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Henry Sohre Kitiabi Mr.
Georgia State University

Lisa Marie Cranmer Dr.
Emory University

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Predictors of TB-mortality among hospitalized HIV-infected children in Kenya

By

Henry Sohre Kitiabi

ABSTRACT

Background: Tuberculosis (TB) is a bacterial disease caused by *Mycobacterium tuberculosis,* resulting in an estimated one million new cases and over 200,000 deaths annually among children. TB is the leading cause of death in HIV-infected children globally (Swaminathan & Rekha, 2010), but few studies have evaluated cofactors of pediatric TB mortality the era ART. We evaluated predictors of TB mortality in a cohort of HIV-infected hospitalized Kenyan children initiating antiretroviral therapy (ART).

Methods: HIV-infected children age ≤12 years were enrolled in four Kenyan hospitals in the Pediatric Urgent Start of HAART (PUSH) trial. Children were ART-naïve and started ART within 2 weeks of enrollment. All children underwent intensified TB case finding at enrollment and were evaluated for TB with symptom screening, physical exam and microbiologic evaluation (two sputum or gastric aspirate samples for AFB, Xpert and culture and one stool Xpert). Children with suspected tuberculosis were treated by hospital clinicians according to Kenyan Ministry of Health guidelines and were followed for six months. We evaluated cofactors of mortality using Kaplan-Meier curves and univariate and multivariate Cox proportional hazard models.

Results: Of 181 ART-naive children enrolled in the study, 14 (8%) had confirmed TB, 81 (45%) had unconfirmed TB, and 86 (47%) had unlikely TB). Overall, mortality was higher among children with confirmed TB compared children with Unlikely TB [HR 3.9, 95% CI 1.50 – 9.97). In multivariate analysis of children with confirmed and unconfirmed TB, higher mortality was observed among participants without anti-TB treatment (aHR 6.5; 95% CI 2.24–18.84; p<0.001), orphans and vulnerable children (OVC) (aHR 4.0; 1.41–11.30; p= 0.009), and children with elevated monocyte-to-lymphocyte ratio >0.378 (aHR 4·5; 1.50 - 13.81; p=0.008).

Conclusion: We observed high mortality among hospitalized HIV-infected children with confirmed TB. Lack of anti-tuberculosis treatment, high monocyte-to-lymphocyte ratio, and OVC status were significant predictors of TB mortality. Earlier identification and treatment of TB/HIV co-infection is urgently needed.

Predictors of TB-mortality among hospitalized HIV-infected children in Kenya

By

Henry Sohre Kitiabi

BSc. Kenyatta University, Nairobi - Kenya

A Thesis Submitted to the Graduate Faculty
of Georgia State University in Partial Fulfillment
of the
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Atlanta, Georgia
30303

APPROVAL PAGE

Predictors of TB-mortality among hospitalized HIV-infected children in Kenya

By

Henry Sohre Kitiabi
Student

Approved:

Prof Richard Rothenberg
Committee Chair

Dr. Lisa Marie Cranmer
Committee Member

04/24/2020
Date of defense

To my loving wife, Maureen Syonthi Linah.

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Author's Statement Page

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Henry Sohre kitiabi

Signature of Author

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INTRODUCTION

1.1 Background

Tuberculosis (TB) is a bacterial disease caused by *Mycobacterium tuberculosis* infecting approximately two billion people, resulting in approximately 1 million annual cases among children (Lawn & Zumla, 2011; WHO, 2018c). TB is a leading cause of death in HIV-infected children globally (Swaminathan & Rekha, 2010). Children more often have more severe forms of disease such as disseminated TB and TB meningitis (CDC, 2014) and high mortality due to immature immunological responses to contain the disease. Diagnosing and confirming TB in children with a laboratory test can be arduous because it is challenging to collect sputum specimens from young children and infants. Additionally, a smaller number of bacteria (paucibacillary disease) is required to cause TB disease in children, which results in low sensitivity of microbiologic testing (Marais, Gie, Hesseling, Obihara, & Nelson, 2004). We studied TB-mortality and its determinants among hospitalized antiretroviral treatment (ART)-naive HIV-infected children in Kenya.

REVIEW OF THE LITERATURE

Epidemiology of TB in Children

TB disease ranks among the top 10 causes of death globally, and is the leading cause of a single infectious agent (*Mycobacterium tuberculosis (Mtb)*), ranking above HIV/AIDS (WHO, 2018a). In 2018, 1.1 million children contracted TB disease globally, and 205 000 child deaths were reported due to TB (including HIV coinfected children) (WHO, 2018b). Pediatric and adolescent TB is challenging to diagnose and many cases are undetected and not treated (Kibel & Hussey, 1990). Children under five years are at higher risk of developing clinical TB after *Mtb* infection and are more likely to develop severe forms of tuberculosis such as tuberculosis meningitis and disseminated tuberculosis (CDC, 2014). Approximately 50% of cases of pediatric TB occur in children less than 5 years old (WHO, 2017). However, studies have shown that the rate of TB progression is highly variable, with the youngest children largely those aged less than two years' experience the greatest risk of severe disease and death (Atalell, Birhan Tebeje, & Ekubagewargies, 2018; Drobac et al., 2012; Jenkins et al., 2017; Marcy et al., 2018).

Burden of TB in Kenya

The true burden of TB in Kenya has not been consistently monitored; the last TB prevalence survey prior to 2015 was conducted six decades ago before independence (MOH & NTLP, 2016). In 2015, the estimated prevalence of all forms of TB for all ages was 426 cases per 100,000 population while the prevalence of bacteriologically confirmed pulmonary TB in the adult population of Kenya was 558 cases per 100,000 population (MOH & NTLP, 2016). A total of 81,518 cases were notified with 83% pulmonary TB cases, of which 45% (36,817) were bacteriologically confirmed. Of notified TB cases, 8.5% were children aged 0 to 14 years (MOH & NTLP, 2016). The 2015 Kenya tuberculosis prevalence survey did not collect data on children below 14 years and the true burden of TB in children may be higher than the estimates of 2016 by the center of health solutions.

Epidemiology of TB/HIV in Kenya

Kenya is categorized by the WHO as a high TB and high TB/HIV burden country (WHO, 2018c). TB disease is the fourth leading cause of death among infectious diseases in Kenya and it is estimated that about thirty-six percent of TB cases remain undetected and untreated (CHSK, 2017). The TB/HIV co-infection rate has been declining over the years from 60% in 2004 to 31% in 2015, while the uptake of antiretroviral therapy among HIV co-infected TB patients has been increasing over time with an uptake of 94% in 2015 (MOH & NTLP, 2016). The primary factor responsible for the enormous TB disease burden in Kenya is the concurrent HIV epidemic. Kenya has an estimated 13,000 new pediatric HIV infections that occur annually (NASCOP, 2014), accounting for 4% of all new pediatric HIV infections globally and 7% of all child deaths (UNAIDS, 2012). The cumulative incidence for HIV/TB was 40,000 among the 51 million population and Incidence rate was 79 cases per 100,000 person years in 2018 (WHO, 2018b).

TB/HIV Mortality in Kenya

According to the World Health Organization, over 95% of tuberculosis-related deaths occur in Less Economically Developed Countries (WHO, 2011) and Kenya is one of those countries. In 2018, cumulative mortality as a result of TB/HIV co-infection was 13,000 cases among the country's 51 million population; mortality rate was 26 cases per 100,000 person years (WHO, 2018b). There is lack of data on epidemiology of TB mortality in children posing a challenge in estimating and comparing incidence and prevalence of TB/HIV mortality in the adult population. However, the high TB/HIV prevalence among Kenyan adults (Enos et al., 2018) puts children at risk of acquiring and dying of the disease.

