Magnitude and Associated Factors of Chronic Liver Disease in Children at Tikur Anbessa Specialized Hospital Five Years Trend Analysis, Addis Ababa, Ethiopia, 2025

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Abstract

Background: Chronic liver disease (CLD) in children, characterized by progressive liver dysfunction lasting over six months, poses significant global health challenges. Pediatric CLD incidence is notably high in Africa (9.9–14.7 per 100,000), with Ethiopia reporting 24 adult CLD deaths per 100,000 population in 2019 [6,9,12]. Limited local data contribute to diagnostic delays, underreporting, and inadequate health policies. This study assessed the magnitude and associated factors of pediatric CLD at Tikur Anbessa Specialized Hospital (TASH), Ethiopia, to address epidemiological and diagnostic gaps.

Methods: A hospital-based cross-sectional study was conducted at TASH from December 2024 to January 2025, involving 240 children with CLD. Retrospective data were extracted from medical charts and the digital iCare system using structured questionnaires. Bivariate and multivariate logistic regression analyses identified factors associated with cirrhotic CLD.

Results: Among participants (55% male, mean age 6.4 years ±4.4 SD), CLD magnitude was 4.8%. Cholestatic liver disease was the most common etiology, yet 60% of cases had undetermined causes. Portal vein thrombosis (5.8%) and autoimmune hepatitis (5.5%) were other etiologies, alongside chronic viral hepatitis (HBV/HCV/CMV: 4.1%) and rare causes like congenital hepatic fibrosis, Gaucher's disease, and schistosomiasis. Factors significantly associated with cirrhotic CLD included age 5–10 years (P=0.02), symptom duration 6–12 months (P=0.007), variceal bleeding (P=0.001), elevated alkaline phosphatase (ALP; P=0.024), prolonged INR/prothrombin time (P=0.037), APRI score >2 (P=0.001), and undetermined etiology. Mortality was 10.8 %, with cirrhosis and undetermined etiology strongly linked to death (AOR=3.2, 95% CI: 0.5–5, P=0.001).

Conclusion: Pediatric CLD burden and mortality are substantial in Ethiopia, with a high proportion of cases remaining etiologically undefined. Findings underscore the urgency for enhanced diagnostic capacity and tailored public health interventions. Prospective multicenter studies with larger samples are recommended to inform national policies for CLD prevention and management.

Contents

Abbreviations/Acronyms

ALP	Alkaline Phosphatase Enzyme
ALT	Alanine Transaminase Enzyme
AOR	Adjusted Odds Ratio
APRI-SCORE	AST-to-Platelet Ratio Index
AST	Aspartate Transaminase Enzyme
CBC	Complete Blood Count
CLD	Chronic Liver Disease
CT	Computed Tomography
GGT	Gamma glutamyl transaminase
Hgb	Hemoglobin
HSM	Hepato-Splenomegaly
LFT	Liver Function Test
NAFLD	Non-alcoholic Fatty Liver Disease
TASH	Tikur Anbessa Specialized Hospital
USG	Ultrasonography

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CHAPTER ONE

1. Introduction

1.1 Background

Chronic liver disease is a progressive deterioration of liver functions for more than six months. Liver functions consist of synthesis of clotting factors, detoxification of harmful products of metabolism, and excretion of bile. End stage of CLD established by structural fibrosis result in cirrhosis. Chronic liver diseases in children signify an emergent public health problem with significant morbidity and mortality [1, 2, 9, 14].

The global incidence of pediatric CLD was 9.4 [6.6 -12.5] per 100,000 population in 2019, showing a 17.9% increase in incidence rate over the past 30 years [3, 4, 5, 9]. In the African continent, the pediatric CLD incidence rate ranged from 9.9-14.7 per 100,000 according to the global burden of disease database 2019. There has been a 102% increment in incidence in East Sub-Saharan Africa over the past 30 years. In Ethiopia, adult chronic liver disease is the 7th leading cause of death, accounting for about 24 deaths per 100,000 population in 2019 [6, 9, 12]. Despite numerous global research efforts, there is a significant research gap in understanding the burden of pediatric chronic liver disease in Ethiopia, with most studies focused on adult chronic liver disease outcomes. This study aimed to address this research gap and provide insight into the specific national prevalence.

Pediatric CLD is spectrum of disorders dependent on age and etiologic indices. Neonatal cholestasis and chronic viral hepatitis were leading reported etiologies of CLD in < 5 years and older children respectively [7]. The most identified etiologies were chronic hepatitis [Infectious/noninfectious], metabolic and genetic liver diseases, cholestasis and congenital liver diseases [8]. Recently, non-alcoholic fatty liver disease (NAFLD) has been described as a common cause of CLD with a pooled mean prevalence of 7.65 % in all children, and 34% in obese children [7]. The approach to the diagnosis and management of CLD has been revolutionized by the advent of better radiological diagnostic techniques, recent advances in the serological diagnosis of hepatotropic viruses, autoimmune markers and improved liver biopsy

technique. Although being an invasive tool, histopathological evaluation of liver biopsy is still considered the cornerstone for diagnosis of CLD [8].

1.2 Problem statement

Chronic liver disease (CLD) in children poses a global health challenge, with protean prevalence and etiologies shaped by age, genetics, and geography [9]. In sub-Saharan Africa, including Ethiopia, pediatric CLD remains understudied despite its heterogeneous burden, compounded by infectious diseases, malnutrition, and limited diagnostic resources. At Tikur Anbessa Specialized Hospital (TASH)—Ethiopia's largest tertiary center an increasing number of children with suspected or confirmed CLD are referred nationwide, yet no institutional or national data exist to quantify its magnitude, clinical profiles, or risk factors.

This gap perpetuates systemic underestimation of CLD-related morbidity and mortality. Primary healthcare providers, lacking evidence-based guidance, may misdiagnose or delay interventions, while policymakers remain uninformed about its public health urgency. Existing studies predominantly focus on adult CLD or high-income settings, neglecting pediatric populations in sub-Saharan Africa, where contextual factors like poverty and healthcare access uniquely influence outcomes.

This study addresses this critical void by investigating pediatric CLD at TASH. It aims to determine the prevalence of CLD, identify demographic, clinical, and etiological factors driving disease, and analyze systemic barriers to care. Though limited to a single referral center, this foundational work highlights an overlooked crisis, advocating for resource allocation and future multi-center research to mitigate CLD's silent burden in low-resource settings.

1.3 Significance of the study

This research, conducted at the TASH pediatric gastroenterology outpatient clinic in Ethiopia, holds critical academic and practical significance as the first institution-based study in the country to assess the magnitude and associated factors of chronic liver disease (CLD) in children. By addressing a notable knowledge gap in Ethiopia—where prior CLD data were limited or unpublished—the study advances pediatric hepatology literature globally, particularly by uncovering underreported or overlooked etiologies of CLD that standard academic resources may have neglected. The findings challenge existing assumptions and provide novel insights into region-specific risk factors, enabling tailored preventative strategies and early detection protocols. Practically, this work empowers healthcare providers to refine diagnostic and management approaches, directly improving clinical outcomes for children in Ethiopia. Societally, it addresses disparities in pediatric healthcare by prioritizing a life-threatening condition disproportionately affecting vulnerable populations, thereby enhancing quality of life and reducing long-term morbidity. Additionally, the evidence generated could inform national health policies, advocating for resource allocation toward CLD screening programs and public health interventions.

Methodologically, the study establishes a foundational framework for future research, serving as a stepping stone for larger, prospective studies across Ethiopia. Its institution-based design offers replicable strategies for data collection and analysis in resource-limited settings, bridging gaps between clinical practice and research. By highlighting locally relevant etiologies, the findings also contribute to global CLD discourse, offering comparative insights for regions with similar healthcare challenges. Ethically, the research underscores the urgency of equitable pediatric care, advocating for inclusive health systems. Economically, early CLD detection could reduce long-term treatment costs, while its scalability promises nationwide health benefits. Ultimately, this work catalyzes interdisciplinary collaboration, inspiring further investigations to transform pediatric liver disease management in Ethiopia and beyond.

1.4 Literature Review

Global burden of pediatric CLD has increased in incidence over the past 30 years according to Chi Zhang et al [9]. Incidence of cirrhosis in pediatric age groups [0-19 yrs.] increased by 17.9 % over 3 decades [1990-2019] with rate of 9.4 per 100,000 per year. However, the prevalence and mortality rate has decreased by 41% and 40% [AAPC= -2.27 and -1.68] respectively over the last 3 decades. In contrary, Mortada H. F et al. reported with similar methodology significant increase in prevalence and mortality among children with CLD in African sub-continent [10]. Ashraf Abou-Taleb et al. and Ayesha Sardar Sr. et al. in their prospective cohort institutional based literatures depicted increasing magnitude and morbidity in pediatric CLD [1.6 % of over-all pediatric admissions in former case] [11,12]. The later published cohorts' compares to Chi Zhang et al. review had limitation in their relative inferiority of study design and sample size for asserting global pediatric CLD prevalence and mortality.

Chi Zhang et al. literature reported the incidence of pediatric cirrhosis were highest in central, western, and eastern Sub-Saharan African countries with the rate 14.1, 14.7 and 9.9 per 100,000 per year in 2019, respectively [Increase of incidence by 134%, 128 % and 102 % over 3 decades, respectively] [9]. However, these reports had limitations of overestimation of figures which are only taken from limited number of countries with weak study designs and sample sizes in order to represent the population of categorized regions. Chi Zhang et al. research did not reflect regional distribution among Sub-Saharan countries and for fact excluded Ethiopia. This retrospective cross-sectional study at TASH may provide insight to region specific prevalence of pediatric CLD.

Chi Zhang et al. reported statistically significant associated factors: age less than 5 years, low socio-economic status, malnutrition, low serum albumin level, low platelet count and presence of portal hypertension and hepatitis B were significantly associated with pediatric CLD and rapid decompensation to ESLD [9]. Comparably, Ashraf Abou-Taleb et al., Anisbel Ruiz Ramos et al. and Prasanth K. Sobhan et al. reported age < 1-year, low birth weight, elevated direct serum bilirubin > 50 % of total, low serum albumin, USG evidence of portal hypertension and histologic and genetic tests for metabolic and genetic etiologies had statistically significant associated with pediatric CLD and rapid decompensation [13, 14, 15]. M.K.R et al. in South

Africa reported that schistomiasis and family history of CLD had statistically significant association with CLD in children [19].

Global trends of pediatric cirrhosis incidence reported highest in age < 5 years with the rate of 14.4 per 100,000 population. However, there was decreased change in incidence by 1.3 % over 3 decades. And the reported incidence in older children and adolescents were highest 6.8 and 8.1 per 100,000 population in 2019 [Increased change in incidence by 22 and 44 % over 3 decades, respectively]. Anisbel Ruiz Ramos et al. and Prasanth K. Sobhan et al. on their cross-sectional institution-based studies reported more than 50 % of pediatric CLD observed in age less than 1 year [9, 13, 14]. Females predominated in Ch Zhang et al. report, in contrary males had highest incidence in other literatures [9, 10, 11, 12, 13, 14].

Aforementioned literatures reported heterogeneous results in socio-demographic trends of pediatric CLD. This research was conducted at TASH incorporated additional variable as socio-demographic condition which is family history of known CLD that reinforced the significance of associated risk factors to be analyzed.

Global trends of clinical profile of children with cirrhosis and CLD is protean from clinically silent to multi-systemic manifestations. Ayesha Sardar et al., Ashraf Abou-Taleb et al., and Anisbel Ruiz Ramos et al. reported the most common presentation were jaundice, hepatomegaly and splenomegaly in all age groups. Complications of portal hypertension [ascites, HSM and variceal bleeding] were also reported with variations [11, 12, 13, 14]. Operational definitions of pediatric CLD in former literatures had not been consistent in setting minimum duration and in standardization of cumulative criteria to reduce statistical bias and unnecessary heterogeneity among literatures. Jismy karakkattu et al., M.K.R et al. and Awais Tahir reported on their cohorts the minimum duration of CLD as 3 months and others with strong study designs reported more than 6 months [9,15,16,17]. Exclusive persistence of clinical profile pertaining to liver disease has never been considered CLD. Non-specific manifestations [abdominal pain, vomiting, fatigue, malnutrition and fever] with transaminases and other investigational variables were regarded as clinical profile of pediatric CLD [9,12,13]. Provided that standard minimum duration for CLD in air, this cross-sectional study was conducted at TASH had comparable limitations like other literatures, but multiple optional operational definitions provided balance to inclusiveness of possible CLD patients.

