International Research Journal of Medicine and Medical Sciences
Vol. 10(1), pp. 1-10, January 2022
ISSN: 2354-211X
Full Length Research Paper

Predictors of mortality among children co-infected with tuberculosis and human immunodeficiency virus in Tigray Region, North Ethiopia: Retrospective follow-up study

Jemberu Nigussie[1]*, Mekuria Kassa[2], Goitom Halefom[3], Haven Hadush[2] and Bekahegn Grima[1]

[1]Department of Nursing, College of Health Science and Medicine, Dilla University, Dilla, Ethiopia.
[2]School of Nursing, College of Health Sciences, Mekelle University, Mekelle, Ethiopia.
[3]School of Public Health, College of Health Sciences, Mekelle University, Mekelle, Ethiopia.

Accepted 3 November, 2021

ABSTRACT

Tuberculosis (TB) and human immunodeficiency virus (HIV) co-infection in the human body potentiate each other by weakening the immune system and causing death, if untreated. Tuberculosis is a major cause of morbidity and mortality in children infected with the human immunodeficiency virus. Evidence on survival and predictors of mortality among TB and HIV co-infection in children is limited and not well documented in Ethiopia. This study aimed to evaluate the predictors of mortality among children with TB and HIV co-infected in general hospitals in two zones of the Tigray region, North Ethiopia, from 2008-2018. An institution-based retrospective follow-up study was conducted. Data were collected from medical records using a data extraction checklist and then entered using epi-data manager 4.4.2.1 and then exported to STATA version 14 for analysis. The Cox regression model was used for both bivariate and multivariate analyses. Of a total of 253 children included in the analysis, 38(15%) children have died. The overall mortality rate was 0.17 (95% CI: 0.12, 0.23) per 1000 child-month observation. Underweight at baseline (AHR=7.9 (95% CI: 1.3, 49.3)), IPT non user (AHR=3.7; 95%CI: 1.3-10.8), Poor adherence to ART (AHR = 3.8 (95% CI:1.4, 10.5)), Extrapulmonary tuberculosis (AHR = 2.9 (95% CI: 1.1, 7.6)), advanced WHO-staging(III&IV) (AHR=6.8 (95% CI: 1.9, 24.9)) and hemoglobin level <10 mg/dl during follow-up (AHR 3.75 (95% CI: 1.06, 13.28)) were predictors of increased mortality. In conclusion, the mortality rate of children co-infected with TB and HIV was high. Early diagnosis and treatment of TB among HIV-infected children is needed. The treatment of malnutrition and anemia should be given emphasis. Strengthening the administration of preventive therapy (IPT, CPT) and counseling on adherence to ART drugs were crucial interventions to reduce mortality among children co-infected with TB and HIV. Children who have extra-pulmonary tuberculosis and advanced clinical staging (III and IV) need special consideration during treatment.

Keywords: Predictors of mortality, co-infection with TB and HIV, children, retrospective follow-up study.

*Corresponding author. E-mail: jemberu2123@gmail.com.

INTRODUCTION

Tuberculosis (TB) and human immunodeficiency virus (HIV) co-infection remain a major global and national health problem that requires substantial action to achieve the Sustainable Development Goals (SDG) and the END-TB strategies (WHO, 2015a). Both TB and HIV are the leading causes of death from infectious diseases worldwide (Adejumo et al., 2015). Mycobacterium tuberculosis and HIV co-infection in the human body, potentiate each other and accelerate to death by deteriorating body immunity causing premature death if

untreated (Bruchfeld et al., 2015). Tuberculosis is a major cause of morbidity and mortality in HIV-infected children (Venturini et al., 2014). In 2015, the World Health Organization (WHO) report showed that nearly 41,000 children died from TB and HIV co-infection. Of which more than 83% were occurring in Africa (WHO, 2015b). The mortality among children, co-infected with TB and HIV varied in different settings and fluctuated widely from 6.2% to 36.5% (Ebonyi et al., 2016; Isaakidis et al., 2013). In Ethiopia, mortality of children co-infected with TB and HIV was 14% (Atalell et al., 2018) and co-infected children had six times greater death than TB disease alone (Palme et al., 2002). Furthermore, more than 1 in 5 TB and HIV co-infected individuals were dead (Abrha et al., 2015), but this huge problem was not specifically known in children.

The prevalence of TB and HIV co-infection in children was under-assured due to the problem of reaching a definitive diagnosis. However, the WHO report showed that HIV prevalence among children with active TB disease ranges from 10 to 60%, depending on the background rates of HIV infection in countries with moderate to high prevalence of TB (UNAIDs and WHO, 2011). The estimated rates of tuberculosis among HIV positive children also had a wide variation, depending on the TB epidemic and the coverage of highly active antiretroviral treatment (HAART) coverage in the area (Venturini et al., 2014).

