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REVIEW

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A brief review of influenza virus infection

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Abstract

Influenza is an acute viral respiratory infection that affects all age groups and is associated with high mortality during pandemics, epidemics, and sporadic outbreaks. Nearly 10% of the world's population is affected by influenza annually, with about half a million deaths each year. Influenza vaccination is the most effective method for preventing influenza infection and its complications. The influenza vaccine's efficacy varies each season based on the circulating influenza strains and vaccine uptake rates. Currently, three antiviral drugs targeting the influenza virus surface glycoprotein neuraminidase are available for treatment and prophylaxis of disease. Given the significant burden of influenza infection globally, this review is focused on the latest findings in the etiology, epidemiology, transmission, clinical manifestation, diagnosis, prevention, and treatment of influenza.

KEYWORDS
antiviral agents, epidemiology, influenza virus, treatment

1 | INTRODUCTION

Influenza is a contagious viral infection in seasonal epidemics, usually in winter.[1–4] Depending on the climatic and geographical situations, seasonal epidemic, and sporadic outbreaks can occur during winter or other seasons. Influenza virus can affect any organs and manifests as an acute febrile illness with variable degrees of systemic and respiratory symptoms.[5] Complications of influenza infection can be severe or life-threatening in high-risk individuals or groups.[6] Symptoms of influenza include fever, feeling chills, headache, weakness, red eyes, sore throat, dry cough, and nasal discharge.[7] Influenza viruses evolve quickly by frequent antigenic variation. Antigenic drift and shift are terms used to describe how the virus mutates and results in new strains. There is a significant change in the virus's genome in antigenic shift resulting in new hemagglutinin (HA) and neuraminidase (NA) protein expression.[8] Antigenic shift rarely occurs, but its role in contributing to and causing pandemics has been confirmed.[2] Due to antigenic shift, influenza infection continues to be an important global communicable disease despite significant improvements in the prevention, control, and management of cases. This review aims to highlight updated information on human influenza (etiology, epidemiology, transmission, clinical manifestation, diagnosis, prevention, and treatment), considering the importance of this infection in causing morbidity and mortality and the general concern and anxiety of health communities regarding future outbreaks, epidemics, and pandemics.

2 | ETIOLOGY

Influenza viruses belong to the family of *Orthomyxoviridae* of RNA viruses.[9] The influenza virus is an enveloped virus with a genome consisting of a segmented, single negative-strand RNA encoding surface glycoproteins of HA and NA.[10,11] The influenza virus infects the host by attaching to the host cell and penetrating the membrane. The HA attaches to cell surface receptors and initiates virus entry into these cells.[12] NA is an enzyme that helps in viral replication and enables the virus to be released from the host cell.[13] Thus, viral

glycoproteins play an essential role in the virulence and pathogenesis of the influenza virus.

Influenza virus strains are categorized as Types A, B, C, and D[14] (Table 1). The majority of influenza epidemics are caused by one or two types of influenza virus. Influenza A is the most common influenza infection during the flu season and causes mild to severe illness and affects humans and animals.[15,16] Type B influenza infection is highly contagious and can sometimes cause serious illness. Influenza B virus is reported to cause minor localized outbreaks.[17] Type B influenza is less common during the flu season than influenza A.[18] Type C viruses primarily infect humans and cause illness in some animals, such as swine.[19] Influenza C viruses cause mild upper respiratory symptoms, sporadic cases, and minor localized outbreaks.[20] The Type D viruses mainly affect pigs and cattle and are not known to cause humans infection.[21]

Type A viruses can be classified based on the antigenic variation in HA and NA antigens. So far, 16 antigenic variants of HA and nine antigenic variants of NA have been identified.[9] Moreover, several HA and NA combinations are possible as subtypes (e.g., H1N1, H5N1, H7N9). In contrast to influenza A viruses, type B viruses are not classified into subtypes.

