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Descriptive and Clinical Characteristics of Non-Survivors in a Tertiary Pediatric Intensive Care Unit in Turkey: 6 Years of Experience

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ABSTRACT

Objectives: To identify the characteristics of non-survivors in a pediatric intensive care unit (PICU) in Turkey.

Methods: This is a retrospective analysis of patients who died in a tertiary PICU over a 6-year period from 2016 to 2021. Data were drawn from electronic medical records and resuscitation notes. Mode of death was categorized as failed cardiopulmonary resuscitation (F-CPR) or brain death (BD).

Results: Among the 161 deaths, 136 non-survivors were included and 30.1% were younger than 1 year old. Severe pneumonia, respiratory failure and ARDS (31.6%) were the most common primary diagnoses. The most common mode of death was F-CPR (86.8%). More than half of the subjects had been admitted from pediatric emergency departments (58.1%), and more than half (53.7%) had died within 7 days in the PICU. Patients admitted from pediatric emergency departments had the lowest frequency of comorbidities ($p<0.001$). Severe pneumonia, respiratory failure and acute respiratory distress syndrome diagnoses were significantly more frequent in those who died after 7 days ($p<0.001$); whereas, septicemia, shock and multiple organ dysfunction were more common among those who died within the first day of PICU admission ($p<0.001$).

Conclusions: It may be important to note that patients referred from wards are highly likely to have comorbidities, while those referred from pediatric emergency departments may be relatively younger. Additionally, patients with septicemia, shock or multiple organ dysfunction were more likely to die earlier (within 7 days), especially compared to those with severe pneumonia, respiratory failure or acute respiratory distress.

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Introduction

Patients hospitalized in pediatric intensive care units (PICU) often have one or more organ failures that require a multidisciplinary approach in addition to close monitoring of vital signs. With advancing technology/knowledge in recent years, important developments have occurred in the care of patients,[1] which has contributed to decreasing mortality rates.[2] Despite these advances, a significant proportion of children still die in hospital due to chronic illnesses after prolonged periods of PICU admission.[3,4]

There are numerous causes of mortality in the PICU, with respiratory failure, sepsis, malignancy, cardiac/neurological diseases being reported as the most common causes.[5] Respiratory failure and neoplastic conditions are reported to be more frequent in developed countries, whereas sepsis-related diagnoses are more commonly reported in developing countries.[5-7] In addition to critical illnesses, complications that develop during follow-up also increase mortality, including mechanical ventilation or nosocomial infections.[8].

Modes of death investigated in the literature include withholding life-sustaining treatment (WLST), brain death (BD), and failed cardiopulmonary resuscitation (F-CPR). Although WLST is the most common mode of death in Europe, the USA and Australia among children in PICU,[9-12] WLST may not be considered ethical in other countries including Turkey. Different cultures, religions, laws, and professional attitudes may also be associated with different rates regarding modes of death;[1,13,14] therefore, obtaining country- and center-specific data is crucial to identify potential measures for different populations.

Published data reveal that more than half of pediatric hospital deaths involve care in the PICU.[15,16] Multiple trauma and nosocomial infections are considered as risk factors;[17,18] however, some studies show that the origin of admission is also associated with death in the PICU. For instance, transfers from wards within the same hospital have been reported to have greater mortality.[17,19]

The number of studies evaluating the features of subjects with mortality after admission to PICUs is limited, and considering the importance of country- and center-specific data, there is a need for descriptive and clinical information about critically ill children who have died in PICU in order to describe potential interventions or policies to reduce mortality. Therefore, the present study aimed to describe the demographic and clinical characteristics of non-survivors in PICU over a 6-year period and to compare various characteristics according to source of admission and length of stay in the PICU before death.

