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Incidence and predictors of mortality among children admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, northwest Ethiopia: A prospective observational cohort study

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Abstract

Objective: To determine the incidence and predictors of mortality among children admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, northwest Ethiopia

Design: An institution based prospective observational cohort study

Participants: All pediatric age group children admitted to the intensive care unit of university of Gondar comprehensive specialized hospital from February 2018 to July 2019 were the study population.

Measurements: Data were collected using structured interviewer-administered questionnaire, physical examination and patient document review. Clinical characteristics like, SBP, pupillary light reflex, SaO_2 need of mechanical ventilator was assessed and documented within the first hour and entered into an electronic App to calculate pediatrics index mortality 2 (PIM2) score. Cox-proportional hazard model was fitted to identify factors associated with mortality.

Result: Based on the 10^{th} version of international classifications of disease (ICD) of WHO, neurologic disorders (22.7%) infectious disease (18.8%) and environmental hazards (11.8%) account for the top three diagnoses. The median observation time was 3 days with IQR of 1 to 6 days. Of the total of 313 participants, 102 (32.6%) died during the follow-up time. This gives the incidence of mortality of 6.9 deaths per 100 person day observation. Caregivers' occupation of government-employed (AHR=0.35, 95%CI: 0.14, 0.89), weekend admission (AHR=1.63, 95%CI: 1.02, 2.62), critical illness (AHR=1.79, 95%CI: 1.13, 2.85) Mechanical ventilation AHR=2.36, 95%CI: 1.39, 4.01) and PIM2 score (AHR=1.53, 95%CI: 1.36, 1.72) were predictors of mortality in the pediatric ICU.

Conclusion: Neurologic disorders were the leading causes of admission followed by infectious diseases, and environmental hazards. Rate of mortality was high and admission over weekends, caregivers' occupation, mechanical ventilation, critical illness diagnosis, and higher PIM2 scores were found to be significant and independent predictors of mortality at the PICU. This suggests that ICU medical equipment and interventions should be available up to the standard.

Strength and limitation of the study

- This study has used prospective cohort study and better statistical function like survival analysis for better estimation and description
- In resource limited setting like Ethiopia this study could help clinicians and health care planners for evidence based interventions
- Some factors like caregivers income which would have association with mortality was not assessed
- The PIM2 scoring was based on 9 out of 11 parameters as there was no Arterial blood gas analyzer in our PICU during the study period which could introduce misclassifications

Introduction

Patients treated by pediatric health professionals exhibit a broad spectrum and frequency of medical and surgical complaints ranging from mild illnesses that can be reassured to those requiring pharmacologic and device-related vital function support in the pediatric intensive care units (PICU).

The range, severity, and response for the treatment of illness is dependent on the age of the patient, biologic, socio-demographic variations, time and place. As per the report of WHO, in low-income countries like Bangladesh, Dominican Republic, Ethiopia, and Indonesia, 90% of children had severe forms of common infectious diseases, especially pneumonia, diarrhea, sepsis, malaria, and meningitis, often complicated with chronic malnutrition [1].

The PICU is a distinct organizational and geographic entity designed for monitoring and support of failing vital functions. It ideally has to be established in an area where an integral medical, surgical, anesthesiology and radiologic intervention is possible.it is a well-staffed and technologically well-equipped than other wards in the hospital. The professional to patient ratio in the ICU is higher considering the severity of illness. There are three levels of care in the PICU ranging from the most intensive Level III where patients have two or more organ failures and require pharmacologic or device interventions that are required to the mildest level I [2, 3].

Patients having one or more failing vital function with a reasonable chance of meaningful recovery and postoperative patients requiring frequent monitoring are candidates for care in the ICU Children having acute neurological deterioration, respiratory distress, cardiovascular compromise, severe infections, and accidental poisoning constitute the major admission in a pediatric intensive care unit [4].

Care in the PICU tremendously improves the success in saving patients having a potentially life-endangering illness but the proportion of survivors with disabilities increased significantly [5]. Its outcome can be measured by standardized mortality ratio (SMR), length of hospital stay, unplanned readmission rate, pain assessment, medication safety practice, and central venous catheter infection prevention practice adoption. Mortality is the most studied outcome measure though data in developing countries is scarce [2]. The mortality rate in the PICU at GUCSH is significantly higher than that of developed countries as to the monthly Mortality-morbidity report. Published data on pediatric critical care in low-income countries remains sparse yet is much needed. This paucity of data makes practice modification and outcome improvement difficult(6).

Most studies done on determinant factors of mortality in the PICU are from western countries and are dependent on clinical and laboratory indices [5]. The few studies that considered epidemiologic and socio-demographic factors are retrospective cross-sectional studies and most did not consider the severity of illness as a factor as they don't apply severity score in retrospective studies [6]. The ICU equipment and set up in developing countries is not well studied [2, 7]. Hence, this study aimed to determine the incidence and predictors of mortality among children admitted to a pediatric intensive care unit at the University of Gondar comprehensive specialized hospital. Findings from this study could help clinicians and case managers for proper management of the diseases.

Methods

Study design, period and setting

An institution-based observation prospective follow up study was conducted among children who aged 1months to 18 years and admitted to pediatric intensive care unit of the University of Gondar comprehensive specialized hospital from February 1, 2018, to July 30, 2019.

The hospital is located in Gondar city, in Amhara Region, 741 km Northwest of Addis Ababa, It is a comprehensive specialized teaching and referral hospital, with a total of 641 beds and 96 beds in the pediatrics side, where a multidisciplinary team of diverse professionals provide a range of health care services for approximately 2806 inpatient and 11986 outpatient children beyond the neonatal age coming from the northwest part of the country including the neighboring administrative regions. The major causes of pediatric admission to the hospital are pneumonia, malaria, neonatal infections, tuberculosis, heart failure, meningitis and other various types of metabolic and organ system-based emergencies according to hospital statistics. On average there are about 25 pediatric critical care admissions per month. The PICU was established in 2013 it has six beds with electronic monitors and one mechanical ventilators. The organizational detail of the PICU in this hospital is lacking. Team composition is often limited to a general pediatrician, resident, interns and a handful of senior-level nurses. Pediatric intensivists, respiratory therapists, pharmacists, and dieticians are not available.

Population and sample

The patients aged 1 month to 18 years admitted to pediatric intensive care unit and stayed more than two hours in the hospital were included in the study. Cases having incomplete data and surgical patients admitted only for recovery purposes was excluded from the study.

The sample size for this study was determined using a single population proportion of P=21%, from previous Bangladesh study [4] 5% margin of error the sample size becomes 254 and after adding 10% contingency, the sample size will be 279. A total of 395 patients were admitted to the

PICU from February 1 2018 to July 30 2019. Data was collected from 327 patients who fulfilled the inclusion criteria, whereas fourteen patients were excluded from the study due to incomplete baseline data.

Data collection procedure

Data was collected by treating physicians using standardized questionnaire after taking consent from caretakers. Clinical characteristics like, SBP, pupillary light reflex, SaO_2 need of mechanical ventilator was assessed and documented within the first hour and entered into an electronic App to calculate pediatrics index mortality 2 (PIM2) score. The PIM2 was used in our research because it doesn't need extensive laboratory investigation and it is not affected by subsequent interventions since it is scored within one hour of admission. Socio-demographic data and medical history were taken by interview. Diagnosis, laboratory indices, and courses in the hospital were filled by chart review at discharge. We used the WHO International Classification of Diseases 10th version for disease category and only the primary diagnosis was used for ICD-10 assignment in patients having multiple diagnoses. The collected data were double-checked by the data collector and the principal investigator. There were orientations and training about data collection and the objective of the study every three months and demonstration every Monday for treating physicians and data collectors. The principal investigators supervised the overall process and check completeness of questionnaires every day.

Variable of the study and operational definitions

The main dependent variable was time to death (event), whereas socio demographic characteristics (age, sex, relation with the caregiver, care giver's educational status, occupation Hospital arrival and admission related factors (duration of illness before admission, time- day and month of admission, source of admission, staff level at admission) clinical characteristics and management-

related factors (diagnosis, admission vital signs, comorbidity, nutritional status, vaccination status, interventions given in the ICU and before admission, PIM2 score, MODS, Complications) were the independent variables.

Event (death): is defined as a patient who died in the hospital during the course of treatment

Censored: discharged alive from the ICU

LOS: refers to the duration of stay in a number of days from the date of admission to the date of discharge

Short term outcome: the outcome of the patient until s/he leaves the hospital

Data processing and analysis

After the data were checked for its consistency and completeness, it was entered into EpiData version 3.1 exported to STATA version 14 for cleaning and analysis. Descriptive statistics like mean, median, proportions were carried out to summarize baseline characteristics and pattern of admission. In addition, summary statistics like life table, log-rank test and Kaplan-Meir curves computed was used to determine the incidence rate (IR) of death and to compare survival curves between the different categories of the explanatory variables.

Both bivariate and multivariate Cox proportional hazard models were used to identify the predictors. Variables with p-value < 0.2 in the bivariate analysis were entered into the multivariate proportional hazard model. Ninety-five percent confidence interval (95% CI) of hazard ratio was computed and variable having p-value < 0.05 in the multivariate Cox proportional hazards model was considered as significantly and independently associated with the dependent variable. Cox proportional hazard model fitness was checked using the Schoenfeld residuals test.

Ethical approval and consent to participate

Ethical clearance was obtained from the Institutional Ethical Review Board of College of Medicine and Health Sciences, University of Gondar (ref.no 20/12/2018). Informed verbal consent was obtained from the caretakers. The name or any other identifying information was not recorded on the questionnaire and all information is taken from the chart was kept strictly for confidential and in a safe place. The information retrieved was used only for the study purpose.

Patient and public involvement

Patients were not involved in the study

Result

Socio-demographic characteristics

A total of 313 patients out of 376 patients admitted during the eighteen-month study period were included in the final analysis. The median age at admission was 48 months with interquartile range (IQR) of 12 to 122 months, about 28.1% were infants followed by adolescents (21.4%). More than half (59.7%) were males, more than three-fourth (77.3%) were from rural areas and parents were the commonest caregivers for the majority (93%) of children. The majority of caregivers had no formal education (77.6%) and 71.2% were farmers, most patients were admitted in the spring season (38. 3%) followed by winter (27.2%) (Table 1).

Table 1: Socio-demographic characteristics of children and caregivers who were admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, from February 1/2018 to July 30/2019, northwest Ethiopia (n=313)

Characteristics	Frequency	Percentages (%)
Age in months		

≤ 12	88	28.1
13-24	29	9.3
25-60	66	21.1
61-132	63	20.1
>132	67	21.4
Sex		
Male	187	59.7
Female	126	40.3
Residence		
Urban	71	22.7
Rural	242	73.3
Caregivers		
Parents	291	93
Grand parents	8	2.6
Siblings	8	2.6
Others	6	1.9
Caregiver level of education		
No formal education	242	77.6
Primary school	32	10.2
Secondary school	17	5.4
College and above	21	6.7
Caregivers occupation		
Farmers	223	71.2
Merchants and private	32	10.2
Government employee	31	9.9
Unemployed	27	8.6
Season of admission		
Summer	63	20.1
Spring	45	14.4
Winter	85	27.2
Autumn	120	38.3

Patterns and causes of admission

More than three-fourth (77%) of patients were admitted over weekdays and about 41.5% in the night shift. Emergency room (60.4%), wards (13.1%) and referrals from other facilities (11.8%) were the commonest sources of admissions to the pediatric intensive care unit. One resident and three nurses were available during 85.6% of admissions and the median number of patients in the ICU was 4 (IQR: 3 to 5 patients). The median duration of illness before any health facility visit and admission to PICU was 3 (IQR: 1 to 7) and 6 (IQR: 3 to 13) days, respectively. The major reason for PICU admission were altered mental status (46.3%), respiratory failure (26.5%), sepsis (18.8%), shock (17.6%), seizure (14.7), DKA (7.7%) and AKI (7.7%). One patient could have more than one reason for the admission. Based on summarized 10th version of ICD of WHO, neurologic disorders (22.7%) infectious disease (18.8%) and environmental hazards (11.8%) account for the top three diagnoses (Table 2).

Table 2: patterns and causes of admission among children and caregivers who were admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, from February 1, 2018 to July 30, 2019, northwest Ethiopia (n=313)

Characteristics	**Frequency**	**Percentages (%)**
Duration of illness before any health facility visit in days		
≤3days	118	37.7
>3days	195	62.3
Duration of illness before PICU admission in days		
≤6 days	71	22.7
>6 days	242	77.7
Day of admission		
Weekday	241	77
Weekend	72	23
Time of admission		
Dayshift	183	58.5
Nightshift	130	41.5
Sources of admission		
Home	36	11.5
Other facilities	37	11.8

Emergency room	189	60.4
Wards and Operating rooms	51	16.3
Vaccination status		
Complete	203	64.9
Incomplete	110	35.1
Comorbid illness		
Yes	43	13.7
No	270	86.3
Comorbidities (n=43)		
Congenital malformations and genetic disorders	23	53.4
Cerebral palsy and epilepsy	11	25.8
Chronic kidney disease	7	16.3
HIV/AIDS	6	14
Reasons for ICU admission		
Altered mental status	145	46.3
Respiratory failure	82	26.5
Sepsis	59	18.8
Shock	55	17.6
Seizure	46	14.7
DKA	24	7
AKI	24	7
CHF	21	6.7
Hemorrhage	14	4.5
Trauma	6	1.9
Others	23	7.3
Interventions given before ICU admission (n=206)		
Intranasal oxygen	206	100
Herbal medications	23	11.2
Fluid resuscitation	164	79.6
Dextrose	35	17
Blood transfusion	30	14.6
Antibiotics	206	100

Clinical characteristics

Only 64.5% of patients were fully vaccinated, 31.9% and 16% of patients had severe and moderate acute malnutrition, respectively. Forty-three (13.7%) patients had at least one comorbid illnesses, of which congenital malformations and genetic disorders (27.9%), cerebral palsy with or without

seizure disorders (25.6%), CKD (16.3%) and HIV/AIDS (14%) are the commonest illnesses. Almost all (98.4%) of patients have vital sign derangement of which 53.4% had more than three vital sign derangements. Summarized based on the 10th version of ICD of WHO, neurologic disorders (22.7%) infectious disease (18.8%) and environmental hazards (11.8%) account for the top three diagnoses.

The baseline severity of diseases was assessed based on the PIM2 score calculated from an android medical app QxMD within one hour after admission. The minimum score was -6.46(with predicted mortality rate = 0.2%) and the maximum score was 2.47(predicted mortality rate =92.2%). The mean predicted mortality rate based on the PIM2 score was 11.14% which gave the standard mortality ratio (SMR) of 2.94. One-third of patients had critical illness diagnosis of which (41%) had sepsis, (47%) septic shock and the remaining (12%) had ARDS. About a third of patients (30.7%) had multiple organ dysfunction syndrome (MODS). Renal failure (57.3%), encephalopathy (49%), cardiac failure (46.9%), respiratory failure (41.7%) were the most common MODS (Table 3).

Table 3: clinical characteristics of children and caregivers who were admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, from February 1, 2018 to July 30, 2019, northwest Ethiopia (n=313)

Characteristics	**Frequency**	**Percentages**
ICD 10 category		
Neurology	71	26.7
Infectious disease	59	18.8
Trauma and environmental	37	11.8
Metabolic diseases	28	8.9
Congenital malformation	23	7.4
Cardiovascular disease	21	6.7

Gastrointestinal	20	6.4
Renal diseases	20	6.4
Respiratory diseases	18	5.7
Neoplasm	18	5.7
Hematology	3	1
MODS(n=96)		
Renal failure	55	57.3
Encephalopathy	47	49
Cardiac failure	45	46.3
Respiratory failure	40	41.7
Hepatic failure	26	27.1
Hematologic failure	18	18.8
Metabolic failure	10	10.4
Critical illness Dx(n=100)		
Sepsis	32	32
Severe sepsis	9	9
Septic shock	47	47
ARDS	12	12
Complications in the PICU(n=56)		
HAS	26	46.4
HAP	10	17.9
Ventilator associated complication	6	10.7
Drug reaction	4	7.1
Other complications	10	17.9
Interventions in the PICU		
Mechanical ventilation	36	11.5
Inotropes	60	19.2
Blood/ blood products	73	23.3
RRT	0	0
Antibiotics	308	98.4

Surgery	9	2.9
Vaccination status		
Complete	203	64.9
Incomplete	110	35.1
Comorbid illness		
Yes	43	13.7
No	270	86.3
Comorbidities (n=43)		
Congenital malformations and genetic disorders	23	53.4
Cerebral palsy and epilepsy	11	25.8
Chronic kidney disease	7	16.3
HIV/AIDS	6	14

Intensive care unit outcomes and the incidence of mortality

Nearly one-third of patients (32.6%) were died at discharge from the PICU. Severe sepsis/MOF (41.2%) was the leading immediate cause of death in the PICU followed by respiratory failure (23.5%) and brain herniation (21.6%). Cardiac arrest accounts for 12.7% of immediate causes of deaths and others accounted to nearly 1%.