3 | EPIDEMIOLOGY

Influenza may occur as pandemics, epidemics, outbreaks, and as isolated sporadic cases. Seasonal epidemics often occur in winter in temperate regions in the northern and southern hemispheres.[22] In tropical areas, influenza outbreaks can occur in all seasons.[10,23] The World Health Organization has estimated that annual influenza epidemics result in about 4 million severe infection cases and about half of million deaths each year.[24] The infection's epidemiologic pattern reflects the virus's changing antigenic properties, resulting in new viral strains that change, the virus's capability to transmit, and the population's susceptibility. An antigenic shift occurs when quick and significant changes in surface glycoproteins (particularly HA of Influenza A virus) occur due to a genetic transfer from some animal strains to human strains.[25] Antigenic shift is very rare, but it is a potential cause of pandemics and epidemics. Antigenic drift refers to minor antigenic changes that occur commonly within HA or NA of the influenza virus, and this is usually associated with localized outbreaks.[26] For Influenza Type B infection, only antigenic drifts in the HA have been recognized. Influenza infection occurs in people in any age group, though the risks of severe complications, hospital admission, and death are higher among people over the age of 65 years.[27] The complications from influenza during pregnancy, such as pneumonia, can be associated with mortality rates and more disabilities in mothers.[28]

It is important to note that the birds make up an essential reservoir of the influenza virus. Subtypes H5, H7, and H9 have all caused avian influenza epidemics in humans. Among these strains, H5N1 has a high mortality rate of around 50%, resulting in many hospitalizations and mortalities.[29] In 2013, there was reported an outbreak of the novel H7N9 influenza virus, despite fewer pathogenic in avian species, resulted in 36 deaths in humans. Therefore, given that the H7N9 pandemic in the human population is possible due to its rapid transmissibility, it is vital to pay more attention to such diseases as future threats to human health.[30,31]

4 | TRANSMISSION

The influenza virus is commonly transmitted from person to person by sneezing and coughing.[32,33] The most important transmission routes are through (1) direct contact with infected individuals, (2) contact with contaminated objects, and/or (3) inhalation of virus-laden aerosols. Respiratory transmission through aerosols containing viral particles can happen during coughing, sneezing, speaking, singing, and even normal breathing.[33,34] Following infection, viral shedding occurs about 24–48 h before symptoms onset.[35,36] Controlling the virus spread through covering the nose and mouth during coughing and sneezing and washing hands with soap, alcohol-based cleaner, or solutions are essential to prevent viral transmission.[37]

5 | CLINICAL MANIFESTATIONS

The standard incubation period for influenza is between 18 and 72 h, although it may vary from case to case.[9] Influenza symptoms often appear suddenly with typical symptoms: high fever and chills, headache, generalized weakness, severe aches in muscles and joints, red eyes, and respiratory signs such as sore throat, dry cough, and

TABLE 1 Different types of influenza virus

Type of influenza	Symptoms	Affect	Subgroups	Epidemiology
A	Mild to severe	Animal and human	Divided based on the antigenic properties (16 hemagglutinin and 9 neuraminidase)	Widespread
B	Mild	Only human	Not classified by subtype	Not cause pandemics
C	Mild	Human and some animals	Not classified by subtype	Not cause epidemics
D	Mild	Animals, unknown in human	Not classified by subtype	Not widespread

rhinitis.[38] The systemic symptoms usually last up to 7 days, but weakness and cough may last for weeks.[27] In adults, fever (38–41°C) typically lasts about 3 days.[9,39] A severe generalized, usually a frontal lobe headache, is common with influenza, worsening with sudden head movement.[40] Influenza cases usually recover from uncomplicated infection after a few days, but prolonged or on-going symptoms may indicate complications. For example, a headache with persistent fever may be due to sinusitis.[41] Ocular symptoms such as pain in eye motion and photophobia may develop in many patients; the eyes can become red, watery, and congested.[42] A sore throat due to influenza usually lasts about 5 days.[38] The symptoms of influenza in children are very similar to those of adults, although children may present with additional symptoms such as nausea, stomach pain, otitis media, and vomiting.

Pneumonia is recognized as the most critical influenza complication, especially in the elderly.[43,44] Complicated influenza infection frequently manifests as primary viral pneumonia, secondary bacterial pneumonia, and/or combined viral and bacterial pneumonia. Primary influenza pneumonia symptoms include high fever, dry cough, headache, sore throat, fatigue, dyspnea, and cyanosis.[43]

Secondary bacterial pneumonia may occur from *Staphylococcus aureus*, *Streptococcus pneumonia*, *Haemophilus influenza*, and other gram-negative bacilli infections.[45,46] Secondary staphylococcal pneumonia usually develops 3 days after the initial presentation of primary influenza pneumonia.[47] The most severe secondary bacterial pneumonia effects include hypoxemia, productive cough, high white blood cell count, and chest radiography may show multiple cavitary infiltrates. Complex viral and bacterial coinfections are the most common pulmonary complications of influenza.[48]

The diagnosis of bacterial coinfection with influenza can be challenging or difficult due to high false-negative rates and sample collection timing. These false-negative rates may not usually coincide when the influenza viruses replicate in the lower respiratory tract.