Methods

This retrospective-descriptive study examined deaths among children aged 1 month-18 years over a period of 6 years (Jan 1, 2016 to December 31, 2021) to determine the demographic and clinical characteristics of non-survivors admitted to the PICU of Goztepe Prof. Dr. Suleyman Yalcin City Hospital. Patients who were declared dead immediately after arrival to the PICU (within 1 hour) were excluded. The study protocol was approved by the Clinical Research Ethics Committee of Istanbul Medeniyet University Göztepe Training and Research Hospital (decision no: 2020/0706, decision date: 16.12.2020).

The data of died patients were collected by a retrospective review of medical records. Information collected as part of the study consisted of basic demographic data (age, sex etc.), annual number of admissions to the PICU, number of deaths in the PICU and origin of admission [in-hospital pediatric emergency room and transfer other emergency rooms (PER), transfers from wards, and transfers from operating rooms (OR)].

Clinical data included the following: mode of death, Pediatric risk of mortality (PRISM III) score, predicted death rate (%), Glasgow coma scale (GCS) (classified into GCS $\leq$ 8 or GCS > 8), time of initiation (days after admission) and duration (hours) of mechanical ventilation (MV), dependence on life support interventions prior to admission (tracheostomy, feeding tube), comorbidities and primary diagnosis at admission. The primary diagnoses were grouped according to the parent diagnostic categories in the International Classification of Disease-10 (ICD-10) classification (World Health Organization, 2005).

In addition to these, we recorded treatments/ therapeutic interventions (renal replacement therapy, therapeutic plasma exchange, Extracorporeal membrane oxygenation (ECMO), use of vasoactive drugs, blood products, inhaled nitric oxide), laboratory parameters; White blood cell and platelet counts, hemoglobin, C-reactive protein (mg/dL) and

Table 1. Demographic and clinical features of non-survivors in PICU

Parameters	**Values**
Age (months), median (min-max)	36.50 (2-216)
Age ≤1 year (n, %)	41 (30. 1%)
Male, n (%)	80 (58. 8%)
Source of admission, n (%)	
Pediatric emergency department (PER)	79 (58.1%)
Operating Room (OR)	9 (6.6%)
Medical Wards	48 (35.3%)
Received CPR before admission (n, %)	21 (15. 4%)
Modes of Death	
Failed cardiopulmonary resuscitation, n (%)	118 (86. 8%)
Brain death, n (%)	18 (13. 2%)
PRISM III Score, median (min-max)	32.00 (4-79)
PDR (%), median (min-max)	76.00% (2-100%)
GCS at admission, median (min-max)	11.00 (3-14)
GCS >8, n (%)	15 (11.0%)
GCS ≤ 8, n (%)	121 (89%)
Intubated before admission, n (%)	104 (76.5%)
Time of initiation of MV after admission (days), median (min-max)	2 (1-60)
Duration of MV (hours), median (min-max)	96 (1-2328)
***Presence of comorbidity, n (%)**	87 (64.0%)
Malignancy	29 (21.3%)
Metabolic/Endocrinological Disease	22 (16.2%)
Cardiac Disease	13 (9.6%)
Congenital anomalies/syndromes	10 (7.4%)
Rheumotological Disease	6 (4.4%)
Neurological Disease	5 (3.7%)
Immune system disease	5 (3.7%)
Kidney disease	2 (1.5%)
Gastrointestinal Disease	2 (1.5%)
Chronic respiratory disease	2 (1.5%)
Primary diagnosis	**n, (%)**
Severe Pneumonia/Respiratory Failure/ARDS	43 (31.6%)
Septicemia/Shock/MODS	34 (25.0%)
Trauma/Traumatic Brain Injury	25 (18.4%)
Central Nervous System Disease/infections	11 (8.1%)
Renal failure	10 (7.4%)
Spontaneous Intracranial Hemorrhage/Stroke	7 (5.1%)
Hepatic Failure	3 (2.2%)
Myocarditis	2 (1.5%)
Poisoning	1 (0.7%)
Treatments/Therapies	
Renal replacement therapy, n (%)	42 (30.9%)
Therapeutic Plasma Exchange, n (%)	16 (11.8%)
ECMO support, n (%)	7 (5.1%)
Vasoactive drug use, n (%)	136 (100.0%)
Need of vasoactive drug within 1 hour of PICU admission, n (%)	99 (72.8%)
Need of transfusion of blood products, n (%)	115 (84.6%)
Inhaled NO treatment, n (%)	27 (19.9%)
Laboratory parameters at admission	**Value**
WBC (*µl/blood*), median (min-max)	11.550 (100-230.000)
Hemoglobin (g/dL), median (min-max)	9.1 (2.6-18.5)
Thrombocyte (*µl*/blood), median (min-max)	172.500 (3.000-799.000)
Thrombocytopenia (n, %)	62 (45.6%)
CRP (mg/dL) , median (min-max)	0.73 (0.00-38.10)
Procalcitonin (ng/mL), median (min-max)	1.00 (0.05-72.51)
LOS at PICU (days), median (min-max)	6.5 (0.08-97)
****Patients died within 24 hours after admission (n, %) ≤ 1 day**	48 (35.3%)
Median (min-max)	0.42 (0.08-1)
>1 day- < 7 days PICU stay prior to death, n (%)	25 (18.4%)
Median(min-max)	4 (2-7)
>7 days stay prior to death, n (%)	63 (46.3%)
Median(min-max)	17 (8 -97)
Organ transplantation n (%)	4 (2.9%)
Brain death (n, %)	3 (16. 7%)

