



Microbes and Infectious Diseases

Journal homepage: <https://mid.journals.ekb.eg/>

Original article

Adverse effects of Oxford–AstraZeneca COVID-19 vaccine among Egyptian healthcare workers

Mai Al-kaffas¹, Amal Aboelnour¹, Manal Aboeela²

1- Department of Medical Microbiology and Immunology, Research Institute of Ophthalmology, Giza, Egypt.

2- Department of Public Health, Research Institute of Ophthalmology, Giza, Egypt.

ARTICLE INFO

Article history:

Received 30 June 2022

Received in revised form 17 August 2022

Accepted 20 August 2022

Keywords:

Vaccine

AstraZeneca

Adverse effects

ABSTRACT

Background: The Coronavirus Severe Acute Respiratory Syndrome 2 (SARS-CoV-2) sparked a global pandemic that resulted in huge health and economic losses. There have been almost two hundred million affirmed cases of COVID-19 to date, with over seven million deaths. Clinical trials on all three vaccines approved for use in the Egypt (Pfizer–Biotech, Oxford–AstraZeneca and Moderna) have demonstrated substantial vaccination efficacy. Numerous research groups had developed possible vaccines as early as December 2020. Despite promises from the World Health Organization and European Medicines Agency (EMA) that there was no evidence tying vaccination to potential adverse events including blood clots, numerous European countries interrupted utilization of the Oxford–AstraZeneca vaccine on March 11, 2021, and noted the adverse effects revealed. We aimed to characterize and analyze the adverse effects associated with the Oxford–AstraZeneca vaccination. **Methods:** This study was done following vaccination of 113 medical healthcare personnel and documentation of each participant's adverse event at the Research Institute of Ophthalmology between March and June 2021. **Results:** 45 (39.8%) patients with no vaccine related adverse effects symptoms, 62 (54.9%) patients with mild/moderate symptoms, and 6 patients with severe side effects (5.3%). The most frequently reported adverse effects in mild/moderate symptoms were bony aches 43 (69.3%), fever 32 (51.6%), localized arm pain 7 (11.3%), and GIT symptoms 2 (3.2%). **Conclusion:** AstraZeneca vaccinations have been associated with mild to moderate adverse events.

Introduction

The Chinese Center for Disease Control spotted in early December 2019 that the outbreak in Wuhan City was initiated by SARS-CoV-2 infection. After MERS-CoV-1 and SARS-CoV-1, the SARS-CoV-2 virus is the third member of the coronavirus family to trigger outbreaks in human history [1]. It is highly contagious and has the potential to spread rapidly over the world. Until 20 July 2022, WHO recorded global situation of 562,672,324 confirmed COVID-19 cases, involving

9,176,657 confirmed cases in Africa and 6,367,793 deaths globally. As of 19 July 2022, 12,166,921,655 vaccine doses have been administered globally [2].

SARS-CoV-2 RNA encodes for four structural proteins including spike (S), membrane (M), envelope (E), and Nucleocapsid (N), with the S protein comprised of two subunits S1 and S2. The receptor binding domain (RBD) is included within the S1 subunit and has high affinity for the angiotensin converting enzyme 2 (ACE2) receptor

DOI: 10.21608/MID.2022.148304.1337

* Corresponding author: Mai Al-kaffas

E-mail address: kaffas_mai@hotmail.com

© 2020 The author (s). Published by Zagazig University. This is an open access article under the CC BY 4.0 license <https://creativecommons.org/licenses/by/4.0/>.

on the cell surface membrane. Infection is mediated by interaction of the SARS-CoV-2 RBD with the ACE2 viral receptor on host cells [3].

The safe, efficient, and economical COVID-19 vaccines stay critical for reducing emerging virus strains in current pandemic emergency [4,5], particularly by early December 2020, numerous research organizations developed potential COVID-19 vaccines [6].

However, an increasing amount of data demonstrates the critical role of cellular responses in COVID-19 patient recovery and encouraged the use of vaccine techniques that stimulate T cell-mediated responses [7]; second-generation SARS-CoV-2 vaccines differ from the currently used vaccines as they are designed to generate immune responses to multiple SARS-CoV-2 proteins and in addition to the spike protein targeted by vaccines that are now in use so they may not necessitate frequent booster immunizations and provide enhanced protection against a wide variety of SARS-CoV-2 variants [8].

