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Aetiology and Antimicrobial Susceptibility Pattern of Bloodstream Infection among Patients with Chronic Kidney Diseases at a Tertiary Hospital in Tanzania

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Abstract

Background

Patients with chronic kidney disease (CKD) are at an increased risk of acquiring bloodstream infections (BSI), particularly during dialysis. Using catheters and other invasive devices can serve as potential sources of infection. Resistant bacteria isolated from CKD patients with BSI significantly contribute to higher morbidity and mortality rates among these patients compared to the general population.

Methodology

A laboratory-based cross-sectional study was conducted to analyse blood samples collected from patients with CKD at Muhimbili National Hospital, Dar es Salaam, Tanzania. Two pairs of blood culture bottles were collected from each patient and incubated in the BACTEC™ FX 04 system. Positive blood cultures were then sub-cultured on solid media for isolation. Gram staining and conventional biochemical tests were performed for bacterial identification. Antimicrobial susceptibility testing was carried out using the Kirby-Bauer disc diffusion method. The patient's clinical data were obtained from their files. The Statistical Package for Social Sciences version 25 was used for data analysis. A p-value < 0.05 was considered statistically significant.

Results

Two hundred participants with CKD receiving care at the nephrology and dialysis wards were enrolled. Most, 90/200 (45.0%), were adults aged 40-60, and males contributed 118/200 (59%). The prevalence of BSI among CKD patients was 75/200(37.5%). BSI was in 43/103 (41.7%) of participants receiving dialysis. Among the isolated bacteria, the Gram-negative bacteria were the predominant contributors, accounting for 43/75 (57.3%). The most frequent Gram-negative bacteria were *Pseudomonas aeruginosa* 13/43 (30.2%) and *Escherichia coli* 12/43 (27.9%). On the other hand, among the isolated Gram-positive bacteria, Coagulase negative staphylococcus (CoNS) was frequent, 23/32 (71.9%). Among the Gram-negative bacteria, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* demonstrated the highest resistance to ciprofloxacin, with rates of 75% and 90%, respectively. Meanwhile, *Escherichia coli* showed the highest resistance to ampicillin at 77%. Among Gram-positive bacteria, CoNS and *Staphylococcus aureus* exhibited the highest resistance to penicillin, with rates of 90% and 85.7%, respectively.

Conclusion

The present study has revealed that a significant proportion of CKD patients have BSI, and the isolated bacteria were resistant to commonly used antibiotics in our settings. These findings underscore the need to address antibiotic resistance through enhanced antimicrobial stewardship in our setting.

Keywords: *Bloodstream Infections, Blood Culture, Antimicrobial Resistance, Chronic Kidney Disease.*

Introduction

Patients with Chronic kidney disease (CKD) are at an increased risk of acquiring bacterial infections such as bloodstream infections (BSI), which plays a major role in increasing the rate of morbidity and mortality among these patients (1,2). BSI is a major contributor to hospitalisation and death among CKD patients, accounting for 20% and 36%, respectively (3). BSI increases in CKD patients due to several reasons, including repeated intravascular interventions exposing them to skin normal flora, impaired immunity caused by renal failure, and in some situations, it could be hospital-acquired due to prolonged hospitalisation, hospital care and treatment, and severe underlying diseases (2,4-6).

BSI in patients with CKD is common globally, including in developed countries, such as the United States (US), where, in 2020, more than 14,000 bloodstream infections were reported to occur in patients on dialysis in the US (7,8). With limited resources and suboptimal adherence to infection prevention and control (IPC) measures and antimicrobial stewardship, the burden of BSI among CKD is greater in developing countries (6,9-11). BSI has been reported in particular subgroups of nephrology patients, for example, those undergoing chronic haemodialysis or kidney transplantation (1,8). The comparison of mortality caused by BSI in patients with end-stage renal disease to the general population shows that dialysis patients are 100-300 times and renal transplant recipients are 20 times (12,13).