PICU: Pediatric Intensive Care Unit, CPR: Cardiopulmonary resuscitation, PRISM: Pediatric risk of mortality score PDR: Predictive death rate GCS: Glasgow coma score MV: mechanical ventilation ARDS: Acute respiratory distress syndrome MODS: Multiple organ dysfunction syndrome, ECMO: extracorporeal membrane oxygenation NO: nitric oxide RBC: Red Blood Cell, WBC: White Blood Cell, CRP: C-Reactive Protein, Thrombocytopenia :< 150.000 LOS: length of stay, *some patients had multiple comorbidities ** Patients who died within 1 hour of admission were excluded, median 10 hours (min-max: 2-24 hours).

stay (days). Time of death after PICU admission was categorized into three groups according to length of stay in the PICU: those who died within 1 day (≤1 day, excluding first 1 hour), >1 day to ≤7 days after admission, and longer length of stay (>7 days).

We defined two modes of death: failed cardiopulmonary resuscitation (F-CPR) and confirmed brain death (BD). WLST and "do not resuscitate" orders are not considered as ethical approaches in our country; therefore, this mode of death did not occur in any of the patients. The Center for Organ Transplant definitions and diagnostic criteria were used to define F-CPR (failure of resuscitation procedures and medications leading to death) and BD (permanent cessation of entire brain function).

Statistical analysis

All continuous variables included in the study were assessed with normality of distribution testing, demonstrating that the great majority of parameters were suitable for non-parametric tests. Absolute and relative frequencies (n, %) were calculated for categorical or ordinal variables. Continuous variables were expressed with median and min-max values. Pearson's chi-square test was used to assess associations between categorical variables. The Mann-Whitney *U* or Kruskal-Wallis analysis of variance were used to compare continuous variables across groups, as appropriate for group count. All statistical tests were two-tailed and $p < 0.05$ was considered to show statistical significance. The Statistical Package for Social Sciences (SPSS) version 28 was used for all data analyses.

Results

We analyzed 1797 admissions in the study period, of which 161 ended in death. The overall mortality was 8.96%. Year-wise variety of mortality rates are given in **Figure 1**. Out of the 161 deaths, 136 were included in the study according to inclusion/exclusion criteria. Patients who were declared dead immediately after arrival to the PICU (within 1 hour, n = 16) and patients with missing data (n = 9) were excluded.

