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The Outcomes of Emergency Admissions and Associated Factors Among Children Admitted to the Pediatric Emergency Unit at Selected Public Hospitals in Addis Ababa, Ethiopia — A Retrospective Cross-Sectional Study

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Abstract

Background: A pediatric emergency condition is a life-threatening process that, without timely and standard clinical intervention, may lead to death. Therefore, this study aimed to assess the outcomes of emergency admissions and associated factors among children admitted to the pediatric emergency of selected public hospitals.

Methods: An institutional-based retrospective cross-sectional study design was conducted on children admitted to the emergency unit/ward from January 02, 2020, to January 08, 2022, in the emergency units of randomly selected public hospitals. Data were extracted with prepared checklists from February 1 to March 1, 2022.

Result: A total of 303 admitted children's charts were reviewed with 100% coverage. The mean age of children was 37.47 months, and the male-to-female ratio was 1.16:1. The study revealed that the most common causes of emergency admission were pneumonia (22.4%), surgical emergencies (14.5%), and late-onset sepsis (9.2%), respectively. More than half (53.8%) of children were admitted to the Pediatric Emergency Department for less than 24 hours, and the mean length of stay was 2 days. 39.6% of children were discharged with clinical improvement. Known comorbidity (AOR=4.65, 95% CI (1.23-17.64)) and length of stay less than 24 hours (AOR=4.2, 95% CI (1.2-14.7)) were strongly associated with the outcome.

Conclusion: Pneumonia is still the most common cause of pediatric emergency admission, and the mortality rate of children at the Pediatric Emergency Department is high, with known comorbidity showing a significant association with mortality. FMOH recommended developing national pediatric emergency care guidelines and providing skill gap training for healthcare workers.

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Running title: The outcome of emergency admissions and associated factors among children admitted to the pediatric emergency unit.

1. Background

The pediatric emergency condition is a broad aspect of pathologies/disorders requiring proper emergency care as it is the only option for management to save lives, avoid/minimize disability. Emergency care, especially for children, is one of the services that would improve their chances of survival. The Pediatrics Emergency Room is a key area of service in every hospital where pediatric emergencies are promptly handled on a regular basis [1].

Globally, 7.4 million children and adolescents died in 2019, primarily from preventable or treatable causes. Furthermore, the burden of child mortality is higher in developing countries. Africa continues to have the highest under-five mortality rate (74 per 1000 live births), which is over 9 times higher than Europe (8 per 1000 live births). Under-five mortality has decreased by 60% globally, from 93 deaths per 1000 live births in 1990 to 38 deaths per 1000 live births in 2019. However, the worldwide burden of child and adolescent fatalities continues to be enormous [2].

The health and survival of children is a concern to every country throughout the globe. However, children under the age of five accounted for 70% of deaths, and a total of 5.2 million deaths occurred among children under the age of 5 in 2019 worldwide. A total of 2.2 million children and adolescents aged greater than 5 died, with 43% of deaths occurring during the adolescent period (ages 10 to 19) [3].

Preventable diseases such as pneumonia, diarrheal diseases, and malaria are major causes of childhood morbidity and mortality globally. Pneumonia, diarrhea, and malaria account for 41% of yearly deaths globally and 49% in Africa [4]. According to the 2019 Ethiopia Mini Demographic and Health Survey (EDHS), the prevalence of under-five mortality rate in Ethiopia is 55 per 1000 live births [5].

There was an increase in overall admissions for children and young people between 2006/7 and 2015/16, from 2.6 million admissions to 2.9 million admissions. Emergency admissions were the most common type of admission, constituting about 39%. There are a number of reasons why children and their families may seek emergency care in a hospital. In

many situations, it is the exact place to go, or it could be the mere option [6].

One of the primary goals of the World Health Assembly is to improve emergency services, particularly for children, through the Millennium Development Goals (MDG) and Sustainable Development Goals (SDG) [7]. In reality, the number of children under the age of five who die every year from preventable causes has dropped from 12.5 million in 1990 to 5.2 million in 2019. A significant goal of the Sustainable Development Goals (SDGs) is to reduce child mortality to less than 2.5 percent in all countries by 2030. Between 2015 and 2030, the global birth rate is predicted to remain around 140 million per year [2]. One hundred twenty-one nations have already achieved the SDGs' objective for under-five mortality, with another 21 expected to do so by 2030 if current trends continue. Efforts to speed development in the remaining 53 nations, two-thirds of which are in Sub-Saharan Africa, must be stepped up [3]. According to the National Strategy for Newborn and Child Survival in Ethiopia, 2015/16 – 2029/20, reducing under-five mortality from the 2013 level of 64/1,000 to 29/1,000 and the infant mortality rate from 44/1000 to 20/1000 by 2019/20 were major goals [8].

