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Survival Analysis of Patients with Multidrug-Resistant Tuberculosis in KwaZulu-Natal, South Africa: A Comparison of Cox Regression and Parametric Models.

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Abstract: Researchers in medical sciences often prefer the Cox semi-parametric model instead of parametric models because of its restrictive distributional assumptions, but under certain circumstances, parametric models estimate the parameters more efficiently and powerful than the Cox model. The objective of this study was to compare the Cox and parametric models by studying a dataset of patients diagnosed with multidrug-resistant tuberculosis (MDR-TB). A total of 1 542 patients were included in the study from four decentralised sites located in rural areas and one centralised hospital in KwaZulu-Natal, South Africa from 1 July 2008 to 30 July 2012. Out of 1 542 patients with MDR-TB, 886 (57.5%) were cured and 245 (15.9%) died. According to the AIC, the Lognormal and Weibull regression models were the best fitting to data and the Cox regression model was the weakest. According to the results from parametric models, baseline weight of patients had an increased risk of death in both univariate and multivariate analysis. Patients with ages 31 – 40, 41 - 50 and >50 years at diagnosis had an increased risk for death in Cox proportional hazards model. In univariate analysis the data strongly supported the Lognormal regression among parametric models, while in multivariate analysis Weibull and Lognormal are approximately similar, according to Akaike Information Criterion. Although it seems that there may not be a single model that is substantially better than others, Lognormal is the most favorable as an alternative to Cox for identifying risk factors for patients with MDR-TB.

Keywords**:** Cox Model, MDR-TB, Parametric Models.

Introduction

Most medical research aim to determine the survival of patients based on demographic and clinical grouping. Studies have been conducted to compare parametric models and semi-parametric models in survival data analysis.

The objective of many survival analysis studies is to look for the different survival distributions that correspond to different subgroups within a heterogeneous population.

Researchers in medical sciences often prefer to use Cox proportional hazards (PH) model as a semiparametric method (Cox, 1972) because of their fewer assumptions, but some researchers have shown that under certain circumstances, parametric models (accelerated failure time models) estimate the parameters more efficiently than Cox PH model (Efron, 1977; Oakes, 1977). Furthermore, parametric models can provide some insight into the shape of the baseline hazard when information is sufficient. Many of the standard parametric models, such as Weibull, exponential and log-normal, are accelerated failure-time models. Accelerated failure time (AFT) models often use the maximum likelihood procedure to estimate the unknown parameters, and the interpretation are familiar to most researchers.

The Weibull model, which was proposed by Weibull (Weibull, 1939), serves as the basic model for survival time and it does not assume a constant hazard rate and therefore has broader applications. It models the rate of failure as time increases (Nelson, 1982). The Weibull distribution is characterized by two parameters: one is shape parameter denoted by γ and the other is scale parameter denoted by λ. The hazard (risk) rate increases when $\gamma > 1$ and decreases when $\gamma < 1$ over the time. When $\gamma = 1$, the hazard rate remains constant over the time and the distribution turns into the exponential. Therefore, Weibull distribution could be used to model the survival distribution of a population that has either increasing or decreasing or constant risk which is typically seen in survival analysis.

Multidrug-resistant tuberculosis (MDR-TB) still represents a challenge for clinicians and staff operating in national TB programmes worldwide (Borisov et al., 2017; Akkerman et al., 2019; Borisov et al., 2019; Lange et al., 2019; Nahid et al., 2019; Migliori, 2019). The World Health Organization (WHO) seeks global evidence on the safety and tolerability of new treatment regimens for DR-TB, including MDR-TB (Halleux et al., 2018). Treatment for MDR-TB is challenging for patients, relatives, healthcare providers and health systems (Lange et al., 2014).

