Journal of Tuberculosis Research, 2022, 10, 1-17
https://www.scirp.org/journal/jtr
ISSN Online: 2329-8448
ISSN Print: 2329-843X

Identifying Factors that Affect the Probability of Being Cured from MDR-TB Disease, KwaZulu-Natal, South Africa: A Competing Risks Analysis

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How to cite this paper: Mbona, S.V., Mwambi, H. and Chifurira, R. (2022) Identifying Factors that Affect the Probability of Being Cured from MDR-TB Disease, KwaZulu-Natal, South Africa: A Competing Risks Analysis. *Journal of Tuberculosis Research*, **10**, 1-17.
https://doi.org/10.4236/jtr.2022.101001

Received: November 20, 2021
Accepted: February 8, 2022
Published: February 11, 2022

Abstract

Setting: Four decentralised sites are located in rural areas and one centralised hospital in KwaZulu-Natal province, South Africa. **Objective:** To analyse risk factors associated with multidrug-resistant tuberculosis (MDR-TB) using competing risks analysis. Understanding factors associated with MDR-TB and obtaining valid parameter estimates could help in designing control and intervention strategies to lower TB mortality. **Method:** A prospective study was performed using a competing risk analysis in patients receiving treatment for MDR-TB. The study focused on 1542 patients (aged 18 years and older) who were diagnosed of MDR-TB between July 2008 and June 2010. Time to cure MDR-TB was used as the dependent variable and time to death was the competing risk event. **Results:** The Fine-Gray regression model indicated that baseline weight was highly significant with sub-distribution hazard ration (SHR) = 1.02, 95% CI: 1.01 - 1.02. This means that weight gain in a month increased chances of curing MDR-TB by 2%. Results show that lower chances to cure MDR-TB were among patients between 41 to 50 years compared to those patients who were between 18 to 30 years old (SHR = 0.80, 95% CI: 0.61 - 1.06). The chances of curing MDR-TB in female patients were low compared to male patients (SHR = 0.84, 95% CI = 0.68 - 1.03), however this was not significant. Furthermore, HIV negative patients had higher chances to cure MDR-TB (SHR = 1.07, 95% CI: 0.85 - 1.35) compared to HIV positive patients. Patients who were treated in the decentralised sites had lower chances to be cured of MDR-TB (SHR = 0.19, 95% CI: 0.07 - 0.54) as compared to patients who were treated in the centralised hospital. **Conclusion:** Identifying key factors associated with TB and specifying strategies to prevent them can

reduce mortality of patients due to TB disease, hence positive treatment outcomes leading to the goal of reducing or end TB deaths. Urgent action is required to improve the coverage and quality of diagnosis, treatment and care for people with drug-resistant TB.

Keywords

Competing Risks, MDR-TB, South Africa

1. Introduction

Tuberculosis (TB) remains the ninth leading cause of death in the world and the leading cause of death among infectious diseases [1], including among persons living with human immunodeficiency virus (HIV) infection [2]. TB is traditionally known as a "disease of poverty". Poverty is associated with several causal and risks factors, for example overcrowding, malnutrition, immigration, HIV, alcohol, or drug use and other factors are widely acknowledged to be risk factors for the TB disease [3]. In 2018, 1.2 million deaths from TB among seronegative individuals and 251,000 deaths among human immunodeficiency virus (HIV) positive people were estimated [1]. The World Health Organisation (WHO) statistics give an estimated incidence of 301,000 cases of active TB in 2018. This is a rate of 520 per 100,000 people. It is estimated that 11,000 people became ill with multidrug resistant tuberculosis (MDR-TB) in 2018 [1].

MDR-TB is a form of TB infection which is resistant to treatment with at least two of the most powerful first-line anti-TB drugs, namely isoniazid and rifampicin and is a growing public health and clinical problem worldwide. Globally, 160,684 cases of MDR-TB were detected and notified in 2017 (a small increase from 153,119 in 2016). Of these, a total of 139,114 people (87%) were enrolled on treatment with a second-line regimen, up from 129,689 in 2016 but still 25% of the estimated 558,000 people developed MDR-TB in 2017 [1].

