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ABSTRACT

Background: Multidrug-resistant tuberculosis (MDR-TB) has a socioeconomic impact and threatens global public health. We assessed treatment outcomes of MDR-TB and predictors of poor treatment outcomes in Sudan given current high prevalence rates.

Methods: Combined retrospective and prospective cohort study at Abu-Anga hospital (TB specialized hospital in Sudan). All patients with MDR-TB between 2013 and 2017 were targeted.

Results: A total of 156 patients were recruited as having good records, 117 (75%) were male, and 152 (97.4%) had pulmonary TB. Patients were followed for a median of 18 months and a total of 2108 person-months. The overall success rate was 63.5% and the mortality rate was 14.1%. Rural residency (P < 0.05) and relapsing on previous treatments (P < 0.05) were determinants of time to poor MDR-TB treatment outcomes.

Conclusion: Overall, more attention needs to be given to special MDR-TB groups that are highly susceptible to poor outcomes, i.e. rural patients. As a result, it is highly recommended to maintain total coverage of medicines for all MDR-TB patients for the entire period of treatment in Sudan. It is also recommended to instigate more treatment centers in rural areas in Sudan together with programs to enhance adherence to treatments including patient counseling to improve future outcomes.

1. Introduction

The World Health Organization (WHO) believes over 10 million people globally fell ill with tuberculosis (TB) in 2017 and 2018, although the number actually reported is only 7 million [1,2]. Drug-resistant TB continues to be a global public health concern with approximately 580,000 cases worldwide and mortality worse than most cancers [1,3–6]. Overall, TB is the leading cause of death among patients with infectious diseases [7,8]. TB is also costly to treat [4,6,9]. In 2015, approximately 480,000 multidrug-resistant tuberculosis (MDR-TB) new cases were notified with 100,000 incidents registered as rifampicin resistant (RR) world-wide, with 250,000 deaths due to MDR/RR-TB [6]. In 2018, there were approximately 500,000 new cases of rifampicin-resistant TB of which 78% were MDR-TB [1]. Previously, the WHO believed that only approximately 25–30% of MDR-TB cases were detected and only approximately 25% of patients accessed second-line medications globally [10]. More recently, progress has been made in testing, detecting and treating MDR/RR-TB resulting in 51% of patients with bacteriologically confirmed TB tested for rifampicin resistance [1]. Despite this progress though, the number of patients actually treated in 2017 and 2018 was only one in three (32%) of approximately 500,000 patients who developed MDR/RR-TB [1,2]. Furthermore, only approximately 50% of those who had received treatment were declared successfully treated [10]. This has risen to 56% with more recent data [1]. In 2017 in Sudan, it was estimated there were 600 MDR/RR-TB among notified pulmonary TB patients. Moreover, it was estimated that 3.5% of new TB cases and 18% of previously treated cases are MDR/RR-TB cases [11].

TB-drug resistance generally occurs due to prescribing malpractice and poor adherence to anti-TB medications, with the spread of resistance enhanced by HIV co-infection [3,12,13]. The consequences of primary infection can also result in drug resistance. Consequently, intensive interventions are typically needed to address this. MDR-TB is characterized by the high cost of treatment, longer duration of therapy, low efficacy compared to susceptible medications, and greater side-effects of treatment [14]. MDR-TB can be prevented bearing in mind that an appreciable number of controlled trials have shown

Article highlights

- Multidrug-resistant tuberculosis (MDR-TB) has an appreciable socio-economic impact and threatens global public health. The current study aimed to assess treatment outcomes of MDR-TB and predictors of poor treatment outcomes in Sudan.
- All MDR-TB patients with complete records admitted between 2013 and 2017 to a leading TB hospital in the capital of Sudan, Khartoum, were included in the study. Overall, 156 patients were included.
- Treatment success for patients with MDR-TB (defined by WHO criteria) was 63.5%, behind the global target of 75%
- Rural residency and relapsing on previous treatments were predictors of poor outcomes of MDR-TB treatment in this study.
- More effort is needed to tackle this disease in Sudan. This should include instigating more treatment centers in rural areas alongside programs to enhance adherence including greater patient counseling especially for patients who have difficulties in reading.

that a 6-month regimen of rifampicin, pyrazinamide, isoniazid, and streptomycin or ethambutol is capable of combating TB with more than 95% of cases reported cured [15].

Overall, the treatment of MDR-TB takes a long time when compared with susceptible TB, and demands administration of at least four second-line anti-TB drugs (SLDs), including parenteral medicines plus pyrazinamide in the intensive phase [16]. However, in view of the costs involved and concerns with adherence, the management of MDR-TB needs both financial and human resources [2,17]. More recently though, the WHO has advocated oral-only treatment regimens to improve adherence rates along with continued patient centered support programs [18]. Fluoroquinolones, bedaquiline, and linezolid are also strongly recommended for use in longer regimens, with tailored treatments including shorter regimens also recommended in some patients to help improve adherence and reduce costs [8,18].

Treatment success of MDR-TB relies on the conversion of the sputum smear of the acid-fast bacilli. The status of mycobacterial cultures is needed for follow-up of treatment in limited resource areas as the findings are considered a robust interim measure for effective treatment [19]. Overall, sputum culture conversion plays a crucial role in the treatment success of MDR-TB [20]. The inability of sputum conversion to negative by the end of the intensive phase of treatment tends to yield poor treatment outcomes, namely failure and death [21,22].

