

Monkeypox Viruses: Resurgence of Global Threat to Mankind

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Abstract

The unprecedented outbreaks of monkeypox viruses in non-endemic regions have created grave concern for global health. The World Health Organization has declared a public health emergency of international concern and stated the seriousness of monkeypox viruses. The gravity of this zoonotic disease cannot be underestimated, owing to the fact that this viral infection can cause pathetic situations if ignored. Keeping these lacunas, the scientific communities have expressed their interest towards the study of monkeypox viruses. Hence the present review discusses the etiological features, historical events, and vaccination along with management strategies to combat and counter the sudden outbreak. The review also highlights the current Indian scenario of the monkeypox virus; with scanty reports available, the present contributes towards the growing scientific knowledge to prevent a future threats to mankind.

Keywords: Monkeypox Virus, Vaccination, Symptoms, Global Threat

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INTRODUCTION

Monkeypox viruses have been one of the top priorities across the globe in recent times.^{1,2} The scientific community has been conducting research on human-virus interactions in response to the recent pandemic outbreak of a new strain of Coronavirus, which has claimed the lives of many people from various regions.³ There is a serious concern about managing the conflict with invisible microorganisms. Monkeypox virus is a zoonotic disease that causes symptoms in animals similar to smallpox infection.^{4,5} Perusal of scientific literature has documented the role of biomagnification of the host among the viruses, and each host is contributing more and more virulent factors, making it one of the deadliest interactions between humans and viruses.⁶ Moving on to the historical aspects of the monkeypox viruses, they were first isolated from monkeys in 1958, which were reported to be incidental hosts, whereas rodents were the prime hosts and were transmitted during the practice of trading.⁷ The first reports of the monkeypox virus

infecting humans were reported in 1970 among the inhabitants of Africa. The cases increased over the years, with approximately 37 cases reported between 1981 and 1986.⁸⁻¹⁰ The rapid expansion of monkeypox was reported during 1996–1997 in the Democratic Republic of the Congo, with 71 new cases reported from different villages in Zaire.¹¹⁻¹³

Scientific research was being conducted to confirm its genetic distribution in terms of virulence, which was later studied with smallpox.¹⁴ The monkeypox viruses belong to the genus Orthopox in the family Poxviridae. The monkeypox virus was reported to replicate within the cytoplasm of the host cell.¹⁵⁻¹⁷ The morphological characteristics of the pox virus were illustrated with electron microscopy, which depicted oval or brick-sized entities with sizes ranging between 200 and 300 nm.^{18,19} The core contains transcribing factors along with DNA and enzymes required for multiplication.^{20,21} This core is packed within the outer member, acting as a protective shield. The genetic studies revealed that the genome is double-stranded, linear DNA with 197kb which is covalently connected at both ends by palindromic

