DOI: https://doi.org/10.54393/pjhs.v7i5.3930

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 7, Issue 05 (May 2026)

Systematic Review

OPEN ACCESS

Role of Cytochrome P450 Enzymes in Pediatric Drug Metabolism: Physiological and Biochemical Perspectives; Systematic Review

Rizwana Kalsoom[1], Zarka Sarwar[2*], Mehreen Nawaz Khan[3], Farzan Hakim[4], Furqan Ali Shah[5] and Najma Fida[6]

[1]Department of Biochemistry, Gomal Medical College, Dera Ismail Khan, Pakistan
[2]Department of Physiology, Bacha Khan Medical College, Mardan, Pakistan
[3]Department of Lifestyle and Integrative Medicine, Regenerative Renaissance, Memphis, United States of America
[4]Department of Biochemistry, Foundation University, Islamabad, Pakistan
[5]Department of Pharmacology, Pak International Medical College, Peshawar, Pakistan
[6]Department of Physiology, Kabir Medical College, Peshawar, Pakistan

ARTICLE INFO

Keywords:
Cytochrome P450, Pediatrics, Ontogeny, Pharmacogenetics, Pharmacokinetics, Therapeutic Drug Monitoring

How to Cite:
Kalsoom, R., Sarwar, Z., Khan, M. N., Hakim, F., Shah, F. A., & Fida, N. (2026). Role of Cytochrome P450 Enzymes in Pediatric Drug Metabolism: Physiological and Biochemical Perspectives; Systematic Review: Role of Cytochrome P450 Enzymes in Pediatric Drug Metabolism. Pakistan Journal of Health Sciences, 7(5), 163-170. https://doi.org/10.54393/pjhs.v7i5.3930

Corresponding Author:
Zarka Sarwar
Department of Physiology, Bacha Khan Medical College, Mardan, Pakistan
zarka.sarwar41@gmail.com

Received Date: 3rd February, 2026
1st Revision Received: 27th February, 2026
Acceptance Date: 24th March, 2026
Published Date: 31st May, 2026

ABSTRACT

Cytochrome P450 (CYP450) enzymes are central to pediatric drug metabolism. However, enzyme maturation (ontogeny) and pharmacogenetic variability produce substantial age-dependent differences in drug clearance, exposure, and toxicity risk across neonatal, infant, and childhood populations. Objectives: To synthesize contemporary evidence (2020–2025) on CYP450 ontogeny and pharmacogenetic variability in children and evaluate their clinical implications for drug clearance, dosing optimization, and safety. Methods: A systematic review was conducted according to PRISMA 2020 guidelines. PubMed, Scopus, Web of Science, and Google Scholar were searched for pediatric studies evaluating CYP450 ontogeny, pharmacokinetics, or pharmacogenetics. Eligible designs included observational studies, physiologically based pharmacokinetic (PBPK)/population PK modeling, real-world analyses, and systematic reviews. Risk of bias was assessed using the Newcastle–Ottawa Scale and AMSTAR. Due to heterogeneity, findings were synthesized narratively. Results: Sixteen studies from Asia, Europe, North America, and Australia were included. CYP2C19, CYP3A4, and CYP2D6 were the most frequently investigated isoforms. Ontogeny demonstrated enzyme-specific maturation patterns: CYP3A4 and CYP2C19 activity increased rapidly during infancy, whereas CYP2D6 and CYP1A2 matured more gradually, contributing to reduced neonatal clearance and prolonged half-life of several substrates. Clinically significant genotype–drug interactions were consistently reported for CYP2D6–codeine and CYP2C19–voriconazole/proton pump inhibitors, where poor or ultrarapid metabolizer phenotypes markedly altered exposure and toxicity risk. Evidence supports genotype-guided dosing and therapeutic drug monitoring for selected high-risk drugs. Conclusions: Pediatric drug clearance is governed by enzyme-specific maturation and functional polymorphisms. Integrating developmental dosing principles with targeted pharmacogenetic strategies may improve therapeutic precision and reduce avoidable toxicity in children.

