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SURVIVAL AND PREDICTORS OF MORTALITY AMONG HIV POSITIVE CHILDREN ON ANTIRETROVIRAL THERAPY IN PUBLIC HOSPITALS, EAST GOJJAM, ETHIOPIA, 2019.

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APPROVAL SHEET BY THE BOARD OF EXAMINERS

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LIST OF ABBREVIATIONS AND ACRONYMS

AAU **Addis Ababa University**

AHR **Adjusted Hazard Ratio;**

ART **Anti-retroviral therapy**

ARV **Antiretroviral**

CHR: **Crude Hazard Ratio**

CD4 **Cluster of differentiation 4**

CD4% **Cluster of differentiation 4 percent**

CI: **Confidence Interval**

CPT **Cotrimoxazole preventive therapy**

DMRH **Debre Markos Referral Hospital**

FMOH **Federal Ministry of Health**

LTFU **Lost time to follow up**

OI **Opportunistic infections**

SMDH **Shegaw Mota District hospital**

TB **Tuberculosis**

UNAIDS **United Nations Program on HIV/AIDS**

WHO **World Health Organization**

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ABSTRACT

Background: Human immunodeficiency virus and acquired immunodeficiency syndrome had created enormous challenges worldwide, continued to be the world's serious health and development challenge. Globally, at the end 2017, there were 1.8 million children (<15 years) living with human immunodeficiency virus. The goal of antiretroviral therapy is to maintain maximal suppression of viral replication, to restore immune function, to reduce human immunodeficiency virus -related morbidity and mortality, and improve quality of life and prolong survival. The survival of HIV positive children treated with ART depends on a variety of factors, which might vary greatly with economic, socio- demographic, behavioral risk and health factor. **Objectives**: To assess Survival status and predictors of mortality among human immunodeficiency virus Positive Children on Antiretroviral Therapy at East Gojjam Zone Public hospitals, Amhara Regional State, Ethiopia 2019.**Methods:** An institution based retrospective cohort study was conducted in selected hospitals of East Gojjam zones among children aged less than 15years who were newly enrolled in human immunodeficiency virus care clinic from January1st 2014 to December 31, 2018. Data was collected using standardized check list. The charts were reviewed during March 1 to 22,2019. Data was entered Epi-Data version 3.1 and then exported to SPSS version 24 for statistical analysis. A Kaplan Meier curve and long rank test were used to estimate the survival time and compare survival curves between variables. Multivariable Cox proportional hazards model was fitted to identify predictors of survival status and variables having p value < 0.05 were considered as statistically significant. **Result:** In this study, a total of 251 HIV positive children on ART were followed up for a total of 60 months, with a mean (SD) survival time of 55.54(+ 0.83), (95% CI:53.90-57.17) months. The overall mortality incidence rate in the cohort during the 626 Child-year-observation (CYO) was 2.56/100 CYO. Kaplan- estimation Meier survival showed that overall estimated survival probability after starting ART was 0 .90 at 60 months of follow up. In this study age, hemoglobin level, CD4 count, cotrimoxazole preventive therapy (CPT), weight for height were statistically significant predictors of survival status (P <0.05). **Conclusion and Recommendation**: Age < 5 years, CD4 count, Hgb <10gm/dl, WFH (z<-3), not taking cotrimoxazole preventive therapy were an independent predictor of mortality. Therefore, concerned stakeholders should focus on above mentioned predictors of mortality and nutritional interventions to enhance survival of HIV-infected children on antiretroviral therapy. **Key words:** Children, antiretroviral therapy, Human immunodeficiency virus, survival, Ethiopia

INTRODUCTION

1.1.Background

Human immunodeficiency virus is a virus that attacks the immune system and damages the body's ability to fight infections. HIV attacks and destroys certain white blood cells that are essential to the body's immune system. The main targets of HIV are CD4+ lymphocytes, monocytes, tissue macrophages, and dendritic cells [1].

Acquired immunodeficiency syndrome is a pattern of devastating infections caused by the human immunodeficiency virus. AIDS is a potentially fatal condition that develops in the most advanced stage of HIV.HIV/AIDS was first identified in the early 1980's. Since then the number of people infected with HIV has increased rapidly throughout the world. HIV/AIDS has become the most widely talked about condition in history[2].

There is no cure for HIV infection. However, effective antiretroviral (ARV) drugs can control the virus and help prevent transmission so that people with HIV, and those at substantial risk, can enjoy healthy, long and productive lives. The goal of antiretroviral therapy (ART) is to restore immune function, to maintain maximal suppression of viral replication, to reduce HIV-related morbidity and mortality and improve quality of life and prolong survival[3].

More than 90 % of pediatrics HIV infection occurs through mother to child transmission and it implies that global distribution of pediatrics HIV infection is similar with the distribution of HIV in women. ART should be initiated for all children living with HIV regardless of WHO clinical stage or at any CD4 cell count[4]. However, only 52% of all children aged 0–14 years living with HIV had access to treatment globally, in 2017[5].

The first evidence of HIV infection in Ethiopia was detected in 1984. Since then, AIDS has claimed the lives of millions and has left behind hundreds of thousands of orphans. HIV/AIDS epidemic has remained one of the important public health challenges[6]. Ethiopia has one of the largest populations of HIV infected people in the world[3].

1.2. Statement of the problem

Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) have created enormous challenges worldwide. HIV has become one of the world's most serious health and development challenges since the first cases were reported in 1981. According to UNAIDS (2018); since the start of the epidemic 77.3 million people have become infected with HIV and 35.4 million people have died from AIDS-related illnesses. Globally, in 2017, there were 36.9million people living with HIV of which 1.8 million children (<15 years). In 2017 new HIV infections among children have declined by 35%, from 270 000 in 2010 to 180 000 in 2017 [5, 7].

The vast majority of people living with HIV are located in the low- and middle- income countries. The WHO African Region is the most affected region, with 25.7 million people living with HIV in 2017. About 91% of children who are HIV positive live in Africa. Limited access to antiretroviral drugs remains an issue across the African continent. Therefore, there are still AIDS-related deaths in Africa [8].

Over the last several years, there has been a dramatic decline in new pediatric infections, but children born infected with HIV are in critical need of lifesaving HIV treatment. Infants and young children infected with HIV have exceptionally higher morbidity & mortality. Up to 52% and 75% of children die before the age of two and five years respectively in the absence of any intervention.[6] Children are being left behind. In 2017, about 180 000 children became infected with HIV, far from the 2018 target of eliminating new HIV infections among children. While the overall HIV treatment level is high, there is a huge injustice being committed against children—only half of under-15s living with HIV were being treated in 2017 [7].

In Ethiopia, around 610, 000 people were living with HIV. Of which 62,000 were children (0-14 ages). In 2017, 16,000 people became newly infected with HIV of which 5,500 were children (0-14 ages). Only 22,438 children were receiving ART as of October, 2017.An estimated 15,000 people died from AIDS-related illnesses of which 3600 were children (0-14 ages). New HIV infections among children declined from 9,600 in 2010 to 5,500 in 2017 [7].

HIV/AIDS continued to be one of the top priorities on the health sector agenda for the Ethiopian government. [9] To this end, the government of Ethiopia took several steps in preventing further disease spread, and in increasing accessibility to HIV care, treatment and support for persons living with HIV and hence to reduce morbidity and mortality[5],[7]. However, in contrast to Ethiopia's progress in reaching HIV epidemic control among adults, identification and treatment of children living with HIV remains a challenge [10].

The mortality rates among children on ART in Ethiopia significantly vary between deferent study areas and ranges from 12.4 deaths per 1000 child-years to 40.0 deaths per 1000 child-years of follow-up period. Predictors of mortality among children on HAART in the country were inconsistently reported by fragmented studies conducted in different study areas [11-18].

The survival of HIV positive children treated with ART depends on a variety of factors, which might vary greatly with economic, socio- demographic, behavioral risk and health factors. Even-though ART has shown significant clinical importance by meeting the goal of therapy, still children were facing a number of deaths that could be avoided by appropriate interventions on certain factors such as socio-economic, demographic, treatment related and health factors which include the child's age, CD4 count / CD4% at ART initiation, WHO stage, hemoglobin level, ART adherence[19 -25].

1.3. Justification of the study

This study was conducted in order to have a nearest five years follow up study periods. In this period, WHO recommend to initiate ART for all children living with HIV regardless of WHO clinical stage or at any CD4 cell count and Ethiopia government is implementing the guideline. This helps to see if there is a change from the previous studies. Moreover, in recent years improved implementation of standardized formats, documentation and recording system in regularly is assumed to be improved.

The survival and predictors of mortality among HIV-infected children on ART had not been studied in the study area. Furthermore, there are inconsistencies of finding among different studies in Ethiopia.

2. SIGNIFICANCE OF THE STUDY

Generally, the rational of studying survival status of children on ART will have practical vital value for patients, providers, researchers and policy-makers in the Ministry of Health. This study will help both society and the individuals at large, to assess progress in HIV/AIDS control and follow-up on HIV/AIDS outcomes.

The study will be an input to policy makers, program managers, health professionals in order to estimate survival rate of patients, to decide based on evidence about HIV/AIDS and to support the planning of systems for enhanced HIV/AIDS control and prevention program. This paper will also provide insight for Nurses in ART treatment centers to know the quality and effectiveness of care they provide. This study will promote nursing research, nursing education and clinical practice so as to provide evidence-based nursing care based on new existing knowledge and estimation of prognosis will be based on evidence and local circumstances. Finally, this paper will also be a base line for future researchers.

3. LITERATURE REVIEW

3.1.Sociodemographic characteristics

A prospective study done in Africa showed that fifty percent of children were females, 22.7% were aged <2 years and 45.1% aged ≥5 years at ART initiation. The median age was 4.2 years. [26] A retrospective cohort study done in Mikelle Hospital indicates, the ages of the cohort at ART initiation were relatively late with median age of 53 months[27]. Similar study done in Wolaita zone states that more half (53.1%) of patients on ART were males. The report showed that median and mean age were 6 and 6.29 years, respectively; 69.3% were living in urban. Parents of 45.6% children were both alive at baseline while 19.7% were both dead [16]. On the contrary, a study done in University of Gondar Hospital states that male patients comprise only 36.65% out of the total 269 ART patients [15].

Another study done in Zewditu Memorial Hospital states that the mean age at initiation of ART was 7.6 years ± 3.8 years, the minimum and the maximum ages being 2.4 months and 15 years, respectively. The median age was 7.9 years. About a quarter (25. 9 %) of the children were under five years, 41% were between 5-10 years and one-third were above ten years of age. There was almost equal male to female proportion (50.3% males). At the initiation of ART, just above a quarter of the children had both parents alive, while either of the parents was alive in 31% and neither of the parents was alive for 19.1% of the children [28]. A study done in Addis Ababa shows Public hospitals, that 49.0% were female. More than seven in ten of the participants were in the age category of 5-14 years [17].