Africa is home to over 1 billion people and is disproportionately affected by TB with 2.6 million of the 10.4 million global TB cases [4], making the continent a key geographical area for health interventions. Sub-Saharan Africa, in particular, saw rates rapidly escalate in the early 1990s due to a delayed response to the emergent HIV epidemic at the time [5] [6]. These failures resulted in incidence rates that are the highest in the world and have made the task to end TB even more challenging. Nevertheless, the tide has changed with the rapid expansion of anti-retroviral therapy resulting in sharp declines in HIV-associated TB incidence in countries in sub-Saharan Africa, thus offering a window of hope [7] [8] [9].

The priorities including public health care workers should be identifying risk factors associated with TB disease. This is essential for assessing programmatic needs and has the potential to contribute to the targeting of interventions and

improvement of treatment monitoring, thus contributing to the End TB Strategy and to reduce TB mortality by 95% [1]. Thus, identifying and understanding most risk factors, if not all, associated with TB may help in developing strategies to assist healthcare workers to reduce or end TB mortality.

Risk factors associate with TB have received much attention in the literature dating back to the past two decades [10]-[15]. In South Africa, studies on the risk factors associated with TB were identified. In the study done between 2008 and 2012 in KwaZulu-Natal, the association between outcomes in patients co-infected with TB/HIV, and health systems performance was strong. The results were found using Pearson product moment correlation coefficients [16].

Results revealed a significant interaction between HIV infection and other risk factors for death during TB treatment in the study done by [17] using a data set collected in Cape Town City between 2009 and 2012. [17] used a Binomial log-linear regression model to obtain results. Results also showed the association between HIV infection and death among young people aged 15 - 24 years. Existing literature is generally addressing risk factors related with TB mortality and does not address specific time to cure MDR-TB after treatment is initiated, taking into account other competing risk factors that can delay or stop the event of interest which is cure MDR-TB. Therefore, this study aimed to analyse factors that delay/stop the curing of MDR-TB taking into account other competing risk, using a competing risks model in a cohort of patients receiving treatment for MDR-TB from 2008 to 2012 in KwaZulu-Natal, South Africa. The study reports the importance of using right statistical method to

This paper is organised as follows: The next section describes the data set used in this paper. Section 3 describes the methods used to analyse the data set. Section 4 reports on the results obtained using a Cox proportional hazards model and a Fine-Gray regression model. The last section discusses findings and conclusion.

2. Data Description

Study Population

This was a prospective health systems study including all patients with confirmed diagnosis of MDR-TB, and who commenced treatment between 1 July 2008 and 30 June 2010. Data were sourced from five sites: The Greytown, Manguzi, Murchison, Thulasizwe (Decentralised sites) and King George (Centralised hospital).

The data set consists of 1542 patients, aged 18 years and older, diagnosed with MDR-TB. The target population was defined as all MDR-TB patients diagnosed and treated in the TB centres during the study period. Patients receiving care at more than one site were excluded in order to guarantee the quality of information on MDR-TB treatment episodes. An automatic monitoring method adopted by [18] sought to eliminate duplicates and correct classification errors of different treatment episodes from the same patient. Inclusion criteria for the compar-

ison study required that patients reside within the catchment area of the site. No data was collected after 1 October 2012 as the study period was from 1 July 2008 to 30 June 2012.

Each participant was examined and followed through regular culture smear sputum tests for MDR-TB outcomes. Conversion of sputum culture from positive to negative was considered a useful early indicator of programme effectiveness, as treatment outcomes were only available 18 - 24 months after treatment started. Culture conversion was defined as two consecutive negative sputum cultures taken at least one month apart [19] [20] [21]. These patients were followed from the date of MDR-TB diagnosis until they became MDR-TB free or until the last follow-up date.

Study Approvals

The study protocol was approved 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 was used in this study. To protect patient confidentiality and anonymity the data bases were de-identified and access strictly limited. 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.

Data Collection

Medical records were reviewed to collect patient-related demographic, clinical, pharmaceutical and laboratory data. All data, was collected prospectively, prior to knowledge of patient treatment outcomes. Health system data was collected from different components of the health system—laboratory, pharmaceutical and transport services and human resources using existing records and databases, structured questionnaires, observation and interviews. An iterative approach was used which enabled team to identify new health system data required and develop appropriate data collection methodologies. Over the four-year study period each site was visited once monthly. During each visit data from each health system component was collected, the functioning of the MDR-TB unit observed and informal discussions held with the nurse-in-charge of the MDR-TB unit, the clinician responsible for MDR-TB and the hospital pharmacist. Through a process of ongoing reflection, feedback and discussion with facility and district level staff problems were investigated to determine their origin and cause and possible solutions identified. Field notes detailing the visit and documenting observations and discussions with staff were written up after returning from the site. Notes were also made of concerns, opinions and issues which needed follow up.

