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ASSESSMENT OF THE STATUS OF TUBERCULOSIS MULTIDRUG-RESISTANCE (MDR-TB) IN ABU-ANGA TB REFERENCE HOSPITAL, SUDAN 2015 - 2021

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Abstract: Scarce information is available regarding the incidence, prevalence, diagnosis, and management outcomes of Multi Drug Resistant-Tuberculosis (MDR-TB) in Sudan. This study aimed to assess MDR-TB diagnosis, management, treatment outcomes and predictors of treatment in Abu-Anga TB Reference Hospital in Sudan between the period 2015 - 2021. A retrospective facility-based study was conducted on the records of 60 patients with MDR-TB. Twenty-three patients with complete file records were enrolled in the study. Data collected from the hospital registry of the 23 MDR-TB case files was analyzed using (SPSS. Ver 24). Descriptive analysis was also used for counts percentages. Results of the study participants showed that among the 23 patients, multiple drug resistance type had the highest percentage (39.1%), Rifampicin resistance was (21.7%), poly-drug resistance represented (26%) with the Pre-XDR percentage (8.7%) and XDR types being at the lowest percentages (4.3%). The outcome of the treatment indicated that 10 patients (43.4%) were cured, 6 patients (26%) were lost to follow up, 4 patients (17.4 %) failed treatment, and 3 (13%) patients died. The findings of this study indicated that good outcome predictors were the adoption of Directly Observed Treatment Strategy, hospitalization treatment model, and in-patient treatment with family support. Poor treatment outcomes were significantly related to rural residency, HIV (human immunodeficiency virus) co-infection, and treatment relapse. It is recommended to increase patient awareness among those living in rural areas to available treatment regimens and improve disease perception to increase treatment compliance and adherence. The study findings highlighted the importance of training of health providers on the proper recording and maintenance of all MDR-TB case files.

Keywords: Tuberculosis, Multidrug resistance, Directly Observed Treatment Strategy, Treatment outcome

Introduction

Tuberculosis (TB) is a worldwide public health problem that continues to affect millions of people each year. It is a major health challenge constituting one of the main causes of death worldwide. Until the coronavirus (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS (Global tuberculosis report 2022). Approximately 10 million new

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TB cases are reported, and 1.5 million deaths occur annually due to the infections, the majority of whom are in resource limited countries (Global tuberculosis report 2022). TB is an infectious disease affecting primarily the respiratory tract and is caused by the bacillus Mycobacterium tuberculosis (M. tuberculosis). Once exposed, approximately 10% of individuals develop active disease characterized by cough, fever, lethargy, loss of appetite, weight loss, and fatigue. Albeit the small percentage of individuals developing active disease, there are an estimated 1.5 million TB related deaths every year worldwide making it the second leading cause of death from an infectious disease behind the human immunodeficiency virus (HIV) (World Health Organization, 2010).

About a quarter of the global population is estimated to have been infected with TB but most people will not go on to develop TB disease and some will clear the infection (Kimbrough *et al.* 2012). As of 2021, most TB cases occurred in the regions of South-East Asia (45%), Africa (22%), the Western Pacific (18%), and Eastern Mediterranean (8.1%) with more than two thirds of cases being diagnosed in eight countries: India (28%), Indonesia (9.2%), China (7.4%), the Philippines (7.0%), Pakistan (5.8%), Nigeria (4.4%), Bangladesh (3.6%) and the Democratic Republic of the Congo (2.9%) (Global tuberculosis report 2022).

The most frequently used diagnostic methods for tuberculosis are the tuberculin skin test, the acid-fast stain, culture test, and the polymerase chain reaction (World Health Organization, 2010). There are several rapid molecular tests that are recommended by WHO as the initial diagnostic test for TB that can detect drug resistance simultaneously as well as tests specifically for the detection of resistance to several first- and second-line anti-TB drugs, and sequencing technologies that can provide a comprehensive individual profile of drug resistance (Global tuberculosis report 2022).