According to a study done in Eastern Ethiopia, more than half of the children were female (52%). At ART initiation, 44.6% were 0 – 5 years of age, the functional status of 52.5% was ambulatory, and 56.4% had CD4 values < 350 cells/mm3. About 15% of the children had history of documented tuberculosis and 49.3% of them were underweight at ART initiation. The mean hemoglobin of the cohort was 10.96 g/dl (SD±1.98) at initiation of ART. More than half of the children (53%) had either mild or moderate to severe anemia[18] On the other hand, a study done in Mekelle Hospital states that nearly equal proportion of male (50.4%) and female (49.6%) subjects were involved in the study. Majority (88%) were above the age of five years. However,

their age ranged from seven months to fourteen years plus two months and the median age was 8.665 years. The reported length of time the children stayed on ART ranged from one to 93 months and the median was 47 months. Furthermore, majority (82.7%) of the children's care takers were males. Age of the care giver ranges from 19 to 84 years and those who were urban and rural dwellers accounted for 79.2% and 20.8% respectively. Those who were illiterates accounted for 39.4%[20].

3.2. **Survival status among children on ART**

Overall mortality rates among HIV-infected children on ART vary greatly around the world. It is higher in less developed countries and minimal in the more-developed countries.

A study done in Swaziland showed the median survival time for children was 78 months.[29] Similar study done in India shows that mortality incidence rate was 30 per 1000 child years (overall); 39 in the <5-year age group; and 25 in 5-9-year age group. Highest mortality (86 per 1000 child years) was encountered among infants.[30]

According to a study done in south Africa showed that mortality incidence rate was 4.7 deaths per 100 child years of follow-up period. [31] while a study done in Nigeria, 4.6% of children had died whereas 95.4% survived. Mortality incidence rate was 1.0 per 100 child-years of follow-up period.[32] Similarly, a study done in four sub Saharan Africa countries showed that 7.6% children died and 38.5% were lost to follow-up. The overall mortality incidence rate was 5.1 per 100 person-years and 1.1 per 100 person-years in the second year of ART use. Mortality decreased over time from 14.3 per 100 person-years during the first three months of therapy to 2.6 per 100 person-years after 6 months of ART use [26].

The mortality incidence rate among children receiving HAART in Ethiopia varies among studies done in different study areas. A study done in Adama showed that a total of 560 children on ART were followed for a median follow-up time of 47 months. At the end of follow up, 65% were alive and 7.6% were reported dead. More than three fourth of the deaths occurred within the first sixth months of starting ART[11]. Another study done in Arba Minich indicates that 15.4% of children died over a follow-up period of 21,175 person-months of observation. The mortality rate of this cohort was 3.07 deaths per 1000 person-months[13]. Another study done in Wolaita Zone showed

that the Cumulative incidence of mortality rate was 21.02 per 1000-person year of observation and estimated mortality was 2, 3, 6, 8 and 16% at 6, 12, 24, 60 and 96 months of follow up, respectively[16].

A study which done in Mekelle, Ethiopia shows that mortality incidence rate was 1.40 per 1000 child-months. Out of the 20 children who died, 2.39 per 1000 child-months died within 12 months of ART initiation while 0.93 per 1000 child-months died after 12 months [27]. Similar study done in Zewditu Memorial Hospital shows that the mortality incidence rate was 2.3 per 100 person-years. The mean survival time was 81.1 months. With regard to time of death, 32.3% died within the first month, 48.4% within the first two months, and 53.2% during the first three months of initiation of treatment.[8] Another study done in Addis Ababa shows that the overall mortality rate was 12.4 deaths per 1000 child-years. The median survival time after initiation of HAART for children who died and censored were 9 months and 72 months, respectively [17].

A retrospective study done in University of Gondar Comprehensive Specialized Hospital showed that 17.1% children died due to the disease, 82.9% were alive or loss to follow-up during the time of data collection [15]. Similar study done in Bahir-Dar shows that the risk of death was found to be 4.0 per 100 child-years of observation. Concerning the time of death, 63.4%, 75.6% and 90.2% of the deaths occurred within the first three, six and twelve months of ART initiation, respectively. The mean survival time was 56.5 months [12].

3.3. **Predictors of mortality in children on ART**

3.3.1. Baseline socio-demographic predictors

Different studies showed that age of the child is considered as predictor of mortality. Studies done in Nigeria[32,33], Malawi[23], Ethiopia[14,15,28] showed that age is statistically significant predictor of mortality. A study done in Swaziland shows that children within the age group of <1 years had higher hazard of death than children within the age group of 1–14 years[29]. A study done in Nigeria shows that age is the main predictor of death, with mortality decreasing by 24% for every 1-year increase in age and the risk of dying being about three and half times more in children <5 years compared to those >5 years[32]. Similarly children within the age group of <1 year had higher hazard of death than children within the age group of 1–14 years. [29] However,

a study done in Uganda shows that there was no enough evidence to suggest that age had a confounding effect on survival[21].

3.3.2. Base line Clinical and laboratory predictors

A study done in Swaziland reveals that active tuberculosis (TB) is predictor of poor survival among children living with HIV[29]. A study done in India shows that mortality rate is significantly higher among children less than five years when the CD4 count at the start of ART is above 200. Additionally, lower CD4 count, HIV clinical stage IV, and lack of functional status seems to be associated with high mortality in children who are on ART[30]. A retrospective study done in four sub Saharan Africa countries shows that immune suppression, HIV clinical stage 3 or 4 are associated with increased rates of mortality, attrition and treatment failure.[26] A study done in Nigeria showed that WHO HIV clinical stage, CD4 count, and year of ART initiation were highly predictive of mortality, while anemia at baseline was not statistically significantly associated[33]. Another study done in Nigeria shows that PTB (100%) and severe immunodeficiency (93.8%) potentially contributed to the increased mortality[32].

A study done in Zewditu Memorial Hospital, Ethiopia showed that on univariate analysis, age, marital status of parents, parental survival, co-trimoxazole prophylaxis, WHO clinical stage, baseline functional status, weight-for-age and height-for-age, were found to be significantly associated with death[28]. Another study done in Gondar hospital showed that age of child (for age <1.5), baseline hemoglobin level, WHO clinical stage, and baseline CD4 count are significant factors for survival of HIV infected children during the 92 months of follow up [15]. On the contrary, a study done in Bahir-Dar found that low baseline CD4 cell count was not a predictor of survival time of HIV infected children[14]. Another study done in Bahir Dare showed that children with low hemoglobin level were almost two and halftimes at risk of death compared to their counterparts. Children with absolute CD4 count below the threshold for severe immunodeficiency were 2.24 times at risk of death. A delayed or regressing developmental milestone at initiation of ART resulted in 6.31 times higher risk of death compared to those with appropriate developmental milestone[12]. A study done in Adama showed that anemia (hemoglobin level<10 gm/dl), absolute CD4 cell count below the threshold, advanced WHO staging (stage IV) and underweight have found to be predictors of mortality after ART initiation[11]. A study done in north west Ethiopia showed that low baseline hemoglobin level, advanced WHO clinical stage and age had

significant impact on the survival of children[14]. Similar study done in Arba Minich stated that delayed and regressed developmental milestone, opportunistic infection at baseline tuberculosis co-infection at base line, low hemoglobin level absolute CD4 below threshold were independent predictors of mortality[13]. Another study done in eastern Ethiopia stated that Children with baseline bed ridden functional status, developing AIDS-defining illnesses and baseline CD4 value <350 cells/mm increased the likelihood of early mortality[18]. However, both presence of OI and WHO clinical stage were not significant predictors of mortality[12].

3.3.3. Treatment (ART and other medication) related predictors

A study done in Swaziland reveals that children who were initiated early on ART had higher survival probability over time ($p < 0.001$) compared to those whose ART initiation was delayed[29]. On adjustment for confounding, absence of co-trimoxazole prophylaxis is strong predictor of mortality[28]. If the child was not on cotrimoxazole preventive therapy at baseline, there was a 4.74 (95% CI: 2.17, 10.34) times increased risk of death[12]. Similar study done in Arba Minich stated that fair and poor adherence to ART, isoniazid preventive therapy and Co-trimoxazole preventive therapy were independent predictors of mortality[13]. Another study done in eastern Ethiopia stated that adherence to ART <85% were factors which increased the likelihood of early mortality. [18] In 2009, WHO recommended that all exposed infants and HIV infected children start cotrimoxazole preventive therapy [34].

3.3.4. Nutritional predictors

A study done in Swaziland reveal that children who were nourished had 88% lower hazard of death than severely malnourished children[29]. A study done in Nigeria shows that severe malnutrition could he contributed to the increased mortality[32]. Underweight was associated with increased rates of mortality[26]. However, baseline nutritional status was not significant predictor of mortality[12].