Anisbel Ruiz Ramos et al. and Ayesha Sardar et al. reported close to 100 % pediatric CLD patients had more than twice elevated transaminases [ALT-AST]. Regardless of the underlying etiology biochemical abnormalities including AST, ALT, GGT, Hgb, Plt, Albumin, PT, PTT, INR and others were elevated in most of literatures including Chi Zhang et al. reports [9, 15, 16, 17]. Clinico-biochemical abnormalities were utilized for operation definition of former literatures. However, Ayesha Sardar et al. reported no age reference biochemical abnormalities as statistically significant to associate with pediatric CLD outcome [11]. In contrary, Ashraf Abou-Taleb et al. and Chi Zhang et al. reported on their respective literatures where degree of AST and ALT abnormality were statistically significant to associate the outcome of CLD in chronic hepatitis [9,12].

Global trends of pediatric CLD based on etiology has been dynamic which is tightly integrated to age, geographical distribution and genetic predisposition. Chi Zhang et al. reported cirrhosis caused by 5 etiologies (alcohol use, hepatitis B, hepatitis C, NAFLD and other causes) increased, among which alcohol use was most obvious, with an increase of 48%, followed by hepatitis C and NAFLD, with 29.8% and 28.7%, respectively over 3 decades. The incidence of hepatitis was reported to be 0.2 per 100,000 population by 2019. Ayesha Sardar et al. and Sr. Awais Tahir et al reported Hepatitis B (31, 22.8%), idiopathic (23, 16.9%), glycogen storage disorder (GSD) (21, 15.4%), and Wilson disease (14, 10.3%) were the most common cause of CLD and Viral hepatitis was the most common cause found in 22 (36.7%) cases respectively with similar prospective cohort studies [11,17].

Ashraf Abou-Taleb et al., Anisbel Ruiz Ramos et al. and Prasanth K. Sobhan et al. reported in agreement the most common etiology of pediatric CLD neonatal cholestasis which is followed by MLD included glycogen storage disease (26.5%), undetermined inborn error of metabolism (5.3%), Gaucher's disease (2.0%), and Niemann Pick disease (1.3%). Other causes of CLD comprised autoimmune hepatitis (8.6%), congenital hepatic fibrosis (5.9%), non-alcoholic fatty liver disease (4.0%), chronic hepatitis C infection (2.7%), and Budd Chiari disease (0.6%) [12, 13, 14, 15]. M.K.R et al. reported in South Africa the most common causes of pediatric CLD were hepatitis B and schistomiasis [19].

2. Objectives

2.1 General objective

To determine the magnitude and associated factors of chronic liver disease in children at Tikur anbessa specialized hospital over the past 5 years.

2.2 Specific objectives

To determine the magnitude of chronic liver disease in children at Tikur anbessa specialized hospital over the past 5 years.

To determine associated factors of chronic liver disease in children at Tikur anbessa specialized hospital over the past 5 years.

- To describe socio-demographic pattern among CLD patients
- To identify clinico-biochemical factors among CLD patients
- To describe etiological pattern among CLD patients
- To determine the mortality rate among CLD patients

3. Conceptual frame-work

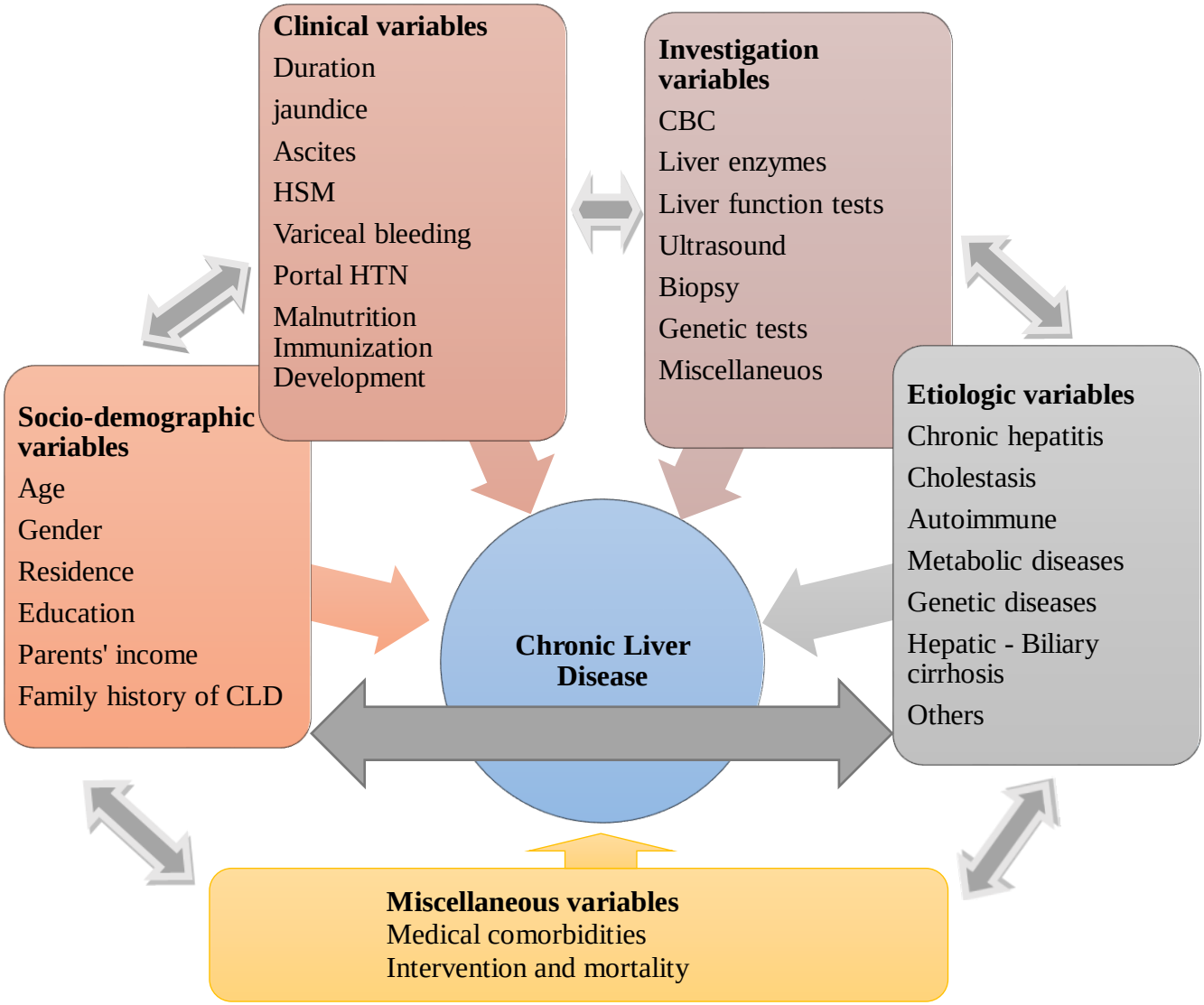

Figure 3.1 Conceptual frame work of CLD in children

CHAPTER TWO

2. Methodology

2.1 Study setting

The study was conducted in Addis Ababa, Ethiopia at Tikur Anbessa Hospital from December 2024 to January 2025. The hospital was established in 1974. It is the teaching hospital of the Addis Ababa University, College of Health Sciences, and School of Medicine, located in Lideta sub-city. It is also the largest referral hospital in Ethiopia with a number of specialties and sub-specialties. It has more than 600 beds and serves about 250,000 patients as outpatients annually.

2.2 Study design

An institution based retrospective cross-sectional study was conducted to determine the magnitude of chronic liver disease in children over the past five years at TASH, Addis Ababa.

2.3 Source population

All pediatric patients who were on follow up at pediatric gastroenterology clinic at Tikur Anbessa specialized hospital for the last 5 years.

2.4 Study population

All pediatric patients who were diagnosed with liver disease at pediatric gastroenterology Tikur Anbessa specialized hospital in the past 5 years.

2.5 Eligibility criteria

2.5.1 Inclusion criteria

a) All pediatric patients age < 18 years old
b) All children with symptoms and signs of CLD persisted for greater than 6 months

2.5.2 Exclusion criteria

a) All pediatric patients less than 18 years old with acute liver disease
b) All children with incomplete investigation and etiologic variables

2.6 Sampling technique

Convenience sampling technique was used

2.7 Sample size

Specific objective 1: To determine the prevalence of CLD in children. The sample size was estimated using a single population proportion formula **[N= $(Z\alpha)^2$ p (1-p)] / d^2]** assuming an expected prevalence of CLD in children, P=9.8 % taken from global disease burden data base in Eastern Sub-Saharan African countries of CLD in children and cross-sectional study in Pakistan [9, 20]. The above formula was used to estimate the sample size. Where Z= level of confidence at 95% certainty (1.96), d= 5% marginal error, Non-response rate 10%, the calculated sample size using the above formula became for prevalence of CLD in children is 136. Considering 10% non-response rate, the overall sample size is 150.

Specific objective 2: To determine associated factors of CLD in children by using double proportion formula by Epi-info software v7**; [n= {$Z\alpha/2\sqrt{(1+1/r)\ p(1-p)}$-$Z\beta\sqrt{p1(1-p_1)}$ +[$p_2(1-p_2)$]/r}2 / p_1-p_2]2**. Where: n: Required sample size per group, Z (alpha/2): Z-score for alpha/2 (1.96 for alpha = 0.05), Zβ: Z-score for power (power = 0.85), p1: 38%, Expected proportion of cholestasis in cirrhotic CLD, p2: 20%, Expected proportion of cholestasis in non-cirrhotic CLD, r=the ratio between cholestasis in cirrhotic non-cirrhotic CLD. Estimate Proportions: Effect size of 18 % differences taken from existing review of global disease burden data base of CLD in children 30 years trend analysis [9]

Therefore, 120 children in each group (with and without cirrhosis) for a total sample size of 240 participants. The total sample size for this study was 240 children (since this was the largest required sample size).

2.8 Study variables

2.8.1 Independent variables

a. Socio-demographic variables; age, gender, religion, residence, family history of CLD
b. Clinical variables; Duration of signs and symptoms, Jaundice, ascites, HSM, variceal bleeding, portal hypertension, malnutrition and others
c. Investigation variables; CBC [Hgb/Plt], Liver Enzymes [ALT, AST, ALP], LFT [Bilirubin, Albumin and coagulation profile], USG [Liver fibrosis or cirrhosis], Miscellaneous [APRI score, CT, Biopsy, Genetic test, metabolic screening]
d. Etiologic variables; Chronic Hepatitis [Neonatal (idiopathic), Autoimmune, Viral, Drug induce], Metabolic diseases: GSD, Gaucher, Niemann Pick Disease, undetermined, Obstruction of bile pathway: Biliary atresia, Paucity of bile ductules, Hepatic fibrosis: Congenital hepatic fibrosis, Parasitic portal tract fibrosis Hepatic Steatosis, Budd Chiari disease, Biliary cirrhosis

2.8.2 Dependent variable

Dependent variable was chronic liver disease in children

2.9 Data collection instruments

Data was collected using medical charts and digital iCare which was adapted from previously published studies with some modification to ensure applicability, validity, reliability to our current study. The questionnaire consisted of questions on socio-demographic factors, Major clinical presenting sign and symptoms and associated factors.

