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Research Article

AN ANALYSIS OF THE PATTERN AND THE RISK FACTORS OF ADVERSE DRUG REACTIONS AT A TERTIARY CARE HOSPITAL

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ABSTRACT

Objective: The objective of the study was to analyze the pattern and risk factors of adverse drug reactions (ADR) in a tertiary care hospital.

Methods: In this retrospective study, all the suspected ADRs reported to ADR monitoring center were analyzed for the demographic details, its temporal association, status of recovery, seriousness and outcome of reaction, details of the suspected and concomitant medications. Data on various predisposing factors responsible for an ADR, such as presence of co-morbidities, use of Fixed Dose Combinations (FDC), improper monitoring, presence of drug interactions, and presence of polypharmacy were also collected. Descriptive statistics and Chi-square were used for data analysis. A p value of <0.05 was taken as level of significance.

Results: Out of the total 233ADRs, 48.9% were reported among geriatric patients. The study showed a female preponderance with 51.9%. The highest number of ADRs was reported from the therapeutic class of antimicrobials 18.9%. The skin and appendages constituted the most common organ system affected with 33.5%. Out of 106 serious ADRs, majority required prolonged hospitalization 62.3%. About 78.1 % of reactions were found to be predictable and 72.5% preventable. A positive association was found between ADR and co-exiting co-morbidity (60%), polypharmacy (66.5%), and use of FDC (18.45%). ADRs secondary to inadequate monitoring was 7.7% and those due to drug-drug interaction was 6.5%.

Conclusion: Female population, age >60 years, and presence of concomitant co-morbidities were the patient related risk factors and polypharmacy, drug-drug interactions, and inadequate monitoring were the drug related risk factors for development of ADRs.

Keywords: Adverse drug reactions, Pharmacovigilance, Preventability.

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INTRODUCTION

Adverse drug reactions (ADRs) accounts for significant cause of morbidity and mortality worldwide, with tremendous impact on health and socioeconomic burden [1]. They culminate in reduced quality of life, increased requirement for physician visits and hospitalizations, and even mortality in extreme case scenario [2]. The definition provided by the World Health Organization (WHO) for ADRs isAdverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product [3].

It has been noted that ADRs account for about 5% of all hospital admissions and occur in 10–20% of hospitalized patients [1,4]. The overall incidence of serious and fatal ADR among hospitalized patients is 6.7% and 0.32%, respectively [5,6]. Surprisingly, there are instances where, ADR-related costs, such as hospitalization, surgery and lost productivity, far exceed the cost of the medications [3,7]. The recent epidemiological studies have reported that ADR are the fourth to sixth leading causes of death [1,8,9].

The WHO defined "Pharmacovigilance" as "The science and activities related to the detection, assessment, understanding and prevention of adverse drug effects or any other possible drug-related problems [3,10]." Despite the various shortcomings of the spontaneous ADR reporting systems, they still remain as the most prevalent method within Pharmacovigilance centers across the world, which permits, ongoing evaluation, and continues to be one of the best ways for early detection and prevention of unexpected and uncommon ADRs [3,10,11]. In the absence of excellent ADR reporting systems, multiple preventable causes of ADRs may remain undetected for significant period of time, which amplifies the unexpected negative outcomes encountered in patient care [9,12-14].

It is well known that elderly population are at higher risk of ADRs due to associated risk factors such as co-morbidities, polypharmacy, irrational use of prescriptions, and improper monitoring [10,11,15,16]. The WHO defines older adults (elderly or geriatrics) as those aged 60 years and older [11,17,18]. Incidence of ADRs in older adults (11–32%) is greater compared to the general population, which results in poor patient compliance and interference with the patient's treatment outcomes and thus, resulting in a higher burden on the health-care system [11,19,20].

The preventive aspect of ADRs is worth probing, as it would positively improve the incidence of complications associated with it. Avoidable adverse events during the hospitalization ranged from 16% to 61% [12]. Preventable ADRs, on further evaluation, was estimated to be 70% of ADRs leading to emergency department visits, which are avoidable [3,21]. Preventable ADRs are postulated to be due to medication errors, drug interactions, underlying diseases or patient characteristics (idiosyncratic reactions and allergies, including unintentional effects happening at recommended doses), prescription or dispensing errors, poor adherence, and ineffective monitoring of patient safety [1,14].