Along with influenza pneumonia, children and adults at high risk can develop some nonpulmonary complications such as heart problems, myositis, myoglobinuria, sinusitis, and ear infections.[49,50] Neurologic complications of influenza include Reye's syndrome, aseptic meningitis, encephalomyelitis, and Guillain-Barré syndrome (GBS).[51] Studies show an association of influenza infections with myocarditis and pericarditis.[52,53] Influenza A and B and enteroviruses are the most commonly reported viruses associated with rare myositis.[54,55] Myoglobinuria infrequently occurs following acute infection with symptoms suggesting an upper respiratory infection (URI) and has been associated with influenza, adenovirus, and parainfluenza.[56–59] Reye's syndrome is an uncommon and potentially life-threatening disease, distinguished by hepatic encephalopathy.[60] This syndrome's symptoms usually begin after viral infections, particularly Influenza B URI and, less frequently, influenza A infection. Long-term use of aspirin in children is another well-recognized risk factor for Reye's syndrome.[61] GBS is another rare disorder that causes acute flaccid paralysis and is preceded by gastrointestinal and URI (such as influenza) in about 60% of GBS patients.[62]

6 | DIAGNOSIS

The diagnosis of influenza is frequently made on clinical grounds, laboratory testing, epidemiology information, and influenza infection symptoms.[63] Cough and fever are the most critical symptomatic predictors of influenza infection, that is, before laboratory confirmation.[64] As the accuracy of clinical diagnosis in outbreaks is high, during an epidemic situation, most cases of influenza are diagnosed on clinical grounds. Laboratory methods include rapid influenza diagnostic tests, polymerase chain reaction (PCR), nucleic acid amplification tests, and virus culture[65] (Table 2).

Reverse transcriptase PCR (RT-PCR) assay is a rapid (<80 min), sensitive, and specific method to diagnose influenza and its subtypes and detect antiviral resistance.[66] RT-PCR is now the first-choice laboratory test for influenza infection because of its high sensitivity and specificity.[67] Nasopharyngeal washes and swab samples are the best specimens for diagnosing the virus by RT-PCR.[68] RT-PCR and other molecular assays may not provide an immediate diagnosis within the limited timeframe of clinical decision making, and RT-PCR assay is not approved for lower respiratory tract samples.

Among the molecular tests, the Loop-mediated isothermal amplification has high accuracy and very quick (about 30 min) to deliver results but is costly.[69] A multiplex real-time PCR assay has been developed in recent years to detect Types A and B influenza strains.[70]

Immunoassays such as rapid antigen tests have been developed to detect the Influenza A and B viral antigens in respiratory specimens. Rapid antigen tests are straightforward to perform and take a short time to complete (<30 min). The specificity of rapid antigen

TABLE 2 Diagnostic methods for identification of influenza virus

Tests	Influenza virus type detected	Samples acceptable	Time needed for test
Rapid influenza diagnostic methods	A and B	Throat swab, nasopharyngeal swab, nasal swab,	<30 min
Reverse transcriptase PCR (RT-PCR) assay	A and B	Throat swab, nasopharyngeal swab, nasal aspirate, sputum	<80 min
Nucleic acid amplification tests	A and B	Nasopharyngeal swab	<30 min
Culture	A and B	Throat swab, nasal swab or wash, sputum	>3 days

tests is high, and false-positive results from the tests are attributed to lower infection activity.[71] However, they have poor sensitivity (about 70% for Type A and <30% for Type B) in comparison to molecular assays and viral culture methods.[72] The sensitivity of rapid antigen tests depends on the disease's course, delivering high sensitivity to 2 days from the symptoms' onset. Nasopharyngeal samples also deliver high sensitivity to the test. Because of the poor sensitivity, rapid antigen tests may not be suitable for making diagnostic and treatment decisions.[71]