2.10 Data collection procedures

This study aimed to identify and analyze pediatric Chronic Liver Disease (CLD) cases from a hospital database spanning 2020-2025. Initial screening identified 260 potential cases, which were then filtered based on inclusion criteria (children under 18 years with CLD, n=247) and exclusion criteria (incomplete charts, n=3; acute liver disease, n=10). Two data collectors independently extracted data using structured forms within Kobo Toolbox, capturing demographics, clinical details, investigations, etiology, and other relevant variables.

Data cleaning and validation involved removing duplicates (n=5) using SPSS, addressing missing values (n=2) via listwise deletion, and cross-verifying 10% of entries for inter-rater reliability. The final dataset comprised 240 participants with clean data, which was then analyzed using SPSS. Descriptive statistics (frequencies, mean, standard deviation) and inferential statistics (chi-square, binary logistic regression) were employed. The results were subsequently exported for inclusion in a thesis report

2.11 Data quality control

Prior to conducting the main study, pre-test was carried out on 5% of the sample size who was not included in the study. Based on the finding of pre-test, the data collectors were reoriented and the questionnaire was revised as needed. To further ensure quality, knowledge on the part of the data collectors, clarification, strict supervision and checking for completeness at the end of each questionnaire was done.

2.12 Data entry, analysis and processing

Data processing was started in the clinic by checking for completeness of the data and performing quality control checks. Decisions was made on how to categorize data particularly with regards to the open-ended questions. Subsequently the data of the completed questionnaires was compiled into a computer using kobo-data-collect statistical software and the 30^{th} version of SPSS software for further processing and analysis. This also required the development of a coding system. Tables, pie chart and bar graphs were used to present the data. Chi-square test was performed to test the existence of significant association of the important factors with chronic liver disease. A p-value was used to compare if there is a significant association between variables.

Regression analysis: Binary logistic regression was chosen because the dependent variables were dichotomized and categorical to suit this model.

2.13 Operational definitions

Chronic liver disease: For this study and standard acceptable definitions [9,11,19]

a. Presence of one or more clinical variables [jaundice, HSM, ascites, variceal bleeding, portal hypertension, malnutrition, others in questionnaire] AND one or more investigation variables [LFT abnormality, Liver enzymes [2 X ALT, AST and ALP], abdominal CT abdominal USG and /or APRI score > 2] for greater than and equal to 6 months [AND/OR]
b. Presence of single imaging evidence of portal hypertension and its complications or cirrhosis [USG, CT or MRI] at any time of diagnosis [AND/OR]
c. Presence of biopsy evidence of cirrhosis or metabolic, genetic or one or more etiologic variables lasting more than 6 months

CLD outcome: Cirrhotic and non-cirrhotic CLD [see the above definition]

Portal hypertension: For this study diagnosed if there are one or more indirect signs of complications of portal hypertension [Ascites, HSM, variceal bleeding, others in questionnaires]

Children: All population less than 18 years old.

2.14 Ethical consideration

An ethical clearance and official letter were obtained from Addis Ababa University, Department of Pediatric and child health. The data collection was anonymous which did not include names of individual participant and any other personal identifiers was not indicated in the study.

2.15 Dissemination plan

The results of the study were presented and submitted to Addis Ababa University, College of Health Sciences, Department of Pediatrics and Child Health. The study abstract was presented in associations like Ethiopian Pediatrics Society (EPS) and the summary of the thesis was submitted to the international or national peer reviewed journal for publication.

CHAPTER THREE

3. RESULTS

3.1 Socio-demographic factors

A total of two hundred forty individuals participated in the study. As Table 1 below shows age ranging between 0-18 years of whom 131 (54.6%) were male and 109 (45.4%) were females. The mean age of respondents was 6.4 with SD= ± 4.4 and most of them have age range of 5 and 10 years.

One hundred sixty (66.7 %) of the participants reside in urban followed by 33.3 % from rural regions. Most of the participants were attending primary school; this group comprised 54.7 percent. About quarter of the children were categorized underage for school. Fourteen percent them were kindergarten students and only 3.3 % were attending secondary school.

Parental income of seventy-six (31.7%) children ranges between 6000-10,000 ETB followed by the parental income of 17 % more than 10,000 ETB. About half percentage of parental income were below 6000 ETB. In regards to family history of chronic liver disease, only fourteen percent of the participants had medically documented family history of CLD.

Table 1. Socio demographic characteristics of the study participants (N=240)

Socio-demographic variables	N (%) or Mean (±2SD*)
Mean age (years) (Range 0-18)	**6.4 (± 4.4)**
Age groups (years)	
≤1	48 (20)
1-5	51 (21.3)
5-10	87 (36.3)
10-15	48 (20)
15-18	6 (2.5)
Sex	
Male	131 (54.6)
Female	109 (45.4)
Residency	
Urban	160 (66.7)
Rural	80 (33.3)
Level of education	
Under age for school	66 (27.5)
Kindergarten	35(14.5)
Primary education	131 (54.7)
Secondary education	8 (3.3)
Parental Income (ETB)	
≤ 3000	74 (30.8)
3000-6000	47 (19.6)
6000-10000	76 (31.7)
>10000	43 (17.9)
Family history of CLD	
Yes	11 (4.6)
No	229 (95.4)

*SD- Standard deviation

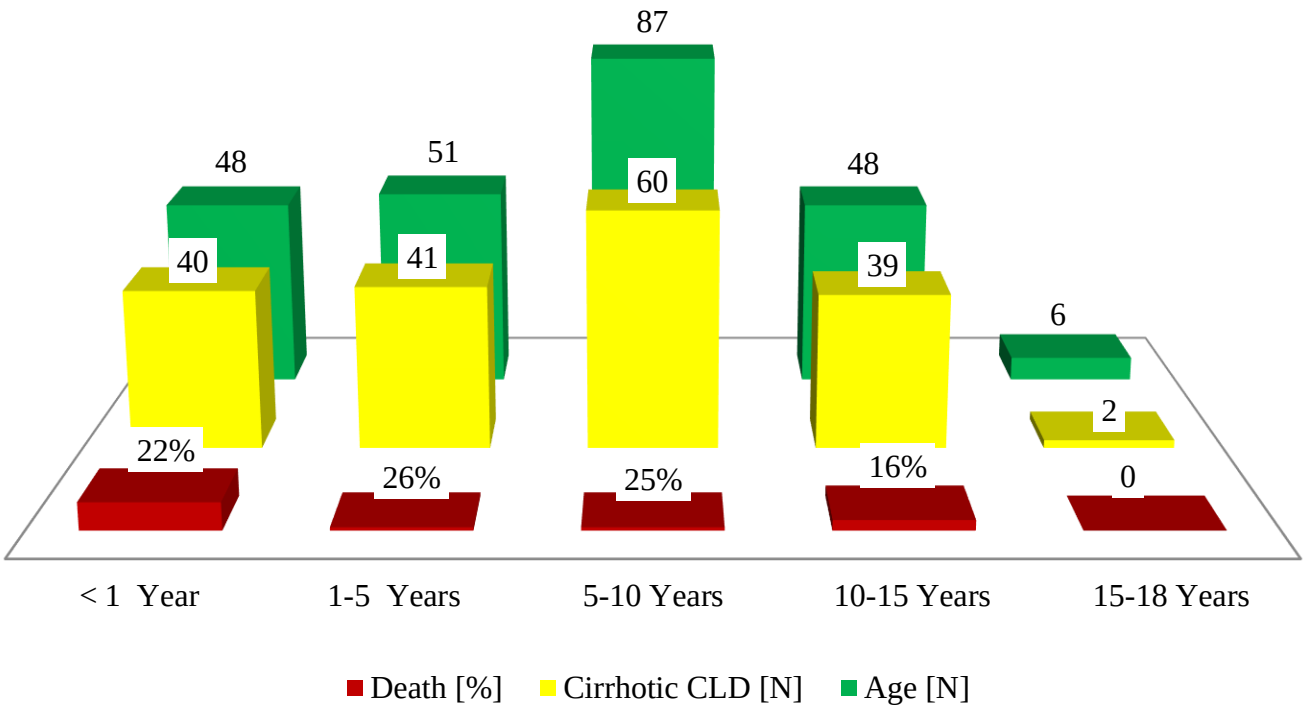

Figure 1. Age groups distribution of the participants [N=240] related with cirrhosis and death

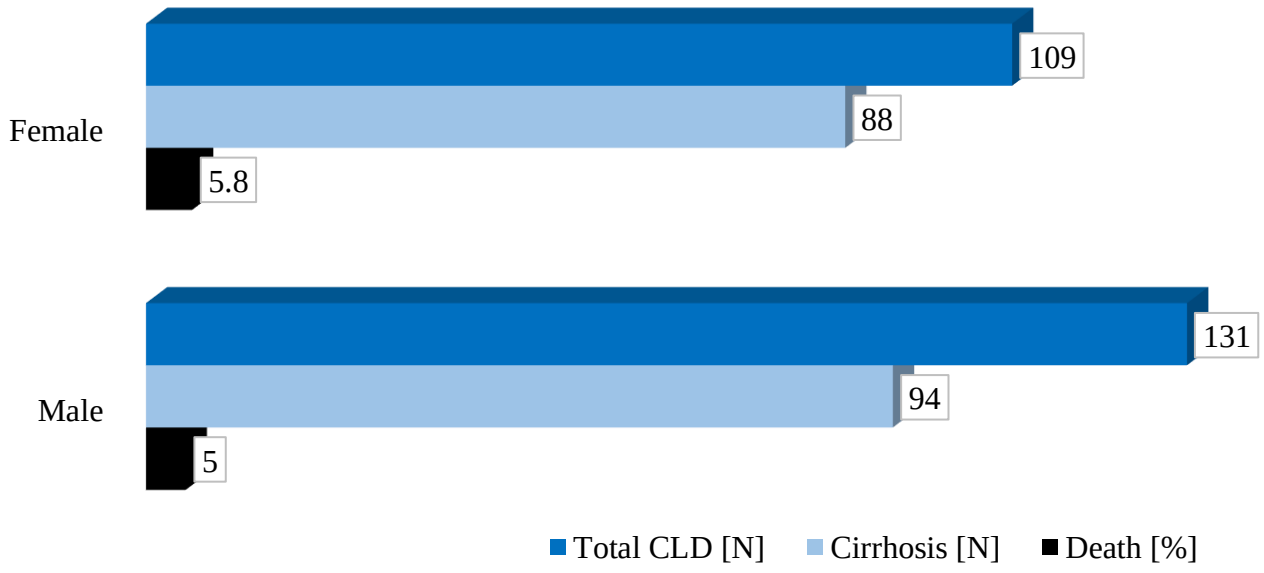

Figure 2. Gender distribution of the participants [N=240] related with cirrhosis and death

Socio-demographic characteristics in relation to the cirrhotic and non-cirrhotic chronic liver disease are reported in Table 2 below. Ninety-four (39.2%) males were reported to have cirrhotic CLD compared to eighty-eight (36.7 %) females. The ratio of male to female is 1.1 in cirrhotic CLD with higher ratio 1.8 in non-cirrhotic CLD group. However, the difference is not statistically significant (*P*=0.081). Regarding the age, sixty-three (26.3%) participants in age range 5-10 years comprised the most cirrhotic CLD compares to other age groups; followed by one third of under 5 years age participants had cirrhotic CLD combined. Participants in age group 5-10 years had more likely of diagnosed to have cirrhotic CLD compares to other age groups and the difference is statistically significant (*P*=0.02).

One hundred one (42%) participants who were attending primary school were reported of having cirrhotic CLD followed by 20% of infants. The least cirrhotic CLD four participants were attending secondary school. Primary school attending participants were more likely having cirrhotic CLD compares to other categories of school and the difference is statistically significant.

Regarding residency status, one hundred twenty-three (51.3%) of urban participants were reported of having cirrhotic CLD compares to participants reside in rural area. The proportion of non-cirrhotic CLD is much higher in rural than urban participants. Urban children were more likely of having cirrhotic CLD compares to rural but the difference is not statistically significant.