ADRs are a growing menace in present day medical practice. A major shortcoming in ADR research is the absence of reliable information on the exact prevalence and burden of ADRs due to extensive under-reporting, rendering accurate assessment of the relative frequencies of different ADRs impractical. The ADR reporting rate is below 1% in India compared to the worldwide rate of 6-10% and most of the studies till date are done in developed countries which makes generalization difficult [15,16]. Detection of ADRs has become more important because of the ever increasing number of drugs entering the drug market, every year over the past two or three decades [17].

The present study was conducted to analyze the pattern, severity, causality, predictability, and outcome of ADR among the hospitalized patients and thereby identify the measure to prevent ADRs which, in turn, improve the patient's quality of life, reduce their economic burden, and promote rational drug use. Given the moderate to high percentages for the preventability of ADRs in the literature and the lack of sufficient studies investigating the most identifiable factors and reasons for ADRs preventability, this study also aimed at exploring the situation of such an important issue.

METHODS

A retrospective, record-based study was conducted in the ADR monitoring center of a tertiary care hospital in South Kerala, working under Pharmacovigilance Programme of India. All the suspected ADRs reported by treating consultants, staff nurses, clinical pharmacists and Junior Pharmacovigilance Associate from Jan 2021 to Dec 2021 were collected in the Central Drug Standard Control Organization Suspected ADR reporting form by WHO from various departments.

The details were sent to the National Coordinating Centre through Vigiflow and simultaneously ADR reports were analyzed for the demographic details and data on the ADR regarding its temporal association, status of recovery, seriousness and outcome of reaction, details of the suspected, and concomitant medications were collected. Data on various predisposing factors responsible for an ADR, such as presence of co-morbidities, use of Fixed Dose Combinations (FDC), and improper monitoring, presence of drug interactions, presence of polypharmacy were also collected.

Causality of ADR

Causality assessment is the method by which the extent of relationship between a drug and a suspected reaction is established and the WHO scale was used in the current study to assess the causality of the adverse reactions [3].

Predictability

Predictability will be determined by classifying the ADRs based on Aronson classification into six types, Type A to Type F [17]. In the current study, Type A, C, D, E, and F are considered predictable. Type B is considered unpredictable.

Preventability

According to the WHO factsheet, it is estimated that at least 60% of ADRs are preventable [3]. In the present study; preventability was assessed using modified Schumock and Thornton scale [18]. An answer of "yes" to any question in this scale suggests that the ADR might have been preventable.

Seriousness of ADR

The criteria for serious ADR have been specified by the WHO and US Food and drug administration and are adopted by CDSCO in suspected ADR reporting form [7] It includes any untoward medical occurrence at any dose that may result in death or life-threatening reaction or requires or prolongs hospitalization or results in persistent or significant disability or incapacity or required intervention to prevent permanent disability or results in congenital abnormality [3,19].

Severity of ADR

In the current study, the modified Hartwig and Siegel scale was used to assess severity. According to this scale, there are seven levels of severity, ranging from "No change in treatment" in level 1to "Death" in level 7 [20].

Outcome of ADR

In the current study, outcome of reaction is categorized as per CDSCO-IPC suspected ADR reporting form. Outcome was categorized as recovered, recovering, not recovered, recovered with sequelae, fatal, and Unknown [7].

Statistics

SPSS V.16 was used for the data analysis. Qualitative variables were expressed as percentages. Quantitative variables were described by mean, frequencies, and percentages. Comparison of quantitative variables was analyzed by Chi-square test. A p value of<0.05 was taken as level of significance.

RESULTS

During the study period, a total of 233 ADRs were collected from the various departments of which 114 ADRs were reported from the age group of >60 years which constitutes 48.9% of the total ADRs. The mean age of the patients was 55.3 years. The study showed a female preponderance with 51.9% (n=121) of ADR being reported in female patients versus 48.1% (n=112) in male patients (Table 1). On the contrary among the geriatric patients higher incidence of ADRs were found to be in male population (62.5%) versus female population (37.2%) (Table 2).

