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Use of drugs that induce osteoporosis or fracture in older adult with myeloma multiple: cross-sectional study

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Abstract

Objective: to describe the frequency of use of medications that induce osteoporosis or fracture (MOF) by old adult with multiple myeloma and evaluate associated factors. **Methods:** cross-sectional study, developed in three settings: a public teaching hospital, a private outpatient onco-hematology service, a public hospital, reference in oncology. Data were collected between April 2019 and March 2020 by means of face-to-face interviews and review of patients' medical records. The dependent variable was the use of MOF. The drugs were identified in pharmacovigilance studies conducted from the Japanese database of adverse drug event reports and the World Health Organization's Vigibase that calculated the reporting odds ratio (ROR) of osteoporosis or fracture for the drugs. Factors associated with MOF by patients of study use were determined by multiple logistic regression. The drugs were classified by the fourth level of Anatomical Therapeutic Chemical (ATC) Classification. **Results:** 153 older adult (≥ 60 years) were included, with a median age of 70.9 years, female predominance (54.2%), and 73.2% of the older adult were using at least one MOF. Most of the older adult (56.9%) were seen in the private health service. The most common comorbidity was hypertension (67.3%), followed by diabetes mellitus (28.8%). The most frequent MOF were proton pump inhibitors (PPIs) (29.2%) and sulfonamides (13.9%) followed by benzodiazepine related drugs (11.9%) and other opioids (10.4%). The older adult who used MOF presented the following characteristics: age up to 70 years, female gender, income up to three salaries, high education (high school or higher), multimorbidity, hypertension and polypharmacy. In multivariate analysis, an independent and positive association was obtained between MOF use and polypharmacy, MOF and high education. **Conclusion:** the frequency of MOF use by the older adult studied was high and was positively and independently associated with polypharmacy and high education. The ATC classes of MOF with the highest frequency of use were: PPIs, high-ceiling diuretic (sulfonamides), benzodiazepines related drugs and other opioids.

Keywords: adverse drug reactions, osteoporosis, fracture, older adult, multiple myeloma.

Utilização de medicamentos que induzem osteoporose ou fratura em idosos com mieloma múltiplo: estudo transversal

Resumo

Objetivo: descrever a frequência de utilização de medicamentos que induzem osteoporose ou fratura (MOF) em idosos com mieloma múltiplo(MM) e avaliar os fatores associados. **Métodos:** estudo transversal, desenvolvido com pacientes em tratamento de MM em três cenários: um hospital público de ensino, um serviço privado ambulatorial de onco-hematologia um hospital público, referência em oncologia. Os dados foram coletados entre abril de 2019 a março de 2020 por meio de entrevistas face a face e revisão de prontuários dos pacientes. A variável dependente foi o uso de MOF, que foram identificados em estudos previamente realizados a partir de duas bases de dados de farmacovigilância: Vigibase da Organização Mundial de Saúde e na *Japanese Adverse Drug Event Report* (JADER), que calcularam o *reporting odds ratio* (ROR) de osteoporose ou fratura para os medicamentos. Os medicamentos foram classificados segundo o nível 4 da sistemática da *Anatomical Therapeutic Chemistry*- ATC. Os fatores associados ao uso de MOF em pacientes com MM incluídos no estudo foram determinados por regressão logística múltipla. **Resultados:** foram incluídos 153 idosos (≥ 60 anos), com mediana de idade de 70,9 anos, predomínio do sexo feminino (54,2%). A maioria dos idosos (56,9%) foi atendida no serviço de saúde privado. A comorbidade mais encontrada foi hipertensão arterial (67,3%) seguida por diabetes mellitus (28,8%). Identificou- se que 73,2% dos idosos faziam uso de pelo menos um MOF. Os MOF mais frequentes foram os inibidores da bomba de prótons (IBPs) (29,2%), sulfonamidas (13,9%) seguidos por medicamentos relacionados a benzoadiazepinicos (11,9%) e outros opioides (10,4%). Os idosos que utilizaram MOF apresentaram as seguintes características: idade até 70 anos, sexo feminino, renda de até três salários, escolaridade alta (ensino médio ou superior), multimorbidade, hipertensão arterial e polifarmácia. Na análise multivariada, obteve-se associação independente e positiva entre uso de MOF e polifarmácia, MOF e escolaridade alta. **Conclusão:** a frequência de utilização de MOF pelos idosos estudados foi elevada e associada de forma positiva e independente com polifarmácia e alta escolaridade. As classes ATC dos MOF com maior frequência de utilização foram: IBP, diuréticos de alça (sulfonamidas), medicamentos relacionados a benzodiazepinicos e opioides.