The AstraZeneca's COVID-19 vaccine is a chimp adenovirus that encodes the spike glycoprotein [9]. It was authorized for utilization in the European Union (EU) by (EMA) on 29 January 2021, regarding European Commission approval; safety and effectiveness of the AstraZeneca vaccine were ascertained through a short-term review of data obtained from clinical trials [10].

Historically, vaccination safety has been monitored using a mixture of active and passive surveillance. The passive surveillance system is the pharmacovigilance foundation; it comprised databases into which physicians and patients spontaneously investigate adverse events following immunization (AEFI) and adverse drug reactions (ADRs) which was not much investigated in Egyptian population [11] which is crucial as clinical trials are frequently made to test the effectiveness of the treatment or vaccine first and foremost; safety is usually a secondary goal. These studies allow for the identification of prevalent negative impacts including local and systemic reactions correlated with the vaccine's immunogenicity [12].

Vaccines based on viral vectors are a comparatively new approach to vaccine development. Innumerable viruses have been altered to decrease their virulence and, in most instances, replication possibility while still infecting human cells [13]. These are designed to carry genetic information from the pathogen to immune

cells, enabling them to represent and reveal antigenic proteins to lymphocytes [14].

Pre-existing immunity to the vector can reduce the magnitude of evoked immune responses, which is one of the drawbacks of utilizing viral vectored vaccines [15]. Consequently, when a multiple vaccination regimen is used, antibodies against the viral vector generated can reduce the booster administrations immunogenicity such as prime-boost vaccinations [16].

Replication-competent viral vectored vaccines and replication-defective viral vectored vaccines are the 2 kinds of viral vectors used to generate vaccines. Because the multiplying vector can culminate with improved antigen presentation, replication vectors need a lower dose to elicit positive responses [17,18]. Replication-defective vectors, on the other hand, should be administered at a higher dose due to their inability to self-promoter [19,20].

COVID-19 vaccines have shown superior efficacy in clinical trials as well as real-world efficacy studies in healthcare workers, older adults, and the general population [21]. After a single dose of Oxford–AstraZeneca vaccine, vaccine efficiency outcomes demonstrate 50–70% protection mild disease, and 75–85% protection against severe diseases. After two doses, the effectiveness against mild disease rises to 65–90% [22,23].

All chronic conditions as diabetes, heart disease, liver disease, chronic kidney disease, neurological disease, and immunosuppressive disease; all been correlated with a higher risk of hospitalization or death when given COVID-19 [24,25]. Individuals with these circumstances have been given priority vaccination in several national programs [26-28].

Materials and Methods

Patients

The present study enrolled 113 medical staff participants and healthcare workers (doctors, nurses and healthcare personnel) at the Research Institute of Ophthalmology, Giza, Cairo, Egypt, between the period of March 2021 till June 2021.

Inclusion criteria of patients:

1. Participants above 18 years old.
2. Vaccination with oxford- AstraZeneca COVID-19 vaccine which was the programed vaccination status by the government to our institute.

3. The vaccination series all within the institute under supervision of the infection prevention control department (IPC).

Exclusion criteria of patients:

1. Participants less than 18 years old.
2. Patients with certain chronic diseases who are not allowed to receive their vaccination with a signed physician report
3. Vaccines other than oxford- AstraZeneca COVID-19 vaccine
4. Vaccination in a place other than the research institute of ophthalmology
5. Participants who had COVID-19 infection at this time.

Ethical approval

The present study was conducted with the Code of Ethics of the World Medical Association, according to the principles expressed in the Declaration of Helsinki 2013. This study has been approved by the Local Research Ethics Committee of Research Institute of Ophthalmology, Giza, Cairo, Egypt. A written informed consent was provided by each participant before their inclusion in the study. Patients' confidentiality was preserved.

Study design and sample size

A cross-sectional, observational study was carried out including all medical staff (113) who agreed to be immunized against COVID-19 using AstraZeneca vaccine between March and June 2021. The following data were gathered from the assessment after first dose of AstraZeneca's COVID-19 vaccine by history taking for symptoms and clinical signs for 12 weeks a follow up between the 2 doses, whether mild/moderate, severe or suggesting infection with COVID-19, all adverse effects were recorded as well as reported cases of positive COVID-19 PCR test.