2.1. Baseline Characteristics of Study Participants

A descriptive analysis was performed to find the summary measures of the variables of interest. In this study, survival time was measured in days between

date of diagnosis and the date of the event of interest (cure MDR-TB), death, defaulted or censoring (end of follow-up period).

During the study period, a total of 1542 patients met the inclusion criteria, including 245 (15.9%) who died during the follow-up period. The median follow-up time of the study period was 26.8 months (IQR: 26.59 - 27.01). The mean baseline weight was 53.12 kg with a standard deviation of 17.01 kg. The majority of patients (35.5% and 35.7%) in this study were in the age groups 18 - 30 and 31 - 40 respectively (**Table 1**). The proportion of males was small compared to females (48.3% vs. 51.7%). Most of the patients (95.7%) in the study had no previous MDR-TB episodes. The type of TB was a pulmonary TB in almost all patients (97.9%). Seventy-four point seven percent (74.7%) of the patients were HIV positive and 25.3% were HIV negative. About (93.6%) of the patients in the study had no other diseases or conditions. The result showed that 56% of patients were cured of MDR-TB disease, and 21.7% were defaulted (**Table 1**).

2.2. Methodology

The Kaplan-Meier estimate

A traditional approach to describe time to event data and estimation of the survival function in the presence of incomplete follow-up, is a Kaplan-Meier (KM) estimate. This statistical method was originally developed to describe mortality in the presence of incomplete follow-up from unrelated causes like study dropout [22]. The KM approach provides a non-parametric estimate of the overall survival probability of an event of interest. Economists, engineers, and scientists have since widely adopted it to describe event-free survival, or time to event, for a number of different outcomes. An important assumption of KM survival analysis is that subjects who have not experienced the primary outcome and cannot be followed to study completion for any reason are censored. Censored subjects are considered "at risk" for the primary outcome for the duration of the study regardless of the reason why they were censored. Every patient in the data set has a follow-up time and status (event or censored). The follow-up times where an event has occurred are ordered from the smallest to the largest (noting that there can be ties since more than one patient may have the event at the same follow-up time). Consider consecutive event times t_{j-1} and t_j. The Kaplan-Meier estimate of the overall survival probability up to event time t_j proceeds as follows. Let n_j be the number of event-free individuals up to time t_j. Suppose d_j events have occurred at time t_j. The estimated survival probability at time t_j is given by the ratio $\left(n_j - d_j\right)/n_j$. The overall survival probability up to time t_j, denoted $S\left(t_j\right)$, is the probability of surviving up to and including time t_j. Therefore, the overall survival probability up to t_j is estimated as the product of the probabilities of survival in all the previous times:
$S\left(t_j\right) = \prod\left(n_j - d_j\right)/n_j = S\left(t_j - 1\right) \times \left(n_j - d_j/n_j\right)$, where the product is over $i = 1, 2, \cdots, j$. The overall survival probability for any time between t_{j-1} and t_j is the same as $S\left(t_{j-1}\right)$, the survival probability up to, but not including t_j.

Table 1. Baseline characteristics of study participants, KwaZulu-Natal, South Africa, 2008 to 2012 (N = 1542).

Factors Categories	Centralised hospital		Decentralised sites		Total		P-value
	No	%	No	%	No	%	
	812	52.7	730	47.3	**1 542**	**100**	
Follow-up time in months	26.8 (26.6 - 27.0)						
Baseline weight (SD)	53.12 (17.0)						
Age, mean (SD)	35.7 (10.8)						
Age at diagnosis							
18 - 30	303	19.7	245	15.9	**548**	**35.5**	0.247
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	4.8	**146**	**9.5**	
Gender							
Male	399	25.9	346	22.4	**745**	**48.3**	0.264
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**	<0.001*
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**	0.001*
Extra-pulmonary TB	8	0.5	24	1.6	**32**	**2.1**	
Comorbidities Conditions							
No other diseases or conditions	780	92.5	9	1.1	**789**	**93.6**	<0.001*
Diabetes	10	1.2	10	1.2	**20**	**2.4**	
Epilepsy	4	0.5	8	1.0	**12**	**1.4**	
Hearing loss prior to start treatment	1	0.1	10	1.2	**11**	**1.3**	
Renal problems	0	0	3	0.4	**3**	**0.4**	
Substance abuse	0	0	4	0.5	**4**	**0.5**	
Psychiatric problems	4	0.5	0	0	**4**	**0.5**	
HIV status							
Positive	576	39.1	524	35.6	**1 100**	**74.7**	0.089**
Negative	211	14.3	162	11.0	**373**	**25.3**	
Status							
Cured	439	28.5	425	27.5	**864**	**56.0**	<0.001*
Died	113	7.3	132	8.6	**245**	**15.9**	
Defaulted	229	14.9	105	6.8	**334**	**21.7**	
Lost to follow-up	31	2.0	68	4.4	**99**	**6.4**	

