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EVALUATING THE RISK FACTORS AFFECTING THE SURVIVAL TIME OF TB/HIV CO-INFECTED PATIENTS TO EARLY DEATH AT RASHID SHEKONI TEACHING HOSPITAL, JIGAWA STATE

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ABSTRACT

Tuberculosis is a serious health threat, especially for people living with HIV. people living with HIV are more likely than others to become sick with TB. Worldwide TB is one of the leading courses of death among people living with HIV (CDC 2015). A retrospective cohort study was conducted in which all patients registered for TB/HIV at Rashid shekoni teaching hospital from 1st January 2017 to 31st December 2021. Kaplan Meier and log rank test were used to determine the survival pattern and the survival experience of two or more different groups. Cox regression was used to identify factors affecting the survival time of the patients. This study consists of 274 TB and HIV co-infected adult patient out of these 120 were died during the study period, and 154 were censored.it was found that massive death occurred at 1.3years of follow up period and the over roll median survival time was (56 months). the multivariate cox regression analysis indicated that an old age patient>39yrs, HIV+, low CD4 cell count<456, weight<42 were significant risk factors associated with death of TB/HIV co-infected patients. In this study the death of TB/HIV adult co-infection was found to be very high at 1.3yr. The risk factors leading to early death of TB/HIV co-infection was associated with age, weight, HIV+ positive, CD4 cell count. The medical decision and policy makers should give these risk factors identified in this study more priority when implementing target improvement in the National TB and HIV program.

Keywords: TB-HIV co-infection, risk factors, Early death, Survival

INTRODUCTION

Tuberculosis is a serious health threat, especially for people living with HIV people living with HIV are more likely than others to become sick with TB. Worldwide tb is one of the leading courses of death among people living with HIV (Center for disease control and prevention 2015). Nigeria is one of the 14 countries that are on the three high-burden country lists for TB, TB/HIV and MDR-TB. The country has an estimated 53,000 incident HIV+TB cases in 2018, which is about 9% of the estimated HIV+ incident TB cases in the African region (2019 Global TB report).

Nigeria has the highest burden of TB+HIV in Africa and is among the eight countries that accounted for two thirds of the Global TB burden. The country in 2018 signed the commitments at the N United Nations High Level Meeting (UNHLM) on TB to successfully treat 1,109,000 people with TB from 2018-2022 and placed 2,193,890 people on TB Preventive Therapy (TPT) within the same period. A National Plan for translating the UNHLM commitments into action was developed and launched during the 2019 World TB Day (2019 Annual report).

The number of HIV positive TB cases detected has been on consistent decrease from 17747 HIV+TB cases in 2010 to 12521 HIV+TB cases in 2019 (see figure below), despite the increase in number of TB patients with known documented HIV status. This consistent decline could reflect the Nigeria's HIV prevalence, which shows downward trend since 2001(Nigeria national HIV/AIDS indicator and impact survey (NSIIS)) 2019.

The HIV positivity rate among TB patients has consistently dropped over the years with increasing number of TB patients tested for HIV. While the Proportion of TB patients with documented HIV status increased from 62% in 2008 to 97% in 2019, that of HIV positivity rate amongTB patients with documented HIV status dropped from 27% in 2008 to 11% in 2019 (2019 Global TB report).

The purpose of this study is to examine the variables that may increase the severity of one or both diseases resulting in the untimely death of a co-infected person. The best estimates from non-parametric and semi-parametric model to identify risk factors and their corresponding hazard scores. The Kaplan-Meier estimator will be used to examine the co-infected patients' survival times, Cox regression will be used to identify risk factors affecting the survival time of TB/HIV patients.

MATERIALS AND MATHOD

Profile of the study area and population

At Rashid Shekoni Teaching Hospital in Jigawa State, Nigeria, data collection for the survey will be conducted. In Nigeria's Jigawa state, this hospital is the biggest healthcare center offering medical services. A referral center for the entire country, the Rashid Shekoni Teaching Hospital has made strides in the delivery of specialized healthcare services using cutting-edge technology. The hospital changed its status to that of a teaching hospital, acting as a training facility for the medical school, nursing school, and school of allied health of Fed. University Dutse in Jigawa state. Record Office under which the study's data will be gathered Mycobacterium tuberculosis-related illnesses are treated by the Chest Unit. The treatment of tuberculosis (TB), chest infections, and HIV management, which are typically associated with TB cases, are well-known specialties of the chest department. The study entails several trips to the Rashid Shekoni chest unit to collect the necessary data from patient records folders (Julius Kwaku 2016).

