Alsayed AR , Abed A, Al Shawabkeh MJ, Aldarawish RR, Al-Shajlawi M, Alabbas N. Human Rhinovirus: Molecular and Clinical Overview. Pharmacy Practice 2024 Jan-Mar;22(1):2925.

https://doi.org/10.18549/PharmPract.2024.1.2925

Review

Human Rhinovirus: Molecular and Clinical Overview

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Received (first version): 09-Jul-2023 Accepted: 07-Aug-2023 Published online: 06-Feb-2024

Abstract

Human rhinoviruses (HRVs) are associated with a wide spectrum of clinical manifestations, ranging from mild cold symptoms to more severe respiratory illnesses, significantly burdening global healthcare systems. At the molecular level, HRVs belong to the Picornaviridae family and are classified into three species: HRV-A, HRV-B, and HRV-C. Advances in genomic sequencing and phylogenetic analysis have revealed a remarkable genetic diversity within HRV species, with over 160 serotypes identified. This genetic variability contributes to the ability of HRVs to evade host immune responses and facilitates their continuous circulation in the population. This review provides an overview of the molecular and clinical aspects of HRV infections.

Keywords: respiratory viruses; rhinovirus; genome; picornaviridae

INTRODUCTION

Human rhinoviruses (HRVs) belong to the family "Picornaviridae", genus "Enterovirus" (EV). HRV is a group of genetically diverse non-enveloped, positive-sense ribonucleic acid (RNA) viruses that can be classified into three serotypes: HRV-A, HRV-B, and HRV-C.[1] Over 160 rhinovirus types have been identified, including 99 classic HRV-A and HRV-B types,[2] in addition to 6, 5, and 51 novel genotypes, for HRV-A, HRV-B, and HRV-C, respectively.

HRV has been identified as a potential causative agent for various respiratory ailments, including pneumonia, asthma attack, exacerbations of chronic obstructive pulmonary disease (COPD), as well as both severe lower respiratory tract illnesses and milder upper respiratory tract disorders like the common cold.[3-5]

Serological procedures were the standard for HRV and EV isolate typing for many years. Serological typing involves cell culture virus isolation, neutralization using intersecting pools of type-specific antisera, and confirmation with a single antiserum. This method took 1-2 weeks and was challenging. In cell culture, HRV requires specific cell lines and growth conditions. Typing in HRV and EV was infrequent.

PCR-based screening methods provide a more convenient and impartial alternative than other methods [6]. As PCR is a universal method in many laboratories, given the abundance of nucleotide sequence data available in online sources, a categorization technique depending on sequence data was optimal [4]. Such a system was established in 1999 for EV.[7]

Employing molecular methods to test the clinical samples is the key way to guarantee the accuracy of the HRV diagnosis. The structural genes or the 5' untranslated region (5'UTR), and in certain instances, a combination of the two, are frequently the specific targets for HRV reverse-transcription (RT) PCR assays. The assay's types categorized by the greatest level of sensitivity are those for which the primers anneal to the highly-conserved motif regions within the 5' UTR. Because of their sensitivity, they can aid in the identification of previously unknown HRV variants[8-11] and prototypic strains.[12-14] It is worth noting that sequence motifs of this nature serve as the primary objective for the majority of primers and probes that have been published. However, it is crucial to acknowledge that each of these methods represents a unique positioning, duration, and assay format. The standard, quantitative, nested, and one-step PCR techniques are employed in this regard.[15]

Utilizing the 5' UTR of the HRV gene for genotyping purposes exhibits several limitations. One illustrative example pertains to the association observed between the 5' UTR and the non-specific amplification of the RNA large regulator known as non-coding RNA B2, or the sequences found in the human genomic DNA chromosome 6. Both of these entities result in the production of a non-specific product with a length of 424 base pairs, which is comparable in size to the virus-specific amplicon measuring 390 base pairs.[11, 16, 17] Non-specific results of this nature are anticipated in clinical samples exhibiting elevated levels of human RNA or in cases where clinical samples have

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https://doi.org/10.18549/PharmPract.2024.1.2925

been contaminated with genomic DNA. The genetic similarity of the 5' UTR sequences for HRV-A and C is attributed to the proposed recombination events between species.[18, 19]

