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ORIGINAL RESEARCH

Medication Appropriateness, Polypharmacy, and Drug-Drug Interactions in Ambulatory Elderly Patients with Cardiovascular Diseases at Tikur Anbessa Specialized Hospital, Ethiopia

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Background: Appropriate prescribing is often challenging in geriatric patients due to age-related pharmacokinetic and pharmacodynamic alterations. Elderly patients with cardiovascular diseases are frequently prescribed multiple medications. Hence, it is imperative to investigate medication appropriateness, polypharmacy, and drug-drug interactions in these groups of patients.

Objective: To assess medication appropriateness using the 2019 American Geriatric Society Beers and Medication Appropriateness Index criteria, polypharmacy and drug-drug interactions among elderly ambulatory patients with cardiovascular diseases at Tikur Anbessa Specialized Hospital.

Methods: A hospital-based retrospective cross-sectional study was conducted among 384 elderly (60 years and older) ambulatory patients with cardiovascular diseases between May 01-August 30, 2021. Data was collected from the patient's medical record using a data abstraction tool. The data were entered and analyzed using the SPSS program. Descriptive and logistic regression models were used to present the findings.

Results: The most frequent diagnosis was hypertension (78.4%) followed by ischemic heart disease (31.3%). Averagely, 4.4 ± 2 medications were prescribed per patient. More than half of (53.1%) the patients received polypharmacy. According to Beer's and medication appropriateness index criteria, over one-third (28.1%) and the majority (95.1%) of the patients were prescribed potentially inappropriate medications, respectively. In addition, 53.1% and 90.1% of patients had polypharmacy, and were exposed to potential drug-drug interactions ranging from mild to major interactions, respectively. Further, polypharmacy was significantly associated with inappropriate medication prescribing.

Conclusion: The study found that more than half of the patients got one or more potentially inappropriate medications in both criteria. The medication appropriateness index tool identified more potentially inappropriate medication than the Beers criteria. In addition, more than half of the patients got polypharmacy and had potential drug-drug interactions. Further, polypharmacy was significantly associated with inappropriate medication prescriptions. These findings highlight the need for interventions to improve appropriate prescribing practice among elderly patients.

Keywords: inappropriate medication, polypharmacy, drug interaction, cardiovascular disease and elderly

Introduction

The world's aging population is speedily increasing from 9% to 16% between 2019 to 2050.[1] Increasing age is associated with higher rates of co-morbidity, disability (cognitive, mental, and functional impairments),[2] and multiple medication use.[3–5] Aging influences heart activities by decreasing cardiac muscle elasticity and the ability to respond to changes in pressure.[6] Hence, it is an independent risk factor for cardiovascular disease (CVD) which poses a great burden to elderly patients.[7] Globally, 32% of the deaths were due to CVD. Of which, three fourth of them were from low and middle-income countries.[8]

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Due to multiple chronic diseases, and age-related physiological changes that affect drugs' pharmacodynamics and pharmacokinetic properties, pharmacotherapy is complex and challenging in the elderly.[9] Polypharmacy, non-adherence, inappropriate medication prescription,[10,11] drug-drug interaction,[12,13] and medication-related problems[14] are frequent in elderly patients with CVD. Due to this, elderly patients are at a higher risk of adverse drug events (ADEs).[15]

Explicit and implicit criteria are used to assess medication safety in the elderly. The explicit criteria (the 2019 American Geriatrics Society (AGS) Beers Criteria)[16] involves six medication appropriateness issues, while the implicit criteria (Medication Appropriate Index (MAI))[17,18] uses ten criteria. The explicit criteria are primarily concerned with medications and assess how well they meet a set of predetermined criteria, criterion-based with rigid standards. On the other hand, the implicit criteria consider healthcare professionals' judgment to assess medication appropriateness.

In Ethiopia, the pooled prevalence of CVD was 5% (1–20%) in the general population,[19] but its prevalence is expected to be higher in the elderly population. Despite CVD is the leading cause of death and disability among the elderly,[20] data are scarce regarding the appropriate use of medication in Tikur Anbessa Specialized Hospital (TASH). Hence, this study aimed to investigate medication appropriateness using both the 2019 AGS and MAI criteria and associated factors in ambulatory elderly cardiac patients at TASH.