Several global studies, including two systematic reviews, have reported higher costs associated with managing MDR-TB patients in hospitals (Fitzpatrick & Floyd, 2012; Floyd et al., 2012; Bassili et al., 2013; Schnippel et al., 2013; Cox et al., 2015). South Africa remains one of the highest burdened countries in all three WHO-defined tuberculosis categories, including drug susceptible TB, MDR-TB, and TB/HIV coinfection cases. A previous tuberculosis drug resistance survey performed in South Africa during 2001 - 2002 reported the prevalence of MDR-TB as 1.6% (95% CI = 1.1 - 2.1) in new TB cases and 6.6% (4.9 - 8.2) in retreatment cases (Weyer et al., 2002). At that time, the prevalence of TB and HIV was rising, a late presentation was common, and tuberculosis-related mortality was high, whereas laboratory testing for drug-resistant tuberculosis was limited. The province of KwaZulu-Natal has the highest prevalence rate of patients with MDR-TB in South Africa (Ismail et al., 2018). In settings with limited resources and a high prevalence of MDR-TB, a decentralised model of care has proven to be effective and is advisable (Loveday et al., 2018). In the latter case, only complicated cases are referred to specialised centres or proposed to local/international TB consilia.

Although several studies on the comparison of Cox model with other parametric models has been discussed including (Pourhoseingholi et al., 2007; Khan & Ababneh, 2016; Nardi & Schemper, 2003; Ravangard et al., 2011) to our best knowledge few studies if none have

compared the Cox semiparametric model with parametric models using MDR-TB data collected in KwaZulu-Natal, South Africa.

In this paper, we compare parametric models versus Cox semiparametric model using data set of patients with a confirmed diagnosis of MDR-TB (KwaZulu-Natal, South Africa) who commenced treatment between 1 July 2008 and 30 June 2012. We show that the task of checking goodness of fit for parametric models is not formidable and that it can be standardized. For this purpose, we use and recommend residuals developed for Cox regression (Nardi & Schemper, 1999). We will be doing this while identifying factors that are related to MDR-TB. The outcome considered here was time from MDR-TB diagnosis until death.

Materials and Methods

Source of Data and Description

This was a prospective mixed methods case study including all patients with a confirmed diagnosis of MDR-TB from five TB centres (four decentralized sites and one centralized hospital in KwaZulu-Natal, South Africa) who commenced treatment between 1 July 2008 and 30 June 2012. The data set consists of 1 542 patients, aged 18 years and older. The response variable of interest is the time to death of an MDR-TB patient. Patients receiving care at more than one site were excluded to guarantee the quality of information on MDR-TB treatment episodes.

According to (Loveday et al., 2018), the study was cleared to use the data by the University of KwaZulu-Natal Biomedical Research Ethics Committee (Ref: BF052/09) and by the KwaZulu-Natal Department of Health. Only secondary data, the data routinely collected by health workers for clinical care using existing records and databases, structured questionnaires, observation and interviews, were used by (Loveday et al., 2018). The authors report that to protect patient confidentiality and anonymity, the databases were deidentified, and access was strictly limited. Furthermore, informed consent was waived by the ethics committee since all patient data used, were previously collected during the course of routine medical care and did not pose any additional risks to the patients.

Univariate and multivariate analysis of prognostic factors was carried out by two methods: Cox proportional hazard model (as semiparametric method) and Weibull, Exponential and Lognormal models (as parametric methods). We briefly recall the definitions of Cox and parametric models. Assume that for a sample of n individuals $(i = 1, 2, \dots, n)$ the survival time t, the status indicator δ (1 for dead and 0 for alive/censored) and a vector of explanatory variables x are recorded. We assume that survival times are continuously distributed. The Cox hazard function for fixed-time covariates, x, is:

$$h(t) = h_0(t)exp\{\beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_p x_p\} = h_0(t)\exp(\beta x)$$

where the hazard function $h(t)$ is dependent on (or determined by) a set of p covariates $(x_1, x_2, \dots, x_p)$, whose impact is measured by the size of the respective coefficients $(\beta_1, \beta_2, \dots, \beta_p)$. The term h_0 is called the baseline hazard and is the value of the hazard if all the x_i are equal to zero. The 't' in $h(t)$ reminds us that the hazard may vary over time. The survival

function may be defined in terms of the hazard function by $S(t) = exp\left(-\int_0^t h(u)du\right) = exp(-H(t))$, where $H(t)$ is the cumulative hazard function defined as the area under the hazard function up to time t. Several methods are available for estimating the cumulative hazard function (Klein & Moeschberger, 2003).