Moreover, the structural genes are unsuitable for universal diagnostic primer usage due to significant sequence variations. However, applying phylogenetic analysis to the capsid-coding regions determining the three HRV species can be distinctly differentiated. The observed variations between these species allow for their effective discrimination.[15, 20-23]

To classify EV by sequence data, the putative molecular determinants of genotype had to be considered. Studies of viral-capsid protein (VP) 1 sequence divergence suggested a 25% nucleotide and 12% amino acid divergence threshold to identify EV types [7]. The aforementioned thresholds are commonly employed in practice, and a substantial number of novel EV types have been categorized utilizing this criterio.[24-28] Because some EV have shown recombination within the capsid region,[29, 30] solitary VP1 is recommended for EV typing. Previous research that used VP2 sequences to categorize EV[31, 32] have been failed.

Molecular categorization of EV isolates has superseded neutralization assays in standard practice. Those methodologies consistently demonstrate superior performance compared to serotyping in terms of accuracy, speed, and the ability to classify novel types.[33]

Classification of the Picornaviridae

The nomenclature of these viruses is based on their diminutive size, as indicated by the prefix "pico," meaning small. They are characterized by their lack of segmentation and possessing a single-stranded RNA genome with positive polarity.[34] Various genera can be found within their family, including HRV, EV, aphthovirus, and cardiovirus. It is worth noting that the latter two genera exclusively impact animals. The dimensions of these entities range from 20 to 30 nanometers. They are classified as naked viruses characterized by their icosahedral capsids.[35, 36] These viruses resist acidic pH conditions enabling them to initiate replication in the oropharynx and successfully traverse the stomach for colonization in the lower digestive tract. EVs undergo reproduction at 37 degrees Celsius, while HRVs replicate at a slightly lower temperature of 33 degrees Celsius.

Picornaviruses belong to the order Picornavirales and are one of the five families of viruses within this order.[37] The order encompasses a heterogeneous assortment of viruses characterized by a single-stranded positive-sense RNA genome. These viruses are classified based on their shared capsid structure and life cycles of the virus. Picornavirales exhibit a broad spectrum of host specificity, encompassing various organisms. Regarding the viral capsid structure, it is observed that these various viruses exhibit a non-enveloped capsid composition comprising 60 protomers. Each protomer is characterized by three distinct domains commonly called "jelly-ron" domains.[38]

The determination of members belonging to the same genus within the Picornaviridae family is based on several criteria. These include the presence of homology among specific polypeptides, structural similarity of the internal ribosomal entry site (IRES) at the RNA level, and a minimum amino acid identity of 40% in the P1 and P2 coding regions, as well as 50% in the P3 coding region.[37]

Classification of HRV based on biological and serological properties

After the isolation of HRV-A1 around 67 years ago,[39, 40] the HRV classification has undertaken several revisions. The categorization of HRV, which relied on characteristics observed in cell cultures conducted in a controlled laboratory setting, has been discontinued and is presently regarded as a subject of historical significance exclusively.

During the 1960s, many HRV isolates with distinct antigenic properties were discovered, necessitating the development of a classification system for these isolates. From 1967 to 1987, a comprehensive collection of HRV isolates was obtained and subjected to serological neutralization assays in order to ascertain their antigenic relationships [2, 41]. The collaborative program was successfully executed in three distinct phases, leading to establishing a comprehensive classification system encompassing 100 HRV serotypes, each assigned a unique sequential number. Given that the recognition of distinct species of HRV was absent during the mentioned period, the sequential numbering system continues to be present across both HRV species, which are currently identified as HRV-A and HRV-B. It has become customary to categorize HRV types by incorporating their species designation, such as HRV-A12 and HRV-B3. The classification of serotypes was initially established by considering their distinct antigenic properties and the absence of substantial cross-reactivity with established HRV serotypes.[41] Nevertheless, subsequent research has revealed several pairs of HRV serotypes that display reciprocal cross-reactivity, such as HRV-1A/1B, 2/49, and 8/95. Additionally, a larger number of serotype pairs have been identified that exhibit non-reciprocal cross-neutralisation.[21, 42, 43] By 1987, the classification of HRV into 100 serotypes had been established based on their neutralization properties.[44]

