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Predictors of Time to Death among TB/HIV Co-Infected Adults on ART at Two Governmental Hospitals in Mekelle, Ethiopia, 2009-2016: A Retrospective Cohort Study

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Abstract

Background: Ethiopia is a country with high burden of Tuberculosis and Human Immunodeficiency Virus (TB-HIV) dual infections in the world. However, little was known so far on predictors of time to death among TB/HIV co-infected adults in the study setting in particular. Therefore, this study was aimed at filling this gap in the region particularly.

Methods: A hospital based retrospective cohort study design was employed on 305 Tuberculosis and Human Immunodeficiency Virus (TB/HIV) co-infected adults who have started Anti-Retroviral Therapy (ART) from January, 2009 to December, 2016 at two governmental hospitals in Mekelle, Ethiopia. Multivariable Cox regression analysis was applied to identify statistically significant predictors of time to death (P< 0.05). Finally, Adjusted Hazard Ratio (AHR) and 95% Confidence Interval (CI) were interpreted and reported in the final Cox model.

Results: Overall, 70 of 305 (23.0%) TB/HIV co-infected adults were died during the entire follow-up period. The study subjects (257 Active TB, 48 Latent TB) were followed for an overall median follow up time of 37 months (Interquartile Range: 10 to 63 months). Baseline Body Mass Index (<18.5 kg/m2) (AHR=2.427; 95% CI: 1.214 to 4.853), and Being Extra-pulmonary TB (Mixed TB) patient (AHR=2.400; 95% CI: 0.220 to 0.697) were predictors of time to death. On the other hand, increasing CD4 cell count (AHR=0.995; 95% CI: 0.991 to 0.999), developing drug side effects (AHR=0.369; 95% CI: 0.194 to 0.701), being co-infected with Latent TB infection (AHR=0.102; 95% CI: 0.023 to 0.449), completing TB treatment (AHR=0.114; 95% CI: 0.060 to 0.16), and being on Cotri-moxazole Prophylactic Therapy (AHR=0.391; 95% CI: 0.220 to 0.697) had prolonged the time to death.

Conclusion: Almost one-fourth of TB/HIV co-infected patients were died with a relatively high mortality rate among those co-infected with active TB since ART initiation. Moreover, being co-infected with active TB/HIV, having low baseline BMI (< 18.5 g/dl), Low CD4 cell count, not developing drug side effects, being on TB treatment, and being off CPT were shortening the time to death and thus, survival of TB-HIV co-infected adults will be improved up on switching off the potential risk factors identified.

Keywords: Adults; Time to death; TB/HIV; ART; AIDS; CD4

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Introduction

Tuberculosis (TB) is the most common opportunistic infection among People Living with Human Immunodeficiency Virus (PLWHIV), and persons co-infected with HIV and TB are highly vulnerable to death as a result of the bidirectional relationship and synergism of the two infections. On the other hand, TB also promotes the progression of HIV infection to Acquired Immunodeficiency Syndrome (AIDS) [1]. The risk of death in co-infected individuals is also approximately twice that of HIV infected individuals alone even considering CD4 cell count and Anti-Retroviral therapy (ART) into account [2].

HIV is the first and TB is the second leading cause of death from infectious disease statistics world widely. Globally, above one-third of the world population were estimated to be latently infected with TB [3]. In the year 2014, above 9 million people developed TB, of which 12% were co-infected with HIV [4]. In 2015, 33% of HIV deaths were due to TB evidencing that it is still a leading

cause of mortality among PLWHIV [5].

In year 2007, 80% of global burden of TB/HIV co-infection was reported from the SSA region followed by the Southeast Asia region which was accounted for 10% of the total burden. Considering the SSA region, South Africa alone accounted for one-third of the global burden of TB/HIV co-infection [6].