Data on the survival of TB and HIV co-infection in children are still lacking and the available information is difficult to interpret due to problems with the diagnosis and selection of study populations (Venturini et al., 2014). In developing countries, including Ethiopia, the management of TB and HIV co-infection in children is very challenging due to the inaccessibility of appropriate formulations of drugs, drug-drug interactions, pill burdens, drug side effects, and poor drug adherence (Pawlowski et al., 2012; Marais et al., 2007; Marais et al., 2011). This may result in high TB incidence and mortality among HIV-positive children.

TB is not only the most commonly reported opportunistic infection (Deribe and Estifanos, 2018), but also a major cause of hospital admission and death in HIV infected children (Tilahun and Gebre-Selassie, 2016). The cause of death is also multifactorial and determined by socio demographic, clinical, laboratory, drug and follow-up related factors (Atalell et al., 2018) which are poorly understood. Therefore, studies on mortality and its predictors in TB and HIV co-infection in children are very significant to designate appropriate action according to their ages.

Most of the studies on TB-HIV co-infection focused on adult, fewer studies on general co-infected population, little is known in pediatrics sub-age group. Still, the problem in children is masked and actions are taken based on findings from studies in the adult population. However, the problem is very alarming in children due to immature immune system and fast deterioration in to death (Ugochukwu, 2010; Newton et al., 2008). A previous study in the comprehensive specialized hospital of Gondar University in Ethiopia lacks a time specification on the TB and HIV co-infection period, rather they prolonged their follow-up after TB was cured (Atalell et al., 2018). This makes the study more biased.

Studies also identify different cause of mortality among TB/HIV co-infected children such as age, sex, CD4 count, under-weight, anemia, type of Tuberculosis, WHO staging, not initiation of ART, ART adherence, ionized preventive therapy (IPT), and co-trimozazole preventive therapy (CPT) (Ebonyi et al., 2016; Atalell et al., 2018; Marcy et al., 2018; Buck et al., 2013; Salvadori et al., 2017; Hicks et al., 2014).

To some extent, there is better evidence on the incidence and predictors of tuberculosis in HIV-infected children (Ayalaw et al., 2015; Endalamaw et al., 2018), but evidence on survival and mortality after co-infection is limited in Ethiopia. Therefore, survival and predictors of mortality among children co-infected with TB and HIV have not been well documented in Ethiopia. Therefore, this study has tried to fill the above gaps by estimating survival and identifying predictors of mortality among children, co-infected with TB / HIV in public general hospitals in Mekelle and the southern zone of Tigray region, northern Ethiopia.

METHODS

Study design, setting and period

A retrospective hospital follow-up study was conducted in two zones of the Tigray Region (Mekelle and Southern), which is located in the northern part of Ethiopia by reviewing 10 years (2008-2018) medical records of children co-infected with TB and HIV in 2019. About 1,179,687 populations lived in these two zones. Of which 515,524 were children (Tigray Regional Health Bureau, 2019). The study was conducted from October 1, 2018 to June 30, 2019 in three selected general hospitals (Mekelle, Alamata, and Maychew).

Population and sampling

Source population

All children infected with TB and HIV co-infected under 15 years of age who received follow-up care from January 1, 2008 to December 30, 2018 in the ant-retroviral treatment (ART) clinic at public general hospitals of the Mekelle and southern zone of the Tigray region, North Ethiopia.

Study population

All children co-infected with TB and HIV, less than 15 years of age and those who followed up from January 1, 2008 to December 30, 2018 in the ART care clinic of selected hospitals in the study area.

Inclusion and exclusion criteria

TB-HIV co-infected children younger than 15 years old, and had follow-up care from January 1, 2008 to December 30, 2018 in selected hospital were included in this study. Children who had missed key information on clinical, immunological, drug information and their outcomes had not been recorded on medical charts were excluded.

Sample size determination and sampling procedure

Sample size determination

The sample size for this study was calculated using Stata statistical package, Version 14 under Cox model based on the following assumptions; the hazard ratio of co-variate (anemia) that gives maximum sample size from previous study was 2.6 when other covariates held constant (28), variability= 0.5, probability of failure (death) observed from previous similar study = 0.14 (28), with 5% marginal error and 95% confidence interval of certainty (α = 0.05) to achieve the power of 80%. Hence our minimum sample size required for this study was 246, and the estimated number of events (E) was 35.

Sampling technique

In the Mekelle and Sothern zones of the Tigray region, five general hospitals were found to provide ART services. These are Mekelle, Quiha, Maychew, Alamata and Korem general hospitals. However, this study used cluster sampling by randomly selecting three hospitals (Mekelle, Alamata and Maychew). Since we used cluster sampling, all children co-infected with TB and HIV who was enrolled in selected hospitals in two zones who met the inclusion criteria were included. The medical charts of children with TB and HIV co-infected from 2008 to 2018 were reviewed.

Data collection and analysis

Data were collected from medical records (charts) using a data extraction checklist developed from the national HIV intake and follow-up form (FMOH, 2017). The checklist consisted of socio-demographic, clinical, and HIV care/ART/ follow-up related information. The Data were collected from April 15/2019 to May 20/2019 from medical charts. If the child is co-infected with TB and HIV, the follow-up should continue for the entire life (for HIV care) even if the child was cured from TB.