The most commonly reported pathogens isolated from BSI in patients with CKD are Gram-negative organisms such as *Klebsiella pneumoniae*, *Escherichia coli* and *Pseudomonas aeruginosa* and Gram-positive bacteria such as *Staphylococcus aureus* (14-16). These organisms have a mechanism that enables them to resist antibiotics; thus, antimicrobial resistance, such as extended-spectrum beta-lactamase production in Enterobacteriaceae, Methicillin resistance in *Staphylococcus aureus,* and carbapenem resistance in Enterobacteriaceae are common (17-19). The accelerating antimicrobial resistance further complicates the treatment of BSI in this vulnerable population and increases the mortality rates (20,21).

Data on the burden of BSI CKD patients in Tanzania is scarce, and antimicrobial resistance is increasing rapidly. Therefore, to address the existing gap, we determined the aetiology of BSI and the antimicrobial susceptibility pattern of the isolated bacteria from CKD patients presenting with BSI. Our findings inform on the need to improve hospital care among patients with CKD and strengthen the IPC measures in Tanzania and other similar settings.

Methods

Study design and area

This cross-sectional study was conducted at Muhimbili National Hospital (MNH) in 2023. MNH is a tertiary referral and teaching hospital in Upanga, Dar es Salaam, Tanzania. The study involved patients admitted to the nephrology and dialysis wards at MNH. The nephrology ward has a capacity of admitting 108 patients per month and 1296 patients per year. The dialysis unit can attend 100 patients per day and 3000 per month.

Study population, sample size, and sampling procedure

The study involved patients with CKD receiving care at nephrology and dialysis wards during the three-month study period (from April to June 2023). We enrolled those who met the inclusion criteria of having a provisional diagnosis of BSI, a sample collected for culture and susceptibility testing, and available clinical data. The sample size of 372 was estimated using the reference of a proportion of patients with BSI of 41% from the study conducted in Uganda in 2022 (3).

Data collection and laboratory procedures

The present study involved the analysis of blood culture samples at the Central Pathology Laboratory (CPL), MNH. The CPL is accredited by the Southern African Development Community Accreditation Service (SADCAS), ensuring that the laboratory adheres to the highest standards of quality and reliability in its reported results. Two blood culture samples were collected by phlebotomists into blood culture bottles under aseptic procedures from patients with CKD in the nephrology and dialysis wards and then sent to CPL for testing. The diagnosis of BSI at the CPL was done using culture methods according to the standard operation procedures (SOP). All the laboratory tests were performed in the Microbiology section at the CPL, MNH. Briefly, the blood culture samples were cultured using an automated blood culture analyser, the BACTEC™ FX 04 blood culture system (Becton Dickinson, USA), at 37℃ for a maximum of five days. The primary Gram stain was performed on positive blood cultures, followed by subcultures using appropriate solid culture media. Positive blood culture samples were subcultured on 5% sheep blood agar and MacConkey agar, then incubated at 5 -10% CO_2 (for blood agar) and 37°C for 18–24 hours. The colony morphology and gram stain were used primarily to identify the bacteria. Then, Gram-negative rods were further identified by Analytical Profile Index (API) 20E (MW, USA) and a set of biochemical tests, including catalase, coagulase, and DNase tests, identified Gram-positive cocci. Antimicrobial susceptibility testing was performed using the Kirby Bauer disc diffusion method on Muller

Hinton agar (22). The selected antibiotics in susceptibility testing were those commonly used in our settings for treating BSI. The clinical data was extracted from the participants' files.

Statistical analysis

The laboratory results from the culture and susceptibility testing of the blood samples, as well as the participant's demographics and clinical data, were entered into Microsoft (MS) Excel software v.2019, and the data were merged, checked and cleaned. Then, the data was transferred to the IBM Statistical Package for Social Sciences version 25 (IBM Corp., Armonk, N.Y., USA). In the present study, the primary outcome was the prevalence of BSI, which was obtained by estimating the total number of patients with true pathogens out of the total number of patients whose blood cultures were performed. Data was summarised and described using tables, graphs and charts. Categorical variables were summarised using proportions. The chi-square test was used to compare differences between proportions. A p-value <0.05 was considered statistically significant for all tests.

Ethical approval

Ethical clearance to conduct the study was obtained from the Senate Research and Publications Committee of the Muhimbili University of Health and Allied Sciences with IRB number Reg. No.2020-04-14692. We requested permission from the Executive Director of Muhimbili National Hospital to access patients' information. The information obtained was handled with confidentiality and privacy, and special identification codes were used instead of the patients' names.