The highest number of ADRs were reported from the therapeutic class of antimicrobials 18.9% (n=44) followed by neurological 17.6% (n=41) and cardiovascular medicines 14.2% (n=33) (Table 3). While beta lactam antibiotics 59% (n=26) were the most common among the antimicrobials group to cause ADRs Psychotropics 51.2% (n=21) and Anti-epileptics 36.6% (n=15) predominated among the neurological medicines. The skin and appendages constituted the most common organ system affected with 33.5% followed by renal disorders (19.3%) and gastrointestinal disorders (12.4%). The detailed description of organ systems affected by ADRs is shown in Table 4. The frequency of ADRs associated with different routes of administration was as follows: Oral (51.5%), parenteral (37.8%), inhalational (9.9%), and topical (0.9%) (Table 5).

The causality assessment was done according to the WHO Causality Assessment Scale and was found that 137 (58.8%) were probable, 90 (38.6%) were possible, and 4 (1.7%) were unlikely. Two reactions belonged to certain in this study (Fig. 1). Out of 106 serious ADRs, while majority required prolonged hospitalization 62.3% (n=66), 34% (n=36) required intervention to prevent permanent impairment/damage, and 3.8% (n=4) were life-threatening ADRs (Fig. 2). As per Modified Hartwig and Siegel scale for severity, majority of the reactions 53.2% (n=124) had level 3 severity followed by level 4 and level 2 with 23.2% (n=54) and 12.4% (n=29), respectively. Assessment of severity showed 12.4%, 76.4%, and 11.2% reactions in mild (levels 1 and 2), moderate (levels 3 and 4), and severe (levels 5, 6, and 7) grades, respectively (Fig. 3).

Assessment of outcome showed 78.1% (n=182) patients recovered from the reaction and 15.5% (n=36) were recovering at the time of reporting ADR. In 4.7% (n=11) reports, patients had not recovered and the reaction was found to be continuing. In 1.7% (n=4) reports outcome was unknown due to loss of follow-up. None of the ADR were reported to be fatal (Fig. 4).

Predictability analysis was done based on Aronson criteria. About 78.1% (182) of reactions belonged to Type A predictable reactions whereas the remaining 21.9% (n=51) belonged to Type B non-predictable reactions.

Table 1: Demographic distribution of patients with adverse drug reactions

Demographic variable	Number (n=233)	Percentage
Age		
0–15	10	4.3
16–30	28	12.0
31–45	31	13.3
46–60	50	21.5
60–75	75	32.2
>75	39	16.7
Gender		
Male	112	48.1
Female	121	51.9

Table 2: Association of adverse drug reactions with age and gender

Gender	Age group		Total	Chi-square test	p-value
	<60	>60			
Male	42 (37.5%)	70 (62.5%)	112 (100%)	14.906	0.001
Female	76 (62.8%)	45 (37.2%)	121 (100%)		

Table 3: Distribution of adverse drug reactions based on therapeutic class of drugs

Therapeutic class	Number (n=233)	Percentage
Antimicrobials	44	18.9
Chemotherapy	9	3.9
Gastrointestinal	6	2.6
Cardiovascular	33	14.2
Neurological	41	17.6
Respiratory	16	6.9
Renal	28	12.0
Hematological	19	8.2
Hormonal	31	13.3
Analgesics	6	2.6

Table 4: Distribution of adverse drug reactions based on system organ class

System organ class	Number (n=233)	Percentage
Skin and appendages	78	33.5
Neuropsychiatric	13	5.6
Cardiovascular	11	4.7
Gastrointestinal	29	12.4
Hematological	23	9.9
Metabolic	18	7.7
Renal	45	19.3
Hepatic	4	1.7
Muscular	1	0.4
Respiratory	3	1.3
Allergy/immunological	3	1.3
General and administration site reaction	2	0.9

Table 5: Distribution of adverse drug reactions among the various routes of administration

Route of administration	Numbers (n=233)	Percentage
Oral	120	51.5
Parenteral	88	37.8
Inhalation	23	9.9
Topical	2	0.9

