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Seasonal influenza vaccination coverage and its association with COVID-19 in Saudi Arabia

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) pandemic is still on-going worldwide. The available information regarding the seasonal influenza vaccine (SIV) coverage during the COVID-19 pandemic and its impact on SARS-CoV-2 spread are limited. Moreover, it is argued that SIV may or may not lessen the COVID-19 severity. No previous studies have been revealed SIV coverage among COVID-19 patients and its association with COVID-19 spread and severity, especially in Saudi Arabia. Hence, this study aimed to estimate the influenza vaccine uptake in confirmed COVID-19 patients and investigate its impact on COVID-19 spread and severity. Accordingly, 1734 COVID-19 confirmed patients were included from three government hospitals in Saudi Arabia (SA). The data were collected electronically through a newly formed, self-administrated questionnaire. Among those patients, 335 were covered with SIV (19.31%), and the coverage rate of females and males was 23.4% and 15.8%, respectively. Severe COVID-19 cases were less in vaccinated patients than in non-vaccinated (2.69% vs. 3.5%, respectively). Additionally, the results showed a significant decrease in getting infected by SARS-CoV-2 after receiving SIV ($P = 0.022$). Even with the tremendous efforts to promote SIV uptake among the general population and high-risk groups, the SIV coverage in SA is not optimal yet. Nevertheless, there is a significant decrease in the probability of getting infected with SARS-CoV-2 after receiving SIV. Such findings with the continuous progression of the COVID-19 pandemic call for a novel approach regarding vaccination policies to increase SIV and COVID-19 vaccine uptake.

1. Introduction

Seasonal influenza is a significant respiratory viral infection caused by influenza A or B virus, manifested as acute upper respiratory tract infection, primary viral pneumonia, secondary bacterial pneumonia, or respiratory failure. During winter, it spreads globally in the northern and southern hemispheres, causing 3–5 million severe cases and 290000–650000 deaths yearly [1]. Influenza viruses belong to the Orthomyxoviridae; their genome consists of negative-sense, single-stranded, segmented RNAs [2]. Influenza virus A is the leading cause of

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seasonal epidemics in humans. This virus is classified based on the similarity of the hemagglutinin (18 subtypes divided into two groups) and neuraminidase sequences (11 subtypes divided into three groups) [3]. To ensure the efficacy of SIV, the vaccine seed viruses are selected periodically by WHO according to the available genetic, antigenic, and epidemiologic information related to current circulating influenza viruses.

In contrast to widely used SARS-CoV-2 messenger RNA vaccines (mRNA vaccines), the licensed influenza vaccines are inactivated vaccines, live attenuated vaccines, or recombinant hemagglutinin vaccines. Inactivated SIV had three types (whole-virion vaccine, split-virion vaccine, and subunit vaccine) and was produced by growing the vaccine seed virus in chicken embryonated eggs [2]. Live attenuated SIV is administered intranasally and mimics a natural infection which elicits a broad immune response and produces IgA and IgG antibodies [4,5]. The recombinant hemagglutinin SIV is produced by a recombinant-protein-expressing system using insect cells and baculovirus [6].

Moreover, Influenza viruses are in continuous genomic changes that result annually in small antigenic changes "antigenic drift", which necessitate a frequent yearly update of seasonal influenza vaccine (SIV). In contrast, significant genomic changes "antigenic shift" occurs less frequently but usually lead to outbreaks or even pandemics caused by a newly emerging strain [7]. The SIV is essential to prevent influenza transmission, reduce health complications from influenza, especially in high-risk patients, and alleviate the resulting economic impact [8]. Saudi MOH has made tremendous efforts before COVID-19 pandemic to increase SIV coverage among patients at risk, pilgrims, and the general population.

As COVID-19 pandemic waves are still on-going and the death toll among infected people is rising worldwide, there is an increasing concern about possible complications in the COVID-19 pandemic course introduced by seasonal influenza outbreaks. The available information regarding the possible impact of influenza coinfection during influenza seasons is limited. The reported coincidence cases raised a concern about the problematic pandemic course [9–11]. On the other hand, some reports are starting to emerge discussing the impact of seasonal influenza vaccination on COVID-19 infection. Two previous studies showed that the SIV lowers the COVID-19 severity, intensive care requirement, ventilator support, and mortality [12,13]. Furthermore, Grossberg et al. [14] showed that the influenza vaccine does not protect against COVID-19; however, it may attenuate the severity of symptoms. In contrast, some reported data suggested that the influenza vaccine is a relevant risk factor for COVID-19 [15,16]. However, no studies have been conducted to determine the SIV coverage during the COVID-19 pandemic in Saudi Arabia and its association with the COVID 19 range. Hence, this study aimed to investigate the SIV coverage among Saudi patients during the COVID-19 pandemic and its association with COVID-19 spread and severity.