Kenya has relied on estimates from WHO to extrapolate incidence and case detection rate of TB (MOH & NTLP, 2016). Risk factors for mortality among children on TB treatment in Kenya have not been well-characterized and few studies have evaluated TB/HIV in children in the context of ART. This study sought to evaluate cofactors of TB mortality in a cohort of HIV-infected hospitalized Kenyan children initiating ART initiation.

Cofactors of TB/HIV mortality in Children

a. HIV and Immunosuppression

HIV infection is known to weaken the immune system, increasing the risk and severity of TB in HIV patients (Marais, Gie, Schaaf, et al., 2004).The increased risk of mortality among HIV-infected children being treated for TB has been demonstrated in several studies , with a study from South Africa reporting that TB/HIV co-infected children were approximately seven times more likely to die than HIV-negative children (Osman et al., 2017). Another study from South Africa among infants aged 0-12 months excluding infants with unknown HIV status showed that the relative incidence of pulmonary tuberculosis was 37.8-fold higher among HIV-infected infants, and the relative incidence of disseminated tuberculosis was 23-fold higher among HIV-infected infants (Hesseling et al., 2009). Studies have shown that the degree of immunodeficiency in TB/HIV coinfected children is highly correlated with mortality (Chintu & Mwaba, 2005). HIV-Infected children at WHO HIV stage three or four presenting with severe immunosuppression in Malawi had a higher risk of death than those on Stages one or two (Buck et al., 2013). While specific mechanisms explaining the vulnerability of HIV infected patients to TB disease are not yet fully understood, the risk of active TB rises correlates with depletion of CD4 T-cells. HIV-infected patients in high TB incidence areas have a higher risk of developing TB disease after HIV seroconversion in their first year (Sonnenberg et al., 2005). Low CD4 cell counts are associated with a higher occurrence of extrapulmonary TB, positive mycobacterial blood cultures, and atypical chest radiographic findings, reflecting the inability of the impaired immune response to manage the infection. The crucial role of CD4 T cells in the production of granulomas, and the depletion of such cells with HIV disease progression, may explain the high risk of extra-pulmonary TB (EPTB) and mortality in HIV-positive patients (Naing, Mak, Maung, Wong, & Kassim, 2013).

b. The role of ART

Early initiation of ART reduces mortality risk in HIV-positive patients co-infected with tuberculosis and is therefore recommended, irrespective of CD4 count (WHO, 2013). The aim of ART is to achieve long-term viral load suppression assessed with regular viral load measurements. To the contrary, delayed ART initiation among patients with TB has been shown to be associated with high mortality. TB/HIV co-infected children in Malawi who had never begun ART treatment had a more than three-fold higher likelihood of death compared to those already on ART (Buck et al., 2013). ART, by lowering a person's viral load and restoring the immune system, significantly reduces HIV transmission and TB acquisition. Evidence from two randomized controlled trials and several observational studies in a systematic review and metanalysis showed that initiating ART at CD4 counts ≤ 350 cells/mm^3 significantly reduces mortality, disease progression and the incidence of opportunistic infections, especially TB (Anglemyer et al., 2014). Although access to ART has significantly increased in both developed and developing countries, many patients are still initiating ART late after significant immunosuppression has already occurred.

c. Age

Age is a significant TB risk factor in various biological and social ways. It shapes social status, social relations, and these behavior aspects are critical in the epidemiology of TB which conforms to population age structure as countries experience demographic shifts (Toru Mori & Chiu, 2010). Several studies have shown that children under the age of five years are at higher risk of developing clinical TB after infection and are more likely to develop severe forms of TB such as TB meningitis and disseminated TB (CDC, 2014; Nelson & Wells, 2004) especially if not protected by Bacillus Calmette-Guérin (BCG) vaccination (Marais, Gie, Hesseling, et al., 2004). Younger age (<2 years) has been associated with over 5-fold increased risk of mortality in HIV-infected children (Marcy et al., 2018). Individuals in different age strata shape the transmission patterns of TB and inform potential implications for the design of age-focused epidemiological interventions.

d. Poverty

Tuberculosis has historically been associated with high levels of poverty and its transmission is enhanced by poor living condition (Bhunu, Mushayabasa, & Smith, 2012). Poverty-stricken people lack food, stable income, access to healthcare, water and sanitation (WHO, 2005). Extreme poverty is predominant among certain subgroups of the population and may be associated with other political and social issues. Vulnerability can emerge from several fronts, including exclusion from access to opportunities and services as a result of education, income, race, gender, ethnic religious

affiliation or underlying help-seeking behavior common among orphans and vulnerable children. UNICEF found out that as of 2015, 13.4 million children and adolescents aged 0 - 17 years in the world had lost one or both parents due to AIDS and at least 80% (10.9 million) of these children live in sub-Saharan Africa (UNICEF 2016)**.** Kenya is one of the sub-Saharan countries facing this significant socio-economic challenge, with 46% of its citizens living below the poverty line (UNICEF 2016) without proper housing and a considerable proportion living in slums and informal settlements. A study in Nigeria found that children living in high-density areas and slum settlements are at high risk for getting TB with nearly half-million new cases are reported each new year (Morrison, Pai, & Hopewell, 2008). Like any other privileged children, orphans and vulnerable children require care and support. However, many families struggle to finance health services. Several studies found that orphaned and vulnerable children lived disproportionately in the poorest households and are more likely to be underweight (Lindblade, Odhiambo, Rosen, & DeCock, 2003; Watts et al., 2007).

e. Nutrition

Malnutrition and TB occur at higher frequency in low- and middle-income countries and have a synergistic relationship affecting child mortality. According to the WHO, these countries account for 95% of malnutrition cases and deaths from tuberculosis (WHO, 2018b). WHO also states that malnutrition is an important risk factor for childhood tuberculosis although there are limited studies to explain the association (WHO, 2006) in part because of the difficult in diagnosing pediatric tuberculosis and the challenge in establishing a causal role of malnutrition on tuberculosis (Jaganath & Mupere, 2012). However, children who are malnourished are more likely to acquire TB and have poor TB outcomes based on available research

f. Disease Severity

Clinical and laboratory markers that indicate higher bacterial burden have been associated with TB mortality. Radiologically severe TB can be defined as evidence of complications resulting from typical radiologic manifestations of TB (including cavities, nodal airway obstruction, expansile pneumonia), or bilateral parenchymal involvement, or overall parenchymal involvement more extensive than the total area of the right upper lobe, and or disseminated (miliary) TB (Walters et al., 2017; Wiseman et al., 2012). An increased risk of mortality was seen among children with miliary TB on chest X-ray (Marcy et al., 2018). Despite major developments in diagnostic methods in the past years with the invention of automated molecular assays, TB treatment response is still evaluated using conventional microbiological techniques such as smear

microscopy and sputum culture. Time to culture positivity can be used as a measure of bacterial burden and disease severity (Bark et al., 2011). Smear microscopy has been shown to reflect the extent of disease progression, with greater smear grades being associated with the presence of cavitary lesions as well as a more extensive lung involvement (Ralph et al., 2010).