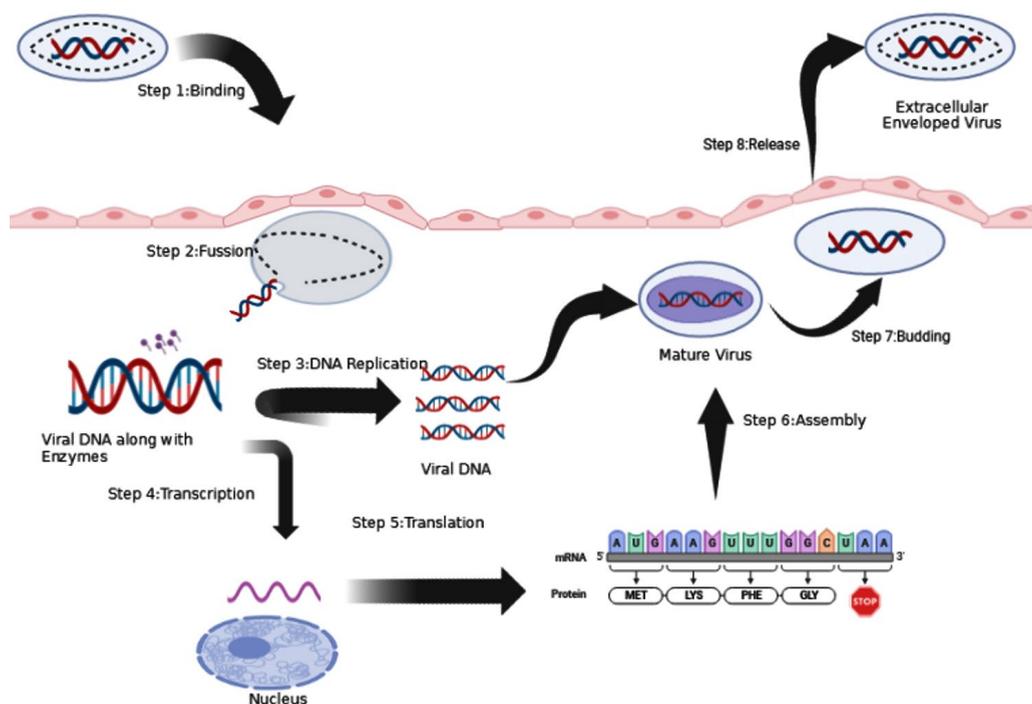


Figure 1. Life cycle of monkeypox and its mechanics within human cells

hairpins.²²⁻²⁴ The genetic material encodes for the proteins responsible for transcription, DNA replication, virion assembly, etc., the highly conserved genes encode for virus-host interaction. The monkeypox viruses have a wide range of hosts, and most of these hosts act as carriers of the virus.²⁵⁻²⁷ The incubation period varies depending on the degree of virulence and type of host, and it may last for 7 to 14 days; in severe cases, it may prolong to 21 days.²⁸

The symptoms vary depending on the host, but fever is a common symptom among all infected people. Other symptoms of infection include rashes and skin lesions all over the body, as well as head and muscle aches, contacting contaminated items, respiratory secretions, lymphadenopathy, skin lesions, genital rashes, pneumonitis, encephalitis, and keratitis.^{29,30} The diagnosis of the monkeypox viruses is achieved with testing of lesions and fluids using polymerase chain reaction. The mode of transmission of the virus is through direct contact with the infected host.³¹ It can easily spread through infected open wounds, sneezing, and the transfusion of infectious body fluids.³² The encounter of an infected animal with healthy humans can lead to infection in different ways, such as through biting, scratching, and the consumption of undercooked

meat from infected animals, etc.³³ The virus can carry itself apart from the host, wherein the infected individual's sneezing results in the release of viral particles, which form droplets, and when these droplets reach a healthy host, they result in indirect transmission.^{34,35} Hence, in order to combat such situations, the infected individual needs to quarantine himself from the healthy surroundings, which can prevent the infection.³⁶ The life cycle of the monkeypox virus and its mode of infection is illustrated in Figure 1.³⁷ Notably, the monkeypox virus completes its entire life cycle within the cytoplasm due to the presence of essential enzymes and factors for DNA replication and protein synthesis. This minimises the intranuclear stage of viral processing. Later, the process of cell lysis releases the viruses to the surrounding environment via different means, as discussed previously.³⁸ The classification of monkeypox virus falls under the family Poxviridae, which contains four genera including the human-infecting species known as poxviruses. Other orthopoxviruses, including mousepox and rabbitpox, aren't considered to cause human diseases, but they're used as an opportunistic infections in animal models that closely simulate human illnesses caused by other orthopoxviruses like smallpox (variola), as shown in Figure 2.³⁹⁻⁴¹