WHO recommended that immunization, exclusive breastfeeding, correct nutrition, and timely and appropriate treatment of common childhood illnesses can all help to avoid many child deaths. Air pollution reductions and improved access to basic hygiene, safely managed drinking water, and sanitation also help to save many child lives [2].

It is obviously clear that the main purpose of pediatric emergency admission is to minimize mortality and disability through the standard of clinical emergency care. The success of the intervention is determined by assessing the outcome of health care intervention. The determinant factors for the outcome of intervention may vary from institution to institution. In Ethiopia, some studies were conducted to assess the pattern and outcome of admissions in children's emergency units, and all the studies have shown a predominance of respiratory diseases as the major causes of morbidities and mortality in children [9][10]. However, there is no current data on the issue that considers the current health care system, and also the existing studies are conducted only in a single hospital, which is difficult for generalization.

The results of this study will help to develop treatment strategies and minimize or prevent disabilities for the major preventable causes of deaths and disabilities among pediatric patients admitted to the pediatric emergency unit. With this understanding, the current study aimed to assess the outcomes of emergency admissions and associated factors among children admitted to the pediatric emergency units of selected public hospitals.

2. Conceptual Framework

By considering the preceding review, causes of emergency admission and factors associated with outcomes among children admitted to the pediatric emergency unit, as depicted in ***figure 1*** below, this shows how the study's unique variables interact with one another and verifies the variables needed for the intended research study. This conceptual framework is built on the assumption that the outcome of pediatric emergency unit-admitted children was correlated to those factors as gleaned from various literatures [7][9][10].