Kaplan-Meier Analysis for MDR-TB

The KM survival estimate for the MDR-TB data is described in the next paragraph. Before analysis, the observed survival times were first sorted in ascending order, starting with the patient with the shortest event time. The estimation of the overall MDR-TB probabilities is illustrated in Table 2. For example, the overall probability estimate of MDR-TB patients not yet cured up to 20 months is $S\left(t_j\right)=0.9510$ and the overall probability estimate of MDR-TB patients not yet cured up to 24 months is $S\left(t_j\right)=0.5069$.

The cumulative incidence of curing MDR-TB by time t_{j+1} is one minus the probability that MDR-TB is not yet cured, that is, $1-S\left(t_{j+1}\right)$. This can be seen in the last column of Table 2. For example, the probability that MDR-TB is not yet cured up to 20 months from diagnosis date is 0.9822. This is equivalent to $1-0.9822=0.0178$ (the probability of curing MDR-TB by this time).

The Fine and Gray regression method

Statistical analysis needs to take into consideration the competing risks. [23] [24] developed competing risk regression (CRR) model, which considers the effect of predictors on the cumulative incidence function (CIF) accounting for the presence of competing risks. This model considers a proportional risk model for the sub-distribution of competing risk, where the covariates directly affect the CIF. That is, for participants in our study that died due to MDR-TB or other diseases, the model considers these risks but with decreasing weight to take into account the reduction of the observations [23].

Table 2. Kaplan-Meier MDR-TB probability estimates, KwaZulu-Natal, South Africa, 2008 to 2012 (N = 1542).

Time in Months	Number at risk	Cured	Cumulative survival $S(t_j)$	Incidence = 1 − $S(t_j)$
0	1542	0	1	0
11	846	2	0.9977	0.0023
17	794	1	0.9964	0.0036
18	779	2	0.9939	0.0061
19	744	9	0.9822	0.0178
20	690	23	0.9510	0.0490
21	642	29	0.9104	0.0896
22	590	42	0.8500	0.1500
23	512	60	0.7608	0.2392
24	309	160	0.5069	0.4931
25	110	162	0.2155	0.7845
26	38	58	0.0877	0.9123
27	14	16	0.0447	0.9553
28	8	5	0.0275	0.9725
29	4	4	0.0118	0.9882
30	3	2	0.0039	0.9961

Table 3. Endpoints for the study.

Endpoint	Measurement	Event of interest	Possible competing risks
Survival	cure MDR-TB	time to cure MDR-TB	Death

In the absence of competing risks, survival data are usually presented as a bivariate random variable or pair (T,C). The censoring variable, C, is 1 if the event of interest was observed, and is 0 if the observation was censored. When $C=1$ the first member of the pair, T, is the time at which the event occurred and when $C=0$, T is the time at which the observation was censored. This definition can be extended to the competing risks situation where $p \geq 2$ types of failures or events are possible. The data are again represented as a pair (T,C), and the censoring indicator C will again be defined as 0 if the observation is censored. In the event that the observation is not censored, though, C will take on the value i, where i is the type of the first failure/event observed ($i=1,2,\cdots,p$). If $C=i$ then T is the time at which the event of type i occurred; otherwise it is the time to censoring [25] [26]. **Table 3** above illustrates the case of competing risks situation.

