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Predictors of Unfavorable Treatment Outcome Among Multidrug-Resistant Tuberculosis Enrollees in Osun State, Nigeria

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Abstract

Background: Multidrug-Resistant Tuberculosis (MDR-TB) poses a significant challenge to Nigeria's efforts in tuberculosis prevention and control, as well as the achievement of Sustainable Development Goal 3 (Good health and well-being). Identifying the predictors of successful MDR-TB treatment outcomes is crucial for guiding health policy implementation and containing the spread of the disease. This study aims to identify the predictors of unfavorable treatment outcomes among patients with multidrug-resistant tuberculosis in Osun State, Nigeria.

Methods: This was a retrospective study that included 181 TB patients from all chest clinics in Osun state's 30 LGAs. Data were collected using a proforma, and analysis was conducted using SPSS version 26. Univariate and bivariate analyses were performed, with the chi-square test used to determine the associations between the categorical variables. The significance level was set at 0.05.

Results: Clinically, majority of the patients had pulmonary MDR-TB (181, 100.0%), were newly diagnosed with DRTB (Drug-resistant TB) (75, 41.4%), and were underweight (89, 49.2%). Regarding the laboratory profiles, nearly all the patients (92.8%) were anemic. More than four-fifths of respondents (156, 86.2%) experienced favorable treatment outcomes (cured or treatment completed), while 25 (13.8%) had unfavorable treatment outcomes. Associations were observed between drug intake (second-line drugs) and treatment outcome (p=0.001, X2=10.53), as well as hemoglobin status (p=0.045, X2=2.245).

Conclusion: Successful treatment was found to be influenced by drug adherence and hemoglobin status. Therefore, there is a need to enhance adherence counseling and ensure early commencement of treatment among patients with MDR-TB.

Keywords: Counseling, Nigeria, Sustainable, Development, Thinness, Treatment Outcome, Tuberculosis, Multidrug-Resistant, Tuberculosis, Pulmonary

Introduction

Tuberculosis (TB) is a contagious bacterial disease caused by an airborne bacterium *Mycobacterium tuberculosis.* It mostly attacks the lungs (pulmonary TB) but can affect any organ in the body, that is, extra Pulmonary TB (1). Despite being preventable and treatable, TB remains a deadly disease. According to the global report from the Centers for Disease Control and Prevention (CDC), one-fourth of the world's population (two billion people) may be infected with TB, with 10.6 million becoming ill each year. Globally, over 3,500 individuals lose their lives to TB each day, totaling 1.3 million deaths each year with Nigeria ranked as the sixth country with the highest burden (2,3). However, Drug-Resistant Tuberculosis (DR-TB) remains a major public health concern, with an estimated 19 million people suffering from multidrug-resistant tuberculosis (MDR-TB) infection (4,5). As reported by the World Health Organization (WHO), there are more than one million rifampicin-susceptible and isoniazid-resistant TB cases annually. Additionally, 3.3% of new cases and 17% of previously treated cases involve Multi Drug Resistant TB (MDR-TB) and Rifampicin-Resistant TB (RR-TB), representing 410,000 cases and resulting in 160,000 deaths each year (6,7) TB was the world's second leading cause of death from a single infectious agent, after coro-navirus disease (COVID-19). As a result, multidrug-resistant TB is contributing to the undesirable increase in TB morbidity and mortality (8).

Drug-resistant TB (DR-TB) comes in various forms, such as mono-resistant tuberculosis and MDR-TB. The former refers to TB resistant to any single first-line anti-tuberculosis drug, while the latter is resistant to key first-line anti-tuberculosis drugs, rifampicin, and isoniazid (9). Poly-resistant tuberculosis is resistant to more than one first-line drug, excluding rifampicin and isoniazid. When MDR-TB is not adequately treated due to various health system challenges in developing countries, it can progress to extensively drug-resistant TB (XDR-TB). Extensively resistant tuberculosis (XDR-TB) involves MDR-TB and additional resistance to any fluoroquinolone and second-line injectable drugs, such as Amikacin, Kanamycin, or Capreomycin (10) bacteriologic, and weight from 439 MDR-TB patients in the Philippines. development presents a major challenge to tuberculosis prevention and control, especially in developing countries like Nigeria (11,12). MDR-TB treatment is commonly linked with unsuccessful outcomes compared to non-MDR-TB therapy (13). However, socio-demographic characteristics such as age, sex, place of residence, occupation, marital status, and HIV co-morbidity are the known predictors of favorable treatment outcomes according to the study conducted in 2020 (14) treatment, prevention and rehabilitation requires frequent update of existing guidelines. This review is aimed at providing clinicians and public health staff with an updated and easy-to-consult document arising from consensus of Global Tuberculosis Network (GTN).