3.4.Conceptual framework

This conceptual framework shows association between dependent variable (survival status) with independent variables which is developed from deferent literatures. For example, HIV-infected children at early age more likely to die than old aged children[15]. Increased WHO clinical stages, low CD4 counts and low hemoglobin level more likely to increase death[11,15]. Similarly not receiving cotrimoxazole preventive therapy at baseline and delayed or regressing developmental history increase mortality[12].Underweight also increases the risk of death.[11,26] Tuberculosis and delayed ART initiation are predictors of poor survival[29].(**Figure 1)**

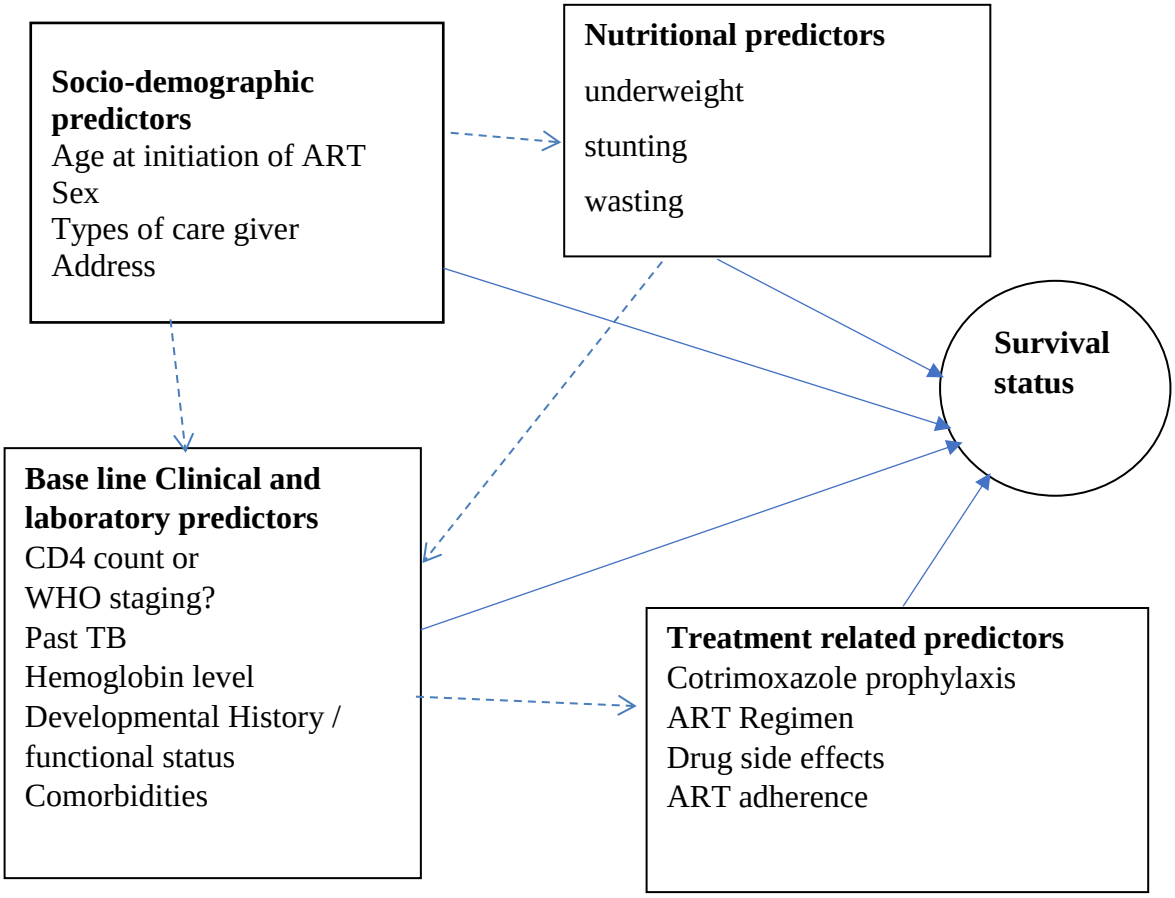

Figure 1 : Conceptual framework for survival status and predictors of mortality among HIV Positive Children on Antiretroviral Therapy in Public hospitals, East Gojjam, Ethiopia.

4. OBJECTIVE

4.1. General objective

To assess Survival status and predictors of mortality among HIV Positive Children on Antiretroviral Therapy in Public hospitals, East Gojjam, Ethiopia.

4.2. Specific objectives

To determine survival of HIV positive children on Antiretroviral Therapy in Public hospitals, East Gojjam, Ethiopia.

To identify predictors of mortality among HIV Positive Children on Antiretroviral Therapy in Public hospitals, East Gojjam, Ethiopia.

5. METHODS AND MATERIALS

5.1.Study area and period

The study was conducted at Debre Markos Referral Hospital and Shegaw Mota District Hospital, East Gojjam zone, Amhara regional state. According to 2007 Census, East Gojjam zone has a total population of 2,153,937, of whom 1,066,716 are men, with an area of 14,004.47 square kilometers. It has a population density of 153.80. While 213,568 or 9.92% are urban inhabitants. The largest ethnic group was the Amhara (99.82%). Amharic is spoken as a first language by 99.81%. while 97.42% of the population practiced Orthodox Christianity, and 2.49% were Muslim [35].

These two hospitals were purposively selected because they are the only hospitals which provide ART services at starting time of study period in the study area. Debre Markos referral hospital is the only referral hospital in East Gojjam zone which is found in Debre Markos town. The town is an administrative city of East Gojjam Administrative Zone. Shegaw Mota District Hospital is one of primary hospitals in east Gojjam zone and found in Mota town of Amhara regional state. DMRH and SMDH are found in Northern direction 299 Kilometers and 370 Kilometers far from Addis Ababa, respectively. According to information obtained from administrative offices of these hospitals, DMRH and SMDH serve more than 3.5 million and 1.5 million populations in their catchment area, respectively. Apart from other services, both hospitals provide ART services [35,36,37].

The data was collected from March 1 to 22, 2019 among records of children on ART registered from 1st of January 2014-December 31st, 2018.

5.2.Study design

Institutional based retrospective cohort study was conducted among children less than 15 years who were living with HIV and initiated for ART from 1st of January 2014-December 31st, 2018.

5.3.Population

5.3.1. Source population

All medical records of all HIV positive children on ART in DMRH and SMDH from 1st of January 2014-December 31st, 2018.

5.3.2. Study population

All medical records of HIV positive children patients who attended the ART unit of DMRH and SMDH from 1st of January 2014-December 31st, 2018 and who fulfilled the inclusion criteria of the study.

5.4. Eligible criteria

5.4.1. Inclusion criteria

All HIV positive children less than 15 years old and who were newly enrolled on ART in DMRH or SMDH from January 1st, 2014- December 31st, 2018 were included.

5.4.2. Exclusion criteria

Children whose medical charts were not found during data collection and /or children's chart having incomplete data on major variables of the study.

5.5. Sample size and sampling procedure

5.5.1. Sample size determination

The sample size was determined using double population proportion formula by considering the covariates. INH prophylaxis, CD4 counts and hemoglobin level are variables that are found to be significantly Predictors of Mortality among Children on Anti-Retroviral Therapy based on study done in Arba Minich, Ethiopia[13] to calculate the required sample size. Finally, it was calculated by using Epi info version 7 statistical package. Moreover, Baseline CD4 count below the threshold was considered as independent predictor since it gives the maximum sample size**. (Table 1)**

***Table 1*: Sample *size determination* of Children on ART in East Gojjam Zone public hospitals, 2019**

Variables	Assumptions	Total sample size	After adding 10%
Baseline CD4 count belo the threshold	P_1=20.99 P_2= 11.25	486	535
Not used INH prophylax	P_1=31.09 P_2=9.27	122	134
Base line hemoglobin level<10.00 gm/dl	P_1=44.87 P_2=9	58	64

P_1: is percent of the outcome in exposed group ,

P_2: is percent of the outcome in non-exposed group,

$Z_{\alpha/2}$: is taking CI 95%, **Z_B**:80% power,

And **r** is the ratio of non-exposed to exposed 1:1,

Then the largest sample size **(N= 535)** was selected as the final sample size for the study.

5.5.2. Sampling procedure

First, the two hospitals; DMRH and SMDH were selected purposely because of their ART service at the starting time of study period, and then the profiles of all HIV positive children who initiated for ART from 1st of January 2014-December 31st, 2018 in the two hospitals were assessed. Study participants who fulfilled the inclusion criteria in the study were identified by data collectors from list of ART charts. However, as there are small number of children enrolled on ART during the study period than that of obtained from the calculated, all the recruited cards in each hospital were selected by using census sampling method. Finally, the selected medical charts were reviewed from March 1 to 22, 2019. (**Figure 2)**

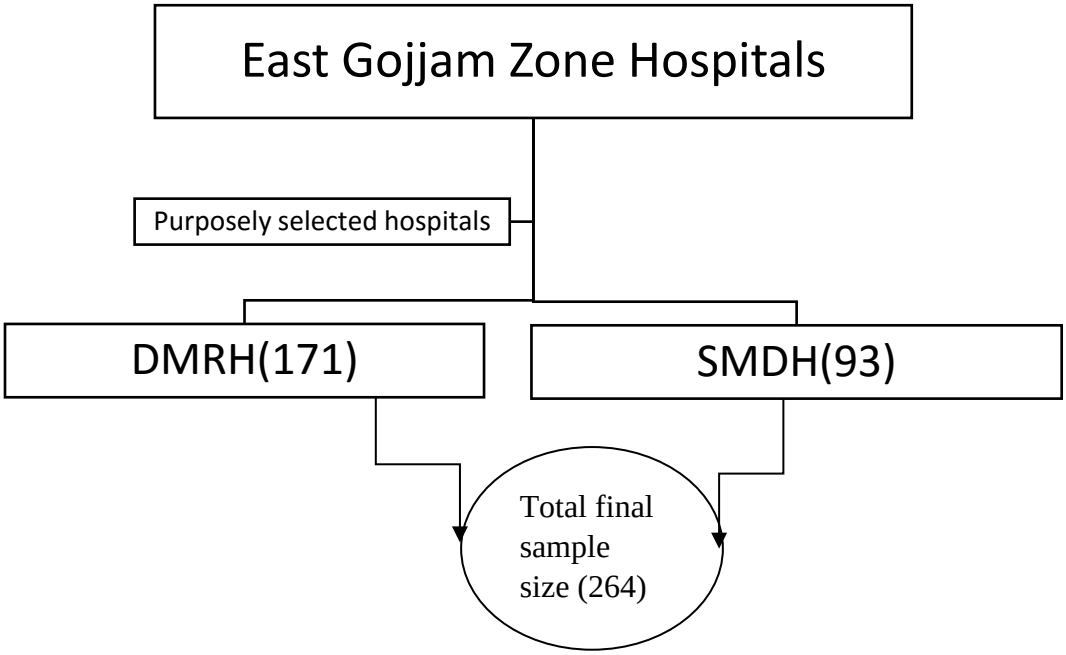

Figure 2: schematic presentation of sampling procedure to assess Survival status and predictors of mortality among HIV Positive Children on Antiretroviral Therapy from (2014-2018) in Public hospitals, East Gojjam, Ethiopia, 2019.

5.6. Study variables

5.6.1. Dependent variable

Survival status (death or censored)

5.6.2. Independent variable

Socio demographic Predictors
Sex
Residential address
Age at initiation of ART
Primary care giver
Religion of care giver
Clinical and laboratory Predictors
Baseline WHO stage
Tuberculosis (TB) positive at baseline
CD4 count/CD4% at baseline
Past opportunistic illness
Hemoglobin level
Treatment related Predictors
Early initiation/delayed initiation
Baseline ART regimen
OI prophylaxis
ART adherence
Drug side effect
Nutritional predictors
underweight
stunting
wasting

5.7. Operational definition and definition of terms

Censored; those HIV positive children who did not develop the outcome of interest (death) until the end of follow-up period, those lost to follow-up or transfer out to a different care unit during the study.

Children: a group of individuals aged less than 15 years.