The prescribing of SLDs began for MDR-TB patients in Sudan in 2008, where the program was adopted for presumptive diagnosis and empirical treatment of such cases. The Green Light Committee (GLC) Initiative Document was signed in 2010 to control MDR-TB by affording access to high-quality SLDs [23]. In Sudan, the treatment of MDR-TB patients is provided at Abu-Anga hospital, Khartoum, for at least 18 months. Medicines including ciprofloxacin, ofloxacin, cycloserine, ethionamide, and amikacin are available free of charge to patients to assist with effective treatment [24]. This compares with high levels of patient co-payment for medicines that is typically the case in developing countries [25].

Improving MDR-TB treatment outcomes is one of the five priority actions suggested by the World Health Organization (WHO) to address the global threat of MDR-TB [2], with a goal of a 75% success rate by the end of 2015 [7,17]. By 2030, the goal is a 90% reduction in the absolute number of deaths due to TB versus 2015 levels achieved for instance by improved identification and management of MDR/RR-TB cases helped by new treatment guidelines from the WHO [2,18]. This includes the provision of only orally administered medicines and more tailored treatments to improve compliance [8,18]. In the literature, there are several factors that affect treatment outcomes. For example, early culture conversion by the end of the first 2 months is associated with better MDR-TB treatment outcomes and vice versa [26]. Moreover, a recent study from China reported that MDR-TB patients who drink, smoke, have ofloxacin resistance, or a high smear grade, were significantly more prone to poor treatment outcomes [27]. Furthermore, it has been reported that male gender, urban residency, aged between 35 and 44 years, and persistence of culture positivity at 2 months were predictors of poor MDR-TB treatment outcomes in Ethiopia [28]. Additionally, extensive drug-resistant TB (XDR), male gender, and a positive smear at the beginning of treatment predicted poor treatment outcomes among Korean patients [29].

However, to date, there have only been a few studies on the outcomes of treatment of patients with MDR-TB in limited resource settings with high prevalence rates such as Sudan [30–33]. We are aware that there have been recent studies researching the incidence of TB as well as success rates for smear-positive TB between different parts of Sudan [34], reasons why TB patients default on their treatment including rural areas, adverse effects of treatment and previous history of TB [35], and that treatment outcomes in Sudan appear to be lagging behind current WHO targets [33]. However, we believe to date that treatment outcomes of MDR-TB, as well as possible factors related with poor treatment outcomes of MDR-TB, have not been reported in Sudan. This study aimed to address this deficit to provide future guidance in this high priority area in Sudan.

2. Method

2.1. Study setting

A hospital-based study was conducted at Abu-Anga hospital, which is the specialized hospital in Sudan to which suspected TB cases are referred to as well as providing health-care services to the population of Khartoum and neighboring states.

Abu-Anga hospital is also the main MDR-TB reference hospital where all recording and reporting processes are gathered and analyzed in Sudan. The hospital in collaboration with the medical colleges in Sudan and the Ministry of Health also facilitates training in the management of patients with TB and provides access to data for research purposes.

2.2. Study design

A combined retrospective and prospective cohort study design was employed. All MDR-TB patients notified between January 2013 and September 2017 attending the hospital were consecutively targeted. Cohorts of 2013, 2014, 2015, 2016, and 2017 were followed up until the end of the treatment period. The cases from 2013, 2014 and 2015 were

reviewed retrospectively. Some cases from 2016 and the cases from 2017 were followed up prospectively until the final outcomes were reported.

Consequently, data collection was started in August 2017 and ended in April 2019. This study design was adopted as the MDR-TB population is a relatively small population and needs a long period for follow-up (i.e. 18 months). Patients were enrolled in the study if they had bacteriologically proven resistance to rifampicin and isoniazid or had clinically evident MDR-TB based on a history of treatment failure or MDR-TB contact defined according to WHO guidance [36,37]. (Table 1). The success rate was defined as the sum of cured and completed patients*100/total cases.

2.3. Molecular screening, treatment regimen, and monitoring

In 2012, the Sudan national tuberculosis control program (NTP) started a molecular screening for TB patients by using Hain MTBDRplus for RIF/INH resistance and MTBDRsl VER 1.0 for fluoroquinolones and injectable second-line anti-TB drugs to screen XDR-TB. In 2014, GeneXpert was launched while MTBDRsl version 2 was brought in during 2017. GeneXpert simultaneously provides rapid detection of TB and resistance to RIF in less than 2 h. In terms of molecular screening, previously the national MDR-TB diagnostic algorithm divided TB presumptive cases into two groups. The first group was the high-risk group, and patients must be screened by GeneXpert. This group includes retreatment TB cases, MDR contacts, HIV-positive patients, health-care

workers, and seriously ill patients. The second group includes the new cases of TB for which screening has not been routinely undertaken. However, currently, all TB presumptive cases are screened by GeneXpert including new cases of TB, extra-pulmonary and childhood TB. Sputum smear microscopy was dedicated to the monitoring of treatment of first-line anti-TB drugs (FLDs). Currently, both conventional and molecular DST are used for both FLDs and SLDs as per the NTP guidance. In practice, molecular screening and DST are not routinely performed for SLDs unless XDR-TB is suspected based on the clinical and microbiological findings. As per the Sudan National TB Management Guideline, the use of sputum smear microscopy and culture to monitor response to treatment are both recommended for the monitoring of patients with MDR-TB [38].

The treatment regimen is selected based on the recommendations of the NTP, which is based on previous WHO guidelines [38,39]. All confirmed MDR-TB cases received an 18-month standardized regimen in two phases: an 8-month intensive and 10-month continuation phase. The medications encompassed a combination of first and second-line anti-TB medicines including kanamycin (Km), levofloxacin (Lev), cycloserine (Cs), ethionamide (Eth), and pyrazinamide (Z). All these medicines are given in the intensive phase, while aminoglycoside is withdrawn during the continuation phase [39]. The enrolled MDR-TB patients are treated under two models of treatment including hospital-based and community-based; both are directly observed treatment (DOT) regimens.