Of the survivors 13.3% were discharged improved home, 20.9% left against medical advice (LAMA) and 62.1% were transferred towards, and 3.3% were transferred to other centers. Fifty-six patients (17.9%) had developed complications during their stay in the PICU, of which hospital-acquired sepsis (46.4%), followed by hospital-acquired pneumonia (17.9%), and mechanical ventilator-associated complications (10.7%) were the most common complications.

Study subjects were followed for different periods which gave a total of 1473 person-day observations (49.1person-months). The median observation time was 3days with IQR of 1 to 6 days. Of the total of 313 participants, 102 (32.6%) died during the follow-up time that gives the

incidence of mortality of 6.9 deaths per 100 person day observations. Of deaths reported more than half (53.9%) died within 24 hours, 13(12.7%) died between 24 and 48 hours and the remaining died after 48 hours of admission. Differences in all variables at baseline between strata were determined using the log-rank ($\chi 2$) test, and the equality of hazard was assessed for the different explanatory variables. Mechanical ventilation (P-value=0.039) and critical illness (P-value= 0.0001) (Figure 1) and (Figure 2).

Predictors of mortality in the ICU

The total follow up time in the intensive care unit were 1473 person day observation (49.1person month) with the median observation time was 3 days with IQR of 1 to 6 days. Of the total of 313 participants, 102 (32.6%) died during the follow-up time, which gives the incidence of mortality 6.9 deaths per 100 person-day observation with (95%CI: 5.34 to 8.34 deaths per 100 person-day).

From bivariable and multivariable cox proportional hazard model caregivers' occupation, day's admission to ICU, critically illnesses, PIM2 score, and mechanical ventilation were predictors of mortality in the PICU. Thus, caregivers of a child whose occupation of government employees the hazard of mortality was decreased by 65% compared to those farmer caregivers (AHR=0.35, 95%CI: 0.14, 0.89). Whereas those children who were admitted to ICU during the weekend the hazard of mortality was 1.63 times higher compared to weekdays (AHR=1.63, 95%CI: 1.02, 2.60). Those patients who had critical illness diagnosis the hazard of mortality were 1.79 times higher compared to those who had such diagnosis(AHR=95%CI:1.13, 2.85). Similarly, a unit increased in the PIM2 score of a child at admission the hazard of mortality was increased by 1.53 times keeping other variables constant (AHR=1.53,95%CI:1.36, 1.72). In addition, those patient who were on mechanical ventilation the hazard of morality were 2.36 times higher compared to those who were not MV(AHR=2.36,95%CI:1.39, 4.01) (Table 4)

Table 4: Bivariate and multivariable Cox proportional hazard model to identify predictors of mortality among patients admitted at the pediatric intensive care unit of University of Gondar comprehensive specialized hospital, northwest Ethiopia, 2019

Variables	Status		CHR (95% CI)	AHR (95% CI)
	Event	Censored		
Age				
≤12	28	60	1	1
13-24	10	19	0.98(0.47 2.12)	1.40(0.65 3.04)
25-60	26	40	1.30(0.75 2.23)	1.15(0.63 2.08)
61-132	20	43	1.07(0.60 1.90)	1.20(0.65 2.21)
>132	18	49	0.92(0.50 1.67)	1.61(0.84 3.08)
Address				
Urban	28	43	1	1
Rural	74	168	0.73(0.47,1.13)	0.63(0.37,1.05)
Caregiver' level of education				
No formal education	96	195	1	1
Primary and above	6	16	0.78(0.34, 1.80)	1.26(0.51,3.13)
Caregivers' occupation				
Farmers	72	151	1	1
Merchants and private	9	23	0.82(0.41, 1.64)	1.06(0.47,2.35)
Government employee	7	24	0.50(0.22, 1.16)	0.35(0.14,0.89)*
Unemployed	14	13	1.61(0.91,2.86)	1.11(0.55,2.24)
Day of admission				
Week day	71	170	1	1
Weekend	31	41	1.47(0.96,2.26)	1.63(1.02,2.60)**
Source of admission				
Home	9	27	1	1
Other facilities	14	23	1.66(0.72,3.86)	1.90(0.76, 4.76)
Emergency room	55	134	1.13(0.56,2.29)	1.59(0.72,3.48)
Wards and OR	24	27	2.11(0.98,4.56)	2.07(0.86,4.99)
Duration of illness before PICU admission				
<6 days	39	107	1	1
≥6 days	63	104	1.43(0.96,2.12)	0.97(0.62,1.54)
Comorbidities				
No	85	185	1	1
Yes	17	26	1.31(0.78 2.21)	0.66(0.36 1.23)
Critical illness DX				
No	53	160	1	1
Yes	49	51	2.05(1.39,3.04)	1.79(1.13, 2.85)**
Nutritional status, Z score				
Normal	45	118	1	1

MAM	15	35	1.19(0.66,2.14)	1.49(0.79,2.82)
SAM	42	58	1.67(1.09,2.55)	1.69(0.94,2.61)
PIM2 score	-3.22±1.81		1.51(1.37,1.67)	1.53(1.36,1.72)**
Mechanical ventilation				
No	79	197	1	1
Yes	23	14	1.93(1.20,3.10)	2.36(1.39,4.01)**
Complications in the PICU				
No	86	190	1	1
Yes	16	21	2.39(1.20,4.73)	1.62(0.79,3.31)
Fluid resuscitation intervention before ICU admission				
No	44	105	1	1
Yes	58	106	1.24(0.83 1.84)	0.92(0.59 1.44)

* show statistical significance at a p-value of 0.05

Discussion

Data from 313 patients admitted during 18 months of study period was analyzed , of which under-five children outnumber any other age groups ,which is supported by other studies in India and Brazil [6, 8] but different from a retrospective study done in our PICU and a general PICU in Ethiopia which shows that above fives outnumber the under-five children [9, 10], which show that admission patterns vary among different regions of the globe, settings of the same country, and even it could be different in time in the same set up. This tells us important information that PICU resource allocation and protocol preparation should be based on settings and revised timely.

Neurologic disorders accounted for nearly a quarter of the total admissions followed by infectious diseases, and environmental hazards. This finding is in line with findings in other studies where neurologic disorder was consistently among the top three causes of admission to PICU [5, 11, 12]. More than half of patients were transferred from the pediatric emergency room which is a consistent finding with studies done in Mekelle, Ethiopia [7], USA [13], Iran [14] and Pakistan [11].

The maximum possible advanced life support interventions given were mechanical ventilation and vasoactive agent infusion. Blood and blood products, antimicrobials, anticonvulsants, Mannitol, steroids, antihypertensive, and insulin were the other commonly used drugs in the PICU.

The median LOS in this study was comparable with the findings of the multi-center study in Europe and USA [15], Japan [16] and South Africa [17], but the proportion of LSP in our study is lower than findings in this studies. But the fact that the proportion of LSP is significantly lower than the findings in these studies could be due to a higher proportion of early deaths and LAMAs on the verge of death there are no life sustain interventions like ECMO in our setting. LOS is not a good indicator of PICU outcome and quality of care as it may vary based on the admission and discharge protocol of each institution. LOS might be short due to increased early mortality or improved quality of care.

This study revealed that the incidence rate of mortality was 6.92deaths (95% CI: 5.68, 8.34) per 100 person-day observations. The cumulative probability of death at the end of the first day was 18.4%, and at the end of the fourth day, the cumulative probability of death was 34.2%. On the other hand, proportion of death in our PICU was 32.6% (95% CI: 27.4,37.8) which is consistent with a retrospective cross-sectional study done in the same PICU from 2013 to 2016(30.9%)[10], Egypt (33.1%)[18], Nigeria (36.1%) [19] and Saudi Arabia (37.4%)[20]. The proportion of mortality in our PICU is lower than the finding of a retrospective cross-sectional study done in Jimma-Ethiopia (40%)[9]. The difference could be attributed to the higher proportion of trauma patients admitted in their PICU as compared to ours. The other possible reason could be that the higher proportion of LAMAs in our study might underestimate the mortality rate in our study.

However, it is higher than the mortality rates in studies done in Pakistan (14%)[11], the average of Latin American countries (13.29%) [21], India (10.58%)[14] and European countries (5%)[22].

The possible explanation the observed discrepancies might be due to a suboptimal care inadequacy of both diagnostic, interventional facilities in our PICU.

In this study, admission over weekends, admission from other facility and emergency room, presence of more than one resident at admission, presence of severe acute malnutrition, MODS, mechanical ventilation, and higher PIM2 scores were found to be significant and independent predictors of mortality at the PICU.

Children who were admitted over weekends had nearly twice an increased risk of mortality than those admitted over weekdays which is consistent with the findings of studies done in Canada, Finland, and Austria [22-24]. This might be due to failure to early recognize deteriorations at wards and other sources as a result of reduced staffing ratios. Access to diagnostic services is also limited in weekends which limits the likelihood of putting correct diagnoses, there could be unrecognized deteriorations during handover round times and delays in giving interventions. The fact that duty teams come from other wards during weekends may contribute to the increased mortality over weekends. But our finding was not supported by three American studies, and studies done in the United Kingdom and the Republic of Ireland [25, 26]. This could be explained by the better standard of care they have and 24 hours around the clock full staffing. This study also reviewed that caregiver occupation of government-employed associated with lower risk mortality compared to caregivers of peasants. This could be explained by differences in health-seeking behavior and early identification and notice of dangers conditions of their children.

The child whose critical illness diagnosis had increased risk of mortality compared to those who had no such history. This could be due to the fact that critical illnesses are associated with an increased probability of death.

Amongst many baseline disease severity assessment tools, we used PIM2 as it doesn't need extensive laboratory investigation and it is not affected by subsequent interventions since it is scored within one hour of admission. Accordingly, A unit increment in PIM2 score had doubled the hazard of mortality and discriminated well between survival and death at our PICU with Area under the curve AUROC of 76.4%. Which shows the score is sensitive in detecting morality. This scoring system is also validated and applicable in many PICUs across the world [27-31]. As to our finding the high observed mortality rate than predicted mortality by PIM2 score cannot be attributed to the severity of illness at admission. It indicates the poor quality of intensive care in our setting. PIM2 Score was found to be nondiscriminatory for the risk of death in studies done in Addis Ababa and India [29, 32].

Patients who were mechanically ventilated had more than two times increased hazard of death. This is in line with the findings of studies[33, 34]. This might be due to the fact that patients who need mechanical ventilation are in advanced stages of the disease. The other explanation for this could be ventilator-associated complications.

Strength and limitations of the study

This study has used prospective cohort study and better statistical function like survival analysis for better estimation and description were strengths of the study. However, the income of caregivers was not assessed because it was difficult to ascertain because the majority of admissions were from a rural area and they usually underreport the assets they have. PIM2 scoring was based on 9 out of 11 parameters as there was no Arterial blood gas analyzer in our PICU during the study period. Availability of medical equipment and PICU quality of care and their impact on survival was not fully assessed using standard parameters. Pediatric critical care is not just about saving

lives, so the degree of physiologic function retained at discharge should have been assessed using a standard checklist for all of the patients discharged.

Conclusion

Neurologic disorders were the leading causes of admission followed by infectious diseases, and environmental hazards. Rate of mortality was high and admission over weekends, caregivers' occupation, mechanical ventilation, critical illness diagnosis, and higher PIM2 scores were found to be significant and independent predictors of mortality at the PICU. This suggests that ICU medical equipment, diagnostics, and interventions should be available up to the standard. Intensivist and full staffing around the clock has to be available in the PICU.

List of abbreviations

AUROC: Area Under the Receiver Operating Curve, AHR: Adjusted Hazard Ratio, AKI: Acute Kidney Injury, CI: Confidence Intervals, CHR: Crude Hazard Ratio, HAS: Hospital Acquired Sepsis, HAP: Hospital Acquired Pneumonia, ICD: International Classifications of Disease, ICU: Intensive Care Unit, IQR: Interquartile Range, IR: Incidence Rate, LAMA: Left Against Medical Advice, LOS: Length of Hospital stay, MAM: Moderate Acute Malnutrition, MODS: Multiple Organ Dysfunction Syndrome, MV: Mechanical Ventilation, PI: Principal Investigator, PICU: Pediatric Intensive Care Unit, PIM: Pediatrics Index Mortality, SAM: Sever Acute Malnutrition, OR: Operation Room, USA: United States of America, WHO, World Health Organization

Declaration

stcox i.ADRESS i.criticalilnnes i.DURICUIL_rec i.sourceadmission i.occupation_recoded i.CAREGIVErecoded i.age_categorized PIM2SCOR i.COMPLICA i.COMORBID i.FLUID i.DAYOFADM i.MV i.ZSCORE

Ethics approval and consent to participate

Ethical clearance was obtained from the Institutional Ethical Review Board of College of Medicine and Health Sciences, University of Gondar (ref.no 20/12/2018). Assent and informed written consent was obtained from the care takers. The name or any other identifying information was not recorded on the questionnaire and all information taken from the chart was kept strictly for confidential and in a safe place. The information retrieved was used only for the study purpose.

Consent for publication

Not applicable

Availability of data and material

Data is available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The study was funded by University of Gondar, Ethiopia. The funder has no role in study design, data collection and analysis, interpretation of data, decision to publish, or preparation of the manuscript.

Authors' contributions

NWT, ATA, and KST participated to design the study, performed data analysis, visualization, validation the whole work and prepared the manuscript. NWT took part in funding acquisition, data collection, supervision and software and other resources. All authors read and approved the final manuscript.