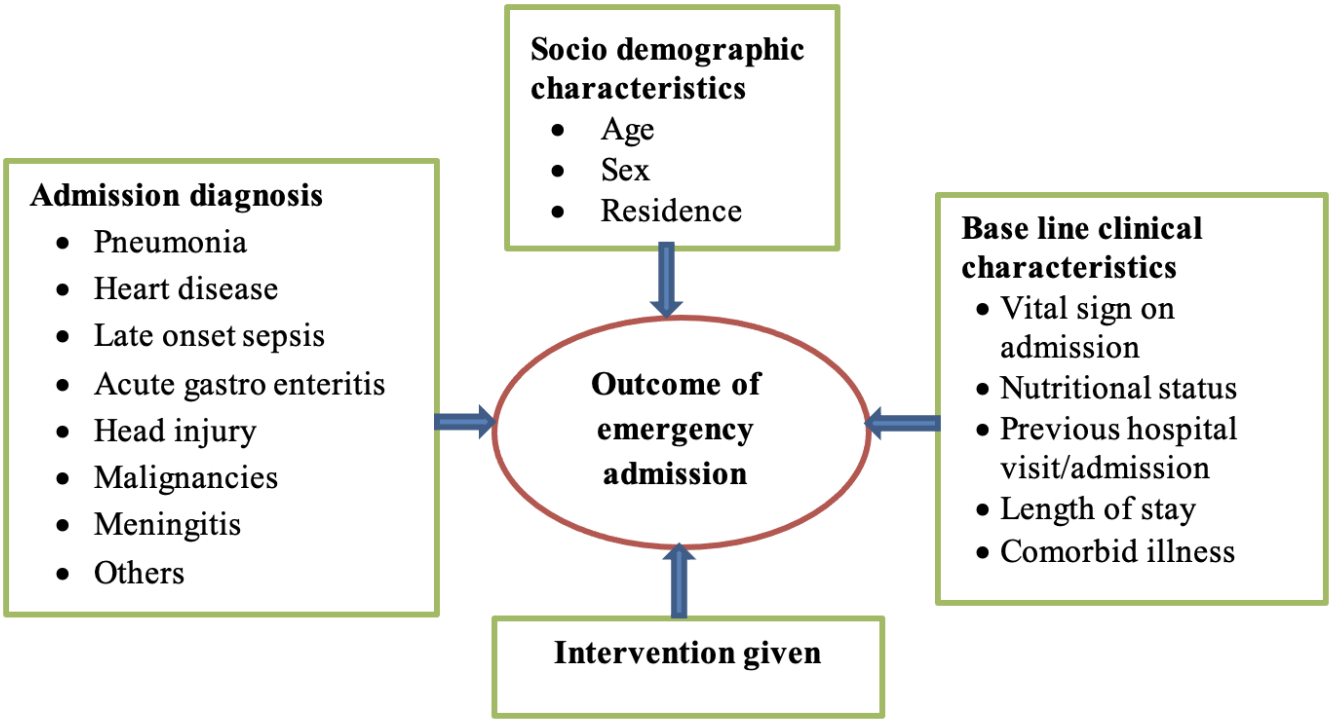

Figure 1. Conceptual framework used for variables predicting the relationship of patient outcomes and associated factors among pediatrics emergency unit patients admitted at public hospitals, Addis Ababa, Ethiopia (January 02, 2020 – January 08, 2022)

3. Materials and Methods

3.1. Study setting

The study was conducted among pediatric patients who were admitted to the pediatric emergency unit of randomly selected public hospitals in Addis Ababa, Ethiopia. Addis Ababa is the capital city of Ethiopia. The city has a total area of 527 square kilometers, administratively divided into 11 sub-cities and 121 districts (known locally as "woredas"), with a population of over 5 million people and a growth rate of 4.4 percent [11]. Addis Ababa has 13 public hospitals spread across 11 sub-cities (five federal hospitals, six under the administration of Addis Ababa health bureau, one operated by the federal police force, and one owned by the armed forces) [12]. The study was conducted in four public hospitals, namely, Tikur Anbesa Specialized Hospital, Zewditu Memorial Hospital, Yekatit 12 Hospital, and St. Peter's Hospital.

3.2. Study design and period

An institution-based retrospective cross-sectional study design was conducted in children admitted from January 02, 2020, to January 08, 2022, in the pediatrics emergency unit of randomly selected public hospitals. Data were extracted with prepared checklists from February 1 to March 1, 2022.

3.3. Source population

Children who were admitted and randomly selected for the pediatric emergency unit of selected public hospitals.

3.4. Study population

Children admitted from January 02, 2020, to January 08, 2022, in the emergency unit of randomly selected public hospitals, and randomly selected admitted children from the logbook and admission charts who fulfilled the eligibility criteria.

3.5. Eligibility criteria

All pediatric age group patients who were admitted to the pediatric emergency unit of selected public hospitals during the study period were included in the study, whereas those who died on arrival or died within two hours of admission, children referred to other hospitals, and children whose charts had incomplete information were not included in the study.

3.6. Sample size determination

A single population proportion formula was used to calculate the sample size by considering the following assumption: - p (proportion in the previous study on a similar topic) as severe pneumonia was a major cause of admission death at the emergency (23.3%) in the study done on the Pattern of Admissions to the Pediatric Emergency Unit of Tikur Anbessa Hospital in Addis Ababa, Ethiopia (2012-2013G.C) [9] and by considering a 95% confidence interval (CI) with a level of precision z = 1.96, a p-value of 0.05, a margin of error of 0.05, and q = 1-p. By adding 10% as non-respondents (by considering lost or incomplete sheets), giving a total sample size n = **303**.

3.7. Sampling procedure

The study population was selected from the charts of four randomly selected public hospitals in Addis Ababa having pediatric emergency units by using a simple random selection technique. To get the study participants, first, the total number of children who were admitted from January 02, 2020, to January 08, 2022, was obtained from each hospital. And sampling units were selected from each hospital by allocating the total sample proportionately. Then the study units were determined by a systematic random sampling technique after getting the sampling frame from the institutional list.

3.8. Data collection tools and procedures

The checklist was adopted and modified from previous related literatures[9][13] to collect data. The sample populations were first identified from registration books in PED. Then the children's medical records were retrieved, and data was collected from medical records/charts using a pre-prepared structured checklist.

3.9. Study variables

Dependent variables: Outcome of emergency admission

Independent variables

- Sociodemographic characteristics of children (age, sex, and address).
- Diagnosis at admission, nutritional status, vital signs on admission, interventions given, previous hospital visit/admission, length of stay, comorbid illness.

3.10. Operational definitions

- **Pediatric emergency admission**: an admission where the physician admits the child to PED due to a sudden and unexpected change in the child.
- **Clinical outcome:** reveals that the patient survived or died at the time of discharge.
- **Pediatric patients survived**: Patients who survived during the pediatric emergency unit stay, including patients who were improved, transferred to the pediatric ward, or discharged.
- **Pediatric patients non-survived**: Patients who are not alive at the time of discharge.
- **Discharge**: the procedure of releasing patients at the completion of their visit.
- **Death**: - the irreversible cessation of all biological function that sustains an organism.

