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Assessment of the Survival Status and Risk Factors for the Mortality among Multidrug Resistant Tuberculosis Patients at Adama and Bishoftu General Hospitals, Oromia, Ethiopia: A Retrospective Cohort Study

Debalke Fantaw[1], Mamo Feyissa[2], Shifa Hamid[3] and Workineh Shibeshi[2*]

[1]*Ethiopian Food, Drug and Healthcare Administration and Control Authority, Ethiopia*
[2]*Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Science, Addis Ababa University, Ethiopia*
[3]*Bishoftu General Hospital, Oromia region, Ethiopia*

Abstract

Background: Multi-drug resistant tuberculosis is a widespread global problem. The magnitude of this disease varies significantly from country to country and the treatment outcomes are inadequately described in Ethiopia.

Objective: To assess the survival status and risk factors for mortality of multidrug resistant tuberculosis patients at Adama and Bishoftu General Hospitals in Ethiopia.

Methods: Retrospective cohort study design was conducted among multidrug resistant tuberculosis patients treated from May, 2013 to August, 2017 at Adama and Bishoftu General Hospitals. Data were collected using standardized data abstraction format. Data were analysed using STATA Version 13 statistical software. Risks were estimated for the entire follow-up time corresponding to each event occurrence using Kaplan-Meier method and the covariates were fitted to Cox Proportional Hazard Regression Model.

Result: Among 164 patients, 74 (45.10%) were male and the mean age was 31.5 years. The participants were followed for a total of 63,141 person-days. The median survival time was 400.5 days. There were 30 (18.30%) known deaths and the survival probability of the study participants at 6, 12, 18 and 24 months of treatment was 84%, 82%, 81% and 72%, respectively. The Cox regression analysis showed that factors independently associated with mortality of patients were: HIV (AHR=2.75, 95% CI(1.23-6.15); low initial body weight(HR=0.44,95% CI (0.22-0.85); co-morbidities and co-infections (AHR=2.28, 95% CI (1.99- 5.26); age (AHR=2.26 ,95% CI (1.35-3.79); and Khat use (AHR=0.41, 95% CI (0.18-0.97).

Conclusion: A lower survival time was found with declining probability of survival across duration of treatment. Higher mortality rate was noted in patients who started MDR-TB treatment with initial low body weight, HIV positive, co-morbidities and co-infections and Khat user.

Keyword: Multidrug resistant tuberculosis; Rifampicin resistant; Survival probability; Isoniazid resistant; Treatment outcome, Risk factors

Abbreviation: MDR-TB: Multi-Drug Resistant Tuberculosis; TB: Tuberculosis; R: Rifampicin; RR: Rifampicin resistance; H: Isoniazid

Introduction

Multidrug Resistant Tuberculosis (MDR-TB) is tuberculosis caused by *Mycobacterium tuberculosis* that does not respond to at least isoniazid and rifampicin [1,2]. It could be new TB cases (primary infection) or resistance may develop while the patient is on course of TB treatment mainly due to human error, major predictor being treatment non-adherence [2]. According to WHO 2017 Global TB report, estimated MDR-TB incidence is 4.1% in new TB patients and 19% in previously treated TB cases globally. According to this report Ethiopia is among the top 20 countries with high MDR-TB burden with overall incidence of 5.7% (3.0%-8.3%) of MDR/RR-TB infection. The estimated incidence is 2.7% (1.5%-4.0%) in new TB cases and 14% (3.5%-25%) in previously treated cases [3].

In Ethiopia among the notified TB cases in 2014, about 1.6% of new and 11.8% previously treated TB cases harbour MDR-TB. Besides, MDR-TB sentinel report in 2013 shows the MDR-TB prevalence of 2.3% among new and 17.8% among previously retreated TB cases [4]. Institution based studies report varying prevalence of MDR-TB in different parts of Ethiopia ranging from 3.0%-46.3% [5]. A facility based cross-sectional study conducted in forty-three public health facilities in Eastern Amhara Regional state of Ethiopia revealed that overall prevalence of drug resistance was 33.5% [6] whereas similar study in West Armachiho and Metema districts of Amhara region in Ethiopia showed that the overall prevalence of MDR-TB was 5.7% [7]. Moreover, a meta-analysis conducted by Eshetie et al. [8] reported an overall prevalence of MDR-TB among newly diagnosed and previously treated TB patients to be 2% and 15%, respectively.