After verifying completeness and consistency, the data were coded and entered into Epi-data manager version 4.4.2.1 and then exported to Stata version 14 for analysis. Kaplan–Meier survival graph and Log-rank test were used to compare the survival difference between intragroups of categorical variables. Mortality rate, person-time observation, and mean survival time were calculated by Stata. The Cox proportional hazard model was used for analysis. Cox Proportional hazard model is used for survival analysis that considered time of event. The Schoenfeld residual test (estat Ph test) or global test was used to check the Cox proportional hazard assumption, it was non-significant (Prob>chi^2 = 0.4179) indicates the hazard was proportionally over time. In time considering analysis, the hazard should be proportional over time. Regarding multi- collinearity, the mean VIF was 1.39 indicates, collinearity between variables was within the acceptable range.

Both bivariate and multivariate analysis was computed to determine the association between predictor variables and the outcome variable. These variables that were significantly associated with a *p*-value of <0.2 in the bivariate analysis were entered into the multivariate analysis. Variables significantly associated with the outcome variable at a *p*-value <0.05 in the multivariate analysis were considered independent predictors of mortality. Finally, the adjusted hazard ratio with 95% CI and ***P*** value was used to measure the significant association between predictors and outcome variable.

Ethical considerations

The study protocol was evaluated and approved by the Institutional Review Board (IRB) of Mekelle University, a college of health sciences, and then ethical clearance was obtained. A cooperation letter was written to the chief executive managers of each hospital. Since the study was retrospective and document review, it did not cause any risk to the study participants.

RESULTS

Socio-demographic characteristics

A total of 282 children with co-infected TB and HIV were enrolled in the general hospitals of Mekelle, Alamata, and Maychew. Of which 29 were excluded from the study due to lost cards or incomplete data. The remaining 253 children co-infected with TB and HIV were included in the study. The median age of the study participants was 8 years with IQR (4-13). One hundred and thirty-one (51.8%) of the children were females (Table 1).

Clinical and immunological related characteristics

Of a total of 253 children co-infected with TB and HIV, 186 (73.6%) of them developed TB after starting ART. At baseline, 165 (65.2%) of the TB and HIV co-infected children had WHO stage III, and 129 (51%) had a CD4 count of less than 350 with a median of 330 cells (IQR (176.50 to 519.50)) cells/µl. During follow-up, 145 (57.3%) of the children co-infected with TB and HIV had improved their WHO staging to stage I & II. However, 66 (26.2%) of the children had a CD4 count of less than 350 with a median of 540 IQR cells (322.50 to 840.50) cells/µl. Thirteen (5.2%) of the children had anemia (HGB <10 mg/dl) with a median HGB level of 13 (IQR (12-14.4)) mg/dl (Table 2).

Medication and follow-up related characteristics

One hundred and ninety-seven (77.9%) of the respondents had taken co-trimoxazole preventive therapy and 145 (57.3%) had also taken isoniazid preventive therapy before developing TB. The initial ART regimen was changed in 59 (23.3%) of the children due to side

Table 1. Socio-demographic characteristics of children co-infected with TB and HIV in general hospitals of two zones of the Tigray region, North Ethiopia, 2019 (n=253).

Characteristics		Total N (%) n=253	Death N (%) n=38	Censored N (%) n=215
Sex of the child	Male	122(48.2)	17(6.7)	105(41.5)
	Female	131(51.8)	21(8.3)	110(43.5)
Age of the child	1-5	72(28.6)	13(5.1)	59(23.3)
	5-10	68(27.1)	9(3.6)	60(23.7)
	10-15	69(27.3)	9(3.6)	60(23.7)
	15-18	43(17)	7(2.8)	36(14.3)
Residence of the child	Urban	186(73.6)	28(11.1)	158(62.5)
	Rural	67(26.4)	10(4.0)	57(22.5)
The child lives with	the parent's	107(81.8)	32(12.6)	175(69.2)
	Grandparents	33(13.1)	4(1.6)	29(11.5)
	Siblings	8(3.1)	1(0.4)	7(2.7)
	Others	5(2)	1(0.4)	4(1.6)
Sex of the care giver's	Male	51(20.1)	11(4.3)	40(15.8)
	Female	202(79.9)	27(10.7)	175(69.2)
Age of care giver's	15-24	17(6.7)	3(1.2)	14(5.5)
	25-34	100(39.5)	18(7.1)	82(32.4)
	35-44	84(32.9)	10(4.0)	73(28.9)
	>=45	53(21)	7(2.8)	46(18.2)
Occupation of the care giver's	Housewife	122(48.2)	15(5.9)	107(42.3)
	Government employer	51(20.2)	11(4.5)	40(15.6)
	Private worker	80(31.6)	12(4.7)	68(26.9)
Educational level of the care giver's	Illiterate	86(34)	9(3.6)	77(30.4)
	Primary school	59(23.4)	10(4.0)	49(19.4)
	Secondary school	47(18.6)	5(2.0)	42(16.6)
	College or University	61(24.1)	14(5.5)	47(18.6)

Table 2. Clinical and immunological characteristics among children co-infected with TB and HIV in general hospitals of two zones of the Tigray region, North Ethiopia, 2019 (n = 253).