The CIF, or sub-distribution, for an event of type $i\left(i=1,2,\cdots,p\right)$ is defined as the joint probability

$$F_i(t)=P(T\leq t,C=i)$$

In other words, the CIF is the probability that an event of type i occurs at or before time t. The overall distribution function is the probability that an event of any type occurs at or before time t. The overall distribution function is equal to the sum of CIFs, for all event types. Hence,

$$F(t)=P(T\leq t)=\sum_{i=1}^{p}P(T\leq t,C=i)=\sum_{i=1}^{p}F_i(t)$$

The sub-survivor function is the probability that an event of type i does not occur by time t and is defined as $S_i(t)=P(T>t,C=i)$. Note here that when the competing risks are not present the overall distribution function spans the interval $[0,1]$. In contrast, in the competing risks environment the CIF can take values only up to $P(C=i)$ because

$$\lim_{t\to\infty}F_i(t)=P(C=i)$$

Therefore, $F_i(t)$ is not a proper distribution, hence the term "sub-distribution". Also note that

$$F_i(t)+S_i(t)=P(C=i)$$

In addition to the CIF and the sub-survivor function, the sub-density function for events of type i is defined as

$$f_i(t)=\frac{\partial F_i(t)}{\partial t}$$

As in the general setting of survival analysis, the sub-hazard function can be

defined in mathematical terms as

$$\tilde{h}_i(t) = \lim_{\delta \to 0} \left\{ \frac{P(t < T \le t + \delta, C = i \mid T > t)}{\delta} \right\}$$

The sub-hazard has the same interpretation as the hazard in the non-competing risks setting—the instantaneous event rate. The overall hazard of an event of any type can be found by summing over all sub-hazards:

$$h(t) = \sum_{i=1}^{p} \tilde{h}_i(t)$$

It is worth pointing out that because the CIF is a joint probability, some of the relationships among the various sub-functions may not be as expected. Based on the definition of the classical approach, one would expect that $\tilde{h}_i(t) = f_i(t) / S_i(t)$. However,

$$\begin{aligned}
\tilde{h}_i(t) &= \lim_{\delta \to 0} \left\{ \frac{P(t < T \le t + \delta, C = i \mid T > t)}{\delta} \right\} \\
&= \lim_{\delta \to 0} \left\{ \frac{P(t < T \le t + \delta, C = i)}{\delta \times P(T > t)} \right\} \\
&= \left\{ P(T > t) \right\}^{-1} \lim_{\delta \to 0} \left\{ \frac{P(t < T \le t + \delta, C = i)}{\delta} \right\} \\
&= \frac{f_i(t)}{S(t)}
\end{aligned}$$

In contrast, the hazard function of the sub-distribution [23] is defined as

$$h_i(t) = \lim_{\delta \to 0} \left\{ \frac{P(t < T \le t + \delta, C = i \mid T > t \text{ or } (T \le t \text{ and } C \ne i))}{\delta} \right\}$$

The relationship between $h_i(t)$ and the sub-density and the sub-distribution can be expressed as

$$h_i(t) = \frac{f_i(t)}{1 - F_i(t)}$$

The cumulative sub-hazard function is defined as

$$H_i(t) = \int_0^t \tilde{h}_i(t) \mathrm{d}x = \int_0^t \left\{ f_i(x) / S(x) \right\} \mathrm{d}x$$

To analyse the cause specific hazard one can employ a traditional approach for the time to event analysis. Thus, the observed time is the time to the first event and the censored variable takes the value 1 when an event of interest occurred and 0 when either the observation is censored or a competing risk event occurred.

The Cox proportional hazard model (which ignores competing risks) was employed to identify factors associated with MDR-TB. The results from the Cox model were then compared with the results obtained using the Fine-Gray sub-distribution hazard model. The Fine-Gray sub-distribution hazard method is also based on the Cox proportional hazards model [27], and it allows for the in-

clusion of time-varying covariates and it takes into account competing risks. Programming for CRR is publicly available using the statistical software R, *cmprsk* package, STATA or other statistical software.

The CIF was used to describe the probability of curing MDR-TB in the presence of competing event (death) and the Gray's test was used to compare the differences between the groups. We tested each of the selected covariates shown in **Table 1**. A p-value < 0.05 is considered to indicate a statistically significant result. The proportionality assumption of the Fine-Gray model was initially checked for CIF and Schoenfeld residuals tests.

2.3. Software Used

The Statistical Package for the Social Sciences 25 (SPSS) was used to organise the data set. We conducted the statistical analysis in STATA software, College Station, TX, USA [28], and free software R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) in the "Survival" [29].

