality and morbidity. In this region, antibiotic therapy and adjunctive steroids are principal to improve clinical outcomes. In addition, antibiotic treatment should not be postponed in patients with a history of papilledema, immunocompromised state, central nervous system disease, and focal neurological deficits (29).

In the present study, the average LOS in PICU and the mortality rate were 10.79 days (range 2-57 days) and 15.5%, respectively. Nevertheless, in a previous retrospective study at the same PICU unit, the mean LOS and the mortality rate were 3.3 days and 16.5 %, respectively (18). In that study, extended LOS in the hospital was significantly associated with mortality. Respiratory diseases and severe infections were the most prevalent causes of mortality and admission in the PICU (18). The quality of pediatric ICU care is improving over time (30). The low mortality rate in the PICU unit of Abuzar Hospital can be due to the development of well-equipped PICU in the recent decade and the absence of trauma patients and those who need surgery (18). The platelet count was significantly lower in the non-survivors compared with survivors in the current study. In contrast, in other studies, hemoglobin level was significantly lower in the non-survivors (7). However, one of the major predictive factors of mortality was white blood cell count in another study (31).

Age was related to PICU mortality in several studies among pediatric patients, and it was indicated that age of fewer than 5 years was related to higher ICU mortality (18,32,33). It may show younger children's vulnerability

to infectious illnesses (14). In addition, it has been reported that there is an association between the outcome of pediatric patients and LOS, while there are contradictory findings regarding the impact of LOS on the outcome (34). It has been indicated that patients who need escalation of care within 24 hours of admission to the hospital have longer LOS in ICU than those who received intensive care from the beginning (35). The existence of the comorbid condition and the severity of the disease before PICU admission are also important factors in the survival of patients (1). The mortality rate in the current study was low. Significant factors that may have an impact on the survival of these patients are sufficient equipment and manpower, as well as consistent medical education on pediatric critical care for staff at the hospital (1).

In this study, 82 and 63 patients were severely and moderately underweight, respectively. Moreover, 72 and 51 patients were severely and moderately stunted, respectively. Undernutrition is common among admitted children to PICUs (36). Few studies evaluated the impact of different nutritional assessments at PICU admission in estimating clinical outcomes (37-39). A prospective study in the southern part of Brazil reported that undernutrition status at PICU admission was a predictor of 60-day mortality and led to a longer time of PICU discharge based on different anthropometric variables (37). In other studies, among critically ill children, BMI-for-age and weight-for-age were related to mortality and clinical outcomes (38,39). However, precise height and weight measurements are often not present for acute critically ill children during their stay in the hospital (40).

Previously, it has been reported that 24-53% of children in PICUs suffered from chronic or acute malnutrition at the time of hospitalization (41,42), and a considerable number of them underwent worsening nutritional status during their stay in the hospital (43). Malnourished patients in the hospital commonly come across several complications, such as infections, extended LOS in PICU, increased mortality, and possibly poor outcomes (43). The nutritional status of patients in ICU tends to worsen due to problems that hamper the supply of optimal nutrition, such as disease severity, interventions and procedures, frequent food breaks, volume restrictions, and the absence of standardized, evidence-based procedures for better nourishment (42).

Early nutritional assessment and intervention were suggested to decrease or prevent complications related to malnutrition (44). Nutritional support is crucial to enhance outcomes in critically ill children. However, well-designed large randomized controlled trials (RCTs) with the assessment of clinically relevant outcomes are rare (45,46). A lack of trials to offer evidence-based guidelines for diverse practices in PICUs globally. Recently, a systematic review summarized the available data and provided practical nutritional direction for pediatric critical care clinicians (47). Regardless of the well-established profits of nutritional support in hospitalized children, insight into disease-related malnutrition is insufficient, and it is a medical burden among numerous PICU patients in Iran (48). In a study among 69 PICU patients of a hospital in Iran, most of the hospitalized children had malnutrition or were at risk (48). There are very limited PICUs in Iran that have a dietitian among their care team members. The underestimation of the important impact of malnutrition and its outcomes by many healthcare specialists in Iran resulted in unsatisfactory awareness of malnutrition among many PICU patients (48).

The ICU serves patients who are extremely ill and undergo several complex interventions. Besides its impact on the death rate, critical care is an expensive part of the hospital budget (49). There has been considerable interest in assessing ICU outcomes in terms of resource utilization and mortality (49). Care enhancement for critically ill patients is an objective in all countries (7). The major goal of PICU is to cure critically ill children and prevent mortality by intensive monitoring. The severity of patients' conditions can be identified by tools like the Pediatric Index of Mortality (PIM) and Pediatric Risk of Mortality (PRISM) and should be a part of the medical records (50). It is required to develop models that estimate the risk of mortality in PICU for monitoring the impact of care. They help to compare different PICUs and determine the relations between disease severity, LOS, and costs (7). Improving and measuring performance is an important component of intensive care medicine. A recent systematic review described the current status of quality improvement in pediatric intensive care medicine (51). There is a lack of interventional studies to improve care in the PICU. However, some professional organizations provided guidelines for PICU admissions (52-54).

This study is one of a few studies related to PICU in Iran. It may improve the insight into the characteristics and outcomes of PICU patients in a Middle-Eastern and middle-income country. The major limitation was the retrospective nature of the study. Additionally, identifying the severity of the disease at PICU admission is required and should be evaluated in upcoming studies. Our study depicted a PICU center experience of over one year. The results of recent studies related to COVID-19

(55,56,22) among pediatric patients in the same hospital may be related to this study.

The evaluation of nutritional status, detection of malnourished patients, regular anthropometric assessment, and initiation of nutrition support are necessary for nutritional management in PICU patients. These data can be useful for policymakers and program managers at the national and regional levels to identify the most cost-effective interventions and reduce the mortality of these patients. We believe that a well-equipped PICU with well-trained staff as well as innovative and modern critical care can significantly facilitate the care of PICU patients to get the desired outcome. Further studies and interventions with multicenter involvement at PICUs could be carried out to develop appropriate therapeutic strategies and improve the outcomes of patients.

In summary, the most prevalent causes of PICU admission were respiratory and neurological diseases. The mortality rate and the mean LOS were 15.5 % and 10.79±6.39 days, respectively. Nearly half of them were under age one. In addition, a quarter of patients required ventilation support, and 377 patients were malnourished. Moreover, significant associations were found between the mortality of patients who had malnutrition, as well as having consanguineous parents. The death rate was significantly higher in patients with infectious disease than non-infectious, as well as in long-stay PICU patients than short-stay patients. Many PICU patients experience a deterioration in their nutritional status during hospitalization, and appropriate nutritional management for these patients is crucial. It is necessary to audit the admissions of children into PICUs and their outcomes, which may help to ameliorate practices and lead to better patient outcomes. The mortality rate in this study was not high but warranted additional studies and interventions related to PICUs at local and national levels.

Acknowledgments

MM and MA conceptualised the study. SHM, MM, MA, SM, SH, and SB participated in data collection and manuscript preparation. SHM analysed the data and prepared the first draft of manuscript. All authors critically reviewed the manuscript.

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