Palavras-chave: reações adversas a medicamentos, osteoporose, fratura, idoso, mieloma múltiplo.

Introduction

Multiple Myeloma (MM) is a hematological neoplasm characterized by the proliferation of abnormal clonal plasmocytes in the bone marrow[1]. According to the worldwide statistics, nearly 86.000 new MM cases are diagnosed per year, representing 0.8% incidence. In addition to that, it is estimated that there are 63,000 deaths due to MM, representing 0.9% of cancer deaths and 10% among hematological neoplasms[2]. Data from the Oncology Panel available at DATASUS show that between 2013 and 2019, approximately 2,600 MM cases were diagnosed in Brazil and that the annual incidence is estimated at 1.24 cases/100,000 inhabitants, for both genders[3]. The patients' age median in Brazil is 63 years old, varying from 18 to 100, according to the Oncology Observatory[3]. In turn, in Europe the age median at the time of diagnosis is 72 years old, indicating that MM is an aged people's disease[4].

Patients with MM usually present hypercalcemia, anemia, kidney injuries, increased risk of infections and pathologic fractures secondary to osteolytic bone loss[2]. The bone marrow microenvironment is a favorable space for the proliferation of tumor cells due to wide vascularization, abundant presence of growth factors and production of prostaglandins[5].

In MM, more than 80% of the newly diagnosed patients will develop detectable bone disease due to osteoclastic bone destruction, reduced osteoblast function and bone restoration blockage[5]. This imbalance, concomitantly with a reduction in Bone Mineral Density (BMD), common in advanced age and factors related to the treatment, can lead to osteoporosis, which is characterized by an increased risk of fractures, mainly in older adults, although this risk can occur at any age[6-7].

Currently, the therapeutic arsenal for the treatment of MM includes treatment regimens that should prioritize drug combinations and may use up to four medications: corticosteroids, alkylating agents, immunomodulators, proteasome inhibitors, histone deacetylase inhibitors and monoclonal antibodies[8]. The treatment options for patients with MM advanced in the last decades and contributed to extending patients' survival and improving their quality of life[8].

Corticosteroids are part of several treatment regimens for MM and their prolonged use leads to fractures and osteoporosis[5,8,9]. In this sense, using this therapeutic class in patients with MM deserves attention due to the bone alterations associated with pathophysiology of the disease[1]. MM is prevalent in older adults, who frequently make use of multiple medications to treat chronic non-communicable diseases[1,10]. Polypharmacy in patients with MM is relevant due to the need to also use medications from different therapeutic classes for supportive therapy to the antineoplastic treatment[1,3,4,5].

Injuries related to bone disease can exert an impact on reducing quality of life, increasing health costs, decreasing functional independence, predisposing older adults to the risk of pathological fractures, disabilities, spinal cord compression, severe bone pain and the need for surgical interventions, posing threats to patient safety and well-being[5,11,12].

Approximately 45% of the patients with multiple myeloma presented fractures in the first year after the diagnosis and 65% during course of the disease[11]. In addition to that, patients with MM who have pathological fractures present 20% higher risk of death in two years when compared to those with no fractures. This type of injury can interfere in functional dependence, reducing the patients' survival[11-12]. Therefore, identifying modifiable risk factors for fractures and osteoporosis, such as medication use, will contribute to improving safety in the treatment of patients with MM. This objective of the current paper is to describe the MOG use frequency in aged people with multiple myeloma, as well as to identify the factors associated with use of these medications.

Methods

This is a cross-sectional study carried out in three settings located in the city of Belo Horizonte, Minas Gerais: a public teaching hospital, High-Complexity Oncology Unit (*Unidade de Alta Complexidade em Oncologia*, UNACON); a private onco-hematology outpatient service; and a public hospital that is a reference in Oncology. The current research is part of the research project entitled "Adverse events, adherence to the treatment and quality of life in patients with multiple myeloma". The patients who took part in the research signed the Free and Informed Consent Form. The research was approved by the Research Ethics Committee of the Federal University of Minas Gerais under CAAE: 05400818.3.0000.5149 and opinion No. 3,186,543.