3.11. Data quality assurance

To ensure the validity and reliability of the data collection tools (checklist) and procedures, the reliability of the data extraction checklist was checked during pretesting by reliable analysis and suggests a reliable tool. A pretest was conducted at Menilik II Hospital on 5% of the total sample size calculated three weeks before the actual data collection period. Based on the findings, appropriate feedback and correction were considered. Data collectors and supervisors were trained for two days on the data collection checklist and data collection procedures.

3.12. Data processing and analysis

Data was entered and cleaned using Epi-Data version 4.6.0.0 statistical software and transferred to SPSS version 23 for further analysis. Narratives, tables, and graphs were used for data presentation. Bivariate logistic regression analysis was used to check variables for association with the dependent variable individually. Variables found to have association with the dependent variable (p-value up to 0.2) were entered into multiple logistic regression models for further analysis, and variables having a p-value of less than 0.05 were considered significantly associated with the dependent variable. The degree of association between dependent and independent variables was expressed by using odds ratios with 95% confidence intervals.

4. Result

4.1. Socio-demographic characteristics of children

This study was undertaken among 303 children from 1 month to 15 years old who were admitted to the pediatrics emergency department/unit for medical record document review, with a 100% response rate (coverage). The majority, 236 (77.9%), of children were aged less than 5 years. The mean (±S. D.) age of the children admitted to the pediatrics emergency department of selected hospitals during the study period was 37.47 (±40.6) months. Of the total admitted patients, 163 (53.8%) were males and 140 (46.2%) were females. The male to female ratio of pediatric emergency unit admissions was 1.16: 1. Over two-thirds, 208 (68.6%), of the admitted children were from urban areas.

4.2. Baseline Information on Clinical and Children Characteristics

From a total of 119 (39.3%) patients who presented to the pediatric emergency department, 77 (25.4%) were referred from public hospitals, and a small number of children (42, 13.9%) were referred to hospitals from private health facilities. More than half of the admitted children (172, 56.8%) had a previous hospital visit, and 41.9% also had a previous hospital admission. Vital signs were deranged during emergency presentation in more than half (171, 56.4%) of the cases. As depicted in **Table 1** below, respiratory rate derangement was seen in 139 (46%) children, and 30% of children also had deranged oxygen saturation. 60 (20%) of children were also experiencing a known comorbid illness; among these, 38.3% had CHD comorbidity. 27 (8.9%) of children were malnourished.

Table 1. Baseline Clinical and children characteristics of pediatrics admitted to public hospitals, Addis Ababa, Ethiopia (January 02, 2020 –January 08, 2022)

Clinical Characteristics			Frequency		Percent	
Source of Referral	Self		119		39.3	
	Public health center		65		21.5	
	Private health facility		42		13.9	
	Public hospital		77		25.4	
Previous hospital visit	Yes		172		56.8	
	No		131		43.2	
Previous hospital admission	Yes		127		41.9	
	No		176		58.1	
Initial vital signs status at PED evaluation	Normal		134		44.2	
	Deranged	RR	139	169	45.9	55.8
		PR	69		22.8	
		Temperature	50		16.5	
		Spo2	91		30	
	Total		303		100	
Known comorbid illness	Yes	CHD	23		7.6	
		Malnutrition	16		5.3	
		Malignancy	6		2.0	
		GDD	1		0.3	
		Other	14		4.6	
	No		243		80.2	
	Total		303		100	
Nutritional status	Well-nourished		276		91.1	
	Malnourished		27		8.9	

4.3. Organ system involvement and major causes of emergency department admission

More than one-third (35.3%) of the children were having respiratory system involvement, followed by gastrointestinal (25.4%), and, as **depicted in figure 2** below, cardiovascular (12%) system involvement by the time of PED admissions.

Pneumonias of different severity (21.4%), surgical emergencies of all categories (14.5%), late onset of sepsis (9.2%), acute gastro-enteritis with hypovolemic states (8.3%), and heart disease of all subtypes (7.6%), seizure disorder (3.3%), meningitis (3%), malignancies (2.6%), type 1 DM (2.6%), and burns (2.3%) were among the top 10 leading causes of PED admissions. TB, anemia, hepatitis, and fractures were among the less frequent causes of PED admissions.