Similarly, retrospective cohort and case control studies conducted in different parts of Ethiopia have reported the bidirectional association between HIV and TB. For instance, a retrospective cohort study conducted nationally has reported that 9.0% of HIV patients on treatment were also co-infected with TB [7]. Another study conducted in Amhara region, Ethiopia has also revealed that 27.7% of HIV patients on ART were developed TB [8]. On the other hand, from a study conducted in Bahirdar, 30.6% of TB patients were also HIV positive and above one fifth of the TB-HIV cases were fatal as well [9]. Moreover, the TB-HIV related deaths were also found to be significant among persons co-infected with HIV/TB and thus, significantly associated with baseline CD4 cell count, baseline functional status, baseline weight, Baseline clinical stage, co-trimoxazole prophylaxis, and co-existence of other OIs in most of the studies [7,9-13].

According to the national annual performance report of Ethiopia, the ART coverage of TB/HIV co-infected patients was 70% unlike the World Health Organization (WHO) recommendation for all TB/HIV co-infected patients to start ART regardless of their baseline CD4 cell count [14]. However, the incidence of mortality among TB/HIV co-infected patients was not yet reduced even in the presence of ART in the country. Thus, this study was aimed at investigating the incidence and predictors of time to death among TB/HIV co-infected adults in the study setting, in particular.

Methods

Study aim, design and setting

An institutionally based retrospective cohort study design was conducted at two governmental hospitals: Ayder Comprehensive Specialized Hospital and Mekelle Hospital to investigate survival and predictors of mortality among TB/HIV co-infected patients on ART. Mekelle is the capital city of Tigray region which is located at a distance of 783 kilometers northern part of Addis Ababa, the capital city of Ethiopia. Ayder Comprehensive Specialized Hospital is the only specialized hospital found in Tigray region, Ethiopia and has begun ART services since January, 2009. On the other hand, Mekelle Hospital has begun the service since September, 2004.

Study population, sample size determination and enrollment procedure

The study subjects were selected consecutively based on their ART initiation and TB/HIV status. TB/HIV co-infected patients who started their ART from January, 2009 to December, 2016 at the two governmental hospitals were eligible for the study. However, medical records with unknown patient status and transfer out cases were excluded from the study.

The minimum sample sized was estimated using a formula for survival data analysis based on the following important assumptions-95% Confidence level, 80% optimum statistical power, CPT as major exposure variable from a similar study that was conducted in Bahir Dar, Northwest Ethiopia [9] (on CPT as exposed groups denoted by q1 (0.88) and Off CPT as non-exposed groups denoted by q0 (0.12)), HR (CPT) =0.33, and cumulative incidence of death =P (death due to TB/HIV co-infection or related causes) reported from the study is 0.22 (22%).

$$Number\ of\ events\exp ected = \frac{(Z_{1-\%} + Z_{\beta})^2}{\log(HR)^2 \times q_1 \times q_0} \approx 61$$

$$where: Z_{1-\%}(Z_{0.975}) = 1.96, Z_{\beta}(Z_{0.80}) = 0.84, HR = \frac{incidence\ of\ death\ on\ CPT}{incidence of\ death\ off\ CPT} = 0.33$$

And 93 of 422 (22%) TB/HIV co-infected adults were died until the end off the follow-up time. Therefore, the minimum sample size was estimated to approximately 278 as follows.

$$Minimum\ sample\ size\ (n)\ needed = \frac{number\ of\ (deaths)\ estimated}{probability\ of\ event\ (death)} = \frac{61}{0.22} \approx 278$$

Eventually, we included 305 TB/HIV co-infected (257 Active TB/HIV, 48 LTBI/HIV) patients were included in the study all consecutively. The overall enrollment of the study subjects was summarized in (Figure 1).

