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Systematic review of the prevalence and nature of drug-related problems in paediatric patients

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Abstract

What is known and objective: A drug-related problem (DRP) is "an event or circumstance involving drug therapy that actually or potentially interferes with the desired health outcome." The paediatric population is easily affected by DRPs. The aim of this study was to evaluate different types and characteristics of DRPs in paediatric patients. This finding can be used as a baseline in epidemiology for assessing potential risk factors for DRPs in paediatric patients.

Methods: An extensive search strategy was designed to retrieve all articles published from the date of inception of the database to 1 May 2020, by combining the terms "drug-related problem" and "paediatric" in several electronic databases (PubMed, Cochrane Library, Embase and Web of Science) and following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Observational and interventional studies report that the epidemiology of DRPs in paediatric patients was included. Two reviewers independently screened studies, extracted data, assessed the quality of the included studies and then qualitatively analysed the results.

Results: Eighteen studies were included in the final analysis, and 6 different classification systems on paediatric-related DRPs were reported. Overall, these studies showed that paediatric patients are easily affected by DRPs. However, the majority of DRPs are considered preventable, and the severity of DRPs in paediatric patients is mostly considered minor and moderate. Dosing-related problems rank highest in terms of frequency, and the number of prescribed drugs has a positive correlation with the occurrence of DRPs.

What is new and conclusion: This study showed that paediatric patients are easily affected by DRPs, but the majority of DRPs are preventable, which indicate that actions should be taken. To reduce DRPs in paediatric patients of the interventions that are noticed, clinical pharmacy services show promising improvement on reducing DRPs compared with other interventions.

KEYWORDS
drug-related problem, medicine-related problem, paediatric, systematic review

Xue Mi, Lingli Zhang have contributed equally to this work.

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1 | WHAT IS KNOWN AND OBJECTIVE

A drug-related problem (DRP) is defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes,"[1] and it can occur at any point in drug use and may result in drug treatment goals not being achieved and/or patient harm[2] and even morbidity and mortality.[3,4] DRPs are different from adverse related problems (ADRs) and medication errors (MEs), and they not only require the promotion of medication safety but also the rational use and cost-effectiveness of drug therapy.[5,6] The rapidly evolving complexity of drug therapy gives increasing challenges to appropriate drug prescribing, highlighting the importance of addressing DRPs.

The paediatric population is unique in drug therapy and is at higher risk of being affected by DRPs, as paediatric patients exhibit significant individual variation in organ development, weight and body surface area (BSA), which are also different from those of adults. Unrecognized and/or unresolved DRPs can potentially lead to hospitalization, emergency department visits and economic burden to the family.[7] Studies have reported that the incidence of DRPs is 39.4% in hospitalized children[8] and 2.7% in children were admitted to emergency departments in the UK.[9] A study from Australia reported that 4.3% of paediatric admissions and 3.3% of emergency department visits were related to DRPs, the direct cost related to DRPs was £100,707,[10] and the emergency department admissions associated with DRP were £764,65.[11] All of the evidence has shown that DRPs constitute a major concern to the paediatric population psychologically and physically and to society as a whole economically.

Drug use and healthcare systems can vary significantly between different countries; consequently, the epidemiology of DRPs and strategies in the reduction of DRPs may be different. However, to date, no study has comprehensively reviewed the characteristics of DRPs in paediatric patients worldwide using a rigorous systematic review approach. Previous studies have mostly focused on one of the primary domains of DRPs, such as adverse drug reactions (ADRs) or prescribing errors.[12–15] Accordingly, the results of such studies are incomplete in representing the overall picture of DRPs. The purpose of this study was to assess and determine all components and the characteristics of DRPs in paediatric patients, and the findings could be used as a baseline for epidemiology and potential associated risk factors for DRPs in paediatric patients.

2 | METHOD

This study is based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for reporting systematic reviews.[16]

2.1 | Selection criteria

Studies were selected based on the following inclusion criteria: (1) eligible study designs included observational epidemiological studies and interventional studies, (2) studies reporting the epidemiology of DRPs in paediatrics (including incidence, type and factors associated with the occurrence of DRPs, severity, preventability, causes, and interventions) and (3) patients aged 0–18 years. The exclusion criteria were as follows: (1) studies published in abstract form only or unoriginal work (letters or reviews) and (2) studies that focused on only one of the primary domains of DRPs, such as studies that reported only ADRs or prescribing errors.