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Figures and legends

Figure 1: Kaplan-Meier failure (death) estimates curves by days of admission among children treated in the pediatric intensive care unit of University of Gondar comprehensive specialized hospital from February 1/2018 to July 30/2019

Figure 2: Kaplan-Meier failure (death) estimates curves by children critical illness admitted to pediatric intensive care unit of University of Gondar comprehensive specialized hospital from February 1/2018 to July 30/2019

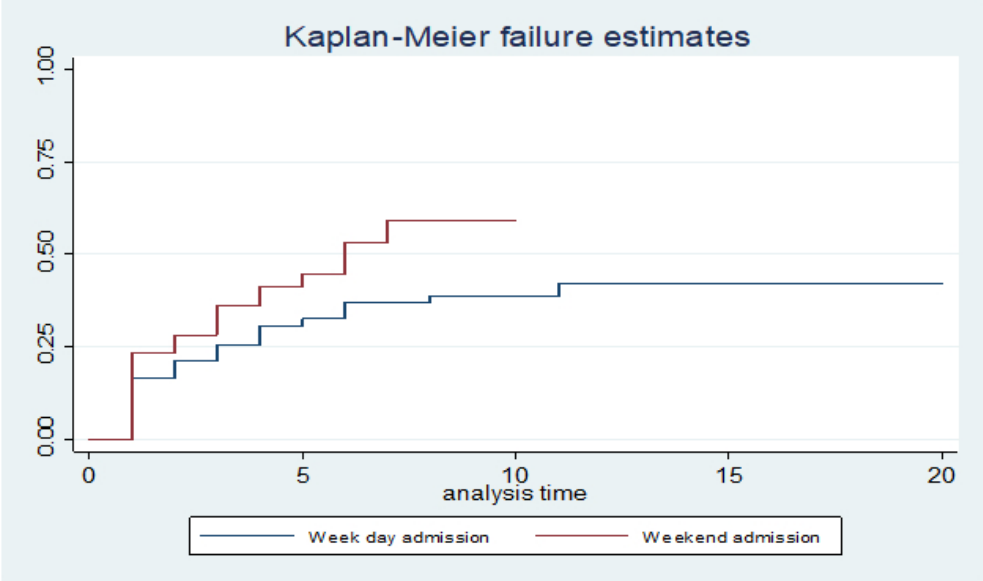

Figure 1: Kaplan-Meier failure (death) estimates curves by days of admission among children treated in the pediatric intensive care unit of University of Gondar comprehensive specialized hospital from February 1/2018 to July 30/2019

168x100mm (96 x 96 DPI)

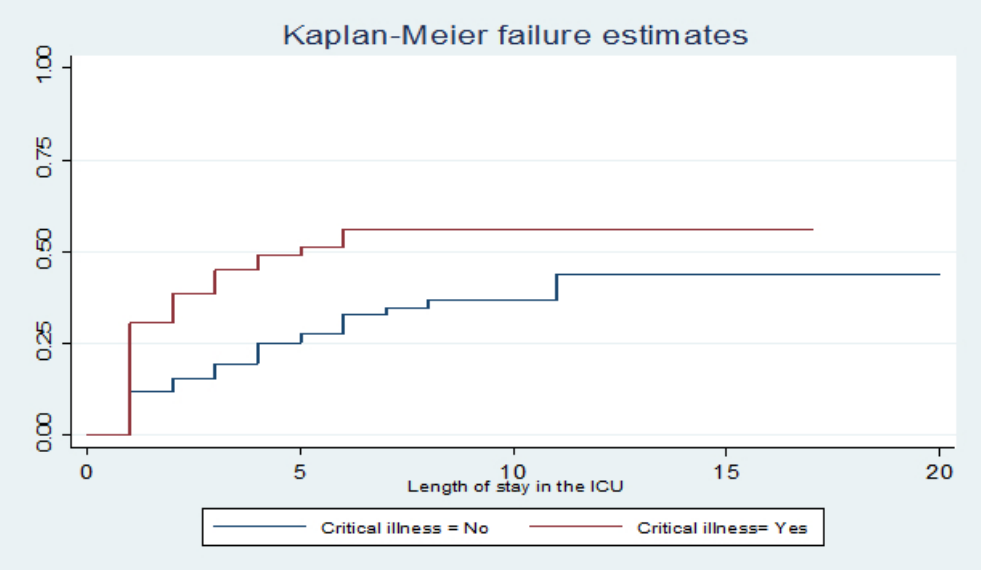

Figure 2: Kaplan-Meier failure (death) estimates curves by children critical illness admitted to pediatric intensive care unit of University of Gondar comprehensive specialized hospital from February 1/2018 to July 30/2019

164x96mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract ***The title describes the study design as* "Incidence and predictors of mortality among children admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, northwest Ethiopia: A prospective observational cohort study". *Page 1***
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ***The abstract describes the method used and Main findings****. page 2, line 19-31*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ***The background and rationale are described in the Background, paragraphs 1, 2, 3, 4, 5 and 6. Page 4-5, Line 64-102***
Objectives	3	State specific objectives, including any pre specified hypotheses ***The specific aims of the study are stated in the Background, paragraphs 6, page 5 ,line 94-104***
Methods		
Study design	4	Present key elements of study design early in the paper ***The study design is discussed in paragraphs 1 of the Methods section, page 6, line 105-107***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ***The institutional setting is described in paragraphs 2 line 108-120 of the Methods section.*** ***Study locations are described in paragraph 1 and 2 of the Methods section; and study timing is discussed in paragraphs of the Methods section. Participant recruitment is mentioned in in population and sample section*****. Page 6**
Participants	6	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants ***Selection of the sample is discussed in paragraph 1 and 2 line 121-130, of population and sample subsection of the Methods section. page 6-7***
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

		Outcomes are discussed in the Outcomes subsection (paragraphs 3 of the Methods section). Data was collected by treating physicians using standardized questionnaire after taking consent from caretakers. Clinical characteristics like, SBP, pupillary light reflex, SaO_2 need of mechanical ventilator was assessed and documented within the first hour and entered into an electronic App to calculate pediatrics index mortality 2 (PIM2) score. **Mentioned in the method section of 131-158, page 7-8**
	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group ***Measurement of the outcomes are discussed in the data collection and measurement of variables subsection. Page 8***
Bias	9	Describe any efforts to address potential sources of bias ***Mentioned in the method section of v*ariable of the study and operational definitions *Page 7-8***
Study size	10	Explain how the study size was arrived at ***Sample size determination was discussed at method, population and sample section. Page 6***
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ***Use of variables is discussed in the data management and analysis subsection. Page 8***
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding ***Statistical methods are discussed in the data management and analysis subsection. Page 8 line 160-178***
		(*b*) Describe any methods used to examine subgroups and interactions Described in in the data management and analysis subsection. ***Results are analysed by socio-demographic and personal attributes like age place of residence .***
		(*c*) Explain how missing data were addressed ***None***
		(*e*) Describe any sensitivity analyses ***None***

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ***At paragraph 1 of result section, page 9***
		(b) Give reasons for non-participation at each stage ***None***
		(c) Consider use of a flow diagram ***None***
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Provider characteristics are presented in Table 1, Table 2, and Table 3.
		(b) Indicate number of participants with missing data for each variable of interest ***None***
Outcome data	15*	*Cross-sectional study*—Report numbers of outcome events or summary measures Both numbers and percentages/proportions are reported throughout the ***Results Section. Page 15-16 line 230-248***
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ***Adjusted results are presented for all outcomes. Page 16-17, table 4***
		(*b*) Report category boundaries when continuous variables were categorized ***Not applicable***
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period ***Not applicable***.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ***None***
Discussion		
Key results	18	Summarise key results with reference to study objectives ***Results are summarized in paragraphs, 1, and 2 of the Discussion section***. Page 18, line 271-283
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ***Strength and limitations are discussed in paragraphs 21, line 344-352***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ***Discussed in discussion and conclusion sub section. 18-22***
Generalizability	21	***Discuss the generalizability (external validity) of the study results*** ***The representativeness of the sample is discussed in the final paragraph of the limitations subsection.***

Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ***Not applicable***

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Incidence and predictors of mortality among children admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, northwest Ethiopia: A prospective observational cohort study

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Abstract

Objective: To determine the incidence and predictors of mortality among children admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, northwest Ethiopia

Design: An institution-based prospective observational cohort study

Participants: A total of 313 children admitted to the intensive care unit of the University of Gondar Comprehensive specialized hospital during one year period were the study population.

Measurements: Data were collected using standard case record form, physical examination, and patient document review. Clinical characteristics like systolic blood pressure, pupillary light reflex, oxygen saturation, and need for mechanical ventilation was assessed and documented within the first hour of admission and entered into an electronic application to calculate the pediatrics index of mortality 2 (PIM 2) score. We fitted the cox-proportional hazard model to identify factors associated with mortality.

Result: The median age at admission was 48 months with interquartile range (IQR: 12 to 122), 28.1% were infants followed by adolescents (21.4%), and 59.7% were males. The median observation time was 3days with (IQR: 1 to 6 days). One hundred two (32.6%) children died during the follow-up time, and the incidence of mortality was 6.9 deaths per 100 person-day observation. Weekend admission [Adjusted Hazard Ratio (AHR) =1.63, 95%CI: 1.02, 2.62], critical illness (AHR=1.79, 95%CI: 1.13, 2.85) ,need of mechanical ventilation (AHR=2.36, 95%CI: 1.39, 4.01) and PIM2 score (AHR=1.53, 95%CI: 1.36, 1.72) were predictors of mortality.

Conclusion: Rate of mortality in the ICU was high, admission over weekends, need for mechanical ventilation, critical illness diagnoses, and higher PIM 2 scores were significant and independent predictors of mortality at the PICU.

Strength and limitation of the study

- This study is a prospective cohort study and has used better statistical functions (survival analysis) for better estimation and description.
- In a resource-limited setting like Ethiopia, this study could help clinicians and health care planners practice evidence-based medicine.
- The PIM2 scoring was based on 9 out of 11 parameters as there was no arterial blood gas analyzer in our PICU during the study period which could introduce misclassifications

Introduction

Patients having one or more failing vital function with a reasonable chance of recovery and postoperative patients requiring frequent monitoring are candidates for care in the intensive care unit (ICU). Children with acute neurological deterioration, respiratory distress, cardiovascular compromise, severe infections, and accidental poisoning constitute primary admissions in pediatric intensive care units [1].

Intensive care units (PICU) tremendously saves the life of patients who had potentially endangering illnesses, but the proportion of survivors with disabilities increased significantly [2]. The outcome of ICU care often measured by standardized mortality ratio (SMR), length of hospital stay, unplanned readmission rate, pain assessment, medication safety practice, and central venous catheter-associated infection prevention practice adoption. Mortality is the most studied outcome measure, though data in developing countries is scarce [3]. The mortality rate in the PICU in Ethiopian hospitals is significantly higher than that of developed countries' health facilities based on annual health sector morbidity and mortality reports. Published data on pediatric critical care in low-income countries remains sparse yet is much needed. This paucity of data makes practice modification and outcome improvement difficult (6).

Most studies done on determinant factors of mortality in the PICU are from western countries and are dependent on clinical and laboratory indices [2]. The few studies that considered epidemiologic and socio-demographic factors were retrospective and cross-sectional studies and most did not consider the severity of illness as a factor as they do not apply severity score in retrospective studies [4]. The ICU equipment and set up in developing countries are not well studied [3, 5]. Hence, this study aimed to determine the incidence and predictors of mortality among children admitted to a pediatric intensive care unit at the University of Gondar comprehensive specialized hospital. Findings from this study could help clinicians and case managers for the proper management of cases. This study could also serve as an entry point for the evaluation of pediatric critical care and assist program planners in evidence-based decision making.

Methods

Study design, period and setting

An institution-based prospective observational follow-up study was conducted among children age 1month to 18 years and admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital from February 1, 2018, to July 30, 2019.

The PICU has six beds with electronic monitors and one mechanical ventilator; on average, there are about 25 pediatric critical care admissions per month. The organizational detail of the PICU in this hospital is lacking. Team composition is often limited to a general pediatrician, resident, interns, and a handful of senior-level nurses, but there are no pediatric intensivists, respiratory therapists, pharmacists, and dieticians in the team.

Population and sample

The patients aged one month to 18 years admitted to the pediatric intensive care unit and stayed for more than two hours in the hospital were included in the study. We excluded cases having incomplete data, and surgical patients admitted only for recovery purposes from the study.

The sample size for this study was determined using a single population proportion of P=21%, from previous Bangladesh study [1] with **a** 5% margin of error the sample size becomes 254 and after adding 10% contingency, the sample became 279. A total of 376 patients were admitted to the PICU from February 1, 2018, to July 30, 2019. We collected data from 327 patients who fulfilled the inclusion criteria. Fourteen patients were excluded from the study due to incomplete data.

Data collection procedure

Data was collected by treating physicians using standard case record form after taking consent from caretakers. Clinical characteristics like systolic blood pressure (SBO), pupillary light reflex, the saturation of oxygen, and need for mechanical ventilation was assessed and documented within the first hour and entered into an electronic application to calculate the pediatrics index of mortality 2 (PIM2) score. We took socio-demographic data and medical history by interview; and diagnosis, laboratory indices, and courses in the hospital by chart review at discharge. We used the WHO International Classification of Diseases 10th version for a disease category, and only the primary diagnoses were used for ICD-10 assignment in patients having multiple diagnoses. The collected data were double-checked by the data collector and the principal investigator. There were orientations and training about data collection and the objective of the study every three months and demonstration every Monday for treating physicians and data collectors. The principal investigator supervised the overall process and checked the completeness of case record forms every day.

Variable of the study and operational definitions

The primary dependent variable was time to death (event). In contrast, socio-demographic characteristics (age, sex, relation with the caregiver, care giver's educational status, occupation) and clinical characteristics (duration of illness before admission, source of admission, critical illness diagnosis, comorbidity, nutritional status, vaccination status, interventions given in the ICU and before admissions like fluid resuscitation, PIM2 score, multi-organ dysfunction syndrome(MODS), and complications) were the independent variables.

Event (death): is defined as a patient who died in the hospital in the course of treatment.

Censored: refers to patients who were discharged alive from the ICU or those with no event of interest

length of stay(LOS): refers to the duration of stay in days from the date of admission to the date of discharge

Short term outcome: the outcome of the patient until he or she leaves the hospital

Critical illness: refers to the presence of sepsis, severe sepsis or septic shock within 24hours of admission or acute respiratory distress syndrome during ICU admission

MODS: refers to a potentially reversible physiologic derangement in two or more organ systems

Data processing and analysis

After we checked the data for its consistency and completeness, we entered it into EpiData version 3.1 and exported to STATA version 14 for cleaning and analysis. Descriptive statistics like mean, median, proportions were carried out to summarize baseline characteristics and patterns of admission. Also, summary statistics like life table, log-rank test, and Kaplan-Meir curves were computed to determine the incidence rate (IR) of death and to compare survival curves between the different categories of the explanatory variables.

Both bivariate and multivariate Cox proportional hazard models were used to identify the predictors. Variables with p-value < 0.2 in the bivariate analysis were entered into the multivariate proportional hazard model. Ninety-five percent confidence interval (95% CI) of hazard ratio was computed, and variable having p-value < 0.05 in the multivariate cox-proportional hazards model was considered as significantly and independently associated with the dependent variable. Cox-proportional hazard model fitness was checked using the Schoenfeld residuals test.

Ethical approval and consent to participate

Ethical clearance was obtained from the Institutional Ethical Review Board of the College of Medicine and Health Sciences, the University of Gondar. Informed verbal consent was obtained from the caretakers. The name or any other identifying information was not recorded on the data collection form, and all information is taken from the chart was kept strictly confidential and in a safe place. The information retrieved was used only for the study purpose.

Patient and public involvement

Patients were not involved in the study

Result

Socio-demographic characteristics

A total of 313 patients out of 376 patients admitted during the eighteen-month study period were included in the final analysis. The median age at admission was 48 months with interquartile range (IQR) of 12 to 122 months, about 28.1% were infants, followed by adolescents (21.4%). More than half (59.7%) were males, more than three-fourth (77.3%) were from rural areas, and parents were the commonest caregivers for the majority (93%) of children. The majority of caregivers had

no formal education (77.6%), and 71.2% were farmers, most patients were admitted in the spring season (38. 3%) followed by winter (27.2%) (Table 1).

Table 1: Socio-demographic characteristics of children and caregivers (n=313)

Characteristics	Frequency	Percentages (%)
Age in months		
≤ 12	88	28.1
13-24	29	9.3
25-60	66	21.1
61-132	63	20.1
>132	67	21.4
Caregivers		
Parents	291	
Grandparentsnts	8	2.6
Siblings	8	2.6
Others	6	1.9
Caregiver level of education		
No formal education	242	77.6
Primary school	32	10.2
Secondary school	17	5.4
College and above	21	6.7
Caregivers occupation		
Farmers	223	71.2
Merchants and private	32	10.2
Government employee	31	9.9
Unemployed	27	8.6
Season of admission		
Summer	63	20.1
Spring	45	14.4
Winter	85	27.2
Autumn	120	38.3

The clinical condition of admitted children

More than three-fourth (77%) of patients were admitted over weekdays, 41.5% in the night shift, and emergency room (60.4%), wards (13.1%) and referrals from other facilities (11.8%) were the primary sources of admissions to the pediatric intensive care unit. The median duration of illness before any health facility visit and admission to PICU was 3 (IQR: 1 to 7) and 6 (IQR: 3 to 13) days, respectively. Forty-three (13.7%) patients had at least one comorbid illnesses, of which, congenital malformations and genetic disorders (27.9%), cerebral palsy with or without seizure disorders (25.6%), CKD (16.3%) and HIV/AIDS (14%) were the comorbid illnesses. One-third of patients had critical illness diagnoses, of which (41%) had sepsis, (47%) septic shock and the remaining (12%) had ARDS. About a third of patients (30.7%) had multiple organ dysfunction syndromes (MODS).

The baseline severity of disease was assessed based on the PIM2 score calculated from an android medical application QxMD within one hour after admission. The minimum score was -6.46 (with predicted mortality rate = 0.2%), and the maximum score was 2.47 (predicted mortality rate =92.2%). The mean predicted mortality rate based on the PIM2 score was 11.14%, which gave the standard mortality ratio (SMR) of 2.94 (Table 2).