Eleven (4.6%) participants with family history of CLD had cirrhotic CLD and none had non-cirrhotic CLD. About three four of cirrhotic CLD had no family history of CLD. Sixty (25 %) of the participants had monthly parental income of 6000-1000 ETB were high likely of reported of having CLD compare to other level of income, but there are no statistically significant differences.

Generally, of the socio demographic characteristics shown in Table 2 except age and educational level there was no statistical difference within the groups as far as prediction of cirrhosis is concerned.

Table 2. Socio-demographic characteristics of the participants in relation to CLD

Variables	Chronic Liver Disease with Cirrhosis		*P* value
	Yes (%) N= 182	No (%) N= 58	
Age groups (years)			
≤1	40 (16.7)	8 (3.3)	
1-5	41 (17.1)	10 (4.2)	
5-10	63 (26.3)	24 (10)	0.020*
10-15	36 (15)	12 (5)	
15-18	2 (0.8)	4 (1.7)	
Gender			
Male	94 (39.2)	37 (15.4)	
Female	88 (36.7)	21 (8.7)	0.081
Residency			
Urban	123 (51.3)	37 (15.4)	
Rural	59 (24.6)	21 (8.7)	0.442
Level of education			
Under age for school	50 (20.8%)	16 (6.6)	
Kindergarten	27 (11.2)	8 (3.3)	
Primary education	101 (42)	30 (12.5)	0.010*
Secondary education	4 (1.7)	4 (1.7)	
Parental Income (ETB)			
< 3000	50 (20.8)	24 (10)	0.280
3000-6000	40 (16.7)	7 (2.9)	
6000-10000	60 (25)	16 (6.7)	
>10000	32 (13.3)	11 (4.6)	
Family history of CLD			
Yes	11 (4.6)	0 (0.0)	0.999
No	171 (71.3)	58 (24.1)	

*statistically significant

3.2 Clinical factors

As table 3 below shows the proportion of clinical factors of the of 240 participants. The clinical characteristics of study participants composed of five factors: duration of symptoms, clinical history and examination, nutritional status, HBV vaccination and developmental status. One hundred seventy-two (71.7%) children were reported to be presented with duration of 6-12 months since the onset of symptoms followed by one fifth of them by 1-5 years. Six percent of study participants with symptoms above 5 years experienced mild nonspecific symptoms until it interfered with daily activity.

Regarding medical history and physical examination findings, half percentage of the study participants with CLD presented with jaundice. Of all study participants 92 % and 79 % of them had hepatomegaly and splenomegaly, respectively. Two third of them had ascites and 28 % of them had variceal bleeding as result of portal hypertension complication. Fort-five (19%) of them had peripheral edema. Twenty-four (10%) of these children with CLD had developed hepatic encephalopathy. Two of the study participants had clubbing and 2 % took unknown type of herbal medications.

Regarding nutritional status of children with CLD, the most common form malnutrition reported was moderate acute malnutrition (20.9%) with comparable difference with severe acute malnutrition (19.2%) and 10.5 % of them with severe stunting overlapped with former forms of malnutrition. No report of overweight or obesity.

Two hundred twenty (91.6%) of children with CLD were vaccinated HBV during their infancy period according to EPI schedule. HBV vaccine status of 8.4 % study participants was reported as unknown. The maternal status of serology of HBsAg of all study participants were negative. Regarding the developmental status of children with CLD, only eleven (4.6%) of them were reported to have global developmental delay with affected motor and language milestones.

Table 3. Clinical characteristics of the study participants (N=240)

Clinical variables	**N** (%)
Duration of symptoms (years)	
≤ 0.5-1	172 (71.7)
1-5	52 (21.7)
>5	16 (6.7)
Medical history and physical exam	
Jaundice	119 (49.6)
Ascites	165 (68.7)
Hepatomegaly	221 (92.1)
Splenomegaly	190 (79.2)
Variceal Bleeding	68 (28.3)
Peripheral edema	45 (18.8)
Hepatic encephalopathy	24 (10)
Clubbing	2 (0.8)
Herbal medicine	5 (2)
Malnutrition	
Severe wasting / acute malnutrition	46 (19.2)
Severe stunting	25 (10.5)
Moderate acute malnutrition	50 (20.9)
HBV vaccination per EPI	
HBV vaccine administered	220 (91.6)
HBV vaccine unknown	20 (8.4)
Developmental Delay	
Global developmental delay	11 (4.6)

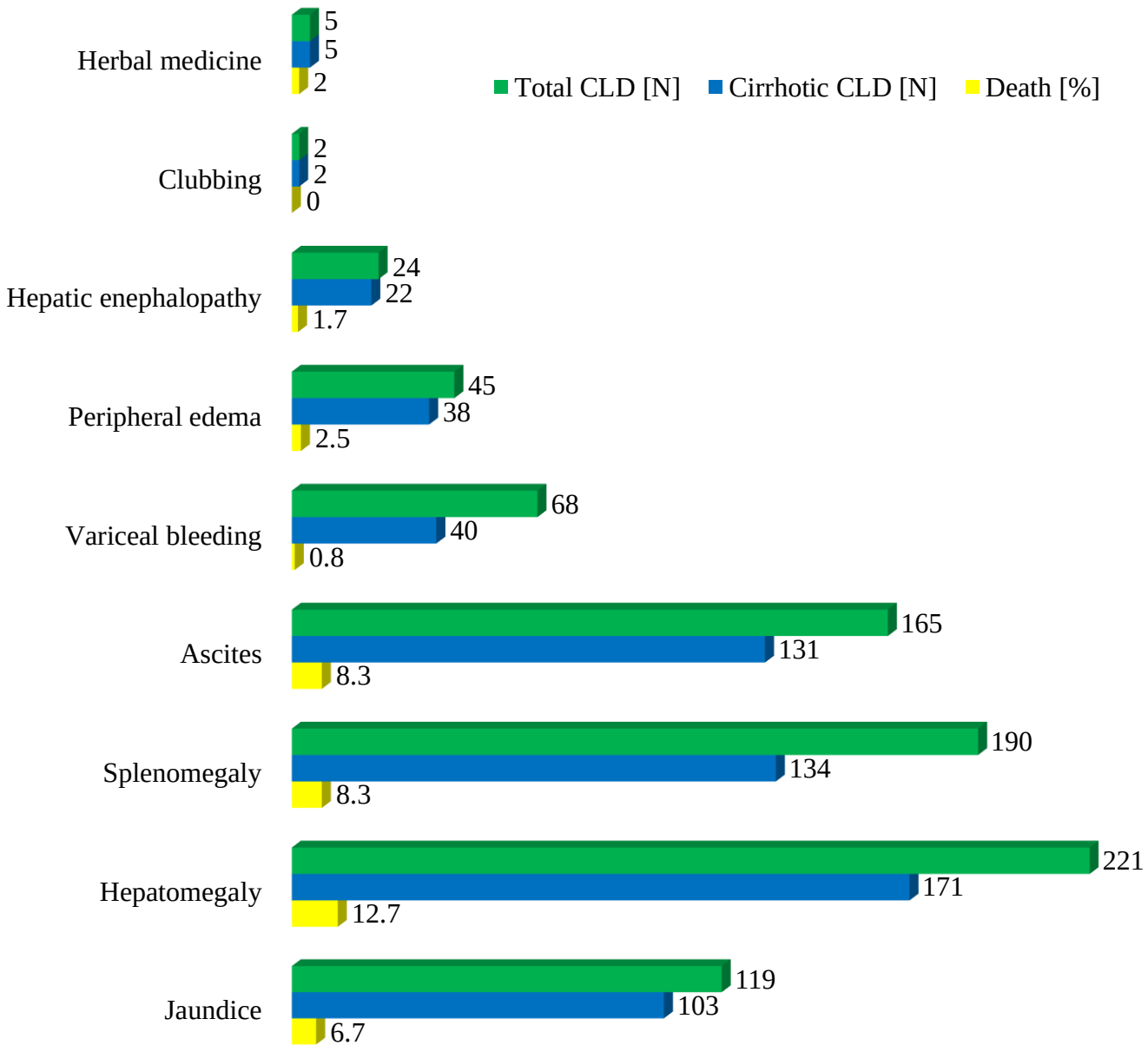

Figure 3. Distribution of clinical characteristics of the participants [N=240] related with cirrhosis and death

Clinical characteristics in relation to the cirrhotic and non-cirrhotic chronic liver disease are reported in table 4 below. Regarding the duration of symptoms, one hundred thirty-four (55.8%) participants presented with duration of symptoms 6-12 months comprised the most cirrhotic CLD participants compares to other groups; followed by 16 % with 1-5 years of duration of symptoms. For those duration symptoms more than 5 years cirrhotic CLD was still prominent. Participants with duration of symptoms of 0.5-1 year had more likely to develop cirrhotic CLD compares to other groups and the difference is statistically significant (*P*=0.007).

Regarding medical history and physical examination findings, study participants with hepatomegaly (71%), splenomegaly (55%), ascites (54%) and jaundice (42%) were reported to have cirrhotic CLD but the difference is not statistically significant. Thirty-eight (15.8 %) and 9.2 % of children had peripheral edema and hepatic encephalopathy, respectively. Forty (16.6 %) of the children with variceal bleeding were more likely to have cirrhotic CLD and the difference is independently statistically significant (*P*=0.001). All of the study participants who had clubbing developed cirrhosis.

Regarding nutritional status of children with CLD, fifteen percent of children with moderate acute malnutrition had cirrhotic liver disease. Severe acute malnutrition in cirrhosis reported in 13 %. None of severely stunted children had non-cirrhotic CLD. All of the participants (4.6%) with global developmental delay had cirrhotic liver disease. And the differences in both nutritional and developmental status of CLD children are not statistically significant.

Generally, out of clinical characteristics shown in table 4 duration of symptoms and variceal bleeding showed statistical significance within the groups as far as prediction of cirrhosis is concerned.

Table 4. Clinical characteristics of the participants in relation to CLD

Variables	Chronic Liver Disease with Cirrhosis		*P* value
	Yes (%) N= 182	No (%) N= 58	
Duration of symptoms (years)			
≤ 0.5-1	134 (55.8)	38 (15.9)	0.007*
1-5	38 (15.9)	14 (5.8)	
>5	10 (4.2)	6 (2.5)	
Medical history/physical exam			
Jaundice	103 (42.9)	16 (6.7)	0.999
Ascites	131 (54.6)	34 (14.1)	0.999
Hepatomegaly	171 (71.3)	50 (20.8)	0.999
Splenomegaly	134 (55.8)	56 (23.4)	0.807
Variceal Bleeding	40 (16.6)	28 (11.7)	0.001*
Peripheral edema	38 (15.8)	7 (3)	0.396
Hepatic encephalopathy	22 (9.2)	2 (0.8)	0.618
Clubbing	2 (0.8)	0 (0)	1.000
Malnutrition			
Severe wasting / acute malnutrition	33 (13.7)	13 (5.5)	0.909
Severe stunting	25 (10.5)	0 (0)	
Moderate acute malnutrition	36 (15)	14 (5.9)	
Developmental Delay			
Global developmental delay	11 (4.6)	0 (0)	0.999

*statistically significant

3.3 Investigational factors

As table 5 below shows the proportion of investigational factors of the of 240 participants. The investigational characteristics of study participants composed of seven factors: complete blood count, liver enzymes, liver function tests, abdominal ultrasound, abdominal CT/liver biopsy, APRI Score and diagnostic tests. One hundred sixteen (48.3%) children were reported to have anemia followed by 40% and 16 % of them had thrombocytopenia and leukopenia, respectively. Sixteen (6.7%) of study participants had thrombocytopenia. Seven percent were reported to have leukocytosis and 6 % of them had pancytopenia.

Regarding liver enzymes, two hundred twenty-four (93.3%) participants had 10 times elevated ALP with 92.9 percent had elevated ALT. One hundred fifty-one (62.9%) of children with CLD had abnormally elevated serum bilirubin level with most being direct hyperbilirubinemia. Severe form of low serum albumin was reported in 55% of participants. Coagulation panel, PT predominantly was affected in 59.5 % of them.