In Cox's PH model, the unknown baseline hazard function h_0 is the non-parametric part, and the unknown β is the parametric part, which together create a semiparametric model. Unfortunately, the simplicity of the Cox PH model imposes unrealistic assumptions on the data. One of the restrictions to using the Cox model with time-fixed covariates is its proportional hazards assumption; it means the hazard ratio between two sets of covariates is constant over time. This is due to the common baseline hazard function canceling out in the ratio of the two hazards. i.e. the hazard ratio of two individuals with different covariates x_1 and x_2 is

$\frac{h(t/x_1)}{h(t/x_2)} = \frac{h_0(t)exp(\beta x_1)}{h_0(t)exp(\beta x_2)} = \frac{exp(\beta_1 x_1)}{exp(\beta_2 x_2)}$ which is constant and independent of time.

A link to parametric survival models comes through alternative functions for the baseline hazard. In this case we can let the baseline hazard be a parametric form such as Exponential, Weibull and Lognormal. For example, in exponential regression the baseline survivorship function is in follows:

$$S(t/x) = exp\left[{}^{-t}/_{exp(\beta_0 + \beta_1 x)}\right]$$

The baseline distribution is completely specified up to an unknown shape parameter. Although the parametric models might be somewhat more efficient, they have more assumptions but if the assumptions are met, the analysis is more powerful. We have considered Weibull and Exponential models with respect to the assumptions of constant and monotone baseline hazard respectively and lognormal model because its baseline hazard has value 0 at $t = 0$, increases to maximum and then decreases, approaching 0 as becomes large. The likelihood value and standardized of parameter estimates were employed to comparison among Cox semiparametric model and parametric models.

In order to compare parametric models and Cox semiparametric model we used Akaike Information Criterion (AIC). The AIC proposed in (Akaike, 1974), is a measure of the goodness of fit of an estimated statistical model (Akaike, 1974). In general, the model with the smaller AIC fits the data better than the one with the larger AIC. The AIC is an operational way of trading off the complexity of an estimated model against how well the model fits the data. The following formula was used to calculate AIC:

$$AIC = -2 * \log(likelihood) + 2(p + k)$$

where p is the number of parameters, $k = 1$ for the exponential model, $k = 2$ for the Weibull, log logistic, and log normal models (Klein & Moeschberger, 2003). All statistical analyses were carried out with SPSS version 25 (IBM Corp., Armonk, New York, USA) and STATA (version 19) statistical software. The statistical significance level was set at p-value < 0.05.

Results and Discussion

In this analysis study, a total of 1 542 patients diagnosed with MDR-TB were included. A total of 812 (52.7%) patients were treated in the centralised hospital and 730 (47.3%) were treated in the decentralised sites located in rural areas. The median follow-up time was 23 months. The median (± SD) age at the time of diagnosis was 34 (±10.8) years, and the patients' ages ranged from 18 to 79 years. Furthermore, the median baseline weight was 50kg. There were 745 (48.3%) males and 797 (51.7%) females in the study. We further observed that 1 475 (95.7%) had no previous MDR-TB episodes, 64 (4.2%) had one MDR-TB episode and 3 (0.2%) had two or more MDR-TB episodes. The results showed that 1 510 (97.9%) patients had pulmonary TB and 31 (2.1%) had extrapulmonary TB. The results also show that 792 (51.4%) patients had no comorbidities and 56 (3.6%) had other conditions. Most of the patients (71.4%) were HIV positive. We observed that 886 (57.5%) of the patients were cured, 245 (15.9%) died, 334 (21.7%) defaulted and 77 (5.0%) were lost to follow-up, during the study period (Table 1).

Table 1: Baseline characteristics of study participants, KwaZulu-Natal, South Africa, 2008 to 2012 (N = 1 542).

