

Developing a Patient-Centered Community-Based Model for Management of Multi-Drug Resistant Tuberculosis in Uganda: A Mixed Methods Study

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Abstract

Background:

The advent of all-oral regimens for the management of multi-drug resistant tuberculosis (MDR-TB) makes the implementation of community-based directly observed therapy (CB-DOT) a possibility for this group of patients. We set out to determine patient preferences for different attributes of a community-based model for the management of MDR-TB in Uganda.

Methods:

The study was conducted at five tertiary referral hospitals. We used a parallel convergent mixed methods study design. To collect quantitative data, we conducted a discrete choice experiment (DCE) with three different attributes of community-based care (provider type, location of care, and type of support) combined into eight choice sets, each with two options and an opt-out. We collected additional qualitative data by eliciting patient reasons for selection of each choice set. We fitted a mixed logit choice model to determine patient preferences for different attributes of community-based care. Thematic analysis using NVivo12 was done to understand the reasons for the choices made.

Results:

From December 2019 to January 2020, we interviewed 103 patients with MDR-TB. Majority (58.3%) were male; 61.2% were HIV negative; and the median age was 37 (IQR 30-47) years. Two thirds (65.1%) earned less than \$1 per day. Study participants preferred at least one of the CB-DOT models of care to none (current standard of care). The most preferred model consisted of a community health worker (CHW) giving DOT at home and travel vouchers to enable attendance at monthly clinic follow-up visits. Qualitative interviews revealed that patients perceived CHWs as knowledgeable and able to offer psychosocial support. Patients also indicated a preference for taking medication at home because it saves both time and money and presents a lower risk of being stigmatized.

Conclusion:

People with MDR-TB prefer to be supported to take their medicine at home by a member of their community. The effectiveness of this model of care will be further evaluated.

Background

Multi-drug resistant tuberculosis (MDR-TB), defined as resistance to both isoniazid and rifampicin, the two major first line anti-TB medicines, threatens global TB control efforts and remains a major public health concern in many countries.¹ Globally, case detection and treatment success rates for MDR-TB are suboptimal. In 2019, only 57% of patients started on second line therapy were successfully treated.² In Uganda, 64% of those started on treatment in 2016 were successfully treated while an estimated 19% died and 15% were lost to follow up.³ These suboptimal treatment outcomes are a potential risk for the development and spread of further resistance to TB treatment.⁴

Uganda currently implements a mixed model of care for MDR-TB characterized by initial hospitalization for two to eight weeks followed by ambulatory directly observed therapy at a public or private health facility near the patient's home.⁵ However, delivery of care through a health facility-based directly observed therapy (HF-DOT) model has been documented to significantly contribute to poor treatment outcomes particularly in resource limited settings⁶. Patients who receive care through this model experience various inconveniences (e.g., travel and waiting times) and incur significant direct (e.g., transport costs) and indirect costs (e.g., time lost from work) that hinder successful treatment completion.⁶ In the management of both drug susceptible and drug resistant TB, community-based treatment support models have been associated with improved treatment outcomes and increased cost effectiveness compared to health facility-based models.^{7,8,9,10}

Since March 2018, the shorter 9–12 months treatment regimen has been the standard of care for patients with MDR-TB without extrapulmonary TB or resistance to fluoroquinolones or second line injectable drugs amongst others. This shorter treatment regimen is better tolerated, and in clinical trials resulted in better treatment outcomes than the two-year treatment regimen.¹¹ However, this regimen also has lower tolerance for lapses in adherence and there is only one chance to complete the shorter regimen.⁵ Provision of effective adherence support for patients receiving the shorter MDR-TB regimen is therefore a priority intervention for the National TB and Leprosy Program (NTLP). Further, the use of community health workers (CHWs) to offer treatment adherence support, particularly in the continuation phase of treatment, is recommended in the Uganda National Guidelines for Programmatic Management of Drug Resistant Tuberculosis⁵ but is yet to be implemented. We therefore set out to assess patient preferences for different attributes of community-based care for MDR-TB.