2. Materials and methods

2.1. Study design

A cross-sectional study design was adopted in this study. Those confirmed COVID-19 infection patients (N = 1734) from the selected governmental hospitals (N = 03) of Saudi Arabia were recruited for this study. This study was conducted between May 1, 2020, and August 31, 2020.

2.2. Samples

Efforts have been taken to select three governmental hospitals from different Saudi Arabia regions to reach the generalizability of the findings. Those hospitals were King Fahd Hospital of the University (Khobar), Qatif central hospital, and Uhud Hospital (Madinah). The COVID-19 infection was confirmed using the Severe Acute Respiratory Syndrome Corona Virus-2 Real-Time reverse transcriptase Polymerase Chain Reaction (SARS-CoV-2 RT-PCR). The authors have adopted a criterion-based sampling approach for including the patients in this study. This study included only those patients administered with the inactive influenza vaccine by Saudi MOH, those with $\geq$ 18 years of age, and laboratory-confirmed COVID-19 by SARS-CoV-2 RT-PCR.

On the other hand, the critically ill patients who could not fill the survey and those with mental or linguistic barriers were excluded. All COVID-19 patients who met the inclusion criteria were invited to participate in this study. The ethical approval for this study was obtained from the Institutional Review Board (IRB) of Imam Abdulrahman Bin Faisal University (IRB-2020-181), Dammam, Saudi Arabia.

2.3. Methods

All participants were administered an online self-administered Arabic version of the questionnaire to collect the demographic and clinical data. In addition, all patients have received phone calls preceding the survey distribution. Furthermore, ethical concerns were followed, and privacy and anonymity were assured. Informed consent was also obtained prior to gathering the data from the participants. All participants were provided with a stipulated duration and frequently reminded to respond to the survey. The demographic data deals with the patient's age, gender, nationality, educational level, and occupation in the questionnaire. The clinical data collected includes the information about receipt of SIV during past influenza season, time of laboratory diagnosis of COVID-19, time of symptom appearance (onset of COVID-19), comorbidities (i.e., chronic lung disease, ischemic heart disease, diabetes mellitus, chronic kidney disease, asthma, chronic liver disease, malignancy, or blood disorders [sickle cell disease, thalassemia]), and disease severity level (i.e., mild, moderate, or severe) of COVID-19. A translated English version of this questionnaire is provided in Appendix 1.

2.4. Data analysis

Descriptive statistics in a simple percentage technique were adopted to describe the patients' demographic characteristics. In addition, a chi-square test was applied to reveal the potential association between the SIV coverage with the spread of COVID-19. Further, the student's t-test was used to determine the difference in the incidence and severity of COVID-19 among vaccinated patients compared with non-vaccinated. All statistical analyses were carried out using SPSS 22.0 (Armonk, NY: IBM Corp.) with a significance level of 0.05.

3. Results

A total of 1734 COVID-19 patients were included, of which 926 (53.4%) were males, the majority of them (N = 1585; 91.4%) were between 21 and 60 years of age, the average age was 37.7 $\pm$ 11.6 (Mean $\pm$ SD). Most of them were Saudis (N = 1564; 90.1%). One thousand thirty-one (59.4%) were carrying university degrees, and 282 (16.3%) were health-care workers (HCWs) (Table 1).

In terms of influenza vaccination, 335 participants have received SIV before or during past influenza season. Vaccine uptake was significantly higher among females 189 (23.4%) compared with males 146 (15.8%) ($P < 0.0001$). Influenza vaccine coverage among Saudis (20.1%) was significantly higher than non-Saudis (11.8%) ($P = 0.009$). Influenza vaccine coverage of patients who had university-level education was significantly higher (20.6%) compared with patients with lower educational levels (illiterates 11.6% and below high school 14%) ($P < 0.001$). Although the study participants included 282 health workers, only 121 (42.9%) received influenza vaccines during the past year (Table 1).

Out of those patients covered (N = 1734), 19.31% already took the

Table 1
Demographic characteristics of the patients in relation with influenza vaccine.