The direct observation for treatment and monitoring of SLDs adverse effects is facilitated by a treatment supporters' network among community-based enrolled MDR-TB patients which provides MDR-TB nurses and specialists with weekly reports and a monthly evaluation regarding second-line anti-TB drug safety. The patients are routinely monitored for adverse effects especially for the most common adverse effects associated with SLDs including gastrointestinal adverse effects, e.g. nausea, vomiting, etc., psychosis, neurotoxicity, nephrotoxicity, thyroid dysfunction, or gouty arthritis. To reduce the incidence of these adverse effects, doses are escalated for SLDs in a period of 4 weeks. Subsequently, the full doses are gradually built to avoid toxicity and increase patient tolerance. If toxicity is reported by a treatment supporter, it is evaluated by the medical panel. Either the concerned medicine is discontinued till symptoms disappear and subsequently escalated. Alternatively, the medicines are replaced by a backup medicine para-aminosalicylic acid (PAS). The backup regimen is composed of PAS with omitting the incriminating medicines, either Cs or Eth (they are the most likely SLDs associated with adverse effects). In the case of Z, the patient with elevated uric acid is treated from gouty arthritis without omitting it.

Table 1. Definition of TB types, resistance, and final treatment outcomes according to WHO

Category	Definition
Pulmonary TB	Lung parenchyma affected by Mycobacterium TB
Extrapulmonary TB	TB affects body organs other than lung
RR	Rifampicin resistance. It also includes other types of rifampicin resistance like MDR-TB and extensive drug resistance (XDR)
MDR-TB	Isolate of Mycobacterium exhibits resistance to at least rifampicin and isoniazid
New patients	Patient who has never exposed to TB drugs or administer TB medications for less than one month
Cure	Is when at least three consecutive sputum samples taken at least 30 days apart are negative during the continuation phase and without evidence of treatment failure
Treatment completed	Patients complete treatment without evidence of three consecutive sputum samples taken at least 30 days apart are negative during the continuation phase and without evidence of treatment failure
Relapse	TB patient remains sputum negative during treatment but becomes smear-positive at the end of the treatment period
Treatment defaulter	Interruption of treatment for at least 2 consecutive months
Treatment failure	Total change of treatment regimen or at least two drugs are terminated due to (a) sputum test remains positive by the end of intensive phase; (b) during continuation phase, reversion after conversion; (c) adverse drug effect; (d) evidence of resistance to fluoroquinolones or parenteral SLD
Lost to follow-up	Treatment outcome is not assigned. It includes transferred out cases and those of unknown treatment outcome
Died	Recorded as died during treatment course irrespective of cause

2.4. Treatment outcomes

Treatment outcomes were assigned based on the definition of WHO as cured, treatment completed, treatment failed, died, and lost to follow-up (Table 1). Treatment success refers to the proportion of patients who were taking their full treatment course for the entire period of treatment and declared cured or completed, whereas poor treatment outcomes were defined as the proportion of death, treatment failure, or treatment default out of the total enrolled patients.

The outcome of interest for the survival analysis was poor treatment outcomes, which included death, treatment failure, or treatment default whichever occurred first. Consequently, patients were assigned censored if declared as a cure, treatment complete, or transferred out. In cases of censoring, we considered the survival time of this category starting from the start of treatment (T0) till the date of being transferred out (T1), and the date of announcing a cure or treatment complete (T2). On the other hand, time to event survival time was computed from T0 up to the date the patient developed the outcome of interest (i.e. the poor treatment outcome) (Ti) [40].

2.5. Sample size

All patients registered in the hospital between 2013 and 2017 of both genders and with different ages were targeted. A total of 200 MDR-TB patients were registered during this period; however, only those with complete records were enrolled in the study (n = 156 patients; 78%). There was no sampling of patients because the total number of patients was limited and thus all patients were recruited.

2.6. Statistical analysis

Data were processed by IBM-SPSS version 24. Statistical tests such as unpaired t-test, chi-square, and Fischer exact test were run to summarize continuous and categorical variables of the sociodemographic and clinical factors. Moreover, the Kaplan–Meier curve was adopted to specify the cumulative survival probability. The log-rank test was processed to assess the influence of different covariates on the survival time of patients.

Cases with event outcome (poor treatment outcomes) were coded as 1, whereas censored cases were coded as 0 (reference category).

A bivariate Cox proportional hazard was first processed, and the significant variables were fitted in the final multivariable Cox proportional hazard model. The ninety-five percent confidence interval (95% CI), crude and adjusted hazard ratios (HR) were computed to estimate the predictors of time to poor treatment outcomes. The transferred out category was excluded from the bivariate and multivariate Cox proportional hazard model. Ultimately, the predictors were identified and considered significant at a P-value less than 0.05.

2.7. Ethical approval

Ethical approval number fmoh/nhrc/rd/ec was granted by the research directorate, Federal Ministry of Health, Sudan (FMOH) dated 29/07/2017. There was no patient consent form with this FMOH approval as the source of information was the TB patient card and TB registry book, with no direct contact with patients.

3. Results

3.1. Socio-demographic characteristics

As mentioned, 156 cases of MDR-TB (78%) were included in the analysis. The average age of enrolled patients was 35 ± 14 years, ranging from 15 to 90. Three-quarters of the patients (n = 117,

75%) were male and just over one third (37.5%) lived in rural locations (Table 2). No statistically significant (P > 0.05) differences in the socio-demographic characteristics were observed among the study variables except for residency (Table 2).