A viral culture may be performed on endotracheal aspirates, nasopharyngeal, and sputum samples. Samples that have dried out are not appropriate for influenza virus isolation. These tests take a long time to detect the virus. Thus, influenza viral isolation does not provide a timely diagnosis to support clinical decision-making. Shell vial culture findings take about 3 days to deliver results, while many traditional tissue-cell viral cultures may take about 10 days.[66,73] The advantage of viral cultures is that they aid strain typing and specific diagnosis of influenza infection. Other types of routine laboratory tests do not help in the specific diagnosis of influenza infection. For example, leukocytosis may indicate the presence of a bacterial infection with influenza.[74] Complete blood count and electrolyte levels or thrombocytopenia are nonspecific but helpful in diagnosing influenza. The differential diagnosis of influenza infection includes acquired immune deficiency syndrome, Legionnaires' disease, dengue fever, and other URIs.

7 | PREVENTION

Influenza vaccination is one of the best public health interventions to prevent infection.[10] Individual and population protection from influenza vaccination depends on vaccine coverage/uptake and the match between the antigen (vaccine strain) and the circulating influenza strains in the particular influenza year/season. Some studies have shown up to 60% efficacy of influenza vaccine against infection with Types A and B viruses.[75] Currently available vaccines for influenza include inactivated influenza vaccine (IIV), live attenuated influenza vaccine (LAIV), and recombinant influenza vaccine (Table 3). The majority of trivalent vaccines available for 2019-2020 contain antigens from two strains of Influenza A (A/Brisbane/02/2018 [H1N1] pdm09-like virus and A/Kansas/14/2017 [H3N2]-like virus) and one strain of Influenza B (B/Colorado/06/2017-like virus as a B/Victoria/2/87 lineage).[76] The quadrivalent vaccines have an extra B virus (B/Phuket/3073/2013-like virus as a B/Yamagata lineage).[77] Influenza vaccinations are safe for anyone aged over 6 months old. Both adjuvanted trivalent influenza vaccine (aTIV) or vaccines without an adjuvant were approved for individuals aged over 65.[78]

The quadrivalent influenza vaccines without adjuvant are approved for anyone over 6 months old.[79] A recombinant quadrivalent influenza vaccine is recommended for individuals over 18 years old. A quadrivalent cell-based influenza vaccine containing viruses grown in cell culture is approved for individuals over 4 years old.[77] A quadrivalent LAIV4 is approved for use in healthy persons aged 2–49 years old.[80] It has been reported that this vaccine is effective in 90% of children unless specifically contraindicated. However, the vaccine is not safe to use during pregnancy or in the case with immunodeficiencies.[5,77] Given that the influenza season runs from October to May in the northern hemisphere, it is recommended that people get vaccinated in the early autumn to ensure protection. Nonetheless, it is recommended, especially for the previously unvaccinated individuals, vaccination even at a later time may be of benefit.

Pregnant women should get IIV even if they were vaccinated during a previous pregnancy. Vaccination of pregnant women can prevent severe illness in the mother during pregnancy and their babies during the first 6 months of life.

Contraindications to the influenza vaccine are previous anaphylactic reactions to influenza vaccines, a history of GBS within 6 weeks of receiving an influenza vaccine, and concurrent infectious illness resulting in fever.[77,81]

There is a potential for influenza antiviral agents to lower the effectiveness of LAIV. Therefore, it is preferable not to use antiviral medicines for at least 2 weeks after receiving the LAIV. For the same reason, LAIV should not be administered within 2 days after discontinuation of influenza antivirals.[82]

8 | TREATMENT

In uncomplicated influenza and low-risk cases, symptomatic and supportive treatment should be offered. Hydration is imperative to replace body fluid loss that usually occurs with a fever. Nonsteroidal

TABLE 3 Recommended influenza vaccines

Vaccine types	Ages	Types of influenza strains protected
Adjuvanted trivalent influenza vaccine (aTIV) or without adjuvant	Adults aged ≥65 years old	3
Quadrivalent influenza vaccines without adjuvant	Persons aged ≥6 months old	4
Quadrivalent cell-based influenza vaccine	Persons aged ≥4 years old	4
Recombinant quadrivalent influenza vaccine	Persons aged ≥18 years old	4
live-attenuated quadrivalent influenza vaccine	Nonpregnant persons aged 2–49 years old	4

anti-inflammatory drugs like aspirin, naproxen, diclofenac sodium, and ibuprofen can be given to reduce symptoms, including fever, headache, and aches in the muscles.[83] Controlling fever can protect the patient from other symptoms such as shivering, myalgia, and tachycardia.