Data collection was carried out through face-to-face interviews and review of patients' medical records from April 2019 to March 2020, using a data collection form. The patients included were those diagnosed with multiple myeloma, aged ≥60 years old (according to the definition of older adults in the Brazilian Statute for Aged People) and who used one or more medications to treat comorbidities and MM (excluding drugs for parenteral antineoplastic therapy)[13].

The study dependent variable was the use of medications that induce osteoporosis or fractures (MOFs), which were identified in two pharmacovigilance studies developed in the following databases: Japanese Adverse Drug Event Reporting Database (JADER), linked to Japan's national drug system and covering data from voluntary reports of adverse drug events since 2012, and in Vigibase, which covers voluntary reports from countries participating in the international WHO drug monitoring program[14-15]. The selected studies used disproportionality analysis carried out in JADER and Vigibase, calculating the Reporting Odds Ratio (ROR) for medications associated with fractures and osteoporosis[14-15]. The medications included were those whose ROR presented p≤0.05. Corticosteroids were not considered in this analysis because they are part of the MM treatment regimens[3].

The independent variables were as follows: sociodemographic ones including age, gender, income ≤3 minimum wages (yes or no) and education (low level: no studies or Elementary School; high level: High School or Higher Education). The clinical variables were multimorbidity (presence of two or more diseases) and comorbidities (hypertension, diabetes *mellitus*, cancer [excluding MM], chronic kidney disease and arthritis), type of health service (private or public), and hospitalization history in the last year (yes or no). In turn, the pharmacotherapeutic variable was polypharmacy, in this study defined as the use of five or more medications, not including parenteral antineoplastics used to treat MM.

The data were introduced into the Questionnaire Development System (QDS), version 2.6.1, and analyzed in the Statistical Package for Social Sciences (SPSS) software, version 25.0. The medications used by the research participants were identified by the name of the drug and classified according to level 4 of the systematic method proposed by the Anatomical Therapeutic Chemical (ATC) classification from the World Health Organization (WHO), recognized by this latter as an international standard for drug utilization studies.

Statistical analysis

Descriptive analyses were carried out using the frequency distribution of the categorical variables and a description of central tendency and dispersion measures of the continuous variables. A univariate analysis was performed to compare patients using at least one MOF to those who did not, using Pearson's chi-square or Fisher's exact tests, respecting the assumptions of the tests. The variables associated with MOF use in the univariate analysis ($p \leq 0.20$) were included in the multiple logistic regression model. The "backward" strategy was employed to obtain the final model, comprising variables with $p<0.05$. In the univariate and multivariate analyses, magnitude of the association was expressed by the Odds Ratio (OR) with a 95% Confidence Interval (CI). Hosmer-Lemeshow test was used to verify fit of the final model of the multiple logistic regression analysis.

Results

The study included 153 aged patients (≥60 years old), with a median age of 70.9 (Interquartile range-IQR=13; Minimum-Min=60 and Maximum-Max=92), with predominance of the female gender (54, 2%). It was verified that 56.9% of the older adults were treated in the private health network and that 46.5% had at least one hospitalization in the last year. The most frequently found comorbidity was arterial hypertension (67.3%), followed by diabetes *mellitus* (28.8%). Polypharmacy was identified in the pharmacotherapy of 70.6% of the study patients. The other characteristics of the research participants are found in Table 1.

Table 1. Sociodemographic and clinical variables of the sample comprised by 153 older adults with multiple myeloma

Characteristics	Values	
Sociodemographic		
Age in years old [Median (Interquartile Range)]	70.9	(13.0)
Gender [Female n (%)]	83	(54.2)
Income[1] [>3 minimum wages n (%)]	82	(53.6)
High schooling levels [High School or Higher Education n (%)]	80	(52.3)
Clinical		
Multimorbidity [Presence of two or more diseases n (%)]	97	(63.4)
Type of service [Private n (%)]	87	(56.9)
Hospitalization history [No n (%)]	117	(46.5)
Arterial hypertension [Yes n (%)]	103	(67.3)
Diabetes *mellitus* [Yes n (%)]	44	(28.8)
Cancer [Yes n (%)]	25	(16.3)
Chronic Kidney Disease [Yes n (%)]	09	(5.9)
Arthritis [Yes n (%)]	2	(1.2)
Pharmacotherapeutic		
Polypharmacy [Use of five or more medications n (%)]	108	(70.5)

[1]One minimum wage = 275 dollars; Dollar exchange rate date: January 2019

Table 2 presents the MOFs used by the research participants, classified according to ATC level 4, the most frequent being: A02BC-Proton Pump Inhibitors (PPIs) (29.2%), C03CA-Sulfonamides (13.9%), N05CF-Benzodiazepine-related medications (11.9%) and N02AX-Other opioids (10.4%).