INTRODUCTION

Cytochrome P450 (CYP450) enzymes play a central role in the metabolism of many medications prescribed in pediatric practice, including sedatives, opioids, antifungals, proton pump inhibitors, immunosuppressants, and antiseizure drugs. Pediatric pharmacotherapy presents unique challenges because drug exposure varies significantly across developmental stages, and the consequences of underdosing or overdosing may be more severe in neonates and infants [1, 2]. A major contributor to this variability is the dynamic change in hepatic metabolic capacity during growth and development, which limits the reliability of direct adult-to-child dose extrapolation [3]. A fundamental determinant of pediatric drug metabolism is ontogeny, defined as the age-

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dependent maturation of enzyme expression and catalytic activity. Importantly, CYP maturation is enzyme-specific and non-uniform, meaning that identical weight-based doses can result in markedly different drug exposures depending on the metabolic pathway involved [4, 5]. Among CYP isoforms, CYP3A4-mediated clearance is particularly sensitive to developmental changes and interacting clinical factors, increasing the likelihood of exposure variability and drug–drug interactions in early life [6, 7]. These observations underscore the need for developmentally tailored dosing strategies rather than simple proportional dose reductions from adult regimens. In addition to maturation, functional pharmacogenetic polymorphisms significantly influence drug exposure, therapeutic response, and toxicity risk, particularly when drug clearance or activation depends predominantly on a single CYP pathway [8, 9]. Clinically meaningful gene–drug interactions, such as CYP2D6 with certain opioids and CYP2C19 with antifungals and acid-suppressing agents, have demonstrated consistent clinical impact. Current evidence and practice guidelines support genotype-guided prescribing and early therapeutic drug monitoring (TDM) for selected high-risk medications to improve target attainment and reduce avoidable adverse effects [10, 11]. However, age and genotype alone do not fully explain variability in pediatric drug metabolism. CYP activity may also be influenced by inflammation, comorbid burden, organ dysfunction, and critical illness, further complicating exposure prediction in real-world clinical settings. Pharmacokinetic modeling studies have shown that dosing predictions are highly sensitive to assumptions regarding enzyme ontogeny functions, emphasizing the need for transparent and evidence-based translation of mechanistic data into clinical recommendations [12]. Additionally, neonatal pharmacokinetic investigations frequently demonstrate substantial inter-individual variability despite standardized dosing approaches, reinforcing the importance of individualized monitoring strategies in vulnerable populations [13]. From a regional perspective, implementation of pharmacogenetic strategies depends partly on allele prevalence and healthcare infrastructure capacity. Population-level pharmacogenomic data suggest clinically relevant frequencies of actionable CYP variants in South Asian populations, supporting the potential utility of targeted pharmacogenetic approaches for selected high-risk drug–gene pairs [14]. Furthermore, synergistic effects of age-dependent maturation and CYP genotype have been demonstrated in high-risk therapies such as transplantation, where dose requirements and target attainment are influenced by both developmental and genetic determinants [15].

Pediatric-specific CYP450 data are very limited, and the majority of the research done is on adults. The populations of South Asia, such as that of Pakistan, are not well represented, even though they have clinically significant genetic variants. There are no uniform age groups in the literature, and no implementation studies in the literature looking at the use of genotype-guided dosing in standard practice. The high degree of methodological heterogeneity does not allow meta-analysis and the synthesis of evidence. The dominance of retrospective and modeling research designs creates bias in selection and dependence on untested assumptions. Small sample sizes reduce statistical power and incomplete evaluation of confounding factors, such as inflammation and the interaction of drugs, which invalidate findings. This systematic review aims to synthesize contemporary evidence on CYP450 ontogeny and pharmacogenetic variability in pediatric populations and evaluate their clinical implications for pharmacokinetics, dosing optimization, drug–drug interactions, safety, and therapeutic outcomes across pediatric age groups.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [16]. The objective was to synthesize contemporary evidence (January 2020–March 2025) regarding cytochrome P450 (CYP450) enzyme ontogeny, pharmacokinetics, and pharmacogenetic variability in pediatric populations (neonates to adolescents). A structured literature search was performed in PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar using combinations of Medical Subject Headings and free-text terms including "CYP450," "cytochrome P450," "pediatric," "neonate," "ontogeny," "pharmacokinetics," and "pharmacogenetics." Only peer-reviewed English-language studies involving pediatric participants and reporting clinically relevant pharmacokinetic, pharmacogenetic, or ontogeny-related outcomes were included. Eligible designs comprised original clinical studies, observational cohorts, population or physiologically based pharmacokinetic (popPK/PBPK) modeling studies, real-world analyses, and systematic reviews. Adult-only studies, animal experiments without clinical correlation, case reports, editorials, and studies lacking methodological clarity were excluded. Two reviewers independently screened titles, abstracts, and full texts, with disagreements resolved by consensus. Data extraction was performed using a standardized template that captured the study design, age group, CYP isoforms evaluated, genotyping/phenotyping methods, drug substrates, pharmacokinetic outcomes, and reported adverse events. Risk of bias was assessed using the