		Influenza vaccination		*P*-values
		Yes	No	
Sex	Male	146 (15.8%)	780 (84.2%)	<0.05
	Female	189 (23.4%)	619 (76.6%)	
Nationality	Saudi	315 (20.1%)	1249 (79.9%)	<0.05
	Non-Saudi	20 (11.8%)	150 (88.2%)	
Educational level	Illiterate	7 (14%)	43 (86%)	<0.05
	Below high school	19 (11.6%)	145 (88.4%)	
	High school	88 (18%)	401 (82%)	
	Bachelor/ diploma	206 (20.6%)	794 (79.4%)	
	PhD	15 (48.4%)	16 (51.6%)	
Occupation	Student	30 (24.2%)	94 (75.8%)	<0.05
	Health worker	121 (42.9%)	161 (57.1%)	
	Employee	120 (14.9%)	688 (85.1%)	
	Unemployed	52 (11.6%)	396 (88.4%)	

Influenza vaccine (N = 335). Among those vaccinated, 20.35% (N = 105) have known comorbidities, whereas 18.88% (N = 230) did not have any known comorbidities. Besides, 26.25% of patients with chronic lung disease, 12% of patients with ischemic heart disease, 11.30% of patients with diabetes, 30.0% of patients with chronic liver disease, and 26.35% of patients with blood disorders (sickle cell disease or thalassemia) were vaccinated against influenza in the past year (Table 2).

The severity of COVID-19 confirmed cases were defined according to the Saudi Ministry of Health (MOH) protocol for patients suspected of/ confirmed with COVID-19. Mild cases present nonspecific (atypical) symptoms and signs (fever, sore throat, headache, loss of taste or smell, or both, cough, nausea, and vomiting). Moderate cases present with shortness of breath, dyspnea, and constitutional symptoms, or severe cases with evidence of pneumonia and one or more of the following findings: Respiratory rate ≥30/min, blood oxygen saturation ≤93%, PaO2/FiO2 ratio <300, or lung infiltrates >50% of the lung fields within 24–48 h [17].

A further attempt was made to study the association between those who received the influenza vaccine in the past year and the severity of COVID-19. 79.1% of patients vaccinated with influenza vaccine past year exhibit a mild COVID 19 disease, whereas 81% of unvaccinated patients show mild symptoms of COVID 19 disease. Similarly, 18.2% of influenza-vaccinated patients showed moderate COVID 19 symptoms when exposed to that virus. It is also found that only 2.69% with severe COVID 19 diseases have received the influenza vaccine in the past year compared with not vaccinated (3.50%) individuals prone to COVID 19 disease (Table 3 and Fig. 1). Even though a decrease of COVID-19 severity is found in the vaccinated group; however, it was not statistically significant (P = 0.345). In terms of SIV impact on SARS-COV-2 spread, our statistical data analysis showed a significant decrease in the probability of getting infected by SARS-COV-2 (P = 0.022) after receiving SIV (Table 4 and Fig. 2).

Table 2
Comorbidities of patients in relation with influenza vaccine.

	Influenza vaccination		Influenza vaccination Coverage (%)
	Yes	No	
Chronic lung disease	21	59	26.25
Ischemic heart disease	12	88	12.00
Diabetes mellitus	13	102	11.30
Chronic liver disease	9	21	30.00
Chronic kidney disease	1	4	20.00
Malignancy	1	5	16.67
Blood disorders (SCD, thalassemia)	44	123	26.35
Multiple comorbidities (≥2)	4	9	30.77
None	230	988	18.88

4. Discussion

Influenza vaccination is the backbone for alleviating influenza outbreaks and disease rigor, particularly in high-risk groups. World Health Organization prioritized certain high-risk groups to have influenza immunization during the COVID-19 pandemic. These high-risk groups include pregnant women, patients with chronic conditions (chronic lung disease, ischemic heart disease, metabolic disorder, chronic liver disease, chronic renal disease, or chronic neurological condition), patients with immunodeficiencies, older people, and health care workers [18,19]. Advisory Committee on Immunization Practices recommends yearly seasonal vaccination against influenza for everyone six months and older [20]. Especially in Saudi Arabia, SIV is usually administered for adults as a single annual dose [21]. Besides, most vaccinated patients in this study have received inactive influenza vaccines, mainly INFLUVAC, which consists of surface inactivated antigens of circulating influenza viruses in the 2019/2020 season.