Demographic and clinical characteristics

The median age of patients was 36.5 (2–216) months, and almost one-third (30.1%, n = 41) of the non-survivors were found to be ≤1 year old (**Table 1**). Patients admitted to PICU were most frequently received from the PER (58.1%, n = 79). 15.4% children were admitted after receiving CPR.

Considering the modes of death, 118 (86.8%) patients died after F-CPR, while BD was reported in 18 (13.2%) of non-survivors. Median GCS was 11.00 (3–14) and 121 (89%) children had a GCS of ≤ 8. 104 (76.5%) children were received in an intubated state before admission, and all of the remaining children required intubation during their stay. Two children were receiving nutritional support via feeding tubes and 6 were ventilator-dependent prior to admission (data not shown).

Table 2. Comparison of non-survivors according to source of admission to PICU

Source of Admission	PER (n: 79)	OR (n: 9)	Wards (n: 48)	Total (n: 136)	P value
Age, months Median (Min-max)	19 (2-103)	110 (12-200)	51 (2-216)	37 (2-216)	0.155
Age≤ 1 year (n, %)	32 (40.5%)	0 (NA)	9 (18.8%)	95 (69.9%)	**0.004****
Gender, Male n (%)	47 (59.5%)	6 (66.7%)	27 (56.3%)	80 (58.8%)	0.829
PRISM III Score Median (Min-max)	40 (4-79)	41 (18-79)	27 (5-62)	32 (4-79)	**0.004****
PDR (%) Median (Min-max)	79 (2.2-429)	78.1 (2-98.3)	61.7 (2-99.8)	76 (2-429)	0.132
Time of initiation of MV, (days), Median (Min-max)	2 (1-5)	0 (N/A)	3 (1-60)	2 (1-60)	0.145
Duration of MV (hours) Median (Min-max)	48 (1-2328)	216 (9-840)	144 (2-1800)	96 (1-2328)	0.466
Presence of comorbid disease (n,%)	38 (48.1%)	5 (55.5%)	44 (91.6%)	87 (64.0%)	**<0.001****
LOS at PICU (Days) Median (Min-max)	3 (0.08-97)	9 (0.38-35)	8 (0.08-90)	6.5 (0.08-97)	0.251
PICU LOS ≤1 day, (n, %)	35 (44.3%)	2 (22.2%)	11 (22.9%)	48 (35.3%)	0.122
PICU LOS >1 day and ≤7 days (n, %)	11 (13.9%)	2 (22.2%)	12 (25.0%)	25 (18.4%)	

Kruskal-Wallis test and Chi-square test were used for comparisons. PICU: Pediatric Intensive Care Unit, PER: Pediatric Emergency Department, OR: Operation Room, PRISM: Pediatric risk of mortality score, PDR: Predictive death rate, MV: Mechanical Ventilation, LOS: Length of Stay * p<0.05, ** p<0.01

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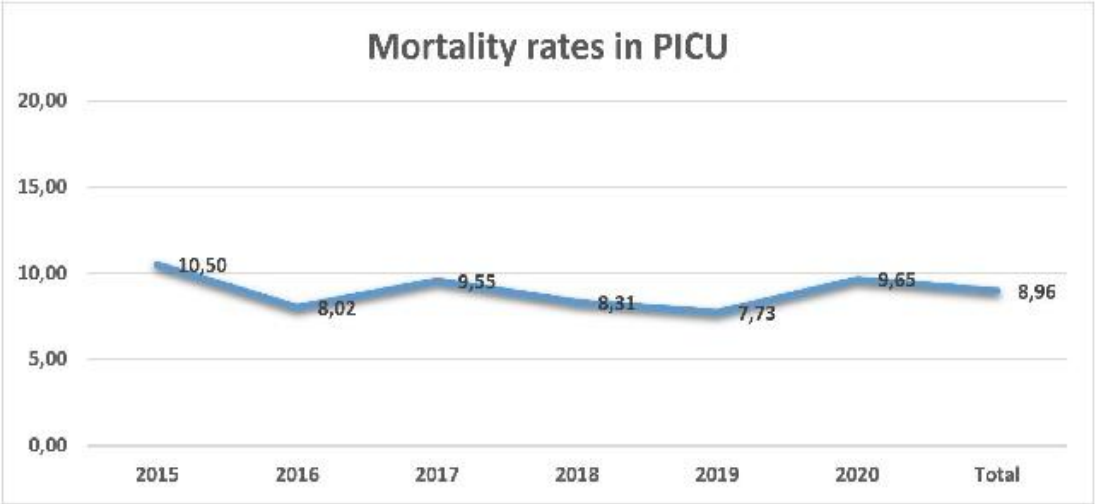