Data source and mode of collection

Retrospective analysis of medical records from January 2017 to December 2021 is being done. the data was collected from the patient treatment folder and the TB registration card which was kept in the Record office department of Rashid shekoni

teaching hospital dutse jigawa state. These records will be used to gather data on some relevant sociodemographic and clinical characteristics, as well as survival information. The following factors will be carefully considered while choosing the subject folder: The Subject is a Rashid Shekoni Teaching Hospital HIV/AIDS patient receiving tuberculosis treatment at the hospital's under chest unit and also Suffering from both HIV/AIDS and Tuberculosis as at January 2017. To maintain the highest level of confidentiality, names of patients whose folders were reviewed not taken but were given an identification number which cannot be traced to their records (Julius Kwaku 2016).

Variables of interest in the study

The main outcome was mortality. The enrollment duration defined as TB diagnosis until either treatment completion, death, or lost to follow-up was considered. Some demographic information about the patients as well as information linked to medicine are included in the predictor variables of interest. The covariates in this study are those that influence the waiting time we want to measure in some way. Age at study start, gender, TB patient category, average CD4 counts for each patient over the course of the study, initial patient weight, marital status, WHO clinical stages, HIV status, functional status, smoking habit, alcohol use, residency, and educational level are the predictor (covariate) variables that are thought to affect the survival of HIV/AIDS and TB patients included in the study. Survival time was months from the start of the study year to death while an individual is on HIV/AIDs and TB treatment, in the case of individuals who did not die, Observations are censored, in the sense that, for some subjects, the event of interest has not occurred at the time the data are analyzed.

METHOD

A retrospective cohort study was conducted in which all patients registered for TB/HIV at the tuberculosis under chest unit in the Rashid shekoni teaching hospital from 1st January 2017 to 31st December 2021 were included 274 TB/HIV co-infection patients in the study cohort. The data were collected from the tuberculosis register and patient treatment card and the data were analyzed only by the use of non-parametric and semi parametric approach i.e. Kaplan Meier and log rank test were used to determine the survival pattern/median survival time of the patient and to compare the survival experience of two or more different groups. Cox regression was used to identify risk factors affecting the survival time of the patients. The entire process of data retrieval and data entry was done by the investigator.

Kaplan-Meier

Kaplan Meier analysis was used to study survival pattern, in which the probability of survival in each month after treatment initiation was calculated followed by calculation of cumulative probability of survival by the end of that particular month. The group variables studied included Age at study start, gender, TB patient category, average CD 4 counts for each patient over the course of the study, initial patient weight, marital status, WHO clinical stages, HIV status, functional status, smoking habit, alcohol use, occupation, residency, and educational level of the patients. The end point studied was death. The time of death was ascertained, The events which were censored were default, treatment completion, cure, failure and transfer.

The Kaplan Meier curve was drawn to arrive at the overall estimate of patients surviving at the end of each month. A vertical gap between two graphs of the survival functions shows that at a given period of time, one group had a higher probability of surviving while a horizontal gap shows that one group took longer to experience an event (Etikan et al., 2017).

$\hat{S}(t) = \prod_{i=1}^{k}(\frac{n_i - d_i}{n_i})$

if the pattern of one survivorship function of one group lies above another group which means the group with the upper curve have a longer survival, or had a more favorable survival experience, than the group defined by the lower curve (Julius Kwaku, 2016).

Log-Rank Test

The difference in the survival patterns over time between different groups was studied using the log rank test. The log-rank test is the most commonly used statistical test for comparing survival functions of two or more groups (Clark et al., 2003; Etikan et al., 2017). A very important assumption for the appropriate use of the log rank test (and the Cox PH regression model) is that the hazards are proportional over time and this implies that the effect of a risk factor is constant over time (Sullivan, 2016).

The log-rank test is used to compare the death rate between two different groups, conditional on the number at risk in the groups. The log-rank test hypothesis is that:

H_0: *survival time between groups are all the same*
H_1: *survival time between groups are not all the same*

The log-rank test compares the observed hazard *O* to the expected hazard *E* just like the chi square test. It is therefore of the relation:

$$x^2 = \frac{\sum_{r=1}^{n}(O_r - E_r)}{E_r}$$

With *r*-1 degrees of freedom, for large values of x^2 the null hypothesis will be rejected.