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Newcastle–Ottawa Scale for observational studies and AMSTAR for systematic reviews; modeling and database analyses were appraised narratively due to methodological heterogeneity. Given substantial clinical and methodological heterogeneity across studies, quantitative meta-analysis was not feasible; therefore, findings were synthesized descriptively with emphasis on developmental maturation patterns, genotype–exposure relationships, and clinical dosing implications. Flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of studies for this systematic review. A total of 659 records were identified through database searching. After removal of 198 duplicate records, 461 records were screened by title and abstract, of which 402 were excluded. Fifty-nine full-text articles were sought for retrieval, 53 were assessed for eligibility, and 37 were excluded for predefined reasons. Finally, 16 studies were included in the qualitative synthesis (Figure 1).

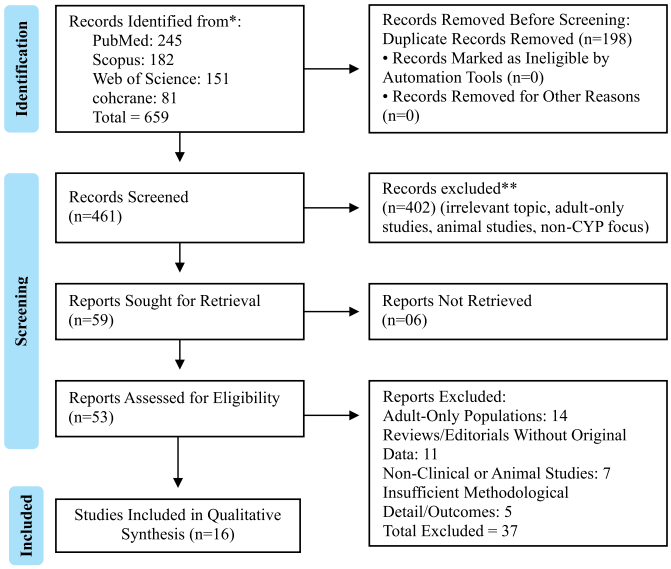

Figure 1: PRISMA 2020 for Study Selection

RESULTS

The included evidence (2020–2025) comprised 16 studies from Asia, Europe, North America, and Australia, with retrospective cohort/observational designs predominating, alongside PBPK/popPK modeling, real-world practice studies, and one systematic review. Across studies, the most frequently investigated isoforms were CYP2C19, CYP3A4, and CYP2D6, reflecting their common involvement in pediatric therapeutics and clinically actionable pharmacogenetic decisions (Table 1).