One hundred eighty-two (75.8%) of the study participants were reported to have abdominal ultrasound findings of coarse echotexture of liver parenchyma with fibrosis and nodularity. One hundred eleven of them showed indirect signs of portal hypertension such as ascites, hepatomegaly, splenomegaly and cavernous transformation of collateral vasculatures. Twenty-six (10.8%) were reported to have small gall bladder and triangular cord signs.

Eight of the participants had CT scan evidence of cirrhosis and four of them had liver biopsy evidence of idiopathic form of cirrhosis. Regarding APRI score, eighty-two (34%) of study participants had APRI score greater than 2. Mild and moderate APRI score were reported in 24% and 18% of the study participants, respectively. However, more than two third children's APRI scores were reported normal.

Regarding diagnostic tests, out of thirteen participants 3.3% and 2% were positive for ASMA and A-LKM1 in conjunction with ANA. Hepatitis B serologic tests consistent with active infection were reported in 6 children. Anti-HCV and CMV PCR were detected in 0.8% for each of them.

Table 5. Investigational variables of the study participants (N=240)

Investigational variables	**N** (%)
Complete Blood Count	
Anemia	116 (48.3)
Thrombocytopenia	97 (40.4)
Leukopenia	40 (16.7)
Leukocytosis	17 (7)
Pancytopenia	16 (6.7)
Liver Enzymes	
Elevated AST	197 (82)
Elevated ALT	223 (92.9)
Elevated ALP	224 (93.3)
Liver Function Tests	
Elevated serum bilirubin	151 (62.9)
Decreased serum albumin (Alb < 3)	132 (55)
Elevated coagulation profile (INR/PT/PTT)	143 (59.5)
Abdominal Ultrasound	
Nodular liver	182 (75.8)
Portal HTN	111 (46.3)
Small gallbladder with triangular cord sign	26 (10.8)
Abdominal CT/Liver biopsy	
CT evidence of cirrhosis	8 (3.3)
Biopsy proven	4 (1.6)
APRI Score	
>2	82 (34.1)
1.5-2	44 (18.3)
0.5-1.5	57 (23.8)
Diagnostic Tests	
Positive HBsAg/HBsAb/HBeAg	6 (2.5)
Positive anti HCV	2 (0.8)
Positive ASMA/ANA	5 (2)
Positive A-LKM1/ANA	8 (3.3)
CMV PCR	2 (0.8)
Stool schistosomiasis and ceruloplasmin	4 (1.6)

Investigational variables in relation to the cirrhotic and non-cirrhotic chronic liver disease are reported in table 6 below. Regarding complete blood count, eighty-three (34%) of participants with anemia were reported to have most cirrhotic CLD compares to other age groups; followed by thrombocytopenia (25%) and leukopenia. However, the difference with in the groups is not statistically significant (*P*=0.317).

Regarding liver enzymes, one hundred sixty-eight (70%) participants with elevated ALP were reported to have cirrhotic CLD. Two third of the children with elevated ALT and AST were reported in cirrhosis. Participants with elevated ALP were more likely to have cirrhotic liver disease compares to other enzymes and the difference is statistically significant (*P*=0.024). And 42% participants with elevated serum prothrombin level and INR reported to have cirrhotic CLD with the difference showed statistical significance (*P*=0.037). More than one third of children with CLD had low serum albumin level with no statistical significance.

Eleven (4.6%) of the participants with ultrasound evidence of portal hypertension had no features of ultrasonographic cirrhosis. And all study participants with CT scan evidence of cirrhosis and liver biopsy evidence of idiopathic form of cirrhosis were reported in cirrhotic CLD; but the difference is not statistically significant. Regarding APRI score, seventy-six (31%) of study participants with APRI score greater than 2 had cirrhotic CLD. Participants with mild and moderate APRI score were reported to have cirrhosis in 17% and 13% of them, respectively. Participants with APRI score greater than 2 were more likely to have cirrhosis than other scores and the difference is statistically significant (*P*=0.001).

Regarding diagnostic tests, out of thirteen participants with positive for ASMA (2%) and A-LKM1(0.4%) in conjunction with ANA had cirrhotic CLD. Most of the participants (2%) with hepatitis B serologic tests consistent with active infection were reported in non-cirrhotic CLD. Participants with anti-HCV and CMV PCR detection were reported as non-cirrhotic CLD. However, the difference in all diagnostic test variables is not statistically significant.

Generally, out of investigational characteristics shown in table 6; elevated ALP, PT and APRI score showed statistical significance within the groups as far as prediction of cirrhosis is concerned.

Table 6. Investigational variables of the participants in relation to CLD

Variables	Chronic Liver Disease with Cirrhosis		*P* value
	Yes (%) N= 182	No (%) N= 58	
Complete Blood Count			
Anemia	83 (34.4)	33 (13.7)	0.317
Thrombocytopenia	61 (25.4)	36 (15)	0.999
Leukopenia	29 (12.1)	11(4.6)	0.542
Leukocytosis	15 (6.2)	2 (0.8)	1.000
Pancytopenia	10 (4.2)	6 (2.5)	0.067
Liver Enzymes			
Elevated AST	154 (64.2)	43 (17.8)	1.000
Elevated ALT	167 (69.6)	56 (23.3)	0.999
Elevated ALP	168 (70)	56 (23.3)	0.024*
Liver Function Tests			
Elevated serum bilirubin	107 (44.6)	44 (18.3)	1.000
Decreased serum albumin (Alb < 3)	89 (37.1)	43 (17.9)	0.999
Elevated coagulation profile (INR/**PT**/PTT)	101 (42)	42 (17.5)	0.037*
Abdominal Ultrasound			
Nodular liver	182 (75.8)	0	0.999
Portal HTN	100 (41.7)	11 (4.6)	1.000
Small gallbladder with triangular cord sign	26 (10.8)	0	0.999
Abdominal CT/Liver biopsy			
CT evidence of cirrhosis	8 (3.3)	0	0.999
Biopsy proven	4 (1.6)	0	
APRI Score			
>2	76 (31.7)	6 (2.4)	0.001*
1.5-2	32 (13.3)	12 (5)	0.181
0.5-1.5	41 (17.1)	16 (6.7)	0.999
Diagnostic Tests			
Positive HBsAg/HBsAb/HBeAg	1 (0.4)	5 (2)	0.999
Positive anti HCV	0	2 (0.8)	
Positive ASMA/ANA	5 (2)	0	
Positive A-LKM1/ANA	1 (0.4)	7 (2.9)	0.999
CMV PCR	0	2 (0.8)	
Ceruloplasmin	1 (0.4)	0	
Stool schistosomiasis	0	3	

*statistically significant

3.4 Etiological factors

As table 7 below shows the proportion of etiological factors of the of 240 participants. The etiological characteristics of study participants composed of six factors: chronic hepatitis, cholestasis, metabolic liver disease, genetic disease, herbal medications and miscellaneous etiology. Thirteen (5.5%) of participants were reported to have autoimmune hepatitis with 2.1% type I and 3.4% type II AIH. Six (2.5%) of children were reported to have HBV infection. Two of study participants each had both HCV and CMV chronic hepatitis.

Cholestasis the second most common etiologic factor of CLD in this study. Thirty-one (12.9%) of children with CLD were reported to be caused by biliary atresia followed by 2.5% of them had progressive familial intrahepatic cholestasis. The least reported etiology was choledochal cyst. Four of the participants had Gaucher disease; one with galactosemia and alpha-1 antitrypsin deficiency each.

Genetic etiologies were rare; only 1 participant with Wilson disease and 5 children with herbal medication. Regarding miscellaneous etiologies, one hundred forty-three (59.6%) children were reported to have CLD caused by undetermined etiologies; which is the most common etiologic factor in this study. Fourteen (6%) of subjects had identified etiology of portal vein thrombosis followed by congenital hepatic fibrosis (CHF) (1.7%), Budd Chiari syndrome (0.8%) and Schistosomiasis (1.3%).

Table 7. Etiological variables of the study participants (N=240)

Etiological variables	**N** (%)
Chronic Hepatitis	
HBV	6 (2.5)
HCV	2 (0.8)
AIH-I	5 (2.1)
AIH-II	8 (3.4)
CMV	2 (0.8)
Drug/Toxo/Giant cell	0
Cholestasis	
Biliary atresia	31 (12.9)
Choledochal cyst	2 (0.8)
PFIHC	6 (2.5)
Metabolic Liver Disease	
Gaucher disease	4 (1.7)
Galactosemia	1 (0.4)
A1 anti trypsin deficiency	1 (0.4)
Genetic disease	
Wilson disease	1 (0.4)
Allagile syndrome	0 (0)
Herbal Medications	5 (2.1)
Miscellaneous Etiology	
Undetermined etiology	143 (59.6)
Congenital hepatic fibrosis	4 (1.7)
Portal vein thrombosis	14 (5.8)
Budd Chiari syndrome	2 (0.8)
Schistosomiasis	3 (1.3)

Etiologic variables in relation to the cirrhotic and non-cirrhotic chronic liver disease are reported in table 8 below. Ninety-seven (40%) of the study participants had identified etiologies; the most common identified etiology was cholestatic liver disease (biliary atresia with 13%) followed by chronic hepatitis with autoimmune hepatitis was leading etiology (5.5%). And rare etiologies were categorized as Wilson disease, portal vein thrombosis and congenital hepatic fibrosis.

Of the identified etiologies, 14% of cholestatic disease; 2.8% of chronic hepatitis; 6.3 of miscellaneous etiologies including chronic portal vein thrombosis and 2% traditional medicines were reported to have cirrhotic CLD. However, the predominant form CLD in chronic hepatitis was reported to be non-cirrhotic CLD with 6.5% of participants. And the ratio of non-cirrhotic to cirrhotic CLD in chronic hepatitis is 2.3. However, the difference in identified etiology of CLD is not statistically significant.

One hundred forty-three (60%) of the study participants had undetermined etiology which was the most common factor reported. Forty-nine percent of the subjects with undetermined etiology had cirrhotic CLD. Participants with undetermined etiology were more likely to have cirrhotic liver disease compares to other groups of identified etiologies and the difference in the undetermined etiology of CLD is statistically significant (P=0.001).

Generally, out of etiological characteristics shown in table 8; except undetermined etiology there was no statistical difference within the groups as far as prediction of cirrhosis is concerned.