3.2. Clinical characteristics

Most of the study sample (n = 152; 97.4%) were smear-positive pulmonary TB (PTB) whereas there were only four extrapulmonary TB (ETB) cases (2.6%). The number of primary and secondary resistant TB was 22 (14.1%) and 134 (85.9%), respectively. The mortality rate among PTB versus ETB patients was 13.8% versus 25%, respectively. The mean hemoglobin concentration of the event category was 15.4 mg/dl ± 1.3, whereas among the censored group this was found to be 14.0 ± 2.1.

The mean level of serum creatinine was assessed to be almost the same in both event and censored categories (0.7 mg/dl). All HIV/AIDS cases (n = 3) included in the study were in the censored group and all were on antiretroviral therapy (ART) (Table 3). Ultimately, there were no statistically significant differences between the two groups in terms of clinical factors except for previous treatment outcome (P < 0.05) and previous exposure to SLDs (P = 0.04) (Table 3).

Table 2. Sociodemographics of MDR-TB patients grouped by treatment outcome.

Variable	Number of patients (%) (n = 156)	Unsuccessful event[a] (%) (n = 55)	Censored[b] (%) (n = 101)	P-value
Age-group (years)				
15–34	97 (62.2)	35 (63.6)	62 (61.4)	0.91
35–54	40 (25.6)	13 (23.6)	27 (26.7)	
≥55	19 (12.2)	7 (12.7)	12 (11.9)	
Sex				
Male	117 (75.0)	43 (78.2)	74 (73.3)	0.50
Female	39 (25.0)	12 (21.8)	27 (26.7)	
Marital status	149			
Single	69 (51.1)	21 (43.8)	48 (55.2)	0.20
Married	66 (48.9)	27 (56.3)	39 (44.8)	
Occupation				
Employee	11 (7.1)	5 (9.1)	6 (6.1)	
Self-employed	45 (29.2)	14 (25.5)	31 (31.3)	0.63
Without job	98 (63.6)	36 (65.5)	62 (62.6)	
Residency				
Rural	57 (37.5)	31 (57.4)	26 (26.5)	<0.05*
Urban	95 (62.5)	23 (42.6)	72 (73.5)	
Number of family members				
≤3	23 (21.3)	7 (20.6)	16 (21.6)	
4– 6	36 (33.3)	8 (23.5)	28 (37.8)	0.27
>6	49 (45.4)	19 (55.9)	30 (40.5)	
Nationality				
Sudanese	137 (87.8)	46 (83.6)	91 (90.1)	
South Sudan	5 (3.2)	2 (3.6)	3 (3.0)	0.43
Others	14 (9.0)	7 (12.7)	7 (6.9)	
Treatment supporter[c]				
Yes	31 (19.9)	14 (25.5)	17 (16.8)	0.29
No	106 (67.9)	33 (60.0)	73 (72.3)	
Not recorded	19 (12.2)	8 (14.5)	11 (10.9)	

NB: The P-value was taken from the Pearson's chi-square (χ^2) test or Fisher's exact test. * = statistical significance; not all variables add up to 156 due to missing data
[a]Event in this study was either death or treatment failure or treatment default.
[b]Censored was either cured or completed or transferred out.
[c]Treatment supporter is the person, i.e. family member, friend or colleague, who takes care of the TB patients.

Table 3. Clinical characteristics of MDR-TB patients grouped by treatment outcome

Variable	Number of patients (n = 156)	Treatment outcome Event[a]* (n = 55)	Treatment outcome Censored[b] (n = 101)	P-value
Site of disease				
Pulmonary	152 (97.4)	54 (98.2)	98 (97.0)	
Extrapulmonary	4 (2.6)	1 (1.8)	3 (3.0)	>0.05
Number of previous TB infection				
New	22 (14.1)	6 (10.9)	16 (15.8)	
Once	74 (47.4)	25 (45.5)	49 (48.5)	0.51
Twice	53 (34.0)	20 (36.4)	33 (32.7)	
Thrice and above	7 (4.5)	4 (7.3)	3 (3.0)	
Previous treatment outcome[c]				
Treatment failure	147 (96.1)	48 (88.9)	99 (100.0)	
Defaulter	1 (0.7)	1 (1.9)	0 (0.0)	<0.05*
Relapse	5 (3.3)	5 (9.3)	0 (0.0)	
HIV/AIDS				
Positive	3 (1.9)	0 (0.0)	3 (3.0)	
Negative	153 (98.1)	55 (100.0)	98 (97.0)	0.55
History of second-line anti-TB				
Positive	3 (1.9)	3 (5.5)	0 (0.0)	<0.05*
Negative	153 (98.1)	52 (94.5)	101 (100)	
History of diabetes mellitus				
Positive	6 (3.8)	1 (1.8)	5 (5.0)	0.13
Negative	2 (1.3)	2 (3.6)	0 (0.0)	
Not recorded	148 (94.9)	52 (94.5)	96 (95.0)	
Treatment side effects				
Positive	55(35.3)	19 (34.5)	36 (35.6)	0.89
Negative	101 (64.7)	36 (65.5)	65 (64.4)	
Initial culture result				
Positive	141 (90.4)	48 (87.3)	93 (92.1)	0.59
Negative	4 (2.6)	2 (3.6)	2 (2.0)	
Not recorded	11 (7.1)	5 (9.1)	6 (5.9)	
Hemoglobin, mean ± SD	14.0 ± 2.0	15.4 ± 1.3	14.0 ± 2.1	0.15
Creatinine (mmol/l), mean ± SD	0.7 ± 0.5	0.7 ± 0.1	0.7 ± 0.5	0.80
White blood cell count, mean ± SD	7200 ± 2300	6200 ± 1900	6400 ± 2400	0.29

NB: The P-value was taken from the Pearson's chi-square (χ^2) test or Fisher's exact test or unpaired t-test. * = statistical significance.
[a]Event in this study was either death or treatment failure or treatment default
[b]Censored was either cured, completed, or transferred out.
[c]The outcome was missing in three cases.