The Cox Proportional Hazards (PH) Model

A semi-parametric model is one whose functional form is unspecified. One of the most popular semi-parametric models is the cox proportional hazard model often called the Cox PH model which was proposed by David Cox (Cox, 1972). The cox model formula gives an expression for the hazard at time t for an individual with a given specification set of explanatory variables represented by X. (Olaosebikan et al. 2020).

$h_i(t/X_i) = h_o(t)exp^{\{X'_i\beta\}}$

here β is a *1 x p* vector of coefficients and $X_i$is a *p x 1* vector of explanatory variables β. In this model $h_o(t)$ is a baseline hazard function that describes the risk for individuals with X_i=*0* and $exp^{\{X'_i\beta\}}$ is the relative risk associated with either increase or decrease in risk of the characteristics X_i.

Ethical Consideration

A letter of ethical clearance was received from the research ethical clearance committee of fed. University dutse. Permission letters were obtained from Rashid shekoni teaching hospitals jigawa state from the Medical Record unit between 2017 and 2021 on patients with TB and TB/HIV co-infection. Data collected from the hospital in support of this analysis commenced immediately after the Ethics board of the University approved it.

RESULT

This study consists of 274 TB and HIV co-infected adult patient. Out of these 120 were died during the study period, and 154 were censored. Among the patient 143 were male and 131 were female; 143 were married,65 were divorced and 66

were single; and the 138 were at younger age while 136 were at older age;157 they were reside in urban area and 117 were reside in rural area; base on education 88 were illiterate,42 attended primary,65 held SSCE, 22 attended NCE program while 57 attended university;212 were infected with HIV+ 62 were non; 233, 41 had pulmonary TB and extrapulmonary TB ;141 light weight and 133 had heavy weight;137 had lower average CD4 while 137 had above average;138, 87,and 49 had working, ambulatory and bed ridden; 124, 61, 51 and 38 for WHO S1,S2,S3 and S4;131 and 143 who were smokers and non-smokers;124 and 206 had alcoholic substance and non. it was found that massively the death occurred at 1.3years of follow up period and the over roll median survival time was (56 months).

From Figure 1 (a) below, indicated that the greatest number of deaths took place in the first 8 to 15 months of admission/follow up. And the median survival time of female patient was (56 months) and the male median survival time was none. we observed that female with TB/HIV-position patients had shorter survival time to live compare to male had a longer survival time.

Figure 1 (b), shows that the greatest number of deaths occurred on the 8 to 15 months of admission/follow up. And the median survival time of a Divorced patient was (23 months) and the Married and Single median survival time was none. From the figure above we discovered that Divorced with TB/HIV-position patients had shorter survival time to live compare to married and single had a longer survival time.

From Figure 1 (c), shows that the largest number of deaths occurred on the 8 to 15 months of admission/follow up. And the median survival time of a pulmonary TB patient was (56 months) and the Extrapulmonary TB median survival time was none. From the figure above, we discovered that pulmonary TB/HIV-position patients had shorter survival time to live compare to Extrapulmonary had a longer survival time.

Figure 1 (d), indicated that the largest number of deaths occurred on the 8 to 15 months of admission/follow up. And the median survival time of a HIV positive patient was (25 months) and the HIV negative patient median survival time was none. From the figure above, we discovered that HIV-positive patients had shorter survival time to live compare to HIV negative had a longer survival time.

Figure 1 (e), indicated that the largest number of deaths occurred on the 8 to 15 months of admission/follow up. And the median survival time of bed ridden patients was (14 months), the median survival time Ambulatory patients was (49 months) and the median survival time of working patients was none. Also, the figure above we discovered that bed ridden patients have a shorter survival time to live compare to Ambulatory and Working patients have a longer survival time.

Figure 1 (f), shows that the most of the largest number of deaths occurred on the 8 to 15 months of admission/follow up. And the median survival time of a stage 4 was (14 months) and the stage 3 was (22 months), stage 2 was (57 months) and the median survival time of stage 1 was none. From the figure above indicated that stage 4,3,2 patients had shorter survival time to live compared to stage 1 had a longer survival time.