Global effort of tuberculosis care and control is threatened by the emergence of drug-resistant tuberculosis particularly in developing countries. MDR-TB patients respond poorly to short course chemotherapy and need to be treated intensively for up to 24 months. The WHO estimated treatment success rate for MDR-TB was 54% [9]. The mortality among MDR-TB patients is high, for instance a study conducted at St. Peter's Hospital in Ethiopia (national MDR-TB specialized Hospital) revealed that 15.43% of patients died and the survival probability of MDR-TB patients at 6, 12, 18 and 24 months of treatment was 88.5%, 85.8%, 82.7% and 79%, respectively. As reported in another study conducted in two hospitals, 10.8% died before the end of the follow-up period and the median survival for MDR-TB patients

***Corresponding author:** Workineh Shibeshi, Associate professor of Pharmacology, Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health science, Addis Ababa University, Addis Ababa, Ethiopia, E-mail: workineh.shibeshi@aau.edu.et

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was 16 months. Different factors have been identified as determinant factors for the survival probability in MDR-TB patients including HIV status, smoking behaviours [10-15], co-morbidities and clinical complication, baseline body weight [16,17] and age. In addition being farmer, known contact history with TB patients, alcohol use, previous known TB history were associated with poor MDR-TB treatment outcome [18,19].

Although Ethiopia is working hard on reduction of MDR-TB, it is still major public health concern in Ethiopia. Determining the survival rate and risk factors of mortality in MDR-TB patients is essential for effective planning and management of MDR-TB treatment. Although, there are few studies that determined survival time among MDR-TB patients in Ethiopia, they are not generalizable since the care and patient related factors may affect outcome. The MDR-TB treatment is started in Adama and Bishoftu general hospitals recently and there is no study conducted to assess the survival time of MDR-TB patients and associated risk factors for their mortality in these two hospitals. Hence, this study aimed to assess the survival time and risk factors for mortality in multidrug resistance tuberculosis patients at Adama and Bishoftu general hospitals in Oromia, Ethiopia.

Materials and Methods

Study setting

This study was conducted in Adama and Bishoftu General Hospitals located in Oromia Regional State, Ethiopia, that provides MDR-TB treatment. Adama General Hospital is located about 100 km south east of Addis Ababa, capital city of Ethiopia, whereas Bishoftu general hospital is located about 45 km from Addis Ababa. Both hospital started treatment of MDR-TB since 2013. Adama Hospital is staffed with medical doctor and two nurses to provide MDR-TB treatment, similarly, two medical doctors and three nurses are providing MDR-TB treatment at Bishoftu General Hospital.

Study design and study population

Retrospective cohort study design based on the patient chart review was conducted among MDR-TB patients who were on second-line treatments from May 2013 up to August 2017 at Adama and Bishoftu General Hospitals.

The study population included all bacteriologically confirmed and clinically diagnosed MDR-TB patients who were on second line anti-TB treatment at Adama and Bishoftu General Hospitals. All other TB patients (susceptible TB or XDR-TB) were excluded in the study.

Considering the numbers of patients in the two hospitals were small, all the patients who started MDR-TB treatment were included in the study to increase the precision of the result. There was a total of 164 eligible MDR-TB patients treated in both hospitals, among which 145 were from Adama general hospital and the rest 19 were from Bishoftu general hospital.

Data collection and quality assurance

Data were extracted from the patient follow up records using standardized data extraction format. Data were collected by three nurses who are working in MDR-TB centres of the hospitals after being trained for one day on the objective of the study and how to properly fill the study data. Socio-demographic variables (age, sex, occupational status, initials weight of the patients, educational status, marital status, smoking, khat and alcohol use) and clinical variables (Tuberculosis treatment history, site of tuberculosis, HIV co-infection and other co- morbidities and the type of drug resistance at baseline, the types of adverse drug reaction occurred after treatment and time to event were recorded. The completeness, consistency, clarity and accuracy of the data were checked daily by the principal investigator. On-site supervision and feedback was given on daily basis for data collectors by principal investigator.