3.3. Treatment outcomes

The treatment outcomes were broken down into successful treatment (cure and treatment complete), poor outcomes (died, treatment failure or defaulters) and the transferred out-group – Table 4. Of the 156 MDR-TB patients, 26 (16.7%) were cured, 73 (44.2%) completed the treatment, 22 (14.1%) died, 30 (19.2%) defaulted on treatment, three (1.9%) were treatment failures and two (1.3%) were transferred out (Table 4).

Consequently, the number of patients with successful treatment outcomes was 99, giving an overall success rate of 63.5%. Poor treatment outcomes were observed to be significantly associated with rural residency as compared with those living in urban facilities (P < 0.05) (Table 4).

3.4. Survival time and treatment outcomes during the follow-up period

The mean survival time for the different categories (i.e. treatment outcomes) during the study period was noted to be significantly shorter among dead and defaulted cases (5 months), whereas relatively longer among treatment failures (15 months) (P < 0.05) (Figure 1).

3.5. The pattern of success rate over the years

The pattern of the success rate was seen to be increasing between 2013 and 2016; however, decreasing after that. Overall, the rate of success rates was 53.3%, 59.1%, 66.7%,

Table 4. Treatment outcomes of patients with multidrug-resistant tuberculosis grouped by residency status and previous treatment outcome.

| Treatment outcome	Status Total patients n = 156 (%)	Residency Rural n = 57 (%)	Residency Non-rural n = 95(%)	Previous treatment outcome Treatment failure = 147 (%)	Previous treatment outcome Relapse n = 5(%)	Previous treatment outcome Defaulters n = 1(%)
Successful treatment						
Cured	26 (16.7)	8 (14.0)	18 (18.9)	25 (17.0)	-	-
Completed	73 (44.2)	17 (29.8)	53 (55.8)	73 (49.7)	-	-
Transferred out	2 (1.3)	1 (1.8)	1 (1.1)	1 (0.7)	-	-
Poor outcome						
Died	22 (14.1)	10 (17.5)	11 (11.6)	20 (13.6)	2 (40)	-
Treatment failure	3 (1.9)	2 (3.5)	1 (1.1)	2 (1.4)	-	1 (100.0)
Defaulted	30 (19.2)	19 (33.3)	11 (11.6)	26 (17.7)	3 (60)	-
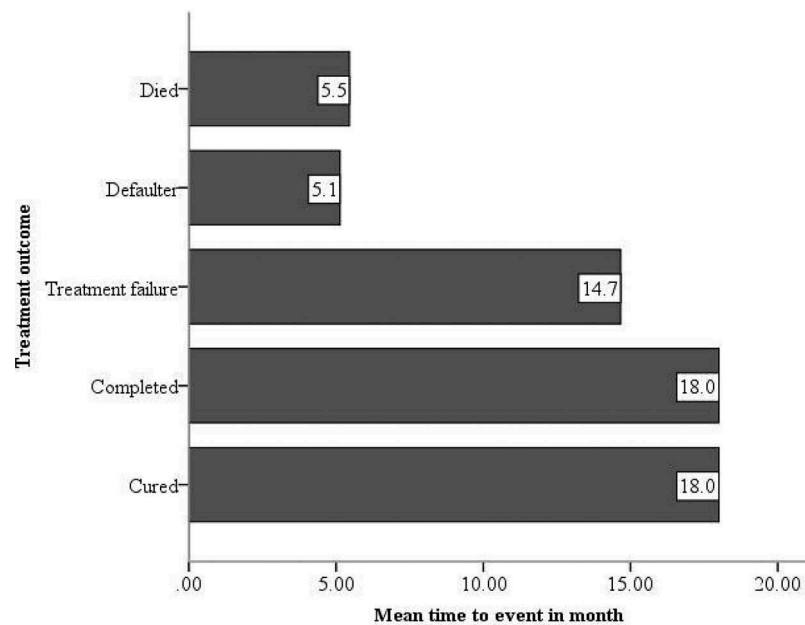
Figure 1. Schematic of survival time and treatment outcomes during the follow-up period.

and 73.1% in 2013, 2014, 2015, and 2016, respectively, before decreasing to 60% in 2017 (Figure 2).

3.6. The probability survival of MDR-TB patients

All the study participants were followed for a median of 18 months [Inter quartile range (IQR): 6 to 18 months] and a total of 2108 person-months. A total of 55 poor treatment events were reported during the study period. These included 22 deaths, 30 defaulters, and three failures that yield 26 poor outcomes per 1000 person-months (Figure 3).

MDR-TB patients living in rural areas had significantly shorter survival times compared with those living in urban facilities (11 and 15 months, $P < 0.05$, respectively). The cumulative probability of survival at the end of the study period among rural residents and urban was noted to be 45% and 76%, respectively (Figure 4).