Figure 1 (g), shows that most of the largest number of deaths occurred on the 8 to 15 months of admission/follow up. And the median survival time of a smoking patients was (50 months) and the non-smoking patients median survival time was (56 months). Also, From the figure above we discovered that the smoking patients had shorter survival time to live compare to those that are non-smoking patient had a longer survival time.

Figure 1 (h), shows that the largest number of deaths occurred on the 8 to 15 months of admission/follow up. And the median survival time of Alcohol patient was (36 months) and the non-Alcohol patient's median survival time was 56 months. Also, From the figure above we discovered that those that are Alcohol drank patients had shorter survival time to live compare to those that are non- Alcohol drunk had a longer survival time.

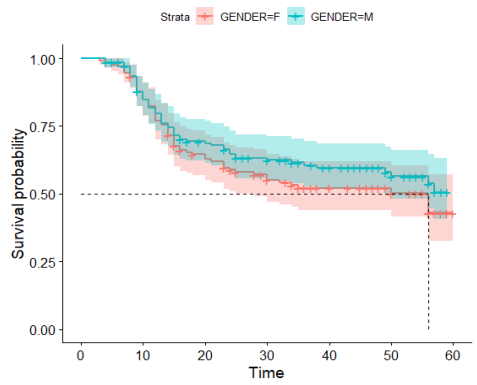
Figure 1 (I) below, shows that most of the largest number of deaths occurred on the 8 to 15 months of admission/follow up. And the median survival time of the Rural patients was (50 months) and the Urban patients median survival time was none. Also From the figure above we discovered that patient's that are living in a Rural area had shorter survival time to live compare to those that are living in an Urban had a longer survival time.

Figure 1 (j) below, shows that the largest number of deaths occurred on the 8 to 15 months of admission/follow up period where the median survival time of a patients who are illiterate was (22 months) followed by primary holders was(30 months), SSCE holders was(55 months) and ND/NCE and university holders median survival time of the patients was not specified And also From the figure above we discovered that patients with illiterate and primary have a shorter survival time to live than those patients that held University qualification have a longer survival time.

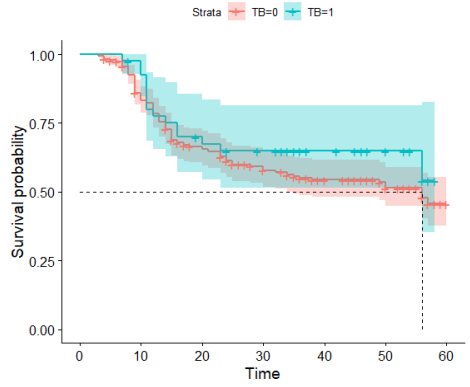
From Figure 1 (k) below, shows that the largest number of deaths occurred on the 8 to 15 months of admission/follow up period where the median survival time of a patients age>39yrs was (18 months) and the median survival time of a patients age<39yrs was not specified And also From the figure above we discovered that patients with age>39yrs have a shorter survival time to live than those patients that have age<39yrs have a longer survival time.

From Figure 1(l) below, shows that most of the largest number of deaths occurred on the 8 to 15 months of admission/follow up. And the median survival time of a patient's weight<42 was (58 months) and the median survival time of a patient with weight>42 was (56 months). From the figure above, we discovered that patients with weight>42 have a shorter survival time to live compare to those patients that have weight<42 have a longer survival time.

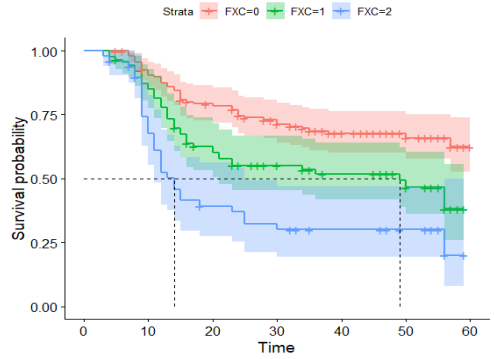
Figure 1(m) below, shows that most of the largest number of deaths occurred on the 8 to 15 months of admission/follow up. And the median survival time of a patients CD4<456.5 was (18 months) and the median survival time of a patient with CD4>456.5 was none. From the figure above, we discovered that patients with CD4<456.5 have a shorter survival time to live compare to those patients that have CD4>456.5 have a longer survival time.



