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MINI-REVIEW

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COVID-19 vaccination challenges: a mini-review

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ABSTRACT

The emergence of SARS-CoV-2 has led to the infection of many people across the globe, over six million deaths, and has placed an unprecedented burden on public health worldwide. The pandemic has led to the high-speed development and production of vaccines against the COVID-19, as vaccines can end the pandemic. At the beginning of the program, vaccinations were initially targeted only at high-risk groups, such as the elderly, those with comorbidities, or healthcare workers. Although most of the mentioned populations have received the two recommended doses, limited resources have left many authorities with an effective vaccine undersupply. Therefore, policies have been implemented to manage the available doses of the vaccines more efficiently. As there is no universally agreed consensus on this topic, we discuss the different recommendations and guidelines regarding the time interval between the two vaccine doses and explain the different scenarios for applying the two doses.

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV -2) has infected many people worldwide, resulted in over six million deaths, and has caused a significant burden on public health worldwide.[1–3] This situation has resulted in an unprecedented international effort to develop effective vaccines, as vaccines can end the pandemic.[4] Although preventive measures, such as social distancing, face masks, quarantine, and lockdowns, have been relatively effective in decreasing the transmission of SARS-CoV-2, coronavirus disease 2019 (COVID-19), vaccines are thought to be the most effective means of preventing infection.[5] Vaccinations have been a practical route for inducing effective and long-lasting immunity against many different diseases,[6] and ideally, they prevent both infection and disease. However, COVID-19 vaccines may also prevent patients from becoming symptomatic or severely infected by decreasing viral loads in a previously vaccinated individual.[7] At the beginning of the vaccination programs, it was planned to vaccinate high-risk groups, such as the elderly, those with comorbidities, and healthcare workers. Although most high-risk groups have received the two vaccine doses, limited resources have left many authorities with an effective vaccine undersupply, at least in most developed countries.

However, due to the evolution of the COVID-19 virus, the rate of development of this virus can be controlled only if a rational vaccination strategy is developed, because in previous mutations such as Delta, not only the mortality rate and morbidity have increased, but also been able to evade diagnosis through diagnostic tests.[8–10] Also, due to breakthrough infections that were first seen in January 2021 in people immunized with the Pfizer-BioNTech vaccine, other breakthrough infections that have been seen, and the occurrence of mutation-induced variables in the viral spike protein acts as the main target of neutralizing antibodies. The virus can cross the protective barrier created by existing vaccines, and even a small number of mutations may prevent the host's protective immunity, making vaccines ineffective.[11–17] So far, RNA vaccines have been the most effective against variants of SARS-COV-2 viruses developed, followed by viral vector vaccines and inactivated virus vaccines.[18–21] Studies have also shown that existing vaccines are still effective against different types, although their effectiveness is generally reduced compared to the original virus.[22]

Since the beginning of the Corona pandemic, several different variants have attracted widespread public attention, including the beta variant (B.1.351), first seen in South Africa, and the alpha variant, which was identified in Britain and based on studies, the effect of BNT162b2 vaccine against them was 75.0% and 92%, respectively.[22–24] In the case of the delta variant, the BNT162b2 vaccine and the AZD1222 vaccine provide 88% and 67% immunity, respectively, in a study by the British.[25] The BNT162b2 vaccine generally has the highest efficacy against different types of variances.[22] Vaccines have varying degrees of effectiveness, ranging from 66% for

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CoronaVac vaccine to 97% immunogenicity for mRNA-1273, regardless of SARS-CoV-2 variants.[26–28] Also, according to evaluations, a single dose of the SARS-CoV-2 vaccine is about 40–60% effective in preventing the clinical situation, but given that the immune response in these people is less than desirable, such an approach can provide an opportunity for the emergence of different types. Provide SARS-CoV-2.[22,29]

Therefore, various policies have been implemented to manage the available doses of the vaccines better. For example, the United Kingdom (UK), and many other countries, decided to administer the second dose of the vaccines with an interval of up to three months.[30] This contrasts recommendations provided by the World Health Organization (WHO) at the time, which suggested a maximum interval of six weeks between vaccine doses.[31] More recently, the WHO has identified the complex issues related to the supply chain and suggests the second dose be given within 8 to 12 weeks.[32] Therefore, due to the lack of agreement on this topic, the present review will discuss the different approaches and guidelines regarding the time interval between the two vaccine doses and explain the different scenarios for applying vaccine doses.