For a considerable period, serological techniques served as the conventional method for characterizing HRV and EV isolates. The process of serological typing encompasses several steps, including the isolation of the virus in cell culture, the neutralization of the virus using intersecting pools of type-specific antisera, and the subsequent confirmation of the virus type using a single antiserum. This method took 1-2 weeks and was challenging. In cell culture, HRV require specific cell lines and growth conditions. Typing in HRV and EV was infrequent.[45]

The screening process commonly employed for EV and HRV using cell culture relied on the subjective assessment of the cytopathic effect through visual inspection. This method posed limitations, especially when applied on a large scale. Serological-based techniques also exhibit subjectivity, even when performed by experienced individuals. According to a survey conducted across twelve laboratories, it was found that

none of the labs accurately reported the expected serotyping results for all ten EV samples included in the study. The overall rate of accurate reporting was approximately 60%.[46]

While HRV classification methods utilizing observable biological characteristics have proven valuable in HRV studies, they necessitate laborious and time-intensive laboratory processes. However, the utilization of phylogenetic techniques relying on easily accessible sequence data has enabled quicker and simpler identification of HRV.

Classification of HRV based on phylogenetic relationships

The recognition that the 100 recognized HRV serotypes were divided into two species (A and B) was attained by phylogenetic analysis. These two apparent species are present throughout the capsid coding region,[15, 22, 47, 48] the 5' UTR,[9] and the 3Dpol region at the 3' end of the coding genome.[48] The confirmation of these two species groupings was further substantiated in 2009 with the conclusion of full genome sequences for all 100 HRV-A and -B strains.[49]

The capsid comprises 60 protomers, each containing a single instance of the four capsid proteins VP4 to VP1. Parechoviruses, in contrast to the majority of viruses, exhibit a distinctive characteristic whereby they possess solely 3 capsid proteins. Specifically, VP2 and VP4 remain in their uncleaved precursor state known as VP0.[50] The external capsid proteins, VP1 to VP3, form an 8-stranded antiparallel beta-barrel "jelly roll" domain, a common feature to other members of the order Picornavirales.[38] The VP4 protein is situated in the intracellular region of the capsid. The arrangement consists of 12 pentamers, each composed of five protomers. These pentamers collectively form a rigid pseudo-spherical structure exhibiting icosahedral symmetry. The present configuration achieves a harmonious equilibrium between the essential attributes of stability and durability necessary for transmission and the requisite characteristics of flexibility required for cell surface binding and virion disassembly. Many studies have indicated that the picornavirus capsid exhibits dynamic characteristics, potentially undergoing a transient exposure of internal proteins, including VP4 and the N-terminus of VP1, through a process resembling "breathing".[51, 52] The release of the RNA genome holds significant importance. The phenomenon of capsid breathing has substantial implications in the field of antiviral therapies. Antibodies that target internal regions of the capsid have been found to neutralize the infectivity of PV-1 effectively. Moreover, these antibodies have the potential to confer cross-serotype neutralization in HRV, as the protein responsible for capsid breathing is highly conserved across different serotypes.[51, 53]

The virion exhibits three axes of symmetry: 5, 3, and a 2-fold axis. The formation of depression, commonly called the "canyon," occurs in most picornaviruses near the five-fold axis of symmetry. This structural feature is attributed to the beta barrels of the VP1 protein. The canyon serves as the binding site for major HRV groups, excluding the minor groups.[54, 55] It has been observed that apthoviruses exhibit an absence of the canyon site.

In contrast, the receptor establishes a binding interaction with a malleable loop that extends outward from the virion's surface.[56] Within the context of EV, a hydrophobic pocket region is situated directly beneath the canyon floor, housing a distinct entity referred to as a "pocket factor".[57, 58] The aforementioned region serves as a target for a range of antiviral drugs. It has been demonstrated that effective binding to this region can impede the uncoating process of the RNA genome and its subsequent transfer into the host cell.[59]

Genome organization and proteolytic processing

The genetic material of all picornaviruses is composed of non-segmented, positive-sense, single-stranded RNA molecules with a length ranging from approximately 7 to 9 kilobases (kB). The genome consists of a solitary coding region bordered by 5' and 3' UTRs of varying lengths. Furthermore, it is worth noting that the length of the 3' polyA tail varies considerably across different genera. Moreover, previous studies have demonstrated that this tail is essential for the infectivity of the virus.[60, 61] The VPg, also known as viral protein genome-linked, is a diminutive protein that forms a covalent bond with the 5' terminus of the genome. Its primary function is to serve as a primer during the replication process of the genome. The VPg is encoded by the 3B genome region, which is known for its brevity and high degree of conservation.