Table 2. Frequency of medication classes that induce osteoporosis and fractures used by older adults with multiple myeloma, according to Level 4 from the ATC classification

ATC Nível 4	Classification	Drug	N	%
A02BC	Proton pump inhibitors	Omeprazole Esomeprazole Pantoprazole	59	29.2
C03CA	Sulfonamides	Furosemida	28	13.9
N05CF	Benzodiazepine related drugs	Zolpidem	24	11.9
N02AX	Other opioids	Tramadol	21	10.4
M05BA	Bisphosphonates	Pamidronate, Zoledronic acid	19	9.4
B01AA	Vitamin K antagonists	Warfarin	8	4.0
N05BA	Benzodiazepine derivatives	Alprazolam	7	3.5
R03BA	Glucocorticoids	Fluticasone +salmeterol	6	3.0
N03AX	Gabapentinoids	Pregabalin	6	3.0
N06AX	Other antidepressants	Duloxetin	6	3.0
N06DA	Anticholinesterasess	Galantamine, Donepezil	4	2.0
G04CB	Testosterone-5-alpha reductase inhibitors	Finasteride, Dutasteride	2	1.0
L02BG	Aromatase inhibitors	Anastrazole	2	1.0
N03AA	Barbiturates and derivatives	Phenobarbital	2	1.0
N03AG	Fatty acid derivatives	Valproic Acid	2	1.0
L01FA	CD20 inhibitors	Rituximabe	1	1.0
L04AA	Selective immunosuppressants	mycophenolic acid	1	0.5
L04AD	Calcineurin inhibitors	Tacrolimus	1	0.5
L04AX	Other immunosuppressants	Azathioprine	1	0.5
M01AH	Coxibs	Celocoxib	1	0.5
N03AF	Carboxamide derivatives	Carbamazepine	1	0.5
Total			**202**	**100%**

The frequency of aged people who used at least one MOF was 112 (73.2%). In the univariate analysis, it was identified that MOF use was more frequent among the older adults with the following characteristics: age up to 70 years old, female gender, income of up to 3 minimum wages, high schooling level (High School or Higher Education), presence of multimorbidity, arterial hypertension and polypharmacy. The association of these characteristics with MOF use presented p-value≤0.20 (Table 3).

In the multivariate analysis, an independent and positive association was obtained between MOF use and polypharmacy (OR=3.19, CI95%=1.46-6.96), as well as between MOF use and high schooling levels (OR=2.08) 95%CI=1.00-4.32) (Table 3).

Discussion

The MOFs most used by research participants were PPIs, loop diuretics (sulfonamides), benzodiazepine-related medications and opioids.

PPIs are prescribed for several clinical conditions even before the MM diagnosis. Recent studies have shown that chronic use of medications from this therapeutic class alters BMD[16,18]. In 2019, Fattahi et al. evaluated the influence of long-term PPI use on BMD in three regions of the human body and demonstrated a drastic reduction in mineral content in all regions investigated, especially in PPI users with no history of previous use, for a period greater than two years[16]. Accordingly, a research study conducted with 25,276 individuals followed-up for five years found that PPI users were 1.27 times more likely to suffer fractures than non-users, including major osteoporotic fractures, hip fractures and vertebral fractures[17].

It is worth mentioning that, according to the AGS/Beers 2023 Criteria, PPIs are classified as inappropriate medications for older adults (IMOAs) when used for more than eight weeks. The classification of PPIs as IMOAs is based on studies showing a significant connection between long-term PPI use and the development of adverse bone-related health outcomes such as osteoporosis and fractures[18].