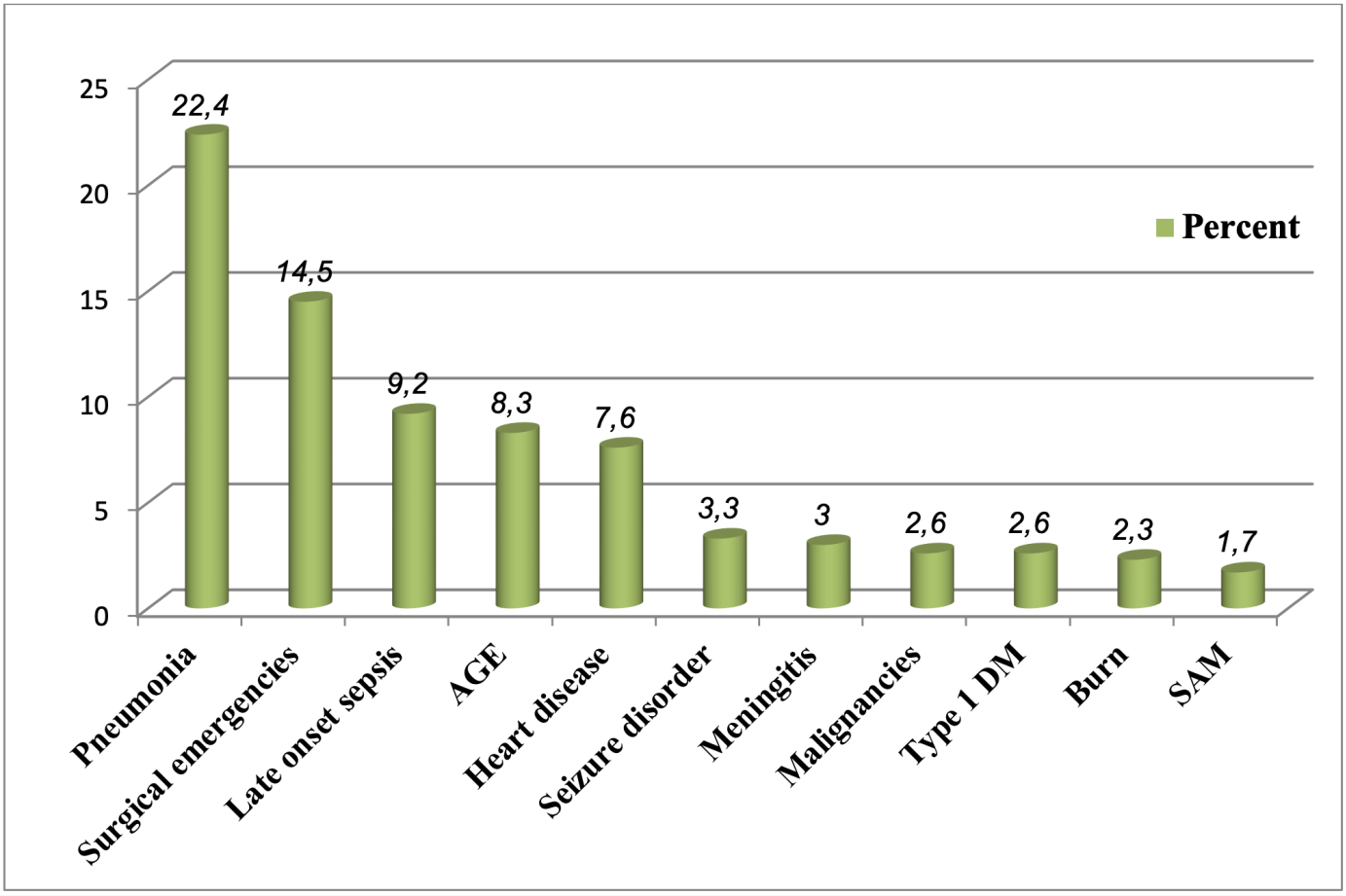

Figure 2. Major causes of pediatrics admitted to public hospitals, Addis Ababa, Ethiopia (January 02, 2020 – January 08, 2022)

4.4. Clinical management and length of stay in pediatric emergency department

Among 303 children admitted to selected public hospitals, more than two-thirds (68.3%) of them were treated with antibiotics, 48.8% got oral or intravenous fluid treatment, and 109 children were treated with oxygen administration. Of all, only 134 (44.2%) of children were seen by a consultant or senior physician during admission.