Methods

Study Setting

The study was conducted at TASH, As Ababa, Ethiopia. It is the largest referral hospital in Ethiopia, established in 1964. It has more than 800 beds and serves over 250,000 outpatient and 48,000 inpatients annually. Several clinics serve ambulatory patients. The cardiac outpatient clinic serves more than thousands of patients with CVDs.

Study Design and Period

A retrospective cross-sectional study was performed in a cardiac clinic of TASH, Addis Ababa, Ethiopia. The study was conducted from May 01– August 30, 2021.

Study Population and Sample Size

All elderly patients (aged ≥ 60 years) with CVD were the source population. The sample population consisted of elderly CVD patients who are on follow-up during 2018–2021. As per the cardiac clinic officer, there were a total of 1993 elderly CVD patients during the mentioned follow-up period in TASH. The sample size was then calculated by using a simple proportion formula by considering a confidence interval of 95%, marginal error of 5%, and, the prevalence of 50%. The calculated sample size was 384. Systematic random sampling method was used to choose 384 patients' medical records. Patients with incomplete medical records were excluded.

Study Variables

The dependent variables were medication appropriateness, polypharmacy and drug-drug interactions (DDIs). On the other hand, the independent variables include socio-demographic characteristics, clinical characteristics (comorbidity, Charlson comorbidity index (CCI)), and prescribed number of medications.

Data Collection Tool and Procedure

The data collection form was prepared based on published study findings and standard tools, which consisted of four sections. The first section included questions on the demographic characteristics of patients. The second section contained clinical and medication-related information. The third section was the AGS Beers Criteria and, the fourth section was MAI tool (Supplementary Table 1).

Data were collected retrospectively from patient medical records. The most recent visit was considered for assessment. Medication appropriateness (Supplementary File) was evaluated according to one explicit (AGS Beers' criteria) and one implicit (MAI) criteria. Both prescription and Over The Counter (OTC) medications were considered. On the contrary, herbal supplements were excluded as they were not well documented. The collected data were thoroughly reviewed and analyzed by experienced clinical pharmacists. DDI was checked using Drugs.com online drug interaction checker. Polypharmacy is considered when the patient is prescribed five or more medications.

Data Quality Control

Before the actual research, a pre-test was done in 5% of patients to check for data collection instrument clarity, consistency, and acceptability. All required changes were made based on the results of the pre-test.

Ethical Consideration

The ethical clearance was obtained from the ethical review committee of the Department of Pharmacology and Clinical Pharmacy (ERB/SOP/315/13/2021), College of Health Sciences, Addis Ababa University. Then, patients, during follow up time, were briefed about the objectives of the study and the confidentiality of their information. In addition, they were informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the patient has understood the information, the data collectors obtained written informed consent.

Statistical Analysis and Interpretation

Data were entered, cleaned analyzed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 23). Descriptive statistics were performed to summarize the sociodemographic and clinical characteristics. The results were presented in frequencies, percentages, tables, and figures. Logistic regression was used to determine factors associated with inappropriate medication use which is assessed by the AGS Beers Criteria. The results of the multivariable logistic analysis were reported using adjusted odds ratio (AOR) and 95% CI. Statistical significance was declared at $p < 0.05$.

Results

Demographic and Clinical Characteristics of the Study Participants

A total of 384 ambulatory elderly cardiac patients were included in the study. The mean age of patients was 68.1 ± 6.5 years, ranging from 60–92 years. Majority (82.6%) of patients were young-old (60 to 74 year age). In addition, 52.6% of them were females, and the majority of (93.7%) the elderly patients had at least one comorbidity (mean 2.68 ±1.2). The average duration of the disease was 8.14 ±7.4 years. Further, 57.6% of patients had ≥ 5 CCI (Table 1).

Disease and Medication Use Pattern

The most frequent CVD encountered were hypertension (78.4%), ischemic heart disease (31.3%), hypertensive heart disease (26.3%), degenerative valvular disease (16.7%), and atrial fibrillation (11.2%).