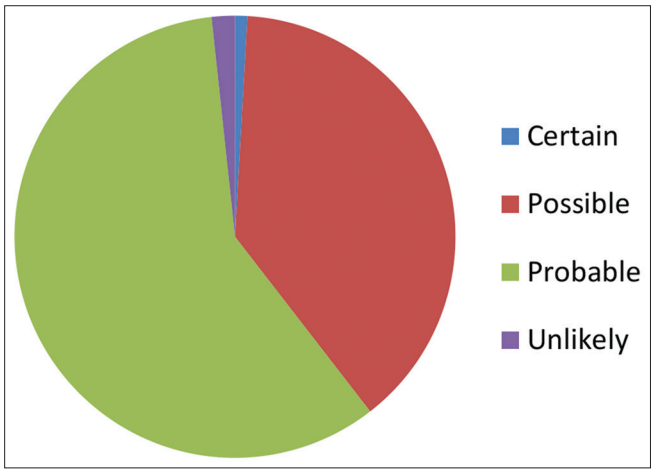

Fig. 1: WHO causality of adverse drug reactions

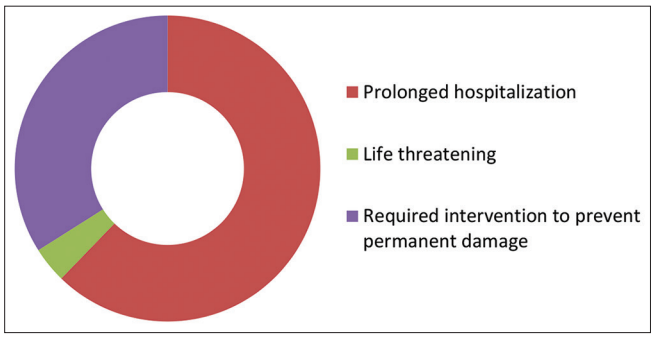

Fig. 2: Seriousness of adverse drug reactions

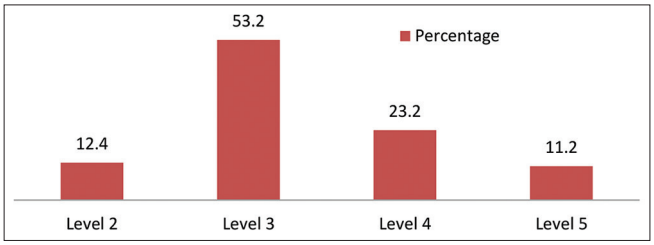

Fig. 3: Severity of adverse drug reaction

No reactions could be attributed to categories C, D or E (Fig. 5). Modified Shumock and Thornton criteria was used to assess the preventability and out of 233 ADRs, majority 169 (72.5%) were probably preventable, 62 (26.6%) ADRs were not preventable, and 2 (0.9%) were definitely preventable (Fig. 6).

75.1% of the patients reported with ADR had an existing co-morbid condition. On an average, each patient had 2.01±0.01 diagnoses. The most commonly associated co-morbid conditions were found to be hypertension, diabetes, coronary artery disease, cerebrovascular disease, chronic kidney disease, and chronic liver disease. ADR among geriatric patients with concomitant co-morbidities were found to be higher (60%) than those without any underlying co-morbidities in whom it was only 10% (p=0.001) (Table 6).

The role of polypharmacy in causing ADR was also assessed and it was found that ADR reported among those with polypharmacy was found to be higher (66.5%). The average number of medications prescribed was 6.45±0.04. On comparing the geriatric population presence of polypharmacy significantly increased the incidence of ADR (54.8%, p=0.018) (Table 6).

18.45% cases of ADRs involved the use of FDC, the commonest being combinations involving antiplatelets, antihypertensives, and diuretics. FDC-related ATT was found to be significantly higher (p=0.022) in the geriatric group (65.1%) as opposed to the patients below 60 years (34.9%) (Table 6). The incidence of DDI-related ADRs found during the study period was 6.4% (n=15). Drugs that act on the cardiovascular system (31.5%) were the most commonly involved followed by the drugs that act on blood and blood-forming organs