Data management and analysis

Time to death was the outcome variable that was measured and coded as 1 for dying and 0 for censored. The patients surviving till the end of the cohort study contributed a censored case. Censorship includes cured, treatment completed, treatment failure, and transfer out, lost to follow-up and treatment completion. Time to event data (survival times) was calculated by subtracting date of treatment started from date of event occurred. Data was analysed using STATA Statistical package, Version 13.0. Hazard ratio with 95% CI and two-sided test of significance were used to measure the association of dependent and independent variables. Survival pattern over the follow up time was described using the Kaplan- Meier survival curve. The covariates were fitted to Cox proportional hazard regression model. Risk on survival curve was estimated for the entire follow-up time corresponding to each event occurrence using Kaplan-Meier survival and life table estimate method. Survival curves were compared between different exposure groups using log-rank test.

Operational definitions

The following operational definitions were based on WHO MDR-TB guideline and National guideline for the management of TB, DR-TB, TB/HIV and Leprosy in Ethiopia.

Multidrug-resistant TB (MDR-TB): TB that does not respond to at least both isoniazid and rifampicin.

Died: A patient who dies for any reason during the course of treatment.

Censored: When the outcome of interest has not been observed for an individual this includes cured, treatment completed, transferred out and lost to follow-up.

Cured: Treatment completed with three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase

Treatment Completed: Treatment completed without evidence of failure but no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.

Transfer Out: Patient who has been transferred to another referral centre and for whom the treatment outcome is not known.

Transfer in: A patient who has been transferred from another treatment site to continue MDR-TB treatment.

Lost to follow-up: A patient whose treatment was interrupted for two consecutive months or more and disappear from the treatment site.

Rifampicin-resistant TB/RR-TB: TB strains resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs and are considered eligible for treatment with MDR-TB regimens.

Bacteriological confirmed TB: is one from whom a biological specimen is positive by smear microscopy, culture or Gene X-pert MTB/RR test.

Clinically diagnosed MDR-TB: is one who does not fulfil the criteria for bacteriological confirmation MDR-TB but has been diagnosed with MDR-TB by a clinician who has decided to give the patient a full course of MDR-TB treatment.

Ethical consideration

The Ethical clearance to conduct the study was obtained from Ethical Review Board of School of Pharmacy, Addis Ababa University (Ref: ERB/SOP/22/09/2017).The permission to conduct research was also obtained from Directors of Adama and Bishoftu General Hospitals. Confidentiality of patient data was assured by coding the personal identifiers of patients. In addition, data collectors were nurse professionals working in the specific centre to avoid external person from accessing patient data.

Results and Discussion

Socio-demographic characteristics

Sociodemographic characteristics study participants are described in Table 1. In this study a total of 164 participants from both hospitals were included in final data analysis. Most of them 90 (54.90%) were females and 113 (68.90%) were between 18-43 years of age and the mean age of the study participants was 31.5 years. In a similar study conducted in Tanzania the mean age of participants was 39.5 years [20]. From these findingsit can be revealed that MDR-TB mostly affecting adult productive age group. Majority of participants 88 (53.70%) were urban residents. In terms of the educational status 77 (47.00%) were illiterates, able to read and write, and completed elementary, junior and high school level 76 (46.30%).

Clinical characteristics of the study partipants

As shown in Table 2, most of the study participants 157 (95.7%) were diagnosed with pulmonary TB. Majority of cases 133(81.10%) were bacteriologically confirmed by Gene Xpert MTB/RIF test and 30 (18.30%) were diagnosed by Line Probe Assay (LPA). The type of resistance identified was RR in 126 (77.00%) followed by resistance to R and H 35 (21.30%). Most of patients 137 (83.50%) had previous history of active TB treatment before diagnosis of MDR-TB indicating acquired resistance. The common comorbidity among the MDR-TB patients was HIV co-infection 39 (23.78%), while type 2 diabetes and hypertension accounted for 12 (7.31%). In similar study in Tanzania 41.45% MDR-TB patients were HIV-positive. However, HIV co-infection among MDR-TB patients in Oromia region, Ethiopia was 19.5% which close to our finding. The differences may be associated with variations in the HIV prevalence across countries. The new MDR-TB was identified in 27 (16.5%) of study participants without history of previous TB treatment indicating primary resistance. This finding is higher than MDR-TB patients in St. Peter's specialized Hospital in Ethiopia where only 6.7% patients were newly infected MDR-TB patients. The probable reason might be increasing transmission of MDR-TB from infected patients to care giver, family member, friends or people in contact with the patient over time.