2.2 | Search strategy

A database search was conducted on May 2020. Relevant studies were identified by electronically searching the following databases: English databases (PubMed, Embase, Cochrane Library and Web of Science), Chinese databases (Chinese Biomedical Literature Database, China National Knowledge Infrastructure, WanFang Database and VIP Database for Chinese Technical Periodicals) and search engines (Google Scholar and Bai Du Scholar). In addition, the bibliographies of relevant identified articles were manually searched. The search terms combined the medical subject headings (MeSH) with free-text words, including "drug-related problem," "medication-related problem," "paediatric" and "children." More details about the search strategy can be found in the supplementary file.

2.3 | Study selection, data extraction and quality assessment

Study selection, data extraction and quality assessment were conducted independently by 2 reviewers. All conflicts were resolved through consensus and, if necessary, consultation with a third reviewer. Data were extracted using standardized forms, including the basic information of the studies and the epidemiological characteristics of DRPs in paediatric patients. The quality of cohort studies was assessed based on the Newcastle-Ottawa Scale (NOS), and cross-sectional studies were assessed based on the tool from the Agency for Healthcare Research and Quality (AHRQ).[17,18]

2.4 | Statistical analysis

A qualitative analysis was conducted in this review to report the epidemiological characteristics and intervention of DRPs in paediatric patients.

3 | RESULTS

3.1 | Search results and study characteristics

A total of 4181 potentially eligible records were identified from the search. Full texts of 35 records were read, and a total of 18 studies met the inclusion criteria.[5,7–11,19–30] The screening process and

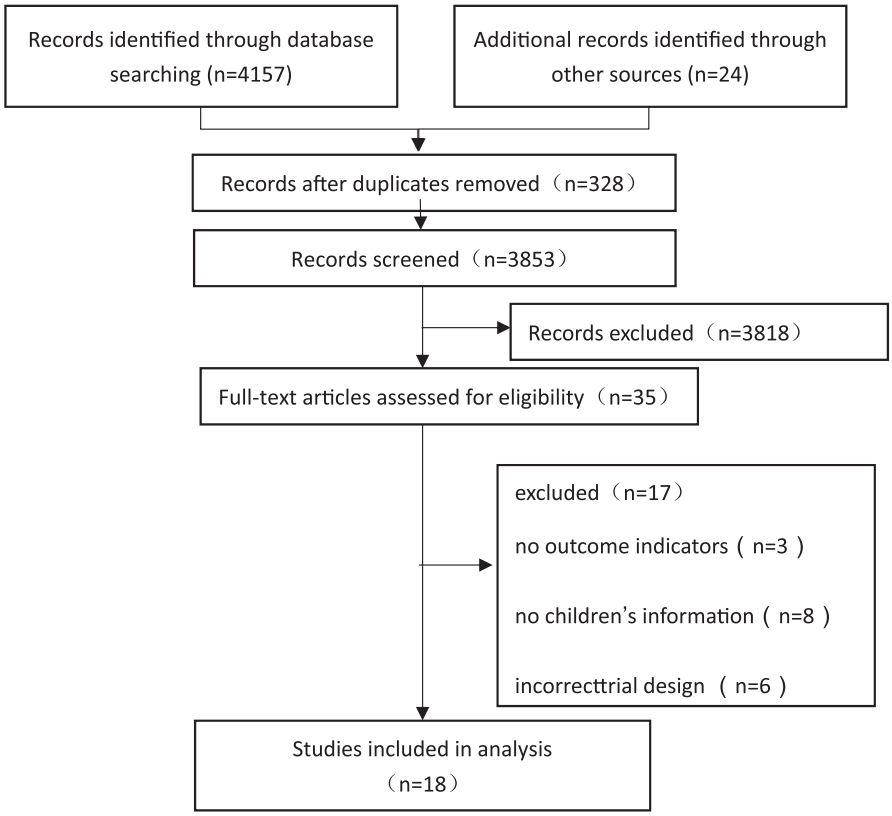

FIGURE 1 Literature search method and screening results

results are shown in Figure 1. The included studies were all published in English; 6 were cohort studies, and 12 were cross-sectional studies. The study period ranged from 3 months to 10 years, and the study size ranged from 60 to 8601 participants. The data were collected in 17 countries, and the main departments included the PICU (paediatric intensive care unit), NICU (neonate intensive care unit), ED (emergency department) and paediatric ward. The characteristics of the 18 included studies are summarized in Table S1.