To capture the susceptibility pattern of all available anti-tuberculosis drugs used to treat the infection, bacteriological analysis for MDR-TB requires utilizing the molecular tests like the Xpert MTB/RIF assay to detect resistance patterns or other rapid Drug Sensitivity Tests (DST) (5). This study aims aimed at identifying the predictors of unfavorable treatment outcomes among the enrollees with MDR-TB in Osun State. The study's results will therefore add to the general field of knowledge and will be useful in developing the policies aimed at improving the treatment outcomes among MDR-TB patients.

Materials and Methods

Study design and participants

This research employed a retrospective study design. A total of 201 clients from Osun State, Nigeria, between 2015 and 2020 were enrolled. Among these, 20 clients were excluded due to incomplete documentation. The treatment regimen administered was standardized and comprised Fluoroquinolones (such as moxifloxacin and levofloxacin), injectable agents (like amikacin, kanamycin, or capreomycin), and Group 4 and 5 drugs (including ethionamide, prothionamide, cycloserine, linezolid, bedaquiline, and clofazimine). This regimen remained consistent throughout the study period. And all the patients had completed their treatment before the survey commenced.

Research tools or measurements

Data collection was performed using a proforma. Data was obtained from the records of clients enrolled in the tuberculosis program in Osun State, selecting only

those with complete documentation. The proforma consisted of four sections: background demographic information, baseline clinical parameters, baseline laboratory parameters, and categorized treatment outcomes based on World Health Organization (WHO) definitions.

Statistical analysis

Following the data collection, the data were cleaned to check for errors and omissions before being analyzed using the Statistical Package for Social Sciences (SPSS), version 26. Records from 181 clients were analyzed, and univariate analysis was performed, with categorical variables expressed as frequencies and percentages. For the continuous variables, summary measures were used. The bivariate analysis employed the chi-square test to examine the relationships between categorical variables (independent variables: socio-demographic status, categorized drug intake, categorized baseline clinical profile, and categorized baseline laboratory profile) and treatment outcomes (dependent variable). Finally, a binary logistic regression analysis was conducted to identify the predictors of favorable treatment outcomes among the clients, using variables that were significant in the bivariate analysis. The p-value was set at 0.05 (95% confidence interval).

Ethical considerations

Ethical approval for the study was obtained from the Health Research Ethics Committee at the College of Health Sciences, Osun State University, Osogbo (UNIOSUNHREC 2021/PBH/017). Additionally, approvals were granted by the Osun State Tuberculosis and Leprosy Control Program and the Osun State Ministry of Health, Osogbo. The confidentiality of clients' information was ensured by not recording any names.

Results

Table 1 shows the socio-demographic characteristics of the study subjects (n=181). The age with the highest percentage was the age group 30-39 years (26.5%). More than half (58.6%) of the clients were male while two-thirds (69.6%) were married.

The treatment outcome of the clients showed that the majority (86.2%) of them had a favorable (cured, treatment completed) treatment outcome (Figure 1).

Table 2 illustrates that all the clients had their site of disease to be pulmonary, 41.4% were new cases of MDR-TB and more than half (54.7%) were underweight. Also, all the clients were detected to be RIF resistant and the majority (88.4%) tested negative for HIV. Half (50.3%) of the clients were tested to be negative for rifampicin resistance when tested by Sputum Acid-Fast Bacilli (AFB). When tested by sputum culture, more than half (57.5%) were tested negative for rifampicin resistance, and