Socio-demographic Characteristics		Numbers (%)
Gender	Male	74 (45.10)
	Female	90 (54.90)
Marital status	Ever married	94 (57.30)
	Never married	70 (42.70)
Age in years	Below 18	18 (11.00)
	18-30	76 (46.30)
	31-43	37 (22..60)
	>=44	33(20.10)
Educational Status	Illiterate, read and write	77 (47.00)
	Elementary, Junior &High school	76 (46.30)
	Diploma and Degree level	11 (6.70)
Residence	Urban	88 (53.70)
	Rural	76 (46.30)
Occupational status	Employed	34 (20.70)
	Daily labours	31 (18.95)
	Farmers	22 (13.41)
	Students	36 (21.95)
	House Wives	26 (15.85)
	Others	15 (9.14)
Social drug use	Non user	103 (62.80)
	Khat	33 (20.10)
	Alcohol	16 (9.80)
	Smoker	12 (7.30)

Table 1: The socio-demographic characteristics of MDR-TB patients at Adama and Bishoftu General Hospitals, Ethiopia.

Clinical Characteristics	Numbers (%)
Types of MDR-TB	
Pulmonary	157 (95.70)
Extra-pulmonary	7 (4.30)
History of TB treatment	
Treated before	137 (83.50)
Not treated before	27 (16.50)
Method of MDR-TB detection	
GeneXpert MTB/RIF	133 (81.10)
Line Probe Assay	30 (18.30)
Clinical suspected	1 (0.60)
Pattern of drug resistance	
R	126 (77.00)
H and R	35 (21.30)
RHE/S	2 (1.10)
HIV status	
Seronegative	125 (76.22)
P Seropositive	39 (23.78)

Table 2: The clinical characteristics of MDR-TB patients at Adama and Bishoftu General Hospitals. RR=Rifampicin Resistant, H=Isoniazid Resistant, E=Ethambutol resistant, S=streptomycin resistant.

Treatment outcomes among participants

Regarding the treatment outcome of the study participants, 103 (62.80%), 30 (18.29%), 22 (13.41%), 5 (3.05%), 4 (2.43%) were cured, died, transferred out, lost to follow-up and treatment completed respectively. The death among MDR-TB patients in our study is higher than finding in study conducted at St. Peter's Specialized Hospital where 15.43% patients were died and in ALERT centre and Gondar University Hospital where 10.80% were died. The treatment success among MDR-TB patients is poor, however, cure rate in present study (62.8%) is better than the global MDR-TB treatment success rate of 55.4%, France national MDR-TB cure rate of 41.5%, cure rate of 41.5% reported in Estonia and cure rate of 25.3% reported by Girum et al. [17] in south Ethiopia. The greater success rate in our study may be due to smaller number samples and it is facility-based study that is not representative of national success rate. Similarly, analysis of adverse drug events reported indicated that 53 (32.31%), 20 (12.19%), 6 (3.64%) and 3 (1.82%) patients developed drug induced gastric manifestation, hypokalemia, peripheral neuropathy, and hearing impairment respectively (Table 3).

Analysis of survival time and predictors of mortality

A total of 164 participants were followed for a total of 63,141 person-days. The median survival time was 400.5 days. Our finding is smaller than studies conducted in France, where median survival probability was 31 months and Lithuanian where median survival time for MDR-TB patients was 4.1 years [21]. However, it is closer to survival probability of 16 months reported by other study in Ethiopia(11). In our study participants, the survival probability at 6, 12, 18, 24 months was 84%, 82%, 81% and 72%, respectively. This is lower than other study conducted at St. Peter's Specialized Hospital, where 6, 12, 18 and 24 months survival probability was 88.53%, 85.83%, 82.71 % and 78.95 % respectively. Generally survival probability of MDR-TB patients showed decreasing trend against follow-up time.