3.2 | Risk of bias within studies

All included cohort studies were considered to be at low risk of bias on all components, and a NOS score ≥7 stars indicated good quality.[5,7–9,27,29] For more than half of the 12 cross-sectional studies, Item 6 "describe any assessments undertaken for quality assurance purposes" and Item 8 "evaluation and/or measures to control confounders" were reported as unclear, and the quality evaluation results of the remaining items were considered good.[10,11,19–26,28,30] Table S2 in the supplementary files shows the assessment of the risk of bias.

3.3 | Epidemiological characteristics of DRPs in children

Eighteen studies analysed the epidemiology of DRPs in paediatric patients in different countries/regions based on the DRP classification system and described problem type, incidence, severity, preventability, causes, driving factors and interventions.

3.3.1 | Classification system

Six different types of DRP classification systems were used in 17 studies (one study did not report the classification system used[30]), including PCNE 5.01 (PCNE, European Pharmaceutical Care Network Foundation), PCNE 6.02, PCNE 8.02,[1] Strand 1990,[6] SPFC (French Society of Clinical Pharmacy) DRP classification[31] and self-developed systems.[28] Among them, PCNE classification systems were used most frequently (72%). There are some differences between different DRP classification systems. The content of each DRP classification system is summarized in Table S3.

3.3.2 | Incidence of DRPs in paediatric patients

Twelve studies examined the incidence of DRPs.[5,7–9,19–26] Bizuneh 2020 assessed DRPs in a paediatric ward in Ethiopia using a prospective observational method; 81 patients were included, and 71 (87.7%) of them had at least one DRP, indicating that the actual incidence of DRPs could be substantially higher than reported.[20] Ibrahim 2015 reported that the incidence of DRPs in paediatric renal inpatients was 19.2% higher than that in paediatric renal outpatients (51.2% vs. 32%, $p = 0.04$).[5] Rashed 2013 reported that the overall incidence of DRPs in paediatric patients who were admitted to a medical ward, PICU or NICU of seven Hong Kong hospitals was 21.0%.[7] The incidence of DRPs in different studies is shown in Table S4.

3.3.3 | Severity of DRPs in paediatric patients

Seven studies reported the severity of DRPs in paediatric patients.[5,7–9,11,22,23] Among them, 5 studies adopted the validated scale for medication errors published by Dean and Barber (1999); to measure the severity of DRPs,[32] the researchers scored the validated DRPs in terms of potential patient outcomes on a scale of 0–10, where 0 represents a case with no potential adverse effect on the patient and 10 a case that would result in death.[5,7–9,22] Easton 2003 (ED) used different criteria,[33] which defined DRP requiring no treatment as "mild," DRP requiring treatment for symptom resolution as "moderate" and DRP requiring hospitalization as "severe."[11] Raman 2019(O)[23] assessed the severity of DRPs based on the tool developed by Lewinski et al.[34] Seven studies showed that the severity of DRPs in paediatric patients was mostly considered minor and moderate. The severity of DRPs is shown in Figure 2.

3.3.4 | Preventability of DRPs in paediatric patients

Seven studies assessed the preventability of DRPs in pediatrics.[7–11,22,23] Among them, 6 studies adopted the criteria provided by Schumock and Thornton (1992) to measure the preventability of DRPs,[35] and Raman 2019(O) used the tool developed by Lewinski et al.[34] Seven studies showed that most identified DRPs in paediatric patients were preventable, and the preventability was between 46.9% and 90.0%. The preventability of DRPs is shown in Figure 3.