Methods

Study setting

The study was carried out at five tertiary referral hospitals purposively selected because they provide care to about 80% of patients started on second line TB treatment in Uganda every year. Second line TB treatment consists of six drugs; kanamycin (Km), moxifloxacin (Mfx), Ethionamide (Eto), clofazimine (Cfz), pyrazinamide (Z), high dose Isoniazid (H) and ethambutol (E) given in two phases; an intensive four-to-six-month period and a five-month

continuation phase. In the initial intensive phase, all seven drugs are given while in the continuation phase only four drugs are given that include Mfx, Cfz, Z and E.⁵

Study Design

We used a parallel convergent mixed methods study design to collect both quantitative and qualitative data on patient preferences for different attributes of community-based care.

Study Variables

The dependent variable was the preferred community-based directly observed therapy (CB-DOT) model, which was the most common chosen combination of the three different CB-DOT attributes that included principal care giver, location of care, and type of additional support. Independent variables included patient demographics, e.g., age, sex, education, duration on MDR-TB treatment, and HIV status.

Data Collection

We included patients 18 years or older who had completed the intensive phase of treatment for MDR-TB. We used stratified sampling to determine the number of patients to be selected from each hospital, and simple random sampling to select the patients to be interviewed at each hospital. We collected quantitative data on patient preferences using a discrete choice experiment (DCE), a technique for eliciting individual preferences for a product or service.¹² We chose three attributes (provider type, location of service, and provision of additional support) each with two or three attribute levels (Table 1). Attributes used in this study were chosen from an initial exploratory study carried out six months prior. Using a fractional factorial design, we chose eight choice sets. Recommendations in the literature^{13,14} have shown that more than eight choice tasks are a cognitive and time burden for participants. We included an opt-out response category so that respondents could choose “neither” choice set to reflect dissatisfaction with either potential CB-DOT model. The final design had 96% d-efficiency (Table 2). To cater for limited literacy levels among the respondents, visual representations of each attribute were developed and used during data collection. Data was collected electronically and entered directly into TB Info, a web-based system.

Additional quantitative data on age, gender, marital status, date of treatment initiation, duration on MDR-TB treatment, and underlying co-morbidities was abstracted from health facility records. Qualitative data was collected through patient interviews carried out after each choice set was presented to find out the reasons for choices made for each set of attributes.

Table 1
DCE attributes and levels

Attribute	Level
Provider type	Expert client
	Family member
	Community health worker
Location	Home
	Work
Support type	SMS reminders
	Call reminders
	Travel vouchers

Table 2
DCE choice sets each with an opt out option.

Choice Set	Choice set alternatives	Attributes		
		Location of care	Provider type	Support type
1	I	work	CHW	Travel vouchers
	II	Home	Expert Client	Call reminders
	III	Neither		
2	I	Home	Family member	SMS reminders
	II	work	Expert Client	Travel vouchers
	III	Neither		
3	I	Home	Family member	SMS reminders
	II	work	CHW	Call reminders
	III	Neither		
4	I	Home	Expert Client	SMS reminders
	II	Home	Family member	Call reminders
	III	Neither		
5	I	Home	Family member	Travel vouchers
	II	Home	CHW	SMS reminders
	III	Neither		
6	I	Work	CHW	SMS reminders
	II	Home	Expert Client	Travel vouchers
	III	Neither		
7	I	Work	Expert Client	SMS reminders
	II	Home	CHW	Call reminders
	III	Neither		
8	I	Work	Expert Client	Call reminders
	II	Home	CHW	Travel vouchers
	III	Neither		

8 choice sets. D-efficiency after iteration 0.9607

Data Analysis

Quantitative data

We described participants' characteristics using descriptive summaries; frequency and percentages for categorical variables, median and inter-quartile range for count data like age, and duration on MDR-TB treatment.

DCE analysis to determine the patients' preferred MDR-TB CB-DOT model

For the primary analysis to determine patients' preferred attributes for community-based care, we used mixed logit choice model (with 1000 Halton simulation draws). We calculated utility scores by substituting coefficients into the model, and computed ranks to determine the most preferred MDR-TB CB-DOT attributes. We estimated the proportion of respondents that had positive relative preference for a certain attribute, using positive proportion = $\Phi(\beta/SD)$. Where, Φ = standard normal cumulative distribution function, and β is positive coefficients from mixed logit choice model, and SD = standard deviation representing level of preference heterogeneity across participants. The following model was used:

$$\text{Utility model (V)} = \beta_0 + \beta_1 \text{ c_chw} + \beta_2 \text{ c_expert} + \beta_3 \text{ l_home} + \beta_4 \text{ s_phcall} + \beta_5 \text{ s_tvouch}$$

Where,

V is utility derived from respondents' preference

β_1 to β_5 are coefficients indicating relative importance of each attribute.¹⁵

For the secondary analysis to determine if these preferences differed by gender, age groups, HIV status, or duration on MDR-TB treatment, we fitted interactions to perform sub-group analysis. The significance level for all the analyses was determined at 5%.