Some infected individuals are shown to have resistant TB to multiple antibiotics (MDR) or even to most known treatments (XDR). Multiple drug resistant tuberculosis (MDR-TB) patients demonstrate resistance to the first line drugs (FLDs) Rifampicin (R) and Isoniazid (I), while extensively drug resistant tuberculosis (XDR-TB) patients have MDR-TB with added resistance to the class of second line drugs (SLDs), fluoroquinolones (FQ), and at least one of the second line injectable agents; amikacin, kanamycin, and/or capreomycin (World Health Organization, 2011). About a quarter of the global population is estimated to have been infected with TB, but most people will not go on to develop TB disease and some will clear the infection (Global tuberculosis report 2022). The infected person has a positive result on immunological testing (e.g., interferon gamma release assays), but shows no symptoms of disease. Furthermore, diagnostic (Chest X-ray tests (CXR) reveals no sign of active TB. These patients are not infectious, but, in the presence of weakened T-cell immunity, the latent TB infection (LTBI) can turn into active disease at any time (Narasimhan *et al.* 2013).

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 (World Health Organization, 2017).

The latest WHO guidelines published in 2022 include a strong recommendation for a 6-month regimen of isoniazid (H), rifampicin (R), ethambutol (E) and pyrazinamide (Z) for people with drug-susceptible TB (both pulmonary and extrapulmonary): all four drugs for the first two months, followed by H and R for the remaining 4 months.

Treatment of MDR-TB takes a long time when compared with susceptible TB and demands administration of at least four secondline anti-TB drugs (SLDs), including parenteral medicines plus pyrazinamide in the intensive phase (Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis: 2011 Update). Treatment success of MDR-TB relies on the conversion of the sputum smear of the acid-fast bacilli. (Nagaraja *et al.* 2012). Recently, WHO issued two new recommendations for treatment of MDR-TB – one for the use of a 6-month BPaLM regimen, composed of bedaquiline, pretomanid, linezolid and moxifloxacin in patients with multidrug-resistant or rifampicin resistant TB (MDR/RR-TB) and those with additional resistance to fluoroquinolones (pre-XDR-TB) and another for a 9-month all oral regimen in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded (WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update).

Sudan has a high burden of tuberculosis with an estimated 50,000 incident cases during 2009, when the estimated prevalence was 209 cases per 100,000 of the population (World Health Organization 2010). In 2017, 21054 cases of TB were notified in Sudan (World Health Organization, 2018). 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 (Adam *et al.* 2017). The treatment of MDR-TB patients is provided by Abu-Anga reference hospital in Omdurman, 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 (Sharaf Eldin *et al.* 2011). 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 (Basit *et al.* 2014). 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 (Lui *et al.* 2018). Male gender, urban residency, age between 35 and 44 years, and persistence of culture positivity at 2 months were predictors of poor MDR-TB treatment outcomes in Ethiopia (Melese and Zeleke 2018). Extensive drug-resistant TB (XDR), male gender, and a positive smear at the beginning of treatment predicted poor treatment outcomes among Korean patients (Jeon *et al.* 2011).

In Sudan, the National Tuberculosis Control Program (NTP) introduced in 2012 molecular screening for TB patients 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 (Ali *et al.* 2019). Both conventional and molecular drug susceptibility testing (DST) are used for both FLDs and SLDs as per the NTP guidance. The treatment regimen is selected based on the recommendations of the NTP, which is based on previous WHO guidelines (Sudan National TB Management Guideline 2018 ; Sudan National TB Management Guideline 2019). All confirmed MDR-TB cases should receive 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 (Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Geneva: World Health Organization; 2014). MDR-TB patients are treated under two models of treatment either hospital-based or 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.

A wide range of classifications are currently being used from the WHO and National TB Control Program based on the disease itself as clinically diagnosed or bacteriologically diagnosed, anatomical site as pulmonary or extra-pulmonary TB, history of previous TB treatment as new case or retreatment case, drug-susceptibility as mono-resistant TB to one first-line anti-TB drug only, polydrug-resistant TB to more than one first line anti-TB drug other than I and R., MDR-TB, XDR-TB and RR-TB, registration groups, history of previous treatment, and treatment outcomes (Manual of Procedures of the National Tuberculosis Control Program, 5th Edition 2022). Patients are classified in two TB disease registration groups as new for those who has never had treatment or as retreatment after relapse, retreatment after failure, retreatment after lost to follow- up, retreatment after previous treatment outcome unknown. Treatment outcomes are assigned based on the definition of WHO as cured, treatment completed, treatment failed, died, and lost to follow-up. 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.