Table 3. Univariate and multivariate analyses of the factors associated with the use of medications that induce osteoporosis and fractures by older adults with multiple myeloma

Variables	MOF use		Univariate analysis		Multivariate analysis	
	Yes (n%)	No (n%)	OR (IC 95%)	P-Value	OR (IC 95%)	p-value
Age						
70 years old	58 (77.3)	17 (22.7)	0.59 (0.28-1.23)	0.162		
>70 years old	54 (66.7)	26 (33.3)	1			
Gender						
Female	63 (75.9)	20 (24.1)	1.35 (0.65-2.76)	0.411		
Male	49 (70.0)	21 (30.0)	1			
Income[1]						
Up to 3 minimum wages	58 (81.7)	13 (18.3)	2.31 (1.08- 4.92)	0.27		
>3 minimum wages	54 (65.9)	28 (34.1)	1			
Schooling						
High – High School or Higher Education	64 (80.0)	16 (20.0)	0.48 (0.23-0.99)	0.047	2.08 (1.00-4.32)	0.047
Low – No studies or Elementary School	48 (65.8)	25 (34.2)	1			
Multimorbidity						
Yes	73 (75.3)	24 (24.7)	1.32 (0.63- 2.75)	0.45		
No	39 (69.6)	17 (30.4)	1			
SAH[2]						
Yes	77 (74.8)	26 (25.2)	1.26 (0.59- 2.68)	0.533		
No	35 (70.0)	15 (30.0)	1			
Diabetes						
Yes	31 (70.5)	13 (29.5)	0.82 (0.37- 1.79)	0.626		
No	81 (74.3)	28 (25.7)	1			
Cancer						
Yes	20 (80.0)	5 (20.0)	1.56 (0.54- 4.48)	0.401		
No	92 (71.9)	36 (28.1)	1			
CKD[3]						
Yes	17 (68.0)	8 (32.0)	0.73 (0.29- 1.86)	0.521		
No	95 (74.2)	33 (25.8)	1			
Arthritis						
Yes	6 (66.7)	3 (33.3)	0.71 (0.17- 3.01)	0.702		
No	106 (73.6)	38 (26.4)	1			
Polypharmacy						
Yes	86 (79.6)	22(20.4)	2.85 (1.34- 6.07)	0.005	3.19 (1.46- 6.96)	0.004
No	26 (57.8)	19 (42.2)	1			

Chi-square: 3.343; Hosmer-Lemeshow test: Degrees of Freedom = 2; p-value = 0,179. [1]One minimum wage = 275 dollars (dollar exchange rate date: January 2019) [2]Systemic Arterial Hypertension. [3]Chronic Kidney Disease

The most prevalent comorbidity among the patients with MM included in the study was hypertension. Anti-hypertensive and diuretic medications are prescribed to more than half of the people in the age group of 60 years old[19]. Loop diuretics, which include sulfonamides, have the adverse effect of increasing renal calcium depletion, which contributes to a greater risk of falls. A cohort study conducted with older adults aged less than 60 years old verified that the risk of fractures was higher among the new users[19].

To guide risk stratification of the patients, a new score was developed to predict fractures in patients with MM, and presence of pain is one of its variables. Paradoxically, opioids used to treat pain are a MOF, especially in older adults in the first days of treatment[20]. The probable reason for the high risk of fractures resulting from opioid use is the increased risk of falls caused by the psychomotor effects. Opioids also influence bone metabolism due to their ability to induce hypogonadism and directly interfere with bone formation[21]. In the current study, among the MOFs with action on the Central Nervous System, in addition to opioids, there are benzodiazepine-related medications, which presented high frequency[14-15].

Currently, due to their safety, effectiveness and tolerability, bisphosphonates (BPhs) are the standard treatment to handle bone disease in MM. This therapeutic class reduces the incidence of adverse events in the skeletal system and improves quality of life and survival in patients with MM[2,5,22]. BPhs mainly act by inhibiting malignant osteolysis through osteoclast activity suppression, inducing osteoclast apoptosis, and impairing MM growth that can result in bone-related events such as fractures and bone pain[22]. The association between atypical fractures and BPhs was evidenced in a disproportionality analysis study conducted using the Japanese pharmacovigilance system database, where eight BPhs were associated with drug-induced atypical femur fractures[14]. Atypical BPh-induced fractures were also reported in studies with patients with MM[15,22,23,24,25].