Methods

Vaccination program

AstraZeneca's COVID-19 vaccine was given intramuscularly (0.5ml each). The first dose was administrated and follow up for any adverse effects was reported 24hrs, 72 hrs and 7 days' after first dose administration up to 12 weeks till administration of second dose. Vaccination program was done under the supervisor of the IPC department at the research institute of ophthalmology who had the authorization for the whole process from handling to vaccination delivery to strictly monitor practice and the assessment at the workplace.

Data collection

Adverse effects were reported after administration of first dose considering the severity whether mild/moderate or severe according to the clinical signs

and symptoms presented and reported by IPC team, actively surveyed after assessment of any adverse effect and investigations done to confirm the diagnosis. All reports were saved to avoid recall bias. Awareness vaccination program was given by IPC department during vaccination time about signs and symptoms of any side effect that could happen to be recorded.

Clinical signs and symptoms were recorded asking every participant about constitutional symptoms (fever, fatigue), respiratory symptoms (cough, dyspnea), neurological symptoms (headache, loss of taste, and loss of smell), and GI symptoms (nausea, vomiting, abdominal pain, and diarrhea). Diarrhea was defined in this study according to the following WHO criteria: three or more loose stools/day or an increase in the number of motions as compared with usual. Frequency, severity, and duration of post COVID vaccination was assessed according to **Kumar et al.** [29]

Statistical analysis

Data was collected from medical records and was statically analyzed using SPSS program. the data was summarized using descriptive measures (e.g., means and standard deviations or median and IQR for continuous variables and percentages for categorical variables.

Chi square test and Mann Whitney U test were used as tests of significance to detect any significant difference between subjects who developed COVID infection after the first dose with those who didn't. p value ≤ 0.05 was considered significant

Results

In the present result, gender distribution in the vaccination program in our institute included 67 (59.3%) males than 46 (40.7%) females. By reporting the adverse effects after the first dose, the results showed 45 out of 113 with no vaccine related adverse effect about (40 %) while mild to moderate adverse effect reported 62 (54.9%) and the lowest for the severe adverse effects reporting 6 cases (5.3%) as shown in **table (1)**.

In the present result, we analyzed the adverse effects of the healthcare staff after the first vaccination dose according to the severity of symptoms and clinical signs; results showed the majority 62 cases was mild to moderate adverse effects. Bony aches reported 43(69.3%) was the highest record followed by fever 32(51.6%) then localized arm pain 7(11.3%) and the least to GIT disorder only 2 cases (3.2%).

Our results reported 6 cases with severe adverse effects with equal analysis reported between GIT and headache 2 cases (33.3%) for each and same results for fever, myositis and bony aches reported 1 case (16.7) for each shown in **table (2)**.

In the present study, we evaluated the distribution of the healthcare vaccinated staff affected by COVID-19 after the first dose to differentiate between infection and vaccination

adverse effects PCR was done for confirmation; reporting 7 cases out of 113 confirmed positive PCR along with signs and symptoms of the disease. Our result showed distribution of males 5 cases (71.4%) to females 2 cases (28.6%) out of the 7 cases.

Our results showed 4 out of 7 cases reported with no vaccine related adverse effects symptoms (57.1%) while 2 cases reported mild to moderate (28.6%) and only 1 case reported severe adverse effect shown in **table (3)**.

Table 1. Demographic and clinical characteristics of the vaccinated group.

Gender n, (%)	
Male	67(59.3)
Female	46(40.7)
Age (years) at 1st dose (median, IQR)	56.4, 23.5
(MIN, MAX)	27, 88
Period between 1st and 2nd dose	
median and IQR	84.0, 1.0
(MIN, MAX)	82.0, 155.0
Side effects following vaccination n, (%)	
No Symptoms reported	45(39.8)
Mild to moderate Symptoms	62(54.9)
Severe Symptoms	6(5.3)

n= number, IQR= interquartile range

Table 2. Adverse effects of the vaccinated staff.