Table 2: The clinical condition of children admitted to the pediatric intensive care unit (n=313)

Characteristics	**Frequency**	**Percentages (%)**
Critical illness diagnosis		
Yes	100	31.9
No	213	68.1
Duration of illness before PICU admission in days		
≤Six days	71	22.7
>6 days	242	77.7
Day of admission		
Weekday	241	77
Weekend	72	23

MODS		
Yes	96	30.6
No	217	69.4
Sources of admission		
Home	36	11.5
Other facilities	37	11.8
Emergency room	189	60.4
Wards and Operating rooms	51	16.3
Vaccination status		
Complete	203	64.9
Incomplete	110	35.1
Need mechanical ventilation		
Yes	37	11.8
No	276	88.2
Nutritional status, Z score		
Normal	163	52.1
MAM	50	16
SAM	100	31.9
Reasons for ICU admission		
Altered mental status	145	46.3
Respiratory failure	82	26.5
Sepsis	59	18.8
Shock	55	17.6
Seizure	46	14.7
DKA	24	7
AKI	24	7
CHF	21	6.7
Hemorrhage	14	4.5
Trauma	6	1.9
Others	23	7.3
Fluid resuscitation before ICU admission		
Yes	164	52.4
No	149	47.6

Intensive care unit outcomes and the incidence of mortality

Nearly one-third of patients (32.6%) died in the PICU, severe sepsis or multi-organ failure (MOF) (41.2%) was the leading immediate cause of death in the PICU followed by respiratory failure (23.5%), brain herniation (21.6%) and cardiac arrest accounts 12.7% of deaths.

Fifty-six patients (17.9%) had developed complications during their stay in the PICU, of which hospital-acquired sepsis (46.4%), followed by hospital-acquired pneumonia (17.9%), and mechanical ventilator-associated complications (10.7%) were the most common complications. Study subjects were followed for a different period, which gave a total of 1473 person-day observations (49.1person-months), and the median length of stay in the ICU was 3 (IQR:1 to 6) days. Of the total of 313 participants, 102 (32.6%) died during the follow-up time that gives the incidence of mortality of 6.9 deaths per 100 person day observations (95%CI: 5.34 to 8.34 deaths per 100 person-day). Of deaths reported, more than half (53.9%) died within 24 hours, 13(12.7%) died between 24 and 48 hours, and the remaining died after 48 hours of admission. Differences in all variables at baseline between strata were determined using the log-rank ($\chi 2$) test, and the equality of hazard was assessed for the different explanatory variables. Mechanical ventilation (P-value=0.039) and critical illness (P-value= 0.0001) (Figure 1) and (Figure 2).

Predictors of mortality in the ICU

The cox-proportional hazard model was fitted to identify predictors of mortality. Thus, caregivers' occupation, weekend admission, critical illness diagnoses, PIM2 score, and need for mechanical ventilation were predictors of mortality. Thus, government employee caregivers' associated with a 65% lower risk of child mortality in the ICU compared to those farmers (AHR=0.35, 95%CI: 0.14, 0.89). Whereas, admission in the weekend and critical illness, the hazard of mortality was 1.63 (AHR=1.63, 95%CI: 1.02, 2.60) and 1.79 (AHR=1.79, 95%CI: 1.13, 2.85) times higher compared to weekday admission and those with critical illness diagnosis, respectively. Similarly, a unit increased in the PIM 2 score of a child at admission, the hazard of mortality was 1.53 times increased, keeping other variables constant (AHR=1.53,95%CI:1.36, 1.72). Also, those patients who need mechanical ventilation (MV), the hazard of mortality was 2.36 times higher compared to those who did not need MV (AHR=2.36, 95%CI: 1.39, 4.01) (Table 3).

198 Table 3: Bivariate and multivariable Cox proportional hazard model to identify predictors of
199 mortality (n=313)

Variables	Status		CHR (95% CI)	AHR (95% CI)
	Event	Censored		
Age				
≤12	28	60	1	1
13-24	10	19	0.98(0.47 2.12)	1.40(0.65 3.04)
25-60	26	40	1.30(0.75 2.23)	1.15(0.63 2.08)
61-132	20	43	1.07(0.60 1.90)	1.20(0.65 2.21)
>132	18	49	0.92(0.50 1.67)	1.61(0.84 3.08)
Address				
Urban	28	43	1	1
Rural	74	168	0.73(0.47,1.13)	0.63(0.37,1.05)
Caregiver' level of education				
No formal education	96	195	1	1
Primary and above	6	16	0.78(0.34, 1.80)	1.26(0.51,3.13)
Caregivers' occupation				
Farmers	72	151	1	1
Merchants and private	9	23	0.82(0.41, 1.64)	1.06(0.47,2.35)
Government employee	7	24	0.50(0.22, 1.16)	0.35(0.14,0.89)*
Unemployed	14	13	1.61(0.91,2.86)	1.11(0.55,2.24)
Day of admission				
Weekday	71	170	1	1
Weekend	31	41	1.47(0.96,2.26)	1.63(1.02,2.60)**
Source of admission				
Home	9	27	1	1
Other facilities	14	23	1.66(0.72,3.86)	1.90(0.76, 4.76)
Emergency room	55	134	1.13(0.56,2.29)	1.59(0.72,3.48)
Wards and OR	24	27	2.11(0.98,4.56)	2.07(0.86,4.99)
Duration of illness before PICU admission				
<6 days	39	107	1	1
≥6 days	63	104	1.43(0.96,2.12)	0.97(0.62,1.54)
Comorbidities				
No	85	185	1	1
Yes	17	26	1.31(0.78 2.21)	0.66(0.36 1.23)
Critical illness diagnosis				
No	53	160	1	1
Yes	49	51	2.05(1.39,3.04)	1.79(1.13, 2.85)**
Nutritional status, Z score				
Normal	45	118	1	1
MAM	15	35	1.19(0.66,2.14)	1.49(0.79,2.82)

SAM	42	58	1.67(1.09,2.55)	1.69(0.94,2.61)
PIM2 score	-3.22±1.81		1.51(1.37,1.67)	1.53(1.36,1.72)**
Mechanical ventilation need				
No	79	197	1	1
Yes	23	14	1.93(1.20,3.10)	2.36(1.39,4.01)**
Complications in the PICU				
No	86	190	1	1
Yes	16	21	2.39(1.20,4.73)	1.62(0.79,3.31)
Fluid resuscitation intervention before ICU admission				
No	44	105	1	1
Yes	58	106	1.24(0.83 1.84)	0.92(0.59 1.44)

* show statistical significance at a p-value of 0.05

Discussion

This study revealed that 32.6% of patients died with a rate of 6.92 deaths per 100 person-day observations. Weekend admission, critical illness diagnosis, pediatrics index of mortality (PIM 2), and need for mechanical ventilation were predictors of child mortality in the ICU. The proportion of mortality in this study was consistent with retrospective cross-sectional studies done in the same PICU from 2013 to 2016(30.9%)[6], Egypt (33.1%)[7], Nigeria (36.1%) [8] and Saudi Arabia (37.4%)[9]. The proportion of mortality in our PICU is lower than the finding of a retrospective cross-sectional study done in Jimma-Ethiopia (40%)[10]. The difference could be attributed to the higher proportion of trauma patients admitted in their PICU as compared to ours. The other possible reason could be that the higher proportion of left against medical advice (LAMAs) in our study might underestimate the mortality rate in our study. However, it is higher than the mortality rates in studies done in Pakistan (14%)[11], the average of Latin American countries (13.29%) [12], India (10.58%)[13] and European countries (5%)[14]. The possible explanation for the observed discrepancies might be due to suboptimal care, the inadequacy of both diagnostic, and interventional facilities in our PICU.

Children who were admitted over the weekends had nearly twice an increased risk of mortality than those admitted over weekdays, which is consistent with the findings of studies done in

Canada, Finland, and Austria [14-16]. This increased mortality over weekends might be due to failure to early recognize deteriorations at wards and other sources as a result of reduced staffing ratios. Access to diagnostic services is limited at weekends, which limits the likelihood of putting correct diagnoses, there could be unrecognized deteriorations during handover round times and delays in giving interventions. The fact that duty teams come from other wards during weekends may contribute to the increased mortality over weekends. However, our finding was not supported by three American studies and studies done in the United Kingdom and the Republic of Ireland [17, 18]. This discrepancy could be explained by the better standard of care they have and 24 hours around the clock full staffing.

This study also reviewed that caregiver occupation of government-employed associated with lower risk mortality compared to caregivers of peasants. This finding could be explained by differences in health-seeking behavior and early identification of danger signs between these groups.

The child who had critical illness diagnosis had an increased risk of mortality compared to those who had not. This difference could be because patients with critical illnesses have a low reserve of physiologic function. This finding was consistent with other studies.

Amongst many disease severity assessment tools at baseline, we used PIM2 as it does not need extensive laboratory investigation, and it is not affected by subsequent interventions since it is scored within one hour of admission. A unit increment in the PIM2 score had doubled the hazard of mortality, which shows the score is sensitive in detecting morality, and this scoring system is also validated and applicable in many PICUs across the world [19-23]. The higher observed mortality rate than the predicted one by PIM2 score in our study indicates the poor quality of intensive care in our setting. PIM 2 Score was found to be nondiscriminatory for the risk of death in studies done in Addis Ababa and India [21, 24].

Patients who needed mechanical ventilation had increased mortality compared to those who did not need it. This finding is in line with the findings of other studies [25, 26]. The explanation for this might be because patients who need mechanical ventilation tend to have advanced disease stages. This can also be attributed to a limited number of mechanical ventilators we had. There might also be unrecognized ventilator-associated complications.

Strength and limitations of the study

This study is a prospective cohort study with a better statistical function (survival analysis). The PIM2 scoring was based on 9 out of 11 parameters as there was no Arterial blood gas analyzer in our PICU during the study period. The availability of medical equipment and PICU quality of care and their impact on patient survival was not adequately assessed using standard parameters. Pediatric critical care is not just about saving lives, so the degree of physiologic function retained at discharge should have been assessed using a standard checklist for all of the patients discharged.

Conclusion

Rate of mortality in the ICU was high, admission over weekends, need for mechanical ventilation, critical illness diagnoses, and higher PIM 2 score were found to be significant and independent predictors of mortality at the PICU. Availing mechanical ventilators up to the standard, intensivist, and full staffing around the clock, including weekends and paying due attention for critical illness and critical illness diagnoses tailored care, may improve PICU outcome. Using PIM 2 score to prognosticate outcomes and tunnel resources to the most in need patients and council caregivers might be advisable.

List of abbreviations

AHR: Adjusted Hazard Ratio, AKI: Acute Kidney Injury, CI: Confidence Intervals, CHR: Crude Hazard Ratio, HAS: Hospital-Acquired Sepsis, HAP: Hospital-Acquired Pneumonia, ICD: International Classifications of Disease, ICU: Intensive Care Unit, IQR: Interquartile Range, IR: Incidence Rate, LAMA: Left Against Medical Advice, LOS: Length of Hospital stay, MAM: Moderate Acute Malnutrition, MODS: Multiple Organ Dysfunction Syndrome, MV: Mechanical Ventilation, PI: Principal Investigator, PICU: Pediatric Intensive Care Unit, PIM: Pediatrics Index Mortality, SAM: Severe Acute Malnutrition, OR: Operation Room, USA: the United States of America, WHO, World Health Organization

Declaration

stcox i.ADRESS i.criticalilnnes i.DURICUIL_rec i.sourceadmission i.occupation_recoded i.CAREGIVErecoded i.age_categorized PIM2SCOR i.COMPLICA i.COMORBID i.FLUID i.DAYOFADM i.MV i. Z SCORE

Ethics approval and consent to participate

Ethical clearance was obtained from the Institutional Ethical Review Board of College of Medicine and Health Sciences, University of Gondar. Assent and informed written consent were obtained from the caretakers. The name or any other identifying information was not recorded on the data collection form. All information taken from the chart was kept strictly confidential in a safe place. The information retrieved was used only for the study purpose.

Consent for publication

Not applicable

Availability of data and material

Data is available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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The study was funded by the University of Gondar, Ethiopia. The funder has no role in study design, data collection, and analysis, interpretation of data, the decision to publish, or preparation of the manuscript.

Authors' contributions

NWT, ATA, and KST participated in designing the study, performed data analysis, visualization, validation of the whole work, and prepared the manuscript. NWT took part in funding acquisition, data collection, supervision and software, and other resources. All authors read and approved the final manuscript.

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Figures and legends

Figure 1: Kaplan-Meier failure (death) estimates curves by days of admission among children treated in the pediatric intensive care unit of University of Gondar comprehensive specialized hospital from February 1/2018 to July 30/2019

Figure 2: Kaplan-Meier failure (death) estimates curves by children critical illness admitted to the pediatric intensive care unit of University of Gondar comprehensive specialized hospital from February 1/2018 to July 30/2019

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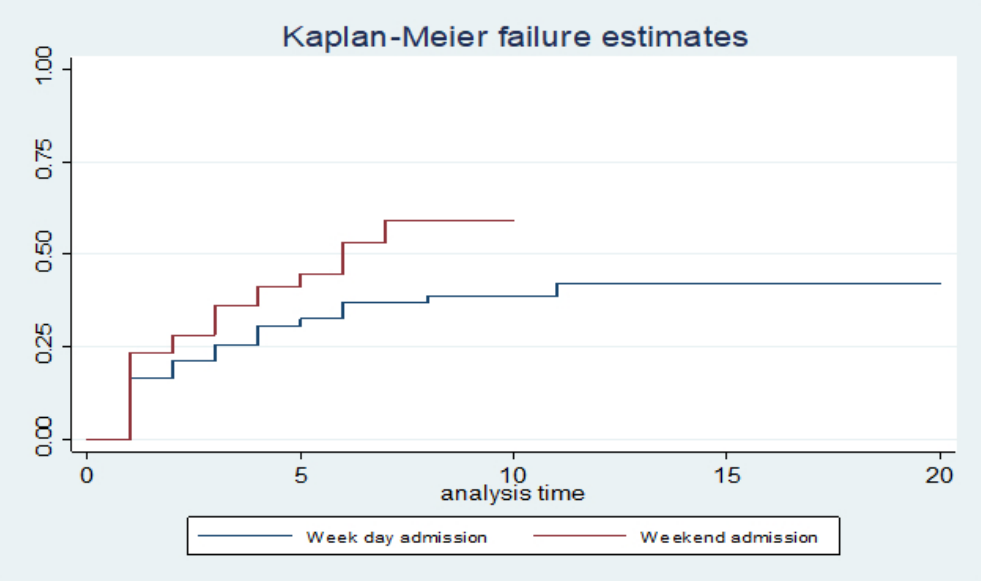

Figure 1: Kaplan-Meier failure (death) estimates curves by days of admission among children treated in the pediatric intensive care unit of University of Gondar comprehensive specialized hospital from February 1/2018 to July 30/2019

168x100mm (96 x 96 DPI)

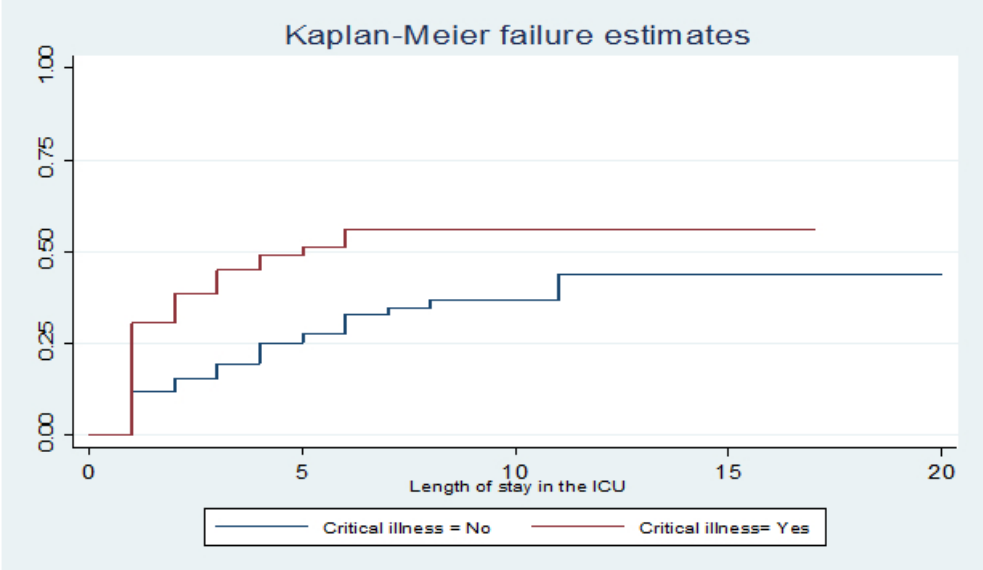

Figure 2: Kaplan-Meier failure (death) estimates curves by children critical illness admitted to pediatric intensive care unit of University of Gondar comprehensive specialized hospital from February 1/2018 to July 30/2019