Table 1: Characteristics of Included Studies and Key Features

References	Region/Country	Design (Brief)	Pediatric Age Group	Main CYP(s)	Main Drug/Drug Class	Key Message
[17]	Europe (Poland)	Retrospective	2–17 y	CYP2C19	Voriconazole	CYP2C19 phenotype strongly affects exposure → TDM helpful
[18]	Asia (China)	Retrospective cohort	6–17 y (plus adults)	CYP2C19	Sertraline	Genotype + clinical factors influence concentrations
[19]	Asia (Japan)	Retrospective + PBPK	Neonates	CYP3A4	Fentanyl	Ontogeny is critical for neonatal exposure/AE prediction
[20]	Europe/Intl	popPK/PD/PGx model	Preterm neonates	CYP3A4	Fentanyl	Model-based dosing improves target attainment
[21]	Australia	Prospective feasibility	6–25 y	CYP3A4 /2C19/2D6	Probe drugs	Demonstrates phenoconversion impact in pediatrics
[22]	USA	Retrospective	Children/adolescents	CYP2C19/2D6	Oncology drugs	PGx testing informs exposure variability
[23]	USA	Ontogeny/tissue-based	Prenatal → adolescence	Multiple CYPs	Scaling factors	Provides pediatric physiology inputs for PBPK
[24]	Asia (China)	Retrospective	Preterm neonates	CYP1A2	Caffeine	Clearance low in preterm → prolonged half-life
[25]	Europe (Switzerland)	Real-world practice	Children	CYP2D6 /2C19/3A4	Mixed drugs	Practical PGx/phenotyping is feasible but heterogeneous
[26]	Europe (Netherlands)	Systematic review	Neonates/infants	CYP2D6 /2C9/2C18	Multiple	Pharmacogenetics clinically relevant early life
[27]	USA	Retrospective chart review	Children/adolescents	CYP2D6/2C19	Opioids/PPIs	PGx testing linked to prescribing decisions
[28]	Asia (Vietnam)	Clinical PGx study	Children	CYP2C19	PPIs (*H. pylori*)	CYP2C19 impacts response/ eradication outcomes
[29]	Europe (Netherlands)	Meeting report	All pediatric ages	Multiple CYPs	Mixed	Highlights PK prediction challenges
[30]	Europe (Switzerland)	Methodological review	Children	CYP1A2 /2D6/3A4	Probe drugs	Pediatric phenotyping approaches summarized

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[31]	USA	Database analysis	Neonate → adolescent	Multiple CYPs	Mixed	Ontogenic patterns reflected in ADE reports
[32]	Europe (Germany)	PopPK modeling	Pediatric extrapolation	CYP3A4	Midazolam	The model integrates induction /inhibition effects

Across pediatric age groups, CYP activity exhibits enzyme-specific maturation, leading to predictable shifts in drug clearance. CYP3A4 and CYP2C19 increase rapidly during infancy and early childhood, whereas CYP1A2 and CYP2D6 mature more slowly, contributing to prolonged half-life and reduced clearance in younger ages (Table 2).

Table 2: Ontogeny-Driven Change in Cytochrome P450 (CYP) Activity Across Pediatric Age Bands (Qualitative Synthesis of Included Studies)

CYP Isoform	Neonate (0–28d)	Infant (1–12mo)	Early Childhood (1–5y)	Late Childhood (6–11y)	Adolescence (12–18y)
CYP3A7	High (fetal)	Moderate (declining)	Low	Very low	Very low
CYP3A4	Low	Moderate	High	Adult-like	Adult-like
CYP2C19	Low	Moderate	High	Adult-like	Adult-like
CYP2D6	Low	Moderate	Moderate	High	Adult-like
CYP1A2	Very low	Low	Moderate	High	Adult-like
CYP3A5	Genotype-dependent	Genotype-dependent	Genotype-dependent	Genotype-dependent	Genotype-dependent

Legend: Very Low, Low, Moderate, High, Adult Like, Genotype Dependent

This heat-map matrix summarizes enzyme-specific developmental trajectories from neonatal to adolescent stages. CYP3A7 demonstrates high fetal/neonatal activity with rapid postnatal decline. CYP3A4 and CYP2C19 show rapid maturation during infancy and early childhood, approaching adult-like activity by early childhood. In contrast, CYP1A2 and CYP2D6 exhibit slower maturation, often reaching adult-like levels later in childhood or adolescence. CYP3A5 activity is primarily genotype-dependent rather than age-dependent. Categories (very low, low, moderate, high, adult-like) represent qualitative synthesis from included studies and are intended for visual comparison rather than exact quantitative enzyme activity. Drug exposure variability in children reflects the combined effect of enzyme maturation (age) and functional polymorphisms (genotype/phenotype). The most clinically significant genotype exposure differences were consistently observed for CYP2D6-opioid bioactivation and CYP2C19-PPI/voriconazole metabolism, supporting genotype-guided dosing and therapeutic drug monitoring (TDM) for selected high-risk therapies (Table 3).