Adverse effects n, (%)	
Mild to moderate symptoms	n = 62
● Bony aches	43(69.3)
● Localized arm pain	7(11.3)
● Fever	32(51.6)
● GIT symptoms	2(3.2)
Severe Symptoms	n = 6
● GIT	2(33.3)
● Headache	2(33.3)
● Fever	1(16.7)
● Myositis	1(16.7)
● Bony aches	1(16.7)

N.B. Some persons had combined side effects.

Table 3. Distribution of vaccinated staff according to COVID-19 infection status.

Variables	COVID 19 after 1st dose		P value
	No (n=106)	Yes (n=7)	
Gender			
Male	62(58.5)	5(71.4)	0.500 ^a
Female	44(41.5)	2(28.6)	
Age(years) at 1st dose (mean, SD)	51.5± 93.5	53.7± 11.1	0.388 ^b
(Min, Max)	27, 88	43, 65	
Severity of Side effects			
No related vaccine side effect symptoms	41(38.7)	4(57.1)	0.268 ^a
Mild to moderate	60(56.6)	2(28.6)	
Severe	5 (4.7)	1(14.3)	

Values are presented as number&% or mean and SD

a Chi square test statistic is used

b Mann-Whitney U test

p value ≤ 0.05 is considered significant

Discussion

The agent responsible for COVID-19, SARS-CoV-2, poses an unprecedented threat to global economics and public health [30]. Safe, efficient, and affordable COVID-19 vaccines' development stays essential to minimize evolving virus strains in the current pandemic crisis and restoring normalcy in the future [31].

In the present study, the distribution of male was higher than females reporting 67 cases out of 113 this was in consistent to a previous study by **Mediu et al.** [32] who documented that gender had an impact factor in the immune response by vaccination in which Females in particular had stronger antibody response to certain vaccines and faster waning of antibody titer compared to men [33]. In addition, previous data has demonstrated the role of estrogen in women as an important down-regulator of angiotensin-converting enzyme 2 which is a known SARS-CoV-2 receptor [34]. In fact, female patients infected with COVID-19 exhibit stronger T cell activation when compared to males [35].

We conducted 45 (39.8%) patients with vaccine related adverse effects symptoms, 62 (54.9%) patients with mild to moderate symptoms, and six patients with severe side effects (5.3%). The most frequently reported adverse effects in mild to moderate symptoms were bony aches 43 (69.3%), fever 32 (51.6%), localized arm pain 7 (11.3%), and GIT disorder in the form of diarrhea 2 (3.2%). however, all symptoms and signs subsided few days

after vaccination, which contrasted with a study by **Voysey et al.** [10] who reported that the most noted negative reactions were injection site myalgia (44.0%), tenderness (63.7%), headache (52.6%), fatigue (53.1%), malaise (44.2%), and. (7.9 %). Furthermore, similar to some of the adverse effects noticed in a study by **Zahid et al.** in Bahrain, where pain at the injection site was observed in (31.03 %), myalgia was observed in (10.3 %), and nausea was observed in (3.45 %) [36]. All symptoms and clinical signs were due to reactogenicity and the physical manifestation of the inflammatory response to vaccination which may differ from person to another.

Following the initial dose, seven participants tested positive for COVID-19 infection. Initially, four of them reported no vaccine related adverse effect symptoms, two reported mild direct side effect symptoms, but one participant over 80 years old developed severe CNS symptoms. This was in line with a study conducted by **Al Khames et al.** which reported only two participants were hospitalized for COVID-19 infection following vaccination [37]. This can be explained by two ways whether the protective value of AstraZeneca vaccine in fully and one dose vaccinated was 76% effective at protecting against COVID-19 with symptoms for at least 90 days, according to late-stage-trial data published in The Lancet on February, 2021[38] as there is no vaccine that provides that level of protection for any disease so we do expect in any vaccine program that there will be cases of disease

among people who were fully vaccinated and certainly among some people who were partially vaccinated or due to antibodies reactions eliciting a slight symptoms of COVID-19 disease [39] or those patients with co-morbidities as hypertension, diabetes, cardiovascular and respiratory system diseases, and other underlying disease are more likely to develop serious illness requiring intensive care treatment associated with poorer clinical outcomes [40].