Therapeutic schemes with nitrogen BPhs are prescribed for long periods[2,5,22]. Impairment of bone remodeling by long-term cumulative effects of treatment with mild bisphosphonates is a hypothesis for atypical fractures[15,25]. According to studies in animal models, nitrogen BPs, used in long-term therapies, prevent bone remodeling and inhibit osteoclasts, resulting in failure to repair micro-cracks in the cortical bone, accumulation of damage and reduced cortical bone tenacity, which may result in atypical fractures[15]. Cumulative BPh doses for the treatment of MM tend to be notably higher than those used for osteoporosis[2,5,22]. A cohort study of Korean patients with MM identified an association between high BPh doses and occurrence of atypical fractures[25]. However, despite the in vivo and in vitro studies, the induction mechanism for BPh-induced atypical fractures is not yet elucidated[15,25].

It is noteworthy that, of the most frequent classes of MOFs in the current study, three (loop diuretics [sulfonamides], opioids and benzodiazepine-related medications) are considered classes of Fall Risk-Increasing Drugs (FRIDs) and that can consequently induce fractures[26].

The high polypharmacy frequency found among the study older adults is in consonance with previous studies conducted with patients with MM[27,28]. Polypharmacy is associated with negative outcomes, including mortality, falls, increased hospitalization times, and risk of adverse events that exert an impact that is proportional to the number of medications used. However, it is important to highlight that, in some individuals, polypharmacy can be clinically appropriate. Pharmacotherapy reviews are a strategy to indicate if the therapy is correct and safe for a given patient[29-30]. One of the strategies indicated to reduce inappropriate polypharmacy is deprescription. Deprescription can be applied to MOFs in patients with MM when there is a therapeutic alternative. If deprescription is not feasible, the patient should be instructed about the risk of falls to avoid fractures. Thus, it is also important to identify the fall-inducing medications and to evaluate safer alternatives[26,29,30].

Polypharmacy and high schooling levels have a positive and independent association with MOF use. This fact can be explained due to the higher schooling level that provides greater access to medications, exposure to polypharmacy and, consequently, greater possibility of MOF use. The association between polypharmacy and schooling level in community-dwelling older adults undergoing non-cancer treatments was also evidenced in a Brazilian study[31].

The current research is innovative in investigating MOF use in patients with MM and classifying them based on diverse evidence from pharmacovigilance studies using disproportionality analysis[14-15]. In addition to that, it is important to note the heterogeneous sample comprised by patients from the public and private health systems in southeastern Brazil.

The research limitations are the impossibility of extrapolating the information to the Brazilian population as a whole, as the research was only limited to a single Brazilian capital city, as well as due to lack of information about the fracture or osteoporosis diagnoses in the medical records, and to the possibility of MOF use under-recording.

Taking into account that osteoporosis affects a large number of aged individuals, that multiple myeloma is a predictor of bone diseases and that, for this type of pathology, medication use can increase the risk of fractures and osteoporosis, including the corticosteroids found in the treatment regimes, this research about MOF use contributes relevance to the scientific community. In addition to that, treatment complexity contributes to reducing the patients' quality of life, imposing new demands on health services.

The development of new studies including variables related to the risk and occurrence of fractures and osteoporosis, and to MOF and corticosteroid use time, will contribute to expanding knowledge, providing more robust evidence to promote interventions targeted at the care of patients exposed to risk of fractures and osteoporosis. Therefore, it is of significant importance of pharmaceutical monitoring and interprofessional work with patients with MM to ensure that MOF use is safe, effective and appropriate to each patient's clinical context.

Conclusion

The MOF use frequency by the research participants was high and positively and independently associated with polypharmacy and high schooling levels. According to ATC level 4, the most frequently used MOF therapeutic classes were the following: PPIs; loop diuretics (sulfonamides); benzodiazepine-related medications; and other opioids.

Collaborators

MLR, CMP and AMR conceived the project; MLR, TLM, PLD, LPS and JSM collected the data; MLR, CMP and AMR analyzed and interpreted the data; MLR, AMR and CMP wrote the article; and MLR, CMP, TLM, PLD, LPS, JSM and AMR critically reviewed the article and approved the final version. The authors are responsible for all the aspects of the paper in ensuring accuracy and integrity of any of its parts.

Declaration of conflict of interests

The authors declare that there are no conflict of interests.

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