Qualitative data

A deductive approach with descriptive thematic coding was used to analyse data using NVivo Version 12. Interview transcripts were reviewed for content related to the research question. Codes were assigned to relevant segments of the text and similar codes aggregated to form themes that were used to develop coherent narratives. Data within and across themes were synthesized to generate an understanding of why certain attribute choices were preferred.

Human subjects' approval

Ethics approval was obtained from the University Research Co., LLC (URC) Ethics Review Board, the Joint Clinical Research Centre (JCRC) Ethics Review Board (Ref. JC1519), and the Uganda National Council of Science and Technology (UNCST) (Ref. HS2684). Prior to interview commencement, written informed consent was voluntarily obtained from all participants. Confidentiality of patients was ensured by using study identification numbers and data storage protection procedures.

Results

Socio-demographics

From December 2019 to January 2020, 103 participants were interviewed, characterized by the following socio-demographics: 58.3% were male, the median age was 37 years (inter-quartile range [IQR] 30 to 47 year), and the majority were farmers (35.9%), HIV negative (61.2%), and earned less than 1\$/day (65.1%). (Table 3).

Table 3
Participants' Characteristics

Characteristics	Number (%), N = 103
Gender	
Female	43 (41.7)
Male	60 (58.3)
Age in years, median (IQR)	
	37 (30–47)
Age categories	
20–34	42 (40.8)
35+	61 (59.2)
Marital status	
Single/Single/Divorced/Separated	48 (46.6)
Married	55 (53.4)
Occupation	
Farmer	37 (35.9)
Business	24 (23.3)
Employed	33 (32.1)
Unemployed	9 (8.7)
Daily income (\$)*	
< 1\$	67 (65.1)
≥ 1\$	36 (34.9)
Educational level	
None	11 (10.8)
Primary	58 (56.9)
Secondary	24 (23.5)
Tertiary	9 (8.8)
HIV status	
Negative	63 (61.2)
Positive	40 (38.8)
Duration on MDR-TB treatment (months)*	
Median (IQR)	10 (5–16)
Categories	
< 6 months	31 (30.4)
≥ 6 months	71 (69.6)
*Missing values; Educational level (1), Duration on MDR-TB treatment (1)	

Discrete choice model analysis

All attributes were significant determinants of participants' preference of the attributes of community-based MDR-TB care. All coefficients had significant P-values (< 0.05) (Table 4) and a positive constant term (coefficient = 0.52) implying that participants preferred at least one of the suggested hypothetical MDR-TB community-based care models to none.

Preference for specific attributes of community-based care

For specific attributes, the positive coefficients indicate that participants preferred: (1) treatment delivered by CHWs or expert clients rather than a family member; (2) treatment delivered at home rather than workplace; and (3) monthly travel vouchers as the form of additional support rather than phone call or SMS reminders. The estimated proportion of respondents with positive preference for CHWs and expert clients as the principal care giver for MDR-TB treatment, compared to a family member, was 73.0% and 69.2%, respectively. The proportion of patients with positive preference for delivery of treatment

at home compared to delivery at workplace was 85.4%, whereas patients with positive preference for phone call reminders and monthly travel vouchers compared to SMS reminders was 99.9% and 99.3%, respectively (Table 4).

Preference for models (combination of attributes) of community-based care

The most preferred community-based care model (i.e., combination of attributes) was a CHW giving treatment at the patient's home and the patient receiving monthly travel vouchers for additional support. The top four preferred MDR-TB CB-DOT models contained travel vouchers or phone call reminders and treatment delivered at home (Table 5).