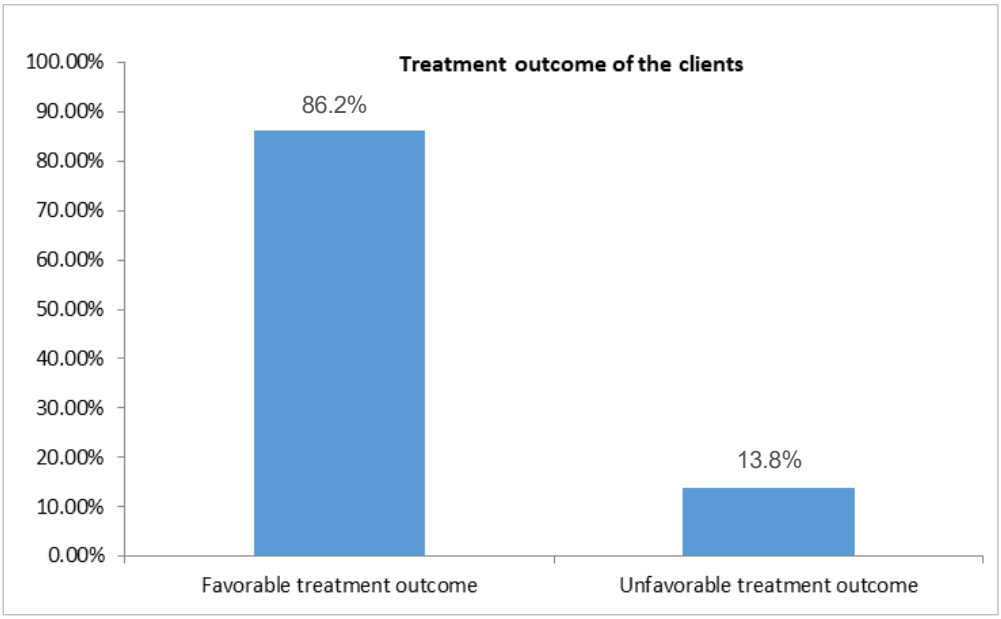

Figure 1. Treatment outcome of the clients.

Table I. Socio-demographic characteristics (n=181)

Variables	Sub-variables	Frequency	Percentage (%)
Age in categories	0-9 years	2	1.1
	10-19 years	11	6.1
	20-29 years	42	23.2
	30-39 years	48	26.5
	40-49 years	43	23.8
	≥50 years	35	19.3
Sex	Male	106	58.6
	Female	75	41.4
Marital status	Single	53	29.3
	Married	126	69.6
	Widowed	2	1.1

Table 2. Clinical profile of clients, baseline laboratory profile

Variables	Sub-variables	Frequency	Percentage (%)
Site of the disease	Pulmonary	181	100
	Extra-Pulmonary	0	0
	Both	0	0
Type of DR TB	New	75	41.4
	Relapse	41	22.7
	Treatment after failure	37	20.4
	Treatment after loss to follow up	19	10.5
	Patient with unknown previous TB treatment history	1	0.6
	Transferred in from another DRTB treatment center	2	1.1
	Others previously treated	6	3.3
Baseline Body Mass Index (BMI)	Underweight (Less than 18.5 kg/m^2)	99	54.7
	Normal (18.5-24.9 kg/m^2)	64	35.4
	Overweight (25-29.9 kg/m^2)	10	5.5
	Obese (30-39.9 kg/m^2)	8	4.4
	Very obese (>40 kg/m^2)	0	0
Gene Xpert	Rif resistance detected	181	100
	Rif resistance not detected	0	0
HIV Test Result	Not done	0	0
	Positive	18	9.9
	Negative	160	88.4
	Unknown	3	1.7
Sputum AFB	Positive	90	49.7
	Negative	91	50.3
Sputum culture	Positive	77	42.5
	Negative	104	57.5
Fasting blood sugar	Normal	128	70.7
	Impaired glucose tolerance	46	25.4
	Diabetics	7	3.9

Cont table 2.