The genome of the picornavirus is composed of a solitary open reading frame that is subsequently translated into a singular polyprotein. Nevertheless, the polyprotein undergoes co-translational cleavage, thereby preventing its detection within the cellular environment.[61] In contrast to mammalian RNA, the RNA of picornaviruses does not possess a methylated 5' cap structure. Instead, the initiation of translation at the ribosome is facilitated by the internal ribosome entry site (IRES) located within the 5' UTR. The polyprotein undergoes translation and subsequent cleavage, forming distinct regions called P1, P2, and P3, encompassing the capsid and non-structural components [62]. The mentioned regions are responsible for encoding a total of four structural proteins and seven non-structural proteins. These proteins undergo cleavage by proteinases encoded by the virus, occurring in a series of proteolytic processing events. Nevertheless, significant distinctions are observed in proteolytic processing events among other genera of picornaviruses.[62]

The requirement for genotypic classification of HRV

Due to their genetic diversity and diverse clinical presentations, treating all HRV types as one biological and clinical entity is no longer feasible or permissible. There are no solid links between HRV types and specific diseases. As the spectrum of serious clinical illnesses attributed to HRV infection becomes more fully understood, it will likely be necessary to routinely screen for HRV in diagnostic settings and initiate large-scale epidemiological studies to determine circulation patterns and strain associations. Implementing a straightforward and pragmatic classification system for HRV - similar to the existing system for EV [63] - would facilitate the study of potential outbreaks and hospital-acquired transmission. Additionally, such a system would enable the examination of type-specific biological characteristics, such as identifying particular types

that may exhibit increased virulence.[15]

The comprehension of genetic variations in viruses, specifically HRV, is of utmost importance in devising efficacious antiviral or vaccine strategies, owing to the substantial genetic diversity exhibited by these pathogens.[64]

The clinical role of HRV

HRV is widely recognized as a primary etiological factor contributing to the occurrence of the common cold. While HRVs are commonly linked to a mild and self-limiting infection of the upper respiratory tract, they have also been recognized as a significant factor in the development of various severe clinical conditions.[3, 15, 65, 66] The association between childhood wheezing caused by HRV infections and the subsequent development of asthma has been extensively studied and established.[4, 67, 68] Moreover, the prevalence of the common cold imposes a significant economic and social burden on affected communities, resulting in diminished productivity, expenditures on over-the-counter treatments, and the unnecessary prescription of antibiotics.[69, 70]

Over the past decade, there has been a notable expansion in the field of HRV research, leading to the identification of a previously unknown species, numerous novel variations, and an escalating correlation with increasingly severe medical conditions. As the extent of the clinical implications of HRV becomes apparent, there is a growing recognition of the need to comprehend the evolutionary mechanisms that have contributed to the vast array of these viruses and to establish formal guidelines for their categorization.

HRV infections may be asymptomatic, but they can also lead to several clinical outcomes, including common colds and severe lower respiratory conditions, for example, bronchiolitis, pneumonia, as well as exacerbating asthma and COPD.[3-5, 71-76] According to the results obtained from studies using PCR and real-time PCR, viral infections are highly prevalent during COPD exacerbations (22–64%).[77-83]

HRV and other respiratory viruses attack the airway epithelium and cause an inflammatory response that can lead to wheezing.[84-87] The virus-induced immune response may modulate host responses to different microorganisms,[88, 89] allergens, stress, and pollution, leading to wheezing and asthma exacerbations in vulnerable individuals.[4] While asthmatic patients are not more susceptible to viral infections than healthy controls, they experience a longer duration of symptoms and a more severe viral-induced respiratory illness.[90] In patients with asthma, host factors are likely to have a role in the increased immune response to viral infections. Influenza and respiratory syncytial virus (RSV) produce cytopathic damage to the airway epithelium, boost inflammatory cytokine and chemokine production, and increase allergen, microbial, and irritant exposure antigen-presenting cells. The release of epithelial mediators such as thymic stromal lymphopoietin (TSLP), interleukin (IL) 25, and IL-33 may also be induced by viral infections. In turn, epithelial cell production of IL-25, IL-33, and TSLP may enhance eosinophilia and stimulate T helper cell type 2 (Th2) responses, advancing the release of allergy cytokines such as IL-4, IL-5, and IL-13, which are known to induce asthma.[91-93]

