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Research Paper

Proton pump inhibitor use and appropriateness analysis: a snapshot from a secondary care hospital

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Abstract

Objectives Proton pump inhibitors (PPIs) have become one of the most frequently prescribed drugs since their introduction 30 years ago. Effectiveness and safety profile of PPIs has led to their overutilization and has exposed patients to a number of potential risks. The objective of this study was to evaluate the use of PPIs in a secondary care hospital in the United Arab Emirates.

Methods This prospective observational drug-utilization study was conducted in patients receiving treatment with PPIs and admitted to internal medicine wards of the study site. Electronic patient case records were reviewed and data on PPI prescribing was collected and analysed. Appropriateness of PPI use was assessed as per international guidelines.

Key findings Out of 172 patients enrolled, 53.5% were females with median age of 57 years (34.3, 71.0). Four different PPIs were prescribed to study patients, pantoprazole (86.6%), esomeprazole (5.8%), rabeprazole (4.1%) and omeprazole (3.5%). Ninety-two (53.5%) patients were prescribed intravenous PPI, whereas 80 (46.5%) patients were given PPI in oral form. Overall, 103 (59.9%) patients had inappropriate PPI prescriptions. Of these inappropriate prescriptions, 22 patients had no clear indication for PPI use and for 16 patients; PPIs were indicated for stress ulcer prophylaxis in low-risk category. Corticosteroid use [odds ratio (OR): 4.34, 95% confidence interval (CI): 1.22–15.46; $P = 0.023$] was significantly associated with greater odds of inappropriate PPI use.

Conclusions We report a high prevalence of inappropriate PPI prescribing among the hospitalized patients in our study. Inappropriate PPI prescribing is a concerning issue and collective efforts should be made to check and minimize the same.

Keywords: proton pump inhibitors; drug utilization; inappropriate; overutilization; guidelines

Introduction

Proton pump inhibitors (PPIs) have become one of the most frequently prescribed drugs since their introduction 30 years ago.[1, 2] Over this span of time, PPIs have proven to be safe and effective therapeutic option for the management of a number of acid-related gastrointestinal disorders like dyspepsia, peptic ulcer disease and gastroesophageal reflux disease.[3] They are also used as an integral part of *Helicobacter pylori* eradication therapy,[4] for prevention of

non-steroidal anti-inflammatory drug (NSAID) associated peptic ulcer in high-risk patients[5] and for the management of Zollinger-Ellison Syndrome.[6]

The effectiveness and safety profile of PPIs has led to their overutilization and has exposed patients to a number of potential risks.[7] Recent observational studies have associated PPI therapy with increased risks of adverse effects, like community-acquired pneumonia,[8] *Clostridium difficile* infection,[9] vitamin B_{12} deficiency,[10] hypomagnesemia,[11] fracture risk,[12] chronic renal failure,[13] cardiovascular events[14] and all-cause mortality[15] and with increased potential for drug–drug interactions.[16, 17]

Clinical guidelines like the National Institute for Health and Clinical Excellence (NICE) guidance for '*Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management*' recommend different doses and duration of PPI use in various clinical indications and guide physicians to prescribe PPIs more judiciously and appropriately.[18] However, many studies have reported inappropriate use of PPIs in the primary care[19] as well as hospital settings.[20] Moreover, this prevalence of inappropriate PPI prescriptions is estimated to be very high and ranges between 40 and 80%.[21–26]

Inappropriate PPI prescribing can be in terms of inappropriate indication or inappropriate dosage. The most common inappropriate indication for PPIs is prophylaxis of stress ulcers outside the intensive care unit.[27] Frequently, admitted patients are prescribed PPIs in the hospital setting, often inappropriately,[28] and following discharge these agents are continued by the physicians in the primary care setting.[25] This irrational prescribing leads to unwanted polypharmacy, increases the risk of drug-related problems like drug–drug interactions and adverse drug reactions as well as increases the overall costs of healthcare.

Prescription pattern studies play a very important role in assessing the prescribing, dispensing and administration of drugs. These studies promote rational use of drugs and discourage irrational prescribing of drugs.[29, 30] While prescription pattern studies focusing on PPIs have been extensively studied in other parts of the world, data from the United Arab Emirates (UAE) are very limited and scarce. Therefore, this study evaluated the use of PPIs in a secondary care hospital in UAE.