Figure 1. Year-wise distribution of mortality rates in our PICU during the study period

Comorbidities were present in 87 (64%) of the subjects. The most common comorbid disease was malignancy (21.3 %) followed by metabolic/ endocrinological disease (16.2 %). Severe pneumonia/ respiratory failure /acute respiratory distress syndrome (ARDS) was the most common primary diagnosis at admission (31.6%) followed by septicemia / shock/ multiple organ dysfunction syndrome (25%). Other common causes, treatments and laboratory parameters are presented in **Table 1**. All children had required vasoactive support to treat hemodynamic imbalance, 72.8% had received within an hour of admission.

Median length of stay prior to death was 6.5 days and 4 (2.9%) children were candidates for organ transplantation. 53.7% (n= 73) of the patients died within 7 days of their PICU admission with a median of 1 day (0.08–7). Forty-eight (35.3 %) patients died within 24 hours after admission.

Comparisons according to origin of admission

Although comparison of age as a continuous variable did not demonstrate significant differences between groups, patients admitted from PERs were more frequently in the <1-year-old age group compared to those admitted from wards ($p = 0.004$). The median PRISM III score of children received from ORs was the highest [41 (18–79)], whereas PRISM III scores of children from medical wards were the lowest [27 (5–62)] ($p = 0.004$). The majority (91.6%) of non-survivors received from medical wards had underlying comorbidity ($p < 0.001$). Although we found that children accepted from PER had shorter MV, shorter PICU stay and earlier death (≤ 7 days), statistical comparisons were non-significant (**Table 2**).

Comparisons according to length of PICU stay before death

The demographic characteristics, clinical scores and comorbidities were similar. Primary diagnoses of severe pneumonia/ respiratory failure / ARDS were significantly more common among subjects with late mortality (>7 days) ($p < 0.001$). Patients with septicemia/ shock/ MODS were found to have more frequently died within 7 days (≤1 day and 1–7 days) ($p < 0.001$). Spontaneous intracranial hemorrhage/ stroke was significantly more common among those who died between 1–7 days ($p = 0.013$) (**Table 3**).

Discussion

The rate of mortality in our PICU was 8.96% during the study period. All non-survivors were critically ill at admission with high PRISM III and PDR values. Our mortality rate was slightly higher than those reported from the United States (4%–6.2%), Canada (7.3%) and United Kingdom (5.1%).[20-22] However, it was lower than other studies in the USA (14.5%), India (16.7%), Taiwan (22%), Pakistan and Turkey (12.9-18%).[6,18,23-25] The differences in these mortality rates can be due to population age range, diagnosis and PICU environment.

The median age of non-survivors was 36.5 months, and 30.1% of patients were ≤1-year-olds, similar to studies reporting greater death frequencies among younger patients.[20-22] It has been found that infants represent a large proportion of children dying in PICU, whereas older children constitute the

majority in non-ICU settings.[26]

In the current study, majority of non-survivors (89%) had low GCS score (≤ 8) and 76.5% were intubated at admission. These results support previous findings by demonstrating that mortality risk is elevated among subjects with worse clinical scores and those who require intubation at admission.