Innate and adaptive antiviral immune responses are triggered by respiratory viral infection and replication, resulting in the generation of proinflammatory cytokines and chemokines and the recruitment of inflammatory cells to the airway. Many viruses can cause wheezing and asthma exacerbations in asthma patients, including human HRV, RSV, influenza, coronavirus, human metapneumovirus (hMPV), parainfluenza, adenovirus, and bocavirus. Wheezing caused by RSV and HRV infection in infants and young children may trigger an inflammatory response in a susceptible host, influencing the later development of asthma.[4, 84, 85, 87, 94-98]

The combination of viruses and bacteria has been related to increased wheezing and asthma symptoms.[99, 100] In children with and without asthma, HRV infection has been found to affect the airway microbiome, with improved detection of *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenza*.[101, 102]

Infections of the respiratory tract with RSV and HRV are associated with the development of asthma in later childhood and early adulthood.[4, 84, 86, 87, 94, 95, 103-107] In a predisposed host, factors such as the time of birth and subsequent exposure to peak bronchiolitis and viral season for RSV and HRV may influence the future development of asthma.[108, 109] However, it is unknown whether specific viral respiratory infections cause asthma or whether wheezing associated with these viruses is a risk factor for developing asthma.[110]

It's uncertain if RSV infections in childhood have a causal effect on the development of asthma later in life. According to observational studies, RSV infections early in life are linked to an increased risk of developing asthma.[94, 95, 111-113] Children who acquire asthma following RSV infection or with chronic asthma symptoms also have asthma risk factors such as maternal history of asthma and increased IgE levels.[114-121]

Asthma development may be influenced by wheezing in the presence of HRV infection.[84, 104] Infants who wheeze due to HRV infection had a higher risk of recurrent wheezing and asthma at three, five, and six years of age.[86, 96] Wheezing with HRV infection within the first three years of life was a substantially higher risk factor for asthma at six years of age than wheezing with RSV infection or the presence of aeroallergen sensitization, according to findings from the Childhood Origins of Asthma Study (COAST).[84]

HRV, unlike RSV and other respiratory viruses, has limited cytopathic effects on airway epithelium or other tissues. Still, it does cause a significant airway inflammatory, immunological response, which may restrict the antiviral interferon (IFN) response in patients during HRV infections.

Several studies have found that HRV interacts with host factors to influence the development of asthma in children, particularly atopic children. Reports suggest that allergic sensitization in the first year of life is the first event that interacts with viral infections, particularly HRV, to promote the development of

asthma in children.[84, 85, 96, 104, 122, 123]

Asthma exacerbations typically manifest in response to various factors, including upper respiratory tract viral infections, pollen, pollutants (specifically tobacco), and limited adherence to controller medication.[76, 124, 125] In the context of asthma exacerbations, it has been observed that infections play a significant role, accounting for over two-thirds of such exacerbations in children and over half in adults. In addition to HRV, several other viruses have been linked to the development of acute asthma. These include RSV, enterovirus, influenza A and B, parainfluenza, adenovirus, and coronavirus. Research has shown that viral infections are responsible for approximately 50-80% of asthma exacerbations, with HRV being detected in about 50-80% of affected patients.[126]

A prospective study by Dinwiddie et al. (2022) observed that individuals with uncontrolled asthma who had viral infections experienced more acute symptoms during exacerbations, particularly among those with allergies. The data suggest a potential correlation between viral infection and allergy in individuals with uncontrolled asthma, as it pertains to acute asthma symptoms and the assessment of biomarkers during an asthma exacerbation.[127]

Although viral infections frequently trigger asthma exacerbations, the current approaches for preventing and treating viral-induced asthma lack complete efficacy. Exacerbations are common within the range of severe asthma and substantially burden healthcare systems and individuals affected by the condition.[128]

In preventing and treating viral-induced asthma exacerbations, notable medications include inhaled corticosteroids (ICS) and the latest iteration of anti-type 2 biologicals.