Methods

Study design and setting

This prospective observational drug-utilization study was done in the internal medicine department of Ibrahim Bin Hamad Obaidallah Hospital, Ras Al Khaimah, UAE. The study site is a secondary care multispecialty hospital with a bed strength of over 100. The hospital has internal medicine, cardiology, neurology, nephrology, gastroenterology, geriatric and psychiatry departments.

Study population

All adult patients, of either gender, receiving treatment with PPIs, admitted to the internal medicine wards of the study site were included in the study. Outpatients, patients admitted to wards other than internal medicine wards and not on PPIs were excluded.

Sample size and sampling technique

One hundred and seventy-two patients satisfying the study criteria were enrolled in the study. Sample size for the study was determined using convenience sampling technique and was based on the number of patients admitted to the internal medicine department of the study site during the 6 months' study period. On an average, eight patients/week were admitted to the internal medicine wards with PPI prescriptions. Therefore, during the 6-month study duration, 192 eligible patients were admitted. Out of these 192 patients, 20 patients with incomplete medical records were not considered for the study.

Data collection

Patient data were collected by reviewing the electronic patient case records. The documented data included age, gender, nationality, smoking and alcohol status, types of PPIs prescribed with common indications, dose, route, dosing frequency and duration of each PPI. PPI doses were also defined as standard dose, double dose or low dose according to the National Institute for Health and Care Excellence (NICE) clinical guidelines. Appropriateness of PPI use was assessed as per the NICE clinical guidelines[18] and the Food and Drug Administration (FDA).[31] The appropriate indications for PPI use are given in Table 1.

Patient characteristics were analysed using descriptive statistics. Categorical variables were reported as frequencies and percentages with 95% confidence intervals (CI). For continuous variables, the normality of distribution was assessed using the Shapiro-Wilk test. Normally distributed variables were expressed as mean ± standard deviation whereas non-normally distributed variables were reported as median and range. Categorical variables were compared using the chi-square test while the continuous variables with normal distribution were compared using Student's *t* test. The Mann–Whitney *U* test was used to compare variables with non-normal distribution. Odds ratio (OR) and 95% CI were used to assess the strength of associations. *P* values < 0.05 were considered statistically significant. All analyses were done using Statistical Package for the Social Sciences (SPSS) version 22.0.

Table 1 Appropriate indications for proton pump inhibitor use[18],[31]

Indications
Gastro-esophageal reflux treatment
Functional dyspepsia treatment, if *Helicobacter pylori* excluded and symptoms persist
Severe esophagitis – treatment and maintenance therapy
Helicobacter pylori eradication therapy
Patients with peptic ulcer disease and tested positive for *Helicobacter pylori*
Patients using NSAIDs with diagnosed peptic ulcer
Peptic ulcer disease treatment for patients tested *Helicobacter pylori* negative and not on NSAIDs
Patients at high risk (previous ulceration) and for whom NSAID continuation is necessary
Hypersecretion (Zollinger-Ellison syndrome and idiopathic hypersecretion)
Risk reduction for gastric ulcers in NSAIDs users with high risk of gastrointestinal complications or with history of upper gastrointestinal bleeding
Stress ulcer prophylaxis in high-risk patients
Critically ill patients, under prolonged mechanical ventilation
Ulcer prophylaxis in high-risk patients on antiplatelets
History of ulcer or upper gastrointestinal bleeding
Age more than 60 years, or dyspepsia/gastro-esophageal reflux disease
Concomitant use of corticosteroids, other antiplatelets, NSAIDs and/or anticoagulants
Dyspepsia
Peptic ulcer disease
Barrett's esophagus

Ethical approval

The ethical approval for the study was obtained from the Research and Ethics Committee of RAK Medical and Health Sciences University [RAKMHSU-REC-47-2016-PG-P] and Ministry of Health and Prevention (MOHAP) Research and Ethics Committee [MOHAP/RAK/SUBC/No-47-2016-PG-P], UAE.