Table 8. Etiological variables of the participants in relation to CLD

Variables	Chronic Liver Disease with Cirrhosis		*P* value
	Yes (%) N= 182	**No (%) N= 58**	
Chronic Hepatitis			
HBV	1 (0.4)	5 (2)	0.790
HCV	0	2 (0.8)	
AIH-I	5 (2)	0	
AIH-II	1 (0.4)	7 (2.9)	
CMV	0	2 (0.8)	
Cholestasis			
Biliary atresia	31 (12.9)	0 (0)	0.868
Choledochal cyst	0	2 (0.8)	0.999
PFIHC	2 (0.8)	4 (1.7)	
Metabolic Liver Disease			
Gaucher disease	0	4 (1.7)	
Galactosemia	0	1 (0.4)	0.999
A1 anti trypsin deficiency	0	1 (0.4)	
Genetic disease			
Wilson disease	1 (0.4)	0	0.999
Allagile syndrome	0	0	
Herbal Medications	5 (2)	0	
Miscellaneous Etiology			
Undetermined etiology	121 (48.7)	22 (9.2)	0.001*
Congenital hepatic fibrosis	4 (1.7)	0	
Portal vein thrombosis	9 (3.8)	5 (2)	
Budd Chiari syndrome	2 (0.8)	0	0.999
Schistosomiasis	0	3 (1.3)	

*statistically significant

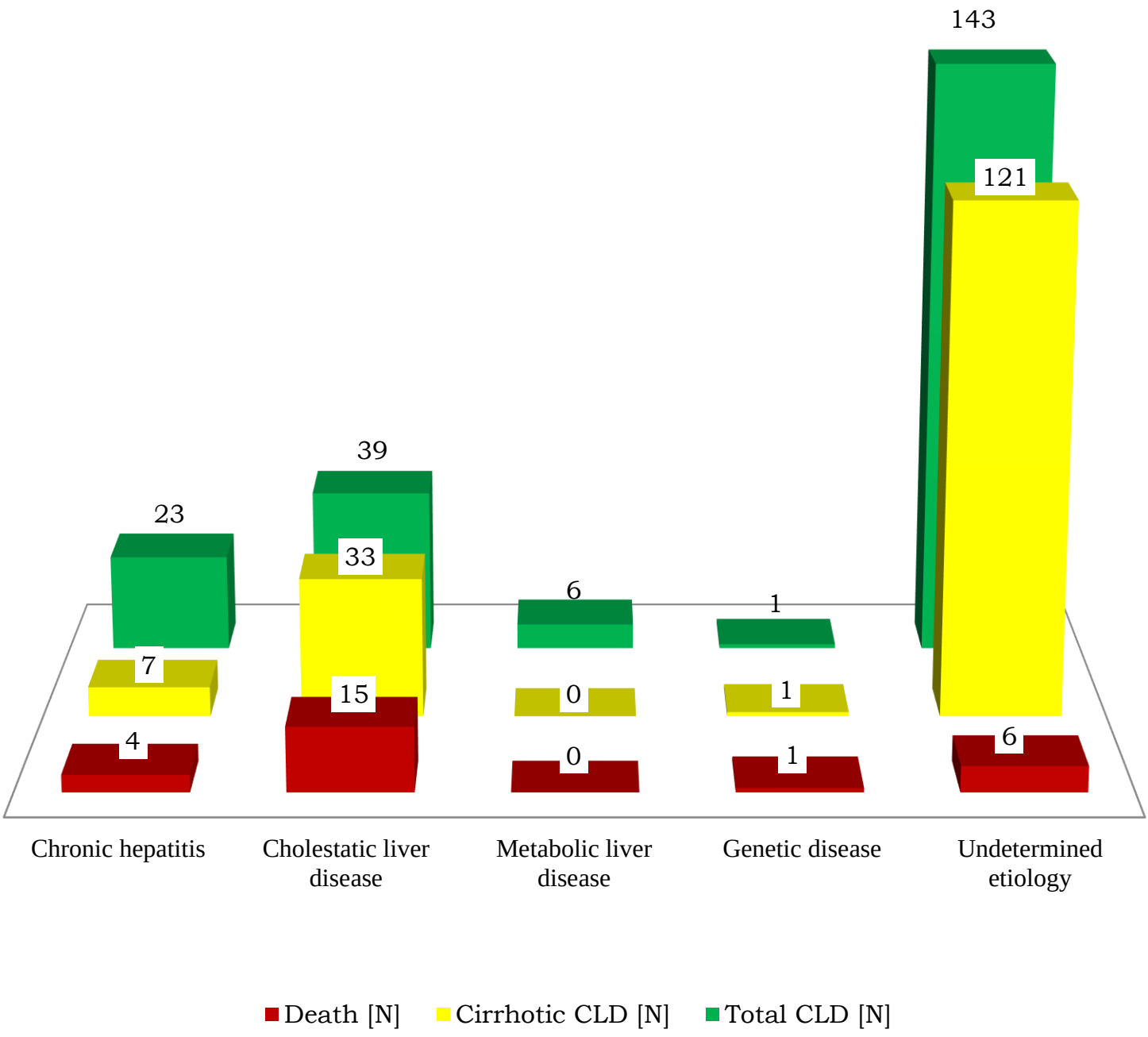

Figure 4. Distribution of etiologic characteristics of the participants [N=240] related with cirrhosis and death

3.5 Miscellaneous factors

As table 9 below shows the proportion of miscellaneous factors of the of 240 participants. The miscellaneous characteristics of study participants composed of three factors: medical comorbidities, intervention and mortality. Two hundred-ten (87.5%) children were reported to whom nonspecific supportive and symptomatic therapy was provided. Five out of 31 participants with biliary atresia had intervention with Kasai procedure (Hepatoportoenterostomy). Eighteen (7.5%) of the participants with high grade varices had variceal band ligation. Two of cirrhotic CLD participants had liver transplant.

Eighteen (7.4%) of the participants were reported to have medical comorbidities; cerebral palsy due to PNA, CRVHD/CHD, polycystic kidney disease, systemic lupus erythematosus, protein C deficiency, malignant fibrosarcoma and septic shock.

Table 9. Miscellaneous variables of the study participants (N=240)

Miscellaneous variables	**N** (%)
Medical comorbidities	
Cerebral Palsy due to PNA	2 (0.8)
CRVHD/CHD	4 (1.7)
Polycystic kidney disease	3 (1.2)
Systemic Lupus Erythematosus	3 (1.2)
Protein C deficiency	1 (0.4)
Malignant fibrosarcoma	1(0.4)
Septic shock	4 (1.7)
Interventions	
Kasai procedure (Hepatoportoenterostomy)	5 (2)
Liver transplant	2 (0.8)
Variceal band ligation	18 (7.5)
Nonspecific Symptomatic Therapy	210 (87.5)
Mortality	
Yes	26 (10.8)
No	214 (89.2)

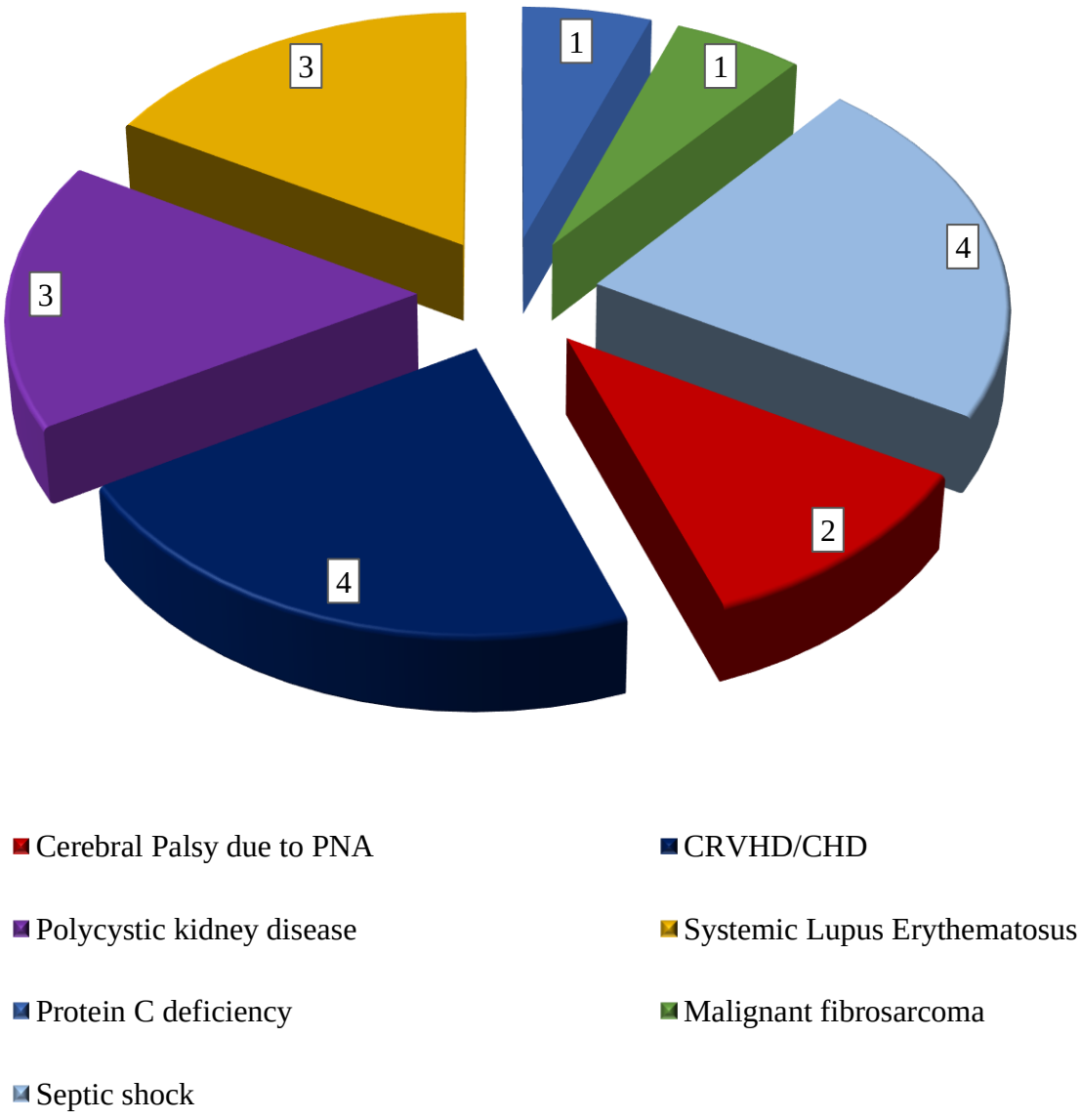

Figure 5. Distribution of comorbid diseases of the participants [N=240] related with cirrhosis and death

3.6 Bivariate and multivariate analysis of associated factors of chronic liver disease

Using method of binary logistic regression, variables entered into the analysis model SPSS soft were include all independent variables with in each section at a time. Criteria for selection being the *p* value equal to or less than 0.25 from the bivariate analysis which included variables age, level of education, duration symptoms, variceal bleeding, serum ALP level, PT and ARPI score.

Table 10 shows the odds of cirrhotic CLD among age group 5-10 years (26.3%) is eight times higher than other level of age groups. And the variation is statistically significant, [*P* value = 0.020*, AOR= 8.1, 95% confidence interval (1.4-46)]. The odds of cirrhosis in children with duration symptoms lasting 0.5-1 year among CLD patients was 2.7 times higher than those with different duration of symptoms, [(p value < 0.007*), AOR= 2.7, 95% confidence interval (1.3-5.7)], the difference being statistically significant. And the difference is statistically significant.

Participants who had variceal bleeding (16.6%) showed 1.5 times greater likelihood to have cirrhotic liver disease compared to those with no variceal bleeding [(*P* value < 0.001), AOR= 1.5, 95% confidence interval (0.7-3.0)], The variation was also statistically significant. Regarding elevated level of ALP, the odds of cirrhosis among children who had ten times elevated ALP was three times higher than participants whose other liver enzymes were abnormally elevated), [(*P* value < 0.024), AOR= 3.2, 95% confidence interval (1.5-6.7)]. And the difference is statistically significant.

The odds of cirrhosis among children who had prolonged PT and INR was five times higher than participants whose other liver functions were abnormally elevated), [(*P* value < 0.037), AOR= 5, 95% confidence interval (1.1-8.2)]. And the difference is statistically significant. Participants whose APRI score was greater than two showed 4.9 times greater likelihood to have cirrhotic liver disease compared to those with lower APRI score [(*P* value < 0.001), AOR= 4.9, 95% confidence interval (1.7-13.6)], The variation was also statistically significant. Regarding etiology, undetermined etiology was 3.2 more likely to cause cirrhotic liver disease than other determined etiologies, [(P value < 0.001), AOR= 3.2, 95% confidence interval (0.5-5)], The variation was also statistically significant.

Table 10. Socio-demographic, clinical, investigational, etiological and miscellaneous factors associated with severity and outcome of chronic liver disease

Variable	Cirrhosis Present	Cirrhosis Absent	AOR (95% CI)	*P* value
Age groups (years)				
≤1	40 (16.7)	8 (3.3)		
1-5	41 (17.1)	10 (4.2)		
5-10	63 (26.3)	24 (10)	8.1 (1.4-46)	0.020*
10-15	36 (15)	12 (5)		
15-18	2 (0.8)	4 (1.7)		
Duration of symptoms				
≤ 0.5-1	134 (55.8)	38 (15.9)	2.7 (1.3-5.7)	0.007*
1-5	38 (15.9)	14 (5.8)		
>5	10 (4.2)	6 (2.5)		
Variceal Bleeding	40 (16.6)	28 (11.7)	1.5 (0.7-3.0)	0.001*
Elevated ALP	168 (70)	56 (23.3)	3.2 (1.5-6.7)	0.024*
Elevated PT/INR	101 (42)	42 (17.5)	5 (1.1-8.2)	0.037*
APRI Score > 2	76 (31.7)	6 (2.4)	4.9 (1.7-13.6)	0.001*
Undetermined etiology	121 (48.7)	22 (9.2)	3.2 (0.5-5)	0.001*

Table 11 shows the odds of case fatality among children with cirrhosis was more than four times higher than those without cirrhosis. And the variation is statistically significant, [*P* value = 0.045, AOR= 4.2, 95% confidence interval (0.9-18)].