Various antiviral influenza medications are available for the treatment and prevention of influenza infection. Among the antivirals, currently, only four have been approved and recommended for use in chemoprophylaxis and treatment of influenza: oseltamivir (Tamiflu), zanamivir (Relenza), peramivir (Rapivab), and baloxavir marboxil (Xofluza)[84,85] (Table 4). These antivirals have demonstrated a good level of effectiveness and efficacy against influenza Types A and B viruses. Three (oseltamivir, zanamivir, peramivir) of these four antivirals are neuraminidase inhibitors (NAIs) and act by blocking the NA enzyme's function and preventing the virus from leaving the infected cells.[86]

Oseltamivir is an orally administered antiviral medication recommended to treat uncomplicated acute influenza up to 48 h after the onset of symptoms in adults and children over 2 weeks old. Oseltamivir is also recommended for chemoprophylaxis in adults and children over 1 year old.[87] Some studies confirmed that treatment with oseltamivir initiated 36 h after onset of symptoms resulted in a 40% reduction in the illness's severity.[88] Some adverse effects reported for oseltamivir include nausea, vomiting, abdominal pain, rash, delirium, and anemia.

Inhaled zanamivir is recommended for treating uncomplicated acute influenza within 2 days after the onset of symptoms in adults and children aged over 7 years old and for chemoprophylaxis of influenza in adults and children aged over 5 years old.[89] Zanamivir is contraindicated in severe milk protein allergy. Early therapy of uncomplicated influenza with zanamivir resulted in a reduction in duration (by up to 2 days) and severity of symptoms. Reported side effects of zanamivir include; cough, headache, bronchospasm, nausea, vomiting, fever, and myalgia.[90]

Intravenous peramivir is recommended for treating uncomplicated acute influenza within 48 h of symptoms onset in patients aged over 18 years old.[91] This antiviral agent has been approved for therapy in adults as an alternative to oral and inhaled medications. Peramivir has not yet been approved for use in children or prophylaxis. Studies in the early administration of a single dose of peramivir reported a decrease in the severity of symptoms and reduced symptoms duration. Adverse effects reported for peramivir include diarrhea, constipation, insomnia, and hypertension.[92] Influenza A has mutated some amino acids, remarkably R292K, N294S, I222V, H274Y, H275Y, and E119V, in NA site activation to need the resistance to NAIs.[93] Such changes modify the condition of the active NA site and decrease NAIs linkage many times.[94] It is important to note that the most common mutation conferring resistance to oseltamivir and peramivir in NA of the H5N1 and H1N1 subtypes was H274Y.[95]

Before 2007, oseltamivir resistance was rarely seen (low resistance rates of <5%), however, oseltamivir-resistant H1N1 started to emerge in the 2007–2008 flu season.[93] In 2009, the H1N1 strain was introduced all over the world. However, in many human cases (lower than 1.5% resistances), continued oseltamivir susceptible primarily.[94] Consequently, in the 2010–2011 influenza seasons in some regions of the world, a growing number of human cases resistant to oseltamivir were recognized. A recent study of three patients of oseltamivir-resistant H1N1 pdm09 in the 2018–2019 influenza seasons revealed that two of the cases recovered with oseltamivir despite whole-genome sequencing, disclosing H275Y mutations in 44% and 100% of the virus population, respectively. The third patient revealed mild clinical improvement with 2 weeks of oseltamivir, after which she was switched to intravenous zanamivir.[96]

Baloxavir marboxil is a cap-dependent endonuclease inhibitor. Baloxavir interferes with viral RNA transcription and inhibits viral replication, stopping the virus from multiplying.[97] A single oral dose of Baloxavir is recommended for the treatment of acute uncomplicated influenza cases up to 48 h after the onset of symptoms in adults and children over 12 years old.[85] Baloxavir has not yet been approved for prophylaxis. Reported adverse events of Baloxavir