Table 2 Socio-demographic and clinical characteristics of the study population

Variable	*N* (%)/Median	95% CI/P_{25}, P_{75}
Age, years	57	34.3, 71.0
Gender		
Female	92 (53.5)	45.9–61.0
Nationality		
UAE Nationals	99 (57.6)	49.4–64.5
Non-smoker	150 (87.2)	82.0–91.9
No alcohol use	167 (97.1)	94.2–99.4
Diagnosis		
Gastrointestinal disease	34 (19.8)	14.0–25.6
Pulmonary disease	29 (16.9)	11.1–22.7
Infectious disease	24 (14.0)	9.3–19.2
Cardiac disease	18 (10.5)	5.8–15.1
Renal disease	15 (8.7)	4.7–13.4
Hepatic disease	14 (8.1)	4.1–12.2
Neurological disease	12 (7.0)	3.5–11.6
Endocrine disease	10 (5.8)	2.9–9.3
Haematological disease	8 (4.7)	1.7–8.1
Others	8 (4.7)	1.7–8.1
Mechanical ventilation	9 (5.2)	2.3–8.7
Number of comorbidities	2	1.0, 4.0
Number of medications	1	0.0, 4.0
Polypharmacy		
No	141 (82.0)	76.2–87.8
Yes	31 (18.0)	12.2–23.8
Concomitant medications		
Antiplatelet	65 (37.8)	30.8–45.3
Anticoagulant	57 (33.1)	26.7–40.7
NSAID	16 (9.3)	5.2–14.0
Corticosteroid	20 (11.6)	7.0–16.3

Polypharmacy is defined as intake of five or more medications per day.

Results

Socio-demographic and clinical characteristics

Out of the 172 patients enrolled in the study, 53.5% (92) were females, 57.6% (99) were UAE nationals, with median age of 57 years. Majority of the patients were non-smoker (87.2%, 150) and non-alcoholic (97.1%, 167). Highest proportion of the patients had a diagnosis of gastrointestinal disease (19.8%, 34) at admission followed by pulmonary disease (16.9%, 29) and infectious disease (14.0%, 24). Almost half of the patients (46.5%, 80) had more than two comorbid conditions. Only 18.0% (31) of the patients were on polypharmacy where polypharmacy was being defined as the intake of more than five or more medications per day. Regarding concomitant medications, 65 (37.8%) patients were co-prescribed antiplatelet agent with the PPI followed by anticoagulant (33.1%, 57 patients), corticosteroid (11.6%, 20 patients) and NSAIDs (9.3%, 16 patients). The socio-demographic and clinical characteristics of the study population are given in Table 2.

Prescriptions of proton pump inhibitors

The study patients were prescribed four different PPIs; pantoprazole to 86.6% (149) patients, esomeprazole to 5.8% (10) patients, rabeprazole to 4.1% (7) patients and omeprazole to 3.5% (6) patients. Only 18.0% (31) patients were on PPI before admission while 82.0% (141) patients received PPI on admission or during hospitalization. More than half of the patients (53.5%) were prescribed PPIs on hospital discharge (Figure 1). Ninety-two (53.5%) patients were given intravenous PPI, whereas 80 (46.5%) patients were given PPI in the oral form. Majority of the study patients (153) received standard doses of the PPIs as per the NICE guidelines. Figure 2 and Table 3 represent the different PPI doses prescribed to the study patients.

Appropriateness of proton pump inhibitor use

Overall, out of the total 172 patients, 103 (59.9%) patients had inappropriate PPI prescriptions. Of these inappropriate prescriptions, 22 (12.8%) patients had no clear indication for PPI use. Other inappropriate indications were stress ulcer prophylaxis in low-risk hospitalized patients (non-intensive care setting) (16 patients, 9.3%), ulcer prophylaxis in patients on antibiotics (13 patients, 7.6%), corticosteroids (13 patients, 7.6%) and NSAIDs (9 patients, 5.2%).