Results

Participants sociodemographic and clinical characteristics

The study involved the analysis of a total of 200 blood culture samples. Most of the participants, 90/200 (45%), were middle-aged adults aged between 40-60 years, followed by elderly, aged > 60 years, 58/200 (29%). More than half, 118/200 (59%) participants, were males. At least half 103/200 (51.5%) of the patients were receiving dialysis treatment, and 23/200 (11.5%) of participants had undergone kidney transplantation. In this study, 95/200 (46.5%) had other diseases (co-morbidities), either diabetes, hypertension or both, anaemia and other diseases. 96 out of 200 (48%) participants were hospitalised, and 5 out of 200 (2.5%) participants were HIV positive. The details of socio-demographic and clinical characteristics are summarised in Table 1.

Table 1: Sociodemographic and clinical characteristics of study participants (N=200)

Participant characteristics	Frequency(n)	Percent (%)
Age (in years)		
<18	10	5.0
18-22	17	8.5
23-39	25	12.5
40-60	90	45.0
>60	58	29.0
Sex		
Male	118	59.0
Female	82	41.0
Hospitalization		
Yes	96	48.0
No	104	52.0
HIV status		
Positive	5	2.5
Negative	195	97.5
Dialysis treatment		
Yes	103	51.5
No	97	48.5
Dialysis treatment frequency		
Once per week	6	5.8
Twice per week	28	27.2
Thrice per week	55	53.4
First time treatment (newly initiated)	14	13.6
History of kidney transplant		
Yes	23	11.5
No	177	88.5
***Kidney transplant duration**		
0 to 6 months	5	21.7
>6 months to 2 years	9	39.1
3 to 5 years	5	21.7
>5 years	4	17.3
Co-morbidities		
Yes	95	47.5
No	105	52.5
***Specific co-morbidities**		
Diabetes	10	10.5
Hypertension	29	30.5
Diabetes and hypertension	18	18.9
Anaemia	8	8.4
Other diseases	30	41.6

**The total of the variable is < 200*

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Prevalence and aetiology of bloodstream infections among patients with CKD

In this study, 75/200 (37.5%) participants with CKD had positive blood culture results. Of isolated pathogenic bacteria, 43/75 (57.3%) were Gram-negative bacteria, and among Gram-negative bacteria, *Pseudomonas aeruginosa* 13/43(30.2%) was frequently isolated, followed by *E. coli* 12/43(27.9%). Gram-positive bacteria contributed 32/75 (42.7%) of the isolated bacteria. Among the Gram-positive bacteria, 23/32 (71.9%) were CoNS, followed by *Staphylococcus aureus* 9/32 (28.1%). Most isolates, 23/75(30.7%), were CoNS species, followed by *Pseudomonas aeruginosa* 13/75 (17.3%). In addition, we isolated the rare bacteria species, including Burkholderia (n=1), Tatumella (n=1), Providencia (n=1) and Serratia (n=1), which we have defined as other Gram-negative rods. The overall distribution of the isolated bacteria regardless of gram reaction, is indicated in Figure 1.