Duration on ART - is defined as the time between the start date of ART and the date of last contact with the health facility.

Event: the occurrence of death from initiation ART to the end of the study.

Moderate stunting: children having Height/ Age Z-score < −2 SD. [38, 39]

Moderate underweight: children having Weight/Age Z-score < − 2 SD. [38, 39]

Moderate wasting: children having Weigh/ Height Z-score < −2 SD. [38, 39]

Severe stunting: children having Height/Age Z-score < −3 SD. [38, 39]

Severe underweight: children having Weigh/Age Z-score < −3 SD. [38, 39]

Severe wasting: children having Weigh/ Height Z-score < −3 SD. [38, 39]

Survival status. In this research, survival status was defined as the outcome of patients was sourced from patient clinical data files and was dichotomized into censored or death.

5.8. **Data collection tool**

A data abstraction format was developed from the standardized ART entry and follow up form that is currently used by the ART clinics of the study hospitals. Data abstraction was designed based on study objectives, and contains three parts; checklist related to socio-demographic information, nutritional factors, checklist related to clinical and laboratory factors, and checklist related to treatment factors which collected from medical records.

5.9. Data collection procedure

All available information on patient records were checked. Then, appropriate data extraction format was adopted in English in order to extract all the relevant variables to meet the study objectives from patient charts. The starting point for retrospective follow-up was the time from initiation of ART, and the end point was date of death, date of lost to follow up, date of transfer out or date of last contact until January 31th, 2018. All charts of HIV positive children, who started ART between 2014 and 2018 at the two hospitals were retrieved from pre-ART, ART and follow up registries. The records of all study participants were selected according to the eligibility criteria. Before collecting the data, the records were reviewed (both baseline and follow up records). Death was confirmed by death certificate complemented by registration and were identified by their medical record number. The most recent laboratory test results before starting ART were used as a baseline value. If there is no pre-treatment laboratory test, results obtained within one month of ART initiation were used as a baseline. In cases where there were two results obtained within a month, the mean value was used.

5.10. Data quality control

To ensure quality of the data, pretest was conducted with 5% of the sample population in Finote Selam Hospital found in west Gojam Zone, Amhara regional state, and data abstraction format was checked to the hospital documentation system to ensure the agreement of the data abstraction format with the need of the study. Any error found during the process of checking was corrected

and modified by the principal investigator at the final version of the data abstraction format. Training on record review was given to data collectors and supervisors for one day before actual data collection task and training guide was prepared to facilitate the training. Data quality was controlled by designing the proper data collection materials and continues supervision. All completed data collection forms were examined for completeness and consistency during data management, storage, cleaning and analysis. Consistency was examined through random selection of cards by the principal investigator and cross checked for their similarity. Four nurses, who have been working on ART unit, participated in data collection. One supervisor in each hospital was assigned to closely supervise the entire data collection process. The overall data collection process was under control of the principal investigator. The data were entered and cleaned by principal investigator before analysis

5.11. Data analysis procedure

Data was coded and then, entered, edited using EPI-data 3.5.3 and transferred to SPSS v 24 statistical software for analysis. Data exploration was undertaken to see if there are odd codes or items that were not logical and then subsequent corrections were made. The actuarial life table was used to estimate probabilities of survival after ART initiation at different time intervals. Kaplan Meier survival curve together with log rank test was used to check the presence of difference in survival among categories of covariates and log rank test was used to compare survival curves. Cox regression was carried out to find predictors of survival status. Patient's cohort characteristics were described in terms of central tendency and dispersion value for continuous data, and frequency distribution for categorical data. Finally, the outcome of each subject was dichotomized into censored or death. Bivariate Cox regression was first fitted and those independent variables which became significant on the bivariate regression having p-value ≤ 0.25 level of significance were included in the multivariable analysis. Cox proportional-hazard regression was fitted at 5% level of significance to determine the net effect of each explanatory variable on time to death after ART initiation (Hazard ratio with its 95% confidence interval and p-values was used to measure strength of association and identify statistically significant result). P-value < 0.05 was considered as statistically significant association. Finally, the results of the study were presented with text, graph and table.

5.12. Ethical considerations

Ethical clearance and paper of approval was obtained from Institutional Review Board of School of nursing and midwifery, College of Health science, Addis Ababa University. The School of nursing and midwifery wrote official letter of co-operation to Amhara regional health bureau, and health bureau, to East Gojjam zone health department and then the health department to Debre Markos Referral Hospital and Shegaw Mota District Hospital. Then, permission was taken from Debre Markos referral hospital and Shegaw Mota district hospital. As the study was conducted through review of medical records, there was no need of taking informed consent from each patient. To keep the confidentiality all collected data were coded and locked in a box. Then, the data were entered to the computer and locked by password, Names and unique numbers were not included in the data collection format, and the data were not disclosed to any person other than principal investigator.

5.13. Dissemination plan

The result of this study will be submitted to school of nursing and midwifery, college of health science, AAU, and it will be disseminating to other concerned bodies after approval, to AAU library and to studied health institutions (DMRH and SMDH). Furthermore, the paper will be present on workshops, seminars and annual nursing association meeting. Finally, the manuscript will be submitted to national or international scientific journals for possible publication

6. RESULT

6.1. Sociodemographic characteristics of study participants on ART

Among HIV positive children (age 0-14 years), who were initiated for ART from January1, 2014 to December 31, 2018, two hundred sixty-four (264) records were reviewed. Of these 251 (95.4%) of records were used in the final analysis, while the remaining 12 (4.6%) records were not included in the final analysis due to missing data from the files. Among 251 children, about half 130(51.8%) of them were males and more than half 143 (57%) of them were from urban area. The mean and median (SD) age of the child at ART initiation was 89.13and 96 (± 47.5) months respectively. The majority of study participants (82.1%) were living with their parents and nearly two third (64.5%) of caregivers of the children were married. The majority of study participants (78.1%) were orthodox Christian religion followers (**Table 2**).

Table 2: socio-demographic characteristics of Children on ART at East Gojjam Zone public hospitals, Amhara regional state, Northwest Ethiopia, 2019**.**

Variables		Outcome of The Child		
		Death	**Censored N %**	**Total N %**
age of the chil	age<12	4(25)	15(6.4)	19(7.6)
	age 12-59	6(37.5)	47(20.0)	53(21.1)
	age 60-179	6(37.5)	173(73.6)	179(71.3)
Sex	Male	6(37.5)	124 (52.8)	130(51.8)
	Female	10(62.5)	111 (47.2)	121(48.2)
Residence	Urban	11(68.8)	132(56.2)	143(57.0)
	rural	5(31.3)	103(43.8)	108(43.0)
Primary care giv	Parents	13(81.3)	193(82.1)	206(82.1)
	relatives	2(12.5)	33(14.0)	35(13.9)
	guardian& orphan	1(6.3)	8(3.4)	9(3.6)
	others	__	1(.4)	1(.4)
religion of care	Orthodox	13(81.5)	183(77.9)	196(78.1)
giver	Muslim	2(12.5)	42(17.9)	44(17.5)
	catholic	1(6.3)	3(1.3)	4(1.6)
	protestant	__	7(3.0)	7(2.8)
Current status c	both alive	10(62.5)	180 (76.6)	190 (75.7)
parents	mother alive, father	3(18.8)	31 (13.2)	34 (13.5)
	died	1(6.3)	13 (5.5)	14 (5.6)
	father alive, mother	2(12.5)	11 (4.7)	13 (5.2)
	died			
	both died			
Marital status c	Single	1(6.7)	21(9.2)	22(9.0)
caregiver	Married	8(53.3)	154(67.2)	162(66.4)
	Divorced	5(33.3)	31(13.5)	36(14.8)
	widowed	1(6.3)	16(7.0)	17(7.0)
	separated	__	7(3.1)	7(2.9)

6.2. Clinical, laboratory and ART information of Children on ART

Of the total 251 cohorts, 155(66.80%) children started ART in mild WHO clinical disease stage of HIV (II or I). After ART initiation, 75 (29.9%) of the children had opportunistic infection. Of the total 54 under -5 years' children, 40(74.1%) had appropriate developmental status at ART initiation while from a total of 197 (5-14 year) children, 132(67%) perform their daily activity. Nearly three fourth 178(73.6 %) of the children had CD4 count or percent above the threshold for severe immunodeficiency. Similarly, three fourth 183(72.9%) of the children have been taking cotrimoxazole preventive therapy. About 51 (20.1%) of children were anemic at ART initiation. Majority of children 217(86.5%) had good ART adherence (**Table 3**).

Regarding baseline opportunistic infection, of the total of 251 children ,32 (12.5) had Diarrhea followed by 29(11.55%) had pneumonia and 28(11.95%) candidiasis (**Figure 3)**

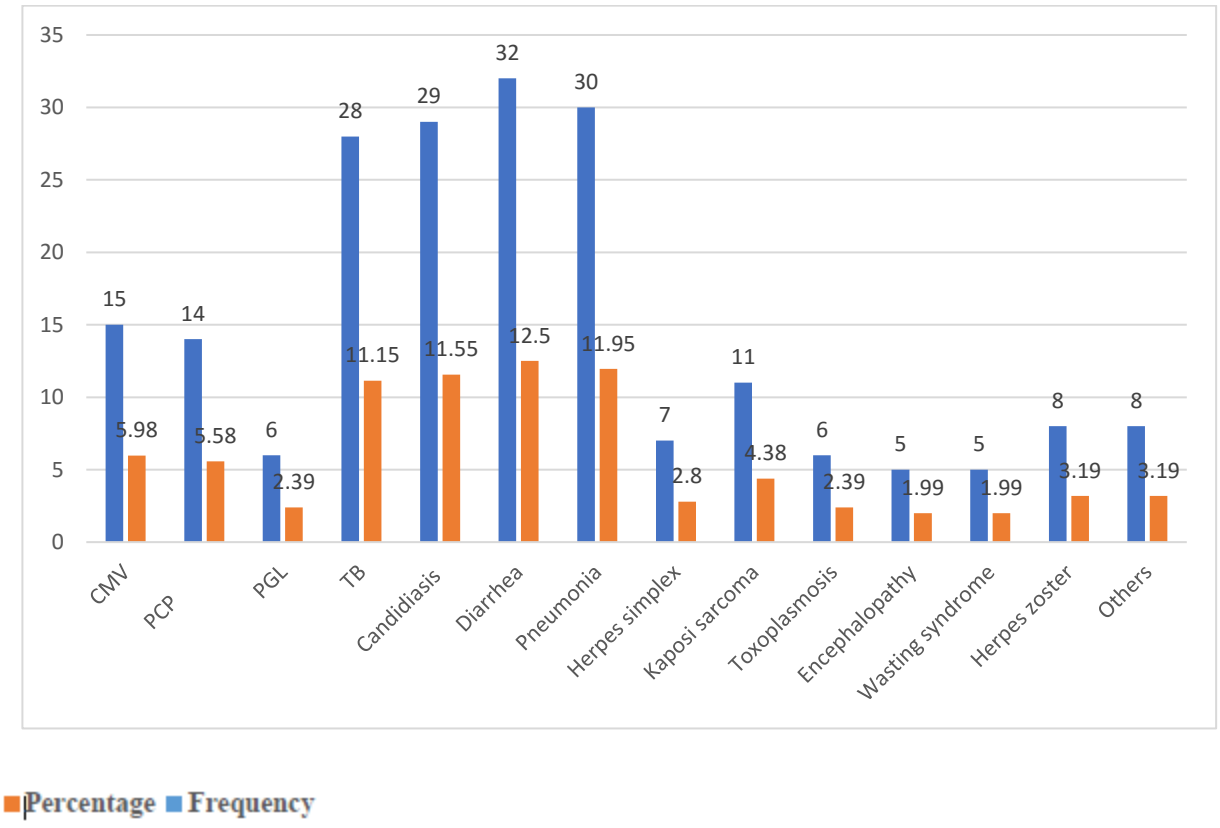

Figure 3 :Baseline opportunistic infection of HIV positive children on ART in East Gojjam zone public hospitals Amhara regional state, Northwest Ethiopia, 2019