Sub-group analysis

Sub-group analysis showed that patients' preference of the CB-DOT model attributes did not differ by gender. More HIV-positive than HIV-negative people with MDR-TB preferred their treatment delivered at home rather than at work (interaction term P-value = 0.04). Older patients aged 35 years and above preferred a CHW more than younger patients (interaction term P-value = 0.02). Those who had been on MDR-TB treatment for a longer duration (6 months or more) preferred a CHW (interaction term P-value = 0.02) or expert client (interaction term P-value = 0.02).

Table 4
Mixed logit choice model estimates and standard deviations with percentage of positive preference for the MDR-TB CB-DOT model attributes

Attributes	Coefficients	95%CI	P-value	SD (SE)	%Positive preference
Constant (CBDOT model)	0.52	0.30–0.74	< 0.01	-	-
Model of delivery					
Family	Reference				
Community health work	1.13	0.68–1.59	< 0.01	1.85 (0.27)	73.0
Expert client	0.89	0.46–1.32	< 0.01	1.77 (0.27)	69.2
Location					
Workplace	Reference				
Home	1.25	0.91–1.59	< 0.01	1.19 (0.20)	85.4
Support					
SMS	Reference				
Phone call reminders	0.70	0.41–0.99	< 0.01	0.19 (0.58)	99.9
Travel vouchers	1.35	1.04–1.653	< 0.01	0.55 (0.26)	99.3

Mix logit choice model with continuous assumption of choices. CI – Confidence interval, SD heterogeneity. – standard deviation for preference heterogeneity, SE – standard error. % positive indicates proportion of patients with positive preference for an attribute.

Table 5
Hypothetical MDR-TB CB DOT models ranks and utility scores

Model	Utility score	Rank
H2 CHW/Treatment delivered at home/Travel voucher	4.25	1
F2 Expert clients/Treatment delivered at home/Travel voucher	4.01	2
G2 CHW/Treatment delivered at home/Phone call reminder	3.61	3
A2 Expert client/Treatment delivered at home/Phone call reminder	3.36	4
E1 Family member/Treatment delivered at home/Travel voucher	3.12	5
A1 CHW/Treatment delivered at work/Monthly travel voucher for monthly appointments	3.00	6
E2 CHW/Treatment delivered at home/SMS reminder for monthly appointments	2.90	7
B2 Expert client/Treatment delivered at work/Monthly travel voucher for monthly appointments	2.76	8
D1 Expert client/Treatment delivered at home/SMS reminder for monthly appointments	2.66	9
D2 Family member/Treatment delivered at home/Phone call reminder for monthly appointments	2.48	10
C2 CHW/Treatment delivered at work/Phone call reminder for monthly appointments	2.36	11
H1 Expert client/Treatment delivered at work/Phone call reminder for monthly appointments	2.11	12
C1 Family member/Treatment delivered at home/SMS reminder for monthly appointments	1.77	13
B1 Family member/Treatment delivered at home/SMS reminders for monthly appointments	1.77	13
C1 Family member/Treatment delivered at home/SMS reminder for monthly appointments	1.66	15
F1 CHW/Treatment delivered at work/SMS reminder for monthly appointments	1.41	16
Utility score (V) = .5230616 + 1.132371 (c_chw) + .8881919 (c_expert) + 1.250887 (L_home) + .7014401 (s_phcall) + 1.346391 (s_tvouch)		

Qualitative results

Several key themes emerged from the data regarding the preferred attributes of community-based model of care.

Provider Type

Respondents reported that a CHW or expert client was preferred because they were trained and knowledgeable. In addition, they had the ability to offer adherence and psychosocial support including guidance on how to take their medications because of their professional or personal experience. Further, patients felt that expert clients could be more empathetic because they have been through similar experiences. They therefore trusted them to maintain confidentiality in the process of offering care.

"A community health worker encourages you to take medicine than any other person. Also provides counselling to the patient and explains the benefit of taking medicines on time." [20 year., Female, Single]

"I prefer an expert client to support me since he has been through the same situation. Expert client has the best experience ever so [I] will be able to share with him." [33 year., Male, Married]

"I prefer a CHW because they are knowledgeable, and I can trust them with my life." [54 year., Male, Married]

Family members were least preferred and viewed as unable to offer the support needed.

"..... family members, they sympathize so much and may discourage you from sticking to your treatment schedules as required and also they lack experience with this type of TB disease." [22 year., Female, Single]

Location of Care

Patients preferred to receive care from home citing privacy and a lower risk of TB-related stigma. They also felt that receiving care at home saves them time and money and presents an opportunity for health education for their family.