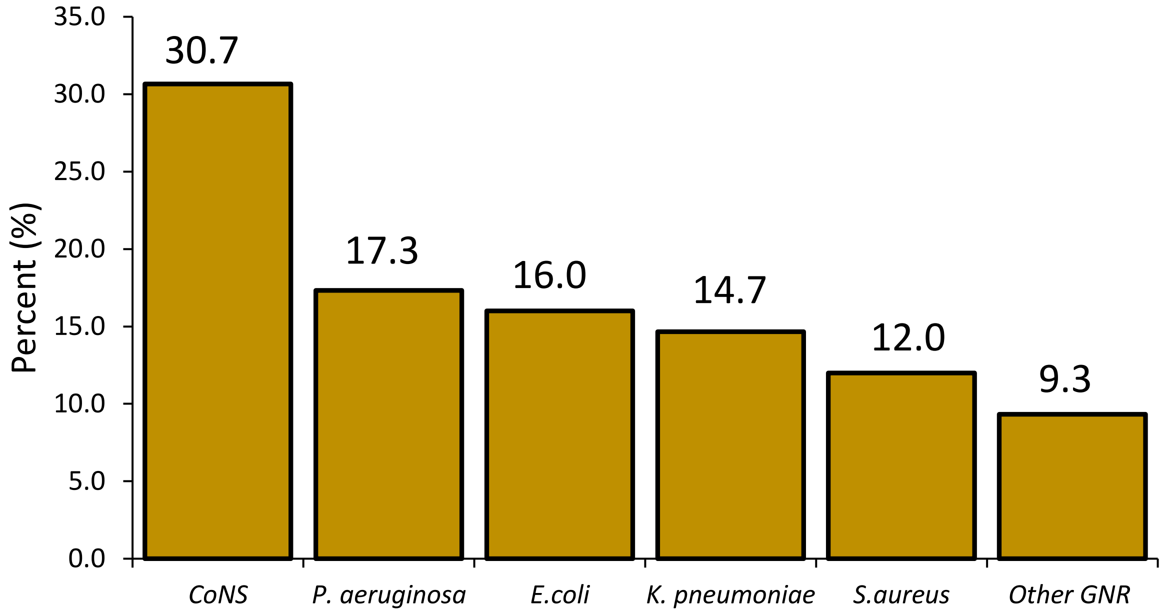

Figure 1. Frequency of bacteria isolated among patients with CKD at MNH

The figure depicts the proportion of distribution of the isolated bacteria from patients with CKD at MNH (n=75). Other GNR is a group of Gram-negative rods that were isolated at a smaller frequency (*Acinetobacter baumanii* (n=1), Enterobacter (n=1), *Salmonella typhi* (n=1), Burkholderia (n=1), Tatumella (n=1), Providencia (n=1) and Serratia (n=1)).

In the present study, the overall prevalence of BSI among patients with CKD was 37.5%. We also observed that BSI was relatively high, 43/103(41.7%) among CKD participants receiving dialysis treatment compared to those not receiving dialysis 32/97(33.0%); however, the difference was not statistically significant. The proportion of BSI across the participants' characteristics is summarised in Table 2.

Table 2: Patterns of Bloodstream infection (BSI) among patients with CKD

Participant characteristics	Total CKD Patients n	BSI positive n (%)	BSI negative n (%)	p-value
Age				
<18	10	3 (30.0)	7 (70.0)	0.63
18-22	17	4 (23.5)	13 (76.5)	
23-39	25	9 (36.0)	16 (64.0)	
40-60	90	38 (42.2)	52 (57.8)	
>60	58	21 (36.2)	37 (63.8)	
Sex				
Male	118	46 (40.0)	72 (60.0)	0.71
Female	82	29 (35.4)	53 (64.6)	
History of hospitalization				
Yes	96	32 (33.3)	64 (66.7)	0.31
No	104	43 (41.3)	61 (58.7)	
HIV status				
Positive	5	1 (20.0)	4 (80.0)	0.73
Negative	195	74 (37.9)	121 (62.1)	
Dialysis treatment				
Yes	103	43 (41.7)	60 (58.3)	0.25
No	97	32 (33.0)	65 (67.0)	
Dialysis treatment				
Once per week	6	4 (66.7)	2 (33.3)	0.31
Twice a week	28	11 (39.3)	17 (60.7)	
Thrice a week	55	20 (36.4)	35 (63.6)	
First time treatment (newly initiated)	14	8 (57.1)	6 (42.9)	
History of kidney transplant				
Yes	23	8 (34.8)	15 (65.2)	0.08
No	177	67 (37.9)	50 (62.1)	
Kidney transplant duration				
0 to 6 months	5	2 (40.0)	3 (60.0)	0.22
>6 months to 2 years	9	5 (55.6)	4 (44.4)	
3 to 5 years	5	1 (20.0)	4 (80.0)	
>5 years	4	0 (0.0)	4 (100.0)	
Co-morbidities				
Yes	95	35 (36.8)	60 (63.2)	1.00
No	105	40 (38.1)	65 (61.9)	
Specific co-morbidities				
Diabetes	10	4 (40.0)	6 (60.0)	0.60

Hypertension	29	10 (34.5)	19 (65.5)
Diabetes and Hypertension	18	7 (38.9)	11 (61.1)
Anaemia	8	1 (12.5)	7 (87.5)
Other diseases	30	13 (43.3)	17 (56.7)