In 2005, Saudi MOH officially recommended SIV for all pilgrims [22]. In 2014, MOH had launched a 3-phase strategic project for five years to increase the vaccination coverage among risk groups up to 30% [23]. Unfortunately, our data show that the SIV coverage rate is far below the MOH targets (Table 2); only 26.25% of patients with chronic lung disease, 12% of patients with ischemic heart disease, 11.30% of patients with diabetics, and 26.35% of patients with blood disorders (sickle cell disease or thalassemia) have been received SIV in the past year. Additionally, overall influenza vaccine coverage was also low (19.31%). The females were more compliant with SIV uptake than males (23.4% vs. 15.8%; P < 0.0001). The coverage of patients who had higher educational levels was significantly higher (P < 0.001). These findings reflect the effect of education on health-seeking behaviours. Thus, getting vaccinated is significantly correlated with a higher knowledge score on the vaccine, participation in educational campaigns, improved access to vaccination, and obligatory immunization policies [24].

From 2006, published studies from Saudi Arabia tried to calculate the SIV coverage rates among some risk groups but not among the general population (Appendix 2). Among those studies, most of them reported that the targeted risk group was HCWs with variable coverage percentages from 5.9% up to 54.5% [25–40]. In this study, the SIV coverage rate of HCWs was 42.9%, which seems higher than the median yearly HCW coverage rate (33.3%) [38]. Further, the SIV coverage rate can be higher among HCWs if a mandatory vaccination policy is applied. Mandatory SIV vaccination of HCWs has been adopted in several countries to prevent influenza transmission in healthcare settings [41]. However, SIV coverage rates of other groups at high risk of developing influenza complications in Saudi Arabia were rarely documented. An earlier study by Alnaheelah IM et al. [36] found SIV uptake was 61% in patients with diabetes compared with 11.30% in our study. This low rate of vaccinated patients with diabetes may be related to change in health priorities and behaviors during the COVID-19 pandemic. In the other

Table 3
Association between influenza vaccination and severity of COVID-19.

Severity of COVID-19	Influenza Vaccination		P-value
	Yes	No	
Mild	265 (79.10%)	1136 (81.08%)	0.345[a]
Moderate	61 (18.20%)	214 (15.29%)	
Severe	9 (2.68%)	49 (3.50%)	

[a] By Chi-square test.

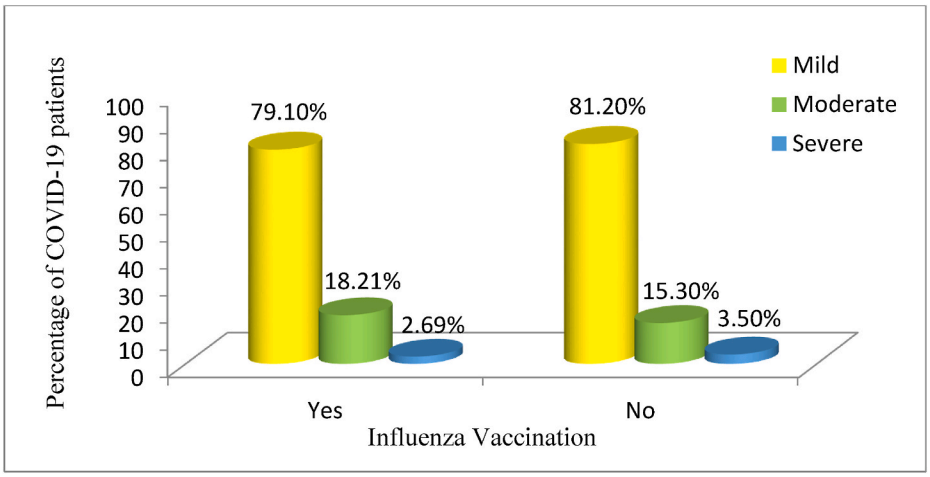

Fig. 1. Percentage of COVID-19 patients with and without Influenza vaccination according to the COVID-19 severity.

Table 4
Association between the onset of disease (COVID-19) and Influenza vaccination.

COVID-19 diagnosed	Influenza vaccine		P-value
	Yes	No	
> 30 days	299 (19.45%)	1238 (80.55%)	0.285*
≤ 30 days	32 (16.24%)	165 (83.76%)	
Mean (±SD)	15.12 (±14.9)	17.5 (±17.02)	0.022** ($p < 0.05$)

*By Chi-square test, ** By *t*-test at 0.05 level of significance.

two studies, the coverage rates of SIV among older people and pregnant women were 47.8% and 18.1%, respectively [33,37].