g. Monocyte to Lymphocyte ratio

Monocytes cells are considered as the target cells of *Mycobacterium tuberculosis*, while lymphocytes are the central effector cells of TB immunity (Naranbhai et al., 2015). Elevated monocyte-to-lymphocyte ratio has been identified as a risk factor in the development of TB disease in HIV co-infected children (Sibley et al., 2019) and has been associated with diagnosis of several diseases; including Hepatitis B (Zhang et al., 2015), HIV (Naranbhai et al., 2014) and tuberculosis (Naranbhai et al., 2014). Elevated monocyte lymphocyte ratio is associated with active TB and may reflect bacterial burden in adults; among HIV-infected children a monocyte-to-lymphocyte ratio of (> 0.378) was associated with TB diagnosis (Choudhary et al., 2019). The monocyte lymphocyte ratio could also be an indicator of treatment response, as demonstrated in a cohort of Chinese adults with tuberculosis (Wang et al., 2015). Of note, monocyte-to-lymphocyte ratio has not yet been evaluated as a predictor of TB mortality.

h. Anti-tuberculosis treatment

TB treatment aims to kill mycobacteria, rapidly stop transmission, and prevent relapse (WHO, 2006). Currently, treatment of tuberculosis involves multiple antibiotics, guided by antibiotic susceptibility testing when available. TB treatment in Kenya is provided free of charge at all public health facilities in Kenya; however, TB continues to be a major health problem and children remain at an increased risk. A significant number of children with TB seeking services at health facilities are not diagnosed due to the low index of suspicion by health care workers (CHSK, 2017). Taking a careful history is essential to explore possible TB exposure, prior TB treatment and to perform adequate symptom characterization (Marais & Schaaf, 2014) to provide unique insight into events following primary *Mycobacterium tuberculosis* infection. According to the CDC, people with recent TB disease infection are at a higher risk of developing TB disease than those who have never had the disease. In Nigeria, a study demonstrated that children who had a history of prior TB treatment of either extra-pulmonary or both extra-pulmonary had a higher risk of death compared to those with no history of TB treatment (Adamu et al., 2017).

2.1 Study Aims

There is a lack of data on epidemiology of TB mortality in children in Kenya and few studies have evaluated TB/HIV in children in the context of ART initiation. Our primary aim is to evaluate cofactors of TB mortality in a cohort of HIV-infected hospitalized Kenyan children initiating ART.

METHODOLOGY

3.1 Study population and procedures

We performed a secondary analysis of data from the Pediatric Urgent Start of HAART (PUSH) randomized clinical trial of delayed (<48 hours) versus urgent (7-14 days) ART initiation among ART-naïve hospitalized children age <12 years in Kenya from April 2013 – December 2015 (NIH R01 HD023412). Children with suspected central nervous system infection (meningitis, encephalitis or other) were excluded from this study. Children underwent intensified TB case finding and were evaluated for TB with symptom screening, physical exam and microbiologic evaluation (two sputum or gastric aspirate samples for AFB, Xpert and culture and one stool Xpert). TB was categorized based on NIH 2015 consensus criteria for confirmed, unconfirmed, and unlikely TB (Graham et al., 2015). Children with suspected tuberculosis were treated by hospital clinicians according to Kenyan Ministry of Health guidelines and were followed for six months. We evaluated cofactors of TB mortality in this cohort. All data received for this analysis are de-identified and do not contain any HIPPA-protected identifiers.

3.2 Statistical analysis

TB mortality was the main outcome of interest, with time from enrolment used in the survival analysis. Follow-up was either until death, loss to follow-up, study withdrawal, or the final study visit at six months, based on which took place first. We described patients' baseline characteristics between TB classification groups. For all children in the study, we estimated the probability of survival by Kaplan-Meier survival analysis and used the log-rank test to compare survival across the three tuberculosis strata as well as ascertain the effect of anti-tuberculosis treatment. We then restricted our analysis to children with confirmed or unconfirmed TB to determine predictors of TB-related mortality. We included variables of interest identified previously as predictors of TB mortality [age, residence classification groups, WAZ, CD4% Log10 HIV-RNA, TB treatment and, prior TB treatment] as well as exploratory variables (OVC status, elevated monocyte-to-lymphocyte ratio >0.378). We entered all variables with a p-value of less than 0.10 into the

multivariate model to identify independent correlates of mortality through the stepwise entry selection of explanatory variables into the model. We considered p-value of less than 0.05 as significant. All analyses were done with SAS software version 9.3 (SAS (r) Proprietary Software 9.3 (TS1M2) Licensed to GEORGIA STATE UNIVERSITY - SFA T&R, Site 70095374).

RESULTS

181 HIV-infected hospitalized ART naïve children were enrolled in the study between April 2013 and May 2013. Of these, 119 (66%), were underweight, and 125 (69%) were severely immunocompromised. Overall, 14 (8%) children had confirmed TB, 81 (45%) had unconfirmed TB and 86 (47%) had unlikely TB. (Table 1). Of the 181, 63 children (35%) started anti-tuberculosis treatment; [11/14 (79%) confirmed, 47/81 (58%) unconfirmed and 5/86 (6%) unlikely TB. Table 1 highlights the baseline characteristics by TB classification groups against mortality. There are significant differences among children who died and those who survived based on the TB classification groups. Significant differences were observed based on Age, WAZ, WHZ, MLR and, log10 HIV-RNA ($p<0.05$). Table 2 highlights baseline characteristics by pooled Confirmed and Unconfirmed TB versus unlikely TB against mortality. Significant differences were observed among children who died and those who survived based on these comparison groups. The differences were seen for Age, WAZ,WHZ, MLR and, Log10 HIV-RNA ($p<0.05$). Median follow-up was 5.6 (IQR 4.2–5·7) months. Overall 6-month mortality was 39 (22%) and most deaths occurred in the first 2 months of follow up. Overall survival probability was lowest among confirmed TB at 50% (7 deaths) compared with unlikely tuberculosis at 76% (21 deaths) and unconfirmed tuberculosis at 86% (11 deaths). There was a significant difference in survival time across the three TB classification groups after 6 months of follow up (Log rank p-value = 0.012**)** as shown in figure 2**.** Not receiving anti-tuberculosis treatment was associated with a significantly increased mortality among children with confirmed and unconfirmed tuberculosis (log-rank $p < 0·03$) as shown in Figure 3. There were significant differences between children who died and those who survived among those who did not receive ant-tuberculosis treatment based on various baseline characteristics including: age, OVC status, Weight-for-age Z-score, Weight-for-height Z-score, malnutrition status, WHO stage 3&4, MLR and log 10 HIV-RNA as shown in Table 3. In Univariate analysis, confirmed tuberculosis was associated with mortality (table 4). Confirmed tuberculosis was associated with a four-times increase in the risk of death compared with unconfirmed tuberculosis (Hazard Ratio 3.90, 95% CI 1.5 – 9.97; p-value 0.005).

Additional factors associated with increased TB-mortality were OVC status (Hazard Ratio 3.15, 1.22 – 8.13; p-value 0.04); lack of anti-TB treatment (Hazard Ratio 2.70, 95% CI 1.10 – 6.81; p-value 0.02) and monocyte-to-lymphocyte ratio greater than 0.378 (Hazard Ratio 4.33, 95% CI 1.70 – 11.20; p-value 0.002). The association between confirmed TB and mortality disappeared after stepwise entry of monocyte to lymphocyte ratio, OVC, and Tuberculosis diagnosis and treatment variables into the multivariate model. Cofactors independently associated with increased TB-mortality, therefore, include Orphans and Vulnerable Children (Adjusted Hazard Ratio 4.00, 95% CI 1.41 – 11.30; p-value 0.009), lack of TB treatment (Adjusted Hazard Ratio 6.50, 95% CI 2.24 – 18.84; p-value 0.0006), and monocyte-to-lymphocyte ratio greater than 0.378 (Adjusted Hazard Ratio 4.54, 95% CI 1.50 – 13.81; p-value 0.008).