Data collection procedure and study variables

We developed data abstraction sheet to collect data from ART registration book and patient medical charts as well. First, variables which were available in the ART registration book were collected which followed by patient medical charts. Thus, a patient charts consisting of ART intake forms, laboratory requests, and physicians clinical diagnosis were reviewed to extract all necessary information included in the data collection checklist. The data collection tool consists of the following important information: 1) Socio-demographic characteristics of TB/HIV co-infected patients; 2) Laboratory and baseline clinical characteristics of the study subjects; 3) Diagnosis and treatment characteristics; and 4) Patient follow up status-during the course of ART treatment the patient was either died or censored (alive, Transfer in, drop out or loss to follow up). Where death was our event and time to death was our outcome variable.

Study variables and measurement

The outcome variable was time to death and death is the event of interest. Therefore, time to death is defined as the time period from ART initiation to death developed.

The starting time (to) for the current study was ART initiation and the follow up time (survival time) was defined as the time period from ART initiation to ART outcome observed (i.e. alive, death, LTFU or stop) Based on their Isoniazid Preventive Therapy (IPT) status and active TB diagnosis, TB/HIV co-infected patients were stratified in to two groups (i.e. LTBI and Active TB). Thus, those who were on IPT were considered as LTBI/HIV co-infected; and those who were not on IPT and diagnosed with active TB were on the other hand treated as active TB/HIV co-infected patients. On the other hand, TB was categorized as Pulmonary TB (PTB), Extra-Pulmonary TB (EPTB) or mixed type TB based on the site where TB has involved. In addition, the presence of at least one ART drug side effect was sufficient to classify the study subject as he/she has "developed drug side effect" otherwise "No". Regarding CPT status, TB-HIV co-infected patients who were taken CPT for at least one month were categorized as "on CPT" and otherwise "off CPT". Similarly, the diagnosis of at least one OI other than TB was considered adequate to classify the patient as having history of OI. Moreover, based on their baseline Hemoglobin level (g/dl), TB/HIV co-infected patients were classified as "Anemic "(≤ 11.0 g/dl) or "Normal" (>11.0 g/dl) regardless of their sex and pregnancy status.

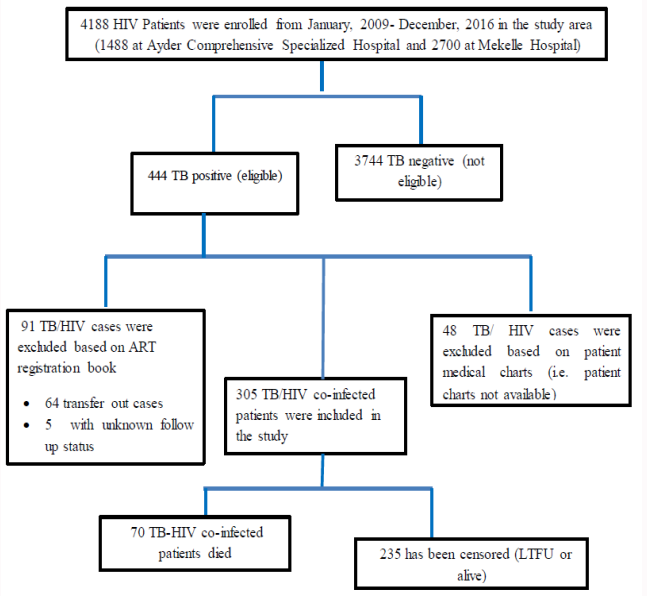

Figure 1: Overall enrollment of TB/HIV co-infected adults on ART at two governmental hospitals in Mekelle, Ethiopia, 2009-2016 (n=305).

Statistical data analysis

First, Data were entered in excel, and then exported to STATA (version 12) statistical software. Categorical variables were labeled and data were declared survival time data prior to analysis. In descriptive statistics, median (IQR), and frequency (%) were computed for numeric and categorical variables respectively. Log rank test and Kaplan Meier curves were used to select potential candidate variables of the final Cox model in univariate analysis. Both multi-collinearity and interaction effects were checked. A multiple Cox regression analysis was fitted to identify statistically significant predictors of mortality due to TB/HIV co-infection and related factors based on Adjusted Hazard Ratio (AHR) and its 95% Confidence Interval (CI).