3.4 | Type of DRPs in paediatric patients

The application of different classification systems to the same patient database of problems has been demonstrated to result in different numbers of DRPs, different category findings and different issues.[36] In this review, 6 different types of DRP classification systems were used in 17 studies, which resulted in different types and numbers of DRPs in paediatric patients. The results showed that DRPs include drug selection, drug dosages, ADR and drug administration. Dosing problems, which include dosages that are too low or too high, are the main types of DRPs identified in many studies. ADR is the second most frequently reported DRP in some studies. The type of DRPs and relative ratio identified in every study are shown in Figure 4.

3.5 | Causes

Eleven studies reported the cause of DRPs in paediatric patients.[5,7,8,19–25,28] The majority were related to the selection of the dosage. The second most frequent causes are drug selection and drug administration processes. Yismaw 2020 reported that the need for prophylactic therapy to reduce the risk of developing new disease conditions is the main cause of the need for additional therapy,[19] Mei 2020 reported that failure to provide necessary prescribing information and medication served without a valid prescription was also the main cause of DRPs[21] and Ibrahim 2015 reported that prescribing errors and the medication-taking behaviour of patients were the main contributing factors for DRPs.[5]

3.5.1 | Factors associated with the occurrence of DRPs

Seven studies evaluated the factors associated with the occurrence of DRPs, and the analysis showed a significant correlation between the number of prescribed drugs and DRP occurrence.[5,7,8,21,22,24,26] Rashed 2013 reported that a patient is more likely to experience DRPs if the patient is diagnosed with "certain infectious and parasitic diseases,"[7] Ramon 2019(P) showed that DRPs are associated with an increased length of stay, number of prescribed drugs and number of clinical problems[24] and Asia 2012 reported that polypharmacy and transition of care (to different hospitals or wards) are the potential risk factors for DRPs.[8]

3.5.2 | Interventions

Eight studies assessed interventions for DRPs.[5,7,8,19,23,25,27,29] Clinical pharmacists are the main workforce delivering interventions, and dose adjustment is the most frequently used intervention. Most recommendations of pharmacists are accepted by the clinical team and produce a significant clinical impact and a positive economic impact. The detailed contents and results of interventions for DRPs are shown in Table S5.

4 | DISCUSSION

The goal of pharmacotherapy is to attain definite therapeutic outcomes, improve patients' quality of life and minimize medication risks. However, inappropriate use of medication is common and exposes paediatric patients to DRPs.[37] The 18 included studies showed that DRPs occur frequently in the paediatric population. The majority of DRPs are preventable, and the severity of DRPs in paediatric patients is mostly minor and moderate.

While classifying DRPs are an important part of pharmaceutical care practice and research, a universally accepted classification system has not been adopted yet.[3,38,39] In this review, 6 different types of DRP classification systems were used in the 17 studies, resulting in difficulties in comparing the numbers and types of DRPs. Many classification systems lack a hierarchical structure and separation of categories identified as causes of DRPs and DRPs, with consequent intermingling of causes of DRP/DRP categories. In this review, the most frequently used system was PCNE (76%), in which a classification scheme was constructed for DRPs during the working

conference of the PCNE in January 1999. After being validated and adapted many times, the current version V8.02 differs from other systems because it separates the problems from the causes.[1] The classification system is important for the identification, resolution and prevention of DRPs, and it is necessary to develop a preferred method of reporting DRP studies, including the development of a reliable, consistent, easily understood and operated and tested system for the classification of DRPs.

Regardless of the classification system used, many studies reported dosing problems to be the most frequently encountered DRPs in their study setting. Compared with the adult population, weight-based dosing, fractional dosing (e.g., mg vs. Gm) and the inaccurate recording of patient weights, which may involve decimals, all contribute to a higher risk of inappropriate dosing in pediatrics.[40–42] Therefore, the high prevalence of dosing problems would highlight it as an important area requiring further attention. Many studies have found that antibiotics result in a higher DRP incidence than other drugs. This may be due to antibiotics, which can be used prophylactically, particularly for patients diagnosed with severe malnutrition, as these patients are at risk of developing infection even with a single microorganism[43]; the absence of national prescribing guidelines and the prevalence of antibiotic resistance also contribute to the high levels of broad-spectrum antibiotics prescribed in paediatric populations.[44,45] Many studies have shown that the high prevalence of DRPs may be attributed to the number of prescribed drugs.[8,19,20,24,26] The more complex drug therapy is, the higher the risk of patients experiencing DRPs. Polypharmacy may increase the chances of drug-drug interactions, which led to increased possibilities for ADRs to occur.[46,47]