"The treatment at home also is a bonus, because the community cannot discriminate if confidentiality is kept by the expert client." [29 year., Female, Divorced/separated]

Treatment at home and monthly travel vouchers for monthly appointments is my preferred choice because there is time management while taking drugs since no out movement.

[66 year., Male, Married]

"It becomes less costly when I get treatment at home." [31 year., Male, Married]

The workplace was not preferred by most of the respondents. It was associated with stigma and fear for loss of employment or clients.

"I feel confidentiality is kept if treatment is given at home compared to my workplace where I could easily be seen and get stigmatized." [22 year., Female, Divorced/separated]

"At home there is no stigma on my condition and yet if visited at work, I could easily suffer from the gossip by workmates when they eventually learn about my condition, this could easily make me lose clients." [55 year., Female, Divorced/separated]

Support Type

Participants felt that monthly travel vouchers were the best way to promote appointment keeping as they provided relief from worrying about transport costs and money left over transport fares could be used to meet other needs like food, other household items, payment of debts, savings and farming amongst others.

"Monthly travel vouchers are the best for me because I will be knowing that transport is readily available and even the ticket will be reminding me of the clinic appointment date." [40 year., Male, Married]

"Because the money given for the travel voucher, the balance from it I can use it to buy other things and also do farming with it." [52 year., Male, Married]

Some of the respondents did not prefer other types of patient support, e.g., SMS or phone calls, due to various limitations surrounding their use which included:

"The message (SMS) reminders would work for me since am partially deaf and cannot easily hear through a phone call....." [43 year., Female, Divorced/separated]

".....SMS reminders are not good for me because I don't know how to read but may be if they call me and give transport to the clinic." [40 year., Male, Married]

Discussion

We carried out a parallel convergent mixed methods study to determine patient preferences for different attributes of community-based care. We found that people with MDR-TB preferred care to be provided at home by a CHW or an expert client who is a member of the community and as additional support, to receive travel vouchers to enable attendance at monthly clinic follow-up visits. MDR-TB patients preferred community-based care to the current standard of care, which is HF-DOT. CHWs and expert clients were viewed as knowledgeable, experienced, empathetic, and skilled to properly counsel and guide patients on how to manage side effects. They were also seen as able to maintain confidentiality in the process of offering care. Family members were viewed as lacking adequate MDR-TB related knowledge and patients were skeptical of their ability to offer the support required.

Preference for and patient satisfaction with lay providers has also been observed elsewhere, such as in rural Swaziland where DOT and administration of injectable forms of MDR-TB medication was delegated to trained community treatment supporters.¹⁶ In that study, preference for lay providers was driven by their ability to offer adherence counselling, confidentiality, and perceived lower treatment costs, reasons similar to those given by patients in our study.

Most patients preferred home care noting it provides privacy, safety, and comfort. Further, patients viewed home-based care as being less costly as it saves on time spent accessing care and daily transportation costs to follow-up health facilities. The workplace was perceived as a possible source of stigma that could lead to loss of clientele for small business owners or loss of employment. Similar to our study, findings from rural northern Uganda¹⁷ showed that home-based care was acceptable to both patients and health providers noting that it is safe, conducive to recovery and time saving. This study further showed that home-based care enabled psychosocial support. In our study, however, psychosocial support was mentioned as a reason for preference for a certain provider type rather than place of care.

In Bangladesh, a decentralized, community-based treatment program for patients with drug-resistant tuberculosis used home-based care DOT to address various needs of MDR-TB patients. It was a patient's preferred approach evidenced by their retention in care resulting into improvement in other treatment outcomes.¹⁸ Similarly, a quasi-experimental study done in India showed home-based care to be associated with low stigma¹⁹ similar to our study findings. In rural South Africa, MDR-TB patients preferred to receive MDR-TB and HIV care at home, and this was associated with reduced levels of rejection creating strong emotional bonds between patients, families and communities that is critical to health.²⁰ The home is seen as a place conducive for recovery and offers both psychological and emotional support needed to enable healing.²¹ In our study, patients preferred to receive care at home noting that home is private, is associated with low levels of stigma, saves time and money, and provides an opportunity for health education including infection prevention and control at the family level. Specifically, patients who were MDR-TB HIV co-infected preferred to be treated from home than those who were HIV negative. This may be related to the fact that in 2017, Uganda rolled out differentiated service delivery models for persons infected with HIV that included community-based drug delivery options.²² It is possible that clients' positive experience with these care delivery models positively influenced their choice for home based care.²³