According to Cox-regression multivariate analysis, initial body weight, age, occupation (daily laborers more affected), HIV positive status, comorbidities and co-infections and Khat use were significant predictor of mortality among MDR-TB patients (Table 4). Similar to our finding, several studies also identified HIV status,smoking, co-morbidities and clinical complication, baseline body weight and age (11) as independent factors that predict the survival probability in MDR-TB patients. However, the Khat use and occupation were independent factors that predict survival in our study but that have not identified in other studies. Multivariate analyses of independent variables indicate that HIV positive patients were 2.75 times more likely to die than HIV negative patients during MDR-TB treatment (HR=2.75, 95% CI (1.23-6.15). The MDR-TB patients co-infected with HIV had less survival probability as compared to HIV negative MDR-TB patients. However, both HIV negative and positive patients MDR-TB patients' survival probability decreases as days of treatment increases and beyond about 600 days it becomes flat (Figure 1). There was higher incidence of death among Khat users (7.1 per 10,000 populations) than non-Khat user (4.2 per 10,000 population) among MDR-TB patients (Figure 2). Khat use is significantly associated with mortality in the present study with AHR=0.41, (95%CI; 0.18-0.97).

The incidence of death was highest in patients aged above 44 years (7.03 per 10,000 populations) followed by age between 31-43 years, 18-30 year and below 18 years with incidences 5.2, 3.8 and 3.3 per 10,000 populations respectively (Figure 3). Based on Cox proportional hazard regression analysis, age of study participants was very significant for low survival probability of the patients with AHR=2.26 (95% CI (1.35-3.79). This finding is in line with other studies in Ethiopia and Lithuania.

MDR-TB patients who had low initial body weight were 56% times more likely to die than other study participants (AHR=0.44, 95% (0.22-0.85). The initial mean body weight of the study participants was 45.85 kg. The incidence of death in patients with weight less than 30 kg, between 30-45 kg and 46-60 kg and greater than 60 kg were 3.2, 8.2, 2.5 and 1.6 per 10,000 populations, respectively (Figure 4). This result was also supported by studies conducted in ALERT center and Gondar university Hospitals in Ethiopia, and studies done in other countries.

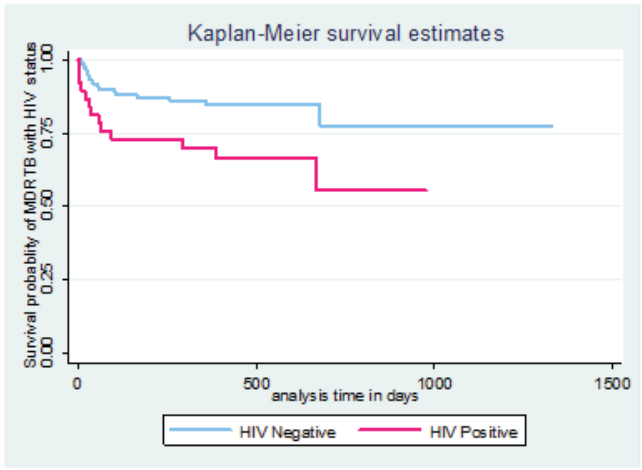

Figure 1: Kaplan-Meier survival estimate among HIV sero-positive and sero-negative MDR-TB patients at Adama and Bishoftu General Hospitals.

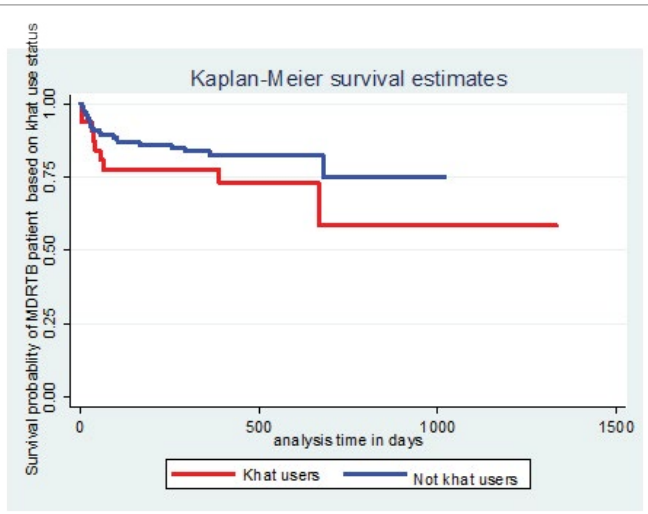

Figure 2: Kaplan-Meier survival estimate among MDR-TB patients based on their Khat use profile at Adama and Bishoftu General Hospitals.