**The total of the variable is < 200*

Antimicrobial resistance pattern of bacteria isolated among patients with CKD

Antimicrobial susceptibility test revealed that *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* expressed resistance to amikacin at 17%, 45.5% and 58.3%, respectively. At least 70% of the Gram-negative bacteria resisted ampicillin, ciprofloxacin, and amoxicillin. At least 40% of the isolates were resistant to ceftazidime, cefepime, meropenem, tazobactam, amoxicillin, gentamicin and sulphamethoxazole-trimethoprim. At least 50% of the isolates were resistant to *amoxicillin-clavulanate* and ceftriaxone. Resistance of up to 90% was observed in *Klebsiella pneumoniae* against ciprofloxacin. *Pseudomonas aeruginosa,* the most predominant GNR isolated, had at least 50% resistance to all the antibiotics tested, including meropenem (Table 3).

Table 3. Antimicrobial susceptibility patterns of Gram-negative bacteria causing BSI

Bacteria isolates	**Antibiotic discs n (%)**										
	AMK	**AMP**	**CIP**	**CAZ**	**CRO**	**FEP**	**MEM**	**TZP**	**AMC**	**CN**	**SXT**
E. coli	2 (17.0)	7 (77.8)	7 (63.6)	5 (41.7)	8 (66.7)	6 (60.0)	6 (50.0)	5 (41.7)	7 (70.0)	3 (27.0)	6 (66.7)
K. pneumoniae	5 (45.5)	8 (80.0)	9 (90.0)	9 (81.8)	8 (80.0)	7 (70.0)	5 (45.5)	7 (63.6)	7 (77.8)	7 (70.0)	8 (88.9)
P. aeruginosa	7 (58.3)		9 (75.0)	7 (53.8)	-	7 (53.8)	6 (50.0)	6 (50.0)	-	7 (58.3)	-
Other GNR	2 (28.6)	5 (71.4)	3 (28.6)	3 (42.9)	4 (57.1)	3 (42.9)	3 (42.9)	5 (57.1)	5 (57.1)	4 (42.9)	3 (42.9)

AMK=amikacin, AMP=ampicillin, CIP=ciprofloxacin, CAZ=ceftazidime, CRO=ceftriaxone, FEP=cefepime, MEM=meropenem, TZP=tazobactam, AMC=amoxicillin-clavulanate, CN=gentamicin, SXT= sulphamethoxazole-trimethoprim

Among the Gram-positive bacteria, the least resistance, 16% and 27%, were observed to erythromycin and clindamycin by *Staphylococcus aureus* and CoNS isolates, respectively. The highest resistance, 85% and 90%, was observed for penicillin by *Staphylococcus aureus* and CoNS isolates, respectively. At least 70% of CoNS isolates expressed resistance to ciprofloxacin, sulphamethoxazole-trimethoprim, erythromycin, azithromycin, and cefoxitin, and at least 45% expressed resistance to gentamicin. Among *Staphylococcus aureus* isolates, at least 70% of isolates expressed resistance to ciprofloxacin and cefoxitin, while 66.7% expressed resistance to azithromycin, 57.1% to gentamicin and 42.9% to clindamycin (Table 4).

Table 4: Antimicrobial susceptibility patterns of Gram-positive bacteria causing BSI

Bacteria Isolates	Antibiotic discs n (%)							
	P	SXT	CIP	E	AZM	CN	FOX	DA
CONS	9 (90.0)	8 (80.0)	5 (71.4)	8 (88.9)	2 (66.7)	5 (45.5)	7 (77.8)	3 (27.3)
S. aureus	6 (85.7)	0 (0.0)	4 (75.0)	1 (16.7)	2 (66.7)	4 (57.1)	5 (71.4)	3 (42.9)

P=penicillin, SXT= sulphamethoxazole-trimethoprim, CIP=ciprofloxacin, E=erythromycin, AZM=azithromycin, CN=gentamicin, FOX=cefoxitin, DA=clindamycin.