Table 3: Baseline clinical, laboratory and ART information of Children on ART at East Gojjam zone public hospitals, Amhara regional state, Northwest Ethiopia, 2019

Variables		Death N %	censored N %	Total N %
Baseline WHO stage	stage I	3 (18.8)	84(35.7)	87 (34.7)
	stage II	3 (18.8)	65(27.7)	68(27.1)
	stage III	5 (31.3)	61(26.0)	66(26.3)
	stage IV	5 (31.1)	25(10.6)	30(12.0)
CD4 count at baseline	below threshol	12 (75)	52(23.0)	64(26.4)
	above threshol	4(25)	174(77.0)	178(73.6)
hemoglobin level	<10 mg/dl	11 68.8)	40(17.2)	51(20.5)
	>=10 mg/dl	5 (31.2)	193(82.8)	198(79.5)
Functional status for	working/functior	2 (28.57)	130(68.4)	132(67.0)
age > =5 years	Ambulatory	1 (14.29)	53(27.9)	54(27.4)
	Bedridden	4 (57.14)	7(3.7)	11(5.6)
	Total	7(100)	190(100.0)	197(100.0)
Developmental status at	Appropriate	6 (66.67)	34(75.6)	40(74.1)
baseline for age <5 years	Delayed	2(22.22)	7(15.6)	9(16.7)
	Regressed	1(11.11)	4(8.9)	5(9.3)
	Total	9(100)	45(100)	54(100.)
Cotrimoxazole	Yes	5(31.25)	178(75.7)	183(72.9)
	No	11(68.75)	57(24.3)	68(27.1)
Opportunistic infections	Yes	10(62.5)	65(27.7)	75(29.9)
	No	6(37.5)	170(72.3)	176(70.1
ART adherence	Good	8(50)	209(88.9)	217(86.5)
	Fair	2(12.5)	17(7.2)	19(7.6)
	Poor	6(37.5)	9(3.8)	15(6.00)
Drug side effect	Yes	4(25)	57(24.3)	61(24.3)
	No	12(75)	178(75.7)	190(75.7)
	Yes	5(31.25)	10(4.3)	15(6.0)
The regimen changed	No	11(68.75)	225(95.7)	236(94.0)

ART regimen given at baseline for HIV positive children

Regarding ART regimen ,115(45.8%) of children have taken a drug of 4c (AZT-3TC-NVP) followed by 42(16.7%) of children have taken a drug of AZT-3TC-EFV (**Figure 4**) .

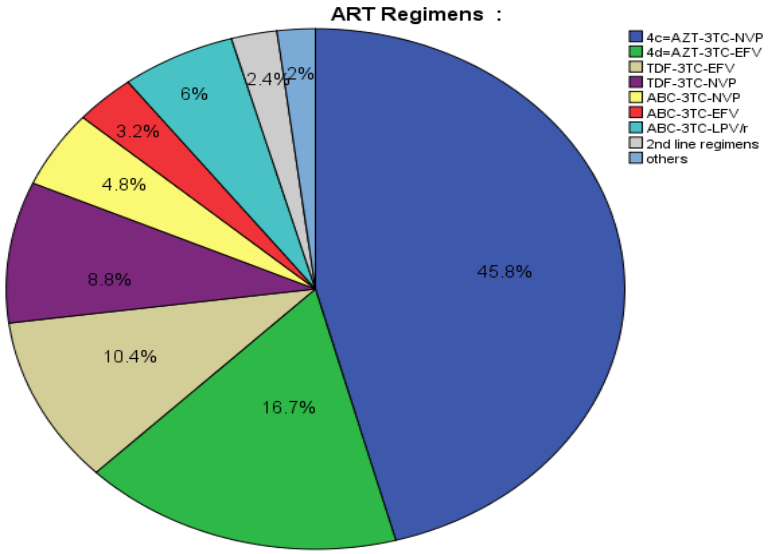

Figure 4 : Baseline ART regimen given for HIV positive children on ART at East Gojjam zone public hospitals Amhara regional state, Northwest Ethiopia, 2019

6.3. Nutritional Status of Children on ART

In this study, the nutritional status of the study participant showed that, 67(26.3 %) were wasted, 72(29.5 %) were stunted and 80 (31.9 %) were underweight (**Table 4**).

Table 4 : Nutritional information of Children on ART at East Gojjam zone public hospitals, Amhara regional state, Northwest Ethiopia, 2019.

		Outcome of The Child					
	Variables	Death N=16(%)		Censored N=235(%)		Total N=251(%)	
Weight for Height	Normal	6	(37.5)	178	(75.7)	184	(73.3)
	moderate wasting	4	(25.0)	52	(22.1)	56	(22.3)
	Severewastng	6	(37.5)	5	(2.1)	11	(4.4)
Height for Age	Normal	6	(37.5)	171	(72.8)	177	(70.5)
	moderate stunting	6	(37.5)	56	(23.8)	62	(24.7)
	severe stunting	4	(25.0)	8	(3.4)	12	(4.8)
Weight for Age	Normal	6	(37.5)	165	(70.2)	171	(68.1)
	moderate underweig	6	(37.5)	59	(25.1)	65	(25.9)
	sever underweight	4	(25.0)	11	(4.7)	15	(6.0)

6.4. Survival status of Children on ART

In this study, a total of 251 HIV positive children on ART were followed up for a total of 60 months, with a mean (SD) survival time of 55.54 (+ 0.83), (95% CI:53.90-57.17) months. The overall mortality incidence rate in the cohort during the 626 Child-year- observation (CYO) was 2.56/100 CYO. Kaplan- Meier estimation survival showed that overall estimated survival after starting ART was 90% at 60 months of follow up. The estimated cumulative survival was 0.98, 0.96, 0.92, 0.90, at 12,24, 36 and 60 months, respectively. Sixteen (6.37%) patients died in the study period, but 235 (93.62%) were censored till the end of the study. Among these, 199(79.3%) were alive, 16 (6.37%) were lost to follow up and 20(8%) were transferred to other health facility. on the Kaplan Meir survival curve for time to death of the child on ART, the probability of survival decreases as the follow-up time increases. This study showed that the highest rate of mortality was occurred between 30 months and 36 months after initiation of ART. (**Figure 5**)

Over all Kaplan-Meir Survival estimate

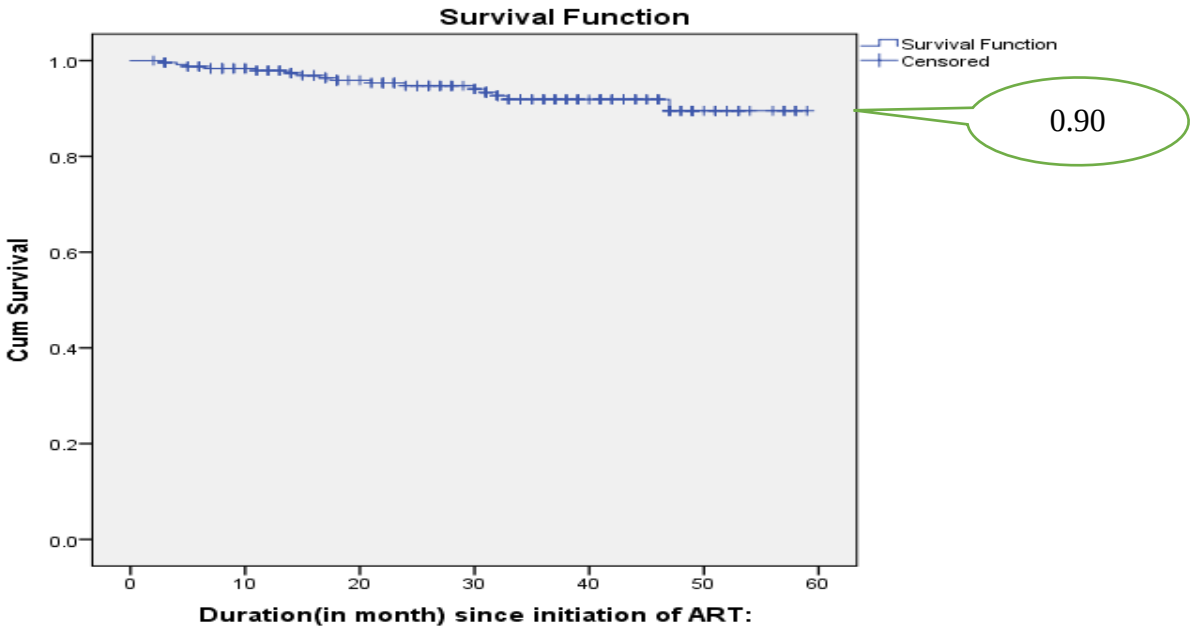

Figure 5 : The overall Kaplan-Meier survival curve with 95% confidence intervals of children on ART at East Gojjam zone public hospitals Amhara regional state, Northern Ethiopia, 2019

Survival time of the study population for different characteristics of children

In this retrospective cohort study, the mean survival time for the younger children had a shorter survival time than those of older children. The mean (SD) survival time for children age less than one year were 39.12(±4.25) months with 95% CI:30.80-47.45, and the mean (SD) survival time for age 5-14 years were 57 .27(±4.69) with 95%CI:55.92-58.63 months. This difference was statistically significant with p-value < 0.000.