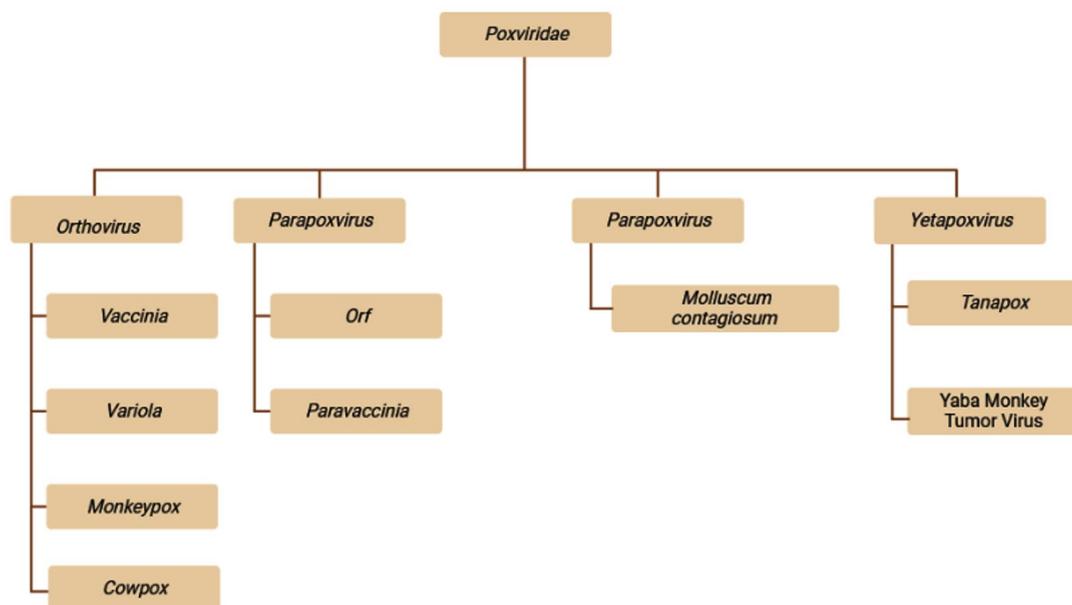


Figure 2. Classification of Monkeypox virus under Poxviridae family

Monkeypox viruses and its global impact

The present review focuses on the key scientific reports that support the severity of monkeypox infection. Monkeypox virus management research has recently accelerated. According to the recent study conducted by Mucker et al.⁴² the outbreaks of monkeypox at the global level have had a serious impact. In this study, enriched inoculums were prepared to inject macaques as hosts and were administered intravenously. The findings revealed that disease caused by enriched inoculums differed from disease caused by an unpurified preparation. The study also marked the importance of inherent factors within the serum influencing the stability of monkeypox extracellular virions. Alshaharani et al. conducted a study to assess medical students' knowledge of monkeypox viruses at King Khalid University in Abha, Saudi Arabia. The self-administered questionnaire was distributed, and statistical data was generated. The findings revealed that 72% of 314 medical professionals had little knowledge of the monkeypox virus. The study concluded that there is an urgent need to create awareness about the possible impact of the monkeypox virus.⁴³

The recent review conducted by Reynolds et al. showed the significant medical complications of monkeypox viruses. The review highlighted the lack of standard or optimized guidelines for clinical management at low-cost, sophisticated facilities. Infected people may become ill for a long time. The review justified the lack of pharmaceutical intervention and medical knowledge if there is a rampage of monkeypox viruses. Hence, there is an urgent need to take up the call from all the scientific resources to develop the needed first-line guidelines against monkeypox viruses.⁴⁴ The review reports of Kaler et al. have documented the endemic regions at the global level and the current scenario of monkeypox viruses with no exact treatment at the first-line level.⁴⁵ The review reported the fear of epidemics surrounding the prevalence of monkeypox viruses, which can be the next big thing after COVID-19. The recent review on the monkeypox virus by Lum et al. has outlined the recent unprecedented outbreak that has surprised the world with sporadic cases mounting to 48,000 and 13 deaths in less than 4 months. The review focuses on the clinical,

epidemiological, and immunological features of monkeypox viruses. The review also highlighted possible opportunities to tackle the ongoing monkeypox threat.⁴⁶ Similarly, the recent review by Haung et al. compiled the recently confirmed outbreak of the monkeypox virus with rapidly increasing cases at the international level, causing a severe threat. The review marked the importance of the monkeypox virus, followed by its clinical manifestations, transmission patterns, and mechanisms of viral infection, diagnosis tools, and treatment measures.⁴⁷ The recent study by Oriz et al. reported the outbreak of the monkeypox virus in Madrid (Spain). The study was conducted with observational features among the infected individuals, followed by confirmation from vesicular lesion swabs and real-time PCR sequencing. The study also performed electron microscopy to confirm the morphological characteristics. In addition, a structured epidemiological questionnaire was also designed to collect the data. The results showed that among 48 patients, all were cisgender men and 87.5% were men having sex with men (MSM), who were at high risk, with 93.8% showing skin lesions, 66.6% showing asthenia, and 52.1 % showing fever.⁴⁸