The mean length of stay in pediatric emergency admission at the study hospitals was 2 days. More than half (53.8%) of children stayed at the pediatric emergency department for less than 24 hours, and only 18.5% stayed for greater than 72 hours.

4.5. Outcome of pediatric emergency department admissions

The large majority of patients admitted to PED were either discharged with improvement (39.6%) or admitted to wards/ICUs (47.5%). As presented in **Figure 3** below, the crude death rate in PED was 5%.

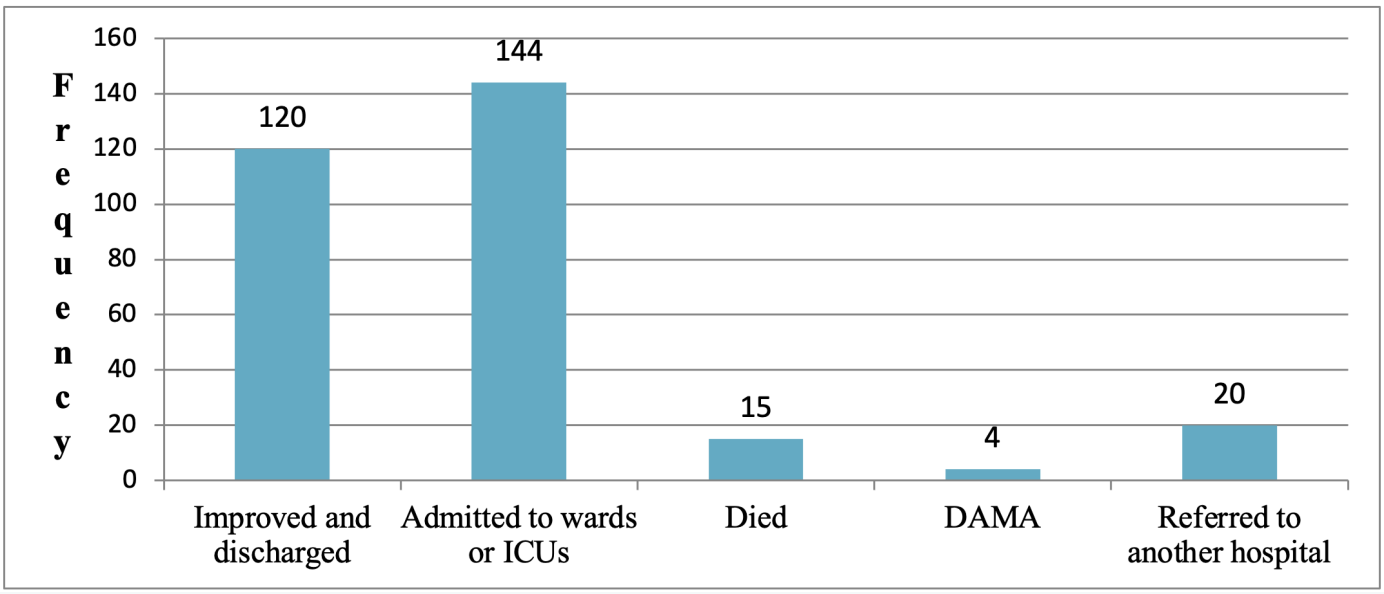

Figure 3. Outcomes of pediatric department admission at public hospitals, Addis Ababa, Ethiopia (January 02, 2020 – January 08, 2022)

4.6. Factors associated with outcomes

Factors associated with the outcomes of children admitted to PED showed that children who had known comorbidities, children who were treated with fluid during admission, and length of stay less than 24 hours were strongly associated with the death of children, with P-values less than 0.05.

As depicted in **Table 2** below, there was a relationship (p=0.024) between known comorbidity and final outcome – those children who had known comorbidities were 5 times more likely to die than children who had no comorbidities. There was also an association seen between fluid administration and treatment outcome; 85.7% of children who received IV fluid treatment during their emergency stay left the emergency department alive. Results also revealed that children who stayed less than 24 hours at the PED were 4 times more likely to die than children who stayed more than 24 hours.