DISCUSSION

We found high TB mortality in our cohort of hospitalized HIV-infected children, despite access to anti-tuberculosis treatment and ART. The overall 6-month mortality among children with confirmed and unconfirmed TB was 19% (18/95), with corresponding mortality rate of 2.3 per 100 person-years. All reported deaths occurred early, within the first two months of follow-up. Our findings were similar to a recent Ethiopian study of hospitalized TB/HIV co-infected children on ART reporting 14.02% mortality and mortality rate of 3.27 cases per 100 child-years (Atalell et al., 2018). Our cohort shared many similarities to this Ethiopian study, including a high proportion of children who were immunosuppressed with underlying malnutrition. We observed a lower mortality compared to a Nigerian cohort of TB/HIV co-infected children who were not on ART, who reported 42% mortality (5.1 cases per 100 person years) (Adamu et al., 2017). Our lower mortality may be due to our exclusion of CNS involvement, as the Nigerian cohort included children with extrapulmonary TB, as well as the effect of ART. To our knowledge, this is the first study addressing predictors of TB mortality in hospitalized HIV-infected Kenyan children starting ART. Mortality was higher in children with confirmed tuberculosis than in those with unconfirmed and unlikely tuberculosis. Our results were consistent with a study among TB/HIV co-infected children in Burkina Faso, Cameroon, and Nigeria (Adamu et al., 2017; Marcy et al., 2018). The high mortality observed in confirmed tuberculosis, even though children had access to treatment could be as a result of higher bacterial burden and disease severity with greater bacillary loads (Marcy et al., 2018).

In HIV-infected children with TB disease, initiation of TB treatment is a priority, but the optimal timing for the initiation of ART during TB treatment is unknown (WHO, 2010). Treatment outcomes in children are improved if treatment is initiated promptly and adherence is maintained until completion. The presentation of TB disease in infants may be more acute, resembling severe acute pneumonia, and should be suspected when there is poor response to antibiotics. Initiating anti-tuberculosis treatment without bacteriologic confirmation diagnosis TB may require first putting children on antibiotics to treat pneumonia and, after that, diagnosing TB only after ruling other possible diagnoses (Onyango, Yuen, Masini, & Borgdorff, 2018). In this study, the decision to treat was not done by the study clinicians. The results were shared with the hospital staff for patients who were confirmed with TB. Most cases who did not receive treatment were too sick and may have be treated but, in some cases, there was not enough time to treat prior to death. The failure to treat in time supports the fact that sometimes clinicians do not recognize TB early and are presented later with cases that are too sick to have good treatment outcomes. We hypothesized that children initiated on anti-TB treatment had better treatment outcomes because they experienced a significant bacteriological burden reduction. Clinical features suggestive of tuberculosis disease that were present at baseline had improved, and there was no new clinical feature suggestive of tuberculosis. Similarly, tolerability to ART treatment might have reduced the degree of immunodeficiency building a stronger immune system that may explain the drastic decrease in mortality after the second month of follow up. Monocyte to lymphocyte ratio previously has been identified as a risk factor in the development of TB disease in HIV in co-infected children and individuals undergoing treatment (Sibley et al., 2019). The association between the monocyte-to-lymphocyte ratio and the risk of developing mycobacterial infections was first seen in rabbits in the 1920s (Cunningham R., Sabin F., Sugiyama S., Kindwall J., & J., 1925; Sabin F. R., Doan C.A., & S., 1926). They demonstrated that the MLR in peripheral blood could reflect the magnitude and progress of TB disease in rabbit models. Recently, several published studies suggest that the elevated MLR may be associated with the risk of active tuberculosis in infants, and in postpartum women infected with HIV (Naranbhai et al., 2014). A prior study in this same cohort of HIV-infected children showed that elevated monocyte lymphocyte ratio above 0.378 was associated with active TB (Choudhary et al., 2019).

Studies have shown that continued replication of the pathogen may result to progression to pulmonary disease and possible dissemination to extra-pulmonary site.

Dissemination of this disease results in severe forms of TB disease and death (CDC, 2014). We hypothesized that elevated monocyte-to-lymphocyte ratio reflected an increased bacteriological burden, and inadequate immune responses may have resulted in death. Tuberculosis transmission has been influenced dramatically by poor living conditions, and vulnerability may be a consequence of multifactorial, including socio-economical, environmental, and biological factors. Orphans and vulnerable children are part of the many community subpopulations that are most times disproportionately affected by TB. These groups of children with TB and HIV often experience severe economic barriers to health care, especially meeting expenses related to diagnosis and treatment. Several studies found that orphaned and vulnerable children lived unfairly in the poorest households and are more likely to be underweight (Lindblade et al., 2003; Watts et al., 2007). All these barriers synergistically aggravate economic challenges and prevent or delay diagnosis, treatment, and successful outcomes, resulting in increased transmission, morbidity, and mortality. We hypothesized that poor treatment adherence may result from socio-economic hardships, which may be essential determinants contributing to low cure rates and high risk of death among poor and vulnerable groups (Storla, Yimer, & Bjune, 2008) but we haven't assessed this association among the OVC in this study. Both poor geographical and financial access to health services synergistically prevent or delay health-seeking among people with TB, especially the poorest (Munro et al., 2007; Storla et al., 2008) and OVC and could experience late diagnosis because of socio-economic challenges.

CONCLUSION

Our study observed high TB mortality among hospitalized HIV-infected children starting ART. Lack of anti-tuberculosis treatment, high monocyte-to-lymphocyte ratio, and OVC status were significant predictors of TB mortality. We recommend earlier identification and treatment of TB/HIV co-infection. Future studies to identify reasons for delays in diagnosis and treatment initiation are needed, and evidence-based interventions will require the involvement of various stakeholders including the Ministry of Health of Kenya, policy makers and public health agencies.

Table 1: Baseline patient characteristics by TB classification for the overall cohort (N=181)