Regarding etiology, participants with undetermined etiology had 4.6 times higher likelihood of death than those with determined etiology; the difference was statistically significant, [(*P* value = 0.002), AOR= 4.6, 95% confidence interval (1.7-12)]. The odds of death among children with APRI score greater than two was four times higher than participants with lower APRI score), but the difference is not statistically significant (*P* value < 0.178).

The odds of death of participants who had Kasai procedure (Hepatoportoenterostomy) was 90 % lower than those who did not receive the intervention; the difference is statistically significant, [(*P* value = 0.043), AOR= 0.1, 95% confidence interval (0.03-0.9)]. The odds of death among female participants was 1.8 times higher than male participants. Two participants who had liver transplantation had 100 % case fatality.

The mortality of children with CLD among age groups, duration of symptoms, clinical signs and symptoms, liver functions and enzymes and determined etiological variables were not associated with statistical significance.

Table 11. Socio-demographic, clinical, investigational, etiological and miscellaneous factors associated with outcome of chronic liver disease

Variable	Death Yes	Death No	AOR (95% CI)	*P* value
Age groups (years)				
≤1	16 (6.7)	32 (13)		
1-5	2 (0.8)	49 (20)		
5-10	2 (0.8)	82 (34.5)	-	0.999
10-15	6 (2.5)	45 (19)		
15-18	0 (0)	6 (2.5)		
Gender				
Male	12 (5)	119 (49.6)		
Female	14 (5.8)	95 (39.6)	1.8 (0.6-5.1)	0.269
Duration of symptoms				
≤ 0.5-1	22 (9.2)	150 (62.5)		
1-5	4(1.7)	48 (20)	-	0.175
>5	0 (0)	16 (6.7)		
Variceal Bleeding	2 (0.8)	14 (5.8)	-	0.999
Cirrhosis	24 (10)	158 (65.8)	4.2 (0.9-18)	0.045*
APRI Score > 2	6 (31.7)	76 (2.4)	4.0 (0.5-30)	0.178
Undetermined etiology	6 (2.5)	137 (57)	4.6 (1.7-12)	0.002*
Kasai procedure	2 (0.8)	3 (1.2)	0.1 (0.03-0.9)	0.043*
Liver transplants	2 (0.8)	0 (0)	-	0.999

CHAPTER FOUR

4. DISCUSSIONS

The main objective of this study was to determine the magnitude and factors associated with chronic liver disease five years trend analysis in Tikur Anbessa specialized hospital.

4.1 The magnitude of chronic liver disease

This study found that the magnitude of chronic liver disease among children (age 0-18 years) who have attended gastroenterology and hepatology clinic for the last five years at TASH is 4.8%. This rate is relatively higher compares to prospectively collected cross sectional study done in Egypt with prevalence of 1.6% [12]. The study done in India at Saisandesh Children's Hospital found 1.1 % rate of children with CLD which is almost one third the rate depicted in this study [4]. In similar study in Pakistan showed the magnitude of CLD 9.8% which far more prevalent than current study. The difference could be attributed to the major socio demographic variation, clinico-etiologic characteristics of the participants and sample size variations related to the diagnosis and intervention of the subjects.

The magnitude of cirrhotic liver disease comprised 75% with case fatality of 10.8% of all participants in this study. Comparable number of children had cirrhotic chronic liver disease depicted in different international cross sectional and cohort studies [4,12,14,16]. Chi Zhang et al. literature reported the incidence of pediatric cirrhosis were highest in central, western, and eastern Sub-Saharan African countries with the rate 14.1, 14.7 and 9.9 per 100,000 per year in 2019, respectively [Increase of incidence by 134%, 128 % and 102 % over 3 decades, respectively] [9]. The mortality and cirrhotic chronic liver disease outcome comparability could be attributable to the spectral continuity of end stage liver disease might be defined universally by the presence of structural cirrhosis despite the heterogenicity of etiological factors. Howe ever, overall mortality was relatively lower in subjects who had definitive intervention despite the severity of chronic liver disease; which was reported in the prospective study done in UK with mortality $< 1\%$ which 10 times lower than figure depicted in this study [22].

4.2 Factors associated with severity and outcome of chronic liver disease

The severity of chronic liver disease was defined in this study as spectral continuity of chronic liver disease with characteristic hepatic ultrasound evidences which is standard for most studies. Prediction of chronic liver disease outcome is mainly dependent on its severity and factors associated with its severity may predict the outcome. This current study found age, educational level, duration of symptoms, presence of variceal bleeding, presence of elevated level of initial ALP, INR/PT and undetermined etiology were statistically significant associated factors that determine cirrhosis in chronic liver disease.

4.2.1 Socio-demographic factors

The most common of CLD in this study 5-10 years with male predominance. Anisbel Ruiz Ramos et al. and Prasanth K. Sobhan et al. on their cross-sectional institution-based studies reported more than 50 % of pediatric CLD observed in age less than 1 year [9, 13, 14]. Females predominated in Ch Zhang et al. report, in contrary males had highest incidence in other literatures.

The odds of cirrhotic CLD among age group 5-10 years (26.3%) is eight times higher than other level of age groups. And the variation is statistically significant, [P value = 0.020*, AOR= 8.1, 95% confidence interval (1.4-46)]. Chi Zhang et al. reported statistically significant associated factor of less than 5 years and comparably, Ashraf Abou-Taleb et al., Anisbel Ruiz Ramos et al. and Prasanth K. Sobhan et al. reported age < 1 year [13,14]. The global and regional studies reported as above had variations in age group of cirrhotic CLD compares to this study. Under five years of age children was predominant in this study but the statistical significance was fallen on higher age group of the study participants. Afore mentioned studies signified the difference might be due to early screening or detection of chronic liver disease compares to this study. This deviation could also be explained by etiological and interventional diversity.

Most educational level were primary school, low parental income, no family history of CLD and residency of urban setting. And similar studies done in Africa depicted comparable socio-demographic characteristics with variations in significance [9].

4.2.2 Clinico-investigational variables

In this study the most common clinical presentations were hepatomegaly, splenomegaly, ascites and jaundice with most of them had elevated liver enzymes, direct hyperbilirubinemia, anemia and elevated PT/PTT/INR. Comparably, Ayesha Sardar et al., Ashraf Abou-Taleb et al., and Anisbel Ruiz Ramos et al. reported the most common presentation were jaundice, hepatomegaly and splenomegaly in all age groups. Complications of portal hypertension [ascites, HSM and variceal bleeding] were also reported with variations [11, 12, 13, 14]. Regardless of the underlying etiology biochemical abnormalities including AST, ALT, GGT, Hgb, Plt, Albumin, PT, PTT, INR and others were elevated in most of literatures including Chi Zhang et al. reports [9, 15, 16, 17]. The comparability showed similar clinico-investigational factors to other studies.

Regarding duration of symptoms in this study, the odds of cirrhosis in children with duration symptoms lasting 0.5-1 year among CLD patients was 2.7 times higher than those with different duration of symptoms, [(p value < 0.007*), AOR= 2.7, 95% confidence interval (1.3-5.7)], the difference being statistically significant. And the difference is statistically significant. The power of association with either onset or persistence symptoms was reported in literatures since its significance was confounded for simple operational definition. And Chi Zhang et al. reported participants with longer duration of symptomatic CLD has higher mortality rate [13]. However, linear comparison is not possible in terms of duration of symptoms for prediction of outcome.

Participants who had variceal bleeding (16.6%) showed 1.5 times greater likelihood to have cirrhotic liver disease compared to those with no variceal bleeding [(*P* value < 0.001), AOR= 1.5, 95% confidence interval (0.7-3.0)], The variation was also statistically significant. Regarding elevated level of ALP, the odds of cirrhosis among children who had ten times elevated ALP was three times higher than participants whose other liver enzymes were abnormally elevated), [(*P* value < 0.024), AOR= 3.2, 95% confidence interval (1.5-6.7)].

The odds of cirrhosis among children who had prolonged PT and INR was five times higher than participants whose other liver functions were abnormally elevated; and the difference is statistically significant. Chi Zhang et al. reported statistically significant associated factors: low serum albumin level, low platelet count and presence of portal hypertension and hepatitis B were significantly associated with pediatric CLD and rapid decompensation to ESLD [9].

Comparably, Ashraf Abou-Taleb et al., Anisbel Ruiz Ramos et al. and Prasanth K. Sobhan et al. reported elevated direct serum bilirubin > 50 % of total, low serum albumin, USG evidence of portal hypertension and histologic and genetic tests for metabolic and genetic etiologies had statistically significant associated with pediatric CLD and rapid decompensation [13, 14, 15].

Factors that are mutually inclusive which were associated with statistical significance were scarce among aforementioned studies; complicated portal hypertension and variceal bleeding specific variable to this study signify statistically significant variation in the progression of chronic liver disease. Abnormal elevation of ALP and PT/INR were implicated as statistically significant associated laboratory factor in prediction of liver cirrhosis; in contrast Chi Zhang et al., study and Ashraf Abou-Taleb et al., Anisbel Ruiz Ramos et al. and Prasanth K. Sobhan et al studies reported serum albumin, low platelet and direct bilirubin level.

The variations of the figures could be attributable to relative etiologic predominance that trajected similar pattern of enzymatic and other laboratory factors. Ashraf Abou-Taleb et al. and Chi Zhang et al. reported on their respective literatures where degree of AST and ALT abnormality were statistically significant to associate the outcome of CLD in chronic hepatitis [9,12]. This study was wriggled with undetermined etiologies. On the hand, Indian and Pakistan cross sectional studies reported elevated ALP and coagulation profiles were associated with progression of CLD [14,17].

Regarding APRI score Participants whose APRI score was greater than two showed 4.9 times greater likelihood to have cirrhotic liver disease compared to those with lower APRI score [(*P* value < 0.001), AOR= 4.9, 95% confidence interval (1.7-13.6)], The variation was also statistically significant. In contrast, studies on association of APRI to prediction CLD in pediatrics were not found. However, adult cross-sectional study in Ethiopia reported APRI prediction of liver fibrosis in chronic viral hepatitis B infection [6]. Though the absence of comparator could affect its statistical power, the association in this study might provide one more bed side predictor of CLD progression in children.

4.2.3 Etiological factors

This study found the most common etiology of CLD in children at TASH in Ethiopia undetermined etiology 60 % followed by cholestasis the second most common etiologic factor. Thirty-one (12.9%) of children with CLD were reported to be caused by biliary atresia followed by 2.5% of them had progressive familial intrahepatic cholestasis. Four of the participants had Gaucher disease; one with galactosemia and alpha-1 antitrypsin deficiency each. Genetic etiologies were rare; only 1 participant with Wilson disease and 5 children with herbal medication. Fourteen (6%) of subjects had identified etiology of portal vein thrombosis followed by congenital hepatic fibrosis (CHF) (1.7%), Budd Chiari syndrome (0.8%) and Schistosomiasis (1.3%).