The mean (SD) survival time for those who have been taking cotrimoxazole preventive therapy (CPT) was found to be 57.47(±.68) months as compared to those who were not taking cotrimoxazole preventive therapy with a mean (SD) survival time of 51.06(±1.93) months. This difference is statistically significant with p-value= 0.003.

Study participants who had a low hemoglobin level (<10gm/dl) have lower survival time as compared to those who had a high hemoglobin level (>=10gm/dl). The mean (SD) survival time for those having a low hemoglobin level was 47.20(±2.84) months and the mean (SD) survival time for those having hemoglobin level >= 10gm/dl was 57.56(±.64) months. The survival time difference between the groups was found statically significant with P-value < 0.000.

The mean (SD) survival time for those who had CD4 count below the threshold at baseline was 48.15 (±2.47) months and 95% C/I 43.32-53.00, but it was 57.79(±.60) months and 56.61-58.96 for those who had CD4 count above the threshold at baseline. This difference was statistically significant with p-value < 0.0001**(Table 5)**

*The Kaplan-Meier survival curves compare survival time of children with different age groups (***Figure 6**), *Children who took CPT and did not took* (**Figure 7**), hemoglobin level(<10gm/dl) and(>=10gm/dl) (**Figure 8),** CD4 count below the threshold and above the threshold at baseline(**Figure 9).**

Table 5: **Survival time, significance and log rank test for the study population for different characteristics of children during 5-year of follow-up (Kaplan-Meier method) of Children on ART at East Gojjam zone public hospitals, Northwest Ethiopia, 2019**

Covariates		Survival time per month, (95% CI)		Log rank test (p–value
		Mean ± SE	95%(CI)	
Age in month	<12	39.12±4.25	30.80-47.45	
	12-59	50.31±2.52	45.38-55.25	19.54(.000)
	age 60-179	57.27±4.69	55.92-58.63	
SEX	Male	55.64+.94	53.80-57.48	2.08(.149)
	Female	54.38+1.38	51.67-57.09	
Residence	Urban	54.98±1.16	52.70-57.25	0.87. (.351)
	Rural	55.48±1.09	53.33-57.62	
CD4 count	below threshold	48.15±2.47	43.32-52.20	21.90(<0.001)
	above thresh hold	57.79±.60	56.61-58.96	
Hemoglobin leve	<10 mg/dl	47.20±2.84	41.63-52.76	
	>=10 mg/dl	57.56±.64	56.31-58.81	25.23(< 0.001)
WHO HIV stage	stage I	57.04±1.11	54.87-59.21	
	stage II	55.85±1.22	53.47-58.23	
	stage III	54.31±1.57	51.23-57.40	10.23(.017)
	stage IV	42.97±3.18	36.73-49.21	
Functional status	working/functional	58.20±.56	57.11-59.30	
>=5 years	Bedridden	37.50±5.14	27.42-47.58	46.96(<0.001)
	Ambulatory	57.12±.87	55.41-58.83	
Developmental	Appropriate	44.49±2.80	39.00-49.98	603 (0.819)
status (<5yrs)	Delayed	36.25±3.28	29.83-42.67	
	Regressed	24.50±4.60	15.49-33.51	
Weight for Heigh	Normal	57.22±.71	55.82-58.62	17.02(0.000)
	Moderate wasting	52.57±2.08	48.49 -56.64	
	Sever wasting	38.60±5.04	28.73-48.48	
Weight for Age	Normal	57.10±.76	55.61-58.59	15.10(.001)
	moderate underweight	53.455±1.76	50.01-56.91	
	Sever underweight	41.20±5.03	31.33-51.06	
Height for Age	Normal	57.17±.73	55.73-58.60	21.79 (< 0.001)
	Moderate stunting	53.19±1.86	49.54-56.83	
	Severe stunting	36.67±5.79	25.33-48.01	
CPT	Yes	57.47±.68	56.14-58.79	10.6 (0.001)
	No	51.06±1.93	47.27-54.85	
ART adherence	Good	56.97±.70	55.60-58.35	29.33(< 0.001)
	Fair	43.34±2.47	38.49-48.1	
	Poor	39.16±4.36	30.61-47.70	
Drug side effect	Yes	52.26±1.81	48.70-55.81	0.004 (0.95)
	No	55.55±.96	53.67-57.42	
Regimen change	Yes	45.67±4.36	37.12-54.23	15. 10 (0.000)
	No	56.45±.75	54.99-57.92	

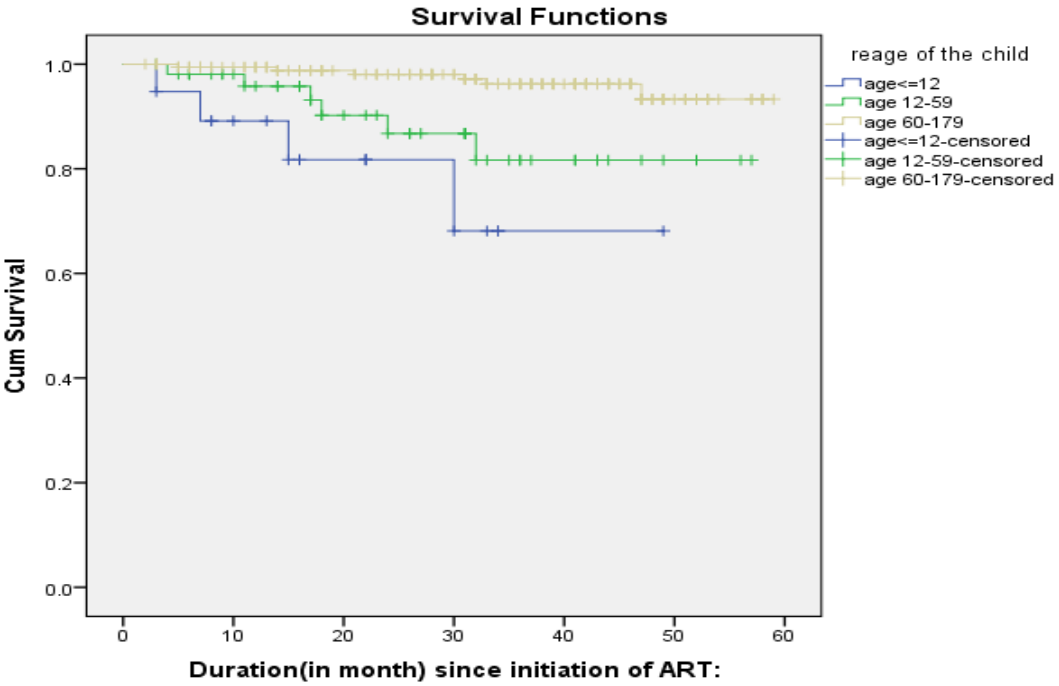

Figure 6: -The Kaplan-Meier survival curves compare survival time with different age groups of Children on ART at East Gojjam zone public hospitals, Amhara regional state, Northwest Ethiopia, 2019

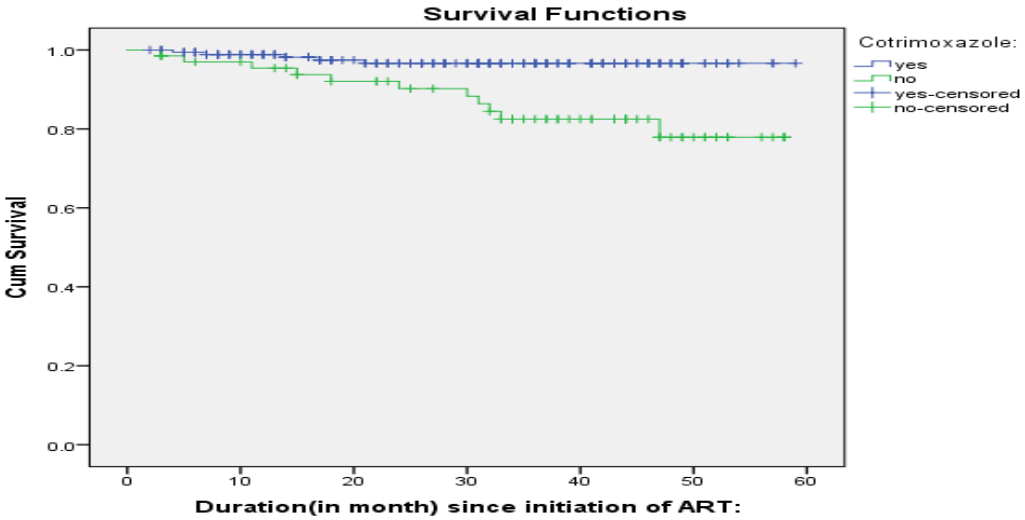

Figure 7 : -The Kaplan-Meier survival curves compare survival time with different groups of Children on ART who took CPT and did not took at East Gojjam zone public hospitals, Amhara regional state, Northwest Ethiopia, 2019.

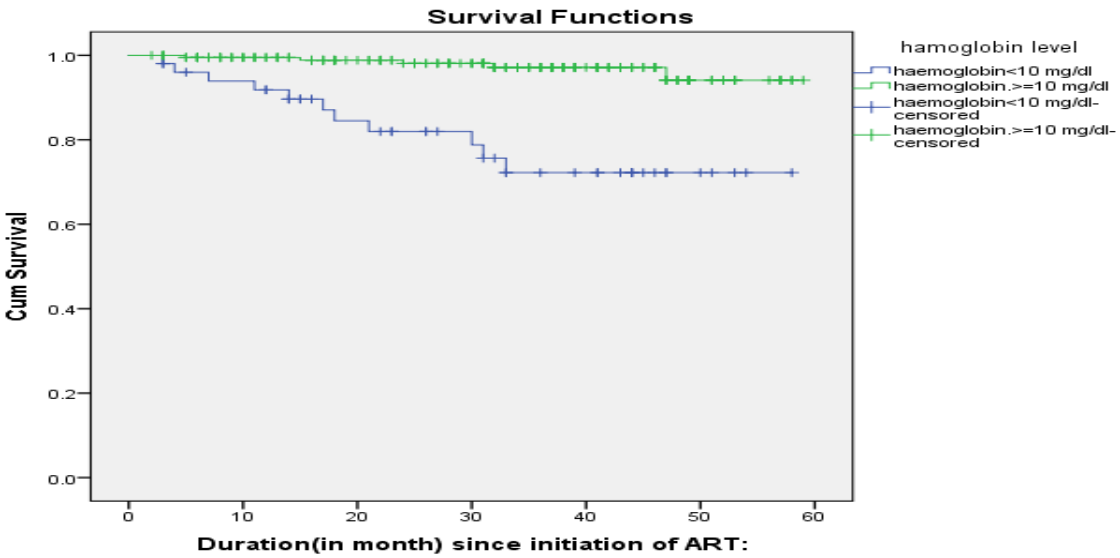

Figure 8 : -The Kaplan-Meier survival curves compare survival time with different hemoglobin level groups of Children on ART at East Gojjam zone public hospitals, Amhara regional state, Northwest Ethiopia, 2019