Patients' Characteristics	Confirmed TB Median (IQR) or n (%)			Unconfirmed TB Median (IQR) or n (%)			Unlikely TB Median (IQR) or n (%)		
	Died (N=7)	Survived (N=7)	p-value	Died (N=11)	Survived (N=70)	p-value	Died (N=21)	survived (N=65)	p-value
Age in years	6.60 (0.60 – 7.71)	4.04 (1.30 – 6.14)	0.65	1.29 (0.48 – 2.00)	2.04 (1.22 – 5.07)	0.05	1.16 (0.49 – 1.65)	2.10 (0.90 – 6.15)	0.006
Residence Nairobi	7 (100)	3 (43)	0.07*	5 (45)	34 (49)	0.85	13 (62)	27 (42)	0.10
Gender Male	4 (57)	5 (71)	1.00*	6 (55)	37 (53)	0.92	13 (62)	35 (54)	0.52
OVC status Yes	5 (71)	5 (71)	1.00*	5 (45)	52 (75)	0.07*	9 (43)	22 (34)	0.45
Weight-for-Age Z score	-4.49 (-5.18, -1.26)	-2.70 (-4.14, -1.26)	0.48	-3.50 (-4.62, -2.70)	-3.32 (-4.27, -2.10)	0.57	-3.23 (-4.19, -2.10)	-1.86 (-2.72, -0.82)	0.002
Weight-for Height Z score	-3.64 (-4.26, -2.61)	-1.98 (-2.31, -1.88)	0.18	-2.96 (-3.58, -2.70)	-2.98 (-4.16, -1.56)	0.44	-2.51 (-3.49, -0.90)	-0.94 (-2.10, 0.38)	0.004
Height-for-Age Z score	-2.79 (-3.80, -2.10)	-1.79 (-2.46, -0.77)	0.15	-2.44 (-3.62, -1.68)	-3.04 (-4.07, -1.59)	0.53	-2.40 (-4.01, -1.35)	-2.11 (-3.32, -0.74)	0.14
Malnourished? Yes	1 (14)	4 (57)	0.27*	6 (55)	28 (40)	0.51*	7 (33)	12 (18)	0.22*
Have Pneumonia? Yes	6 (86)	5 (71)	1.00*	8 (73)	55 (79)	0.71*	9 (43)	31 (48)	0.70*
WHO HIV Stage 3 & 4	7 (100)	7 (100)	–	10 (91)	51 (74)	0.44*	14 (67)	35 (54)	0.30
Monocyte-Lymphocyte Ratio	0.56 (0.40 – 0.67)	0.40 (0.23 – 0.82)	0.48	0.29 (0.23 – 0.59)	0.21 (0.15 – 0.35)	0.02	0.55 (0.24 – 0.65)	0.20 (0.14 – 0.33)	0.002
CD4%	11.80 (4.00 –25.20)	11.00 (6.00 – 15.00)	0.61	15.60 (3.60 – 25.63)	13.00 (8.90 – 19.20)	0.82	12.00 (7.80 – 18.00)	18.00 (11.00 – 24.50)	0.08
Severely Immuno-suppressed? Yes	4 (57)	6 (86)	0.56*	8 (73)	51 (74)	1.00*	17 (81)	39 (60)	0.08
Log 10 HIV-RNA	5.52 (4.92 – 5.61)	5.65 (5.37 – 5.75)	0.32	5.94 (5.51 – 6.51)	5.59 (5.01 – 6.25)	0.17	6.27 (5.91 – 6.71)	5.59 (4.86 – 6.09)	0.0002
Hemoglobin (g/dL)	8.80 (7.90 – 10.90)	6.90 (5.30 – 8.90)	0.11	8.10 (7.90 – 9.20)	8.90 (7.90 – 10.0)	0.56	9.60 (7.80 – 10.2)	8.70 (6.90 – 9.60)	0.07
Have Anemia? Yes	2 (29)	2 (29)	1.00*	3 (27)	7 (10)	0.13*	5 (24)	23 (35)	0.33

Is TST Negative?			1.00*			1.00*		0.21
Yes	6 (100)	6 (86)		5 (100)	59 (91)		15 (94)	61 (100)	
HAART Initiation			1.00*			0.92		0.54
Urgent (< 2 days)	4 (57)	3(43)		6 (55)	37 (53)		11 (52)	29 (45)	

*Fisher exact test Abbreviations: IQR – Interquartile range

Table 2: Baseline patient characteristics by TB classification for the overall cohort (N=181)

Patient's Characteristics	Confirmed TB + Unconfirmed TB Median (IQR) or n (%)			Unlikely TB Median (IQR) or n (%)		
	Died (N=18)	Survived (N=77)	p-value	Died (N=21)	Survived (N=65)	p-value
Age in years	1.51 (0.60 – 3.84)	2.05 (1.26 – 5.07)	0.21	1.16 (0.49 – 1.65)	2.10 (0.90 – 6.15)	0.006
Residence Nairobi	12 (67)	37 (48)	0.15	13 (62)	27 (42)	0.10
Gender Male	10 (56)	42 (55)	0.94	13 (62)	35 (54)	0.52
OVC status Yes	11 (61)	22 (29)	0.01	9 (43)	22 (34)	0.45
Weight-for-Age Z-score	-3.73 (-4.75, -2.70)	-3.29 (-4.29, -1.97)	0.32	-3.23 (-4.19, -2.10)	-1.86 (-2.72, -0.82)	0.002
Weight-for-Height Z-score	-2.61 (-3.51, -1.32)	-2.45 (-3.81, -1.15)	0.89	-2.51 (-3.49, -0.90)	-0.94 (-2.10, 0.38)	0.004
Height-for-Age Z-score	-2.96 (-3.69, -2.40)	-2.55 (-3.71, -1.41)	0.14	-2.40 (-4.01, -1.35)	-2.11 (-3.32, -0.74)	0.14
Malnourished? Yes	7 (39)	32 (42)	0.84	7 (33)	12 (18)	0.22*
Have Pneumonia? Yes	14 (78)	60 (78)	0.99	9 (43)	31 (48)	0.70*
WHO HIV Stage 3 & 4	17 (94)	58 (76)	0.11	14 (67)	35 (54)	0.30
Monocyte-lymphocyte ratio	0.44 (0.26 – 0.59)	0.21 (0.15 – 0.36)	0.003	0.55 (0.24 – 0.65)	0.20 (0.14 – 0.33)	0.002
CD4% at enrollment	15.10 (4.00 – 25.20)	13.00 (8.45 – 19.10)	0.76	12.00 (7.80 – 18.00)	18.00 (11.00 – 24.50)	0.08
Severely Immuno-suppressed? Yes	12 (67)	57 (75)	0.55*	17 (81)	39 (60)	0.08
Log 10 HIV VL	5.59 (5.44 – 6.33)	5.59 (5.03 – 6.19)	0.54	6.27 (5.91 – 6.71)	5.59 (4.86 – 6.09)	0.0002
Hemoglobin (g/dl)	8.50 (7.90 – 9.80)	8.80 (7.70 – 9.90)	0.94	9.60 (7.80 – 10.2)	8.70 (6.90 – 9.60)	0.07
Have Anemia? Yes	5 (28)	9 (12)	0.13*	5 (24)	23 (35)	0.33

				1.00*			0.21
Is TST Negative?	Yes	20 (95)	120 (95)		15 (94)	61 (100)	
HAART Initiation				0.78			0.54
Urgent (< 2 days)		10 (56)	40 (52)		11 (52)	29 (45)	

*Fisher exact test Abbreviations: IQR – Interquartile range

Table 3: Baseline patient characteristics by Treatment status for the overall cohort (N=181)