Drug-related problems are common in paediatric patients; however, the majority of identified DRPs are preventable and minor or moderate in severity. Easton 2002 showed that the total direct costs associated with DRPs were £100707, of which £61543.20 was associated with DRPs determined to be preventable. Easton 2003 reported that the direct costs associated with preventable DRP were $A44455.01.[10,11] These studies highlighted that it is necessary to act to reduce the consequences of DRPs in paediatric patients and

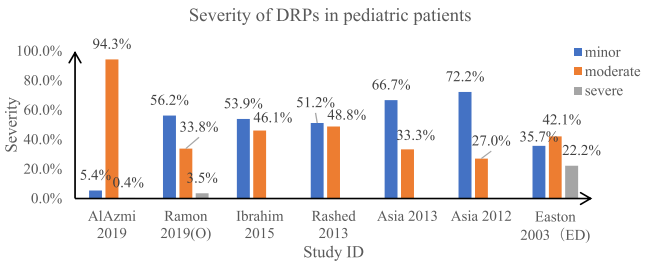

FIGURE 2 Severity of DRPs in paediatric patients at included studies

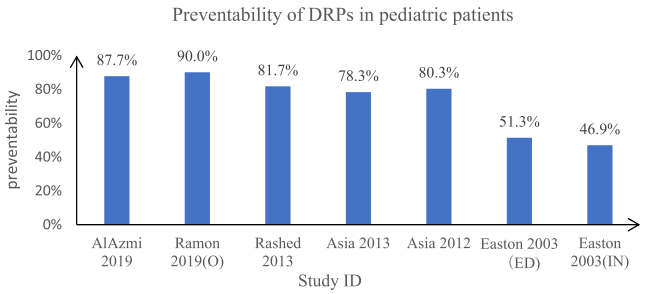

FIGURE 3 Preventability of DRPs in paediatric patients at included studies

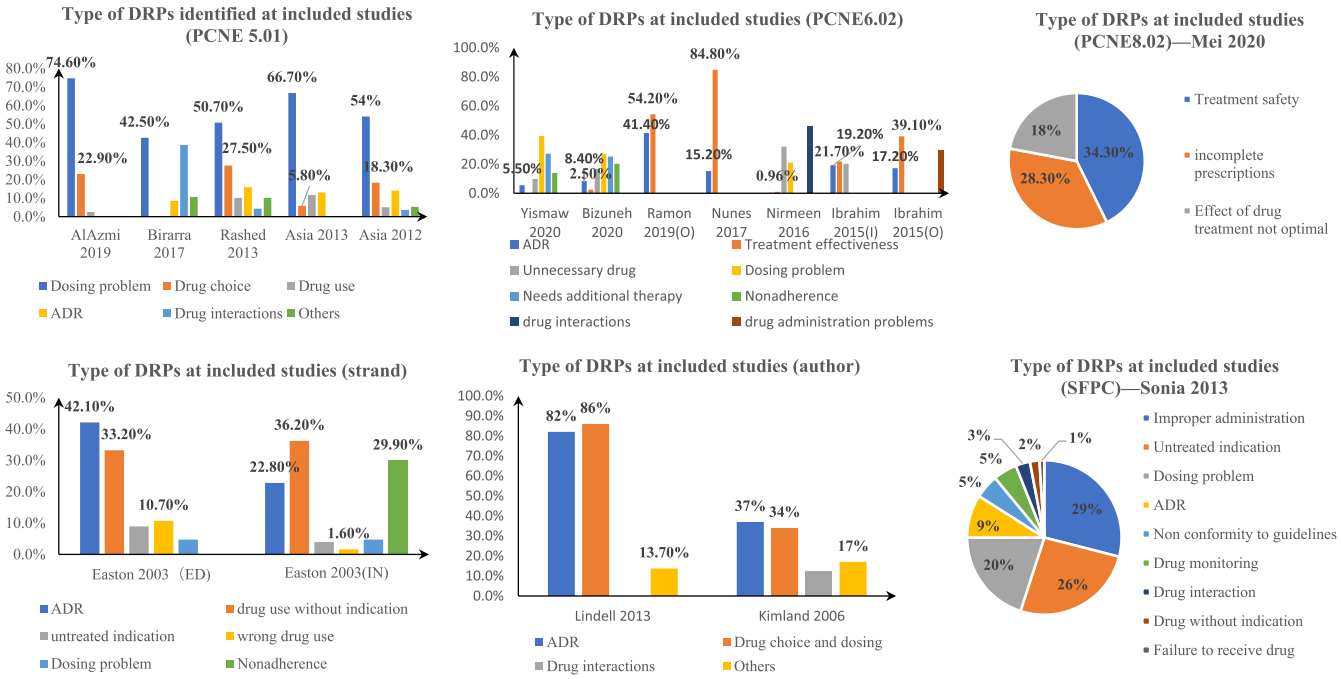

FIGURE 4 Type of DRPs in pediatric patients identified at included studies

the significant burden that DRPs place on our healthcare system.[48,49] Clinical pharmacists can effectively identify, prevent and resolve DRPs, and their interventions have largely been endorsed by physician colleagues.[29,50] Nirmeen 2016 reported that pharmacists' intervention resulted in a significant reduction in prescribing error down to 35.2% ($p < 0.001$), and 65% of pharmacists' suggestions were accepted by physicians.[27] Sonia 2013 found that clinical pharmacists intervened to address a total of 996 DRPs relating to 270 patients, and 98% of their proposals were accepted.[29] Aiming at the main type and causes of DRPs in paediatric patients, clinical pharmacists need to pay more attention to antimicrobial stewardship activities to encourage physicians' prudent use of antibiotics by educational interventions and information provision and especially reduce unnecessary antibiotic use. To reduce DRPs in paediatric patients, the suggested strategies include using computer-aided prescribing as well as unit dose-dispensing systems, computerized physician order entry and educational/risk management programmes, implementing drug information centres and utilizing different software to detect drug interactions, all of which clinical pharmacists can play a significant role in.[51–53]

Understanding the epidemiology of DRPs in paediatric patients is important to gathering efforts from researchers, healthcare professionals and patients to mitigate these problems through the implementation and improvement of interventions. This is the first time the epidemiology of DRPs in paediatric patients has been reviewed in such depth based on a strong conceptual framework. The results of this study provide a breakthrough point for future studies to analyse and quantify potential risk factors and interventions for DRPs and provide more information to paediatricians about clinical and economic considerations while providing healthcare services.