Results

Socio-demographic characteristics of TB/HIV co-infected adults

A total of 305 TB/HIV co-infected patients (257 Active TB/HIV, 48 LTBI/HIV) were included in the study. Of the total study subjects, 157 (51.5%) of they were females and the median age was also 35years (IQR: 29-40 years). Regarding the other socio-demographic characteristics, 129 (42.3%), and 119 (39.0%) of the study subjects had baseline married status, and secondary educational level respectively. Moreover, 293 (96.1%), and 222 (72.8%) were orthodox followers and urban dwellers respectively. The ART follow up site for 172 (56.4%) of the study subjects was Mekelle Hospital (Table 1).

Baseline clinical characteristics of TB/HIV co-infected patients

On the other hand, 141 (46.2%), 142 (46.6%), and 114 (37.4%) TB/HIV co-infected had baseline: working functional status; clinical stage-IV, and anemic status. The median baseline CD4 count was also 86 Cells/mm^3 (IQR: 38 to 167 Cells/mm^3) respectively (Table 2).

Diagnosis and treatment characteristics of TB/HIV co-infected adults

Based on their diagnosis and treatment characteristics, approximately two-third (63.0%) of TB/HIV co-infected patients had developed at least one ART drug side effect. Regarding TB diagnosis site, above half (56.7%) of the study subjects were diagnosed with EPTB or both EPTB and PTB involving different organs besides the lung. Moreover, at least one or more OIs other than TB were also diagnosed in 243 of 305 (79.7%) patients. Our findings also revealed that 283 (83.0%), and 251 (82.3%) of TB/HIV co-infected patients were completed their treatment, and on CPT respectively (Table 3).

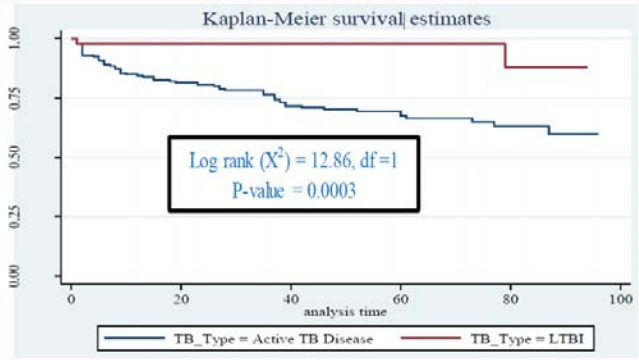

Figure 2: Survival experience of TB/HIV co-infected adults on ART at Ayder comprehensive Specialized Hospital and Mekelle Hospital, Ethiopia, 2017 stratified by TB type (n=305).

Table 1: Socio-demographic characteristics of TB/HIV co-infected adults on ART at two governmental hospitals in Mekelle, Ethiopia, 2009-2016 (n=305).

Variable	Active TB Disease (n=257)	LTBI (n=48)	Total (n=305)
Sex			
Female	129 (50.2%)	28 (58.3%)	157 (51.5%)
Male	128 (49.8%)	20 (41.7%)	148 (48.5%)
Baseline Age (Years)			
>35.0	113 (44.0%)	16 (33.3%)	129 (42.3%)
≤ 35.0	144 (56.0%)	32 (66.7%)	176 (57.7%)
Marital Status			
Single	60 (23.4%)	9 (18.8%)	69 (22.6%)
Married	108 (42.0%)	21 (43.8%)	129 (42.3%)
*Others	89 (34.6%)	18 (37.5%)	107 (35.1%)
Educational Level			
No formal education	56 (21.8%)	9 (18.8%)	65 (21.3%)
Primary	75 (29.2%)	15 (31.2%)	90 (29.5%)
Secondary	100 (38.9%)	19 (39.6%)	119 (39.0%)
Tertiary	26 (10.1%)	5 (10.4%)	31 (10.2%)
Religion			
Orthodox	247 (96.1%)	46 (95.8%)	293 (96.1%)
Muslim	10 (3.9%)	2 (4.2%)	12 (3.9%)
Place of Residence			
Rural	71 (27.6%)	12 (25.0%)	83 (27.2%)
Urban	186 (72.4%)	36 (75.0%)	222 (72.8%)