Hemoglobin	Normal	13	7.2
	Anemic	168	92.8
	Renal function test		
(K+)	Normal (3.5-5 *mmol/L*)	99	54.7
	Abnormal (<3.5 *mmol/L* & >5 *mmol/L*)	82	45.3
(Na+)	Normal (120-140)	153	84.5
	Abnormal (<120 & >140)	28	15.5
(Serum urea)	Normal (6-24 *mg/dl*)/(2.1-8.5 *mmol/dl*)	106	58.6
	Abnormal (<6 *mg/dl* & >24 *mg/dl*)/(2.1 *mmol/L* & 8.5 *mmol/L*)	75	41.4
(Serum Creatinine)	Normal Men (0.74-1.35 *mg/dl*)/(65.4-119.3 *mmol/L*) Women (0.59-1.04 *mg/dl*)/(52.2-91.9 *mmol/L*)	120	66.3
	Abnormal Men (<0.74 *mg/dl* & >1.35 *mg/dl*)/(<65.4 *mmol/L* & >119.3 *mmol/L*) Women (<0.59 *mg/dl* & >1.04 *mg/dl*)/(<52.2 *mmol/L* & >91.9 *mmol/L*)	61	33.7
	Liver function test		
ALT [_up to 56 _]	Normal (7-56)	157	86.7
	Deranged (<7 or>56)	24	13.3
AST [_up to 40_]	Normal (5-40)	167	92.3
	Deranged (<5 or>40)	14	7.7
Albumin [_less than 35_]	Normal (3.4-5.4 *g/dl*)/(34-54 *g/L*)	145	80.1
	Abnormal (<3.4 *g/dl* or >5.4 *g/dl*)/(<34 *g/L* or >54 *g/L*)	36	19.9
Bilirubin	Normal (0.2-1 *mg/dl*)	153	84.5
	Abnormal (<0.2 *mg/dl* & >1 *mg/dl*)	28	15.5

almost all the clients (92.8%) were discovered to be anemic when their hemoglobin was tested. The fasting blood sugar of the majority (70.7%) of the clients was normal. As for the renal function test, the potassium (K+) and serum urea levels are normal in more than half (54.7, and 58.6% respectively) of the clients, and sodium (Na+) is normal in the majority (84.5%). Also, serum creatinine is normal in two-thirds of the clients. The test for ALT, AST, Albumin, and Bilirubin (Liver function test) is normal among the majority (86.7%, 92.3, 80.1%, and 84.5%) of the clients.

Table 3 shows that there is no association between the socio-demographic characteristics of the clients and treatment outcomes. However, an association exists between drug intake and treatment outcome (p=0.001, X2–10.583) while there is no association between the baseline clinical parameters and treatment outcome.

Table 4 below shows that the only baseline laboratory profile that has a significant association with the patients' treatment outcome was the hemoglobin level of the patients and their treatment outcome (p= 0.045, X2–2.245).

Table 5, clients with adherence to drug intake are 4.3 times more likely to have a favorable outcome compared to clients with non-adherence to drug intake (OR 4.3, CI -1.74 to 10.75).

Explanation of the results: Clinically, the majority had pulmonary MDR-TB-181(100.0%), a new type of DRTB 75(41.4%), and were under-weight 89(49.2%). Concerning the laboratory profile, almost all (92.8%) were anemic, more than four-fifths of clients, 156(86.2%) had a favorable treatment outcome (cured and treatment completed) while 25(13.8%) had an unfavorable treatment outcome. There was an association between drug intake (second-line drugs) and treatment outcome (p=0.001, X2–10.583) as well as hemoglobin status (p=0.045, X2 – 2.245).

Table 3. The association between socio-demographic status, drug intake and baseline clinical parameters, and treatment outcome

Variables	Sub-variable	Treatment outcome		df	Statistics (x2),(p)
		Favorable	Unfavorable		
Sex	Male	95(89.6%)	11(10.4%)	1	X2=2.535 p=0.111
	Female	61(81.3%)	14(18.7%)		
Age	0-9	2(100.0%)	0(0.0%)	5	X2=5.300 p=0.380
	10-19	10(90.9%)	1(9.1%)		
	20-29	35(83.3%)	7(16.7%)		
	30-39	40(83.3%)	8(16.7%)		
	40-49	41(95.3%)	2(4.7%)		
	50 and above	28(80.0%)	7(20.0%)		
Marital status	Single	46(86.8%)	7(13.2%)	2	X2=0.361 p=0.835
	Married	108(85.7%)	18(14.3%)		
	Divorced	2(100.0%)	0(0.0%)		
Drug intake	Adherence	131(90.3%)	14(9.7%)	1	X2=10.583 p=0.001
	Non-adherence	25(69.4%)	11(30.6%)		
Type of Disease	New	65(86.7%)	10(13.3%)	6	X2=2.782 p=0.836
	Relapse	35(85.4%)	6(14.6%)		
	Treatment after failure	33(89.2%)	4(10.8%)		
	Treatment after loss to follow up	16(84.2%)	3(15.8%)		
	Patient with unknown previous TB treatment history	1(100.0%)	0(0.0%)		
	Transferred in from another DRTB treatment center	1(50.0%)	1(50.0%)		
	Others previously treated	5(83.3%)	1(16.7%)		
Body Mass Index (BMI)	Underweight (Less than 18.5 *kg/m²*)	84(84.8%)	15(15.2%)	3	X2=1.845 p=0.605
	Normal (18.5-24.9 *kg/m²*)	56(87.5%)	8(12.5%)		
	Overweight (25-29.9 *kg/m²*)	8(80.0%)	2(20.0%)		
	Obese (30-39.9 *kg/m²*)	8(100.0%)	0(0.0%)		
	Very obese (>40 *kg/m²*)	0(0.0%)	0(0.0%)		