Table 2. Factors associated with outcome of children admitted to public hospitals, Addis Ababa, Ethiopia (January 02, 2020 –January 08, 2022)

Variables	Value	Outcome		COR	AOR	P-value
		Death	Alive			
Age	<1 year	11	119	3(0.65-13.97)	0.4(0.10-2.27)	0.298
	1-5 years	2	104	0.63(0.09-4.55)	1.87(0.22-16.1)	0.571
	>5 years	2	65	1	1	
Previous hospital admission	Yes	9	118	2.16(0.75-6.23)	1.22(0.33-4.55)	0.772
	No	6	170	1	1	
Vital sign at presentation	Deranged	13	156	0.18(0.04-0.82)	1.94(0.32-11.73)	0.469
	Normal	2	132	1	1	
Known comorbidity	Yes	8	51	5.32(1.84-15.31)	4.65(1.23-17.64)	**0.024***
	No	7	237	1	1	
Heart diseases	Yes	3	20	3.35(0.87-12.84)	4.59(0.90-23.5)	0.067
	No	12	268	1	1	
Late onset sepsis	Yes	3	25	2.63(0.70-9.94)	2.77(0.55-13.86)	0.215
	No	12	263	1	1	
AGE	Yes	2	23	1.77(0.38-8.34)	6.73(0.67-67.3)	0.105
	No	13	265	1	1	
Fluid treatment	Yes	2	135	0.17(0.04-0.79)	0.14(0.02-0.93)	**0.041***
	No	13	153	1	1	
Length of stay	<24 hours	10	119	2.84(0.95-8.52)	4.2(1.2-14.7)	**0.025***
	>=24 hours	5	169	1		

5. Discussion

This study assessed the causes of admission into the emergency unit, treatment outcomes, and associated factors at Public Hospitals in Addis Ababa, Ethiopia. A total of 303 pediatric emergency unit-admitted children's medical records (charts) were reviewed during the study period.

This finding reveals that the common causes of morbidity among admitted children in the study public hospitals were pneumonia (22.4%), surgical emergencies (14.5%), late onset sepsis (9.2%), AGE (8.3%), and heart diseases (7.6%), which were the major diagnoses of pediatric emergency admission. This is different from the study done in Singapore [14], which showed that the major diagnoses of emergency admission were URTI (19.9%), unspecified fever (7.1%), gastroenteritis (6.5%), and fracture (3.7%), and the study done in Nigeria [15], which indicated that malaria 29.6%, broncho-pneumonia 9.6%, diarrhea 9.0%, septicemia 8.5%, and surgical emergencies 5.8% were the major diagnoses of admission. This might be due to differences in socio-economic and disease prevention methods between the two settings. This is also slightly different from the previous study conducted in Ethiopia [9], where severe pneumonia (27.4%), heart diseases (13.2%), late onset sepsis (8.5%), AGE (8%), and head injury (4.7%) were the major diagnoses of admission. This may be due to the advancement of cardiac centers in Ethiopia.

In this study, 39.6% of admitted children were successfully managed at PED and discharged with improvement. This is

much lower than the study done in Italy (88.2%) and in Nigeria (79%) [16][17], which may be due to differences in the quality of care between these two settings. And also, this result is much lower than the study done in Ethiopia (84.5%) [9]. This might be due to the high admission rate to pediatric wards/ICUs because the emergency stay protocol for most hospitals is 24 hours.

This study clearly showed mixed outcomes of emergency admission. A higher proportion (47.5%, n=144) of cases required admission to the wards/ICUs, indicating the seriousness of diseases. This result is lower than the study done in Tanzania (72%) and Nigeria (50%) [7][18] and higher than the study done in Italy (10.94%)[16]. This might be due to different emergency treatment setups. There was 8.5% admission in the previous study done in Ethiopia, which is lower than in this study [9]. This may be due to a change in emergency admission protocol, and this study includes an additional 3 referral hospitals.

This study also showed that 1.3% of children were discharged against medical advice, which is lower than the study done in Nigeria (4.7%) [15], may be due to difference in level of patient satisfaction between the two settings. 6.6% of children were referred to other hospitals for further treatment, which is higher than in the previous study in Ethiopia (0.2%) [9]. This may be due to an increase in division of specialties to different hospitals, and the previous study was done only in one hospital.

In this study, the crude PED mortality rate of 5% is much lower than the findings of similar studies conducted in Nigeria (11.6%) and Tanzania (9%) [7][18]. This could be due to differences in disease patterns and quality of emergency care between these settings. Also, this result is slightly higher than the study done in Ethiopia (4.1%) [13]. This might be due to the previous study being done only in one hospital and the difference in study period.