Prevention of TB involves screening those at high risk, early detection and treatment of cases, and vaccination with the bacillus Calmette-Guérin (BCG) vaccine. Those at high risk include household, workplace, and social contacts of people with active TB (Chakaya *et al.* 2021). 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 (World Health Organization, 2018).

The rate of multidrug resistant pulmonary TB is increasing in Sudan. The exact information regarding the incidence, prevalence, diagnosis, and management outcomes of MDR-TB patients in Sudan needs to be known. The general objective of this study was to assess the outcomes of diagnosis and management protocols of MDR-TB in Abu-Anga Reference TB Hospital in Sudan between the period 2015 - 2021. The specific objectives were to determine how MDR-TB cases are treated in Abu-Anga hospital and to assess the different management plans, determine the outcomes of treatment following diagnosis of MDR-TB, and detect factors hindering success in management of MDR-TB. Assessing and evaluating Abu-Anga TB Reference Hospital records would reveal and detect drawbacks to improve early diagnosis and effective management of MDR-TB.

Materials and Methods

A retrospective facility-based study was conducted. All the case files of MDR-TB patients registered in Abu-Anga TB Reference Hospital during the period 2015-2021 were studied. Abu-Anga referral hospital, is a TB tertiary hospital in Omdurman City with over 300 beds. Suspected TB cases are referred to the hospital from Khartoum state and nearby states. Records of patients enrolled in the study who were initially confirmed to have bacteriologically proven resistance to rifampicin and isoniazid or have clinical evidence of MDR-TB based on a history of treatment failure or MDR-TB defined according to WHO guidance (Manual of Procedures of the National Tuberculosis Control Program, 5th Edition 2022). Exclusion Criteria were the incomplete records of patient information.

A total of 60 MDR-TB patients were registered during this period. The case files of 23 patients with complete records were enrolled in the study. The population size is manageable and is a well-defined subgroup. Data sheet of TB registry was filled from the hospital records of all 23 patients who had a complete record. Data analysis was performed using statistical package for social sciences (SPSS ver. 24). Descriptive analysis was used for counts and percentages.

Ethical approval number fmoh/nhrc/rd/ec was granted by the IRB of the Federal Ministry of Health, Sudan (FMOH) dated 16/10/2021. 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. Approval of medical director of the hospital was granted.

Results

The results of a retrospective facility-based study on the assessment of the status of tuberculosis MDR in Abu-Anga TB Reference Hospital between 2015 and 2021 are presented. Sixty patient case files of MDR-TB were registered during this period. Upon examination of the records, it was revealed that only 23 case files (38.3%) included complete records of patients' information, history, laboratory investigation, treatment plans and outcomes. The remainder of thirty-seven incomplete case files (61.7%) were discarded and excluded from the study because they were missing important data in their records. This may have introduced bias if having missing records is related to certain risk factors.

Socio-demographic Characteristics:

Gender distribution showed that the majority of the participants were males 17 (74%). The age of participants ranged between 17 – 40 years. The age group of participants between 20-30 years represented the highest number of MDR-TB patients (47.8%). In regard to marital status, most of the patients 11 (47.8%) were either separated or divorced. Data on the level of education of participants indicated that primary school graduates had the highest percentage of MDR-TB among participants (34.7%) followed by non-educated participants (30.4%), while secondary school graduates had the lowest percentage of (13%). Regarding occupation, most of the participants occupations were unspecified (47.8%), 6 participants were housewives (26%) and 4 were merchants (17.4%), private employees and farmers represented (4.3%) respectively. Regarding residence distribution, 14 participants were from Khartoum State (60.8%) and 9 (39.2%) patients were referred from other nearby states i.e., El Gezira and White Nile state.