Factors Categories	Centralised hospital		Decentralised sites		Total	
	No	**%**	**No**	**%**	**No**	**%**
	812	52.7	730	47.3	**1 542**	**100**
Median age (SD) 34 (10.8)						
Age at diagnosis (years)						
18 - 30	303	19.7	245	15.9	**548**	**35.5**
31 - 40	292	18.9	258	16.7	**550**	**35.7**
41 - 50	145	9.4	153	9.9	**298**	**19.3**
51 or more	72	4.7	74	4.9	**146**	**9.5**
Gender						
Male	399	25.9	346	22.4	**745**	**48.3**
Female	413	26.8	384	24.9	**797**	**51.7**
Previous MDR-TB episodes						
No previous MDR-TB episodes	802	52.0	673	43.6	**1 475**	**95.7**
1 previous MDR-TB episode	9	0.6	55	3.6	**64**	**4.2**
2 or more previous MDR-TB episodes	1	0.1	2	0.1	**3**	**0.2**
Type of TB						
Pulmonary TB	804	52.1	706	45.8	**1 510**	**97.9**
Extra-pulmonary TB	7	0.5	24	1.6	**31**	**2.1**
Comorbidities or other conditions						
No other diseases or conditions	780	50.6	12	0.8	**792**	**51.4**
Diabetes	10	0.6	10	0.6	**20**	**1.2**
Epilepsy	4	0.3	8	0.5	**12**	**0.8**
Hearing loss prior to start treatment	1	0.1	10	0.6	**11**	**0.7**
Renal problems	0	0.0	3	0.2	**3**	**0.2**
Substance abuse	0	0.0	4	0.3	**4**	**0.3**
Liver problems	1	0.1	1	0.1	**2**	**0.2**
Psychiatric problems	4	0.3	0	0.0	**4**	**0.3**
HIV status						
Positive	576	37.4	524	34.0	**1 100**	**71.4**

Negative	211	13.7	162	10.5	**373**	**24.2**
TB outcomes						
Cured	441	28.6	445	28.9	**886**	**57.5**
Died	113	7.3	132	8.6	**245**	**15.9**
Defaulted	229	14.9	105	6.8	**334**	**21.7**
Lost to follow-up	29	1.9	48	3.1	**77**	**5.0**

*SD = Standard deviation; median follow-up time = 22.6 months; median baseline weight = 50 kg

We compared Cox semiparametric and parametric models by using AIC. Before using the Cox regression model, proportional hazards assumption for each of the variables were investigated. The result of Schoenfeld test showed that none of the variables violated the proportional hazard assumption ($p > 0.05$) (Table 2).

Table 2: Test of proportional-hazards assumption.

Factors	χ^2	**df**	**p-value**
Baseline weight	4.66	1	0.09
Age (years)	0.02	1	0.88
Gender	1.48	1	0.22
HIV status	0.41	1	0.52
Type of TB	0.04	1	0.84
Comorbidities	0.18	1	0.67
Previous MDR-TB	0.03	1	0.85
Study site	0.07	1	0.79
global test	**5.36**	**8**	**0.72**

*df = degrees of freedom

Tables 3 and 4 show the results of univariate and multivariate analyses using Cox PH model and alternative parametric models. Based on AIC, the Lognormal model in univariate analysis fit the data better among parametric models and Cox semiparametric model. We further observe that all parametric models showed better likelihood compared to Cox semiparametric model. Patients with ages 31 – 40, 41 - 50 and >50 years at diagnosis had an increased risk for death in Cox PH models, while in the parametric models' patients with ages 31 – 40, 41 - 50 and >50 years at diagnosis had a decreased risk for death. The results in Table 2 also show that HIV negative patients had an increased risk for death (parametric models). Previous MDR-TB is significant in Exponential, but insignificant in Cox regression and other parametric models (Table 3).

The Weibull and Lognormal model in multivariate analysis are the best. But with respect to lower variability Exponential seems better (Table 4). According to the results from parametric models, baseline weight of patients had an increased risk of death in both univariate and multivariate analysis, and female had a decreased risk of death in term of relative risk in multivariate analysis ($p < 0.05$). The results in the Cox regression strike different (see table 4). In univariate and multivariate models, all parametric models are better than Cox with respect to AIC and standardized variability. Neither Cox, nor parametric models in both univariate and multivariate analysis show any evidence about significant differences in type of TB, comorbidities and study sites.