Characteristics		Total N (%) n= 253	Death N %) n=38	Censored N (%) n= 215
Baseline WHO staging	Stage III	165(65.2)	18(7.1)	147(58.1)
	Stage IV	88(34.8)	20(7.9)	68(26.9)
WHO Staging- during follow-up	Stage I &II	145(57.3)	6(2.4)	139(54.9)
	Stage III &IV	108(42.7)	32(12.7)	76(30.0)
Baseline HGB	<10	47(18.6)	17(6.7)	30(11.9)
	≥10	206(81.4)	21(8.3)	185(73.1)

Table 2. Continues.

HGB level during-follow-up	<10	13(5.2)	7(2.8)	6(2.4)
	≥10	240(94.8)	31(12.3)	209(82.6)
Weight for age at baseline	Greater than 1	78(30.8)	3(1.2)	75(29.6)
	Between -1 & 1	65(25.7)	8(3.2)	57(22.5)
	Between -2 &-1	60(23.8)	9(3.6)	51(20.2)
	Less than -2	50(19.8)	18(7.2)	32(12.6)
Malnutrition at baseline	No	166(65.6)	11(4.3)	155(61.3)
	Yes	87(34.4)	27(10.7)	60(23.7)
	Under-weight	29(11.5)	6(2.4)	23(9.1)
	Sever-underweight	36(14.2)	14(5.5)	22(8.7)
	Moderate wasting	7(2.8)	4(1.6)	3(1.2)
	Sever wasting	23(9)	13(5.2)	10(3.8)
	Moderate stunting	6(2.4)	0	6(2.4)
	Severe stunting	10(4)	3(1.2)	7(2.8)
Malnutrition treatment	Yes	83(32.8)	27(10.7)	56(22.1)
	No	4(1.6)	3(1.2)	1(0.4)
Past TB treatment history	No	219(86.6)	26(10.3)	193(76.3)
	Yes	34(13.4)	12(4.7)	22(8.7)
	Past TB treatment was completed	31(12.3)	12(4.8)	19(7.5)
History of OI	No	145(57.3)	8(3.2)	137(54.1)
	Yes	108(42.7)	30(11.9)	78(30.8)
HIV confirmed	Before TB	184(72.8)	30(11.9)	154(60.9)
	After TB	69(27.2)	8(3.2)	61(24.1)
Weight for age during-follow-up	Greater than 1	105(41.5)	5(2.0)	100(39.5)
	Between -1&1	100(39.5)	19(7.5)	81(32.0)
	Between -2 &-1	35(13.9)	9(3.6)	26(10.3)
	Less than -2	13(5.1)	5(2.0)	8(3.2)
OIS other than TB during the follow-up time	No	197(78.9)	23(9.1)	174(68.8)
	Yes	56(22.1)	15(5.9)	41(16.2)
Type of TB	PTB	193(76.2)	20(7.9)	173(68.4)
	EPTB	60(23.8)	18(7.1)	42(16.6)
Time of TB occurrence	Pre ART	67(26.4)	9(3.6)	58(22.9)
	During ART	186(73.6)	29(11.5)	157(62.1)

effects 35 (13.9%), TB 9 (3.6%), treatment failure 13 (5.1%) and other reasons 4 (1.6%) such as drug toxicity. First-line ART treatment failure was observed in 13 (5.1%) children. Of these, 10 (76.9%) of them initiated second-line ART regimens. Regarding ART adherence, 211 (88.4%) of the children had good ART adherence (Table 3).

Table 3. Medication and follow-up related characteristics among children co-infected with TB and HIV in general hospitals of two zones of the Tigray region, North Ethiopia, 2019 (n = 253).

Characteristics		Total N (%) n=253	Death N (%) n=38	Censored N (%) n= 215
Taken INH at baseline	No	108(42.7)	26(10.3)	82(32.4)
	Yes	145(57.3)	12(4.7)	133(52.6)
Taken CPT at baseline	No	56(22.1)	13(5.1)	43(17.0)
	Yes	197(77.9)	25(9.9)	172(68.0)
First-line treatment failure	No	240(94.9)	29(11.5)	211(83.4)
	Yes	13(5.1)	9(3.6)	4(1.6)
	Immunological failure	11(4.4)	8(3.2)	3(1.2)
	Virological failure	5(2)	2(0.8)	3(1.2)
	Clinical failure	9(3.6)	7(2.8)	2(0.8)
	The second-line regimen was started	10(3.9)	6(2.4)	4(1.6)
Child HIV disclosure status	Fully disclosed	99(39.1)	18(7.1)	81(31)
	Partially disclosed	67(26.5)	9(3.6)	58(22.9)
	Not disclosed	87(34.4)	11(4.4)	76(30.0)
Eligibility criteria	Age	21(8.3)	3(1.2)	18(7.1)
	CD4 count	7(2.8)	4(1.6)	3(1.2)
	WHO staging	98(38.7)	9(3.6)	89(35.1)
	Both CD4 and WHO staging	127(50.2)	22(8.7)	105(41.5)
Taken CPT during the follow-up time	No	25(9.9)	1(0.4)	24(9.5)
	Yes	218(90.1)	37(14.6)	191(75.5)
Child's ART adherence	Good	211(88.4)	14(5.5)	197(77.9)
	Poor	42(16.6)	24(9.5)	18(7.1)