Medical History of MDR Tuberculosis Patients at Admission:

Medical history of the participants Table 1 indicated that 7 (30.4%) of the participants were suspected to have MDR-TB when attended to the hospital, while 3 (13%) were bacteriologically confirmed to have MDR-TB at admission. The rest of 13 participants (56.5%) were confirmed to have MDR-TB by GeneXpert. Sixteen out of the 23 registered participants (69.65%) had previous First Line Drug history. On the other hand, Most of the MDR-TB patients 20 (86.9%) had already taken the SLDs; (Kanamycin, Levofloxacin and Cycloserine) at the start of treatment for more than a month. Sixteen of the participants were HIV tested. Three of whom were HIV positive (18.8%). Two of those HIV positive participants have started taking antiretroviral therapy (ART). Regarding smoking history, 12

of the participants were smokers (52.2 %), 8 participants were nonsmokers (34.7 %) and 3 participants had unspecified records. The records of two patients (8.70%) indicated that they were previously managed at Abu-Anga Hospital, one patient at Al Shaab Hospital, one at Alhosh, and one at Kosti TB center. Eighteen patients (72.26%) did not report the name of their previous Tuberculosis Management Unit (TBMU). Recorded as NA; not available.

Table 1: Results on Medical history of participants in Abu-Anga Reference Hospital 2015-2021.

Variable	Status	Number N=23	%
MDR-TB at the start of treatment	Confirmed MDR	3	13%
	Suspected MDR	7	30.4%
	Not known	13	56.5%
Taken second line drugs for more than a month	Yes	20	86.9%
	No	3	13%
HIV test	Yes	16	69.5%
	No	7	30.4%
HIV result n=16	Positive	3	18.8%
	Negative	13	81.2%
Started on ART n=3	Yes	2	66.6%
	No	1	33.3%
Smoking History	Yes	12	52.2%
	No	8	34.7%
	Unspecified	3	13%
Previous Tuberculosis FLD treatment history	Yes	16	69.6%
	No	7	30.4%

Laboratory Findings and Treatment:

Results presented in Table 2 show the classification of MDR-TB patients based on anatomical site, registration group, drug susceptibility test, resistance type, and laboratory findings. Classification of the participants showed that 18 patients (78.3%) had pulmonary TB and 5 (21.7%) had extrapulmonary TB. Twelve of the patients who had pulmonary TB were smokers (66.6%), while 2 of those with extra pulmonary TB were non-smokers. Patient classification based on history of previous TB treatment (patient registration group) showed 8 participants (34.7%) were Retreatment relapse cases, 6 participants (26%) were Retreatment after failure, 5 (21.7%) were lost to follow-up, 3 (13%) were registered as Retreatment after Previous Treatment Outcome Unknown (PTOU) and one participant (4.3%) was a new case. In regard to (DST) resistance type, results estimated that 21 patients (91.3%) were resistant while 2 patients (8.7%) were susceptible. While 9 of the patients (39.1%) drug resistance type was MDR, 6 patients were Rifampicin resistant (26%), 5 patients (21.7%) were polydrug resistant, two patients (8.2%) had preextensive resistance type (Pre-XDR) and only one patient had the XDR type (4.3%). Laboratory tests of the participants of Abu-Anga Hospital,

showed that 13 (56.5%) were tested by Gene Expert, 5 patients (21.7%) did the smear microscopy test, and 5 patients (21.7%) did the AFB Sputum culture test.

Table 2: Tuberculosis classification based on anatomical site, registration group, drug susceptibility test, resistance type, and laboratory findings of participants in Abu-Anga Hospital 2015 - 2021.

Variable	Status	Number N=23	%
Disease classification based on anatomical site	Pulmonary	18	78.3%
	Extra Pulmonary	5	21.7%
TB patient classification based on registration group i.e., previous TB treatment history.	Retreatment Relapse	8	34.7%
	Retreatment after Failure	6	26%
	Retreatment after Lost to Follow-up (TALF)	5	21.7%
	Previous Treatment Outcome unknown (PTOU)	3	13%
	New case	1	4.3%
Drug Susceptibility test for FLDs	Resistant	21	91.3%
	Susceptible	2	8.7%
Type of Resistance	Rifampicin resistance	6	26%
	Poly drug resistance	6	26%
	Multiple drug resistance	9	39.1%
	Pre-XDR	2	8.7%
Lab Test	Gene Expert	13	56.5%
	AFB – Sputum culture	5	21.7%
	Smear	5	21.7%

The Types of Regimens Used for Treatment of Participants in Abu-Anga TB Hospital:

Figure 1 shows the treatment regimens followed in the treatment of the participants in Abu-Anga TB Hospital. Five patients received the standard oral treatment type (21.7%), 3 patients received the standard long injectable treatment (13%), 3 received the standard short injectable medication (13%) and 3 received the standard long oral medication treatment (13%). The Pre-XDR regimen type was given to 8 patients (34.7%) and the XDR Regimen was given to one patient (4.3%).