Our study found no vaccine related adverse effect of thrombosis, in contrast to a latest single study obtained from a study by **Pulanić et al.** from Croatia that found an elevation in the incidence of mixed pulmonary embolism (PE) and deep venous thrombosis (DVT), but not extracted PE or extracted DVT [41] Pandemic lockdowns and restrictions on physical activity were postulated to be the cause [42].

Muscle pain (inflammatory myositis), Fever, and injection site inflammation are all common side effects of foreign drug injection. They are the result of the innate immune system's interaction. When the body's macrophages or neutrophils detect vaccine molecules, they release cytokines, which are chemical signals that cause fever, chills, nausea, and muscle pain. If a foreign agent is implemented into the bloodstream, this cytokine response is anticipated [43]. Active immunizing antigens, preservatives, stabilisers, adjuvants, conjugating agents, and culture media used in vaccine preparation are all prospective allergens. Type III hypersensitivity reactions include a wide range of delayed reactions that are primarily induced by the immune complexes encompassing T cells' formation. The most typical symptoms of postponed reactions are rashes, which include erythema, angioedema, and urticaria [44].

Study's limitations

Involve the small number of possible negative events, the vaccine's restricted safety data, and also the requirement to quantify each participant's antibodies and immunogenicity. This study, on the other hand, collected valuable data on this current topic. It found a very small number of adverse reactions correlated with the AstraZeneca's COVID-19 Vaccine that could have been caused by a variety of factors other than the vaccines. Underreporting combined with investigation biases. It deduced the vaccine seemed to be effective and safe, with benefits outweighing risks, and urged

individuals to acknowledge vaccination when offered.

Conclusions

Out of 54,571 adverse reactions reported in the electric vehicle database, this study found mild to moderate adverse effects with few severe symptoms linked to the AstraZeneca's COVID-19 Vaccine. This finding should be interpreted with caution because underreporting combined with investigation biases may limit the findings' generalizability.

Recommendations

A potential COVID-19 vaccine must address these safety concerns to stop the current pandemic, avoid its recurrence, and avoid future epidemics with eliciting long lasting immunity and avoid disease progression.

Additional analyses predicated on more detailed adverse event findings, which include patient features and comorbidities, may allow for a more precise determination of causality.

Clinical trials examining the vaccine's efficacy in limiting disease, seeking to avoid infection, and reducing infectiousness, as well as studies investigating the vaccine's indirect impacts, can be used to evaluate these vaccine effects

Conflict of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Funding source

This research has not been funded with any specific grant from any funding agency.

References

- 1-**Abdool Karim SS, de Oliveira T.** New SARS-CoV-2 Variants: Clinical, Public Health, and Vaccine Implications. *N Engl J Med* 2021;384(19):1866-1868.
- 2-**WHO.** Coronavirus disease (COVID-19) situation report,181. World Health Organization, Geneva (2020)
- 3-**Dai L, Gao GF.** Viral targets for vaccines against COVID-19. *Nat Rev Immunol* 2021;21(2):73-82.
- 4-**Tobaiqy M, Elkout H, MacLure K.** Analysis of Thrombotic Adverse Reactions of COVID-