Table 4. Association between baseline laboratory profile and treatment outcome

Variables	Sub-variable	Treatment outcome			Statistics (x2), (p)
		Favorable	Unfavorable		
HIV	Positive Negative Unknown	14(77.8%) 140(87.5%) 2(66.7%)	4(22.2%) 20(12.5%) 1(33.3%)	2	X2=2.261 p=0.323
Hb	Normal Abnormal	13(100%) 143(85.1%)	0(0.0%) 25(14.9%)	1	X2=2.245 p=0.045

Cont Table 4.

Fasting blood sugar	Impaired glucose tolerance (100-125 *mg/dl*) Diabetic (>126 *mg/dl*) Normal (70-99 *mg/dl*)	40(87.0%) 6(85.7%) 110(85.9%)	6(13.0%) 1(14.3%) 18(14.1%)	2	X2=0.031 p=0.985
		Liver function			
ALT[_up to 56]	Normal (7-56) Deranged (<7 &>56)	136(86.6%) 20(83.3%)	21(13.4%) 4(16.7%)	1	X2=0.189 p=0.663
AST[_up to 40]	Normal (5-40) Deranged (<5 &>40)	142(85.0%) 14(100.0%)	25(15.0%) 0(0.0%)	1	X2=2.432 p=0.119
Albumin	Normal (3.4-5.4 *g/dl*)/(34-54 *g/L*) Deranged (<3.4 *g/dl* & >5.4 *g/dl*)/ (<34 *g/L* & >54 *g/L*)	126(86.9%) 30(83.3%)	19(13.1%) 6(16.7%)	1	X2=0.308 p=0.579
Bilirubin	Normal (0.2-1*mg/dl*) Deranged (<0.2 *mg/dl* & >1*mg/dl*)	134(87.6%) 22(78.6%)	19(12.4%) 6(21.4%)	1	X2=1.614 p=0.204
		Renal function			
K+	Normal (3.5-5 *mmol/L*) Deranged (<3.5 *mmol/L* & >5 *mmol/L*)	89(89.9%) 67(81.7%)	10(10.1%) 15(18.3%)	1	X2=2.528 p=0.112
Na+	Normal (120-140) Deranged (<120 &>140)	133(86.9%) 23(82.1%)	20(13.1%) 5(17.9%)	1	X2=0.455 p=0.500
Serum creatinine	Normal Men (0.74-1.35 *mg/dl*)/ (65.4-119.3 *mmol/L*) Women (0.59-1.04 *mg/dl*)/ (52.2-91.9 *mmol/L*)	103(85.8%)	17(14.2%)	1	X2=0.038 p=0.846
	Deranged Men (<0.74 *mg/dl* & >1.35 *mg/dl*)/ (<65.4 *mmol/L* & >119.3 *mmol/L*) Women (<0.59 *mg/dl* & >1.04 *mg/dl*)/ (<52.2 *mmol/L* & >91.9 *mmol/L*)	53(86.9%)	8(13.1%)		

Table 5. Predictors of favorable treatment outcome (n-181)

Variables	Sub-variable	Treatment outcome		Odd ratio (Confidence interval)
		Favorable (n=156)	Unfavorable (n=25)	
Drug intake	Adherence	131(90.3%)	14(9.7%)	4.3(1.74-10.75)
	Non-adherence (R)	25(69.4%)	11(30.6%)	