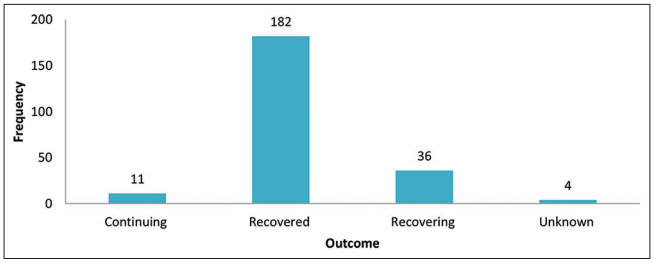

Fig. 4: Outcome of adverse drug reaction

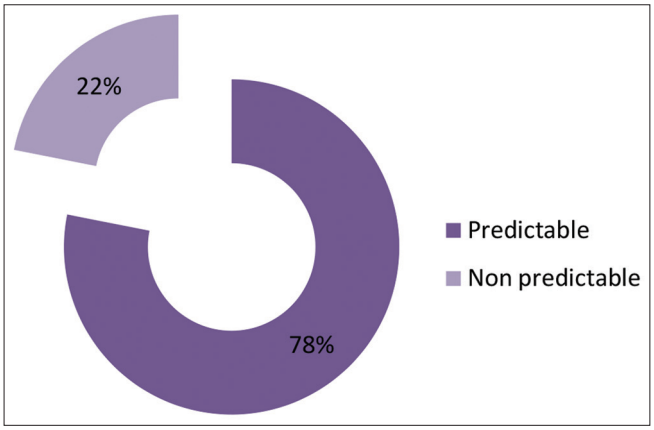

Fig. 5: Predictability of adverse drug reactions

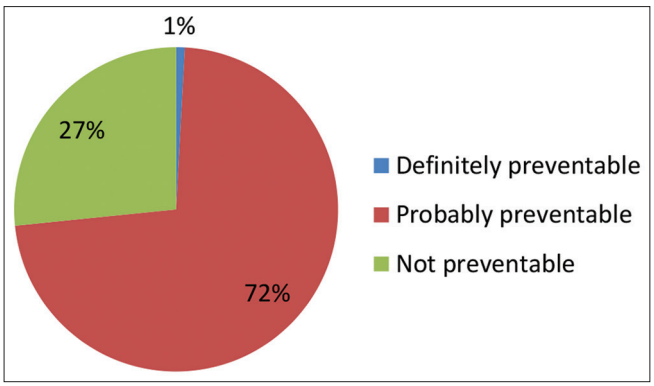

Fig. 6: Preventability of adverse drug reactions

(21%). ADR due to inadequate monitoring accounted to 7.7% (n=18) (Table 7).

DISCUSSION

The study aimed at a descriptive analysis of the ADRs reported in a tertiary care hospital and also to identify the predisposing risk factors. The mean age of the study population was 55.3 years and 48.9% of the ADRs were reported in the age group of >60 years. Similar findings were shown in a study by Oliver Pascale *et al.* and could be due to the fact that this population is attending hospital more frequently and is a major population receiving drug therapy [21]. A positive association between incidence of ADR and increasing age was as well found which was consistent with the findings of Barbate *et al.* [9].

Regarding the association between sex and ADRs Rademaker *et al.* found females had a 1.5–1.7 times greater risk of experiencing ADRs which is similar to our results which could be due to the anatomical and physiological variations in the females which alter the pharmacokinetic and pharmacodynamics of the drugs and predispose them to more ADRs compared to males [8,22].

Table 6: Association of risk factors with adverse drug reactions

Risk factors	Age group		Total	Chi-square test	p-value
	<60	>60			
Comorbidity					
Yes	70 (40.0%)	105 (60.0%)	175 (100%)	31.863	0.001
No	48 (82.8%)	10 (17.2%)	58 (100%)		
FDC					
Yes	15 (34.9%)	28 (65.1%)	43 (100%)	5.240	0.022
No	103 (54.2%)	87 (45.8%)	190 (100%)		
Polypharmacy					
Yes	70 (45.2%)	85 (54.8%)	155 (100%)	5.568	0.018
No	48 (61.5%)	30 (38.5%)	78 (100%)		

Table 7: Adverse drug reaction versus drug interaction and inadequate monitoring

Risk factors	Numbers	Percentage
Drug interaction		
Yes	15	6.4%
No	218	93.6%
Inadequate monitoring		
Yes	18	7.7%
No	215	92.3%

Antimicrobials accounted for the majority of ADRs in the present study and similar which could be due to the fact that antimicrobial drugs are the commonly prescribed drugs. This was consistent with study by Alenzi *et al.* whereas on the contrary antineoplastic drugs predominated in a study by Digra *et al.* [10,23,24]. The skin and appendages constituted the most common organ system affected with commonest reaction between rash and urticaria. This was consistent with the results in a study by Digra and Shivaraj Patil wherein dermatological reactions predominated with 67.3% and 42.9%, respectively [23,24].