Characteristics	TB Treatment Median (IQR) or n (%)			No TB Treatment Median (IQR) or n (%)		
	Died (N=11)	Survived (N=52)	p-value	Died (N=28)	Survived (N=85)	p-value
Age in years	2.00 (1.34 – 7.19)	2.10 (1.23 – 6.12)	0.90	1.01 (0.42 – 1.78)	2.04 (0.90 – 5.10)	0.002
Residence Nairobi	9 (82)	19 (37)	0.008	16 (57)	47 (55)	0.62
Gender Male	5 (45)	26 (50)	0.78	18 (64)	53 (58)	0.40
Is the child OVC? Yes	7 (64)	20 (39)	0.19	13 (46)	24 (28)	0.08
Weight-for-Age Z-score	-3.04 (-4.98, -2.12)	-3.65 (-4.67, -2.05)	0.88	-3.34 (-4.55, -2.13)	-2.02 (-2.88, -1.14)	0.001
Weight-for-Height Z-score	-2.65 (-3.64, -0.52)	-3.09 (-4.08, 1.51)	0.42	-2.54 (-3.50, 0.98)	-1.02 (-2.27, 0.59)	0.002
Height-for-Age Z-score	-3.13 (-4.07, -2.15)	-2.53 (-3.56, -0.95)	0.32	-2.71 (-3.76, -1.48)	-2.24 (-3.44, -1.15)	0.25
Malnourished? Yes	3 (27)	26 (50)	0.17	11 (39)	17 (20)	0.04
Have Pneumonia? Yes	10 (91)	43 (83)	0.68*	13 (46)	45 (53)	0.55
WHO HIV Stage 3 & 4	11 (100)	43 (84)	0.33*	20 (71)	45 (53)	0.09
Monocyte-lymphocyte ratio	0.56 (0.29 – 0.68)	0.25 (0.15 – 0.38)	0.009	0.44 (0.23 – 0.62)	0.20 (0.13 – 0.29)	0.0002
CD4% at enrollment	10.00 (3.00 –25.00)	12.90 (6.00 – 19.00)	0.80	14.78 (6.50 – 21.90)	16.10 (10.00 – 24.00)	0.29
Severely Immuno-suppressed? Yes	8 (73)	40 (78)	0.70*	21 (75)	53 (62)	0.22
Log 10 HIV VL	5.97 (5.52 – 6.56)	5.71 (5.30 – 6.30)	0.40	6.09 (5.57 – 6.60)	5.56 (4.75 – 6.05)	0.001
Hemoglobin (g/dl)	8.90 (7.90 – 11.40)	8.85 (7.95 – 9.75)	0.37	8.85 (7.85 – 10.00)	8.70 (6.90 – 9.80)	0.31

Have Anemia?	Yes	4 (36)	7 (13)	0.09*	6 (21)	23 (27)	0.55
Is TST Negative?	Yes	9 (100)	46 (94)	1.00*	17 (94)	79 (98)	0.46*
HAART Initiation				0.48			0.79
Urgent (< 2 days)		7 (64)	27 (52)		14 (50)	40 (47)	

*Fisher exact test Abbreviations: IQR – Interquartile range

Table 4: Factors associated with TB-mortality among ART-Naïve Kenyan children (N = 95)

	Univariate analysis		**Multivariate analysis**	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Patients' Tuberculosis Status		**0.005**		0.17
Confirmed tuberculosis	3.90 (1.50 – 9.97)		2.34 (0.70 – 7.91)	
Unconfirmed tuberculosis	Ref			
Tuberculosis diagnosis and treatment		**0.04**		**0.0006**
Did not receive TB Treatment	2.70 (1.10 – 6.81)		6.50 (2.24 – 18.84)	
Received TB treatment	Ref		Ref	
Prior Pulmonary TB Treatment	1.72 (0.50 – 5.95)	0.40	-	-
Yes	Ref			
No				
Age in years		0.60	-	
Less than 5 years	1.40 (0.45 – 4.14)			
5 to 12 years	Ref			
Residence		0.20	-	-
Nairobi	1.91 (0.72 – 5.10)			
Kisumu	Ref			
Orphans or Vulnerable Children Status		**0.02**		**0.009**
Yes	3.15 (1.22 – 8.13)		4.00 (1.41 – 11.30)	
No	Ref		Ref	
Weight-for-Age Z-score		0.42	-	-
Less than –2SD	1.67 (0.48 – 5.80)			
Greater or equal to –2SD	Ref			
Weight-for-Height Z-score		0.85		-
Less than –2SD	1.10 (0.39 – 3.10)		-	
Greater or equal to –2SD	Ref			
Monocyte-to-Lymphocyte Ratio		**0.002**		**0.008**
Greater than 0.378	4.33 (1.70 – 11.20)		4.54 (1.50 – 13.81)	
Less than or equal to 0.378	Ref		Ref	
Hospitalized due to Malaria		0.64	-	-
Yes	0.62 (0.08 – 4.65)			
No	Ref			
CD4 Percentage		0.56	-	-
Less or equal to 15%	1.31 (0.52 – 3.31)			
More than 15%	Ref			
Log10-HIV-RNA		0.55	-	-
More than 5-log10	0.74 (0.28 – 1.97)			
Less or equal to 5-log10	Ref			
Severely immunocompromised		0.51	-	-
Yes	0.72 (0.27 – 1.92)			
No	Ref			

Analysis Flow Chart

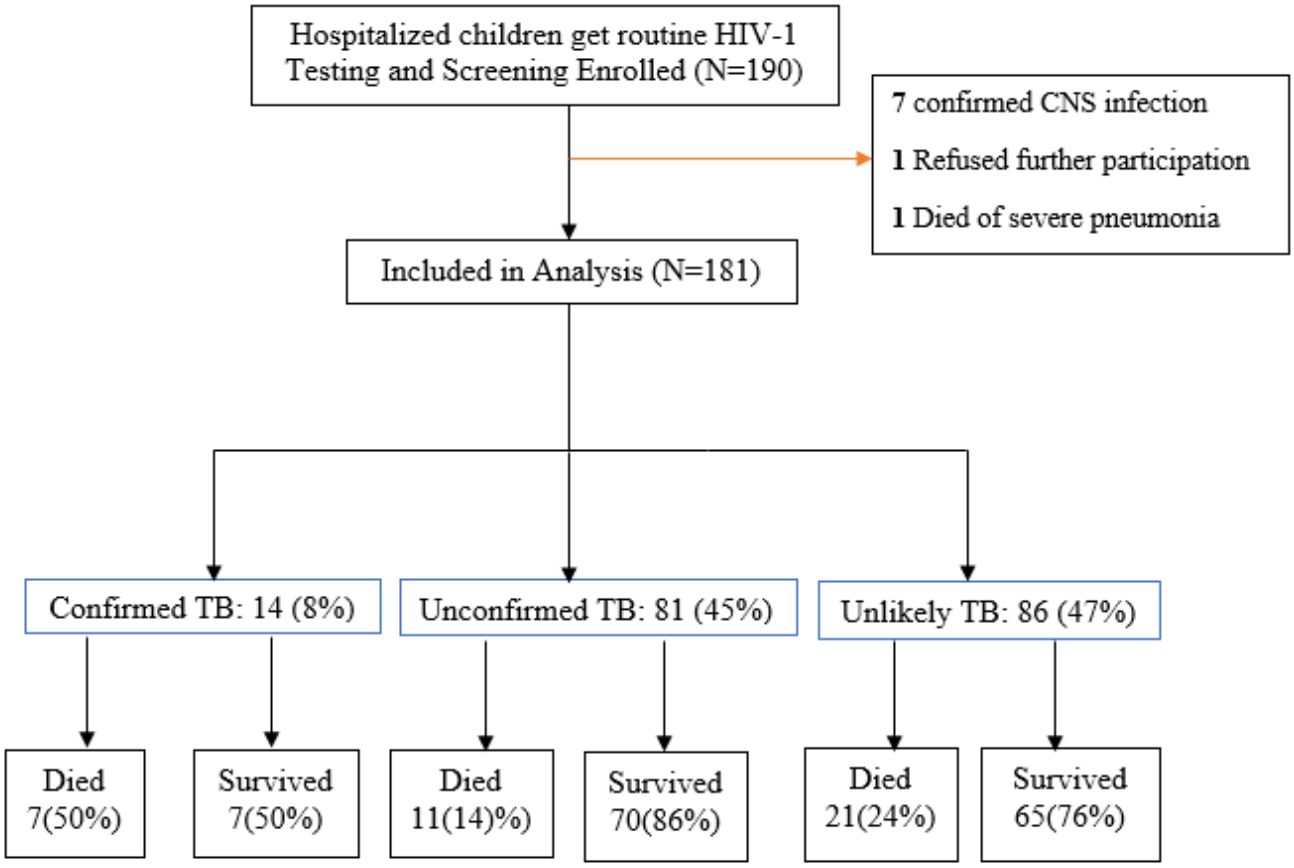

Figure 1: Kaplan-Meier survival estimates for the overall antiretroviral therapy-naive cohort