The clinical presentations of influenza and COVID-19 can be similar [42]. Also, lymphopenia has been observed in patients with severe influenza. [41] Coinfections with a severe course or a fatal outcome have been reported [43–46]. The risk for in-hospital death in patients with COVID-19 is five times higher than that of influenza hospitalized patients [47]; however, the outcome of Influenza-COVID-19 coinfections seems to be comparable with the outcome of COVID-19 alone [41].

A vaccine-induced change in innate immunity could explain the mechanisms behind the protective effect of SIV. Immunological memory cells are found in the innate immune compartment and tissue-resident stem cells and can be triggered by infections and vaccines [48–50]. As a result, these cells will defend the body against multiple pathogens, including those not targeted by the vaccine itself. This explanation is supported by the evidence that frequent childhood vaccinations and repeated pathogen infections might be resulting in trained immunity of innate immune cells, immune fitness of adaptive immune cells, or cross-protection of antibodies [51]. Furthermore, activation of innate immunity is also supported by the fact that innate immune system adaptations after SIV may be compromised by the aging process, which correlates with the observed lower protection rate of SIV vaccine in elderly patients [52,53].

The available data regarding the correlation between SIV and COVID-19 are limited; recently published studies showed increased influenza vaccine uptake during the COVID-19 pandemic correlates with reduced SARS-CoV-2 spread and decreased COVID-19 morbidity and mortality [54–56]. Furthermore, a study by Fink et al. [13] found that more than 53,000 patients with COVID-19 who had influenza vaccine demonstrated lower odds of requiring intensive care and ventilatory support in about 8% and 20%, respectively, with lower mortality in all age groups. Our findings also support a significant correlation between increased SIV coverage rate and decreased COVID-19 incidence. However, the results showed a decrease of COVID-19 severity percentage in

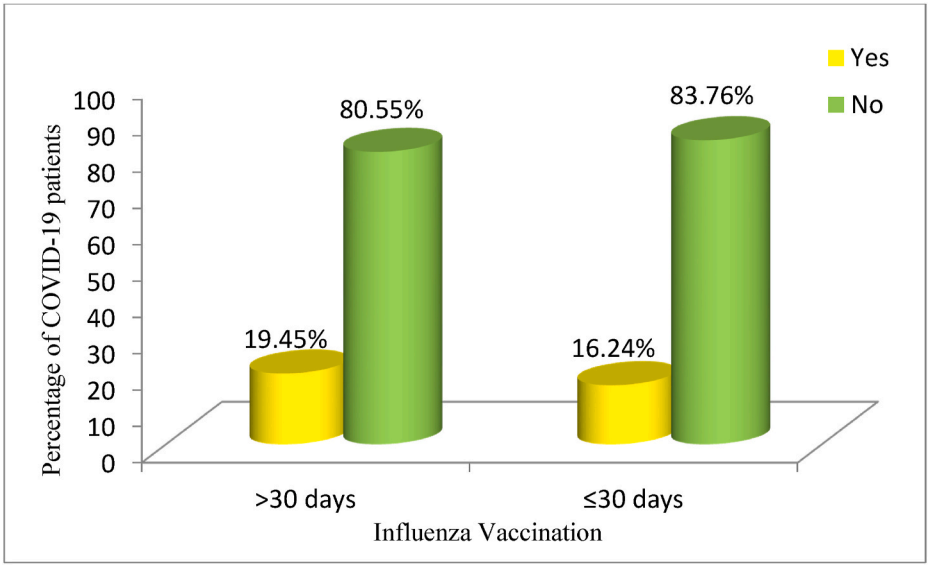

Fig. 2. Percentage of COVID-19 patients with and without Influenza vaccination according to the onset of COVID-19.

the vaccinated group compared with non-vaccinated, but it was not significant (P = 0.345).

Even infection with one pathogen does not preclude coinfections with other pathogens, and humans have suffered from influenza for thousands of years [41,57], COVID-19 pandemic waves can be more complicated during influenza seasons by influenza outbreaks and coinfections. However, in the real world, seasonal influenza spread seems less than expected during the 2020–2021 influenza season; some countries reported sporadic influenza cases, others even reported no influenza detection in specific seasonal periods [58,59]. Furthermore, despite increasing influenza testing in some countries, the percentages of positive results remain lower than in past seasons; the influenza B virus caused most reported cases [58]. Nevertheless, the evaluation or disappearance of specific virus and epidemiological behaviors depends on multifactorial ecological virome changes that need more investigations. One should interpret recent global influenza surveillance findings with caution; it seems that multiple factors are interplaying with influenza transmission during the COVID-19 pandemic. These include, but are not limited to, change of health-seeking behaviors among infected patients, the changes in laboratory practices regarding influenza testing, the effect of COVID-19 on sentinel sites, and implementation of various hygiene measures and physical distancing to reduce SARS-CoV-2 virus transmission [58,59].