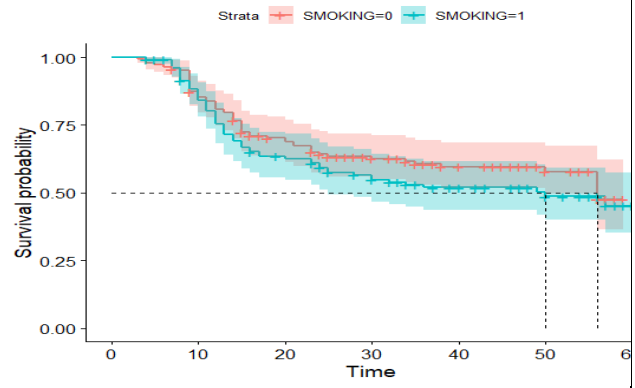
1. Gender



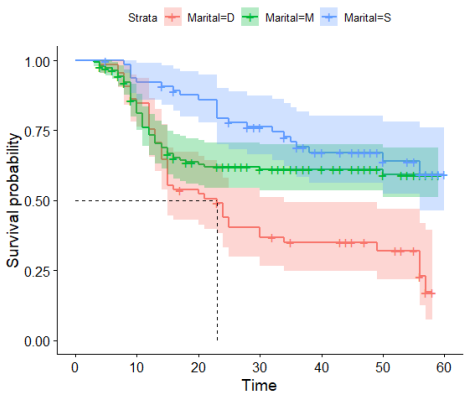
2. TB status



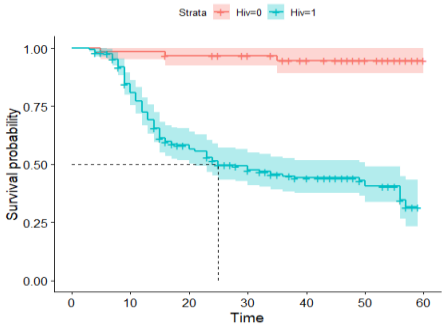
(e) Functional status



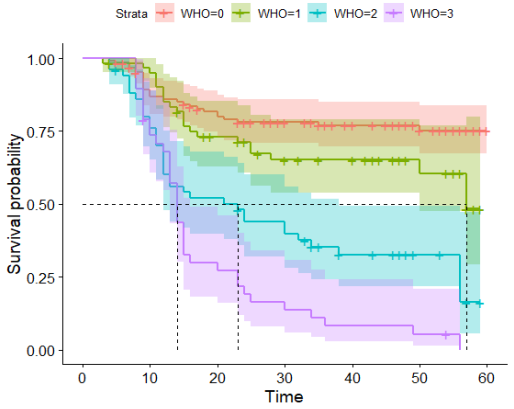
(g) Smoking habit



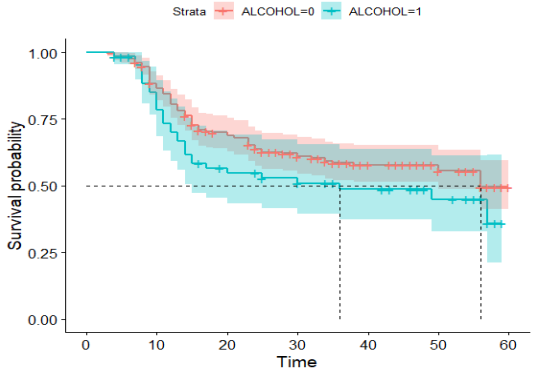
3. Marital status



(d) HIV status



(f) WHO clinical stages



(h) Alcohol used

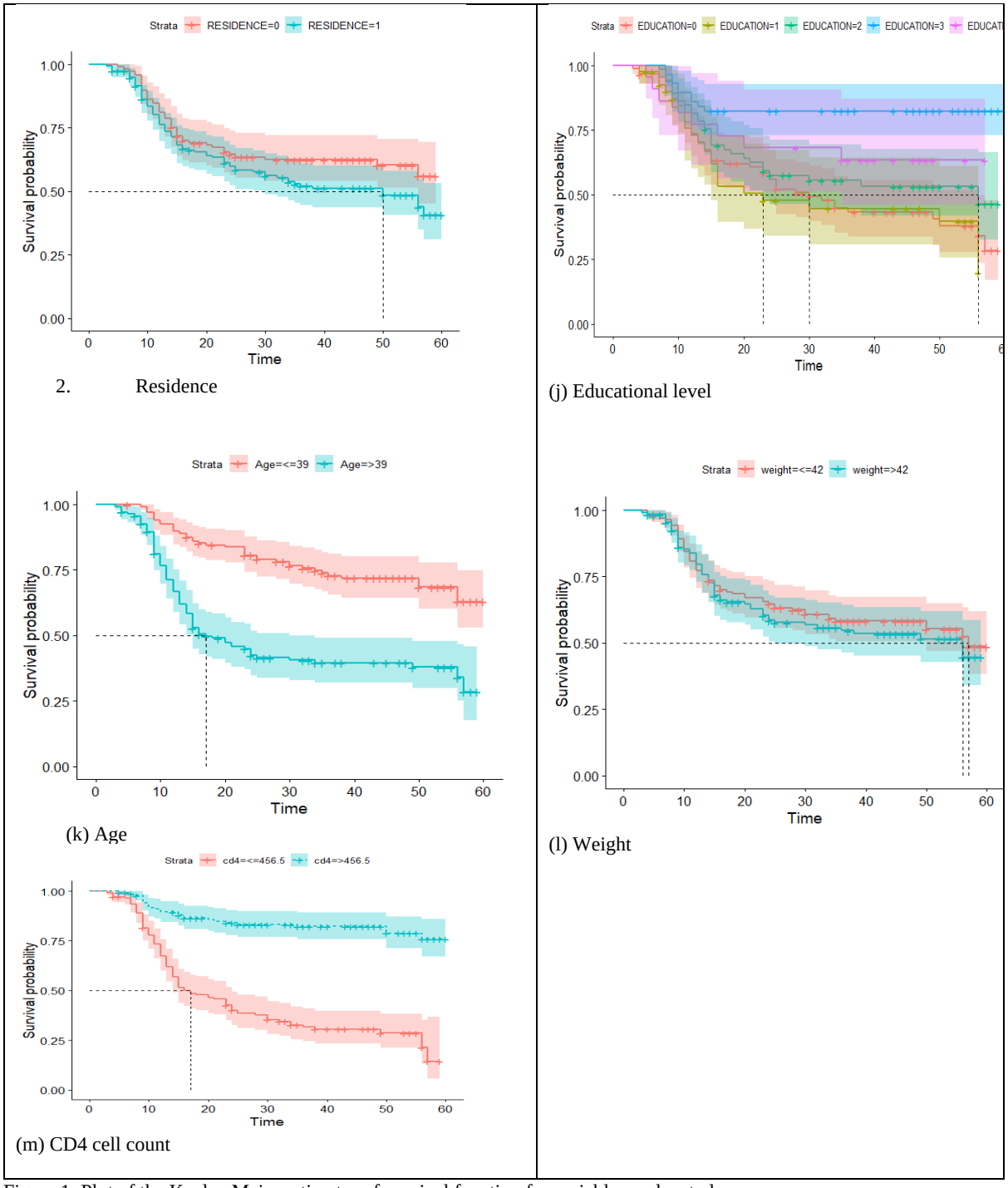


Figure 1: Plot of the Kaplan Meier estimates of survival function for variables under study

Table 1: Result of the log-rank test for Comparing the Difference of survival time Between the Category of Variables of TB/HIV Co-infection patients

Variables	Df	Chi-Square value	P-value	Decision
Age	1	35.6	0.0000	RejectH_0
Gender	1	1.3	0.3	AcceptH_0
Marital status	2	18.9	0.0008	RejectH_0
Weight	1	0.5	0.5	AcceptH_0
TB status	1	1	0.3	AcceptH_0
CD4 Cell	1	73.2	0.0000	RejectH_0
HIV status	1	45.6	0.0000	RejectH_0
Functional s	2	31.4	0.0000	RejectH_0
WHO Stages	3	87.5	0.0000	RejectH_0
Smoking	1	1.2	0.3	AcceptH_0

Alcohol	1	2.8	0.1	AcceptH_0
Resident	1	2.7	0.1	AcceptH_0
Educational Lvl	4	24	0.00008	RejectH_0