164x96mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract ***The title describes the study design as* "Incidence and predictors of mortality among children admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, northwest Ethiopia: A prospective observational cohort study". *Page 1***
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ***The abstract describes the method used and Main findings****. page 2, line 19-31*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ***The background and rationale are described in the Background, paragraphs 1, 2, 3, 4, 5 and 6. Page 4-5, Line 64-102***
Objectives	3	State specific objectives, including any pre specified hypotheses ***The specific aims of the study are stated in the Background, paragraphs 6, page 5 ,line 94-104***
Methods		
Study design	4	Present key elements of study design early in the paper ***The study design is discussed in paragraphs 1 of the Methods section, page 6, line 105-107***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ***The institutional setting is described in paragraphs 2 line 108-120 of the Methods section.*** ***Study locations are described in paragraph 1 and 2 of the Methods section; and study timing is discussed in paragraphs of the Methods section. Participant recruitment is mentioned in in population and sample section*****. Page 6**
Participants	6	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants ***Selection of the sample is discussed in paragraph 1 and 2 line 121-130, of population and sample subsection of the Methods section. page 6-7***
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

		Outcomes are discussed in the Outcomes subsection (paragraphs 3 of the Methods section). Data was collected by treating physicians using standardized questionnaire after taking consent from caretakers. Clinical characteristics like, SBP, pupillary light reflex, SaO_2 need of mechanical ventilator was assessed and documented within the first hour and entered into an electronic App to calculate pediatrics index mortality 2 (PIM2) score. **Mentioned in the method section of 131-158, page 7-8**
	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group ***Measurement of the outcomes are discussed in the data collection and measurement of variables subsection. Page 8***
Bias	9	Describe any efforts to address potential sources of bias ***Mentioned in the method section of v*ariable of the study and operational definitions *Page 7-8***
Study size	10	Explain how the study size was arrived at ***Sample size determination was discussed at method, population and sample section. Page 6***
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ***Use of variables is discussed in the data management and analysis subsection. Page 8***
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding ***Statistical methods are discussed in the data management and analysis subsection. Page 8 line 160-178***
		(*b*) Describe any methods used to examine subgroups and interactions Described in in the data management and analysis subsection. ***Results are analysed by socio-demographic and personal attributes like age place of residence .***
		(*c*) Explain how missing data were addressed ***None***
		(*e*) Describe any sensitivity analyses ***None***

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ***At paragraph 1 of result section, page 9***
		(b) Give reasons for non-participation at each stage ***None***
		(c) Consider use of a flow diagram ***None***
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Provider characteristics are presented in Table 1, Table 2, and Table 3.
		(b) Indicate number of participants with missing data for each variable of interest ***None***
Outcome data	15*	*Cross-sectional study*—Report numbers of outcome events or summary measures Both numbers and percentages/proportions are reported throughout the ***Results Section. Page 15-16 line 230-248***
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ***Adjusted results are presented for all outcomes. Page 16-17, table 4***
		(*b*) Report category boundaries when continuous variables were categorized ***Not applicable***
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period ***Not applicable***.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ***None***
Discussion		
Key results	18	Summarise key results with reference to study objectives ***Results are summarized in paragraphs, 1, and 2 of the Discussion section***. Page 18, line 271-283
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ***Strength and limitations are discussed in paragraphs 21, line 344-352***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ***Discussed in discussion and conclusion sub section. 18-22***
Generalizability	21	***Discuss the generalizability (external validity) of the study results*** ***The representativeness of the sample is discussed in the final paragraph of the limitations subsection.***

Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ***Not applicable***

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Incidence and predictors of mortality among children admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, northwest Ethiopia: A prospective observational cohort study

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Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Emergency medicine
Keywords:	Paediatric intensive & critical care < ANAESTHETICS, ACCIDENT & EMERGENCY MEDICINE, INTENSIVE & CRITICAL CARE

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Incidence and predictors of mortality among children admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, northwest Ethiopia: A prospective observational cohort study

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Abstract

Objective: To determine the incidence and predictors of mortality among children admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, northwest Ethiopia

Design: A single-center prospective observational cohort study

Participants: A total of 313 children admitted to the intensive care unit of the University of Gondar comprehensive specialized hospital during one-and-a-half-year period.

Measurements: Data were collected using standard case record form, physical examination, and patient document review. Clinical characteristics like systolic blood pressure, pupillary light reflex, oxygen saturation, and need for mechanical ventilation were assessed and documented within the first hour of admission and entered into an electronic application to calculate the Pediatric Index of Mortality 2 (PIM 2) score. We fitted the Cox proportional hazards model to identify predictors of mortality.

Result: The median age at admission was 48 months with interquartile range (IQR: 12 to 122), 28.1% were infants, and adolescents accounted for 21.4%. Of the total patients studied, 59.7% were males. The median observation time was three days with (IQR: 1 to 6). One hundred two (32.6%) children died during the follow-up time, and the incidence of mortality was 6.9 deaths per 100 person-day observation. Weekend admission [Adjusted Hazard Ratio (AHR) =1.63, 95%CI: 1.02, 2.62], critical illness diagnoses (AHR=1.79, 95%CI: 1.13, 2.85), need for mechanical ventilation (AHR=2.36, 95%CI: 1.39, 4.01) and PIM 2 score (AHR=1.53, 95%CI: 1.36, 1.72) were the predictors of mortality.

Conclusion: The rate of mortality in the Pediatric intensive care unit (PICU) was high, admission over weekends, need for mechanical ventilation, critical illness diagnoses, and higher Pediatric Index of Mortality 2 scores were significant and independent predictors of mortality.

Strength and limitation of the study

- This study was a prospective cohort study and had used better statistical functions (survival analysis) for better estimation and prediction of mortality.
- This study could help clinicians and health care planners practice evidence-based medicine in a resource-limited setting like ours.
- The PIM 2 scoring was done based on 9 out of 11 parameters as there was no arterial blood gas analyzer in our set up during the study period that might result in misclassification.

Introduction

Pediatric intensive care units (PICUs) are essential areas of service to save the lives of children with life-threatening conditions. Children with acute neurological deterioration, respiratory distress, cardiovascular compromise, severe infections, and accidental poisoning constitute primary admissions in PICUs [1].

Children admitted to the PICU may die or survive with or without permanent sequelae, and the proportion of survivors with disabilities has increased significantly [2]. It is essential to prioritize and tunnel resources to the most fruitful practice based on the prediction of patient outcomes, especially in resource-limited setups.

The outcome of intensive care is often measured by standardized mortality ratio (SMR), length of hospital stays, unplanned readmission rate, pain assessment, medication safety practice, and central venous catheter-associated infection prevention practice adoption.

Mortality is the most studied outcome measure within PICUs, though data from developing countries are scarce [3]. The mortality rate among PICUs in Ethiopian hospitals is thought to be significantly higher than in developed countries based on annual health sector morbidity and mortality reports. Published data on pediatric critical care in low-income countries remains sparse. This paucity of data makes practice modification and outcome improvement difficult. Also, most studies done on predictors of mortality in the PICUs are from high-income countries and are dependent on clinical and laboratory indices, which are not readily available in low-income countries [2]. The few studies that considered epidemiologic and sociodemographic factors were retrospective and cross-sectional, and most did not consider important parameters[4].

This study aimed to determine the incidence and predictors of mortality among children admitted to a pediatric intensive care unit at the University of Gondar comprehensive specialized hospital. It might add to the knowledge of mortality and its predictors, thereby hoping to plan the most efficient method of intervention for those at higher mortality risk, thus contributing to recovery as well as making the assessment of the performance of the services delivered.

Methods

Study design, period and setting

A single-center prospective cohort study was conducted among children aged one month to 18 years admitted to the PICU at the University of Gondar comprehensive specialized hospital from February 1, 2018, to July 30, 2019.

The PICU has six beds with electronic monitors and one mechanical ventilator; on average, there are about 25 pediatric critical care admissions per month. The organizational detail of the PICU in this hospital is lacking. Team composition is often limited to a general pediatrician, resident,

interns, and a handful of senior-level nurses, but there are no pediatric intensivists, respiratory therapists, pharmacists, and dieticians in the team.

Population and sample

Patients who stayed for more than two hours in the hospital were included in the study. We excluded patients having incomplete data, and surgical patients admitted only for recovery purposes from the study.

The sample size for this study was determined using a single population proportion of P=21%, from previous Bangladesh study [1] with a 5% margin of error; the sample size became 254, and after adding 10% contingency, the sample became 279. A total of 376 patients were admitted to the PICU during the study period. We collected data from 327 patients who fulfilled the inclusion criteria. Fourteen patients were excluded from the study due to incomplete data.

Data collection procedure

Data was collected by treating physicians using standard case record form after receiving consent from caretakers. Clinical characteristics like systolic blood pressure (SBP), pupillary light reflex, the saturation of oxygen, and need for mechanical ventilation was assessed and documented within the first hour and entered into an electronic application to calculate the Pediatric Index of Mortality 2 (PIM 2) score. We took sociodemographic data and medical history by interview; and diagnosis, laboratory indices, and the clinical course during the hospital by chart review at discharge. We used the World Health Organization (WHO) International Classification of Diseases 10th version (ICD-10) for disease category, and only the primary diagnoses were used for ICD-10 assignment in patients having multiple diagnoses. The collected data were double-checked by the data collector and the principal investigator. There were orientations and training about data collection and the objective of the study every three months and demonstration every Monday for treating

physicians and data collectors. The principal investigator supervised the overall process and checked the completeness of case record forms every day. No direct patient care was provided by investigators, who only accessed patients' records.

Variable of the study and operational definitions

The primary dependent variable was time to death (event). In contrast, sociodemographic characteristics included age, sex, relation with the caregiver, caregiver's educational status, and occupation. Clinical characteristics included duration of illness before admission, source of admission, critical illness diagnosis, comorbidity, nutritional status, vaccination status, interventions given in the PICU, and before admissions like fluid resuscitation, PIM 2 score, multi-organ dysfunction syndrome (MODS), and complications.

Event (death): is defined as a patient who died in the hospital during treatment.

Censored: refers to patients who were discharged alive from the PICU or those with no event of interest.

Length of stay (LOS): refers to the duration of stay in days from the date of admission to the date of discharge.

Short term outcome: the outcome of the patient until he or she leaves the hospital

Critical illness: refers to the presence of sepsis, severe sepsis or septic shock within 24 hours of admission or acute respiratory distress syndrome during PICU admission

MODS: refers to a potentially reversible physiologic derangement in two or more organ systems

Data processing and analysis

After we checked the data for its consistency and completeness, we entered data into EpiData version 3.1 and exported to STATA version 14 for cleaning and analysis. Descriptive statistics like

mean, median, and proportions were carried out to summarize baseline characteristics and patterns of admission. Also, summary statistics like life table, log-rank test, and Kaplan-Meir curves were computed to determine the incidence rate (IR) of death and to compare survival curves between the different categories of the explanatory variables.

Both bivariate and multivariate Cox proportional hazards models were used to identify the predictors. Variables with p-value < 0.2 in the bivariate analysis were entered into the multivariate proportional hazard model. Ninety-five percent confidence intervals (95% CI) of hazard ratio were computed, and variables having p-value < 0.05 in the multivariate Cox proportional hazards model were considered as significantly and independently associated with the dependent variable. Cox proportional hazards model fitness was checked using the Schoenfeld residuals test.

Ethical approval and consent to participate

Ethical clearance was obtained from the Institutional Ethical Review Board of the University of Gondar's College of Medicine and Health Sciences. Informed verbal consent was obtained from the caretakers. The name or any other identifying information was not recorded on the data collection form, and all information taken from the chart was kept strictly confidential and in a safe place. The information retrieved was used only for the study purpose.

Patient and public involvement

There was no direct patient contact, and investigators accessed only patient records.

Result

Sociodemographic characteristics

A total of 313 patients out of 376 admitted during the 18-month study period were included in the final analysis. The median age at admission was 48 months with interquartile range (IQR: 12 to 122), with a male to female ratio of 1.7:1, as shown in Table 1. The majority of caregivers (92.9%)

were parents. More than three-fourth (77.6%) of caregivers had no formal education, and 71.2% were farmers. Most patients were admitted in the spring season (38. 3%), followed by winter (27.2%) (Table 1).

Table 1: Sociodemographic characteristics of patients

Characteristics	**Frequency**	**Percentages (%)**
Age in months		
≤ 12	88	28.1
13-24	29	9.3
25-60	66	21.1
61-132	63	20.1
>132	67	21.4
Sex		
Male	188	59.7
Female	125	39.3
Season of admission		
Summer	63	20.1
Spring	45	14.4
Winter	85	27.2
Autumn	120	38.3
Vaccination status		
Complete	203	64.9
Incomplete/unvaccinated	110	35.1
Comorbid illness (n=43)		
Congenital malformations/genetic disorders	12	27.9
Cerebral palsy with or without seizure disorders	11	25.6
Chronic kidney disease	7	16.3
HIV/AIDS	6	14
Others	7	16.3

HIV/AIDS: Human immunodeficiency virus infection and acquired immune deficiency syndrome

The clinical condition of admitted children

The primary source of admissions in the PICU was the emergency room (60.4%), inpatient pediatrics wards (13.1%), and referrals from other facilities (11.8%). More than three-fourth (77%) of patients were admitted over weekdays and 41.5% in the night shift. The median duration of illness before any health facility visit and admission to PICU was 3 (IQR: 1 to 7) and 6 (IQR: 3 to 13) days, respectively.

One-third of patients had critical illness diagnoses, of which (41%) had sepsis, (47%) septic shock, and the remaining (12%) had acute respiratory distress syndrome. About one-third of patients (30.7%) had multiple organ dysfunction syndromes (MODS).

The minimum PIM 2score was -6.46 (with predicted mortality rate = 0.2%), and the maximum score was 2.47 (predicted mortality rate =92.2%). The mean predicted mortality rate based on the PIM 2 score was 11.14%, which gave the standard mortality ratio (SMR) of 2.94 (Table 2).

Table 2: Clinical condition of patients

Characteristics	**Frequency**	**Percentages (%)**
Critical illness diagnosis		
Yes	100	31.9
No	213	68.1
Duration of illness before PICU admission in days		
≤6 days	71	22.7
>6 days	242	77.7
Day of admission		
Weekday	241	77
Weekend	72	23
Multi-organ dysfunction syndrome		
Yes	96	30.6
No	217	69.4
Sources of admission		
Home	36	11.5
Other facilities	37	11.8
Emergency room	189	60.4
Wards and Operating rooms	51	16.3
Need for mechanical ventilation		
Yes	37	11.8

No	276	88.2
Nutritional status, Z score		
Normal	163	52.1
Moderate acute malnutrition	50	16
Severe acute malnutrition	100	31.9
Reasons for PICU admission		
Altered mental status	145	46.3
Respiratory failure	82	26.5
Sepsis	59	18.8
Shock	55	17.6
Seizure	46	14.7
Diabetic ketoacidosis	24	7
Acute kidney injury	24	7
Congestive heart failure	21	6.7
Hemorrhage	14	4.5
Trauma	6	1.9
Others	23	7.3
Fluid resuscitation before PICU admission		
Yes	164	52.4
No	149	47.6

PICU: Pediatric intensive care unit

Intensive care unit outcomes and the incidence of mortality

Nearly one-third of patients (32.6%) died in the PICU. Severe sepsis or multi-organ failure (MOF) (41.2%) was the leading immediate cause of death in the PICU followed by respiratory failure (23.5%), brain herniation (21.6%), and cardiac arrest (12.7%).