3. Results

In this section, we apply the above methods to the MDR-TB cohort study, which is described in more detail in section 3.

The cumulative incidence functions for the sub-distribution hazard ratio (SHR) of curing MDR-TB disease and death due to MDR-TB or other diseases, in a competing risk structure are presented in **Figure 1**. The CIF of death was higher than that of curing MDR-TB disease from the beginning of the study follow-up period until about 23 months. Immediately after 24 months, we observe a gradual increase of the CIF of curing MDR-TB becoming higher than that of death.

The cumulative incidence curves [23] give an overall idea about the survival distribution. **Figure 1** summarizes the cumulative incidence estimates for the two possible events, taking competing risks into account. The probability of death was significantly high in decentralised sites than in the centralised hospital (**Figure 2**). Gray's test showed a significant difference between the sites (decentralised and centralised) in curing MDR-TB. Patients treated in the centralised hospital had a higher probability of becoming MDR-TB free compared to those patients who were treated in the decentralised sites (**Figure 3**).

Table 4 shows results obtained using the Cox proportional hazard model and Fine-Gray regression model with 95% confidence interval (95% CI) for the covariates which could be factors that affect the probability of being cured from MDR-TB. The Cox model reported baseline weight, age group, comorbidities conditions and study sites as significant covariates. The Cox results show that an increase in weight in one month results in an increase chances of curing MDR-TB by 0.8%. The results also show that patients between 41 to 50 years of age had lower chances of curing MDR-TB compared to those between 18 to 30 years (HR = 0.739, 95% CI: 1.541 - 3.009). Furthermore, the result showed that

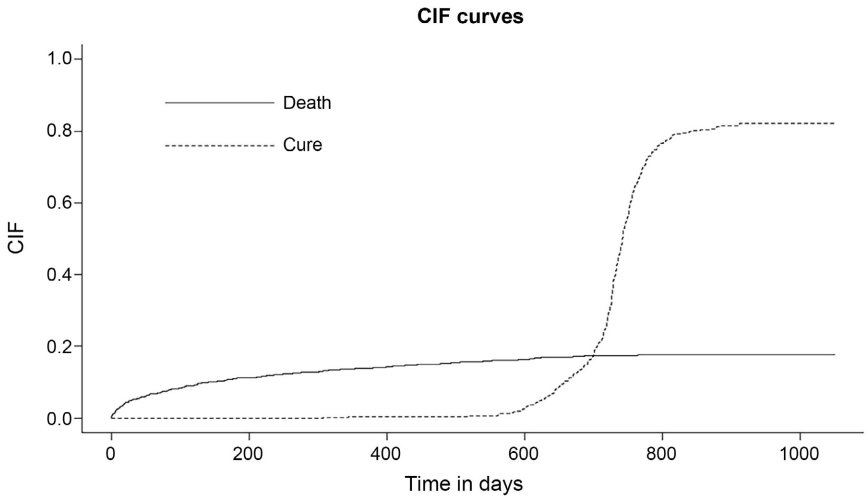

Figure 1. Survival curves estimated by the Cumulative Incidence Functions (CIF) of the sub-distribution of risks proposed by Fine and Gray.

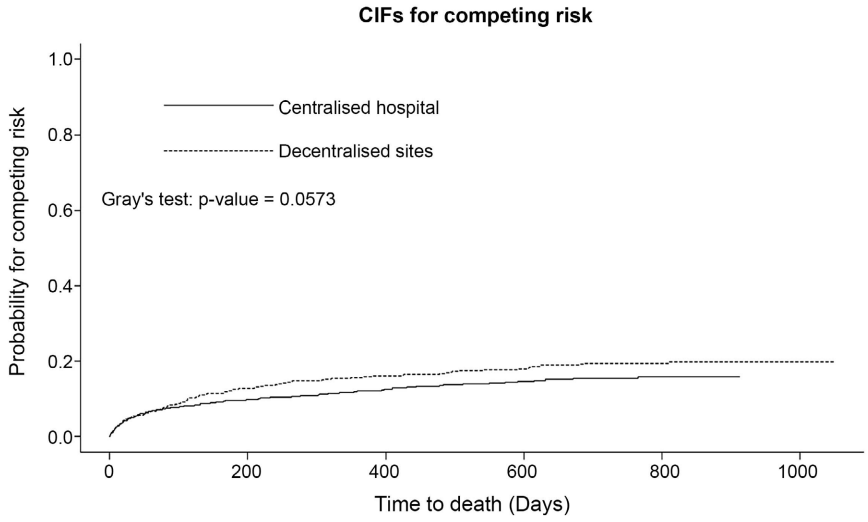

Figure 2. Cumulative incidence functions for death (Competing risk).