In this study, the causal relation for 58.8% per cent ADRs with drug was probable, corroborating with results by multiple studies [2,16]. About 45.5% of the reactions were considered serious and the commonest reason for seriousness was prolongation of hospitalization (62.3%) which was consistent with a study by Jihana *et al.* wherein 39% of the reactions were reported to be serious [15]. Severity assessment showed 12.4%, 76.4%, and 11.2% reactions in mild, moderate, and severe grades, respectively. In a study by Geer *et al.*, a similar severity pattern of 23.68%, 69.29%, and 7.01% was found in respective grades [2,14]. Assessment of outcome showed 78.1% patients recovered from the reaction and 15.5% were recovering at the time of reporting ADR which was consistent with the study by Badyal *et al.*, with 95.5% recovery rate [25].

The higher incidence of moderate reactions and improved recovery rate could be due to the better quality of health care which helped in early identification, effective treatment, and thereby reducing the complications.

Predictability analysis showed 78.1% (182) of reactions belonged to Type A Predictable reactions and a similar pattern was found in a study by Gholami *et al.* with a predictability rate of 96% [26]. On the contrary study by Jihana *et al.* had a low predictability rate of 40% as majority of the reactions reported were hypersensitivity reactions with the low predictability [15]. Preventability was a promising finding in our study whereby 72.5% of reactions were found to be preventable which was in agreement with the results of a study by Al Daman *et al.* wherein preventability rate was found to be 50% [27].

Co-morbidity, the concomitant presence of multiple coexisting diseases in the same individual, is a major issue in geriatrics and is associated with an increased risk of ADR [28]. The study showed that 75.1% of the patients reported with ADRs had an existing co-morbid condition and 60% of them belonged to an age group of >60 years (p=0.001).This was consistent with the findings of study by Jennings *et al.* [29].

Polypharmacy or concurrent use of five or more medications was the most consistently identified predicting risk factor of ADR among hospitalized older adults [30]. The average number of medications prescribed in the current study was 6.45±0.04 and it significantly increased the incidence of ADRs (54.8%, p=0.018) among the geriatric study population. Similar results were found in a study by Olivier Pascale *et al.* [21].

In the current study, 18.45% cases were attributed to FDC related ADRs and the incidence was higher among the geriatric population (65.1%, p=0.022) which is consistent with the results of a study by Yades *et al.* [11].

A higher incidence (19.7%) of drug-drug interactions (DDI) related ADRs was found in a study by Olivier Pascale *et al* contrary to the findings of the current study wherein it was only 6.5% [21]. ADRs due to inadequate monitoring accounted to only 7.7%. This was contrary to the findings by Al Daman *et al* where it accounted to 29.4% [27]. The lower incidence of ADRs due to insufficient monitoring as well as DDI-related ADRs could be explained by the improved monitoring and prescription audits carried out by the clinical pharmacists in our hospital.

Limitations of the study

This is a retrospective observational study design and hence the actual incidence of ADRs could not be estimated. Shorter study duration and a smaller sample could have resulted in missing out of multiple ADRs. The main limitation of this study is that it represents only the ADRs spontaneously reported to the ADR Monitoring Centre and hence does not reveal complete picture of ADR in this tertiary care teaching hospital.

CONCLUSION

This retrospective observational study in addition to analyzing the pattern of ADRs also throws light on the important contributing factors in causing the identified ADRs. Female population and age >60 years were found have a higher preponderance for the development of ADRs and hence were identified as patient related risk factors for development of ADRs. The role of various drug related factors in the development of ADRs was also analyzed and a positive association was found between polypharmacy, concomitant co-morbidities, DDI, and inadequate monitoring in the development of ADRs. This information helps in initiation of preventive strategies that can be followed by health-care professionals to reduce the incidence of ADRs and thereby ensure medication safety and improve the quality of life.

AUTHORS CONTRIBUTIONS

All authors have contributed critically to the preparation of the manuscript.

CONFLICT OF INTEREST

None declared.

AUTHOR FUNDING

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ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

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