Given the uncertainties of SARS-CoV-2 mutations, extends of COVID-19 epidemic waves, and the epidemiological impact of transmission of influenza viruses, SIV will remain of critical importance and an integral component of COVID-19 pandemic response plans, it will reduce the spread of influenza viruses and prevent influenza SARS-CoV-2 coinfections, especially in high-risk groups [60].

This study has some limitations, which are described as follows: First, it is a cross-sectional study using a self-administrated questionnaire, and the accuracy of findings is based on participant responses that may be inaccurate. Second, excluding a small portion of critically ill patients may affect the overall conclusions of disease severity. In addition, SIV uptake during the 2019–2020 influenza season may be influenced by outreach obstacles because of lockdown and other government measures to reduce SARS-CoV-2 spread. More studies are needed to tailor evidence-based response plans and increase SIV uptake among HCWs and other risk groups. Finally, future studies should answer emerging questions about COVID-19 pandemic and ecological virome changes that may lead to the spread of a single predominant pathogen, the need for dual vaccination in the next influenza season, and reliable policies to improve vaccination coverage for SARS-CoV-2 and influenza simultaneously. Furthermore, it is recommended to include more hospitals in Saudi Arabia with a larger sample size of COVID-19 confirmed cases in future studies. Such an attempt would further aid the researchers in determining the protective effect of the SIV against COVID-19.

5. Conclusions

Even with the tremendous efforts to promote SIV uptake among the general population and high-risk groups, the SIV coverage in SA is still not optimal yet. Out of all those diagnosed with COVID-19 disease (N = 1734), only 19% (N = 335) have prior vaccination with SIV. Our study clearly showed no association between the SIV coverage and the severity of COVID-19 compared to other studies that show an association of decreased severity of COVID-19 among vaccinated patients. However, this study found a significant decrease in the probability of getting infected with SARS-CoV-2 after receiving SIV. Such a study with the continuous progression of the COVID-19 pandemic calls for a novel approach regarding general vaccination policies to increase uptake of SIV and COVID-19 vaccines.

Ethical statement

The ethical approval for this study was obtained from the Institutional Review Board (IRB) of Imam Abdulrahman Bin Faisal University (IRB-2020-181), Dammam, Saudi Arabia.

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Author contributions

Dr. Marwan Jabr Alwazzeh (M.A.), Dr. Laila Mohammed Telmesani (L.T.), Dr. Abdulaziz Saud AlEnazi (A.A.), Dr. Lamia Abdulwahab Buohliqah (L.B.), Dr. Roa Talal Halawani (R.H.), Dr. Noor-Ahmed Jatoi (N.J.), Dr. Arun Vijay Subbarayalu (A.S.), Dr. Fahd Abdulaziz Almuhanna (F.A.)

Conceptualization - M.A., L.T. and A.A.; Methodology - M.A., L.T., A. A., L.B., and R.H.; Software - A.A., L.B. and R.H.; Validation - L.T., L.B and R.H.; Formal analysis - M.A., A.A., N.J. and F.A.; Investigation - A. A., L.B., and R.H.; Resources - M.A., A.S., and N.J.; Data -M.A., A.A., L.B., and R.H.; Writing—original draft preparation - M.A., and N.J.; Writing—review and editing - M.A., L.T, A.S., and F.A.; Visualization - M. A., A.S., and F.A.; Supervision - L.T., F.A.; Project administration - M.A., and A.S.; Funding acquisition - None.

Data availability statements

The data presented in this study are available on request from the corresponding author.

Informed consent statement

Informed consent was obtained from all participants involved in the study.

Sources of funding for your research

This research received no external funding.

Consent

Informed consent was obtained from all participants involved in the study.

The ethical approval for this study was obtained from the Institutional Review Board (IRB) of Imam Abdulrahman Bin Faisal University (IRB-2020-181), Dammam, Saudi Arabia.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Nothing to report.

Appendix A. Supplementary data

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