2. Timing of the vaccine doses

It was speculated that one of the reasons for the delay in introducing COVID-19 vaccines was the greater interest in developing more effective medications. However, even delivering a less effective vaccine sooner would benefit the world's population more than delaying the vaccination program to wait for a more effective vaccine.[33] For example, since the incidence of viral infections peaks in the colder months, administering a relatively effective vaccine before winter might have significantly reduced last year's incidence peaks, leading to less morbidity and mortality and decreasing the burden on healthcare personnel.[34,35]

3. Different vaccine platforms and doses

In general, anti-SARS-CoV-2 vaccine platforms are classified as either classic or next-generation. The classical platforms include inactivated viruses, live-attenuated viruses, protein subunits, and virus-like particles, while the next-generation vaccines include nucleic acids (RNA and DNA), viral vectors (non-replicating and replicating), recombinant protein, and antigen-presenting cells (18).

A group of COVID-19 vaccines contains nucleoside-modified messengers based on which the two mRNA-1273 and BNT162 vaccines were developed. The mRNA-1273 vaccine, based on the experience of Moderna's previous studies on coronaviruses such as SARS and MERS, is a lipid nanoparticle (LNP) mRNA vaccine capable of encoding the stabilized viral perfusion form of Spike (S) protein, thus preventing COVID-19 infection. BNT162 by Pfizer and BioNTech companies, which has a history of making mRNA-based vaccines for influenza in 2018; Was made. The two companies announced an agreement to develop four candidates for the COVID-19 vaccine, including modified nucleoside mRNA (modRNA), uridine-containing mRNA-based (uRNA), and self-amplifying mRNA (saRNA). With its lipid nanoparticle formula, BNT162 encodes a full-length spike on the surface of the SARS-CoV- 2 mutated form during perfusion. The vaccine is 95% effective in preventing mild to severe cases and is 94% effective in adults over 65 years of age without any particular concern. Another group of vaccines is the viral vector vaccine, and one of the key benefits of these vaccines is their ability to promote T cell progression and the humoral immune response.[36] This group includes the ChAdOx1 nCoV-19 vaccine (AZD1222) developed by the University of Oxford and AstraZeneca. The vaccine is based on the MERS-CoV experiment and consists of the non-reproducible chimpanzee adenovirus vector ChAdOx1, which contains the gene for the spike protein. On 23 April 2020, the clinical trial phase I of this vaccine began with a trial of 543 volunteers aged 18–55 years with no severe adverse effects (NCT04324606).[4,37] The immunogenicity of this vaccine had previously been observed in pigs and mice.[38] According to the results obtained after the first dose in 91% of participants neutralizing antibody and in 100% after the second dose of this antibody was created and thus caused immunogenicity.[37] Other vaccines in this group are Gam-COVID-Vac and Ad26.COV2.S. Gam-COVID–Vac (Sputnik V) vaccine is made by the Gamaleya Research Institute of Epidemiology and Microbiology/Ministry of Health of the Russian Federation from two non-reproducible vectors called Adenovirus 26 (Ad26) and Adenovirus 5 (Ad5) as transporters for the SARS-CoV-2 Spike protein expression gene.[39] Overcoming previous immunity in the population against adenovirus was the reason for using two different serotypes, and among the available vaccines, only this vaccine has used this method.[40] And Ad26.COV2.S, produced by Johnson & Johnson by a recombinant and non-replicating adenovirus vector of serotype 26 (Ad26) in the PER.C6 cell line.[4,41] Virus-like particles (VLPs) are another class of vaccines that are a subset of protein subunit vaccines and are produced artificially by virus-like nanoparticles.[42] This category includes the NVX-CoV2373 vaccine, which Novavax manufactures with funding from CEPI and US Operation Warp Speed. The vaccine uses engineered baculovirus to infect insect cells. This vaccine requires two doses to create its maximum immunization and the addition of Matrix-M adjuvants to achieve 100% seroconversion.[4,36,43] Another company is working on a plant-based system called Nicotiana benthamiana for vaccine production.[44]