Table 3: Clinically Actionable Drug–Gene Pairs in Children

Drugs	Key CYP	Pediatric Group	Key Polymorphism/ Phenotype	PK/Clinical Significance (Short)	Practical Implication	References
Codeine	CYP2D6	Children	PM vs UM	UM → ↑ morphine formation, toxicity risk; PM → poor analgesia	Avoid/contraindicate high- risk use; prefer alternatives	[25, 26]
Voriconazole	CYP2C19	Children/ Adolescents	PM/IM vs RM	PM/IM → higher troughs, hepatotoxicity/ neurotoxicity risk	Genotype-guided start + mandatory TDM	[16, 33]
PPIs (omeprazole/ esomeprazole)	CYP2C19	Children	LOF vs GOF Alleles	Large exposure differences affecting response/adverse effects	Dose adjustment by phenotype, where feasible	[27]
Tacrolimus	CYP3A5 (±3A4)	Pediatric Transplant	Expressers vs non-expressers	Expressers often need a higher dose to reach the target	Higher initial dose + TDM	[15]
Midazolam	CYP3A4	Neonates/Infants	Ontogeny-Dominant	Low clearance early life → prolonged sedation/resp. depression risk	Age-stratified dosing + interaction vigilance	[12, 31]
Caffeine	CYP1A2	Preterm Neonates	Ontogeny-Dominant	Very slow clearance → prolonged half-life	Monitor toxicity; dose spacing as needed	[13, 23]

Overall certainty of evidence was affected by the predominance of retrospective and modeling-based designs, which tend to increase susceptibility to selection bias, incomplete covariate capture, and assumption-dependent estimates. However, outcome measures were often objective (TDM levels, PK parameters, genotyping), reducing measurement bias. In general, most studies were rated moderate risk of bias, while structured clinical pharmacogenetic studies showed lower risk (Table 4).

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Table 4: Overall Risk of Bias Summary

References	Study Type	Main Bias Concern	Overall Risk	Tool
[17, 18]	Retrospective cohorts	Selection/covariates	Low–Moderate	NOS
[19, 20]	PBPK/popPK modeling	Assumption-dependent ontogeny + inputs	Moderate	NOS/Model appraisal
[21, 25]	Feasibility/real-world	Comparability + heterogeneity	Moderate	NOS
[23]	Tissue-based ontogeny	Generalizability	Low	NOS
[26]	Systematic review	Review process quality	Low	AMSTAR
[28]	Clinical PGx	Stronger design/standard methods	Low	NOS
[29, 31]	Report/database	Reporting + selection	Moderate	Narrative/NOS