Fifty-six patients (17.9%) developed complications during their stay in the PICU, including hospital-acquired sepsis (46.4%), hospital-acquired pneumonia (17.9%), and mechanical ventilator-associated complications (10.7%).

Study subjects were followed during the study period, which gave a total of 1473 person-day observations (49.1 person-months), and the median length of stay in the ICU was 3 (IQR:1 to 6) days. Of the total of 313 participants, 102 (32.6%) died during the follow-up time. The incidence of mortality was 6.9 deaths per 100-person day observations (95%CI: 5.34 to 8.34 deaths per 100

person-day). Among deaths reported, more than half (53.9%) died within 24 hours, 13 (12.7%) died between 24 and 48 hours, and the remaining died after 48 hours of admission. Differences in all variables at baseline between strata were determined using the log-rank ($\chi 2$) test, and the equality of hazard was assessed for the different explanatory variables. Kaplan Meir failure curve was plotted for weekend admission (P-value=0.039) and critical illness (P-value= 0.0001) shows significant difference. (Figure 1) and (Figure 2).

Predictors of mortality in the PICU

The Cox proportional hazards model was fitted to identify predictors of mortality. From the multivariate analysis, caregivers' occupation, weekend admission, critical illness diagnoses, PIM 2 score, and need for mechanical ventilation were predictors of mortality. Mortality was 65% lower for those whose caregivers were government employees compared to farmers (AHR=0.35, 95%CI: 0.14, 0.89). The hazard of mortality was 1.63 times higher for patients admitted over weekends (AHR=1.63, 95%CI: 1.02, 2.60) and 1.79 times higher in patients who had critical illness diagnoses(AHR=1.79, 95%CI: 1.13, 2.85) compared to weekday admission and those without critical illness diagnosis, respectively. Similarly, each one-unit increase in the PIM 2 score increased the hazard of mortality 1.53 times, keeping other variables constant (AHR=1.53, 95%CI:1.36, 1.72). Also, those patients who met the criteria for mechanical ventilation (MV), the hazard of mortality was 2.36 times higher compared to those who did not need MV (AHR=2.36, 95%CI: 1.39, 4.01) (Table 3).

Table 3: Bivariate and multivariate Cox proportional hazard model Fit for different independent variables

Variables	**Status**		**CHR (95% CI)**	**AHR (95% CI)**
	Event	**Censored**		
Age (months)				
≤12	28	60	1	1

13-24	10	19	0.98(0.47 ,2.12)	1.40(0.65 ,3.04)
25-60	26	40	1.30(0.75, 2.23)	1.15(0.63 ,2.08)
61-132	20	43	1.07(0.60 ,1.90)	1.20(0.65, 2.21)
>132	18	49	0.92(0.50 ,1.67)	1.61(0.84 ,3.08)
Address				
Urban	28	43	1	1
Rural	74	168	0.73(0.47,1.13)	0.63(0.37,1.05)
Caregiver' level of education				
No formal education	96	195	1	1
Primary and above	6	16	0.78(0.34, 1.80)	1.26(0.51,3.13)
Caregivers' occupation				
Farmers	72	151	1	1
Merchants and private	9	23	0.82(0.41, 1.64)	1.06(0.47,2.35)
Government employee	7	24	0.50(0.22, 1.16)	0.35(0.14,0.89) *
Unemployed	14	13	1.61(0.91,2.86)	1.11(0.55,2.24)
Day of admission				
Weekday	71	170	1	1
Weekend	31	41	1.47(0.96,2.26)	1.63(1.02,2.60) *
Source of admission				
Home	9	27	1	1
Other facilities	14	23	1.66(0.72,3.86)	1.90(0.76, 4.76)
Emergency room	55	134	1.13(0.56,2.29)	1.59(0.72,3.48)
Wards and OR	24	27	2.11(0.98,4.56)	2.07(0.86,4.99)
Duration of illness before PICU admission				
<6 days	39	107	1	1
≥6 days	63	104	1.43(0.96,2.12)	0.97(0.62,1.54)
Comorbidities				
No	85	185	1	1
Yes	17	26	1.31(0.78 ,2.21)	0.66(0.36, 1.23)
Critical illness diagnosis				
No	53	160	1	1
Yes	49	51	2.05(1.39,3.04)	1.79(1.13, 2.85) *
Nutritional status, Z score				
Normal	45	118	1	1
Moderate acute malnutrition	15	35	1.19(0.66,2.14)	1.49(0.79,2.82)
Severe acute malnutrition	42	58	1.67(1.09,2.55)	1.69(0.94,2.61)
Pediatric Index of Mortality 2	-3.22±1.81		1.51(1.37,1.67)	1.53(1.36,1.72) *
Mechanical ventilation need				
No	79	197	1	1
Yes	23	14	1.93(1.20,3.10)	2.36(1.39,4.01) *
Complications in the PICU				
No	86	190	1	1
Yes	16	21	2.39(1.20,4.73)	1.62(0.79,3.31)
Fluid resuscitation intervention before PICU admission				

No	44	105	1	1
Yes	58	106	1.24(0.83, 1.84)	0.92(0.59 ,1.44)

* Shows statistical significance at a p-value of 0.05, AHR: Adjusted hazard ratio, CHR: Crude hazard ratio PICU: Pediatric intensive care unit

Discussion

Our study is the first report from a prospective study from PICU in Ethiopia that demonstrates the mortality is high. Our analysis demonstrated that lack of appropriate human resources (weekend admission), critical illness diagnosis, and need for mechanical ventilation were important risk factors for death.

The proportion of mortality(32.6%) in this study with a rate of 6.92 deaths per 100 person-day observation was consistent with retrospective cross-sectional studies done in same PICU from 2013 to 2016 (30.9%)[5], and other countries like Egypt (33.1%)[6], Nigeria (36.1%) [7] and Saudi Arabia (37.4%)[8]. However, it is lower than the finding of a retrospective cross-sectional study done in Jimma, Ethiopia (40%)[9]. The difference could be attributed to the higher proportion of trauma patients admitted in their PICU as compared to ours. When we compare it with other lower and middle-income countries the mortality rate in our PICU is higher than the mortality rates in studies done in Pakistan (14%)[10], the average of Latin American countries (13.29%) [11], and India (10.58%)[12]. The possible explanation for the observed discrepancies might be due to suboptimal care, the inadequacy of both diagnostic, and interventional facilities in our PICU.

Children who were admitted over the weekends had nearly twice an increased risk of mortality than those admitted over weekdays, which is consistent with the findings of studies done in Canada, Finland, and Austria [13-15]. This increased mortality over weekends might be due to failure to promptly recognize deteriorations among patients in the wards and other sources as a result of reduced staffing ratios. Access to diagnostic services is limited during weekends, which

limits the likelihood of arriving at diagnoses. Furthermore, there could be unrecognized deteriorations during handoff and round times and delays in administering interventions. However, our finding was not supported by three American studies and studies done in the United Kingdom and the Republic of Ireland [16, 17]. This discrepancy could be explained by the better standard of care they have and 24 hours around the clock staffing.

This study also highlighted how being a caregiver who is a government employee was associated with lower risk mortality compared to caregivers of peasants. This finding could be explained by differences in health-seeking behavior, access to funds for transportation, and early identification of danger signs between these groups.

The child who had a critical illness diagnosis had an increased risk of mortality compared to those who had not. This difference could be because patients with critical illnesses have a low reserve of physiologic function. This finding was consistent with other studies [18, 19].

Amongst many disease severity assessment tools at baseline, PIM 2 does not need extensive laboratory investigation, and it is not affected by subsequent interventions since it is scored within one hour of admission resulting in early identification of the severity of illness and stratification of children for necessary intervention [20], which in turn helps in counseling caregivers of sick children. A unit increment in the PIM 2 score doubled the hazard of mortality, which shows the score is sensitive in detecting morality, and this scoring system is also validated and applicable in many PICUs across the world [21-25]. The higher observed mortality rate than the predicted one by PIM 2 score in our study indicates the poor quality of intensive care in our setting.

Patients who had respiratory failure, and those who met the criteria for mechanical ventilation had increased mortality compared to those who did not have indications for ventilation. This finding is consistent with the findings from other studies [26, 27]. Patients who need mechanical

ventilation tend to have advanced disease stages. This finding can also be attributed to a limited number of mechanical ventilators in our PICU. There might also be unrecognized ventilator-associated complications in those who were placed on a mechanical ventilator.

Strength and limitations of the study

This study is a prospective cohort study with a better statistical function (survival analysis). The PIM 2 scoring was based on 9 out of 11 parameters as there was no arterial blood gas analyzer in our PICU during the study period. The availability of medical equipment and PICU quality of care and their impact on patient survival was not adequately assessed using standard parameters. Pediatric critical care is not just about saving lives, so the degree of physiologic function retained at discharge should have been assessed using a standard checklist for all discharged patients.

Conclusion

Rate of mortality in the PICU was high, and admission during weekends, need for mechanical ventilation, critical illness diagnoses, and higher PIM 2 score were significant and independent predictors of mortality. Availing mechanical ventilators, providing care by intensivists, full staffing around the clock, and paying due attention for early signs of critical illness may improve intensive care outcomes. Using the PIM 2 score to prognosticate outcomes and tunnel resources to the most in need patients and counseling of caregivers might be advisable.

List of abbreviations

AHR: Adjusted Hazard Ratio, AKI: Acute Kidney Injury, CI: Confidence Intervals, CHR: Crude Hazard Ratio, HAS: Hospital-Acquired Sepsis, HAP: Hospital-Acquired Pneumonia, ICD: International Classifications of Disease, ICU: Intensive Care Unit, IQR: Interquartile Range, IR: Incidence Rate, LAMA: Left Against Medical Advice, LOS: Length of Hospital stay, MAM: Moderate Acute Malnutrition, MODS: Multiple Organ Dysfunction Syndrome, MV: Mechanical

Ventilation, PI: Principal Investigator, PICU: Pediatric Intensive Care Unit, PIM 2: Pediatrics Index of Mortality 2, SAM: Severe Acute Malnutrition, OR: Operation Room, USA: the United States of America, WHO: World Health Organization

Declaration

Ethical approval and consent to participate

Ethical clearance was obtained from the Institutional Ethical Review Board of College of Medicine and Health Sciences, University of Gondar. Assent and informed written consent were obtained from the caretakers. The name or any other identifying information was not recorded on the data collection form. All information taken from the chart was kept strictly confidential in a safe place. The information retrieved was used only for the study purpose.

Consent for publication

Not applicable

Availability of data and material

Data is available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

NWT, ATA, and KST participated in designing the study, performing data analysis and visualization, validating the work, and preparing the manuscript. NWT took part in funding acquisition, data collection, supervision and software, and other resources. All authors read and approved the final manuscript.

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Figures and legends

Figure 1: Kaplan-Meier failure (death) estimates curves by days of admission

Figure 2: Kaplan-Meier failure (death) estimates curves by critical illness

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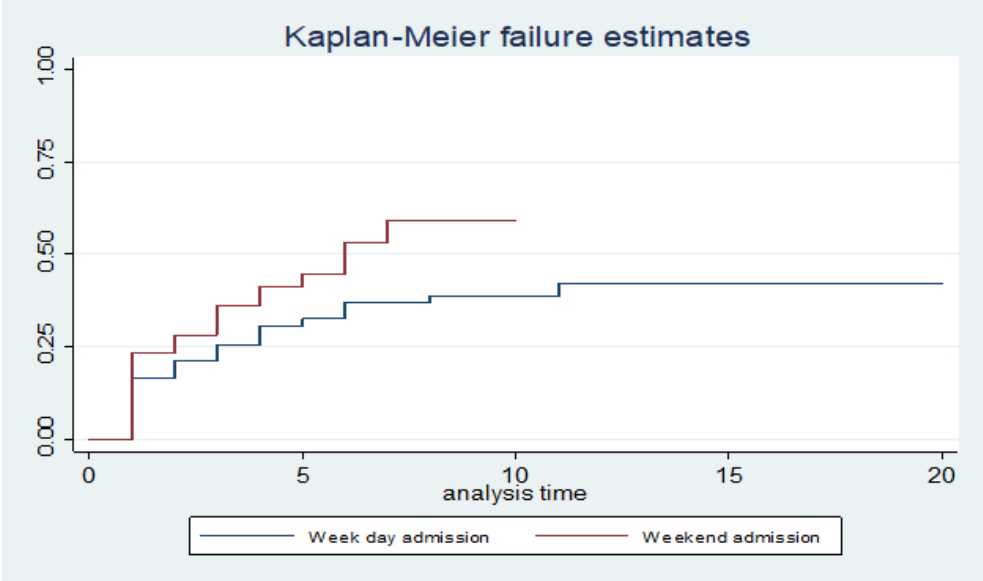

Figure 1: Kaplan-Meier failure (death) estimates curves by days of admission among children treated in the pediatric intensive care unit of University of Gondar comprehensive specialized hospital from February 1/2018 to July 30/2019

168x100mm (96 x 96 DPI)

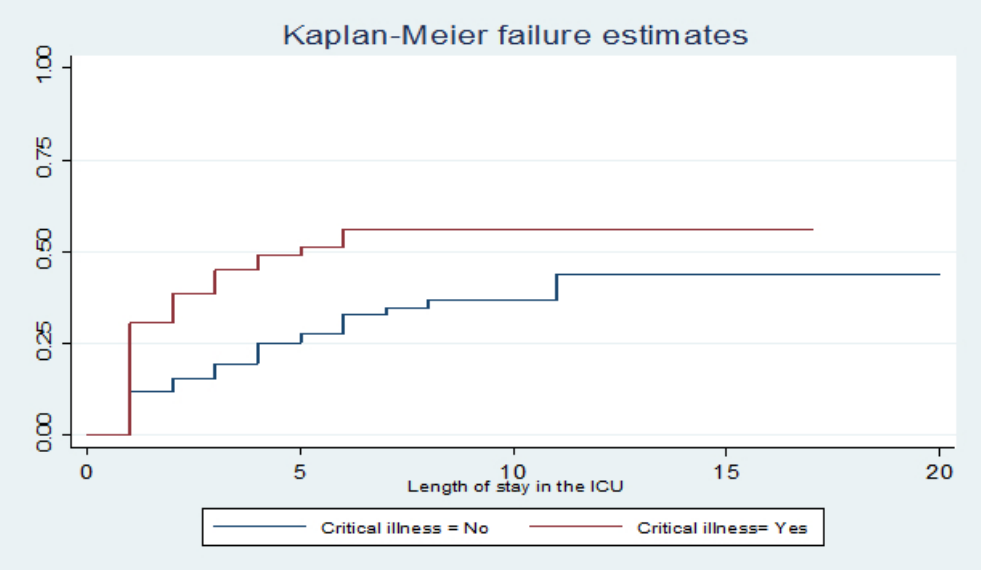

Figure 2: Kaplan-Meier failure (death) estimates curves by children critical illness admitted to pediatric intensive care unit of University of Gondar comprehensive specialized hospital from February 1/2018 to July 30/2019

164x96mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract ***The title describes the study design as* "Incidence and predictors of mortality among children admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, northwest Ethiopia: A prospective observational cohort study". *Page 1***
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ***The abstract describes the method used and Main findings****. page 2, line 19-31*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ***The background and rationale are described in the Background, paragraphs 1, 2, 3, 4, 5 and 6. Page 4-5, Line 64-102***
Objectives	3	State specific objectives, including any pre specified hypotheses ***The specific aims of the study are stated in the Background, paragraphs 6, page 5 ,line 94-104***
Methods		
Study design	4	Present key elements of study design early in the paper ***The study design is discussed in paragraphs 1 of the Methods section, page 6, line 105-107***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ***The institutional setting is described in paragraphs 2 line 108-120 of the Methods section.*** ***Study locations are described in paragraph 1 and 2 of the Methods section; and study timing is discussed in paragraphs of the Methods section. Participant recruitment is mentioned in in population and sample section*****. Page 6**
Participants	6	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants ***Selection of the sample is discussed in paragraph 1 and 2 line 121-130, of population and sample subsection of the Methods section. page 6-7***
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

		Outcomes are discussed in the Outcomes subsection (paragraphs 3 of the Methods section). Data was collected by treating physicians using standardized questionnaire after taking consent from caretakers. Clinical characteristics like, SBP, pupillary light reflex, SaO_2 need of mechanical ventilator was assessed and documented within the first hour and entered into an electronic App to calculate pediatrics index mortality 2 (PIM2) score. **Mentioned in the method section of 131-158, page 7-8**
	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group ***Measurement of the outcomes are discussed in the data collection and measurement of variables subsection. Page 8***
Bias	9	Describe any efforts to address potential sources of bias ***Mentioned in the method section of v*ariable of the study and operational definitions *Page 7-8***
Study size	10	Explain how the study size was arrived at ***Sample size determination was discussed at method, population and sample section. Page 6***
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ***Use of variables is discussed in the data management and analysis subsection. Page 8***
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding ***Statistical methods are discussed in the data management and analysis subsection. Page 8 line 160-178***
		(*b*) Describe any methods used to examine subgroups and interactions Described in in the data management and analysis subsection. ***Results are analysed by socio-demographic and personal attributes like age place of residence .***
		(*c*) Explain how missing data were addressed ***None***
		(*e*) Describe any sensitivity analyses ***None***

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ***At paragraph 1 of result section, page 9***
		(b) Give reasons for non-participation at each stage ***None***
		(c) Consider use of a flow diagram ***None***
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Provider characteristics are presented in Table 1, Table 2, and Table 3.
		(b) Indicate number of participants with missing data for each variable of interest ***None***
Outcome data	15*	*Cross-sectional study*—Report numbers of outcome events or summary measures Both numbers and percentages/proportions are reported throughout the ***Results Section. Page 15-16 line 230-248***
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ***Adjusted results are presented for all outcomes. Page 16-17, table 4***
		(*b*) Report category boundaries when continuous variables were categorized ***Not applicable***
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period ***Not applicable***.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ***None***
Discussion		
Key results	18	Summarise key results with reference to study objectives ***Results are summarized in paragraphs, 1, and 2 of the Discussion section***. Page 18, line 271-283
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ***Strength and limitations are discussed in paragraphs 21, line 344-352***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ***Discussed in discussion and conclusion sub section. 18-22***
Generalizability	21	***Discuss the generalizability (external validity) of the study results*** ***The representativeness of the sample is discussed in the final paragraph of the limitations subsection.***

Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ***Not applicable***

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Incidence and predictors of mortality among children admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, northwest Ethiopia: A prospective observational cohort study

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Incidence and predictors of mortality among children admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, northwest Ethiopia: A prospective observational cohort study.