Discussion

Globally, patients with CKD have an increased risk of acquiring BSIs due to factors such as repeated intravascular interventions, impaired immunity, and prolonged hospital stays (5). Therefore, the present study aimed to determine the aetiology and the antimicrobial susceptibility pattern of bacteria causing bloodstream infection among patients with CKD at a tertiary hospital in Dar es Salaam, Tanzania.

Overall, our findings indicate a relatively high proportion of BSIs among CKD patients, with a relatively high frequency in those receiving dialysis. This observation supports previous reports of an increased risk of BSIs in CKD patients (3). In our study, Gram-negative bacteria were the most prevalent pathogens, accounting for 57.3% of the isolates, with *Pseudomonas aeruginosa* (30.2%) and *Escherichia coli* (27.9%) being the most common. These findings are consistent with studies from Uganda, Madrid, and Israel, where Gram-negative bacteria predominated, and *Escherichia coli* was frequently isolated (2, 3, 23). The higher prevalence of Gram-negative bacteria in our setting might be related to specific hospital practices or the unique characteristics of the patient population. In contrast, Gram-positive bacteria contributed to 42.7% of the total isolates, whereby the CoNS was the predominant (71.9%) bacteria. Although CoNS are often considered contaminants, in this study, they were considered pathogenic and significant contributors to BSIs. Similar trends have been reported in other studies, highlighting the role of CoNS in CKD patients, particularly those undergoing repeated invasive procedures like dialysis (2, 24, 25). Our study's high incidence of CoNS contrasts with some reports where Gram-positive bacteria had a higher overall incidence rate in BSIs (24, 26, 27). These variations could be due to differences in study populations, such as age, with adult patients being more susceptible to Gram-positive BSIs (28). Our study also identified rarely isolated bacteria, such as *Providencia* and *Serratia*. These findings align with studies from the islands of Saipan and Glasgow, where similar pathogens were reported (29). The presence of *Providencia* in our study might be linked to environmental contamination or prolonged use of dialysis instruments, highlighting the need for stringent infection control measures in our setting.

Regarding antimicrobial resistance, we observed alarmingly high resistance rates among both Gram-negative and Gram-positive bacteria. For Gram-negative bacteria, such as *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae*, resistance to commonly used antibiotics exceeded 40%. The observed resistance rates were higher than those reported in Uganda and Turkey in 2022 (3, 30). Additionally, *Staphylococcus aureus* and CoNS demonstrated substantial resistance to penicillin, 85% and 90%, respectively and other commonly used antibiotics. CoNS exhibited at least 70% resistance to ciprofloxacin, sulphamethoxazole-trimethoprim, erythromycin, azithromycin, and cefoxitin. These findings align with other studies and underscore the significant burden of resistance bacteria in BSIs among CKD patients (31, 32). The high levels of antibiotic resistance observed in this study highlight the urgent need to strengthen infection prevention and control strategies and antibiotic stewardship programs to mitigate the impact of antimicrobial-resistant bacteria in this vulnerable population.

The present study has some limitations. First, the number of bacteria isolated is less than 25 and we could not collectively report the antimicrobial susceptibility data of all the isolated bacteria because the bacterial isolates were not all tested to the same panel of antibiotic agents. Nonetheless, we believe our results are reliable as they concur with other previous studies.

Conclusion

The present study has revealed the significant burden of bloodstream infections among CKD patients, with a concerning level of antibiotic resistance. These findings emphasise the urgent need to strengthen infection prevention and control measures to curb the risk of bloodstream infections among patients with CKD, especially those undergoing dialysis and implement robust antimicrobial stewardship strategies in our local healthcare setting.

Abbreviations

BSI	Bloodstream infections
CKD	Chronic Kidney Disease

CoNS	Coagulase negative Staphylococcus
IPC	Infection Prevention and Control
SADCAS	Southern African Development Community Accreditation Service
MNH	Muhimbili National Hospital
CPL	Central Pathology Laboratory

Declarations

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The study did not receive any funding.

Authors Contribution

DK, EH, VJS, RK, NS, UOK, AMM, SSM, JM, AJ and MM contributed to the study's design, analysis, and interpretation of data. DK, EH and RK collected the data. DK drafted the manuscript while UOK, AMM, SSM, JM, AJ and MM critically reviewed the manuscript. All authors read and approved the manuscript.

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