DISCUSSION

Age-dependent ontogeny of CYP450 enzymes is a fundamental determinant of pediatric drug clearance. In early life, hepatic metabolic capacity is reduced due to immature enzyme expression, resulting in lower intrinsic clearance and prolonged half-life for many CYP substrates. As children grow, enzyme expression increases in an isoform-specific manner, producing predictable but non-uniform changes in systemic exposure. This maturation trajectory directly influences dosing requirements across neonatal, infant, and childhood populations and explains why simple weight-based extrapolation from adult dosing often leads to overexposure in neonates and underexposure in older children [4, 5]. CYP3A4, one of the most clinically relevant isoforms, demonstrates a rapid postnatal increase in activity. Neonatal clearance of CYP3A4 substrates such as midazolam and fentanyl is markedly reduced compared with later childhood, a finding consistently supported by physiologically based pharmacokinetic (PBPK) modeling and in vivo data [32, 33]. Modeling analyses confirm that predicted and observed midazolam clearance from birth to adolescence is highly sensitive to assumptions regarding CYP3A4 ontogeny curves [12]. These findings reinforce that neonatal and early infancy dosing must account for immature CYP3A4 activity to avoid respiratory depression and drug accumulation. Similar ontogeny-dependent variability has been demonstrated for fentanyl in preterm infants, where developmental physiology significantly alters exposure–response relationships [19, 20]. CYP2C19 maturation also has major clinical implications, particularly for antifungals and proton pump inhibitors. Pediatric voriconazole studies demonstrate that CYP2C19 poor metabolizers exhibit significantly higher trough concentrations and increased risk of hepatotoxicity and neurotoxicity, necessitating genotype-guided dosing and early therapeutic drug monitoring (TDM) [17, 34]. In contrast, rapid metabolizers may require higher starting doses to achieve target concentrations. These findings highlight how ontogeny and genotype interact: in younger children, incomplete maturation may amplify genotype effects, whereas in older children, genotype may become the dominant determinant of exposure variability. CYP2D6 presents a different pattern, characterized by gradual maturation through early childhood combined with strong genetic influence. For prodrugs such as codeine, ultrarapid metabolizers convert codeine to morphine more efficiently, increasing toxicity risk, while poor metabolizers experience inadequate analgesia. International pharmacogenetic guidelines, therefore, recommend avoiding codeine in high-risk phenotypes [35]. The clinical relevance of CYP2D6 polymorphisms becomes increasingly pronounced as metabolic capacity matures, demonstrating the shifting balance between developmental and genetic determinants of clearance across age groups. Slower-maturing enzymes such as CYP1A2 further illustrate ontogeny-dependent clearance. In preterm neonates, caffeine elimination half-life may extend to 80–100 hours due to immature CYP1A2 activity [13, 24]. Population pharmacokinetic studies confirm substantial inter-individual variability despite standardized dosing, supporting model-informed dose adjustments and close monitoring in vulnerable populations [13]. These examples collectively demonstrate that enzyme maturation is not uniform across isoforms and that clearance trajectories differ substantially by pathway. Beyond ontogeny and genotype, drug clearance in children is influenced by inflammation, comedication, organ dysfunction, and "phenoconversion," whereby environmental or disease-related factors temporarily alter CYP activity [21, 25]. Modeling studies suggest that assumptions regarding ontogeny functions significantly influence dose predictions, underscoring the need for transparent integration of mechanistic data into clinical dosing frameworks [12]. Real-world studies further show that drug–drug interactions are particularly impactful in early life, when metabolic reserve is limited. Regional considerations are also relevant. Pharmacogenomic data from South Asian populations demonstrate clinically meaningful frequencies of actionable CYP variants, suggesting that genotype-guided strategies may have practical relevance beyond Western cohorts [14]. In pediatric transplantation, for example, CYP3A5 genotype combined with age significantly influences tacrolimus dose requirements and time to target concentration [15].

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These findings support the concept that both developmental stage and population genetics must be considered in individualized dosing strategies. Taken together, the literature consistently supports a dual framework in which pediatric drug clearance is governed by enzyme-specific maturation and functional polymorphisms. In neonates and infants, ontogeny predominates; in older children, genotype becomes increasingly influential. This developmental transition explains much of the observed variability in exposure, efficacy, and toxicity across pediatric age groups.

This review is limited by substantial heterogeneity in study design, age stratification, endpoints, and reporting quality, which precluded quantitative meta-analysis. The predominance of retrospective and modeling-based studies introduces potential selection bias and reliance on ontogeny assumptions. In addition, inconsistent reporting of genotype frequencies and sample sizes limits cross-study comparability. Future research should prioritize prospective multicenter pediatric cohorts with standardized age bands, uniform genotype definitions, and clinically meaningful endpoints such as target attainment and toxicity. Implementation studies evaluating the cost-effectiveness and feasibility of integrating genotype-guided dosing with therapeutic drug monitoring in routine pediatric practice are also warranted.

CONCLUSIONS

Pediatric CYP450-mediated drug clearance is governed by enzyme-specific ontogeny combined with functional genetic polymorphisms. Age-dependent maturation strongly influences clearance in neonates and infants, whereas genotype becomes increasingly important in older children. Integrating developmental dosing principles, therapeutic drug monitoring, and targeted pharmacogenetic guidance, particularly for opioids, azole antifungals, calcineurin inhibitors, and antiseizure medications, has the potential to reduce preventable toxicity and improve therapeutic precision in pediatric populations.

Authors' Contribution

Conceptualization: RK
Methodology: MNK, FAS
Formal analysis: RK
Writing and Drafting: RK, ZS, MNK, FH, FAS, NF
Review and Editing: RK, ZS, MNK, FH, FAS, NF

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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