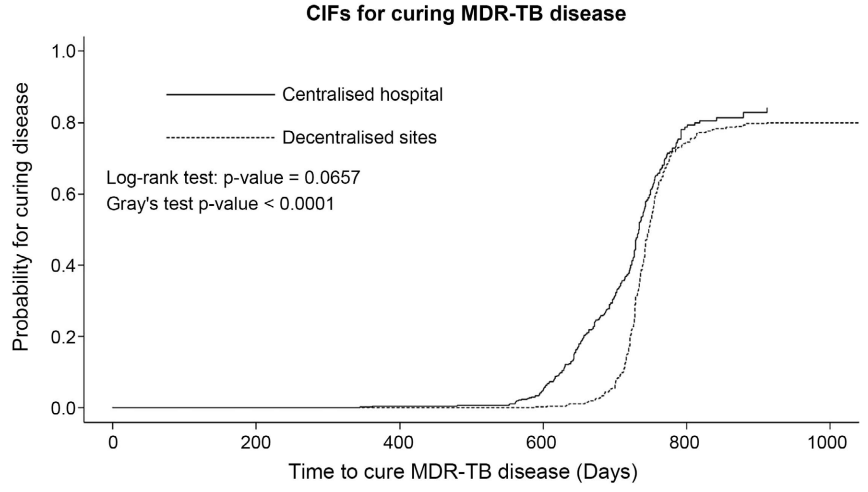

Figure 3. Cumulative incidence for curing MDR-TB disease in patients by sites.

Table 4. Cox Proportional Hazard Model with hazard ratios (HR) and Fine-Gray Regression Model with the sub-distribution hazard ratio (SHR) and confidence interval (95% CI) of reported cases of MDR-TB, KwaZulu-Natal, South Africa, 2008 to 2012 (N = 1542).

Variables	Cox Proportional Hazard Method					Competing Risk Regression Method				
	Coef.	Std.error	HR	P-value	95% CI	Coef.	Std.error	SHR	P-value	95% CI
Baseline weight (kg)	0.008	0.754	1.008	0.026*	1.001 - 2.014	0.015	0.328	1.015	<0.001*	1.009 - 3.021
Age group (years)										
18 to 30 (Ref)										
31 to 40	−0.021	0.912	0.979	0.868	0.760 - 1.260	0.599	0.522	1.821	0.111	0.643 - 1.046
41 to 50	−0.303	0.763	0.739	0.057*	1.541 - 3.009	-0.219	0.337	0.803	0.035*	1.606 - 2.063
>50	−0.101	0.744	0.904	0.622	0.603 - 1.353	0.582	0.461	1.790	0.244	0.531 - 2.175
Gender										
Male (Ref)										
Female	0.052	0.865	1.053	0.638	0.849 - 1.307	-0.175	0.246	0.840	0.098	0.683 - 1.033
Previous MDR-TB										
No (Ref)										
Yes	0.751	0.559	2.118	0.319	0.575 - 7.802	0.667	0.295	1.949	0.223	0.326 - 2.758
Comorbidities conditions										
No (Ref)										
Yes	−0.229	0.831	0.795	0.015*	1.225 - 6.378	−0.144	0.362	0.866	0.004*	1.400 - 5.865
HIV status										
Positive (Ref)										
Negative	0.096	0.750	1.100	0.045*	1.859 - 2.410	0.068	0.278	1.070	0.041*	1.851 - 2.346
Study sites										
Centralised hospital (Ref)										
Decentralised sites	−1.290	0.924	0.275	0.024*	1.090 - 4.842	−1.667	0.499	0.189	0.002*	1.067 - 4.536

*Significance at the 95% level.

patients with other comorbidities had lower chances to cure MDR-TB (HR = 0.795, 95% CI: 1.225 - 6.378) than those with no other comorbidities. HIV negative patients had higher chances of being cured of MDR-TB than those patients who were HIV positive (HR = 1.100, 95% CI: 1.859 - 2.410). The Cox regression model also reported that patients treated in decentralised sites had lower chances (HR = 0.275, 95% CI: 1.090 - 4.842) of curing MDR-TB compared to those patients who were treated in the centralised hospital.