- 19 AstraZeneca Vaccine Reported to EudraVigilanceDatabase. *Vaccines* (Basel) 2021;9(4):393.
- 5-**Morin L, Savale L, Pham T, Colle R, Figueiredo S, Harrois A, et al.** Four-Month Clinical Status of a Cohort of Patients After Hospitalization for COVID-19. *JAMA* 2021;325(15):1525-1534.
- 6-**Kyriakidis NC, López-Cortés A, González EV, Grimaldos AB, Prado EO.** SARS-CoV-2 vaccines strategies: a comprehensive review of phase 3 candidates. *NPJ Vaccines*. 2021;6(1):28.
- 7-**Moss P.** The T cell immune response against SARS-CoV-2. *Nat Immunol* 2022;23:186–193.
- 8-**Turner JS, O’Halloran JA, Kalaidina E, Kim W, Schmitz AJ, Zhou JQ, et al.** SARS-CoV-2 mRNA vaccines induce persistent human germinal centre responses. *Nature* 2021;596: 109–113.
- 9-**Sayedahmed EE, Elkashif A, Alhashimi M, Sambhara S, Mittal SK.** Adenoviral Vector-Based Vaccine Platforms for Developing the Next Generation of Influenza Vaccines 2020; 8(4):574.
- 10-**Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK., et al.** Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; 397:99-111.
- 11-**Lei J, Balakrishnan MR, Gidudu JF, Zuber PLF.** Use of a new global indicator for vaccine safety surveillance and trends in adverse events following immunization reporting 2000–2015. *Vaccine* 2018; 36 (12): 1577–1582.
- 12-**Sebastian J, Gurumurthy P, Ravi MD, Ramesh M.** Active surveillance of adverse events following immunization (AEFI): a prospective 3-year vaccine safety study. *TherAdv Vaccines Immunother* 2019;21(7):2515135519889000.
- 13-**Uddin M, Mustafa F, Rizvi TA, Loney T, Suwaidi HA, Al-Marzouqi AHH, et al.** SARS-CoV-2/COVID-19: Viral Genomics, Epidemiology, Vaccines, and Therapeutic Interventions. *Viruses*. 2020;12(5):526.
- 14-**Matić, Z. and Šantak, M.** Current view on novel vaccine technologies to combat human infectious diseases. *ApplMicrobiolBiotechnol* 2022;106: 25–56.
- 15-**McIntyre PB, Aggarwal R, Jani I, Jawad J, Kochhar S, MacDonald N, et al.** COVID-19 vaccine strategies must focus on severe disease and global equity. *Lancet* 2022;399(10322):406-410.
- 16-**Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al.** Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet* 2021;397(10275):671-681.
- 17-**Rodrigues AF, Soares HR, Guerreiro MR, Alves PM, Coroadinha AS.** Viral vaccines and their manufacturing cell substrates: New trends and designs in modern vaccinology. *Biotechnol J* 2015;10(9):1329-1344.
- 18-**Kallert SM, Darbre S, Bonilla WV, Kreutzfeldt M, Page N, Müller P, et al.** Replicating viral vector platform exploits alarmin signals for potent CD8⁺ T cell-mediated tumour immunotherapy. *Nat Commun* 2017; 8:15327.
- 19-**Ura T, Okuda K, Shimada M.** Developments in Viral Vector-Based Vaccines. *Vaccines* (Basel) 2014;2(3):624-641.