Among these, the following vaccines have thus far been approved by the healthcare authorities for public use: Moderna mRNA 1273 (RNA), Sinopharm and Sinovac (inactivated virus), Novavax NVX CoV2373 (protein subunit), Oxford AstraZeneca AZD1222 (ChAdOx1-S [recombinant]) (non-replicating viral vector), Covaxin (inactivated virus), Pfizer-BioNTech BNT162 (RNA), Sputnik V (non-replicating viral vector), and Johnson & Johnson Ad26.COV2.S vaccine (non-replicating viral vector).[4,45,46] However, the Food and Drug Administration (FDA) has only approved the Pfizer-BioNTech vaccine (reported efficacy of 95%), the Moderna vaccine (efficacy of 94%), and the Johnson & Johnson vaccine (efficacy of 66%),[47] all of which are administered in two doses with a minimum interval of 21–28 days,[48,49] except the Johnson & Johnson vaccine which is administered in a single dose.[50] However, regulatory bodies across countries have different

vaccination schedules to service the population. For example, in Australia, the Therapeutic Goods Administration approved the use of Pfizer BNT162b2 mRNA vaccine and AstraZeneca viral vector vaccine in early 2021 for individuals aged over 16 years and 18 years, respectively. Around June, the Janssen-Cilag viral vector vaccine was also provided with a provision registration for use in individuals aged 18 years and over, with an update to the Pfizer schedule for individuals aged 12 years and over in July. As of September 2021, the Moderna mRNA vaccine was also made available for individuals aged 12 and over.[51]

4. The reason for developing the "two-dose" vaccine regimen

All the mentioned vaccine types, except the Johnson & Johnson vaccine, need to be administered in at least two doses since the efficacy of a single dose is expected to be suboptimal. Thus, a second dose should elicit a more durable and more potent antibody response.[52] For example, the neutralizing antibody responses induced by the one-dose Ad26.COV2.S vaccine is stable for at least 14 weeks, while a second dose provokes a significant surge in antibody concentrations and causes a more durable immune response.[52] Booster doses are designed to trigger B-cell affinity maturation, elevate the concentration of neutralizing antibodies, and improve memory *T*-cell resources.[53] Regarding the role of memory T cells, recent studies have shown strong and highly functional T cell-mediated responses in the fight against the SARS-CoV-2 virus, even in individuals with negative neutralizing antibodies, which can help create protective immunity. Protective immunity, a stronger and faster protective response to the pathogen after the first encounter, is mediated by B and T cells and provides the basis for herd safety.[54] In addition, the lower neutralizing antibody responses against new variants, such as alpha (B.1.1.7), beta (B.1.351), gamma (P.1), and epsilon (B.1.429), following a single dose of the vaccine, seem to improve significantly after the second dose.[55]

5. The need for a COVID-19 vaccine booster

The emergence of new SARS-CoV-2 variants such as Omicron (B.1.1.529) that show decreased susceptibility to current vaccine-induced antibodies may warrant extra vaccine doses to prevent further disease incidence peaks.[56] In addition, the reported waning antibody levels following natural infection or vaccination seem to be a justification for periodic immunity boosters.[57] On 1 April 2021, the Chief Executive Officer of Pfizer, Albert Bourla, has publicly reported that a third vaccine dose within 12-months of getting the first vaccine is likely to be needed, with annual vaccinations from there out.[58] However, there is a strong argument that vaccines should be made available to other countries before offering domestic booster vaccinations or run the risk of further exacerbating vaccine inequality.[59]

6. The necessity of dose modification of the vaccines

According to reports, shortage of vaccine resources can be attributed to poor or underdeveloped countries such as Congo, South Sudan, Nigeria, Yemen, and Burundi, where the number of vaccines injected into the population is the lowest per 100 people.[60] Vaccination in countries such as India is also associated with many challenges, and as seen, the limited number of vaccines in this country has led to fewer prescriptions during the first 5 months of their vaccination program, followed by concerns about the increase in daily cases following the accumulation in vaccination centers.[61]