The Fine-Gray regression model indicated that baseline weight was highly significant with sub-distribution hazard ration (SHR) = 1.015, 95% CI: 1.009 - 3.021. This means that weight gain in a month increased chances of curing MDR-TB by almost 2%. Results shows that lower chances to cure MDR-TB was among patients between 41 to 50 years compared to those patients who were

between 18 to 30 years old (SHR = 0.803, 95% CI: 1.606 - 2.063). The chances of curing MDR-TB in female patients was low compared to male patients (SHR = 0.840, 95% CI = 0.683 - 1.033), however this was not significant. The result showed that patients with other comorbidities had lower chances to cure MDR-TB (SHR = 0.866, 95% CI: 1.400 - 5.865) than those with no other comorbidities. Furthermore, HIV negative patients had higher chances to cure MDR-TB (SHR = 1.070, 95% CI: 1.851 - 2.346) compared to HIV positive patients. Patients who were treated in the decentralised sites had lower chances to be cured of MDR-TB (SHR = 0.189, 95% CI: 1.067 - 4.536) as compared to patients who were treated in the centralised hospital.

The signs of the regression coefficients differed for the effect of age group 31 - 40, >50 and the effect of female in the Cox Proportional regression model and the Fine and Gray model as can be seen in Table 4. Even though these effects are not statistically significant, this opposite effect would not be detected by fitting a standard Cox model. This is because the standard Cox model is not designed to answer risk factors in the presence of the competing risks. We further noticed that the standard errors of the estimates in the Fine and Gray model were small compared to those in the Cox regression model.

4. Discussion and Conclusions

Competing risks occur frequently in clinical studies even though their presence may not always be recognized at the time of analysis. In the analysis of competing risk data, it is important to present both the results of the event of interest and the results of competing risks. Competing risk regression analysis is used to analyse the factors that affect the probability of the event of interest to occur. A number of surprising results were found in this study. Standard errors of the regression estimates turned to be small in the Fine and Gray model. We further observed parameter estimates striking in opposite directions indicating that Cox regression model did not take into account competing risk event.

Using a Cox regression model may give incorrect estimates because it ignores competing risks and treats them as censored. Fitting a competing risk regression model is important to confirm whether the difference seen in the cumulative incidence curves is true or confounded by other risk factors. It is important when analysing survival data to first recognise that competing risks are present. Following this, the analysis should include a calculation of cumulative incidence of an event of interest in the presence of competing risks, a proper test for cumulative incidence curves of an event, and competing risk regression analyses.

In this paper, we have presented two methods of analysing survival data: 1) analysis of the event of interest ignoring competing risks, 2) analysis of competing risks. We have noticed that the effect of other risk factors changed significantly. The first approach may lead to insufficient or erroneous results. The magnitude of the error could be large if the incidence of competing risk is high, or could be minimal if the incidence of competing risk is low. However, one

could not know the effect of competing risks prior unless a competing risk analysis is done. The second approach is more preferable because it caters for competing risks and gives unbiased results. Future research is needed to include analysis of joint events as a single end point.

Conclusion, in survival analysis, it is important to assume that there are two or more failure types in addition to censoring. Fitting models separately (not jointly) for each type of failure, treating other failure types as censored data could result in difficulties in comparing parameter estimates corresponding to different failure types.

Declarations

Ethics Approval and Consent to Participate

The study protocol was approved 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 was used in this study. To protect patient confidentiality and anonymity the data bases were de-identified and access strictly limited. 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.

Consent for Publication

Not applicable.

Availability of Data and Materials

Data will be made available upon request but will be controlled.

Funding

The National Research Foundation (NRF) Grant (SFH160712177401) of South Africa has funded me to be able to expand my knowledge in data analysis using different statistical methods and programs.

Authors' Contributions

All the authors made contribution to the study. SVM planned the study and wrote the initial draft of the article and did the analysis. HW and RC assisted with data analysis and interpretation. SVM did the revisions to the paper assisted by HW and RC. All authors approved submission of this article. The author(s) read and approved the final manuscript.

Acknowledgements

We thank Dr Marian Loveday and Prof Glenda Matthews for allowing us to use their dataset. We thank all facility level managers, doctors, nurses and data capturers at the study sites for their assistance. Thank you all very much!

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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