*others: Widowed/Divorced/Separated; TB: Tuberculosis; LTBI: Latent TB Infection

Survival estimate and follow up status of TB/HIV co-infected patients

TB/HIV co-infected patients on ART were followed for an overall median follow-up time of 37 months (IQR: 10-63 months). Moreover, the median survival time was 9 months among the study subjects who

Table 2: Baseline clinical characteristics of TB/HIV co-infected adults on ART at two governmental hospitals in Mekelle, Ethiopia, 2009-2016 (n=305).

Variable	Active TB Disease (n=257)	LTBI (n=48)	Total (n=305)
Baseline BMI (kg/m²)			
>18.5	90 (35.0%)	15 (31.3%)	105 (34.4%)
≤ 18.5	167 (65.0%)	33 (68.7%)	200 (65.6%)
Baseline Weight (kg)			
>47	130 (50.6%)	22 (45.8%)	152 (49.8%)
≤ 47	127 (49.4%)	26 (54.2%)	153 (50.2%)
Functional Status			
Working	115 (44.7%)	26 (54.1%)	141 (46.2%)
Ambulatory	91 (35.4%)	19 (39.6%)	110 (36.1%)
Bedridden	51 (19.8%)	3 (6.3%)	54 (17.7%)
WHO Clinical Stage			
I or II	27 (10.5%)	5 (10.4%)	32 (10.5%)
III	101 (39.3%)	30 (62.5%)	131 (42.9%)
IV	129 (50.2%)	13 (27.1%)	142 (46.6%)
Baseline Hemoglobin (g/dl)			
>11.0	157 (61.1%)	34 (70.8%)	191 (62.6%)
≤ 11.0	100 (38.9%)	14 (29.2%)	114 (37.4%)

Table 3: Diagnosis and treatment characteristics of TB/HIV co-infected adults on ART at two governmental hospitals in Mekelle, Ethiopia, 2009-2016 (n=305).

Variable	Active TB Disease (n=257)	LTBI (n=48)	Total (n=305)
ART Drug Side Effects'			
Yes	92 (35.8%)	21 (43.8%)	113 (37.0%)
No	165 (64.2%)	27 (56.2%)	192 (63.0%)
TB diagnosis			
PTB	104 (40.5%)	28 (58.3%)	132 (43.3%)
EPTB/Mixed	153 (59.5%)	20 (41.7%)	173 (56.7%)
History of OI			
Yes	210 (81.7%)	33 (68.8%)	243 (79.7%)
No	47 (18.3%)	15 (31.2%)	62 (20.3%)
TB Treatment Completion			
Yes	209 (81.3%)	44 (91.7%)	253 (83.0%)
No	48 (14.4%)	4 (8.3%)	52 (17.0%)
CPT			
On	214 (83.3%)	40 (82.3%)	254 (83.3%)
Off	43 (16.7%)	8 (17.7%)	51 (16.7%)

CPT: Co-trimoxazole Prophylactic Therapy; Tb: Tuberculosis; LTBI: Latent Tuberculosis Infection; PTB: Pulmonary TB; EPTB: Extra-Pulmonary TB

have developed the event of interest. Furthermore, the study subjects contributed a total of 11 933 (9 381 by active TB/HIV, 2 552 by LTBI/HIV) Person Months (PMs). Of the total study subjects, 70(23.0%) of them were died due to TB/HIV co-infection or associated factors with an incidence rate of 5.9 new deaths per 1000 PMs where the mortality rate was 9 times higher among those diagnosed with active TB as compared to LTB/HIV co-infected patients. On the other hand, LTBI/HIV co-infected patients had better survival as compared to active TB/HIV co-infected patients (Figure 2).