Due to the lack of vaccines, the decision on injection strategy should be made to achieve the two main goals of vaccines, including protecting vaccinated people against SARS-CoV-2 infection and indirectly protecting unvaccinated people through herd safety and reduced transmission.[62] One of the strategies to cope with the vaccine shortage could be using fractional doses of the vaccines. However, as the elderly are more vulnerable to severe and fatal forms of SARS-CoV-2 infection, a fractional dosing strategy might fail because of their lower immunogenicity. In contrast, lower vaccine doses can suffice in younger individuals with higher vaccine reactogenicity.[63]

7. The optimal interval between the vaccine doses

Since the beginning of the COVID-19 vaccination programs, the two-dose vaccines have been delivered at 21–28 days intervals. However, as previously mentioned, the scarcity of supplies has led some countries and territories to delay the second dose. Despite potentially leading to the waning of first-dose efficacy, the main advantage of a 12-week dose interval would be the more extensive population coverage in situations where there is not enough supply for all people to get the two doses of vaccines earlier.[64] Nevertheless, it does not mean that the second dose is unnecessary since it is needed to develop a more potent and long-lasting immunity.[53] Computer-based modeling has been used to identify optimal vaccination policies[65]and the optimal delay between the first and second vaccine dose.[66] The latter study identified that the second dose could be delayed for up to eight weeks in infection-blocking vaccines providing the efficacy of the first dose, according to serological testing, was greater than 50%. While for symptom-alleviating vaccines, the efficacy of the first dose needed to be > 70%.[66] However, these results suggest that delaying the second dose is feasible from a public health perspective.

8. Delay in the second dose administration

While the United States (US) had the required number of vaccine doses to stick to the recommended 3–4 weeks schedule, at the end of 2020, the United Kingdom (UK) was the first country to recommend an interval of 12 weeks between the two doses, rather than the previously recommended 3–4 weeks for the Pfizer-BioNTech and AstraZeneca vaccines.[67] The rationale behind the delay was to protect the most significant number of at-risk people in the shortest time possible. The idea was that even with weaker immunity, this strategy would reduce COVID-19-related morbidity, mortality, and hospitalizations. Moreover, the best way to handle the waning immunity of the vaccines over time can be to delay the second dose so that the vaccine-induced immune response lasts longer.[68] Furthermore, research has found that the efficacy of the two-

dose vaccine is higher with an interval of more than six weeks than it is for less than six weeks.[30,69] Hence, some authorities believe that using a single-dose vaccine with lower efficacy and delaying the second dose can end the pandemic sooner since the first doses are provided earlier to more people.[70]

Another issue is the emergence of the new SARS-CoV-2 variants, which reduce the efficacy of the currently available vaccines. Therefore, delaying the second dose could also give researchers additional time to produce more potent and effective vaccines against these variants. Nonetheless, it is also worth noting that researchers have hypothesized that partial vaccination may lead to a less potent immune response and, therefore, an increased risk of mutations.[71] Furthermore, there have been some arguments against delaying the second dose, as this might trigger more cases of breakthrough infections 21–28 days after the first vaccine dose. Another significant concern is whether these single-dose vaccine recipients may develop asymptomatic infection and become a transmission source in the interval between the first and the delayed second dose of the vaccine.[72] Moreover, extending the between-doses interval will result in some people forgetting to return for their second dose, thus necessitating a reminder system to reduce this problem.[29] In addition, delaying the second dose can cause concerns for healthcare personnel working in high-risk environments since they may not be highly protected.[73] Nevertheless, it seems possible to delay the second dose of the vaccine in individuals with a history of prior SARS-CoV -2 infection since these people have been shown to respond more rapidly and more potently to a single-dose vaccine, indicating there is no need for a second dose, in the short-term at least.[74]

9. The persistence of the vaccine-induced immunity or antibody response

Studies have demonstrated that antibodies provoked by the mRNA vaccines can remain for up to six months, or even more than one year after the second dose.[75,76] However, vaccine-induced immunity diminishes over time because of the immunologic memory weakening or evolution of new variants.[77] Therefore, booster doses are needed to maintain adequate protection and durability.