According to the study of Alakunle et al. the re-emergence of the monkeypox virus was reported in Nigeria between 2018 and 2019 which has raised serious concern in different parts of Nigeria. The studies emphasize the role of recombination and mutation in the evolution of monkeypox viruses, which resulted in gene loss and gene gain. The report also reported the genome-wide phylogenetic analysis from 2017. The report concluded with knowledge gaps for monkeypox viruses.⁴⁹ Similarly, Luna et al. reported the phylogenetic analysis of available monkeypox viruses in order to determine their evolution and diversity. The phylogenetic analysis was grouped into three monophyletic clades based on the previously reported outbreaks in comparison with the 2022 outbreak. The analysis was conducted to integrate the pertinent epidemiological information to help inform public health decisions to mitigate the outbreak.⁵⁰

Factors influencing the Monkeypox

There are wide ranges of hosts for

monkeypox viruses; both vertebrates and invertebrates are infected with this virus. The clinical manifestation may differ among rodents, humans, birds, and other mammals.⁵¹ When it comes to human beings, individuals who have compromised immune systems are at high risk, along with patients who have pre-existing ailments.⁵² People who engage in wildlife poaching, for example, are particularly vulnerable because the virus can quickly spread from an infected animal to a healthy individual.⁵³ The site of infection plays a very important role in the virulence of the disease. The direct contact of the body fluids of an infected person or animal with a healthy individual may lead to contamination of the serum, which may increase the lesions and rash all over the body.⁵⁴ One of the diagnostic features is lesion formation, which is very significant for disease development. The lesion progresses through four different stages, which include macular, papular, vesicular, and pustular, and later form scabs and falls off. Individuals with skin infections and allergies are particularly vulnerable to direct contact with contaminated serum.⁵⁵⁻⁵⁷

Inhalation of droplets oozing out from the coughing and sneezing of an infected individual carries viral particles, which, upon reaching the oral tract and lungs, can cause ulcers and impart the normal functioning of the lungs.⁵⁶ Individuals with lung infections and diseases are more likely to contract monkeypox infection if exposed. The population with MSM, i.e., men having sex with men, has a higher risk of infection when having sex with infected individuals, which may result in sores and lesions forming in their private parts of the body.⁵⁸⁻⁶⁰ The severity of the disease can be gauged by the higher lesion counts. Infected individuals with lesions can also get infected with bacterial skin infections. The bacteria, along with the monkeypox virus, can cause severe health implications such as respiratory tract infection and septicemia.⁶¹ In some severe cases, there might be ocular infections leading to permanent vision loss. Along with this geographic area, habitual behaviour also plays an important role in the transmission of disease.^{56,62} Since the first report of the monkeypox virus from Africa, there have been numerous outbreaks with increased virus virulence. This could be attributed to geographical

areas and lifestyle choices. During pregnancy, monkeypox viruses can be transmitted from the mother to the fetus; there is a risk of miscarriage, and lesions can be seen across the placenta.⁵³

Diagnosis of Monkeypox virus

The detection of monkeypox virus requires a well-equipped laboratory staffed by technicians who have received adequate training in technical and safety protocols.^{63,64} In order to identify the MPXV agent and/or particular viral DNA sequences, either real-time or traditional Polymerase Chain Reaction (PCR) techniques should be utilised.^{64,65} The diagnosis of monkeypox virus routinely is done by real-time PCR, where the DNA of monkeypox virus from human and animal samples is done by RT-PCR targeting conserved areas of extracellular-envelope protein gene.⁶⁶⁻⁶⁸ In the phenotypic method of diagnosis, the physical parameter are being taken into consideration, for instance, the incubation period of monkeypox virus is 4-21 days and normally it is followed by prodromal illness where symptoms like pharyngitis, malaise, back pain, intense asthenia, myalgia, headache, and fever.^{69,70} In the exanthema phase rashes and pea-sized lesions are seen; these are found to be different from smallpox lesions. The immunological identification of viruses is carried out with ELISA technique which detects IgG and IgM antibodies, whereas viral antigens can be identified with immunohistochemistry.⁶⁵⁻⁷⁰