A total of 1698 medications were prescribed, averagely 4.4 ± 1.9 per patient (range; 1–12 medications). The most frequently prescribed medications were atorvastatin (65%), enalapril (58.6%), aspirin (46.9%), furosemide (44.3%), and amlodipine (37.2%) (Table 2).

Medication Appropriateness Among Ambulatory Elderly Patients

Explicit Beer's Criteria (AGS Beers Criteria)

Over one-third of (28.1%) of elderly CVD patients were prescribed at least one potentially inappropriate medication (PIM), averagely 1.51 ±1.3 per patient. Of these patients, 19.8%, 26.6%, 17.4%, and 6% were prescribed one, two, three, and four or more PIM, respectively. A total of 617 medication-related issues were identified. 54.9% (277), 28.1% (108), 13.4% (38), 4.6% (18) and 1% (4) of patients prescribed medications that should be used with caution, PIM as per the Beers criteria, medications that should be avoided or reduce dose in renal failure, potentially inappropriate medications to avoid in older adults with certain conditions, and medications with clinically important DDIs to be avoided, respectively.

Table 1 Demographic and Clinical Characteristics of the Study Participants (N=384)

Variables	Description	Frequency (%)
Gender	Male	182 (47.4)
	Female	202 (52.6)
Age (years)	60–74 (young-old)	317 (82.6)
	75–83 (middle old)	59 (15.4)
	≥ 84 (oldest-old)	8 (2.1)
	Mean age ±SD	68.09 ±6.5
Presence of comorbidity	Yes	361 (93.7)
Number of comorbidities	< 5	364 (94.8)
	≥ 5	20 (4.2)
CCI	< 5	163 (42.4)
	≥ 5	221 (57.6)
Duration of the disease	< 5 yrs	159 (41.2)
	≥ 5 yrs	225 (58.6)

Abbreviations: CCI, Charlson comorbidity index; SD, standard deviation.

Table 2 The Most Frequent CVD Medications Prescribed Among Study Participants

	Top Ten Medications	Frequency (%)
1	Atorvastatin	250 (65)
2	Enalapril	225 (58.6)
3	Aspirin	180 (46.9)
4	Furosemide	170 (44.3)
5	Amlodipine	143 (37.2)
6	Metoprolol	119 (31.6)
7	Spironolactone	79 (20.6)
8	Hydrochlorothiazide	63 (16.4)
9	Warfarin	43 (11.2)
10	Digoxin	23 (6)

The frequently prescribed inappropriate medications were diuretics (46.29%) and antiplatelet agents (31.5%). (Figure 1) In addition, the frequently prescribed medications that should be avoided in the elderly were amitriptyline (29.6%), proton pump inhibitors (21.3%), digoxin (20.3%), glibenclamide (16.3%), and non-steroidal anti-inflammatory medications (NSAIDs) (12.3%).

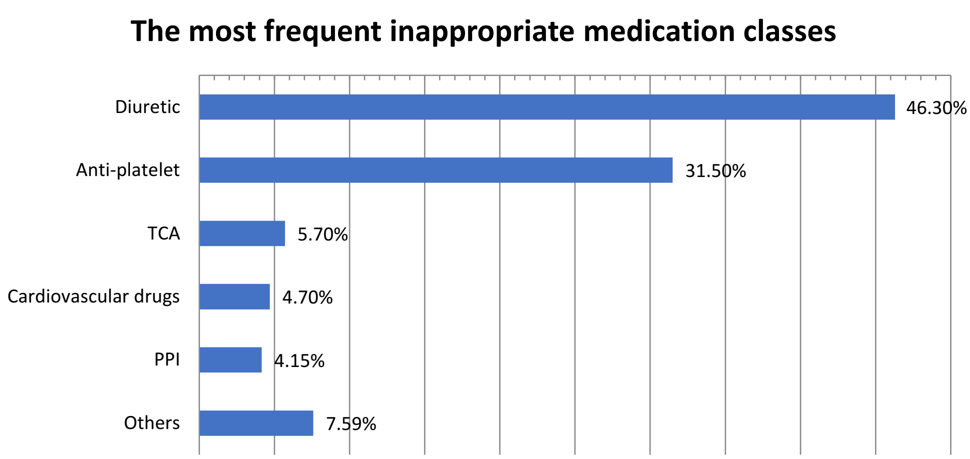

Figure 1 Inappropriate drug classes based on the AGS Beers criteria.