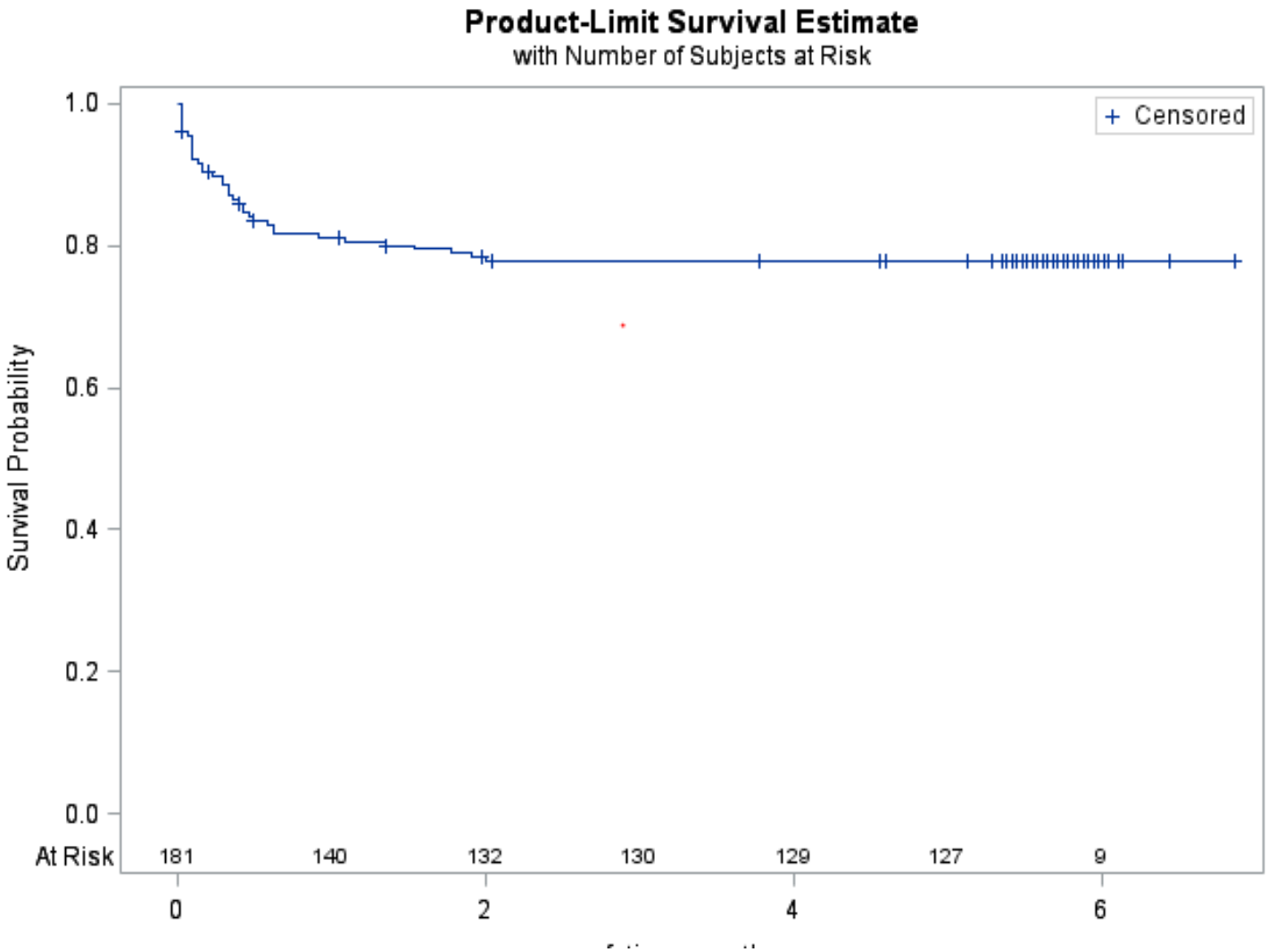

Figure 2: Kaplan-Meier survival analysis on time to death by TB classification groups