The table above described that there were no significant difference between the categories of variables Gender, Weight, TB category, Smoking, Alcohol, Resident with their p values (0.3,0.5,0.3,0.3,0.1,0.1) greater than the level of significant α=0.05 likewise there were an existing of significant difference between the categories of the variable Age, Marital status, CD4 cell count, HIV status, Functional status, WHO stages, Educational level with their P-values (0.000,0.0001,0.0000,0.000008,0.00000,0.00000,0.0001) are Less than the level of significant α=0.05

Multivariate Cox regression was used to calculate HR. HR indicates the instantaneous risk or hazard (hazard per unit time, usually 1 day) of an event (e.g., death) in a test group relative to a reference group, A narrow CI indicates good precision in our HR estimate; a wider CI would indicate more uncertainty (Neus Valveny). The central statistical output is the variable that has p-values less than the level of significant at 0.05 and hazard ratio (falmata et.al.2019).

Table 2: Estimates variables of cox regression

Variables	coef	HR	se(coef)	z	p	low95%	Upp95%
GENDER M	-0.16524	0.84769	0.22104	-0.748	0.45473	0.5153	1.2096
Marital M	-0.25297	0.77649	0.21326	-1.186	0.23553	0.4279	1.0154
Marital S	0.53468	1.70691	0.36324	1.472	0.14102	0.8619	2.9869
TB	-0.11609	0.89039	0.28419	-0.408	0.68291	0.6127	1.8902
HIV	1.99637	7.36231	0.63776	3.130	0.00175	0.3670	8.3280
FXC	0.19038	1.20970	0.12663	1.503	0.13274	0.7286	1.2604
WHO	0.20986	1.23350	0.12368	1.697	0.08974	0.8076	1.3733
SMOKING	0.05914	1.06092	0.23659	0.250	0.80262	0.6126	1.4794
ALCOHOL	0.06627	1.06851	0.26338	0.252	0.80135	0.5830	1.6589
RESIDENCE	0.03162	1.03212	0.22473	0.141	0.88811	0.7378	1.7656
EDUCATION	0.04316	1.04411	0.09063	0.476	0.63391	0.9056	1.3065
Age>39	0.89446	2.44600	0.28229	3.169	0.00153	1.0236	1.0620
weight>42	-0.39957	0.67061	0.19599	-2.039	0.04148	0.9710	1.0031
cd4<456.5	-0.74051	0.47687	0.30438	-2.433	0.01498	0.9950	0.9986

From the above table 4.3 COX regression estimates indicated that there is no clear evidence of high risk of death between the variable at different level and reference category with respect to gender, marital status, TB category, functional status, WHO stages, Smoking, Alcohol, education status because their p-values is greater than the standard level of significant 0.05.While on the other hand there is an evidence of high risk of death between the variable at different level and reference category those variables are age<39, HIV+, Weight>42, CD4 cell count<456.5 because their P-values is less than the standard level of significant 0.05.

In the remaining part of this section interpretations of the results are given using estimated hazard ratios and their respective estimated 95% confidence interval (Hailu Refera Eshetu Wencheko).

CD4 cell count: For CD4 cell count the estimated hazard ratio, HR=0.46787 [95% CI: 0.9950 to 0.9986 p<0.01498]. This means that patients whose CD4 cell count was lower by 456.5cells/mm3 had a greater risk of dying 0.46787 times more than those that had CD4 greater than 456.5cell/mm3.

Age: the estimated hazard ratio age>39 compared to age<39yrs was HR=2.446, (95% CI=1.0236 -1.0620 P= 0.00153). Indicated that Patients with Age>39yrs had a high risk of dying 2.446 times higher compared to those patients with Age<39yrs.

Weight: For Weight the estimated hazard ratio of weight>42kg compared to weight<42kg was HR=0.19599 [95% CI: 0.9710 – 1.0031, p<0.04148]. This means that patients whose Weight was lower by 42 had a greater risk of dying 0.19599 times more than those that has weight greater than 42kg.

HIV+: the estimated hazard ratio of HIV+ compared to HIV- was HR=7.36231, (95% CI= 0.3670 – 8.3280 P=0.00175).this means that Patients with HIV+ had a high risk of dying 7.3631 times higher compared to those patients with HIV-.