Most non-survivors were admitted through the PER (from same or outside hospital) (58.1%), which is similar to other studies.[6,27] These patients also had the highest PRISM III score and they were generally infants. As our study did not compare non-survivors with survivors we cannot compare death rates among patients originating from different sources; however, it is possible to suggest that children received from PER should be more carefully managed. Of note, some studies have reported that referral from distant centers is risk factors for increased mortality.[17,28]

Researchers from the USA found that the likelihood of death was two-times higher in patients originating from the same hospital's wards when compared with PER.[17] The underlying hypothesis is that patients transferred from wards had severe comorbidities or acute diseases with poor response to routine treatment.[29] Furthermore, these patients are also more likely to have had prolonged hospitalization prior to PICU which may have facilitated colonization by resistant microorganisms.[29] In addition, possibility of delayed shifting of patients to PICU can cause worse prognosis. Similarly in our study majority of patients received from medical ward had underlying comorbidity (91.6 %) that supports these hypothesis although we could not evaluate LOS at medical ward prior to PICU admission.

The most common admission diagnosis was severe pneumonia / respiratory failure / ARDS followed by septicemia / shock / MODS. Since respiratory problems/infections and sepsis are the most common cause of death in most ICUs,[6,18,27] our results appear to be in line with the literature.

There is a wide variation in the patterns of mortality among critically-ill patients.[5,11,25] Various studies have identified WLST as the most frequent mode of death[22] followed by FCPR.[6,21,22] In other studies, F-CPR is reported as the most common mode of death.[1,27] Similarly we also found F-CPR as the most common mode of death of non-survivors. The differences between studies could be related to a number of factors, including relevant laws and regulations, the types/severity of cases, and the differences in PICU referral/ admittance. We had no cases that died with "do not resuscitate" order or

Table 3. Comparison of characteristics of non-survivors according to LOS at PICU

Parameters	LOS in PICU ≤ 1 day (n: 48)	LOS in PICU in >1-<7 days (n: 25)	LOS in PICU > 7 days (n: 63)	Total (n: 136)	P value
Age, months Median (min-max)	50 (2-216)	47 (2 -204)	18 (2 -207)	37 (2 -216)	0.178
Gender, Male n (%)	25 (52.1%)	16 (64.0%)	39 (61.9%)	80 (58.8%)	0.491
PRISM Score Median (min-max)	40 (7 -79)	33 (7 -79)	32 (4 -79)	32 (4 -79)	0.279
PDR (%) Median (min-max)	76.50 (2-100)	72.40 (2 -99.80)	66 (2 -99.8)	74.2 (2-100)	0.267
GCS ≤ 8, n (%)	43 (89.6%)	19 (76.0%)	59 (93.7%)	121 (89.0%)	0.058
Presence of comorbid disease (n, %)	26 (54.2%)	18 (0.72%)	43 (68.3%)	87 (64.0%)	0.202
Severe pneumonia / Respiratory Failure/ ARDS, n (%)	6 (12.5%)	4 (16.0%)	33 (52.4%)	43 (31.6%)	**<0.001****
Septicaemia / Shock / MODS, n (%)	19 (39.6%)	9 (36.0%)	6 (9.5%)	34 (25.0%)	**<0.001****
Trauma/Traumatic Brain Injury, n (%)	13 (27.1%)	4 (16.0%)	8 (12.7%)	25 (18.4%)	0.144
CNS disease, n (%)	5 (10.4%)	1 (4.0%)	5 (8.0%)	11 (8.1%)	0.484
Renal Failure, n (%)	3 (6.3%)	2 (8.0%)	5 (7.9%)	10 (7.4%)	0.581
Spontaneous Intracranial hemorrhage/stroke, n (%)	0 (0.0%)	4 (16.0%)	3 (4.8%)	7 (5.1%)	**0.013***
Hepatic Failure, n (%)	0 (0.0%)	1 (4.0%)	2 (3.2%)	3 (2.2%)	0.753
Myocarditis, n (%)	1 (2.1%)	0 (0.0%)	1 (1.6%)	2 (1.5%)	0.777
Poisoning, n (%)	1 (2.1%)	0 (0.0%)	0 (0.0%)	1 (0.7%)	0.397