TABLE 4 Antiviral medications recommended for influenza

Drug	Use	Recommended for	Dosage
Oral Oseltamivir (Tamiflu)	Therapy	Individuals aged ≥2 weeks	Adults: 75 mg bid for 5 days Children 1–12 years: 30–75 mg bid, depending on weight for 5 days
	Prophylaxis	Individuals aged ≥1 year old	Adults: 75 mg/d Children ≥1 year: 30–75 mg/d, depending on weight
Inhaled Zanamivir (Relenza)	Therapy	Persons aged ≥7 years old	Adults and children ≥7 years: 10 mg bid for 5 days
	Prophylaxis	Persons aged ≥5 years old	Adults and children ≥ 5 years: 10 mg/d
Intravenous Peramivir (Rapivab)	Therapy	Patients aged ≥18 years old	Adult: 600 mg once
	Prophylaxis	–	–
Oral Baloxavir marboxil (Xofluza)	Therapy	Patients aged ≥12 years old	Adults: 80 mg once Children ≥12 years and <80 kg: 40 mg once
	Prophylaxis	–	–

include headache, nausea, and diarrhea. Evidence regarding baloxavir resistance is limited. Some research of healthy individuals with Influenza A and B treated with this drug revealed that about 10% developed a specific mutation (PA/I38X) after treatment. It has also been shown that PA/I38X variants were related to higher viral loads and long-term symptoms.[98]

Other antivirals like adamantanes (amantadine and rimantadine) target the M2 ion channel protein of type influenza. However, adamantanes are no longer recommended for the prophylaxis and treatment of influenza due to reports of a high degree of resistance.[99,100] In general, antiviral treatment is recommended for severe influenza cases hospitalized and at high risk of severe infection or complications.[101] Antiviral treatment can reduce the fever and illness duration and the rate of complications associated with influenza infection. Oseltamivir is recommended for severe infection and complicated influenza cases that have not been admitted to hospitals or people in the community.[102] Antivirals have a significant beneficial impact for groups at high-risk infection or of complications: children under 4 years of age; people over 65 years of age; immunosuppressed individuals; patients with cancer, stroke, chronic conditions such as cardiovascular, pulmonary, renal, neurologic disorders; pregnant women; women who have delivered infants (postpartum) less than 14 days ago; patients under 19 years old receiving long-term aspirin therapy; individuals with obesity (body mass index ≥40); and residents of care homes [103] (Table 5).

It is necessary to mention that broadly neutralizing antibodies against several viruses have been documented, such as dengue, hepatitis C virus, respiratory syncytial virus, and influenza. Notably, antibodies against the sialic binding pocket and stem of influenza HA have been recognized.[104,105] In other words, some influenza virus-neutralizing antibodies bind to the HA and block the interaction between the viral sialic acid receptors and the host cells. Numerous studies have found that these antibodies targeting the influenza virus's conserved epitopes can provide alternative medicine.[106]

TABLE 5 Individuals at the highest risk of influenza complications

Adults aged 65 years and older
Children aged 4 years old and younger
Women who have delivered babies ≤14 days ago
Pregnant women during influenza season
Residents of long-term care facilities
People with cardiovascular, pulmonary, renal, and neurologic disorders
Individuals with a weakened immune system due to HIV or AIDS and cancers
Children 6 months to 18 years old receiving long-term aspirin medications
Persons with a body mass index (BMI) over 40 or more
Alaska Natives and American Indians

Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus.

9 | CONCLUSION

Influenza is a contagious respiratory disease and is preventable. Influenza can cause severe complications and death in healthy individuals of all ages. It is challenging to distinguish influenza from other viral or bacterial respiratory infections within antivirals' effectiveness, leading to delays in treatment with antivirals. Influenza vaccine remains the most effective means of preventing influenza disease and complications. However, in addition to antivirals, more effective interventions are needed in older people, in whom the burden of influenza is highest, and vaccine effectiveness against a severe outcome is lowest.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Mostafa Javanian and Soheil Ebrahimpour were involved in review concepts, design, and critical revision for important intellectual content. Mohammad Barary, Sam Ghebrehewet, Veerendra Koppolu, VeneelaKrishnaRekha Vasigala, and Soheil Ebrahimpour performed the literature search and drafted the manuscript. Mohammad Barary and Soheil Ebrahimpour were involved critical revision of the manuscript.

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DATA AVAILABILITY STATEMENT

All data are available upon reasonable request to the corresponding author.

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