3.7. Predictors of poor MDR-TB treatment outcomes

On bivariate analysis, rural residency and being a relapse patient from previous treatments were significantly associated with poor MDR-TB treatment outcomes (Table 5).
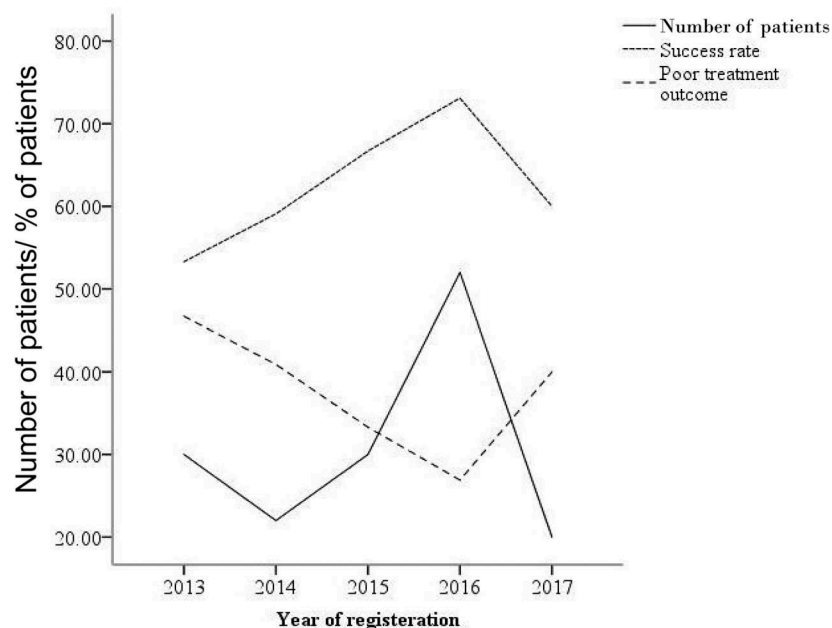

Figure 2. Number of MDR-TB patients, successful treatment outcomes, and poor treatment outcomes grouped by year.

Furthermore, multivariate analysis showed that the same factors, i.e. being rural and relapses from previous treatments, were significantly associated with a poor outcome from treating MDR-TB. Rural residents had more than twice the risk of a poor treatment outcome (AHR = 2.5, 95 CI: 1.4–4.58). Similarly, a relapsed patient from the previous treatments was five times more likely to have a poor treatment outcome (AHR = 4.9, 95% CI: 1.8–12.9) (Table 6).

4. Discussion

Our study aimed to assess the treatment outcomes of MDR-TB patients at the leading TB hospital in Sudan and to assess the determinants of poor treatment outcomes. Identifying these determinants in a high prevalence country such as Sudan should help improve the overall performance of the TB program. As a result, reducing future morbidity and mortality associated with MDR-TB. This could be achieved by the instigation of pertinent interventions and strategies that will help to successfully improve treatment outcomes in the future building on the recent changes in suggested regimens by the WHO [18].

By 2015, the Stop TB Partnership Global Plan stated that one million MDR-TB patients worldwide were to be targeted with respect to detection and treatment coverage. Moreover, success rates of at least 75% need to be achieved as the global target [17,41]. Our study shows that the overall success rate of 63.5% was lower than the 2015 global target [17]. Having said this, the treatment success rate of MDR-TB patients in our study was comparable to other low-resource countries such as Egypt (69.3%) [42] and Pakistan (71.6%) [43], although lower than high-income countries such as the United States

(78%) [44], and Switzerland (76%) [45]. There was an improvement in the pattern of success rates from 2013 up to 2016; however, unfortunately, this declined to only 60% in 2017 (Figure 2). This decline could be due to recent political and economic issues in Sudan that severely affected the healthcare system [46]. However, further research is needed before we can say this with certainty. In view of this decline in this high priority disease area, we believe there is an urgent need for the health authorities in Sudan to take the initiative and maximize efforts and resources to achieve the global target of a 75% success rate for MDR-TB, and we will be making a number of suggestions under recommendations.

Our findings that patients living in rural areas had poorer treatment outcomes are similar to the findings of Ali and Prins [35]. Poorer outcomes could potentially be attributed to the distance to the treatment center and the cost of transportation despite the medicines being provided free of charge. We have seen this phenomenon in studies assessing factors impacting on adherence to antihypertensive medicines [47,48]. However, few studies to date have described the association between residency and poor treatment outcomes among patients with MDR-TB. Similar to our findings, a case–control study undertaken in Khartoum state investigating the factors associated with treatment interruption among TB patients also reported that rural residency was significantly associated with treatment default in Sudanese patients [49]. In this study, patients recorded as relapses were five times as likely to have poor treatment outcomes. Ahmed et al. also concluded that a poor previous treatment outcome was also significantly correlated with treatment default among Sudanese patients [49]. Chen et al. also found that 65% of
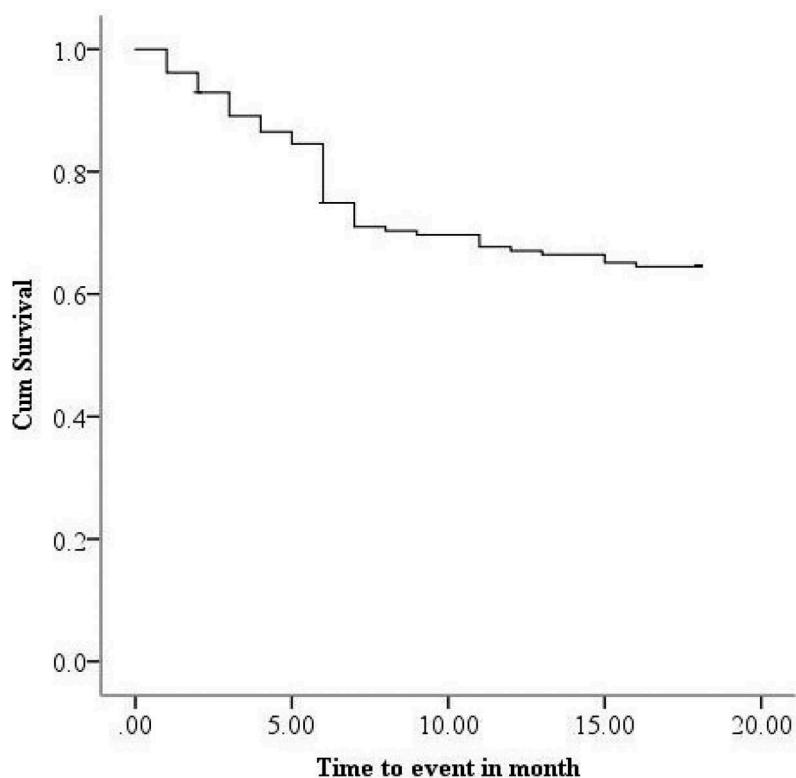