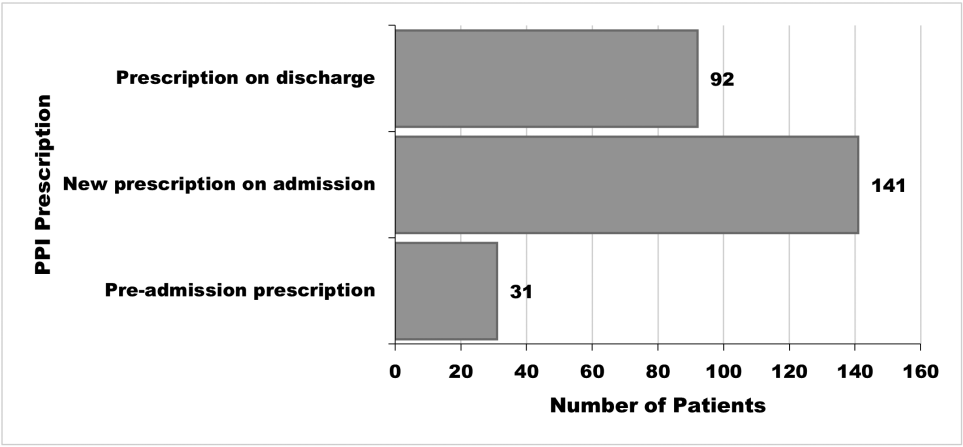

Figure 1 PPI prescriptions in the study population.

On the other hand, the most predominant appropriate PPI use was for ulcer prophylaxis in high-risk patients on antiplatelets (39 patients, 22.7%) followed by dyspepsia and stress ulcer prophylaxis in high-risk patients (each with 10 patients, 5.8%) (Table 4).

Analysis of factors associated with inappropriate PPI use revealed that corticosteroid use (OR: 4.34, 95% CI: 1.22–15.46; $P = 0.023$) was significantly associated with greater odds of inappropriate PPI use, whereas antiplatelet use (OR: 0.042, 95% CI: 0.02–0.11; $P < 0.001$) and anticoagulant use (OR: 0.21, 95% CI: 0.08–0.54; $P = 0.001$) were significantly associated with lesser odds of inappropriate PPI use. Anticoagulant use ($P < 0.001$) and antiplatelet use ($P < 0.001$) were identified to be the significant predictors of appropriate PPI use (Table 5). Regarding the dose, overall PPI dose was inappropriate only for nine (5.2%) patients.

Discussion

This study represents the pattern of PPI usage in a secondary care hospital in UAE. The study identified a high prevalence (59.9%) of inappropriate PPI prescribing among the hospitalized patients at the study site. This finding is in line with the findings of previous studies conducted in different parts of the world, which reported the prevalence of inappropriate PPI prescriptions between 40 and 80%.[21–26] A prospective cross-sectional study conducted in Thailand reported that 50.6% of the patients admitted to a tertiary care hospital were inappropriately prescribed PPIs.[21] Similar inappropriate and overutilization of PPIs was reported by a Swiss study where 72% of the admitted patients received PPIs for unjustified indications.[32] A recent large retrospective study conducted in China also reported that 50% of the PPI prescriptions were inappropriate.[33]

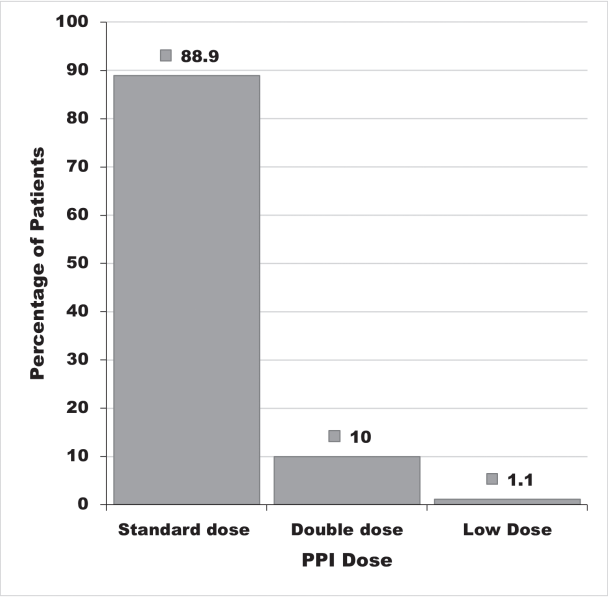

Figure 2 PPI doses used in the study population. PPI doses are defined as standard/full dose, double dose or low dose as per National Institute for Health and Care Excellence clinical guidelines.