Predictors of time to death among TB-HIV co-infected adults

Upon running the multivariable Cox regression analysis: 7 variables (ART drug side effects, Baseline CD4 cell count, TB type, Baseline BMI, TB treatment Completion, TB diagnosis, and CPT) were identified as statistically significant predictors of mortality. By holding the effect of other variables constant, the development of ART drug side effects has reduced the risk of death due to TB-HIV co-infection by 63.1%. Moreover, completing TB treatment phase, being co-infected with LTBI, and being on CPT had protective effects and thus reduced the risk of TB-HIV mortality by 88.6%, 89.8%, and 60.9% respectively as compared to their prospective comparative groups. Besides to this, a 10 unit increase in baseline CD4 cell count decreased the risk of death due to TB/HIV co-infection by 5.0%. Unlikely, having baseline BMI (<18.5 kg/m²), and being an EPTB (mixed TB) patient increased the risk of death by approximately 143.0%, and 140.0%, respectively (Table 4).

Discussion

The current study was investigated the median survival time, mortality rate, and predictors of mortality among TB/HIV co-infected patients. Consequently, the overall median survival time was 37 months (IQR: 10-63 months). But, it was 9 months among those who developed death. The survival time was higher as compared to similar studies conducted in Brazil, Peru, Ambo Referral hospital, and Bahir Dar [9,12,15,16]. This might be due to the fact that some TB/HIV co-infected patients who were not basically on ART were included in most of these studies.

Based on the event of interest, 70 of 305 (23.0%) of TB/HIV co-infected patients were died with an incidence rate of 5.9 new TB and HIV deaths per 1000 PMs. The mortality rate was nine times higher among those diagnosed with Active TB disease status as compared to those with LTBI. The overall incidence rate in the study is lower than similar study conducted in Bahir Dar [9] which had reported an overall mortality rate of 4.1 new cases per 100 PMs. The discrepancy might be being not on ART for some participants from Bahir Dar contribute a lot for the high incidence of mortality.

However, the Cumulative mortality finding in the study was slightly lower than the results of the studies reported from Peru and not on-ART mortality in Zambia, and Bahir Dar [9,16,17] where cumulative death was above one-fourth in all the studies. However, the magnitude of TB-HIV and related mortality was higher as compared to similar studies conducted in China, Brazil, on ART death in Zambia, on ART death in Bahir Dar, Awassa, Jimma, Ambo, Bahir Dar, and Ethiopia which had been reported 8.1%, 13%, 9%, 18%, 13.5%, 20.2%, 15.8%, 18%, and 15.5% deaths respectively [7,9-13,15,17,18].

The predictors associated significantly with TB/HIV related mortality in the final Cox model were: baseline BMI (<18.5 kg/m², baseline CD4 cell count, presence of drug side effects, being diagnosed with EPTB/Mixed TB, co-infected with LTBI and HIV, completing TB treatment, and being on CPT. Some of them potential risk effect (I.e. baseline BMI (<18.5 kg/m²), and being EPTB or mixed TB patient, whereas, the rest had protective effect against TB/HIV mortality.

Based on the baseline BMI, 59 of 197 (29.9%) of TB/HIV co-infected patients with Baseline BMI (<18.5 kg/m²) were died and hence, it had increased the risk of mortality by approximately 143% keeping the effect of other variables constant. On the other hand, TB/HIV co-infected patients with BMI (<18.5 kg/m²) had approximately

Table 4: Predictors of time to death among TB/HIV co-infected adults on ART at two governmental hospitals in Mekelle, Ethiopia, 2009-2016 (n=305).