Figure 3. Kaplan–Meier curve showing the probability survival of MDR-TB patients since the commencement of treatment to end of the study period.
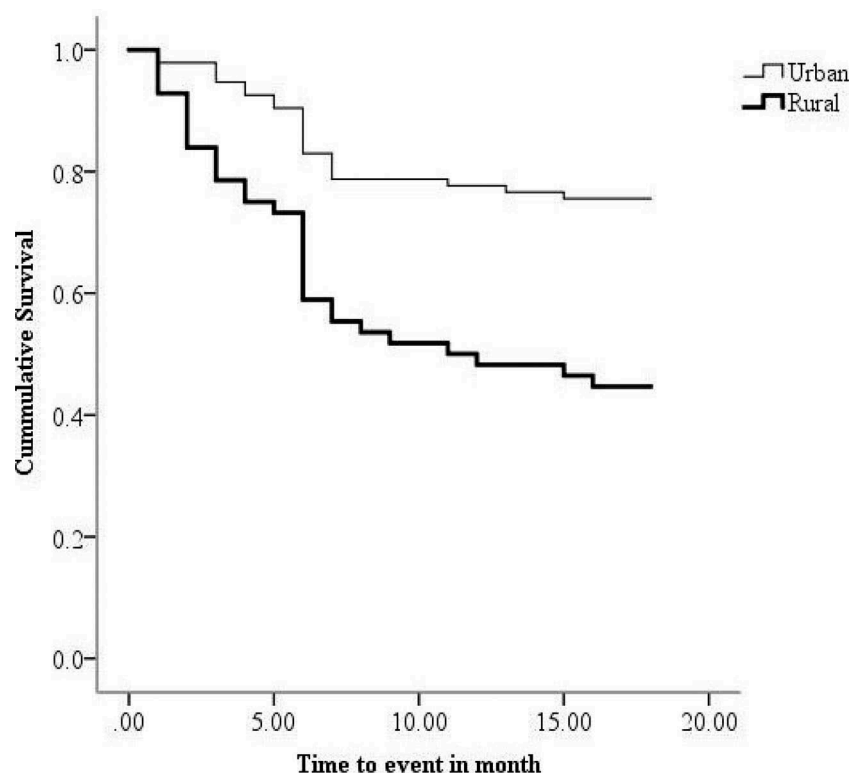
Figure 4. Kaplan–Meier survival probability curve for rural and urban MDR-TB patients.

MDR-TB cases had poor treatment outcomes including relapses before becoming MDR-TB. Moreover, unlike new cases, chest radiograph findings of re-treated cases revealed significantly more cavitation when compared to new cases [50]. In contrast, our regression model did not predict any association between most of the sociodemographic factors and the time to poor MDR-TB treatment outcomes (Table 5). These findings though are consistent with a number of other studies that confirmed no association for instance with gender or age and poor MDR-TB treatment outcomes [51–53].

On the other hand, anemia was not found to impact on poor treatment outcomes in our study. This is unlike Alene et al. who found that anemic patients were more than twice as likely to have poor treatment outcomes from their MDR-TB [40]. The positive association between anemia and death among MDR-TB patients has also been reported in a number of other published studies [54–56]. This association could be attributed to delayed presentation [40]. Despite this, the National TB program (NTP) in Sudan has recently introduced investigations including complete blood count (CBC) as a routine before treatment to help improve the outcomes in these patients, and we will be investigating this further in future studies.

Previous exposure to SLDs including fluoroquinolones and aminoglycosides was not associated with poor treatment outcomes in our study. However, the findings of a prospective cohort study undertaken in eight countries suggested that the rate of resistance to SLDs and the precipitation of extensive drug resistance-TB (XDR-TB) were seen among those patients who were previously prescribed SLDs [57]. Consequently, increased prescribing of SLD such as amikacin and ofloxacin

for infectious diseases other than TB might increase the incidence of XDR-TB. As a result, we will be researching potential ways to reduce their prescribing in future studies in Sudan.

We know that the rate of treatment failure and death of patients with MDR-TB are associated with clinical factors as well as sociodemographic factors, which include unemployment, imprisonment, and alcoholism [58]. Our findings suggest that 19 out of 30 defaulters were rural residents (Table 4). Moreover, 65.5% of poor MDR-TB outcome events were seen in unemployed patients (Table 2). Consequently, we will be looking at a number of different measures to improve patient adherence in the future including home visits, disability stipends, monthly incentives, and assistance with transportation costs. In addition, looking at potential changes in treatment regimens following changes in WHO recommendations [18]. This will be the subject of future research projects. We will also be investigating issues of education as this can impact on issues of adherence and treatment ourtcomes in these patients [59,60].

The current study included only three patients with HIV/AIDS (Table 3). However, we are aware that HIV/AIDS contributes to poor treatment outcomes [3,13,54], and that patients taking ART have a lower risk of dying [5]. Girum et al. found that HIV/AIDS positive patients with MDR-TB were three times more liable to die compared with seronegative patients [61]. This is most probably due to severe interactions between SLDs and ART, and the accompanying adverse effects which in turn might affect patient's adherence to treatment. Moreover, independent predictors of failure and death such as age, HIV/AIDS, comorbidities, and persistent positive cultures by the third month of treatment should draw the attention of clinicians to examine the potential for additional interventions.