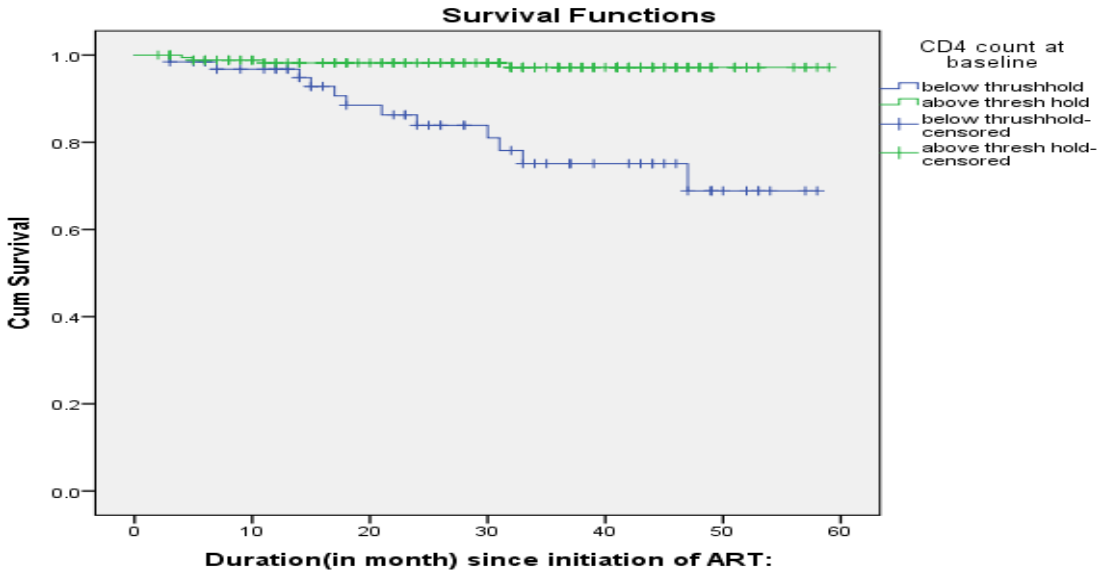

Figure 9 : -The Kaplan-Meier survival curves compare survival time with different CD4 count groups of Children on ART at East Gojjam zone public hospitals, Amhara regional state, Northwest Ethiopia, 2019

6.5. Predictors of mortality among children on ART

The bivariate cox proportional Hazard regression model indicated that age, WHO clinical stage, hemoglobin level, CD4 count, cotrimoxazole preventive therapy (CPT), nutrition status indicators (weight for height, weight for age, and height for age), ART adherence, and regimen change during follow-up were all associated with survival status (P <0.05). In multivariate Cox regression analysis those variables with p-value <0.25 in the bivariate analysis and non-collinear independent variables were included. However, other Socio demographic, clinical and laboratory variables were not associated to be the predictors of mortality, as a result they were not fitted to multivariate analysis

In multivariable cox proportional hazards model, five variables were associated with HIV mortality for children on ART. The result of multivariable analysis revealed that children who were less than 1year were 8.92 times more likely to die as compared to those of older children >/= 5 years (AHR; 8.92, 95% CI:2.62-30.36). Children who have age 1-5 years were also 6.42 times more likely to die as compared to children with age>/= 5 years (AHR:6.42, 95%CI: 1.40,30.36). Children having a hemoglobin level less than 10 gm/dl were 5.04 times more likely to die as compared to those having hemoglobin level greater than or equal to 10 gm/dl (AHR: 5.04, 95% CI: 1.54-16.55). Similarly, children having a CD4 count below threshold were 3.55 times more likely to die as compared to those of having a CD4 count above threshold (AHR: 3.55, 95% CI: 1.08-11.67). Children who were not takin\g cotrimoxazole preventive therapy were at risk of mortality by 2.5 times compared to those who has been taking cotrimoxazole preventive therapy (AHR: 2.5, 95% CI: 1.16-8.20). Furthermore, children who were severe wasting were 5.18 times more likely to die as compared to those who are normal (A HR:5.18, 95% CI: 1.25-21.42). Moderate wasting was associated to predict mortality in the bivariate but not statistically significant in the multivariate analysis (**Table 5)**

Table 6: Cox regression analysis of predictors of mortality among children on ART at East Gojjam zone public hospitals, Amhara regional state, North West Ethiopia, 2019. (N=251)

Variables		Death N (%)	Censored N (%)	CHR (95%CI)	AHR (95%CI)	p-value
Age	< 1 year	4(25)	15(6.4)	10.57(2.94, 8.02)	**8.92(2.62,30.36)**	**0.000**
	1-5 year	6(37.5)	47(20.0)	4.54 (1.46, 14.16)	**6.42(1.4, 29.5)**	**0.017**
	>=5 year	6(37.5)	173(73.6)	1	**1**	
CD4 count	below threshold	12 (75)	52(23.0)	9.27 (2.98, 28.76)	**3.55(1.08, 11.67)**	**0.037**
	Above threshold	4(25)	174(77.0)	1	1	
Hemoglobin	<10mg/dl	11 68.8)	40(17.2)	9.26(2.98, 28.76)	**5.04(1.54,16.55)**	**0.008**
	>10mg/dl	5 (31.2)	193(82.8)	1	1	
Baseline WHO Stage	Stage I &II	6(37.5)	149(63.4)	0.36(.13-.99)	0.45(.16,1.28)	0.113
	Stage III & IV	10(62.5)	86(36.6)	1	1	
Taking CPT	Yes	5(31.3)	178(75.7)	1	1	
	No	11(68.8)	57(24.3)	4.95 (1.71,14.30)	**2.5(1.16, 8.20)**	**0.034**
Opportunistic Infections	Yes	10(62.5)	65(27.7)	3.78 (1.37,10.38)	2.18(.63,7.57)	0.222
	No	6(37.5)	170(72.3)	1	1	
Weight for height	Normal	6(37.5)	178(75.7)	1	1	
	Moderate wasting	4(25.0)	52(22.1)	2.07 (.58, 7.35)	1.82(.53, 6.16)	0.336
	Sever wasting	6(37.5)	5(2.1)	21.39(6.86, 66.72)	**5.18(1.25, 21.42)**	**0.023**
Height for age	Normal	6(37.5)	171(72.8)	1	1	0.996
	Moderate stunting	6(37.5)	56(23.8)	2.71(.87, 8.40)	1.01(.01,241.00)	0.998
	Sever stunting	4(25.0)	8(3.4)	12.24(3.44, 43.59)	0.70(.01,1476.91)	0.928
Weight for age	Normal	6(37.5)	165(70.2)	1	1	
	under weight	6(37.5)	59(25.1)	2.45 (.79, 7.59)	2.33(.54, 6.41)	0.431
	Sever under weight	4(25.0)	11(4.7)	8.89 (2.49, 31.66)	2.66(.65,13.45)	0.311
ART adherence	Good	8(50.0)	209(88.9)	1	1	
	Fair	2(12.5)	17(7.2)	2.72 (.58, 12.83)	1.27(.65,8.22)	0.847
	Poor	6(37.5)	9(3.8)	10.89 (3.76, 1.54)	1.49(.83,7.54)	0.733
The regimen Changed	No	11(68.8)	225(95.7)	6.26 (2.17, 18.07)	5.62(2.34, 82)	0.972
	Yes	5(31.3)	10(4.3)	1	1	

The bold font indicates significantly associated predictors in multivariable cox regression analysis

6.6. Test of proportional hazard assumption

Testing the proportional hazard assumption is vital for interpretation and use of fitted proportional hazard models. Therefore, in this study goodness-of-fit (GOF) particularly the Schoenfeld residuals proportional hazard assumption test for the individual covariates and global tests was used. If P-Value < 0.05, then the proportional hazard assumption is rejected. The findings indicated that all variable included in the model were satisfy PH assumptions (p-value>0.05) (see **Table 6).**

Table 7 : Test of proportional-hazards assumption

Variable	Rho	chi2	Df	Prob >chi2
Age	0.03	0.01	1	0.90
Haemoglon	0.15	0.49	1	0.48
Cd4count	-0.05	0.07	1	0.79
Weight for height	-24	0.06	1	0.80
Height for age	0.17	0.06	1	0.81
Weight for age	0.10	0.2	1	0.90
WHO stage	-0.14	0.37	1	0.54
CPT	0.10	0.17	1	0.68
OI	-0.22	0.69	1	0.40
ART adherence	0.17	0.61	1	0.44
The regimen changed	-0.25	1.40	1	0.24
global test		11.96	11	0.37

7. DISCUSSION

This study was aimed to assess survival status and predictors of mortality among HIV Positive children on Antiretroviral Therapy. Socio demographic, clinical, nutritional and treatment related determinant of survival were assessed.

The result of the study showed that at the end of follow up, 16 children on ART were died and 235 children on ART were censored, resulting in a total death prevalence of 6.37% and an incidence rate of 2.56 per 100 child-years -observation. The overall mortality rate that occurred in this study was consistent with previous studies done in Ethiopia, 2.1% in Wolaita Zone [16], (2.3%) in Zewditu Memorial Hospital [28]. The reason that the findings of this study consistent with above mentioned studies might be due to having nearly similar study periods.

However, the overall mortality rate that occurred in this study was lower than other studies conducted in different countries; (3%) in India [30], (5.1%) in four sub Saharan Africa countries [26], 3.4 deaths per 100 patient years (PYs) Malawi[23], 4.7 deaths per 100 child years in South Africa [31], 3.8 per 1000 child-months in Eastern Ethiopia [18], 4% CYO in North west Ethiopia [12] and 3.6% CYO in Arba Minich [13].