Discussion

Findings of this study indicate that more than three-quarters of the clients had favorable treatment outcomes (cured or treatment completed), while the remaining had unfavorable outcomes (treatment failure, death, loss to follow-up, or not evaluated). This is similar to a study conducted in Southern Ethiopia, which reported less than one-quarter of MDR-TB patients with unfavorable treatment outcomes (15). Positive drug adherence was linked to favorable treatment outcomes, echoing results from a case-control study in Serbia, which found that non-adherence to treatment can result in patients remaining infectious, experiencing increased risk

of TB recurrence, TB-related mortality, or higher likelihood of acquired drug resistance (16). Both drug adherence and patients' hemoglobin levels were significant factors associated with favorable treatment outcomes. Among all the laboratory parameters, only hemoglobin showed a statistically significant association with treatment outcomes (p-value of 0.045, x^2=2.245). There was also a strong association between consistent drug intake and favorable treatment outcomes (p-value<0.001, x^2=10.583), with clients who were consistent in their drug intake being four times more likely to achieve favorable treatment outcomes compared to those who were inconsistent.

Furthermore, all the subjects in this study had pulmonary TB, with a majority being new cases of MDR-TB. This contrasts with a study from Tanzania, where most clients were previously treated for TB cases (13). Additionally, more than half of the MDR-TB clients in this study were underweight, differing from a study on malnutrition's impact on MDR-TB, which found only 20% of the patients were underweight. This suggests that pulmonary multidrug-resistant tuberculosis is particularly prevalent (17). However, it is revealed that pulmonary multidrug-resistant tuberculosis is particularly prevalent.

Regarding the laboratory parameters, the data for this study were extracted from registered reviews of patient follow-ups. While sputum culture is the gold standard for confirming the MDR-TB infection, all the laboratory parameters tested were RIF-resistant using GeneXpert. More than half of the patients tested negative for both sputum AFB and sputum culture, contrasting with a study from Southern Ethiopia, where more clients tested positive for these parameters (15).

A study on MDR-TB predictors found HIV to be an independent predictor of MDR-TB (18), behavioral and clinical risk factors using a structured questionnaire and clinical record reviewing. The data were entered and analyzed using SPSS windows version 16. Descriptive analysis was done to generate summary values for the variables and those significant variables in the bivariate analysis at p-value less than 0.25 were entered to multivariable logistic regression to identify independent determinants. Statistical significance was declared at p-value less than or equal to 0.05. Results: A total of 90 cases and 90 controls were included in the study. Age of respondents (adjusted odds ratio [AOR]=7; 95% confidence interval [CI]: 2.6–24.5. Although no significant association was found between clients' HIV status and their treatment outcomes in this study, those who tested negative had more favorable outcomes than those who tested positive. Most clients had normal fasting blood sugar levels, with less than half having diabetes or impaired glucose tolerance. This is comparable to a study from Tanzania, which found that clients with normal fasting blood sugar levels tended to have more favorable treatment outcomes than those with impaired glucose tolerance or diabetes (13). Low hemoglobin levels predicted unfavorable treatment outcomes, similar to findings from Southern Ethiopia (15). The majority of clients with normal liver function tests (ALT, AST, albumin, bilirubin) had favorable treatment outcomes, consistent with the Southern Ethiopia study. Additionally, our findings on renal function tests in multidrug-resistant tuberculosis clients demonstrated that more than half had normal renal function tests.

The strength of this retrospective study design lies in its ability to establish an association between favorable treatment outcomes and both medication adherence and hemoglobin status. However, the study's limitation excludes the clients with incomplete documentation regarding follow-up laboratory investigations and medication adherence. This exclusion was necessary to ensure an accurate analysis of the treatment outcomes.

Conclusion

Conclusively, the majority of MDR-TB patients in Osun State were classified clinically as pulmonary, anemic, and underweight. A significant number of the clients experienced unfavorable outcomes, such as treatment failure, transfer out, death, loss of follow-up, and not being evaluated. However, the successful treatment was found to be influenced by high baseline hemoglobin levels and good drug adherence.

Therefore, it is recommended to encourage early initiation of treatment among MDR-TB clients, along with continuous education on medication adherence.

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Conflict of Interest

There was no conflict of interest in this manuscript.

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