Table 5. Bivariate–Cox regression analysis of determinants for time to poor treatment outcome among 154 patients.

Variable	Patients with poor treatment outcome (%)[a]	Unadjusted hazard ratio (95% CI)	P-value
Sex			
Male	43/116 (37.1)	1.2 (0.7–2.4)	0.50
Female	12/38 (31.6)	1	
Residency			
Rural	31/56 (55.4)	2.8 (1.6–4.8)	<0.05*
Urban	23/94 (24.5)	1	
Marital status			
Married	27/66 (40.9)	1.4 (0.8–2.5)	0.23
Single	21/68 (30.9)	1	
Occupation of the patient			
Without work	36/96 (37.5)	0.73 (0.3–1.8)	0.50
Self-employed	14/45 (31.1)	0.6 (0.2–1.7)	0.35
Employee	5/11 (45.5)	1	
Treatment supporter			
Not recorded	8/19 (42.1)	1	
No	33/104 (31.7)	0.6 (0.3–1.3)	0.20
Yes	14/31 (45.2)	0.9 (0.4–2.1)	0.78
Previous treatment outcome			
Relapse	5/5 (100)	8.2 (3.2–21.1)	<0.05*
Defaulter	1/1 (100)	2.6 (0.4–19.1)	0.34
Treatment failure	48/146 (32.9)	1	
History of second-line anti-TB			
Positive	3/3 (100)	2.6 (0.8–8.4)	0.10
Negative	52/151 (34.4)	1	
History of diabetes mellitus			
Positive	1/6 (16.7)	0.4 (0.1–3.1)	0.39
Negative	2/2 (100)	3.9 (0.9–15.9)	0.06
Not recorded	51/140 (36.4)	1	
HIV/AIDS			
Positive	0/3 (0.0)	0.0 (0.0–116.7)	0.45
Negative	55/151 (36.4)	1	
Hemaglobin status			
Anemic	0/8 (0.0)	0.0 (0.0–495.7)	0.49
Normal	5/34 (14.7)	1	

NB: In this analysis, two transferred outpatients were excluded from the analysis. * = statistical significance
[a]Values are poor treatment outcome/total number of patients in the category (%)

Table 6. Multivariate Cox regression analysis of determinants for time to poor treatment outcome among 154 patients.

Variable	Patients with poor treatment outcome (%)[a]	Adjusted hazard ratio (95% CI)	P-value
Residency			
Rural	31/56 (55.4)	2.5 (1.4–4.58)	<0.05*
Urban	23/94 (24.5)	1	
Previous treatment outcome			
Relapse	5/5 (100)	4.9 (1.8–12.9)	<0.05*
Defaulter	1/1 (100)	1.5 (0.2–11.3)	0.68
Treatment failure	48/146 (32.9)	1	

[a]In this analysis, two transferred outpatients were excluded from the analysis. * = statistical significance

Older age, HIV/AIDS, and the frequency of XDR-TB increase the death rate among TB patients [62]. SLDs are more toxic when compared with first-line anti-TB treatments, and this might also affect patient adherence [63]. The adverse effects comprise gastrointestinal (GI) disturbances, psychosis, peripheral neuropsychiatric disorders, and hearing disturbance [54]. Consequently, adverse effects need to be considered by clinicians when prescribing medicines for patients with MDR-TB, and necessary interventions should also be considered to improve adherence rates. Interventions could include greater education of patients regarding the different regimens and the need to complete the course of treatment, particularly among those patients with more limited education.

We are aware that there are several limitations to this study. Firstly, the information in some patient cards was often incomplete. In addition, information was only collected once during the study period. We also did not consider other sociodemographic and clinical factors impacting on outcomes including smoking, alcohol, asthma, heart diseases, and drug addiction as the primary source of data was the patient cards. In addition, the immunovirological status of HIV-patients was not considered in this study because the test data were not recorded in TB registries. The study scope focused on the treatment outcomes of MDR-TB patients and the factors associated with poor treatment outcomes, and provided useful data for future guidance of these patients in Sudan given the limited data to date in this important area. However, other aspects such as the adverse reactions of drugs used to treat patients with MDR-TB was out of the scope of this study. Future studies will though be undertaken to explore this aspect further. Despite these limitations, we believe our findings are robust in view of the fact that this is the leading hospital treating MDR-TB patients in Sudan and we included all the patients during the period of 2013–2017.

5. Conclusion and recommendations

In conclusion, we believe based on our findings that the current situation of TB in general and MDR-TB, in particular, in Sudan is a concern especially with a decline in the success rate of MDR-TB in recent years. We also ascertained that patients living in rural areas and relapse patients from previous treatments were associated with poorer outcomes.

In view of our findings, we recommend more care to be given to MDR-TB patient groups that are highly susceptible to death and default in Sudan, which should include greater educational input especially in those patients with limited education. Moreover, it is highly recommended that the authorities in Sudan continue to maintain total coverage of the drug supply for all MDR-TB patients for the entire period of their treatment. The authorities should also look to instigate more treatment centers in rural areas alongside programs to enhance adherence to prescribed treatments including patient counseling. We will be exploring these options in the Ministry of Health in the coming months alongside their other priority areas. Moreover, in light of these findings and as Sudan is lacking behind the global target, further studies are recommended to tackle other variable aspects and barriers to successful MDR-TB treatment outcomes in Sudan. We will also be pursuing these as well with relevant personnel and authorities

in Sudan and reporting on developments and their impact in the future.

Declaration of interest

Hamdan Mustafa Hamdan Ali works for the National Tuberculosis Control Program, Federal Ministry of Health, Sudan.

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