Implicit Criteria (MAI Criteria)

The majority (365, 95.1%) of elderly patients were prescribed one or more PIM. The average MAI score per patient was 18.2 ±12.3 (median 17; range 0–90). The criteria with the highest MAI score were effectiveness, correct dosage, unnecessary duplication, and indication-related issues. On the other hand, the lowest score was the duration of therapy. Considering the cumulative MAI, 320 medications (84.4%) met inappropriate ratings of 0–30 weighted average MAI, 57 (14.8%) met inappropriate ratings of 31–60 weighted average MAI and 3 (0.8%) met inappropriate rating of ≥ 61 weighted average MAI (Table 3).

Polypharmacy and Drug-Drug Interactions in the Elderly

More than half the study participants had polypharmacy (53.1%, 212) and, the majority had (90.1%, 346) potential DDIs which can range from mild to major interactions. Of all DDIs, 15.1%, 75%, and 83.3% were major, moderate, and minor interactions, respectively. (Table 4) The most frequently prescribed major DDIs were enalapril and spironolactone (73%, 46) (causes hyperkalemia), amlodipine and carbamazepine (11.1%, 7) (reduces the blood levels of amlodipine), and enalapril and allopurinol (3.2%, 2) (increases hypersensitivity to allopurinol) (Table 5).

Factors Associated with Inappropriate Medication Prescription

Patients with polypharmacy were 5.1 times riskier to have inappropriate prescriptions (AOR=5.1, 95% CI [0.110,0.386] p<0.001) than patients having less than five medications (Table 6).

Discussion

This study analyzed medication appropriateness, polypharmacy and DDI in the ambulatory elderly (aged 60 years and above) patients with CVD at TASH, Addis Ababa with a focus on prevalence and associated factors of PIM.

Table 3 Distribution of Inappropriate Prescriptions Using MAI Criteria

	MAI Criteria	Sum (Range)	Mean (SD)
1	Is there an indication for the drug?	703 (0–12)	1.83 ±2.5
2	Is the medication effective for the condition?	2285 (0–24)	6 ±3.6
3	Is the dosage correct?	1215 (0–10)	3.2 ±2.2
4	Are the directions correct?	491 (0–6)	1.3 ±1.3
5	Are there clinically significant drug-drug interactions	408 (1–16)	1.1 ±2.0
6	Are there clinically significant drug-disease/condition interactions?	635 (0–10)	1.7 ±1.65
7	Are the directions practical?	415 (0–5)	1.1 ±0.9
8	Is there unnecessary duplication with another drug (s)?	732 (0–7)	2 ± 1.3
9	Is the duration of therapy acceptable?	111 (0–3)	0.3 ±0.6
	The average weight of MAI	Frequency (%)	
	0–30 points	324 (84.4%)	
	31–60 points	57 (14.8%)	
	61 and above points	3 (0.8%)	

Table 4 Polypharmacy and Drug-Drug Interaction in the Study Participants

Variables		Frequency (%)
Number of drugs prescribed	1–4 medications	180 (46.9)
	≥ 5 medications	204 (53.1)
Presence of drug-drug interaction	Yes	346 (90.1)
Type of drug-drug interaction	Severe	58 (15.1)
	Moderate	288 (75)
	Mild	320 (83.3)

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Table 5 List of Severe DDI, Their Prevalence, and Expected Negative Effects