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Abstract

Objective: To determine the incidence and predictors of mortality among children admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, northwest Ethiopia

Design: A single-center prospective observational cohort study

Participants: A total of 313 children admitted to the intensive care unit of the University of Gondar comprehensive specialized hospital during a one-and-a-half-year period.

Measurements: Data were collected using standard case record form, physical examination, and patient document review. Clinical characteristics like systolic blood pressure, pupillary light reflex, oxygen saturation, and need for mechanical ventilation were assessed and documented within the first hour of admission and entered into an electronic application to calculate the modified Pediatric Index of Mortality 2 (PIM 2) score. We fitted the Cox proportional hazards model to identify predictors of mortality.

Result: The median age at admission was 48 months with interquartile range (IQR: 12 to 122), 28.1% were infants, and adolescents accounted for 21.4%. Of the total patients studied, 59.7% were males. The median observation time was three days with (IQR: 1 to 6). One hundred two (32.6%) children died during the follow-up time, and the incidence of mortality was 6.9 deaths per 100 person-day observation. Weekend admission [Adjusted Hazard Ratio (AHR) =1.63, 95%CI: 1.02, 2.62], critical illness diagnoses (AHR=1.79, 95%CI: 1.13, 2.85), need for mechanical ventilation (AHR=2.36, 95%CI: 1.39, 4.01) and modified PIM 2 score (AHR=1.53, 95%CI: 1.36, 1.72) were the predictors of mortality.

Conclusion: The rate of mortality in the Pediatric intensive care unit (PICU) was high, admission over weekends, need for mechanical ventilation, critical illness diagnoses, and higher Pediatric Index of Mortality 2 scores were significant and independent predictors of mortality.

Strength and limitation of the study

- This study was a prospective cohort study and had used better statistical functions (survival analysis) for better estimation and prediction of mortality.
- This study could help clinicians and health care planners practice evidence-based medicine in a resource-limited setting like ours.
- The PIM 2 scoring was done based on 9 out of 11 parameters as there was no arterial blood gas analyzer in our set up during the study period that might result in misclassification.

Introduction

Though pediatric intensive care units (PICUs) are essential areas of service to save the lives of children with acute neurological deterioration, respiratory distress, cardiovascular compromise, severe infections, accidental poisoning, and other life-threatening conditions; organizational details of pediatric ICUs in low-income settings are lacking [1, 2].

Published data on pediatric critical care in low-income countries remains sparse, making practice modification and outcome improvement difficult. Also, most studies done on predictors of mortality in the PICUs are from high-income countries and are dependent on clinical and laboratory indices, which are not readily available in low-income countries [3]. The few studies that considered epidemiologic and sociodemographic factors were retrospective and cross-sectional, and most did not consider essential parameters [4]. Determining the risk factors of mortality among children admitted to the pediatric intensive care will be crucial to prioritize and

tunnel resources to the most fruitful practice based on the prediction of patient outcomes, especially in resource-limited setups like ours.

This study aimed to determine the incidence and predictors of mortality among children admitted to a pediatric intensive care unit at the University of Gondar comprehensive specialized hospital. It will add to the knowledge of mortality and its predictors, thereby hoping to plan the most efficient method of intervention for those at higher mortality risk, thus contributing to recovery as well as making the assessment of the performance of the services delivered.

Methods

Study design, period and setting

A single-center prospective cohort study was conducted among children aged one month to 18 years admitted to the PICU at the University of Gondar comprehensive specialized hospital from February 1, 2018, to July 30, 2019.

The PICU has six beds with electronic monitors and one mechanical ventilator; on average, there are about 25 pediatric critical care admissions per month. The organizational detail of the PICU in this hospital is lacking. Team composition is often limited to a general pediatrician, resident, interns, and a handful of senior-level nurses, but there are no pediatric intensivists, respiratory therapists, pharmacists, and dieticians.

Population and sample

Patients who stayed for more than two hours in the hospital were included in the study. We excluded patients having incomplete data, and surgical patients admitted only for recovery purposes from the study.

The sample size for this study was determined using a single population proportion of P=21%, from previous Bangladesh study [2] with a 5% margin of error; the sample size became 254, and

after adding 10% contingency, the sample became 279. A total of 376 patients were admitted to the PICU during the study period. We collected data from 327 patients who fulfilled the inclusion criteria. Fourteen patients were excluded from the study due to incomplete data.

Data collection procedure

Data was collected by treating physicians using standard case record form after receiving consent from caretakers. Clinical characteristics like systolic blood pressure (SBP), pupillary light reflex, oxygen saturation, and need for mechanical ventilation were assessed and documented within the first hour and entered into an electronic application to calculate the modified Pediatric Index of Mortality 2 (PIM 2) score. We took sociodemographic data and medical history by interview; and diagnosis, laboratory indices, and the clinical course during the hospital by chart review at discharge. We used the World Health Organization (WHO) International Classification of Diseases 10th version (ICD-10) for disease category, and only the primary diagnoses were used for ICD-10 assignment in patients having multiple diagnoses. The collected data were double-checked by the data collector and the principal investigator. There were orientations and training about data collection and the study's objective every three months and demonstration every Monday for treating physicians and data collectors. The principal investigator supervised the overall process and checked the completeness of case record forms every day. No direct patient care was provided by investigators, who only accessed patients' records.

Variable of the study and operational definitions

The primary dependent variable was time to death (event). In contrast, sociodemographic characteristics included age, sex, relation with the caregiver, caregiver's educational status, and occupation. Clinical characteristics included duration of illness before admission, source of admission, critical illness diagnosis, comorbidity, nutritional status, vaccination status,

interventions given in the PICU, and before admissions like fluid resuscitation, modified PIM 2 score, multi-organ dysfunction syndrome (MODS), and complications.

Event (death): is defined as a patient who died in the hospital during treatment.

Censored: refers to patients who were discharged alive from the PICU or those with no event of interest.

Length of stay (LOS): refers to the duration of stay in days from the date of admission to the date of discharge.

Short term outcome: the outcome of the patient until he or she leaves the hospital

Critical illness: refers to sepsis, severe sepsis, or septic shock within 24 hours of admission or acute respiratory distress syndrome during PICU admission.

MODS: refers to a potentially reversible physiologic derangement in two or more organ systems

Data processing and analysis

After we checked the data for its consistency and completeness, we entered data into EpiData version 3.1 and exported to STATA version 14 for cleaning and analysis. Descriptive statistics like mean, median, and proportions were carried out to summarize baseline characteristics and admission patterns. Also, summary statistics like life table, log-rank test, and Kaplan-Meir curves were computed to determine the incidence rate (IR) of death and to compare survival curves between the different categories of the explanatory variables.

Both bivariate and multivariate Cox proportional hazards models were used to identify the predictors. Variables with p-value < 0.2 in the bivariate analysis were entered into the multivariate proportional hazard model. Ninety-five percent confidence intervals (95% CI) of hazard ratios were computed, and variables with p-value < 0.05 in the multivariate Cox proportional hazards

model were considered significantly and independently associated with the dependent variable. Cox proportional hazards model fitness was checked using the Schoenfeld residuals test.

Ethical approval and consent to participate

Ethical clearance was obtained from the Institutional Ethical Review Board of the University of Gondar's College of Medicine and Health Sciences. Informed verbal consent was obtained from the caretakers. The name or any other identifying information was not recorded on the data collection form, and all information taken from the chart was kept strictly confidential and in a safe place. The information retrieved was used only for the study purpose.

Patient and public involvement

There was no direct patient contact, and investigators accessed only patient records.

Result

Sociodemographic characteristics

A total of 313 patients out of 376 admitted during the 18-month study period were included in the final analysis. The median age at admission was 48 months with interquartile range (IQR: 12 to 122), with a male to female ratio of 1.7:1, as shown in Table 1. The majority of caregivers (92.9%) were parents. More than three-fourth (77.6%) of caregivers had no formal education, and 71.2% were farmers. Most patients were admitted in the spring season (38. 3%), followed by winter (27.2%) (Table 1).

Table 1: Sociodemographic characteristics of patients

Characteristics	**Frequency**	**Percentages (%)**
Age in months		
≤ 12	88	28.1
13-24	29	9.3
25-60	66	21.1
61-132	63	20.1

>132	67	21.4
Sex		
Male	188	59.7
Vaccination status		
Complete	203	64.9
Incomplete/unvaccinated	110	35.1
Comorbid illness (n=43)		
Congenital malformations/genetic disorders	12	27.9
Cerebral palsy with or without seizure disorders	11	25.6
Chronic kidney disease	7	16.3
HIV/AIDS	6	14
Others	7	16.3

HIV/AIDS: Human immunodeficiency virus infection and acquired immune deficiency syndrome

The clinical condition of admitted children

The primary source of admissions in the PICU was the emergency room (60.4%), inpatient pediatrics wards (13.1%), and referrals from other facilities (11.8%). More than three-fourth (77%) of patients were admitted over weekdays and 41.5% in the night shift. The median duration of illness before any health facility visit and admission to PICU was 3 (IQR: 1 to 7) and 6 (IQR: 3 to 13) days. One-third of patients had critical illness diagnoses, of which (41%) had sepsis, (47%) septic shock, and the remaining (12%) had acute respiratory distress syndrome. About one-third of patients (30.7%) had multiple organ dysfunction syndromes (MODS). The minimum modified PIM 2 score was -6.46 (with predicted mortality rate = 0.2%), and the maximum score was 2.47 (predicted mortality rate =92.2%). The mean predicted mortality rate based on the modified PIM 2 score was 11.14%, which gave the standard mortality ratio (SMR) of 2.94 (Table 2).

Table 2: Clinical condition of patients

Characteristics	**Frequency**	**Percentages (%)**
Duration of illness before PICU admission in days		
≤6 days	71	22.7
>6 days	242	77.7

Multi-organ dysfunction syndrome		
Yes	96	30.6
No	217	69.4
Sources of admission		
Home	36	11.5
Other facilities	37	11.8
Emergency room	189	60.4
Wards and Operating rooms	51	16.3
Need for mechanical ventilation		
Yes	37	11.8
No	276	88.2
Nutritional status, Z score		
Normal	163	52.1
Moderate acute malnutrition	50	16
Severe acute malnutrition	100	31.9
Reasons for PICU admission		
Altered mental status	145	46.3
Respiratory failure	82	26.5
Sepsis	59	18.8
Shock	55	17.6
Seizure	46	14.7
Diabetic ketoacidosis	24	7
Acute kidney injury	24	7
Congestive heart failure	21	6.7
Hemorrhage	14	4.5
Trauma	6	1.9
Others	23	7.3

PICU: Pediatric intensive care unit

Intensive care unit outcomes and the incidence of mortality

Nearly one-third of patients (32.6%) died in the PICU. Severe sepsis or multi-organ failure (MOF) (41.2%) was the leading immediate cause of death in the PICU followed by respiratory failure (23.5%), brain herniation (21.6%), and cardiac arrest (12.7%). Fifty-six patients (17.9%) developed complications during their stay in the PICU, including hospital-acquired sepsis (46.4%), hospital-acquired pneumonia (17.9%), and mechanical ventilator-associated complications (10.7%).

Study subjects were followed during the study period, which gave a total of 1473 person-day observations (49.1 person-months), and the median length of stay in the ICU was 3 (IQR:1 to 6) days. Of the total of 313 participants, 102 (32.6%) died during the follow-up time. The incidence of mortality was 6.9 deaths per 100-person day observations (95%CI: 5.34 to 8.34 deaths per 100 person-day). Among deaths reported, more than half (53.9%) died within 24 hours, 13 (12.7%) died between 24 and 48 hours, and the remaining died after 48 hours of admission. Differences in all variables at baseline between strata were determined using the log-rank ($\chi 2$) test, and the equality of hazard was assessed for the different explanatory variables. Kaplan Meier failure curve was plotted for weekend admission (P-value=0.039), and critical illness (P-value= 0.0001) shows a significant difference (Figure 1) and (Figure 2).

Predictors of mortality in the PICU

The Cox proportional hazards model was fitted to identify predictors of mortality. From the multivariate analysis, caregivers' occupation, weekend admission, critical illness diagnoses, PIM 2 score, and need for mechanical ventilation were predictors of mortality. Mortality was 65% lower for those whose caregivers were government employees than farmers (AHR=0.35, 95%CI: 0.14, 0.89). The hazard of mortality was 1.63 times higher for patients admitted over weekends (AHR=1.63, 95%CI: 1.02, 2.60) and 1.79 times higher in patients who had critical illness diagnoses (AHR=1.79, 95%CI: 1.13, 2.85) compared to weekday admission and those without critical illness diagnosis, respectively. Similarly, each one-unit increase in the modified PIM 2 score increased the hazard of mortality 1.53 times, keeping other variables constant (AHR=1.53, 95%CI:1.36, 1.72). Also, those patients who met the criteria for mechanical ventilation (MV), the hazard of mortality was 2.36 times higher compared to those who did not need MV (AHR=2.36, 95%CI: 1.39, 4.01) (Table 3).