DISCUSSION

The current study found that initial weight, baseline CD4, Age, HIV+ were significant Risk factors that affect the survival life time of TB-HIV co-infected patients to early death.

The impact of weigh on survival rate had been compared with other studies. The findings of which showed that the depletion of weight was associated with high risk of death. A retrospective cohort study was carried out in eastern zone of Tigray region Ethiopia reveals that patient with body weight<50kg was the predictors of mortality of HIV/TB co-infection (Mulugeta geremew geleso). Another study was conducted in Ethiopia region indicated that Based on loglogistic model, age, weight, were found to be the most prognostic factors of time-to-death. Similarly. A retrospective cohort study was conducted where it reveals that lower weight was predictors associated with higher risk of death. Another retrospective cohort study was carried out at Maiduguri teaching hospital showed that the Exp(β) value is 1.467 which means that the risk of death in patients with weight less than 45kg is 1.467 times higher than patients with weight> 45kg. in fact our current study also evaluated that weight has a strong association with the risk factor of death.

The CD4 cell count was among the risk factors of mortality especially patients that has CD4 less than 456.5. this finding is supported by the studies conducted in northwest, Ethiopia indicated that CD4 count below threshold [AHR=2.1(95%CI:1.21-6.45)] was a significant predictor of mortality. A retrospective cohort study research was conducted in Ethiopia where it reveals that the patients with lower CD4 cell was predictors associated with higher risk of

death. Another retrospective cohort study was carried out at Maiduguri teaching hospital showed that the Exp(β) value is 2.861 which means that the risk of death in patients with CD4 count less than 200 is 2.861 times higher than the patients with CD4 greater than 200 (falmata alhaji et al). Also retrospective cohort study was carried out in brazil stated that CD4 diagnostic criteria (HR = 0.64) was the predictor of death. A cohort study was conducted in in Almaty, Kazakhstan showed that CD4 count < 499 (HR 2.398, 95%CI 1.191, 4.830, p < 0.014) was associated with mortality(Zhandybayeva et al.). likewise, our current study revealed that patient with CD4 less than 456.5 has a shorter survival time.

The age the hazards of mortality in patient age less than 39yrs compared with age>39 were 2.446 times higher than those with age>39. This finding is supported by the studies conducted. A retrospective cohort study was carried out in eastern zone of Tigray region Ethiopia reveals that patient with age>45(hr:5.315 95%CI=1.231-22.959) was the predictors of mortality of HIV/TB co-infection (Mulugeta geremew geleso). Another study was carried out in Mizan-Tepi University, Tepi, Ethiopia the result showed that age>40yrs was among the predictors of mortality meaning that a younger has a longer survival time than an older age. A retrospective cohort study was conducted in Rio de Janeiro,Brazil the studty indicated that age>40yrs was significant association of death. A Study was carried out in Suriname The study showed that older age (HR: 5.84, 95%CI: 3.00 – 11.4) was statistically associated with higher mortality For the TB/HIV co-infected patients (Stijnberg et al.2019) Another cohort study was carried out in southwest Ethiopia showed that aged between 35–44 years (AHR=2.9; 95 % CI: 1.08–7.6) was predictors of mortality of HIV/TB co-infected(Hailay Gesesew et al.).

The HIV: the estimated hazard ratio of HIV+ compared to HIV- was HR=7.36231, (95% CI= 0.3670 – 8.3280 P=0.00175).this means that Patients with HIV+ had a high risk of dying 7.3631 times higher compared to those patients with HIV-. This finding is supported by different research conducted from different countries. A Study was carried out in Suriname Ethiopia. The study showed that HIV-seropositivity (HR: 2.08, 95%CI: 1.48 – 2.92) was statistically associated with higher mortality. For the TB/HIV co infected patients (Stijnberg et al.2019). Another retrospective cohort study was carried out in eastern zone of Tigray region Ethiopia reveals that patient with body HIV+ was the predictors of mortality of hiv/tb co-infection (Mulugeta geremew geleso). Likewise our current study found that HIV+ was statistically associated with early mortality.

CONCLUSION

in this study the death of TB/HIV adult co-infection was found to be very high. The risk factors leading to early death among TB/HIV co-infection was associated with age, HIV+ positive, CD4 cell count, initial weight. The medical decision and policy makers should give these risk factors identified in this study more priority when implementing target improvement in the National TB and HIV program.

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