The mortality rate among children co-infected with TB and HIV

Of a total of 253 children co-infected with TB and HIV included in the study, 38 (15%) deaths and 215 (85%) censored were recorded. Of the censored cases, 186 (73.5%) were alive until the end of the follow-up period, 14 (5.5%) were transferred out, 15 (5.9%) were dropped out of follow-up, and the rest were in TB treatment. Those 253 TB and HIV co-infected children were followed for different periods (1 month to 12 months), which provides 226 child-month observations with a mean survival time of 10.75 (95% CI; 10.37 -11.14) months. In this study, the mortality rate was 0.17 (95% CI 0.12 to 0.23) per 1,000 child-month observations. The majority (73.7%) of the deaths occurred in the first six months of follow-up period and 15 (40%) occurred during the initial phase of TB treatment. All deaths 38 (15.02%) had occurred during ART. The cumulative probability of survival at the end of 2 months, 6 months, 9 months and 12 months was 94.0, 88.0, 85.0 and 82.9%, respectively (Figure 1).

Predictors of mortality among children co-infected with TB and HIV

Bivariate and multivariate analyzes were used to assess the significant association between exposure variables and the outcome variable. Underweight at baseline, moderate/severe wasting at baseline, IPT, CPT, baseline hemoglobin level, level of adherence to ART, type of tuberculosis, WHO staging during follow-up, and hemoglobin level during follow-up were statistically significant at 0.2 level of significance in bivariate analysis. In multivariate analysis; underweight at baseline, IPT user/not/, ART adherence level, type of TB, WHO staging during follow-up, and hemoglobin level during follow-up were statistically significant at 0.05 significance level (Table 4).

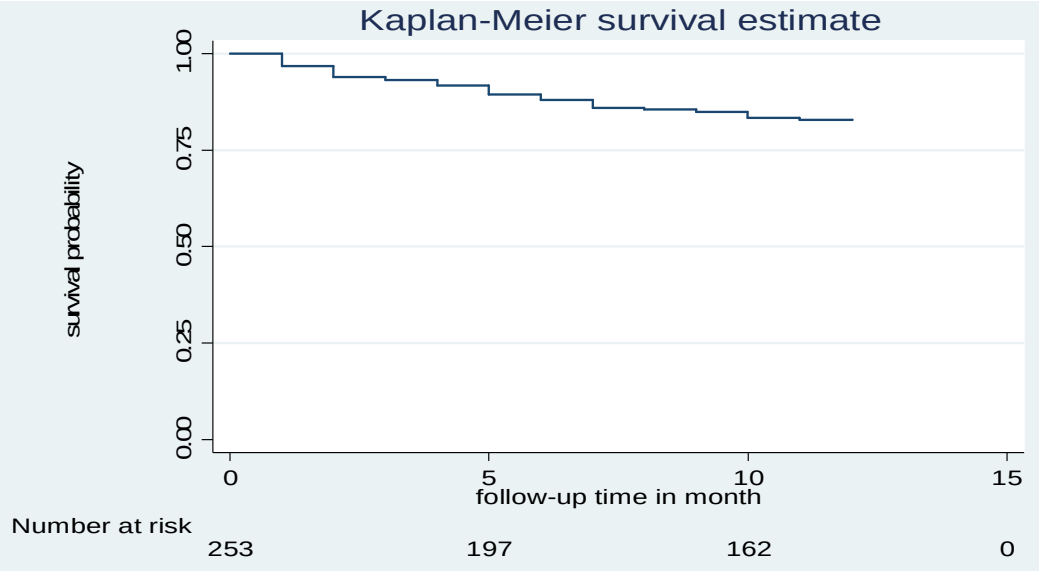

Figure 1. Kaplan-Meier cumulative survival estimate of children co-infected with TB and HIV in general hospitals of two zones of the Tigray region, North Ethiopia, 2019.

Table 4. Results of the bivariate and multivariate analysis among children infected with TB and HIV in general hospitals of two zones of the Tigray region, North Ethiopia, 2019 (n = 253).