Table 3: Bivariate and multivariate Cox proportional hazard model Fit for different independent variables

Variables	Status		CHR (95% CI)	AHR (95% CI)
	Event	Censored		
Age (months)				
≤12	28	60	1	1
13-24	10	19	0.98(0.47 ,2.12)	1.40(0.65 ,3.04)
25-60	26	40	1.30(0.75, 2.23)	1.15(0.63 ,2.08)
61-132	20	43	1.07(0.60 ,1.90)	1.20(0.65, 2.21)
>132	18	49	0.92(0.50 ,1.67)	1.61(0.84 ,3.08)
Address				
Urban	28	43	1	1
Rural	74	168	0.73(0.47,1.13)	0.63(0.37,1.05)
Caregiver' level of education				
No formal education	96	195	1	1
Primary and above	6	16	0.78(0.34, 1.80)	1.26(0.51,3.13)
Caregivers' occupation				
Farmers	72	151	1	1
Merchants and private	9	23	0.82(0.41, 1.64)	1.06(0.47,2.35)
Government employee	7	24	0.50(0.22, 1.16)	0.35(0.14,0.89) *
Unemployed	14	13	1.61(0.91,2.86)	1.11(0.55,2.24)
Day of admission				
Weekday	71	170	1	1
Weekend	31	41	1.47(0.96,2.26)	1.63(1.02,2.60) *
Source of admission				
Home	9	27	1	1
Other facilities	14	23	1.66(0.72,3.86)	1.90(0.76, 4.76)
Emergency room	55	134	1.13(0.56,2.29)	1.59(0.72,3.48)
Wards and OR	24	27	2.11(0.98,4.56)	2.07(0.86,4.99)
Duration of illness before PICU admission				
<6 days	39	107	1	1
≥6 days	63	104	1.43(0.96,2.12)	0.97(0.62,1.54)
Comorbidities				
No	85	185	1	1
Yes	17	26	1.31(0.78 ,2.21)	0.66(0.36, 1.23)
Critical illness diagnosis				
No	53	160	1	1
Yes	49	51	2.05(1.39,3.04)	1.79(1.13, 2.85) *
Nutritional status, Z score				
Normal	45	118	1	1
Moderate acute malnutrition	15	35	1.19(0.66,2.14)	1.49(0.79,2.82)
Severe acute malnutrition	42	58	1.67(1.09,2.55)	1.69(0.94,2.61)

Modified Pediatric Index of Mortality 2	-3.22±1.81		1.51(1.37,1.67)	1.53(1.36,1.72) *
Mechanical ventilation need				
No	79	197	1	1
Yes	23	14	1.93(1.20,3.10)	2.36(1.39,4.01) *
Complications in the PICU				
No	86	190	1	1
Yes	16	21	2.39(1.20,4.73)	1.62(0.79,3.31)
Fluid resuscitation intervention before PICU admission				
No	44	105	1	1
Yes	58	106	1.24(0.83, 1.84)	0.92(0.59 ,1.44)

* Shows statistical significance at a p-value of 0.05, AHR: Adjusted hazard ratio, CHR: Crude hazard ratio
PICU: Pediatric intensive care unit

Discussion

Our study is the first report from a prospective study in a PICU in Ethiopia that demonstrates the mortality is high and identified predictors of mortality like lack of appropriate human resources (weekend admission), critical illness diagnosis, and need for mechanical ventilation. Thes findings help clinicians, and health care planners practice evidence-based medicine in a resource-limited setting and effective prognosis tailored care and resource utilization.

The proportion of mortality(32.6%) in this study with a rate of 6.92 deaths per 100 person-day observation was consistent with the mortality rate in retrospective cross-sectional studies done in the same PICU from 2013 to 2016 (30.9%) [5], and other studies in low-income countries in Africa which ranged from 25% in Mozambique to 50% in Rwanda [6-8]. However, it is lower than the finding of a retrospective cross-sectional study done in Jimma, Ethiopia (40%)[9]. The difference could be attributed to the higher proportion of trauma patients admitted in their PICU compared to ours. When we compare it with other lower and middle-income countries, the mortality rate in our PICU is higher than the mortality rates in studies done in Pakistan (14%)[10] and India (10.58%)[11]. The possible explanation for the observed discrepancies might be suboptimal care, the inadequacy of diagnostic and interventional facilities in our PICU.

Children admitted over the weekends had nearly twice increased risk of mortality than those admitted over weekdays, consistent with the findings of studies done in Canada, Finland, and Austria [12-14]. This increased mortality over weekends might be due to failure to promptly recognize deteriorations among patients in the wards and other sources as a result of reduced staffing ratios. Access to diagnostic services is limited during weekends, which limits the likelihood of arriving at diagnoses. Furthermore, there could be unrecognized deteriorations during handoff and round times and delays in administering interventions. However, our finding was not supported by three American studies and studies done in the United Kingdom and the Republic of Ireland [15, 16]. This discrepancy could be explained by the better standard of care they have and 24 hours around the clock staffing. Better weekend coverage and full hour staffing is recommended for aa better critical care delivery.

This study also highlighted how being a caregiver who is a government employee was associated with lower risk mortality compared to caregivers of peasants. This finding could be explained by differences in health-seeking behavior, access to funds for transportation, and early identification of danger signs between them.

The child who had a critical illness diagnosis had an increased risk of mortality than those who had not. This difference could be because patients with critical illnesses have a low reserve of physiologic function. This finding was consistent with other studies [17, 18].

Amongst many disease severity assessment tools at baseline, PIM 2 does not need extensive laboratory investigation, and it is not affected by subsequent interventions since it is scored within one hour of admission resulting in early identification of the severity of illness and stratification of children for necessary intervention [19], which in turn helps in counseling caregivers of sick children. We used a modified PIM2 score as there was no arterial blood gas analyzer in our PICU during the study period. A unit increment in the modified PIM 2 score doubled the hazard of mortality, which shows the

score is sensitive in detecting morality, and this scoring system is also validated and applicable in many PICUs across the world [20-24]. The higher observed mortality rate than the predicted ones by the modified PIM 2 score in our study indicates the poor quality of intensive care in our setting. Using the modified PIM 2 score to focus the care on those with dangerous modified PIM2 scores, prognosticate outcomes, and tunnel resources to the most in need patients will improve the critical care outcome in low-income settings.

Patients who had respiratory failure, and those who met the criteria for mechanical ventilation had increased mortality than those who did not have indications for ventilation. This finding is consistent with the findings from other studies [25, 26]. Patients who need mechanical ventilation tend to have advanced disease stages. This finding can also be attributed to a limited number of mechanical ventilators in our PICU. There might also be unrecognized ventilator-associated complications in those who were placed on a mechanical ventilator.

Strength and limitations of the study

This study is a prospective cohort study with a better statistical function (survival analysis). The PIM 2 scoring was based on 9 out of 11 parameters as there was no arterial blood gas analyzer in our PICU during the study period. The availability of medical equipment and PICU quality of care and their impact on patient survival was not adequately assessed using standard parameters. Pediatric critical care is not just about saving lives, so the degree of physiologic function retained at discharge should have been assessed using a standard checklist for all discharged patients.

Conclusion

Rate of mortality in the PICU was high, and admission during weekends, need for mechanical ventilation, critical illness diagnoses, and higher modified PIM 2 score were significant and independent predictors of mortality. Full staffing around the clock including better weekend

coverages, and paying due attention for early signs of critical illness may improve intensive care outcomes. Using the modified PIM 2 score to focus the care on those with risky scores, and tunnel resources to the most in need patients and counseling of caregivers might be advisable.

List of abbreviations

AHR: Adjusted Hazard Ratio, AKI: Acute Kidney Injury, CI: Confidence Intervals, CHR: Crude Hazard Ratio, HAS: Hospital-Acquired Sepsis, HAP: Hospital-Acquired Pneumonia, ICD: International Classifications of Disease, ICU: Intensive Care Unit, IQR: Interquartile Range, IR: Incidence Rate, LAMA: Left Against Medical Advice, LOS: Length of Hospital stay, MAM: Moderate Acute Malnutrition, MODS: Multiple Organ Dysfunction Syndrome, MV: Mechanical Ventilation, PI: Principal Investigator, PICU: Pediatric Intensive Care Unit, PIM 2: Pediatrics Index of Mortality 2, SAM: Severe Acute Malnutrition, OR: Operation Room, USA: the United States of America, WHO: World Health Organization

Declaration

Ethical approval and consent to participate

Ethical clearance was obtained from the Institutional Ethical Review Board of College of Medicine and Health Sciences, University of Gondar. Assent and informed written consent were obtained from the caretakers. The name or any other identifying information was not recorded on the data collection form. All information taken from the chart was kept strictly confidential in a safe place. The information retrieved was used only for the study purpose.

Consent for publication

Not applicable

Availability of data and material

Data is available from the corresponding author upon reasonable request.

Competing interests

None declared

Funding

The study was funded by the University of Gondar, Ethiopia. The funder has no role in study design, data collection, and analysis, interpretation of data, the decision to publish, or preparation of the manuscript.

Authors' contributions

NWT, ATA, and KST participated in designing the study, performing data analysis and visualization, validating the work, and preparing the manuscript. NWT took part in funding acquisition, data collection, supervision and software, and other resources. All authors read and approved the final manuscript.

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Figures and legends

Figure 1: Kaplan-Meier failure (death) estimates curves by days of admission

Figure 2: Kaplan-Meier failure (death) estimates curves by critical illness

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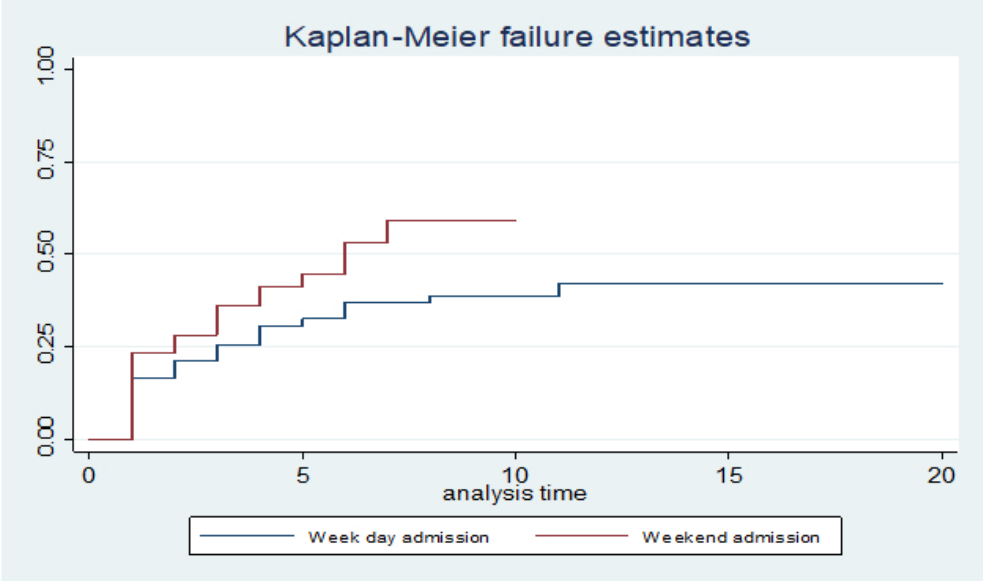

Figure 1: Kaplan-Meier failure (death) estimates curves by days of admission among children treated in the pediatric intensive care unit of University of Gondar comprehensive specialized hospital from February 1/2018 to July 30/2019

53x32mm (300 x 300 DPI)

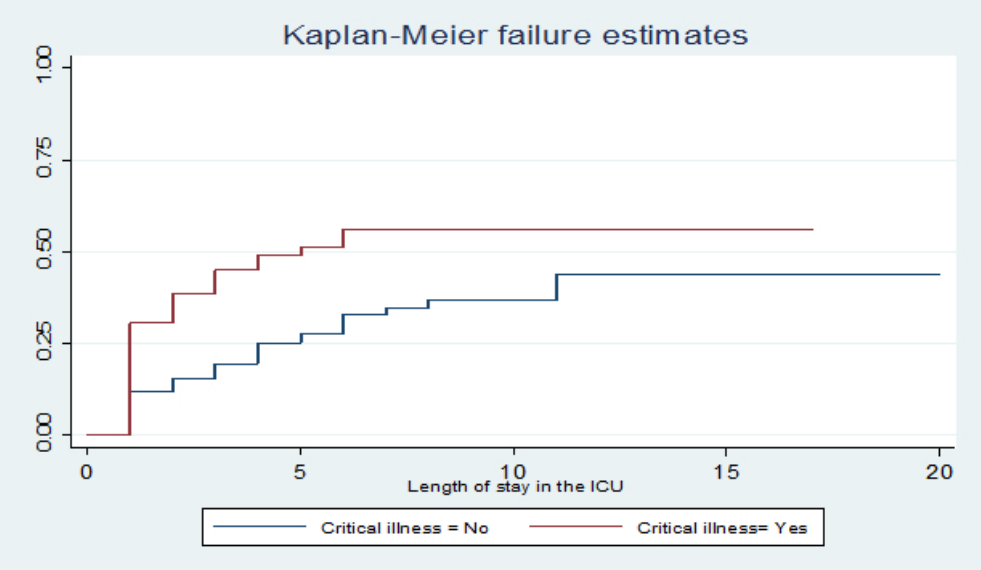

Figure 2: Kaplan-Meier failure (death) estimates curves by children critical illness admitted to pediatric intensive care unit of University of Gondar comprehensive specialized hospital from February 1/2018 to July 30/2019

52x30mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	Indicate the study's design with a commonly used term in the title or the abstract ***The title describes the study design as* "Incidence and predictors of mortality among children admitted to the pediatric intensive care unit at the University of Gondar comprehensive specialized hospital, northwest Ethiopia: A prospective observational cohort study". *Page 1***
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found ***The abstract describes the method used and Main findings****. page 2, line 19-31*
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported ***The background and rationale are described in the Background, paragraphs 1, 2, 3, 4, 5 and 6. Page 4-5, Line 64-102***
Objectives	3	State specific objectives, including any pre specified hypotheses ***The specific aims of the study are stated in the Background, paragraphs 6, page 5 ,line 94-104***
Methods		
Study design	4	Present key elements of study design early in the paper ***The study design is discussed in paragraphs 1 of the Methods section, page 6, line 105-107***
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection ***The institutional setting is described in paragraphs 2 line 108-120 of the Methods section.*** ***Study locations are described in paragraph 1 and 2 of the Methods section; and study timing is discussed in paragraphs of the Methods section. Participant recruitment is mentioned in in population and sample section*****. Page 6**
Participants	6	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants ***Selection of the sample is discussed in paragraph 1 and 2 line 121-130, of population and sample subsection of the Methods section. page 6-7***
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

		Outcomes are discussed in the Outcomes subsection (paragraphs 3 of the Methods section). Data was collected by treating physicians using standardized questionnaire after taking consent from caretakers. Clinical characteristics like, SBP, pupillary light reflex, SaO_2 need of mechanical ventilator was assessed and documented within the first hour and entered into an electronic App to calculate pediatrics index mortality 2 (PIM2) score. **Mentioned in the method section of 131-158, page 7-8**
	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group ***Measurement of the outcomes are discussed in the data collection and measurement of variables subsection. Page 8***
Bias	9	Describe any efforts to address potential sources of bias ***Mentioned in the method section of v*ariable of the study and operational definitions *Page 7-8***
Study size	10	Explain how the study size was arrived at ***Sample size determination was discussed at method, population and sample section. Page 6***
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why ***Use of variables is discussed in the data management and analysis subsection. Page 8***
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding ***Statistical methods are discussed in the data management and analysis subsection. Page 8 line 160-178***
		(*b*) Describe any methods used to examine subgroups and interactions Described in in the data management and analysis subsection. ***Results are analysed by socio-demographic and personal attributes like age place of residence .***
		(*c*) Explain how missing data were addressed ***None***
		(*e*) Describe any sensitivity analyses ***None***

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed ***At paragraph 1 of result section, page 9***
		(b) Give reasons for non-participation at each stage ***None***
		(c) Consider use of a flow diagram ***None***
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Provider characteristics are presented in Table 1, Table 2, and Table 3.
		(b) Indicate number of participants with missing data for each variable of interest ***None***
Outcome data	15*	*Cross-sectional study*—Report numbers of outcome events or summary measures Both numbers and percentages/proportions are reported throughout the ***Results Section. Page 15-16 line 230-248***
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included ***Adjusted results are presented for all outcomes. Page 16-17, table 4***
		(*b*) Report category boundaries when continuous variables were categorized ***Not applicable***
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period ***Not applicable***.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses ***None***
Discussion		
Key results	18	Summarise key results with reference to study objectives ***Results are summarized in paragraphs, 1, and 2 of the Discussion section***. Page 18, line 271-283
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias ***Strength and limitations are discussed in paragraphs 21, line 344-352***
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence ***Discussed in discussion and conclusion sub section. 18-22***
Generalizability	21	***Discuss the generalizability (external validity) of the study results*** ***The representativeness of the sample is discussed in the final paragraph of the limitations subsection.***

Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based ***Not applicable***

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.