List of Severe DDI	Prevalence of the DDI	Clinical Presentation
Enalapril and spironolactone	46 (73%)	Hyperkalemia
Amlodipine and carbamazepine	7 (11.1%)	Significantly reduce the blood levels of amlodipine
Enalapril and allopurinol	2 (3.2%)	Increased hypersensitivity to allopurinol
Amiodarone and furosemide	1 (1.6%)	Increase the risk of an irregular heart rhythm that may be serious.
Amiodarone and verapamil	1 (1.6%)	The additive effect, blood pressure may need to be checked more frequently
Amiodarone and warfarin	1 (1.6%)	Cause bleed more easily
Aspirin and rivaroxaban	1 (1.6%)	Increase the risk of bleeding, including severe and sometimes fatal hemorrhage.
Candesartan and spironolactone	1 (1.6%)	Increase potassium level in the blood.
Clopidogrel and omeprazole	1 (1.6%)	Reduce the effectiveness of clopidogrel in preventing heart attack or stroke.
Enalapril and losartan	1 (1.6%)	Increase the risk of side effects such as low blood pressure, kidney function impairment, and hyperkalemia
Verapamil and metoprolol	1 (1.6%)	Bradycardia or complete AV block

Abbreviation: AV, atrioventricular.

Table 6 Factors Associated with Inappropriate Medication Use

Variables	Description	COR (95% CI)	P-value	AOR (95% CI)	P-value
Age	Young old	1	0.27	1	0.53
	Middle old	0.613 (0.317,1.186)	0.152	0.362 (0.373,1.734)	0.761
	Oldest-old	1.302 (0.305,5.555)	0.721	3.873 (0.390,12.143)	0.234
Gender	Male	1	1	1	1
	Female	0.602 (0.814,2.414)	0.583		
Presence of comorbidity	No	1	1	1	1
	Yes	5.587 (1.985,11.734)	0.004	0.425 (0.296,1.594)	0.066
CCI	<5	1	1	1	1
	≥ 5	0.437 (0.280,0.681)	0.00	0.694 (0.411,1.174)	0.154
Number of comorbidities	<	1876 (0.283,3.281)	0.012	1.340 (0.642,2.785)	0.745
	≥ 5	1	1	1	1
Number of medications	< 5 medications	1	1	1	1
	≥ 5 medications	0.123 (0.14,0.3)	0.00	5.1 (0.110,0.386)	0.00

Note: P=0.00 is when p <0.0001.
Abbreviation: CCI, Charlson comorbidity index.

Our findings showed that 28.1% of the patients received at least one PIM according to the AGS Beers Criteria. Ethiopian studies conducted in geriatric patients at Tirunesh Beijing Hospital, University of Gondar Teaching Hospital chronic care clinic, and Jimma Medical Center reported that 46.9%,[21] 47.2%,[22] and 83.1%[23] of older adults were prescribed at least one PIM, respectively. In these studies, medication appropriateness was assessed using Beers criteria in two studies,[22,23] while the remaining study[21] used both WHO core prescribing indicators and Beers criteria. In addition, our finding was lower than a study done in the United States, with 87.4% of the patients receiving at least one PIM.[24] As it is seen in different studies, PIM is common in the elderly. However, the different prevalence may be due to variation in case-mix, availability of medications, type and number of comorbidities.

Our study also revealed that more PIM was detected using MAI than Beers criteria (MAI:95.1%, Beers criteria: 28.1%), which is comparable to a study conducted in Spain (94.1% PIM by MAI, 68.8% by Beers criteria).[25] In addition, Awad et al[26] detected more cases of PIMs using MAI (74%) than Beers criteria (53.1%). The reason for this could be the Beers criteria have rigid criteria that focus on the drug/drug class, and it does not address patient preference, while MAI focuses on the patients who address the entire medication regimen with the clinical conditions.

Diuretics (46.3%), antiplatelets (31.5%), and tricyclic antidepressants (5.7%) were the frequently prescribed PIMs in our study. However, angiotensin-converting enzyme inhibitors (ACEIs) (15.6%), a combination of aspirin and Vitamin K Antagonist (14%), and statins (3.16%) were the common PIMs reported by Abegaz et al.[27] In addition, Tesfaye et al[23] found diuretics (46.3%), antiplatelets (31.5%) and tricyclic antidepressants were the common PIMs. Further, a study conducted in Serbia showed that proton pump inhibitors (15.7%) were the frequent PIM according to Beers criteria.[28] Such variation may be due to the different clinical conditions, comorbidities, and disease severity of the studied population.