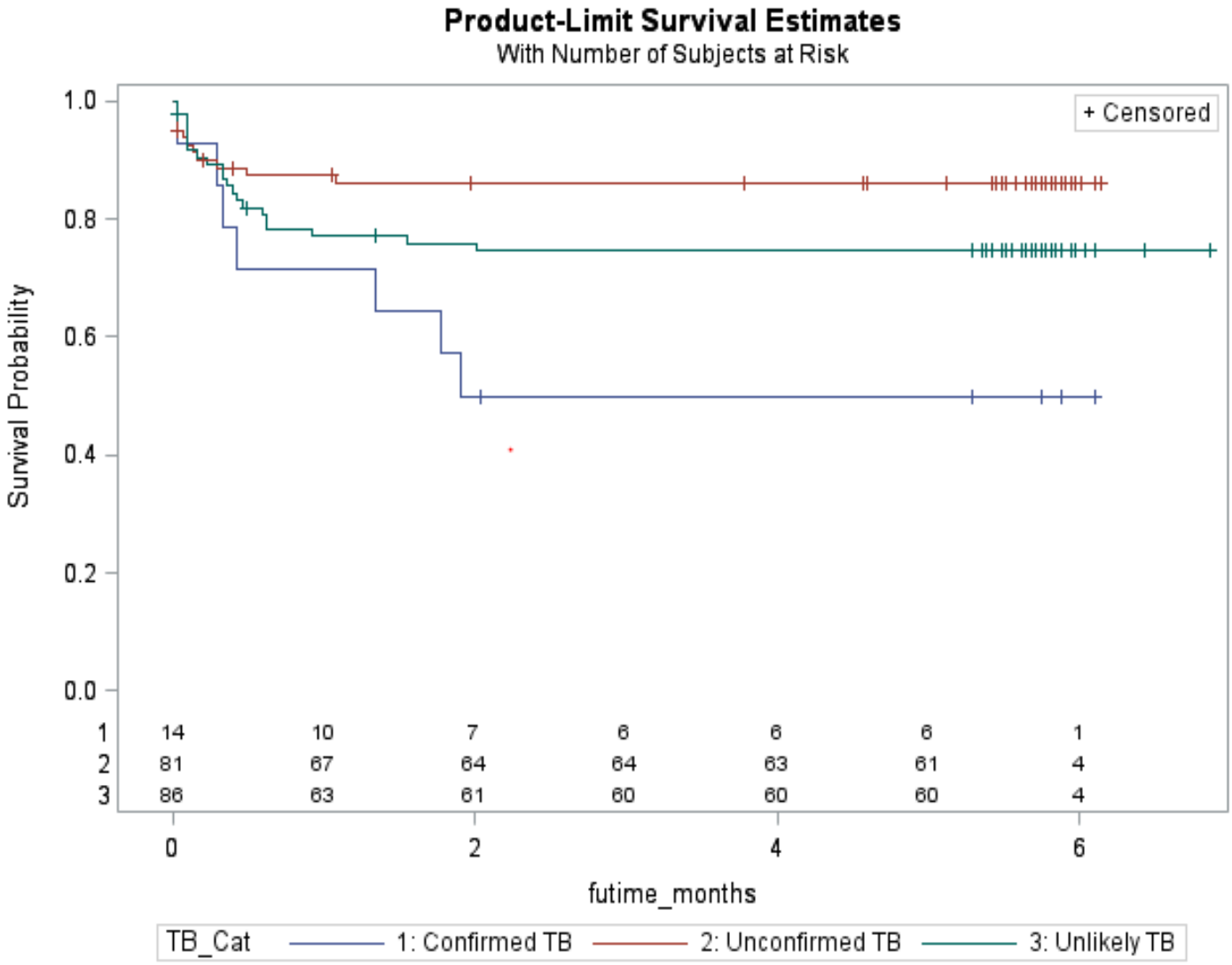

Fig 2: There is a significant difference in survival time across TB classification groups in 6.6 months of follow up (**Log rank p-value = 0.012).**

Figure 3: Kaplan-Meier survival analysis on time to death by Anti-TB treatment Status

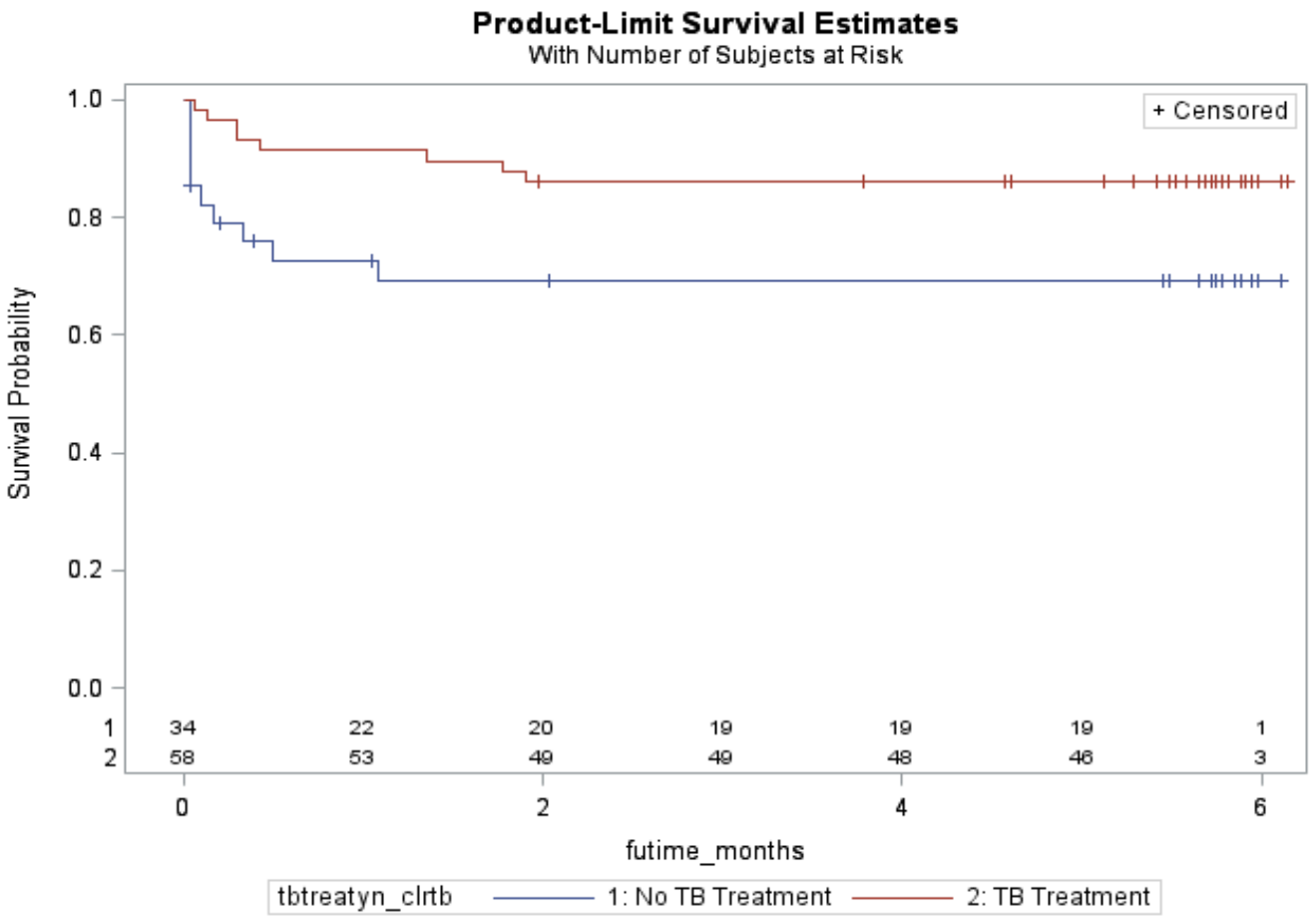

Fig. 3: Anti-tuberculosis treatment was associated with significantly increased survival in a pooled cohort of children with either confirmed and or unconfirmed tuberculosis. **(log-rank p<0·03**).

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APPENDICES

Table 5: Supplementary table on baseline patient characteristics by mortality

Patient's Characteristics	Died (N=39) Median (IQR) or n (%)	Survived (N=142) Median (IQR) or n (%)	P-Value
Age in years	1.29 (0.49 – 2.14)	2.05 (1.15 – 5.95)	0.003
Residence - Nairobi	19 (49)	70 (49)	0.95
Gender - Male	22 (56)	78 (55)	0.87
OVC - Yes	20 (51)	44 (31)	0.02
Weight-for-Age Z-score	-3.35 (-4.62, -2.12)	-2.51 (-3.65, -1.36)	0.02
Weight-for-Height Z-score	-2.55 (-3.51, 0.90)	-1.57 (-3.03, -0.20)	0.09
Height-for-Age Z-score	-2.80 (-3.82, -1.75)	-2.32 (-3.42, -1.15)	0.12
Malnourished? - Yes	15 (38)	43 (30)	0.33
Have Pneumonia? Yes	23 (59)	91 (64)	0.56
WHO HIV Stage 3 & 4	31 (79)	93 (66)	0.11
MLR at enrollment	0.45 (0.24 – 0.65)	0.21 (0.15 –0.35)	<.0001
CD4% at enrollment	12.74 (4.00 – 22.00)	14.90 (9.00 – 22.00)	0.36
Severely Immuno-suppressed? Yes	29 (74)	96 (68)	0.45
Log 10 HIV VL	6.09 (5.55 – 6.60)	5.59 (4.96 – 6.14)	0.001
Hemoglobin (g/dl)	8.90 (7.90 – 10.20)	8.80 (7.30 – 9.80)	0.22
Have Anemia? Yes	10 (26)	32 (23)	0.68
Is TST Negative? Yes	26 (96)	126 (95)	0.73
HAART Initiation Urgent < 2 days	17 (44)	73 (51)	0.39