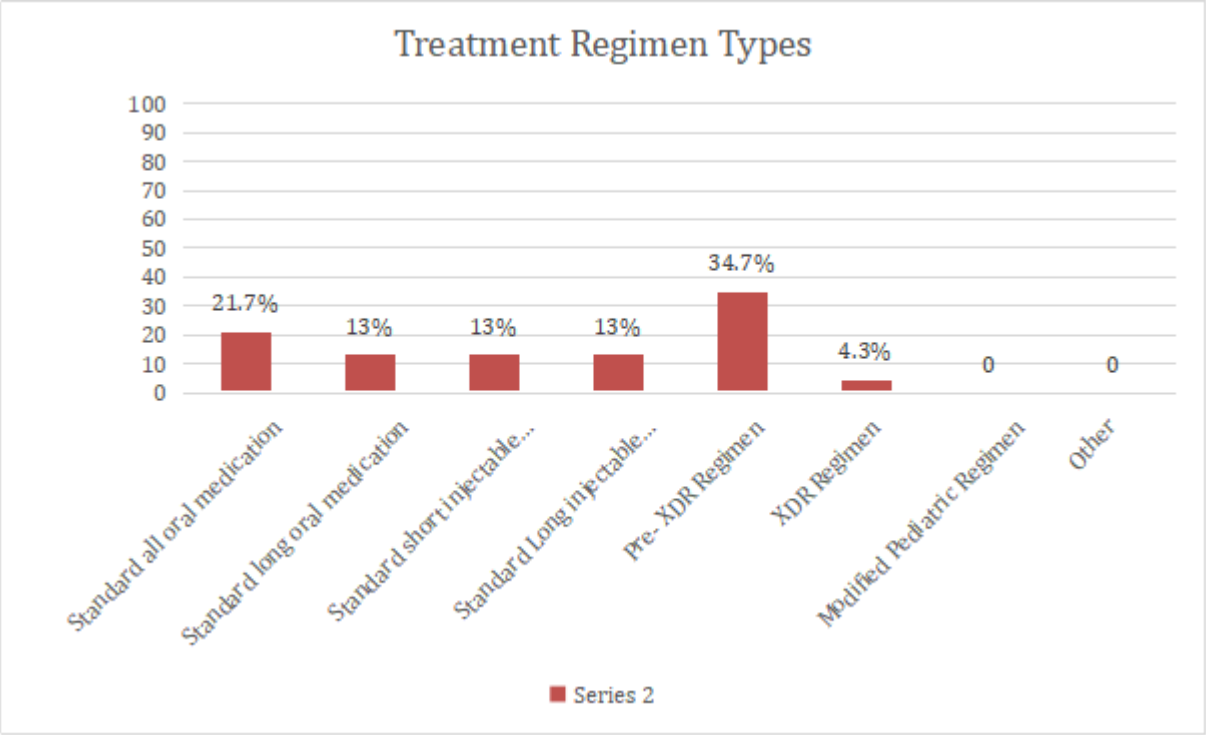

Figure 1: Types of Regimens used for participants in Abu-Anga TB Hospital in Omdurman 2015-2021.

Treatment Model, Support Type, Adverse Effects, and Treatment Outcomes

Regarding treatment model, 16 participants were treated as inpatient (69.5%) and were supported by family members, 7 (30.4%) were treated at home supported by community volunteers. Most of the participants (82.6%) did not encounter adverse effects during management, while only four (17.3%) encountered side effects; (nausea, vomiting and diarrhea) during the management period. The success rate of the treatment plans was estimated at (43.4%), i.e., 10 patients completed the treatment plan. Four patients (17.4%) were treatment failure of TB, 6 patients were lost to follow-up (26%), 3 patients (13%) reported as died.

Good treatment outcome was associated with inpatient treatment model with family support, while community support at home treatment model was associated with poor outcomes.