10. Single-Dose versus two-dose vaccine

The shortage and limited supply of COVID-19 vaccines is still a significant problem, for which some solutions have been proposed. One of these includes changing the vaccination program from two doses to a single-dose program. However, we should first identify whether a single-dose vaccine can be as effective as a two-dose one.[78] Recently, it has been demonstrated that even a single dose of mRNA COVID-19 vaccines, such as the mRNA-1273 (Moderna) or BNT162b2 (Pfizer/BioNTech) vaccines, can confer significant protection and reduce new infections, reaching an efficacy of 75% 15 days after the first dose, and up to 83% after 36 days.[79,80] These results also highlight the lower level of protection 15 days post-vaccination.[81] Thus, the European Medicines Agency (EMA) has discouraged intervals of more than 42 days between the first and second doses of the Pfizer-BioNTech vaccine.[82] Nevertheless, the Oxford-AstraZeneca vaccine has been shown to provide high short-term immunity against severe disease, especially between 3 weeks after the first dose to two weeks after the second dose, and the efficacy of one dose of this vaccine is greater than 70%.[83]

Also, single doses of the Pfizer and AstraZeneca vaccines have significantly decreased the risk of COVID-19-related hospitalizations at 28–34 days after the first dose by conferring 91% and 88% efficacy, respectively.[84] Moreover, it has been shown that a single-dose vaccine can provide short-term protection against asymptomatic SARS-CoV-2 infection, leading to decreased transmission and consequently a lower disease burden.[85] Nevertheless, there is likely to be some form of negative emotional impact on vulnerable or at-risk individuals caused by postponing the second dose.[86]

11. Single-Dose vaccine patients who have recovered from SARS-CoV-2 infection

At the beginning of the pandemic, it was thought that infection with SARS-CoV-2 would confer lifetime immunity to the virus. However, with the increasing rate of reinfections, the theory of long-lasting immunity has proven incorrect. Therefore, vaccination is necessary even for previously infected individuals and should not be deferred in these people.[87] Antigenic drift, waning antibody response, and heterogenic immune responses to the primary infection are reasons why vaccination is still required, even after SARS-CoV-2 infection.[88] Furthermore, in the absence of data comparing the clinical and biologic responses to the vaccines among patients who have recovered from the infection versus infection-naive individuals, it is still unknown whether a single-dose vaccine would be sufficient for previously infected SARS-CoV-2 individuals. It has been demonstrated that the post-vaccination antibody response in those with prior SARS-CoV-2 infection is significantly higher than among those without prior infection.[89] The hypothesis is that this single-dose vaccine could serve as a booster for these patients' previously stimulated immune systems, equating to antibody levels induced in infection-naive people following double-dose vaccination.[90] In addition, these previously infected individuals do not show a further increase in circulating antibodies or memory B cells following the second dose, and antigen-specific responses to the second dose of the vaccine are negligible in people with prior exposure to SARS-CoV-2, in comparison to those without prior infection.[91] Nonetheless, the vaccine antibody response of those patients who have survived SARS-CoV-2 infection depends on the pre-vaccination IgG titer and the symptoms of their infection, such as anosmia or dysgeusia.[92,93] Therefore, perhaps a single-dose vaccination program could serve as a reasonable strategy to maximize vaccine supplies for those more vulnerable to COVD-19-related morbidity and mortality and accelerate herd immunity achievement.[94] Thus, since the seroprevalence of antibodies differs geographically, active antibody screening could help identify individuals with a history of infection and allow vaccines to be deployed elsewhere.[95]

12. When to vaccinate after SARS-CoV-2 infection?

As immunity induced by a naturally acquired SARS-CoV-2 infection has been reported to last up to several months following the primary infection, the optimal timing of vaccination following a COVID-19 infection cannot be determined.[96] However, in areas with low vaccine supplies, perhaps vaccination can be temporarily delayed in individuals with a recent history of SARS-CoV-2 infection,[97] as assessed using SARS-CoV-2 specific antibody testing to define who has already acquired adequate protective antibodies.[98] Nevertheless, an important point is how accurate and reliable these antibody tests are, making such decisions challenging.