Characteristics		Death	Censored	CHR (95% CI)	AHR (95% CI)
Taken INH at baseline	No	26	82	3.66 (1.83 - 7.30)	3.68 (1.26-10.7)**
	Yes	12	133	1.00	1.00
Taken CPT at baseline	No	13	43	2.33 (1.18 - 4.60)	1.77 (0.73-5.30)
	Yes	25	172	1.00	1.00
WHO Staging- during our follow-up	Stage I & II	6	139	1.00	1.00
	III & IV	32	76	8.64 (3.59-20.77)	6.79 (1.85-24.65)**
HGB level at baseline	<10	17	30	4.49 (2.34- 8.61)	0.44 (0.12-1.56)
	≥10	21	185	1.00	1.00
HGB level during our follow-up	<10	7	6	7.89 (3.30-18.86)	3.75 (1.06-13.28)**
	≥10	31	209	1.00	1.00
Weight for age at baseline	>1	3	75	1.00	1.00
	B/n -1 &1	8	57	3.74 (0.98 - 14.16)	3.59 (0.6-21.41)
	B/n -2& -1	9	51	4.39 (1.18 -16.31)	1.84 (0.29-11.86)
	≤-2	18	32	12.15 (3.55- 41.58)	7.86 (1.25-49.2)**
Moderate /severe wasting at baseline	No	22	202	1.00	1.00
	Yes	16	13	7.69 (4.01- 14.74)	2.54 (0.60-10.78)*
Child's ART adherence	Good	14	197	1.00	1.00
	Poor	24	18	20.32 (10.13-40.75)	3.82 (1.38-10.5)**

Table 4. Continues.

Type of TB	PTB	20	173	1.00	1.00
	EPTB	18	42	3.06 (1.60-5.84)	2.87 (1.08-7.58)**

** = significant variables in multivariate analysis at p<0.05
CPT - co-trimoxazole preventive therapy; EPTB - extrapulmonary TB; OT- opportunistic infection; CHR- crude hazard ratio; AHR- Adjusted Hazard Ratio; IPT-isoniazid preventive therapy; PTB - pulmonary tuberculosis.

The risk of death among children with TB and HIV co-infected with underweight was approximately 8 times higher than children with normal weight at baseline (AHR=7.9 (95% CI 1.26, 49.3)). Children who did not take IPT were approximately 4 times more likely to experience death than children who had taken IPT (AHR=3.69 (95% CI=1.26, 10.8)). The risk of child death with poor adherence to ART was approximately 4 times higher than children with good adherence to ART (AHR = 3.82 (95% CI: 1.38, 10.54)). The risk of death among children infected with extra-pulmonary TB was also approximately 3 times higher than infected children with pulmonary TB (AHR = 2.9 (95% CI: 1.1, 7.6)). During follow-up, children with advanced WHO staging (III and IV) were approximately 7 times higher risk of death than children with stage I and II (AHR=6.79 (95% CI= 1.85, 24.9)). Anemic children were approximately four times more likely to experience death compared to non-anemic children during follow-up (AHR=3.76 (95% CI=1.06, 13.27)).

DISCUSSION

The study provides information on the overwhelming problem of high mortality and associated predictors among children with TB and HIV co-infected. The mortality rate in this study was 0.17 (95% CI 0.12–0.23) per 1000 child-month observations. The result was lower than the mortality rate reported from a single study conducted in four developing countries (Burkina Faso, Cambodia, Cameroon and Vietnam), which is 0.370 per 1000 child- month observations (Marcy et al., 2018). The difference may depend on the sample size difference used by the studies.

In this study, mortality was higher in underweight children at baseline. A similar finding was reported from a study conducted in Thailand (Salvadori et al., 2017). This might be the effect of underweight by reducing body metabolic process results inadequate energy acquisition that increases disease progression, which may end up in death. Furthermore, inadequate weight gain in TB treatment indicates a poor response to treatment (Hicks et al., 2014). However, stunting and wasting were not significant in this study. This could be due to a higher proportion (90%) of children diagnosed with malnutrition in this study who received treatment for malnutrition.

The study also revealed that children who did not take IPT were three times more likely to experience death than children who did take IPT. This was in line with a study conducted in Gondar, Ethiopia (Atalell et al., 2018). The possible reason might be that IPT reduces the severity and spread of TB disease. However, CPT was not found to be statistically significant in this study, which was reported as a protective factor for death in a study conducted in Gondar, Ethiopia (Atalell et al., 2018). This may be that a higher proportion (78%) of our respondents had taken CPT that unable to make a difference.. The number of children who did not take the CPT and died was too little (5.1%). For better survival, HIV positive children should take both CPT and IPT as preventive prophylaxis.

In this study, the hazard of death among extra-pulmonary TB infected children were three times, most likely higher than pulmonary TB infected children. This result was in line with a study conducted in Gondar, Ethiopia (Atalell et al., 2018). The reason might be that the easy diagnostic technique for EPTB is not available in most of our clinical settings, resulting in delayed initiation of anti-TB treatment leading to rapid disease progression and easy involvement of vital organs.