First line defence

The initial steps taken by an infected individual can prevent the further spreading of the virus. Since primitive treatments are always supportive, early identification of individuals with symptoms should be kept in observation and if confirmed, the ring vaccination should be performed.⁷¹⁻⁷³ The administration of vaccine like vaccinia vaccine, Jynneos' Imvamune at the initial stage can reduce the severity of symptoms and also can prevent the disease. Vaccination with vaccinia vaccine is not recommended for those with certain medical conditions, including severe allergies, immunosuppression, pregnancy, breastfeeding, preexisting heart disease, and a background of atopic dermatitis (AD) or the other exfoliative skin disease.^{74,75} Alternative suggested treatment includes administration of antiviral

like tecovirimat which is approved antiviral in the treatment of smallpox, particularly adults patients. Antiviral brincidofovir, used for treating severe smallpox viruses for both children and adults, is undergoing evaluation for EA-IND used in treating monkeypox.^{75,76}

Vaccination

Researchers have discovered that the smallpox vaccine provides protection against many orthopox virus species, including orthomyxoviruses.⁷⁷⁻⁷⁹ The World Health Organization declared the elimination of found natural smallpox in 1980. Still, new vaccinia-based smallpox vaccinations were licensed in the early 21st century in response to worries about bioterrorism and monkeypox outbreaks.⁷⁹⁻⁸³ First-generation smallpox vaccinations, like Dryvax, were lymph derived and developed on the skin of animals. These vaccines contained vaccinia virus strains from the New York City Board of Health (NYCBH), Lister/Elstree, and Ikeda. Cell culture methods were used to develop second and third-generation vaccines in an effort to make them safer.⁸⁴⁻⁸⁸ Two smallpox vaccinations have been approved for use in the United States. Further, ACAM2000 was licensed in 2007 by USFDA which was a second-generation vaccinia virus-based smallpox vaccine, and it is a derivative of Dryvax.⁸⁴⁻⁸⁶ which is said to be effective against smallpox but not on monkeypox. An adverse reaction such as myopericarditis in smallpox affect individual, and this was found to be a threat to immune-compromised patients. Further attenuated vaccinia virus-based vaccines were developed in cell culture Eggs as means of attenuation. In 2019, the FDA approved Jynneos, a live, attenuated, third-generation smallpox vaccine.⁸⁶⁻⁸⁸ To create the attenuated Modified Vaccinia Ankara (MVA) strain, the vaccinia virus Ankara strain was cultured in chick embryo fibroblast cells for almost five hundred successive cycles. Jynneos is suggested to treat the individual of aged 18, and the individual with above age of 18 were insisted to be at high risk for both monkeypox and smallpox virus. Jynneos was previously approved by European Medicine Agency in 2013 against smallpox for the age of 18 and older with the name MVANEX.⁸⁷⁻⁹¹ IMVAMUNE is the trade name by Public Health Agency of Canada (PHAC)

in 2013. In 2020 PHAC added monkeypox and other orthopoxvirus infection to their previous indications, and EMA did the same in 2022 when it extended its indication of IMVANEX by adding monkeypox and vaccinia virus-causing diseases. In 1975 researchers in Japan developed a live, replicating attenuated vaccine derived from the Lister strain of vaccinia which was said to be the third generation and was licensed.⁸⁶⁻⁹³ In 2022 added the monkeypox to their existing indication of the vaccine. These above vaccines have a safety profile because these vaccines are attenuated phenotype and can be administrated to immunosuppressed patients. Since these vaccines are proven safe in clinical trials demonstrated, and found effective against monkeypox viruses under ethical guidance, hence in recent years, monkeypox is also being incorporated in the list of indications.⁸⁹⁻⁹⁴

Management of Monkeypox virus

Frequent ventilation of the area where the infected patient is staying, vacuuming of dust, and cleaning of floors, surfaces, and cloths in touch with the body of the infected patient should be performed to reduce the risk of environmental contamination.⁹⁵⁻⁹⁷ When symptoms appears on the infected person, then such individuals needs to be taken care at room with sufficient ventilation. Need to avoid sharing of washroom and restroom with healthy people, and standard disinfectant and detergent should be used for thorough cleaning after each instance of contact.⁹⁸⁻¹⁰⁰ Intercourse without proper remedies should be avoided, and sharing of clothes and room with the infected individual should not be practised. It is imperative that anyone with a compromised immune system is kept far away from the home of a monkeypox virus sufferer. Depending on how many and where the lesions are, it may be necessary to cover them with a bandage.⁹⁶⁻⁹⁹ Wearing a surgical mask is compulsory to avoid the airborne spread of viruses and viral particles. To avoid the possible spread of disease from a human to a mammal, or vice-versa pets should be kept away from the affected person's house.⁹⁹⁻¹⁰²