13. The risk factors of low antibody response following COVID-19 vaccines administration

Previous research has found that central obesity, hypertension, and smoking are associated with lower immunogenicity from anti-SARS-CoV-2 vaccines.[99] Furthermore, glucocorticoids and B cell depleting agents can significantly impair vaccines' immunogenicity.[100] Interestingly, sleep deprivation and psychological stress may also lead to less robust antibody production following vaccination.[101,102] However, it has been demonstrated that adding a particular adjuvant (a subunit vaccine comprising the SARS-CoV-2 spike protein receptor-binding domain displayed on an I53–50 protein nanoparticle scaffold) to SARS-CoV-2 vaccines can boost the vaccine-induced protective immunity, even against the newly emerged variants.[103]

14. The need for serology tests before vaccination

As previously stated, the shortage of vaccine supplies is why some authorities have sought strategies to change from a two-dose to a single-dose regimen in individuals previously infected with SARS-CoV-2. The only way to confirm prior infection would be via antibody testing before administering the first dose of the vaccine so that those with high antibody titers can be excluded from getting a second dose. This strategy can be cost-effective and easy to perform and reallocate the additional vaccine doses.[104] However, some studies have suggested that vaccinations should only be carried out in seronegative individuals while neglecting the fact that past exposure alone is not sufficiently protective and even those with a history of prior SARS-CoV-2 infection are vulnerable to reinfections, meaning that these individuals should not be excluded from the vaccination program.[105] Nonetheless, this approach can be performed in higher-income countries with more readily available point-of-care tests.

15. The need for serology tests after vaccination

Many people enquire whether they have produced an adequate immune response after being vaccinated. Therefore, it is a reasonable strategy to identify low-or non-responders to the vaccine as early as possible to consider additional interventions, such as administering booster doses or taking more protective measures against infection.[106,107] Thus, although circulating antibody levels alone are sufficient to indicate immune protection, point-of-care tests for SARS-CoV-2 antibodies can be used to easily self-assess the immunogenicity level and the efficacy of the vaccination or natural exposure at home.[108,109] There are currently promising serological, saliva, and finger stick assays for evaluating post-vaccination antibody levels.[110–113]

16. Administration of different first and second vaccine doses

Several studies have proposed giving doses of the first and second COVID-19 vaccines using different vaccine types. The rationale for this alternate vaccine strategy is to provide additional protection. It has been shown that antibody responses following a two-dose heterologous COVID-19 vaccine regimen are more robust than a single-dose or two-dose homologous regimen.[114] Moreover, in situations with limited vaccine supply, this can help confer broader population coverage. In addition, if concerns about the efficacy or safety of the first vaccine were raised, changing to another vaccine type would be a reasonable option.[115]

17. Conclusion

This is the first time in history that the world has been subjected to a vaccination campaign as extensive as the present COVID-19 immunization exercise. Because of the specific issues identified and highlighted in this assessment, various difficulties that might jeopardize the ongoing mass COVID-19 immunization campaign must be addressed appropriately first. In conclusion, while there are many identified challenges to the current COVID-19 vaccination campaigns, holistic and timely planning and execution of such plans, rigorous community involvement, and a robust multi-sectoral partnership will help to yield beneficial results in the global efforts to vaccinate the people against COVID-19.

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Disclosure statement

TTS reports that he provides strategic and scientific recommendations as a member of the Advisory Board and speaker for Novocure, Inc. and also as a member of the Advisory Board to Galera Therapeutics, which are not in any way associated with the content or disease site as presented in this manuscript. All other authors have no relevant financial interests to be declared.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author contributions

Zeinab Mohseni Afshar: Conceptualization, Writing—Original Draft; **Mohammad Barary**: Investigation, Writing—Original Draft, Writing—Review & Editing; **Rezvan Hosseinzadeh**: Investigation, Writing—Original Draft; **Bardia Karim**: Investigation, Writing—Review & Editing; **Soheil Ebrahimpour**: Investigation, Writing—Original Draft; **Kosar Nazary**: Investigation, Writing—Review & Editing; **Terence T. Sio**: Writing—Review & Editing **Mark J. M. Sullman**: Writing—Review & Editing; **Kristin Carson-Chahhoud**: Writing—Review & Editing; **Emaduddin Moudi**: Investigation, Writing—Original Draft; **Arefeh Babazadeh**: Conceptualization, Writing—Original Draft, Supervision.

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