Variable	CHR [75% CI]	AHR [95% CI]	P-Value
Baseline BMI (kg/m^2)			
>18.5	1	1	
≤ 18.5	3.617 [2.476, 5.284]	**2.427 [1.214, 4.853]**	0.012*
Baseline functional status			
Working	1	1	
Ambulatory	1.838 [1.324, 2.552]	1.411 [0.768, 2.593]	0.267
Bedridden	3.332 [2.330, 4.766]	1.706 [0.868, 3.356]	0.122
Clinical stage			
I or II	1	1	
III	2.291 [1.136, 4.621]	1.681 [0.490, 5.761]	0.409
IV	3.812 [1.915, 7.587]	1.255 [0.363, 4.340]	0.719
Baseline CD4 count (Cells/mm^3)	0.993 [0.991, 0.995]	**0.995 [0.991, 0.999]**	0.015*
Baseline hemoglobin (g/dl)			
>11.0 (Normal)	1	1	
≤ 11.0 (Anemic)	2.486 [1.884, 3.281]	1.358 [0.801, 2.291]	0.252
ART drug side effects"			
No	1	1	
Yes	0.327 [0.227, 0.470]	0.369 [0.194, 0.701]	0.002*
History of OIs			
No	1	1	
Yes	2.069 [1.343, 3.189]	1.811 [0.839, 3.908]	0.13
TB treatment completion			
No	1	1	
Yes	0.0927 [0.068, 0.127]	**0.114 [0.060, 0.216]**	<0.001*
TB diagnosis			
PTB	1	1	
EPTB/Mixed	2.575 [1.887, 3.515]	**2.400 [1.348, 4.273]**	0.003*
TB type			
Active TB Disease	1	1	
LTBI	0.119 [.0519, 0.271]	**0.102 [0.023, 0.449]**	0.003*
CPT status			
Off	1	1	
On	0.347 [0.258, 0.465]	**0.391 [0.220, 0.697]**	0.001*

1: Reference group; CHR: Crude Hazard Ratio; AHR: Adjusted Hazard Ratio

two times extra risk of death as compared to their comparative groups (BMI ≥ 18.5 kg/m^2). The finding of this study was in line with a study conducted in Lesotho [19], which had reported the risk increment by at least 275%.

Similarly, baseline CD4 cell count was statistically associated with mortality among TB/HIV co-infected patients on ART, which is consistent with other studies conducted in Ambo, Bahir Dar, South Africa, and Malaysia which have all reported the protective effect of increasing CD4 cell count against TB/HIV or related mortality [9,12,20]. This might be due to the fact that high CD4 cell count indicates intact immunity and thus, limiting the occurrence of OIs that speeds up the risk of mortality.

ART drug side effect was also statistically related with TB/HIV co-infected mortality or more associated causes and as a result, more deaths were reported among TB/HIV co-infected patients who were not developed drug side effects. Keeping the effect of other covariates constant, 63.1% of death among TB/HIV co-infected patients was prevented upon the development of drug side effect. This is probably related to the high care seeking behavior and adherence to treatment of TB/HIV co-infected patients among those reported ART drug side effects.

TB diagnosis was statistically associated with mortality due to TB/HIV co-infection mortality and related causes and hence, EPTB /mixed TB increased the risk of mortality by 240%. The finding of our study was in consistent with a study conducted in Bahir Dar, Ethiopia [9] in which persons co-infected with EPTB had increased the risk by 140%. Unlikely, the results of our study was different from the findings of similar study conducted in Ambo Referral Hospital, Ethiopia which had reported PTB patients were 2.33 times more likely to die than EPTB patients [12]. Possible justification for this finding might be EPTB or mixed TB (PTB and EPTB) cases have greater chance to be disseminated to different body organs which may result in treatment failure and finally, leads to multi-drug resistance and mortality.