During follow-up, this study revealed that anemia was associated with higher child death. No previous studies examined anemia during follow-up, but at the beginning of the study, it was identified as a predictor of mortality in studies conducted in Gondar (Ethiopia) and Thailand (Atalell et al., 2018; Salvadori et al., 2017). Higher mortality with anemia may be associated with decreased oxygen and nutrient care capacity of the blood, resulting in inadequate oxygen and nutrient supply to vital organs that become synergistic with TB and HIV (Atalell et al., 2018).

In contrast to other studies in Gondar (Ethiopia) (Atalell et al., 2018), Thailand (Salvadori et al., 2017), Nigeria (Ebonyi et al., 2016), Malawi (Buck et al., 2013), and a single study of four developing countries (Marcy et al., 2018); WHO staging, CD4 count, and hemoglobin level at baseline were not significantly associated with mortality in this study. The reason might be that unlike these studies, our study assessed the effect of these variables during

follow-up time and at baseline. Most of these variables were significantly associated during follow-up, which shows a better effect on the outcome variable than at baseline. This is one of the strengths of this study. Assessing the effect of these variables during follow-up enables us to overlook the more accurate effects of exposure variables on the outcome variable. The study also considered the time of the event, which enables us to consider the contribution of censored cases.

Limitation of the study

Since the study was a retrospective review of the chart (secondary data), some variables not documented in the child's medical records were missing. A further prospective study is needed to address other important issues not addressed by this study.

Conclusions

The mortality rate of children co-infected with TB and HIV in two zones of the Tigray region was high. Most deaths occurred within the first six months of the follow-up period. Underweight at baseline, IPT non-user, poor ART adherence, extrapulmonary TB, advanced WHO staging during follow-up, advanced/severe immunosuppression status during follow-up, and hemoglobin level < 10mg/dl during follow-up were predictors of increased mortality. This study is important for planning and decision making by pointing out gaps to make a successful strategy to combat TB and HIV and related consequences to increase the overall effectiveness of therapy in TB and HIV co-infected infected children. The treatment of malnutrition and anemia should be given emphasis. Strengthening the administration of preventive therapy (IPT, CPT) and counseling on adherence to ART drugs were crucial interventions to reduce mortality among children co-infected with TB and HIV. Children who have extra-pulmonary tuberculosis and advanced clinical staging (III and IV) need special consideration during treatment.

ABBREVIATIONS: AIDS - Acquired immune deficiency syndrome; **AHR** - adjusted risk ratio; **CHR** - crude risk ratio; **ART** - anti-retroviral therapy; **CI** - confidence interval; **CPT** - co-trimoxazole preventive therapy; **ART** - anti-retroviral therapy; **HGB** – hemoglobin; HIV - human immunodeficiency virus; EPTB - extrapulmonary tuberculosis; PTB - lung tuberculosis; IPT - isoniazid preventive therapy; OI - Opportunistic infections; **PLHIV**- people living with HIV; **TB** - tuberculosis; **TB and HIV - tuberculosis** and human immunodeficiency virus; **WHO -** World Health Organizations.

DECLARATIONS

Ethical approval and consent to participate

Ethical approval was obtained from the Institutional Review Board of the College of Health Sciences, Mekelle University. A letter of cooperation from the School of Nursing and a permission letter from hospitals were also secured before data collection. The name of the respondent was not mentioned during data collection.

Consent for publication: Not applicable

Competing interests: The authors declare that they have no competing interest.

Funding: There is no source of funding.

Availability of data and materials

The data set analyzed during the current study is available from the cross-pondering author on reasonable request.

ACKNOWLEDGEMENTS

We greatly acknowledge and appreciate data collectors, hospital staff, hospital administrators, and Tigray Regional Health Bureau; without them, this work cannot be real. We also acknowledge the School of Nursing College Health Sciences, Mekelle University, for their financial and technical support.

REFERENCES

Abrha H, Tsehayneh B, Massa D, Tesfay A, Kahsay H, **2015**. Survival experience and its predictors among TB/HIV Co-infected patients in Southwest Ethiopia. Epidemiol (Sunnyvale), 5: 191.

Adejumo OA, Daniel OJ, Adebayo BI, Adejumo EN, Jaiyesimi EO, Akang G, Awe A, **2015**. Treatment outcomes of childhood TB in Lagos, Nigeria. J Trop Pediatr, 62(2): 131-138.

Atalell KA, Birhan Tebeje N, Ekubagewargies DT, **2018**. Survival and predictors of mortality among children co-infected with tuberculosis and human immunodeficiency virus at University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia. A retrospective follow-up study. PloS One, 13(5): e0197145.

Ayalaw SG, Alene KA, Adane AA, **2015**. Incidence and Predictors of Tuberculosis among HIV Positive Children at University of Gondar Referral Hospital, Northwest Ethiopia: A Retrospective Follow-Up Study. Int Sch Res Notices, 307810. doi: 10.1155/2015/307810.

Bruchfeld J, Correia-Neves M, Källenius G, **2015**. Tuberculosis and

HIV coinfection. Cold Spring Harb Perspect Med, 5(7): a017871. doi: 10.1101/cshperspect.a017871..