The finding in this study revealed that children who had known comorbidity were 5 times more likely to die than children who had no known comorbidity. This result is supported by the study done in the USA [19]. Also, in this study, children who were in fluid treatment during their emergency stay were less likely to die than children who were not in fluid treatment. However, this result is not in agreement with the study conducted in (Kenya, Uganda, and Tanzania) [20]; their result shows that children who took fluid treatment were more likely to die than those who did not take fluid. The number of deaths in this study showed a fourfold increment trend after children were admitted for a length of stay less than 24 hours in the PED (p=0.025; CI=(1.2-14.7); AOR=4.2), which is similar to the study done in Ethiopia [9].

6. Limitations of the study

The possible limitation of our study is that it is a retrospective study conducted in selected public hospitals that do not include private hospitals. The study needs to be conducted in multi-center settings (to include both the public and private hospitals with pediatric emergency admissions) in the future.

7. Conclusion and Recommendations

7.1. Conclusion

This study reveals that the major prevalent causes of disease morbidity and mortality of pediatric emergency department admissions are pneumonia, followed by surgical emergencies and late onset sepsis, all of which are preventable and treatable through early detection and risk reduction. Mortality at the pediatric emergency department is also high (5%). Children who had known comorbidities and a length of stay less than 24 hours in the emergency department had a significant association with the mortality of children at the pediatric emergency department.

7.2. Recommendations

All health care workers in the pediatric emergency department and parents of children should be involved in early case detection and management, including risk reduction, which is vital for the success of health interventions. Based on the findings, the authors would like to recommend the following major points:

- All health care professionals who are working in the pediatric emergency department should emphasize timely case detection and treatment.
- Provide UpToDate and skill gap training through technology support for health care workers, and all stakeholders should work together to strengthen the quality of pediatric intensive care unit services.
- Children's parents should be informed of the importance of seeking early clinical diagnosis and treatment for clinical cases, risk reduction, and the benefits acquired from regular follow-up to limit early deaths of children related to comorbidities.
- FMOH and policymakers should develop national pediatric emergency care guidelines for the appropriate management and timely intervention.

Abbreviation and Aeronomy

AGE-Acute Gastroenteritis, **AOR-**Adjusted Odds Ratio, **CI-**Confidence Interval, **DAMA-** Discharged Against Medical Advice, **FMOH-**Federal Ministry of Health, **MDG-**Millennium Development Goal, **PED-**Pediatric Emergency Department, **PI-**Principal Investigator **, PICU-** Pediatric Intensive Care Unit, **SDG-** Sustainable Development Goal, **TASH-** Tikur Anbesa Specialized Hospital, **URTI-**Upper Respiratory Tract Infection, **WHO-** World Health Organization, **ZMH-** Zewditu Memorial Hospital.

Statements and Declarations

Availability of data and materials

All relevant data are included within the manuscript document. If necessary, it is possible to contact the corresponding author to get additional materials.

Ethics approval and consent to participate

Written ethical clearance was obtained with ref. number 01/22/SNM from the Institutional Review Board (IRB) of Addis Ababa University (AAU), College of Health Sciences, School of Nursing and Midwifery, and written permission was obtained from Tikur Anbessa Specialized Hospital, Zewditu Memorial Hospital, Yekatit-12 Hospital, and St. Peters Hospital. Informed consent was obtained from the respective children's caregivers after a detailed explanation of the aim of the study, procedures, potential risks, benefits, and rights of the participants was given to the participants, and written consent from the participants was obtained. Confidentiality of information was maintained; no unauthorized person had access to the information, and names or other identifiers were not recorded. Methods were carried out in accordance with Helsinki guidelines and regulations.

Authors' Contributions

The paper is the result of joint research, and the contribution of all authors is comparable to the others.**Tsegaye Asinakew** searched the literature, trained field researchers for data collection, and wrote the draft results and review of the manuscript, and **Teshome Habte** supervised and reviewed the report, conceptualized the report, and participated in validation and manuscript preparation. The respective authors read and approved the final manuscript.

Competing interests

All authors reported no conflicts of interest for this work. The authors followed all ethical principles of scholarship in the preparation, data collection, analysis, interpretation, and completion of this thesis. All scholarly matter addressed in the thesis has been given recognition through citation (cited and referenced) of all sources used to prepare this document. This thesis is in partial fulfillment of the requirements for graduation as a Master's degree from the School of Nursing and Midwifery post-graduate Studies at Addis Ababa University. We did not receive any financial support from our organization, and we confirm that this work is original and has not been published elsewhere nor is it currently under consideration for publication by any journal.

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Availability of data and materials

All relevant data are included within the manuscript document. If it is necessary, it is possible to contact the corresponding author to get additional materials.

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