ICS, a key asthma treatment, reduces the likelihood of future asthma exacerbations induced by the virus, as can long-acting β-2 agonists.[124] The Cochrane Database review suggests that increasing oral steroid dosage in adults and children with mild to severe asthma in the presence of the first clinical symptoms of an exacerbation is unlikely.[129] Eosinophilic inflammatory asthma responds well to steroids whereas non-eosinophilic inflammation responds mildly.[130]

The anti-type 2 newer biologicals have demonstrated remarkable effectiveness in mitigating the frequency of acute asthma exacerbations. In addition, they can potentially enhance the antiviral response and thus exhibit efficacy in the context of viral infections.[128] The mechanisms of action of these newly developed biological medications target various essential aspects of bronchial inflammation by inhibiting different cytokines and/or their specific receptors. As a result, these medications effectively manage symptoms and decrease the reliance on systemic steroids. Several examples of biologicals can be found in the field of medicine. These include Omalizumab, which specifically targets IgE. Mepolizumab and Reslizumab both target IL-5, Benralizumab, which targets the interleukin 5 alpha receptor, and Dupilumab, which targets both IL-4 and IL-13. Furthermore, there have been recent introductions of new medications to this category, such as Itepekimab, which specifically targets IL-33, Tezepelumab, a monoclonal antibody that inhibits thymic stromal lymphopoietin, and Astegolimab, an agent that acts as an anti-TSLP (thymic stromal lymphopoietin) 2.[131]

Furthermore, research into whether palivizumab, a monoclonal antibody directed against RSV antigen, can prevent the onset of recurrent wheeze has shown conflicting results.[113, 132, 133] RSV prophylaxis reduced the incidence of recurrent wheezing in children without a family history of atopy but had no effect in children from atopic families, according to findings from a prospective cohort analysis of preterm infants, 146 treated with palivizumab and 171 untreated.[113] Treatment of healthy preterm newborns with palivizumab to prevent severe RSV infection was related to a lower rate of recurrent wheezing in a randomized study of 429 high-risk infants.[132]

Numerous studies suggest that plasmacytoid airway mucosa dendritic cells are the antigen-presenting cells that mediate the synergistic inflammation caused by atopy and viral infections.[134-136] Upregulation and cross-linking of the Fc epsilon receptor on lung dendritic cells, which binds IgE, has been shown to enhance Th2 inflammation and modify type I and type III IFN antiviral responses.[134-136] In clinical trials, Omalizumab has been shown to increase IFN-alpha production by HRV-stimulated peripheral blood mononuclear cells, associated with fewer asthma exacerbations.[137]

The PROSE (Preventative Omalizumab or Step-up Therapy for Severe 429 Fall Exacerbations) study examined 478 children (6-17 years old) with allergic asthma. Omalizumab treatment reduced HRV infections and HRV-induced diseases during asthma exacerbations. IgE blocking reduces HRV infection susceptibility in asthma exacerbations [138]. A double placebo-controlled, multicentric clinical trial was done among inner-city asthmatic children aged 6-17 having one or more recent exacerbations in the fall due to viral infections. This study found that a 4–6-week pre-seasonal Omalizumab treatment reduced exacerbation rates and enhanced HRV INF-α response.[139]

A 2020 meta-analysis of randomized controlled trial studies on children and teenagers with asthma found that Omalizumab reduces asthma exacerbations on a 30-week + treatment program with low adverse effects.[140]

CONCLUSION

Given the genetic variability and diverse clinical manifestations observed, considering all types of HRV as a single biological and clinical entity is no longer feasible or appropriate. There is no strong association between any specific type of HRV and a particular disease. Nevertheless, as understanding the extensive spectrum of severe clinical diseases linked to HRV infection deepens, it is anticipated that regular screening for HRV in diagnostic settings and the initiation of comprehensive epidemiological investigations will be imperative to reveal circulation patterns and establish associations with specific strains. The implementation of a straightforward and pragmatic classification system for HRV, akin to the existing system

employed for EV, would facilitate the examination of potential outbreaks, nosocomial transmission, and the identification of type-specific biological characteristics, including the detection of types exhibiting potentially heightened virulence.

FUNDING

Authors received no specific funding for this work.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

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