Table 3: Cox and parametric models of MDR-TB survival in univariate analysis.

Factors	Cox standardized variability			Weibull standardized variability			Exponential standardized variability			Lognormal standardized variability		
	HR (S.E)	**p-value**	**AIC**	**RR (S.E)**	**p-value**	**AIC**	**RR (S.E)**	**p-value**	**AIC**	**RR (S.E)**	**p-value**	**AIC**
Baseline weight	0.98 (0.00)	< 0.01*	**2584**	1.05 (0.01)	< 0.01*	**1647**	1.02 (0.00)	< 0.01*	**1790**	1.05 (0.01)	< 0.01*	**1635**
Age (years)												
18 - 30 (Ref)												
31 - 40	1.53 (0.27)	0.02*		0.40 (0.15)	0.02*		0.64 (0.11)	0.01*		0.40 (0.16)	0.02*	
41 - 50	1.71 (0.34)	0.01*	**3111**	0.31 (0.13)	0.01*	**1941**	0.58 (0.11)	0.01*	**2132**	0.29 (0.13)	0.01*	**1926**
> 50	2.39 (0.51)	< 0.01*		0.15 (0.07)	< 0.01*		0.40 (0.09)	< 0.01*		0.14 (0.08)	< 0.01*	
Gender												
Male (Ref)												
Female	1.06 (0.14)	0.65	**3124**	0.89 (0.25)	0.67	**1955**	0.94 (0.13)	0.66	**2147**	0.83 (0.27)	0.57	**1938**
HIV status												
Positive (Ref)												
Negative	0.69 (0.12)	0.04*	**2807**	2.21 (0.86)	0.04*	**1785**	1.46 (0.26)	0.03*	**1954**	2.32 (0.96)	0.04*	**1772**
Type of TB												
Pulmonary (Ref)												
Extrapulmonary	1.22 (0.47)	0.6	**3124**	0.64 (0.53)	0.59	**1954**	0.79 (0.30)	0.55	**2147**	0.83 (0.82)	0.85	**1938**
Comorbidities												
No (Ref)												
Yes	1.31 (0.42)	0.4	**1367**	0.55 (0.39)	0.4	**965**	0.77 (0.24)	0.41	**1066**	0.53 (0.44)	0.44	**958**
Previous MDR-TB												
No (Ref)												
Yes	1.65 (0.44)	0.06	**3121**	0.33 (0.19)	0.06	**1952**	0.57 (0.15)	0.04*	**2143**	0.29 (0.21)	0.08	**1935**
Study site												
Centralized (Ref)												
Decentralized	1.17 (0.16)	0.25	**3123**	0.72 (0.21)	0.26	**1953**	0.87 (0.12)	0.31	**2146**	0.75 (0.24)	0.36	**1937**

*HR = hazard ratios; RR = relative risk; S.E = standard error

Table 4: Cox and parametric models of MDR-TB survival in multivariate analysis.

Factors	Cox standardized variability		Weibull standardized variability		Exponential standardized variability		Lognormal standardized variability	
	HR (S.E)	**p-value**	**RR (S.E)**	**p-value**	**RR (S.E)**	**p-value**	**RR (S.E)**	**p-value**
Baseline weight	0.97 (0.00)	< 0.01*	1.06 (0.01)	< 0.01*	1.03 (0.01)	< 0.01*	1.06 (0.01)	< 0.01*
Age (years)								
18 - 30 (Ref)								
31 - 40	1.70 (0.45)	0.04*	0.32 (0.18)	0.05	0.58 (0.15)	0.04*	0.24 (0.15)	0.02*
41 - 50	1.82 (0.56)	0.05	0.27 (0.18)	0.05	0.50 (0.16)	0.03*	0.32 (0.23)	0.12
> 50	1.61 (0.62)	0.21	0.36 (0.30)	0.22	0.63 (0.24)	0.22	0.28 (0.25)	0.15
Gender								
Male (Ref)								
Female	1.69 (0.38)	0.02*	0.32 (0.16)	0.02*	0.58 (0.13)	0.01*	0.27 (0.14)	0.01*
HIV status								
Positive (Ref)								
Negative	0.94 (0.24)	0.82	1.12 (0.62)	0.84	1.05 (0.27)	0.86	1.18 (0.69)	0.77
Type of TB								
Pulmonary (Ref)								
Extrapulmonary	1.28 (0.93)	0.73	0.58 (0.91)	0.73	0.79 (0.58)	0.75	0.49 (0.86)	0.68
Comorbidities								
No (Ref)								
Yes	0.72 (0.40)	0.55	2.10 (2.52)	0.54	1.44 (0.81)	0.52	2.35 (3.63)	0.58