Nevertheless, this study had some limitations. First, not all relevant studies may have been identified by our search strategy although we followed systematic review guidelines, and to identify further articles for inclusion, we examined all citation lists from the assessed articles. Second, 6 different types of DRP classification systems were used in the 17 studies, which resulted in the results of these studies not being comparable. We only compared the results of studies using the same DRP classification system, but we examined and analysed every study that reported the types and causes of DRPs in detail. Third, epidemiological and economic data on DRPs in paediatric patients are limited in Asia, especially in mainland China; however, most of the published studies were conducted in Europe. Fourth, different studies utilized different criteria to report the severity and preventability of DRPs in children. For example, in Asia 2012, the preventability criteria were originally developed for ADR assessment, and the severity scale used was originally established to assess medication errors.[8] Therefore, the question remains as to whether these tools are adequate for assessing DRPs or whether specific tools should be developed; thus, validating specific tools for assessing DRPs could be an area of interest for further studies.

Further research is needed to explore the epidemiology and factors associated with DRPs in Asia to prevent and avoid their occurrence. Future studies should also represent the broader picture of DRPs by focusing on the definition of the term "DRP" itself and the difference and connection between DRP and other drug safety terms (such as ADRs and MEs). Additionally, areas with the highest potential for reducing DRPs and requiring targeted clinical pharmacy interventions should be highlighted and further explored.

5 | WHAT IS NEW AND CONCLUSION

This study showed that paediatric patients are easily affected by DRPs, but the majority of DRPs are preventable, and the severity is mostly minor or moderate. Actions are needed to reduce the consequences of DRP in paediatric patients. Of the interventions that are given emphasis, clinical pharmacy services show promising improvement in reducing DRPs compared with other interventions.

CONFLICT OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article.

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