Indian Scenario

India has recovered and countered the recent COVID-19 pandemic attack, and the historical

scenario of India facing microbial infections has been difficult due to overpopulation, crowded areas, poor sanitary and hygienic conditions, and malnutrition. In spite of these drawbacks, the Indian medical fraternities have done their best to manage every situation and incidence precisely. Even when India was recovering from COVID-19, in the second half of 2022, reports of monkeypox virus infection surfaced, which can be a major threat if ignored. With the WHO declaring a public health emergency of international concern about the spread of the monkeypox virus at a global level, all countries are on high alert. On July 15, 2022, the first suspected case of monkeypox virus was reported in the southern Indian state of Kerala in a 35-year-old man with a travel history from Middle Eastern countries. Later, within the span of 90 days, there were more reports of the suspected monkeypox virus infecting diverse groups of the population, and the major infection was reported by an individual with travel history. There were reports of patients succumbing to the monkeypox virus with preexisting ailments or travelled to the cluster countries. This led to an increase in the investigation and diagnosis of monkeypox viruses for people returning to or visiting India, especially from the Middle East and African countries. The emergency meeting of the Ministry of Health and Family Welfare, Government of India, along with other governing bodies like AYUSH, National Institute of Virology, designated the monkeypox virus as one of the potential threats to the country, intensified the early surveillance, and released guidelines for the management of monkeypox viruses. The medical communities were guided with training programmes to create awareness about the monkeypox viruses, and if needed, designated or isolated centres may be set up just like COVID-19 to control the spread of infection. Different committees were set up under the rapid response team to review and strengthen the facilities.¹⁰³⁻¹⁰⁵

Future prospective

The monkeypox virus is considered to be one of the world's most serious threats. The world has recently witnessed the COVID-19 pandemic, which has closed down various progressive domains around the world, particularly in

developing and underdeveloped countries. Ever since the eradication of smallpox viruses, global health has been haunted by different zoonotic diseases caused by viruses. Despite advances in medical fields and advancements in management strategies, there is an urgent need to counter sudden outbreaks. The frequent emergence of the monkeypox virus from different parts of the globe needs to be addressed with immense care, with international governing bodies working together with the cluster countries to gather more information, especially with its genetic diversity, which has a greater influence on the virulent factor and transmission. Every country needs to be ready with a response team and analysis tools, even in remote areas, especially with biosensing tools that can be operated with minimal infrastructure. Further creating awareness in the public domain by utilizing resources to reach populations in different parts of the globe. The scientific community must update research-oriented works on the monkeypox virus so that medical professionals can use appropriate first-line defence medications in an early diagnosis. Also, the use of traditional knowledge coupled with scientific advances in nanotechnology can boost the ongoing progress to develop nano-vaccines, which can be robust with cost-effective measures. The phylogenetic comparison and lineage of recent outbreaks with previously reported monkeypox viruses need to be made available on a portal that can be accessed by different countries to gather sufficient data. One of the greatest challenges that need to be looked into is the way monkeypox viruses are sexually transmitted. Hence, there is a great demand for developing novel strategies to be implemented right from the screening stage to the management level. Furthermore, more scientific literature in this specific area of science needs to be published in order to advance scientific knowledge.

CONCLUSION

Overall, the present review highlights the gravity of the monkeypox virus with respect to its frequent re-occurrence. The review makes an important call for the governing bodies and scientific authorities to work under one roof to prepare the strategies to combat monkeypox

infection to prevent future possible pandemics. Finally, the present review adds information towards the growing scientific knowledge of the monkeypox virus.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

SB conceptualized the study. HKR collected the data. RSC, AP, CNK performed data curation. SB, HKR, SS, RSC, KM wrote the manuscript. SS, MNPN, SNR, RSC reviewed the manuscript. BPH, SCN, MNPN, SNR edited the manuscript. All authors read and approved the final manuscript for publication.

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DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not Applicable.

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