Despite documented evidence that digital mobile technologies are useful in supporting TB care,²⁴ majority of participants preferred monthly travel vouchers over mobile-based support, such as SMS and phone call reminders. In our study, varying degrees of literacy and hearing loss due to drug toxicity probably decreased the preference for mobile technologies. In addition, the utility of the travel voucher in meeting other household needs besides travel to the monthly hospital appointment served as a main driver for this choice. The majority of our respondents earned only about a dollar a day and were receiving a transport voucher worth about 50 dollars a month from the NTLP under its ongoing “enabler program”. The travel voucher therefore shielded them against incurring catastrophic costs during their treatment. In Uganda, a recent study done to examine costs incurred during TB treatment showed that that more than half of households affected by TB experienced catastrophic costs, defined as spending more than 20% of their annual income on TB and these costs were 30 times higher among MDR-TB patients compared to drug sensitive tuberculosis (DS-TB) patients.²⁵ The major drivers of cost according to the Uganda TB cost survey were non-medical and included transportation, food, and nutritional supplements. Many respondents in our study reported that they could use the travel voucher to buy food.

The study had several strengths and limitations. We had regional representation across the country, involved MDR-TB treatment centers that treat more than 80% of the MDR-TB cases. The results presented here are therefore applicable to MDR TB patients diagnosed across the country. In addition, we used patients who had been on treatment for MDR-TB. Their opinions therefore are grounded in their lived experiences. However, the retrospective nature of the study may have resulted in some recall bias which could have resulted in under reporting. However, we tried to minimize this by using hospital records for non DCE variables. In addition, DCE experiments are sometimes prone to DCE bias which could result in misrepresentation of preferences. This was minimized by using pictorial questionnaires to aide understanding of choice sets. Further, the study used routinely collected data which is prone to missing data. However, efforts were made to minimize this by training research assistants on quality data collection and respective standard operating procedures prior to data collection. Finally, data collected did not include children and other risk populations, like pregnant women. Future studies could include children and other vulnerable populations so that their views are taken into consideration.

Conclusions And Recommendations

Our respondents preferred to take their medicines at home supported by a member of their community but revealed a critical need for additional support to help mitigate the costs of accessing care. Due to the current COVID-19 pandemic, innovations that reduce the need for health facility visits while still providing additional support to meet client needs will become increasingly relevant.² The feasibility and effectiveness of these models of care should be further evaluated. Studies to determine the feasibility and effectiveness of our preferred patient care model are underway.

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This research was performed in accordance with the Declaration of Helsinki guidelines. It was approved by the Joint Clinical Research Centre (JC1519) Institutional Review Board (IRB), and by the Uganda National Council of Science and Technology (HS2684) prior to study conduct. Administrative permission to collect this data were provided by the National TB and Leprosy Program. Prior to interview commencement, written informed consent was voluntarily obtained from all participants. Confidentiality of patients was ensured by using study identification numbers and data storage protection procedures.

AUTHOR CONTRIBUTIONS

RMM- Study conceptualization, protocol development, supervision of data collection process, qualitative data analysis, preparation of initial draft

JM- Protocol review, quantitative data analysis, manuscript revisions

SZM- Study conceptualization, protocol review, supervision of data collection process, manuscript revisions

EK: protocol review, supervision of data collection process, MDR TB technical input, manuscript revisions

HN: Supervision of data collection process, data management, manuscript revisions

PA: Supervision of data collection process, data management, manuscript revisions

DC- Protocol review, manuscript revisions, review of qualitative data analysis output, overall study supervision

DBFL- Protocol review, manuscript revisions, overall study supervision

HB- Protocol review, qualitative data analysis, manuscript revisions

ST- Study conceptualization, protocol review, overall study supervision, manuscript revisions.

AN- Study conceptualization, protocol review, overall study supervision, manuscript revisions.

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AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study available from the corresponding author on request.

CONSENT FOR PUBLICATION

Not applicable

COMPETING INTERESTS

The authors declare that they have no competing interests.

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