The majority of inappropriate PPI prescriptions in our study had no clear indication of PPI followed by prescriptions for stress ulcer prophylaxis in low-risk hospitalized patients. Previous studies have highlighted similar inappropriate PPI use in non-intensive care unit patients.[27, 34] Other predominant inappropriate PPI indications in our study were ulcer prophylaxis in patients on antibiotics, corticosteroids and NSAIDs. These findings are in coherence with previous studies conducted in Germany[35] and Thailand,[21] which reported inappropriate PPI use for ulcer prophylaxis in low-risk patients receiving NSAIDs, corticosteroids and oral anticoagulants.

Furthermore, corticosteroid use was the significant predictor of inappropriate PPI use in our study population. Studies have shown that corticosteroid therapy is rarely associated with peptic ulcers and therefore, there is no rationale for PPI use for ulcer prophylaxis with corticosteroid therapy in the absence of concomitant NSAIDs and/or concomitant antiplatelet therapy.[36, 37] Co-prescribing PPI and corticosteroids for low-risk patients is a matter of concern, as corticosteroid use is associated with an increase the risk of fractures and infection, which are also the adverse effects related with PPI use.[38, 39]

A number of possible reasons contribute to overutilization and inappropriate use of PPIs in the hospitals. First and the foremost being the physicians' perception that PPIs are safe, long-term medications, which are free from adverse effects. Second, lack of awareness towards the evidence-based guidelines and recommendations on PPI use. Third, physicians tend to prescribe PPI for ulcer prophylaxis because of their defensive approach towards medicine without considering the risks factors for ulcer development in hospitalized patients. Fourth, physicians seldom review and document PPI indications and duration, which often result in inappropriate long-term use of PPIs.

Regarding appropriate PPI prescriptions, the most common appropriate indication was ulcer prophylaxis in high-risk patients on antiplatelets. Similar utilization of PPIs for the ulcer prophylaxis in high-risk patients on antiplatelets were reported by studies conducted in China,[33] Thailand[21] and Portugal.[40] Different evidence-based guidelines like American College of Cardiology, American College of Gastroenterology, and American Heart Association (ACCF/ACG/AHA)[41] and European Society of Cardiology (ESC)[42] recommend the use of PPI for ulcer and gastrointestinal bleed prophylaxis in patients with history of ulcer or upper gastrointestinal bleeding, patients above 60 years of age, or dyspepsia/gastro-esophageal reflux disease, or concomitant use of corticosteroids, other antiplatelets, NSAIDs and/or anticoagulants.

Table 3 PPIs and their doses prescribed to the study population

PPI	ATC	DDD	PDD	Standard dose[a]	Double dose[a]	Low dose[a]
Pantoprazole	A02BC02	40 mg	36.6 mg	40 mg once a day	40 mg twice a day	20 mg once a day
Esomeprazole	A02BC05	30 mg	36.0 mg	20 mg once a day	40 mg once a day	Not available
Omeprazole	A02BC01	20 mg	26.6 mg	20 mg once a day	40 mg once a day	10 mg once a day
Rabeprazole	A02BC04	20 mg	18.3 mg	20 mg once a day	20 mg twice a day	10 mg once a day

ATC, anatomical therapeutic chemical classification; DDD, defined daily dose; PDD, prescribed daily dose.
[a]PPI doses are defined as standard/full dose, double dose or low dose as per National Institute for Health and Care Excellence clinical guidelines.

Table 4 Appropriate and inappropriate PPI indications in the study population

	N (%)	95% CI
Appropriate PPI indications	69 (40.1)	33.1–47.1
Ulcer prophylaxis in high-risk patients on antiplatelets	39 (22.7)	16.3–28.5
Ulcer prophylaxis in high-risk patients on NSAIDs	3 (1.7)	0.0–4.1
Dyspepsia	10 (5.8)	2.3–9.3
Peptic ulcer	4 (2.3)	0.6–4.7
Upper gastrointestinal bleeding	3 (1.7)	0.0–4.1
Stress ulcer prophylaxis in high-risk patients	10 (5.8)	2.3–9.9
Inappropriate PPI indications	103 (59.9)	52.9–66.9
Stress ulcer prophylaxis in low-risk hospitalized patients	16 (9.3)	5.2–13.4
Gastroenteritis	8 (4.7)	1.7–8.1
Pancreatic disease	7 (4.1)	1.2–7.0
Ulcer prophylaxis in patients		
On antibiotics	13 (7.6)	3.5–11.6
On corticosteroids	13 (7.6)	3.5–11.6
On NSAIDs	9 (5.2)	2.3–8.7
On antiplatelets	8 (4.7)	1.7–8.1
On anticoagulants	7 (4.1)	1.7–7.6
No clear indication of PPI	22 (12.8)	8.1–18.6