Table 3: Treatment model, support type, adverse effects, end date and treatment outcomes.

Variable	Status	Number n=23	%
Treatment Model	Hospitalization; In-patient Model	16	69.5%
	Community Model	7	30.4%
Treatment Support Type	Community member	7	30.4%
	Family member	16	69.5%
Drug Administration	Directly observed	14	60.8%
	Not observed / Not Taken	9	39.1%
Adverse Effects during management	Yes	4	17.3%
	No	19	82.6%
Treatment Outcome	Failure	4	17.4%
	Complete	10	43.4%
	Died	3	13%
	Lost to follow up	6	26%

Drug Administration:

Regarding drug administration, 14 participants (60.8%) were directly observed while taking the medication and 9 (39.1%) of the participants were not observed taking drugs or did not take the drugs.

Contact Screening and Evaluation:

On screening of patient contacts of MDR-TB patients, 11 patients contacts accepted to do the screening (48%) and 2 of them were found to be positive for TB. On the other hand, the remaining 12 contacts (52%) refused to be screened.

Discussion

The study results indicated that the overall treatment success rate of 23 MDR-TB patients was estimated as (43.4%) as only 10 MDR-TB patients recovered after completion of treatment. The findings illustrate the contribution of many factors to poor diagnosis, treatment, and treatment outcomes of MDR-TB. One of the contributing factors included socio-demographic characteristics as poor socioeconomic status and ill disease perception correlated with noncompliance to medications, relapsing to treatment, drug resistance and the refusal of inpatient household contacts to be screened. Good treatment outcome was found to be associated with presence of family member support and implementation of reliable directly observed treatment strategy.

The study also revealed that there was shortage in the information of records of MDR-TB patients, this is more likely due to the under reporting of the treatment plans and outcomes as only 23 patients (38.3%) had complete file records out of the 60 registered MDR-TB case files. Thus, the limitation in the proper interpretation of the results due to the incomplete file records that were excluded from the

study and the small sample size of 23 records which did not allow the estimation of statistically significant accurate associations between the different variables. Hence, the interpretation of the results of this study relied only on descriptive statistical analysis.

In a study conducted by Sharaf Eldin et al. (2011) investigating drug susceptibility of M. tuberculosis isolates from 235 Sudanese patients, 127 isolates (54%) were found fully susceptible to the first line drugs, isoniazid, rifampicin, ethambutol and streptomycin, while 108 isolates (46%) had resistance to at least one of the four drugs tested, and 26 isolates (11%) were classified as MDR-TB, being resistant to at least isoniazid and rifampicin.

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 (Ali et al. 2019). In a recent systematic review and met-analysis paper on the prevalence of drug-resistant tuberculosis in Sudan, Hajissa et al. (2021) estimated the overall prevalence of MDR-TB at 22.8%. In agreement with our findings in this study, they also reported that the resistance profile of the previously treated patients was found to be remarkably high compared with the newly diagnosed TB patients.

The total number of registered MDR-TB patients (n=60) who sought treatment in Abu-Anga TB Reference Hospital in Sudan during 2015-2021 and included in our study was lower than what we expected, taking into consideration the high incidence of MDR-TB in Sudan in 2017 as reported by Ali et al. (2019).

Conclusion

Good outcome predictors of successful treatment of MDR-TB in the present study were the implementation of directly observed treatment strategy, hospitalization treatment model and presence of family member treatment support. The treatment success rate of MDR-TB patients of 43.4% in the present study was below the target. Hence, it is recommended to provide effective MDR-TB diagnosis and treatment strategies to facilitate prevention and disease control among patients. It is highly recommended to maintain coverage of medications for all MDR-TB patients for the whole duration of management in Sudan, and to increase coverage and access to GeneXpert testing for confirmatory diagnosis of MDR-TB. The refusal of 52% household contacts of MDR-TB patients to be screened for TB due to stigma and ill disease perception highlights the need for awareness and health education of individuals at risk and the general public in Sudan.

It is also recommended to train health care providers at Abu-Anga Hospital on the proper recording and maintenance of MDR-TB case files for future research purposes.

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Declaration of Interest Statement

The authors declare that they have no conflict of interests.

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