Chi Zhang et al. reported cirrhosis caused by 5 etiologies (alcohol use, hepatitis B, hepatitis C, NAFLD and other causes) Ayesha Sardar et al. and Sr. Awais Tahir et al reported Hepatitis B (31, 22.8%), idiopathic (23, 16.9%), glycogen storage disorder (GSD) (21, 15.4%), and Wilson disease (14, 10.3%) were the most common cause of CLD and Viral hepatitis was the most common cause found in 22 (36.7%) cases respectively. Ashraf Abou-Taleb et al., Anisbel Ruiz Ramos et al. and Prasanth K. Sobhan et al. reported in agreement the most common etiology of pediatric CLD neonatal cholestasis which is followed by MLD included glycogen storage disease (26.5%), undetermined inborn error of metabolism (5.3%), Gaucher's disease (2.0%), and Niemann Pick disease (1.3%) [9,11,17].

The major disparity shown in the respective studies is undetermined etiology labeled this study provided diverse blind assumptions for progression of CLD and invalid comparison to similar studies. Almost 60% of the participants in this study had no identified etiology to attribute the variations observed in other similar studies. However, participants with identified etiologies (40%) had relatively comparable number to sample sizes of similar studies. And this provided small room for statistical association with CLD progression and outcome. Forty-nine percent of the subjects with undetermined etiology had cirrhotic CLD. Participants with undetermined etiology were more likely to have cirrhotic liver disease compares to other groups of identified etiologies and the difference in the undetermined etiology of CLD is statistically significant (P=0.001).

This study did not report statistically significant difference of both etiologies cholestatic liver disease and chronic hepatitis (HBV and HCV); unlike Chi Zhang et al. and Ayesha Sardar et al.

4.2.4 Miscellaneous factors

This study found that the odds of case fatality among children with cirrhosis was more than four times higher than those without cirrhosis. And the variation is statistically significant, [*P* value = 0.045, AOR= 4.2, 95% confidence interval (0.9-18)]. Similarly, Chi Zhang et al. reported mortality significantly associated with severe form of CLD [9].

The mortality of participants who had Kasai procedure (Hepatoportoenterostomy) was 90 % lower than those who did not receive the intervention; the difference is statistically significant, [(*P* value = 0.043), AOR= 0.1, 95% confidence interval (0.03-0.9)]. Two participants who had liver transplantation had 100 % case fatality. In large prospective cohort study done in UK death after liver transplant was reported less than 1% and the difference is not statistically significant. The variation in survival of children with CLD could be dependent of definitive intervention [22].

Eighteen (7.4%) of the participants were reported to have medical comorbidities; cerebral palsy due to PNA, CRVHD/CHD, polycystic kidney disease, systemic lupus erythematosus, protein C deficiency, malignant fibrosarcoma and septic shock. No report of studies showed statistically significant variation in the survival of children with CLD. One of the participants in this study had post liver transplant complication of severe infection which led to shock and death.

4.3 Limitations of the study

First, its cross-sectional design prevents establishing causality or disease progression timelines. Second, selection bias from single-center recruitment may underrepresent early-stage CLD cases, skewing risk assessments. Third, reliance on caregiver-reported symptom durations introduces recall bias. Fourth, unmeasured confounders like genetic or environmental factors may distort associations, particularly in undetermined etiologies. Fifth, diagnostic reliance on non-invasive biomarkers (e.g., APRI) over biopsies risks misclassifying fibrosis severity, while incomplete etiological evaluations inflate undetermined cases. Sixth, short follow-up limits mortality data's reflection of long-term outcomes.

CHAPTER FIVE

5. CONCLUSION AND RECOMMENDATIONS

5.1 Conclusions

Based on result findings and discussion the following conclusions were extended:

This study reveals a substantial burden of chronic liver disease (CLD) among children (0–18 years) at Tikur Anbessa Hospital, with a prevalence of 4.8%, exceeding rates in comparable African studies but remaining below those reported in South Asian cohorts. Key determinants of cirrhosis progression included age 5–10 years, symptom duration 6–12 months, variceal bleeding, elevated ALP, prolonged PT/INR, APRI scores >2, and undetermined etiology, all identified as robust prognostic markers. Mortality (10.8%) correlated strongly with cirrhosis and undetermined etiology, underscoring their clinical gravity.

Surgical intervention significantly reduced mortality risk by 90% in cholestatic CLD, though limited access to liver transplantation—a definitive therapy—precluded conclusive analysis of its impact. These findings advocate for prioritization of early non-invasive prognostic indices (APRI, PT/INR), etiological clarification protocols, and scalable surgical access to mitigate poor outcomes in resource-constrained settings. The data underscore an urgent need for region-specific CLD management frameworks addressing multifactorial determinants and healthcare inequities.

5.2 Recommendations

The following recommendations have been made based on result findings and discussions:

1. Prioritize Multicenter Longitudinal Studies: Given the elevated prevalence of pediatric CLD at TASH, rigorous prospective cohorts with expanded sample sizes are imperative to inform evidence-based national policies for prevention, early intervention, and outcome optimization.

2. Standardize Prognostic Biomarker Integration: Elevated APRI scores, PT/INR, and ALP should be embedded into routine clinical algorithms to stratify disease severity and guide timely definitive interventions (e.g., transplantation eligibility).

3. Accelerate Etiological Diagnostics: Undetermined etiology—a critical driver of mortality (10.8%)—demands protocolized, tiered diagnostic workflows incorporating genomic, metabolic, and infectious assays to enable targeted therapies and improve survival.

These strategies address the study's epidemiological gaps, prognostic predictors, and etiological ambiguities, aligning with global mandates to reduce CLD mortality through precision diagnostics and scalable health system reforms

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Annex

Annex-1 Questionnaire

General Information

Date: ...../...../ …….

Questionnaire serial No: .....

MRN: .....

Part I. Socio-demographic variables

1. Age 1. < 1 yr. 2. 1-5 yr. 3. 5-10 yr. 4. 10-15 yr. 5. 15-18 yr.
2. Gender
   1. Male 2. Female
3. Residency
   1. Rural 2. Urban
4. Parental income
   1. < 3000 ETB 2. 3000-6000 ETB 3. 6000-10000 ETB 4. > 10000 ETB
5. Education level
   1. KG 2. Primary 3. Secondary 4. Others
6. Family history of CLD 1. Yes 2. No

If yes, Specify _____

Part II. Clinical-variables

7. Duration of symptoms
   1. < 6 months 2. > 6 months 3. 6-12 months 3. Specify duration _____
8. Symptoms [History] and Signs [Physical Exam]

1. Jaundice

2. Ascites

3. Hepatomegaly

4. Splenomegaly

5. Variceal bleeding

6. Clubbing

7. Peripheral edema

8. Hepatic encephalopathy

9. Usage of traditional medicine

Others specify all _____

9. Malnutrition

1. Severe stunting [Age/Height < -3] 2. S.wasting [MUAC ≤ 11.5 cm BMI/A< -3]

3. Severe underweight [Wgt/Age < -3] 4. Over weight [BMI/Age > 2 Z score]

10. Maternal HBV status during pregnancy

1. Active infection 2. Past infection 3. Chronic infection 4. Inactive phase

11. EPI vaccine to HBV to child

1. Yes 2. No

12. Is there developmental mile stones delay comparable to child's age

1. Yes, Developmental delay 2. No, Developmental delay

If yes, 1. GDD 2. Language alone 3. Motor 4. Social 5. Cognition

Part III. Investigational-variables

13. CBC

1. Anemia 2. Thrombocytopenia [<100,000 / ul] 3. Leukopenia [< 4000 /ul]

4. HgB in g/dl _____ 5. Platelet in /Ul _____ 6. WBC in /ul _____

Normal reference [21]

[HgB in g/dl 0-30 days 15.0-24.0 , 1-23 mo 10.5-14.0 , 2-9 yr 11.5-14.5 , 10-18 yr M 12.5-16.1 , F 12.0-15.0] [Platelets in per ul 150,000-400,000] [WBC per ul x 1000 1-23 mo 6.0-14.0 , 2-9 yr 4.0-12.0 , 10-18 yr 4.0-10.5]

14. Liver enzymes

1. Elevated AST > 2x 2. Elevated AST > 3-4x 3. Elevated AST > 5-6x

4. Elevated ALT > 2x 5. Elevated ALT > 3-4x 6. Elevated ALT > 5-6x

7. Elevated ALP > 2x 8. Elevated ALP > 3-4x 9. Elevated ALP > 5-6x

Normal References [21]

AST [in u/l 1-12 mo 22-63,1-3 yr 20-60 , 3-9 yr 15-50, 10-15 yr 10-40,

16-19 yr M 15-45 , F 5-30]

ALT [Age < 1 yr. 12-45 u/l, > 1 yr. 5-45]

ALP [in u/l 1-9 yr 145-420, 10-11 yr 140-560, 12-13 yr M 200-

495 F 105-420, 14-15 yr M 130-525 F 70-230, 16-19 yr M 65-260 F 50-130]

15. Liver function Test

1. Direct bilirubin > 20 % T.Bilirubin 2. Serum Albumin < 3.4 g/dl

3. PT > 14 sec 4. aPTT > 34 sec 5. INR > 1.5

6. T/D bil in mg/dl ___ 7. S.Albumin in g/dl _____ 8. PT,PTT,INR_____

Normal references [21]

Total bilirubin [1month -adult < 1 mg/dl] Serum albumin [g/dl 8 days-1 yr 1.9-4.9, 1-3 yr 3.4-4.2, 4-19 yr 3.5-5.6] [PT, INR and aPTT 12-15 sec, 1.1-1.2 , 28-34 sec]

16. Abdominal Ultra-sonography

1. Portal hypertension with cirrhosis [Atrophied liver lobe, coarse echogenicity, nodules]

2. Portal hypertension with no cirrhosis [Dilated portal vein > 13-15 mm and operation def.]

3. Non visualized gall bladder with or without triangular cord signs

Specify all findings

_____

_____

17. Miscellaneous [APRI score, CT, Biopsy, Genetic test, metabolic screening]

17.1 Viral/ToRCH/Genetic/Metabolic/Autoimmunity tests

1. HBsAg/Anti HeAG 2. HCV 3. CMV titer 4x more than mother 4. Toxoplasmosis antobidy 4x more than mother 5. Low ceruloplasmin 6. A 1 anti trypsin deficiency 7. ANA positive 8. ASMA positive 9. Anti-LKM1 positive 10. Stool schistosoma positive 11. Others mention _____

17.2 APRI score [Calculate Average =AST level/AST upper normal] validated only for > 10yr.

. Platelet count [10^9/L]

1. 0.5-1.5 Likely liver fibrosis 2. 1.5-2 Fibrosis – cirrhosis 3. > 2 Cirrhosis

17.3 Biopsy _____

17.4 CT scan_____

Part IV. Etiological-variables

18. Chronic hepatitis,

1. HBV 2. HCV 3. CMV 4. Autoimmune type 1 5. Autoimmune type 2 6. Drug induced 7. Toxoplasma 8. TB 9. Idiopathic [Giant cell, Neonatal]

Other specify the diagnosis _____

19. Cholestasis,

1. Biliary atresia 2. Allagile syndrome 3. Progressive familial intra hepatic cholestasis 4. Choledochal cyst Others specify the diagnosis_____

20. Metabolic diseases,

1. Gaucher disease 2. Galactosemia 3. A1 antitrypsin deficiency

4. Tyrosinemia 5. GSD 6. Neimann pick disease

Others specify the diagnosis_____

21. Genetic diseases,

1. Wilson's disease 2. Allagile syndrome 3. A1 antitrypsin deficiency

Others specify the diagnosis_____

22. Traditional medicines, specify the names _____

23. Miscellaneous etiologies,

1. Congenital hepatic fibrosis 2. Parasitic portal tract fibrosis 3. Schistomiasis 3. Budd Chiari syndrome 4. Portal vein thrombosis 5.Undetermined etiology

Others specify the diagnosis_____

Part V. Miscellaneous Variables

24. Associated medical diseases:_____

25. Interventions done:_____

26. Mortality 1. Yes 2. No

Annex-2 Declaration of Own Work

I the undersigned senior pediatrics and child health specialty resident does hereby declare that all the work presented in this topic is my own work unless otherwise acknowledged. So I hence forth present it for Addis Ababa University, College of health sciences school of medicine department of Pediatrics and child health at Tikur Anbessa specialized hospital.

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