The discrepancy of results that has been seen among studies might be due to difference in the study period as there were changes in treatment modality recently recommended to treat all HIV positive children regardless their WHO clinical stage and CD4 count. Another possible explanation might be difference in the stage of HIV/AIDS at ignition of ART. In this study, the majority of the study participants-initiated ART at WHO clinical stage (I&II) but not in others. Children who were initiated ART at early phase had a longer survival time as compared to their counterparts. Furthermore, the differences of the results might be the difference in the duration study. Another possible explanation might be the difference in sample size. There was also a study which was reported to have lower findings (1%) in Nigeria [32], 12.4 deaths per 1000 child-year in Addis Ababa. [17], in Mekelle, Ethiopia (1.40 per 1000 child-months) [27].

In this study, age was found to be a significant predictor of mortality among HIV positive children on ART. The mortality rate was higher amongst the youngest children less than five years than those among the older children. Children <1-year-old were 8.92 times more likely to die as

compared to children >/= 5 years old. This finding is consistent with other previous studies conducted in Swaziland [29], India [30], Nigeria [32, 33], Malawi [23] and Ethiopia [14, 15, 28]. Children 1-5 years old were also 6.42 times more likely to die as compared to children >/= 5 years old. This finding was also consistent with other previous studies conducted in Ethiopia [14]. This variation among different age groups might be due to fragility of infants and younger children that end up high mortality rate among children in this age group. Children starting ART before 2 years of age are more likely to have rapid disease progression [32] and this may also be the cause of high mortality in the young children. Further research is needed to identify factors impacting health outcomes among this highly vulnerable group of children. However, this study was not supported by a study done in Uganda which stated there was no enough evidence to suggest that age had a confounding effect on survival [21].

Children with CD4 count below the threshold level at initiation of ART have higher risk of death (3.55 times) than those children with CD4 count above threshold. This might be due to the fact that HIV attacks CD4 cells, as a result child with the lower CD4 count could have the chances of acquiring serious diseases which end up in death. This finding is consistent with previous studies conducted in different areas of Ethiopia [11,12,13,15,33]. On the contrary, a study done in Bahir-Dar found that low baseline CD4 cell count was not a predictor of survival time of HIV infected children [14].

Similarly, in this study the risk of mortality increased among children with low hemoglobin level at baseline. Children with Low hemoglobin level (<10 gm/dl) were 5.04 times at risk of death as compared with their counter parts. This study was supported by other findings [11,12,13,14,15]. This might be the dual effect of anemic condition and some drugs that aggravate anemia which leads to other comorbidity and death.

The findings of present study revealed that malnutrition in the form of severe wasting was significant predictor of mortality among children on ART. Children who were severely wasted at the time of ART initiation were 5.18 times more likely to die as compared to those who were normal (not wasted) at the time of ART initiation. This finding is consistent with other previous studies.[29,32] However, baseline nutritional status was not significant predictor of mortality [12].

In this study cotrimoxazole preventive therapy was found to be an independent predictor of survival that becomes statistically significant in the cox proportional hazard model. Cotrimoxazole was found to have a protective effect for children on ART. Children not taking cotrimoxazole have

(AHR,2.5,95% CI :1.16 -8.20**).** This finding is consistent with previous findings in different studies [12], [28].This study also supported WHO recommendation that states all exposed infants and HIV infected children start cotrimoxazole preventive therapy[34].

Unlike most of previous findings [11,14,15,18,26,28,32,33], it was found that WHO clinical-stages at baseline were not found to be an independent predictors of survival in this study. In this study, WHO clinical-stages was associated with survival of children in bivariate analysis however it is not found to be statistically significant in multivariable analysis in the cox proportional hazard model.

This discrepancy could be changes in treatment modality recommended to treat all HIV positive children regardless their WHO clinical stage and CD4 count. As a result, this cohort reveals a high proportion child in mild WHO clinical-stages at baseline. About two third (66%) of the children were WHO clinical stage I&II at initiation of ART. This study in line with a previous study done in Ethiopia [12].

8. STRENGTH OF THE STUDY AND LIMITATION

8.1. Strength of the study

This study has the following strengths. The data were collected over the period 2014-2018 and it reflects current utilization of treatment methods and new medications, which might be the opportunity to improve survival probability in the study population.

8.2. Limitation of the study

Since the data were collected from medical records, charts of some children were not found during data collection and hence these charts were not included in the study. In the same way, missing values for some of the variables were inevitable. Therefore, those study subjects whose charts were not included in the study and with missing value may undermine the result if it is related with death. Some children who were lost to follow-up were not addressed by tracing mechanism and those study subjects may under estimate mortality rate as they might end up in death.

9. CONCLUSION

This study found that the overall mortality rate was 2.56 per 100 children years' observation. The mortality rate was lower when compared with previous studies done in Ethiopia as well as from other countries. CD4 count below threshold, children age which were <1 year and 1-5 years, baseline malnutrition in the form of sever wasting (WFH<-3z), children who were not taking cotrimoxazole preventive therapy and Hgb<10gm/dl were significant predictor of mortality among HIV positive children after initiation of ART.

10. RECOMMENDATION

Based on the findings of this research, the following recommendations were forwarded;

To federal minister of health and other stake holders

To maintain “treat for all HIV positive children “treatment program; and to reduce mortality of HIV children more.

Encourage Health professionals to properly documenting patients’ health care data being used for studies.

To health care providers working ART clinics of East Gojjam zone public hospitals

Close monitoring and follow-up should be given for children who are under-5 years at initiation of ART, children who were not taking cotrimoxazole preventive therapy, for children with malnutrition in the form of wasting (WFH<-3), Hemoglobin level <10gm/dl and CD4 count blow threshold.

To improve the completeness and reliability of base line data being collected.

To researchers

Further studies on survival status among children on ART that can address the limitations of this study and design strategies to improve completeness by using prospective study design.

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12. APPENDIX**.**

Annexes: Data extraction form (Checklist)of English version

Table. Data extraction form for the Assessment of Survival and predictors of mortality among HIV Positive Children on Antiretroviral Therapy in Public hospitals ART Unit, East Gojjam, Ethiopia, 2014 -20118.

This tool is prepared for the collection of socio-demographic, clinical, laboratory, treatment and outcome related information that are important for the assessment of Survival and predictors of mortality among HIV Positive Children on Antiretroviral Therapy at East Gojjam Zone selected Hospitals, Amhara Regional State, 2019.This information was retrieved from the clients ART and pre-ART registration book and from individual patient card without mentioning the name of clients. This information was collected by BSc Nurses working in the ART clinic of the hospitals.

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Data collection date----------month----------Year----------

Name of the Hospital ----------

Name of data collector---------- signature----------

Name of supervisor----------signature----------

Code no----------

Part I: Socio demographic characteristic			
NO	Socio demographic of child	Possible answers	Skip
101	Age of the child at initiation of ART	----------in month	
102	Sex	1 male 2.female	
103	Place of residence	1.Urban (regional town, zonal town, district town) 2. Rural	
104	Primary care giver	1. Parents 2. Relatives 3. Guardians & Orphan 4. others	
105	Religion of care giver	1. Orthodox 2. Muslim 3. Catholic 4. Protestant	

		5. Others specify-----	
106	Current status of parents	1. both alive 2. mother alive but father dead 3. mother dead but father alive 4.both dead	
107	Marital status of care giver	1. Single 2. Married 3. Divorced 4. Widowed 5. Separated	
Part II: - Clinical and laboratory characteristics at baseline			
201	Baseline WHO stage	1. I 2. II 3. III 4. IV	
202	Baseline CD4 count or Baseline CD4%	(---------) date----------/------- /--	
203	If CD4 count or CD4% is lower at base lin when become normal?	----------months	
205	Hemoglobin level at base line	---------- ----------	
206	Weight at base line	(----------) kg	
207	Height/length at base line	(----------) cm	
208	Functional status at baseline for age ≥ 5 years	1. Ambulatory 2. Bedridden 3. Functional 4. Not determined	
209	Developmental status at baseline for age <5 years	1. Appropriate 2. Delayed 3. Regressed 4. Not determined	
210	Past opportunistic illness	1. No 2. CMV 3. PCP 4. PGL 5. PML 6. TB 7. Candidiasis 8. Diarrhea 9. Pneumonia 10. Herpes simplex 11. Kaposi sarcoma 12. Toxoplasmosis 13. Encephalopathy 14. Wasting syndrome 15.Herpes zoster 16. Other specify------	
Part III: treatment related and follow-up characteristics.			
301	Date of confirmed HIV positive	(----------/----------/---------)	
302	Starting date of ART	(----------/----------/---------)	
303	Last follow up date	(----------/----------/---------)	
304	Duration since initiation of ART	(----------) month	

305	OI prophylaxis given	1. Not given 2. Cotrimoxazole 3. INH 4. Others specify----------	
309	Regimens given at follow up time	1. D4t-3TC-NVP 2. D4t-3TC-EFV 3. AZT-3TC-NVP 4. AZT-3TC-EFV 5. ABC-3TC-NVP 6. ABC-3TC- EFV 7. TDF-3TC-NVP 8. TDF-3TC- EFV 9. 2nd line regimens 10. Others specify (----------	
312	Opportunistic infections during follow up	1. No 2. Herpes zoster 3. Pneumonia 4. TB 5. Oral thrush 6. Diarrhea 7. Cryptococcus meningitis 6. Others specify------	
313	Cotrimoxazole preventive therapy	1. given 2. not given	
314	Recent ART adherence	1. Good 2. Fair 3. Poor	
315	From Q no313 if fair/poor reason for fair/poor adherence	A. Toxicity/SE B. Share with others C. Forgot D. Felt better E. Too ill F. Stigma G. Drug stoke out H. Travelling problem I. Depression J. Others specify-----	
314		1. Yes 2. No	
315	From Q no 314 if yes which Drug side effect the child had?	3. Nausea 4. Diarrhea 5. Fatigue 6. Headache 7. Numbness 8. Rash	

		9. Anemia 10. Fat change 11. Nightmare 12. Dizziness 13. Others specify-------	
316	Does the regimen changed?	1.No 2.Yes	
317	From Q no316 if yes, reason for regimen change	1. Toxicity/SE 2. New drug available 3. Drug out of stoke 4. Clinical failure 5. Immunologic failure 6. Virologic failure 7. New TB 8.Other specify	
318	Does the regimen stopped?	1. No 2. Yes	
319	From Q no318 if yes, reason for stopping regimen.	1. Toxicity/SE 2. Treatment failure 3. Poor adherence 4. Drug out of stock 5. Other patient decision 6. Planned treatment interruption 7. Other specify----------	
320	Current status	1. Alive 2. Dead 3. Lost follow up 4. Transfer to other health facility	
321	From Q no 320 if dead when after initiation of ART	(----------) month	
322	From Q no 320 if lost to follow up when after initiation of ART	(----------) month	
323	From Q no 320 if transfer to other facility when after initiation of ART	(----------) month	