Half (50.0%) of TB/HIV co-infected patients were died during TB Treatment or before TB treatment completion that was supported by another study conducted in Ethiopia [7], which had reported almost two-third of TB/HIV deaths were during TB treatment. The survival experience of TB/HIV co-infected patients on ART was improved up on the completion of TB treatment phase and the hazard of death among TB/HIV co-infected patients was decreased by 88.6% (AHR=0.114) upon completing TB treatment in relation to the study subjects who were on treatment or not completed their treatment. This might be probably due to the fact that regular completion of TB treatment would be broken the synergistic and bidirectional positive relationship of the two infections.

HIV patients co-infected with LTB at enrollment were less likely to develop death as compared to those co-infected with active TB disease. On the other hand, the TB/HIV or related mortality in the study was minimized by 89.8% (AHR=0.102) despite IPT administration among those co-infected with LTBI. Therefore, the reduced risk of mortality among patients with LTBI could be associated with the role of IPT in preventing LTBI reactivation (active TB disease development) which in turn prevents early mortality among PLWHIV [21].

Finally, the most important predictor variable in the final Cox model was CPT. TB/HIV co-infected patients on CPT had better survival and reduced the risk of mortality by approximately 61%. Our finding was in line with similar studies conducted in Zambia, Lusaka, Uganda, and Bahir Dar [9,17,22,23]. The studies from Zambia, Lusaka and Uganda had reported the protective effect of CPT on all causes of mortality by 90%, 21%, and 46% respectively. On the other hand, the study conducted in Bahir Dar revealed the risk of death being off CPT was increased by 203%. In addition, a systematic review and meta-analysis study had reported the 50% protective effect of CPT among adults co-infected with TB and HIV [24]. The high protective effect of CPT in the study conducted in Zambia might be due to the fact that only TB/HIV co-infected patients with baseline CD4 cell count (>350 cells/mm^3) were included and provision of co-trimoxazole is a minimum standard of care in TB/HIV co-infected persons in Zambia [25]. However, the protective effect of CPT could be its important role in preventing the occurrence of OIs and thus, improves the survival

experience of TB/HIV co-infected patients.

Despite its public health importance, the study had the following limitations because of its retrospective nature. Therefore, variables like adherence to treatment, care seeking behavior, TB drug resistance, and viral loads were not investigated and thus, their effect on TB/HIV or related mortality was not reported. Moreover, there might be also possibility of misclassification based on exposure status as TB/HIV co-infected patients were stratified into LTBI and Active TB disease based on their IPT status and active TB diagnosis. In addition, the deaths were not also attributable to TB/HIV co-infections alone as other causes of death might be seen at the same time.

Conclusion

Almost 1 in 4 (23.0%) of TB/HIV co-infected patients were died during the entire follow up time. HIV patients co-infected with LTBI had better survival as compared to those co-infected with Active TB. Moreover, having low baseline BMI (<18.5 g/dl), Low CD4 cell count, not developing drug side effects, failure to complete TB treatment/being on treatment, and being off CPT were aggravating the risk of mortality among TB/HIV co-infected patients. Thus, TB/HIV co-infected patients, and health care providers are advisable to prevent early mortality up on switching off the potential risk factors identified in the study. Moreover, further prospective studies were recommended to observe the unbiased temporal relationship between exposure status and outcome (mortality) among TB/HIV co-infected patients.

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Ethics Approval

Ethics approval was issued by the research ethics review committee of Mekelle University, College of Health Sciences and the consent to participate was also waived by the ethics review committee since an already existing data were used. However, confidentiality, privacy and anonymity were all assured.

Availability of Data and Materials

The dataset used in this study was not released to public. However, it can be obtained from the corresponding author up on reasonable request.

Authors' Contributions

KEG, the principal investigator, has participated in planning, designing, analyzing the research and preparing the manuscript. HTA and LGG have assisted in planning, designing and analyzing the study. All authors read and approved the final manuscript. AKG participated in data collection, statistical data analysis and write up.

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