- 20-**Richterman A, Meyerowitz EA, Cevik M.** Indirect Protection by Reducing Transmission: Ending the Pandemic with Severe Acute Respiratory Syndrome Coronavirus 2 Vaccination, *Open Forum Infectious Diseases* 2022;9(2):259
- 21-**Munster VJ, Wells D, Lambe T, Wright D, Fischer RJ, Bushmaker T, et al.** Protective efficacy of a novel simian adenovirus vaccine against lethal MERS-CoV challenge in a transgenic human DPP4 mouse model. *NPJ Vaccines* 2017;16; 2:28.
- 22-**Bennet BM, Wolf J, Laureano R, Sellers RS.** Review of current vaccine development strategies to prevent coronavirus disease 2019 (COVID-19). *Toxicol Pathol* 2020;48: 800-809.
- 23-**Whitaker HJ, Tsang RS, Byford R, Andrews NJ, Sherlock J, Sebastian P, et al.** Pfizer-BioNTech and Oxford AstraZeneca COVID-19 vaccine effectiveness and immune response amongst individuals in clinical risk groups. *The Journal of Infection*. 2022;84(5):675-683.
- 24-**Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, Desai P, et al.** Comorbidity and its Impact on Patients with COVID-19. *SN Compr Clin Med* 2020;2(8):1069-1076.
- 25-**Fast HE, Zell E, Murthy BP, Murthy N, Meng L, Scharf LG, et al.** Booster and Additional Primary Dose COVID-19 Vaccinations Among Adults Aged ≥ 65 Years. *MMWR Morb Mortal Wkly Rep* 2021;17;70(50):1735-1739.
- 26-**Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al.** Factors associated with COVID-19 related death using Open safely. *Nature*. 2020;584(7821):430-436.
- 27-**Sjöwall J, Hjorth M, Gustafsson A, Göransson R, Larsson M, Waller H, et al.** SARS-CoV-2 Specific Antibody Response and T Cell-Immunity in Immunocompromised Patients up to Six Months Post COVID: A Pilot Study. *J Clin Med* 2022, 11, 3535
- 28-**Seebacher NA.** The antibody response of haematological malignancies to COVID-19 infection and vaccination. *Br J Cancer* 2022; 126:691–692.
- 29-**Kumar R, Botwin G, Horizon A.** American Journal of Gastroenterology 2021;116:427-S428.
- 30-**Coronaviridae Study Group of the International Committee on Taxonomy of Viruses.** The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol* 2020;5(4):536-544.
- 31-**Giovanetti M, Benedetti F, Campisi G, Ciccozzi A, Fabris S, Ceccarelli G, et al.** Evolution patterns of SARS-CoV-2: Snapshot on its genome variants. *Biochem Biophys. Res Commun* 2021 ;29:538:88-91.
- 32-**Mediu R, Rama A, Puca E.** Evaluation of neutrophil-to-lymphocyte ratio and immune response in patients vaccinated with Pfizer-Biontech vaccine. *J Infect Dev Ctries* 2022 ;30;16(5):745-751.
- 33-**Zimmermann P, Curtis N.** Factors That Influence the Immune Response to Vaccination. *Clin Microbiol Rev* 2019;32(2): e00084-18.
- 34-**Klein S, Cortese M, Winter SL, Wachsmuth-Melm M, Neufeldt CJ, Cerikan B, et al.** SARS-CoV-2 structure and replication characterized by in situ cryo-electron tomography. *Nat Commun* 2020;11(1):5885.
- 35-**McCartney PR.** Sex-based vaccine response in the context of COVID-19. *J Obstet Gynecol Neonatal Nurs* 2020; 49: 405–408.

- 36-**Zahid MN**. Unfolding the Mild to Moderate Short-Term Side Effects of Four COVID-19 Vaccines Used in Bahrain: A Cross-Sectional Study. *Vaccines (Basel)* 2021;9(11):1369.
- 37-**Al Khames Aga QA, Alkhaffaf WH, Hatem TH, Nassir KF, Batineh Y, Dahham AT, et al**. Safety of COVID-19 vaccines. *J Med Virol* 2021;93(12):6588-6594.
- 38-**Chenchula S, Karunakaran P, Sharma S and Chavan M**. Current evidence on efficacy of COVID-19 booster dose vaccination against the Omicron variant: A systematic review. *J Med Virol* 2022;94(7):2969-2976.
- 39-**World Health Organization**. Statement for healthcare professionals: How COVID-19 vaccines are regulated for safety and effectiveness. March, 2021.
- 40-**Puca E, Čivljak R, Arapović J, Popescu C, Christova I, Raka L, et al**. Short epidemiological overview of the current situation on COVID-19 pandemic in Southeast European (SEE) countries. *J Infect Dev Ctries* 2020;14(5):433-437.
- 41-**Pulanić D, Gverić-Krečak V, Nemet-Lojan Z, Holik H, Coha B, Babok-Flegarić R, et al**. Venous thromboembolism in Croatia - Croatian Cooperative Group for Hematologic Diseases (CROHEM) study. *Croat Med J* 2015;56(6):550-7.
- 42-**Wilke J, Mohr L, Tenforde AS, Edouard P, Fossati C, González-Gross M, et al**. A Pandemic within the Pandemic. Physical Activity Levels Substantially Decreased in Countries Affected by COVID-19. *Int J Environ Res Public Health* 2021;18(5):2235.
- 43-**Hervé C, Laupèze B, Del Giudice G, Didierlaurent AM, Tavares Da, Silva F, et al**. The how's and what's of vaccine reactogenicity. *NPJ Vaccines* 2019; 4:39.
- 44-**Kim MA, Lee YW, Kim SR, Kim JH, Min TK, Park HS, et al**. COVID-19 Vaccine-associated Anaphylaxis and Allergic Reactions: Consensus Statements of the KAAACI Urticaria/Angioedema/Anaphylaxis Working Group. *Allergy Asthma Immunol Res* 2021;13(4):526-544.