More than half the patients (53.1%) were prescribed polypharmacy, which is higher than the studies conducted in various parts of Ethiopia (10.8–42.5%).[21–23] As aging is associated with multiple comorbidities,[29,30] polypharmacy is common in the elderly. Similarly, DDI is common in elderly patients.[30] Our study revealed that 90.1% of patients had potential mild to major DDIs, which lies in the recent systematic review finding (DDIs: 80.5–90.5%).[31] However, it is higher than Bhagavathula et al (2.8%)[22] and Assefa et al (84.3%) studies. Of all the DDIs, enalapril and spironolactone interactions (73%) were the most frequent DDI like de Oliveira et al study result.[31] On the other hand, van Heerden et al found that central nervous system medications (30.6%) were the frequent causes of DDIs.[32] The variation could be due to differences in geriatric circumstances as well as methodological discrepancies, particularly in the methods/software utilized to detect DDIs. In addition, our study revealed that 15.1% of patients had major DDIs, which is relatively lower than the studies conducted in studies conducted at Ethiopian Yekatit 12 medical college hospital (17.3%),[12] and in the South African elderly ambulatory patients (25.8%).[32] The difference could be due to the variation in the case-mix of targeted patients, and professional expertise.

Regarding risk factors, polypharmacy is significantly associated with PIM (AOR=5.1 95 CI [0.110,0.386], p=0.000). Polypharmacy, which was more common with older people, is recognized as the primary contributor of PIM in the Serbian study.[33] In addition, a study done in France reported that the presence of comorbidities, taking multiple medications, and the higher CCI were associated with the likelihood of PIM.[34] As the number of medications is increased, the possibility of potential DDIs and drug-disease interactions are increased. This predisposes the patient to have PIM. The variation of PIM risk factors could be due to the type and number of comorbidities, and the case mix of the study population.

The strengths of our study include; firstly, patient-specific factors were considered to evaluate PIM. Secondly, two methods of medication appropriateness were used. On the other hand, there were certain limitations which include (i) doctors were not interviewed to identify their reasons for prescribing the identified PIMs; (ii) the exclusion of herbal supplements may have resulted in an underestimation of PIMs; (iii) the study was done in a single study, and (iv) some medication appropriateness lists were difficult to analyze due to the retrospective nature of the study.

Conclusion

The study found a considerable number of patients prescribed PIM. MAI identified more PIM than the Beers criteria. More than half of the patients prescribed polypharmacy. In addition, the majority of the patients experienced potential mild to major DDIs. Of which, around 15% had major potential DDIs. Moreover, PIM is significantly associated with polypharmacy. These findings highlight the need for interventions that improve appropriate prescription in elderly patients, reduce the number of medications and reduce DDIs.

Abbreviations

ACEi, angiotensin-converting enzyme inhibitors; ADE, adverse drug event; ADR, adverse drug reaction; AGS, American Geriatrics Society; AHA, American Heart Association; AOR, adjusted odds ratio; CCI, Charlson comorbidity index; CHS, College of Health Science; CI, confidence interval; CNS, central nervous system; COR, crude odds ratio; CVD, cardiovascular disease; DDI, drug-drug interaction; HR, hazard ratio; IPET, improving prescribing in the elderly tool; MAI, medication appropriateness index; NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; OTC, over the counter; PIDP, potentially inappropriate drug prescribing; PIMs, potentially inappropriate medications; PIP, potentially inappropriate prescribing; PP, polypharmacy; PPI, proton pump inhibitors; PPO, potential prescription omissions; SD, standard deviation; SPSS, Statistical Package for Social Sciences; START, Screening Tool of Older People's

Prescription; STOPP, Screening Tool to Alert Doctors to Right Treatment; TASH, Tikur Anbessa Specialized Hospital; TCA, tricyclic antidepressants; WHO, World Health Organization.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

Ethical approval was obtained from the Ethical Review Committee of the School of Pharmacy (ERB/SOP/315/13/2021), College of Health Sciences, Addis Ababa University. Then, patients, during follow up time, were briefed about the objectives of the study and the confidentiality of their information. In addition, they were informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the patient has understood the information, the data collectors obtained written informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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