Table 5 Patient characteristics compared between groups with appropriate and inappropriate PPI use

Characteristics	Appropriate use *n* = 69 (40.1%)	Inappropriate use *n* = 103 (59.9%)	*P*-value
Gender, *n* (%)			0.777[a]
Female	36 (52.2%)	56 (54.4%)	
Male	33 (47.8%)	47 (45.6%)	
Age, median (P_{25}, P_{75})	62 (43.5, 74)	51 (31, 71)	0.090[b] (*U* = 3010.500)
Number of comorbidities, median (P_{25}, P_{75})	2.0 (1.0, 4.0)	2.0 (1.0, 4.0)	0.734[b] (*U* = 3446.500)
Number of medications, median (P_{25}, P_{75})	1.0 (0.0, 4.5)	1.0 (0.0, 4.0)	0.581[b] (*U* = 3386.000)
Polypharmacy	14 (20.3%)	17 (16.5%)	0.527 [a]
Concomitant medications, *n* (%)			
Antiplatelet	55 (79.7%)	10 (9.7%)	<0.001[a]
Anticoagulant	44 (63.8%)	13 (12.6%)	<0.001 [a]
NSAID	4 (5.8%)	12 (11.7%)	0.195 [a]
Corticosteroid	3 (4.3%)	17 (16.5%)	0.015 [a]
PPI prescription, *n* (%)			
Pre-admission prescription	14 (20.3%)	17 (16.5%)	0.527[a]
New prescription on admission	55 (79.7%)	86 (83.5%)	0.527[a]
Prescription on discharge	37 (53.6%)	55 (53.4%)	0.977[a]

Polypharmacy is defined as intake of five or more medications per day.
[a]Pearson's chi-square test.
[b]Mann–Whitney *U* test.

Despite more than 30 years of extensive literature on PPIs and several studies, large and small scale, advocating appropriate use and highlighting problems associated with inappropriate use, PPI overutilization remains consistently high in the clinical practice. Inappropriate PPI prescribing is a concerning issue as it leads to unwanted polypharmacy and increases the risk of drug-related problems like drug–drug interactions and adverse drug reactions. In addition to this, it adds substantial financial burden on the country's healthcare system.

Several approaches can be adopted by the hospitals to check and reduce the over prescribing of PPIs, including collaborative approach involving clinical pharmacists and physicians in developing hospital specific evidence-based guidelines, educational interventions aimed at increasing the awareness of physicians and patients, hospital policies targeted at restricting unnecessary PPI prescriptions, financial measures like incentives to the physicians, and audit and feedback approach. Studies have identified that multiple approach strategy has been successful in reducing the inappropriate use of PPI.[43, 44]

This study has a number of limitations. First, it is a single-centre study limited to a government secondary care hospital; therefore, the findings cannot be generalized to tertiary care and private hospital settings. Second, observational research design of the study might have resulted in bias due to unknown confounders. Third, since the data were collected from the electronic patient case records, data

analysis was limited by the documentation quality. Lastly, for some of the patients, PPI indications were not clearly mentioned and had to be implied indirectly from laboratory investigations and medical history.

Conclusion

We report a high prevalence of inappropriate PPI prescribing among the hospitalized patients at our study site. The majority of inappropriate PPI prescriptions in our study had no clear indication of PPI followed by prescriptions for stress ulcer prophylaxis in low-risk hospitalized patients. Corticosteroid use was significantly associated with inappropriate PPI use in the study population. Inappropriate PPI prescribing is a concerning issue and collective efforts should be made to check and minimize this.

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Author Contributions

S.A.R. was involved in conceptualization of study, study design, literature search, data analysis and manuscript preparation, editing and review. S.S.D. was involved in literature search, conduct of the study and data acquisition for the study. P.G.M.R. was involved conceptualization of the study, study design, manuscript editing and review. A.R.B. was involved conceptualization of the study, manuscript editing and review. All authors approved final version of the manuscript, and all authors are accountable for the accuracy and integrity of the manuscript.

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Conflict of Interest

None declared.

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