Kruskal-Wallis test and Chi-square test was used for the analysis of comparison as appropriate. PICU: Pediatric Intensive Care Unit, PRISM: Pediatric risk of mortality score, PDR: Predictive death rate, GCS: Glaskow coma score, MV: Mechanical Ventilation, ARDS: Acute respiratory distress syndrome, MODS: Multiple organ dysfunction Syndrome, CNS: Central Nervous System, LOS: Length of Stay PICU: Pediatric Intensive Care Unit, CNS: Central Nervous System. * p<0.05, ** p<0.01

WLST since these approaches are not possible due to legal regulations in Turkey.

In the current study, the median length of stay between admission and death was 6.5 days. More than half (53.7 %) of the patients died in less than one week of their admission and 48 non-survivors had died within 1 day. Other studies have found that patients have a median admission length ranging from 2.1 to 3 days.[22] Many factors may influence admission length. It was suggested that this may be related to modes of death/ end of life processes.[22] In our study, no patients had WLST, and therefore, the relatively longer period before death can be attributed to intense life support to the critically ill patients.

In a previous study from the US, those who died later (>7 days) tended to have pre-existing diagnoses and were more likely to have "do not resuscitate" orders/ WLST.[5] These findings correlate with data showing that children with chronic conditions are more likely to die after a longer period of MV.[4] Although we did not find significant results that could elucidate the causes associated with later fatal outcome, children with underlying comorbidities had longer length of stay before death. Additionally, children who died later were more likely to have been diagnosed with severe pneumonia/ respiratory failure/ ARDS. In contrast, those with hemodynamic imbalance, septicemia and circulatory problems (e.g., shock) and those with multiple organ involvement were found to have died earlier. In a recent study from Turkey Botan et al. found that rates of neurological findings, hypotension, oliguria, acidosis, coagulopathy, cardiac arrest and PRISM III scores were higher in children who died early compared to those who died later. In the same study multi-organ failure and cardiac diseases were common causes in patients who died early.[30] Another recent study reported sepsis and septic shock as the common cause of early decedents.[31] So our study findings are in line with the recent literature.

The mode of death was recorded to be BD in 13.2% of our patients. The low ratio of BD in some countries may be due to under-diagnosis of BD cases.[32] Meanwhile, data from New Zealand and Australia revealed an incremental increase in the rate of BD diagnoses by 0.72% per year (10), which may indeed be associated with an increased frequency of diagnosis.

Limitations of the study

Although this study fulfils its aim in describing the characteristics of non-survivors in the PICU, there are a number of limitations that should be discussed. First, the study was based on retrospective data extracted from the database of a single center, and although PICU records are highly accurate, some discrepancies may have been present. Second, the database lacked information concerning length of stay in wards / other hospitals prior to PICU admission. The absence of autopsy-based confirmation of the cause of death was another limitation due to legal limitations. Information about children discharged from PICU and died elsewhere was not included, thus limiting other possible analyses. Geographical and legal differences in end-of-life care also limit generalizability of our findings.

Conclusion

Our study contributes to the limited literature concerning direct evaluations of children who have died within PICUs. Relatively speaking, mortality rate was slightly higher than developed countries, but lower than developing countries and other studies from Turkey. Although our patient group's demographics, clinical characteristics and modes of death appear to be similar to previous studies, it is notable that we identified a very high incidence of F-CPR-related deaths, possibly due to aggressive treatments. The clinical scores of all non-survivors included in this study demonstrated increased likelihood of poor outcomes. We also found that death in the PICU follows differing profiles based on length of stay. Earlier deaths are often associated with septicemia, shock or MODS; whereas later deaths occurred in patients with known comorbidities who were often diagnosed with severe pneumonia, respiratory failure or ARDS.

Declarations

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Conflict of Interest

None declared.

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