Buck WC, Olson D, Kabue M, Ahmed S, Nchama L, Munthali A, Hosseinipour M, Kazembe P, **2013**. Risk factors for mortality in Malawian children with human immunodeficiency virus and tuberculosis co-infection. Int J Tuberc Lung Dis, 17(11): 1389-1395.

Deribe A, **Estifanos** W, **2018**. Magnitude and determinants of opportunistic infections among Hiv/aids patients in Sphmmc, Addis Ababa, Ethiopia: Retrospective study. J Public Health, 4.

Ebonyi AO, Oguche S, Agbaji OO, Sagay AS, Okonkwo PI, Idoko JA, Kanki PJ, **2016**. Mortality among pulmonary tuberculosis and HIV-1 co-infected Nigerian children being treated for pulmonary tuberculosis and on antiretroviral therapy: a retrospective cohort study. Germs, 6(4): 139.

Endalamaw A, Engeda EH, Tezera N, **2018**. Incidence of tuberculosis in children on antiretroviral therapy: a retrospective cohort study. BMC Res notes, 11(1): 745.

FMOH, **2017**. Federal ministry of health Ethiopia National guidelines for comprehensive HIV prevention, care, and treatment. In. Addis Ababa, Ethiopia.

Hicks R, Padayatchi N, Shah N, Wolf A, Werner L, Sunkari V, O'Donnell M, **2014**. Malnutrition associated with unfavorable outcome and death among South African MDR-TB and HIV co-infected children. Int J Tuberc Lung Dis, 18(9): 1074-1083.

Isaakidis P, Paryani R, Khan S, Mansoor H, Manglani M, Valiyakath A, Saranchuk P, Furin J, **2013**. Poor outcomes in a cohort of HIV-infected adolescents undergoing treatment for multidrug-resistant tuberculosis in Mumbai, India. PLoS One, 8(7): e68869.

Marais B, Graham S, Cotton M, Beyers N, **2007**. Diagnostic and management challenges for childhood tuberculosis in the era of HIV. J Infect Dis, 196(Supplement_1): S76-S85.

Marais B, Rabie H, Cotton M, **2011**. TB and HIV in children–advances in prevention and management. Paediatr Respirat Rev, 12(1): 39-45.

Marcy O, Tejiokem M, Msellati P, Huu KT, Do Chau V, Ngoc DT, Nacro B, Ateba-Ndongo F, Tetang-Ndiang S, Ung V, **2018**. Mortality and its determinants in antiretroviral treatment-naive HIV-infected children with suspected tuberculosis: an observational cohort study. Lancet HIV, 5(2): e87-e95.

Newton SM, Brent AJ, Anderson S, Whittaker E, Kampmann B, **2008**. Paediatric tuberculosis. Lancet Infect Dis, 8(8): 498-510.

Palme IB, Gudetta B, Bruchfeld J, Muhe L, Giesecke J, **2002**. Impact of human immunodeficiency virus 1 infection on clinical presentation, treatment outcome and survival in a cohort of Ethiopian children with tuberculosis. Pediatr Infect Dis J, 21(11): 1053-1061.

Pawlowski A, Jansson M, Sköld M, Rottenberg ME, Källenius G, **2012**. Tuberculosis and HIV co-infection. PLoS Pathog, 8(2): e1002464.

Salvadori N, Ngo-Giang-Huong N, Duclercq C, Kanjanavanit S, Ngampiyaskul C, Techakunakorn P, Puangsombat A, Figoni J, Mary J-Y, Collins IJ, **2017**. Incidence of tuberculosis and associated mortality in a cohort of human immunodeficiency virus-infected children initiating antiretroviral therapy. J Pediatric Infect Dis Soc, 6(2): 161-167.

Tigray Regional Health Bureau, **2019**. Demographic data of Tigray region and public health facilities, Ethiopia.

Tilahun G, **Gebre-Selassie** S, **2016**. Treatment outcomes of childhood tuberculosis in Addis Ababa: a five-year retrospective analysis. BMC Public Health, 16(1): 1-10.

Ugochukwu EF, **2010**. HIV/TB Co-infection in Nigerian children. Nig Med J, 51(3): 120.

UNAIDs, **WHO**, **2011**. Global HIV/AIDS response: epidemic update and health sector progress towards universal access: progress report 2011. Global HIV/AIDS response: epidemic update and health sector progress towards universal access: progress report 2011.

Venturini E, Turkova A, Chiappini E, Galli L, de Martino M, Thorne C, **2014**. Tuberculosis and HIV co-infection in children. BMC Infect Dis, 14(1): S5.

WHO, **2015a**. Implementing the end TB strategy: the essentials. In.: World Health Organization.

WHO, **2015b**. Global tuberculosis report 2015: World Health Organization.

Citation: Nigussie J, Kassa M, Halefom G, Hadush H, Grima B, 2021. Predictors of mortality among children co-infected with tuberculosis and human immunodeficiency virus in Tigray Region, North Ethiopia, retrospective follow-up study. Int Res J Med Med Sci, 10(1): 1-10.