Previous MDR-TB								
No (Ref)								
Yes	0.83 (0.60)	0.80	1.39 (2.19)	0.83	1.09 (0.80)	0.90	1.61 (2.98)	0.80
Study site								
Centralized (Ref)								
Decentralized	1.57 (0.77)	0.36	0.38 (0.40)	0.36	0.66 (0.33)	0.40	0.29 (0.42)	0.40
AIC	**1186**		**849**		**932**		**844**	

*HR = hazard ratio; RR = relative risk; S.E = standard error

Although Cox regression model is the most common method of analyzing prognostic factors in clinical research, applied statisticians seem to be concerned about the required assumptions on the baseline distribution and the assumed effort in arriving at an appropriate model. The Cox PH model is preferable due to the fact that the model allows us to estimate and make inference about the parameters without assuming any distribution for the lifetime, whose distribution is often unknown. However, PH assumption (Altman et al., 1995; Paoletti & Asselain, 2010) need to be met in order to use this model, which is not always satisfied by the data. If this assumption does not hold, the Cox model can lead to the unreliable conclusions, so parametric models such as Lognormal, Weibull and Exponential are the common choices. These models provide the interpretation based on a specific distribution for duration times without need to PH assumption. The results of a systematic review revealed that only 5% of the journals which used Cox model assessed PH assumption (Altman et al., 1995).

In this study, global PH assumption was assessed and satisfied the data but results of AIC showed that Cox regression model had the poorest fit to data as compared with the parametric models. The results of AIC showed that Weibull and Lognormal models had fitted better than Exponential. The AIC and Cox-Snell residuals used by (Zare et al., 2013) to compare Cox model and parametric models in modeling transition rates of a multi-state model. They showed that parametric models have often been more reliable and less biased. Also, some studies showed when the data were generated by a Lognormal model with an exponential conditional mean function, the Cox model performed poorly (Basu et al., 2004). The group of Ferreira and Nunez-Anton conducted a simulation study to comparing Cox and accelerated failure time models they also presented this comparison in a gastric cancer data set that the proportional hazard assumption did not hold. The findings showed a perfect fitting for lognormal (Orbe et al., 2002). Although it seems that there may not be a single model that is substantially better than others, the data strongly supported the Lognormal regression among parametric models in both univariate and multivariate analysis and it can be led to more precise results as an alternative for Cox.

A good discrimination among parametric models requires the censoring percentage not to exceed 40-50% (Nardi & Schemper, 2003). In our data, the percent of censoring was 26.7%. Age at diagnosis was a strong and independent prognostic factor for MDR-TB, and our finding in univariate analysis is in conformity with previous reports indicated better survival for young patients (Pillay et al., 2001; Finlay et al., 2012; Osman et al., 2015). The results in multivariate analysis showed a lower relative risk of death for female patients with MDR-TB. Our findings

agree with these observations showing an association with MDR-TB, which is maintained in multivariate analysis (Borgdorff et al., 2000; Holmes et al., 1998).

Limitations and Suggestions for Future Research

The limitation of this study is related to incomplete patients' record. Some of variable such as comorbidities, baseline weight, type of TB and HIV status there was missing data. Future research studies should be carried out to evaluate the effects of practical cases such as small sample size and large censoring.

Conclusions

In conclusion, although regression coefficients are not all the same, baseline weight, age at diagnosis and gender should be considered as most important prognostic factors that affect life of patients with MDR-TB.

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