Types of adverse drug reactions	Numbers (%)
Drug induced gastric manifestation	53 (32.31)
Hypo kalmia	20 (12.19)
Drug induced psychosis	3 (1.82)
Hearing impairment	3 (1.82)
Peripheral Neuropathy	6 (3.64)
Renal toxicity	3 (1.82)
Drug induced hepatitis	2 (1.22)
Hypothyroidism	1 (0.61)

Table 3: The type of adverse drug reaction reported among MDR-TB patients at Adama and Bishoftu General Hospitals.

Predictors	P-value	HR	95.0% CI for AHR	
			Lower	Upper
Initial weight	0.02	0.44	0.22	0.85
Age of patients	0	2.26	1.35	3.79
occupation	0.01	1.31	1.06	1.63
Co-morbidities and co-infection	0.05	2.28	0.99	5.26
HIV status	0.01	2.75	1.23	6.15
Khat	0.04	0.41	0.18	0.97

Table 4: The independent predictors for the mortality of MDR-TB patients at Adama and Bishoftu General Hospitals.

Conclusion

The mortality among MDR-TB patients was high. The major risk factors for mortality of MDR-TB patients were initial low body weight, HIV positive status, co-morbidities and co-infections, age and Khat

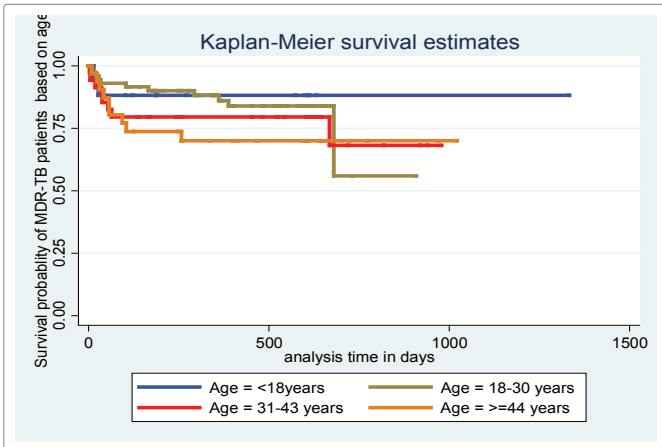

Figure 3: Kaplan-Meier survival estimates of MDR-TB patients based on age at Adama and Bishoftu General Hospital.

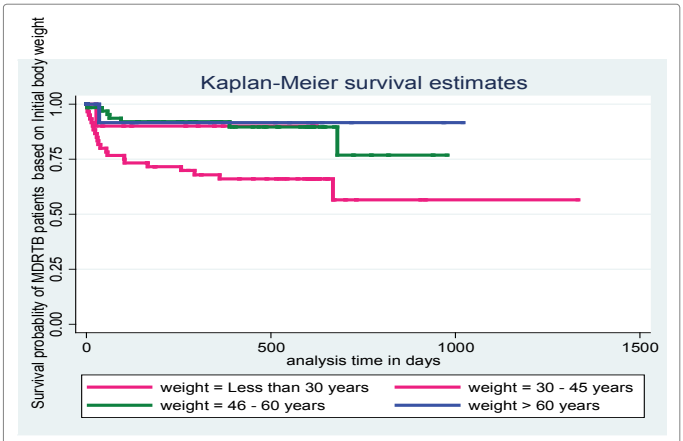

Figure 4: Kaplan-Meier survival estimates of MDR-TB patients based on initial body weight of MDRTB patients at Adama and Bishoftu General Hospitals.

use. The survival probability of MDR-TB patients at 24 months was lower indicating poor survival.

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Authors' Contribution

DF generated the idea, designed and conducted data collection; analyzed and interpreted the results. MF involved in supervision of the research and prepared the draft manuscript. WS involved in primary supervision of the study and final proof-reading and submission of manuscript. SH co-supervised the study.

Conflict of Interest

The authors declare that there is no conflict of interest.

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