# العلاقة بين الزمر الدموية الأساسية وأنواعها الفرعية بتشكيل الأضداد عند الأفراد السوريين الملقحين ضد فيورس كورونا المستجد سارس كوفيد ٢-

**The relationship between the essential blood groups and their subtypes with the formation of antibodies in Syrian individuals vaccinated against SARS-CoV-2**

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**الملخص:** حاولت العديد من الدراسات ايجاد علاقة بين أنواع الزمر الدموية (A,B, and O) وإمكانية الإصابة بفيروس كورونا المستجد COVID-19. حاولنا اكتشاف العلاقة بين الزمر الدموية الأساسية (A,B, and O) وأنواعها الفرعية ($Rh^+$) و ($Rh^-$) مع عيارات الأجسام المضادة التي أحدثتها لقاحات فيروس كورونا المستجد SARS-CoV2، في مجموعة من المجتمع السوري.

**الطرائق**: بلغ عدد المشاركين في هذه الدراسة ٢٤٣ مشارك. منهم ١٥٣ شخصا تلقى اللقاح، و٩٠ شخص غير متلقي للقاح. استخدم ثلاثة أنواع من اللقاحات. اختيرت مستويات الأضداد IgM و IgG بعد عشرة أيام من كل جرعة اللقاح الأولى والثانية.

**النتائج:** بعد الجرعة الثانية من اللقاح اعتمدت مستويات الأضداد IgG كمؤشرات مناعية، حددت فروق معنوية تفضيلية للقاح استرازينكا وزمرة الدم A بالمقارنة مع زمرة الدم O. لأكثر من ذلك أظهر الذكور حاملي زمرة الدم A مستويات أعلى من الأضداد IgG مقارنة مع الإناث حاملي الزمرة A. أبدى المشاركون من الشريحة العمرية بين (٣٣-٤٦ سنة) وحاملي الزمرة الدموية O الذين تلقوا لقاح أسترازينكا مستويات الأضداد IgG أعلى من غيرهم. أخيرا لوحظ وجود فروق مهمة بين الأفراد حاملي الزمرة الفرعية $Rh^+$ الذين تم تلقيهم لقاح استرازينكا والأفراد حاملي نفس الزمرة $Rh^+$ الذين تلقوا الأنواع الأخرى من اللقاح. **الخلاصة:** قد تعطي مستويات الأضداد IgG فكرة عن احتياج اللقاح المعزز ضد فيروس كورونا SARS-CoV-2. حيث من الممكن اعتبار نتائج الدراسة كمؤشر إيجابي لفعالية اللقاح والحماية الكاملة.

**الكلمات المفتاحية:** سارس كوفيد -٢، سوريا، المناعة، مستوى IgG ، مستوى IgM، الزمر الدموية A,B, &O,$Rh^+$, $Rh^-$

## The relationship between the essential blood groups and their subtypes with the formation of antibodies in Syrian individuals vaccinated against SARS-CoV-2

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**Abstract**

**Background:** Several studies tried to find a relationship between AB & O blood types and susceptibility to COVID-19. In this study, we attempted to detect a relationship between essential ABO blood groups and their subtypes $Rh^+$ and $Rh^-$ with the antibody titers elicited by SARS-CoV2 vaccines in a group of Syrian society.

**Methods:** A total of 243 participants were included in this study, comprising 153 vaccinated individuals and 90 unvaccinated individuals. Three types of vaccines were used. IgM & IgG titers were tested 10 days after the vaccine's first and second doses**.**

**Results:** After the $^{2nd}$dose of vaccine, IgG titers were used as indicators of immunogenicity, significant differences were detected in the advantage of AstraZeneca and type A blood group as compared to blood type O. Furthermore, males with type A blood group presented higher IgG titers than females with type A. Vaccinated participants belonging to age-group 33-46ys with type O who received AstraZeneca expressed IgG titers more than others. Finally, significant differences were obtained between $Rh^+$ vaccinated subjects receiving AstraZeneca compared with $Rh^+$ vaccinated individuals using other vaccines.

**Conclusion:** IgG titers may give an idea about the requirement of a booster vaccine against SARS-CoV-2. Our findings could be considered positive predictors of vaccine effectiveness and full protection.

**Keywords:** SARS-CoV-2 vaccine, Syria, immunogenicity, IgG titers, IgM titers, ABO blood groups, $Rh^+$, $Rh^-$.

## Introduction

The world has faced the most frightening pandemic of the twentieth century, it is sars-cov 2 (COVID-19). The virus disrupted social and economic life systems and put pressure on health systems around the world. An outbreak shook the globe, caused by SARS-CoV-2 [1].

In 2021, COVID-19 caused the death of 2.5 million worldwide. In the Syrian Arab Republic, 57,743 confirmed cases have been reported, of which 3,165 deaths have occurred until 4/10/2022 [2]. Treatment is primarily supportive and symptomatic after suitable isolation of patients to prevent infecting others.

At the beginning of 2021, the US Food and Drug Administration granted emergency use authorization for COVID-19 vaccines, based on a smaller amount of data than typical. A lot of results showed that there is a relationship between the type of blood Group and vaccination,

To date, there are no biomarker-predicting factors that increase the chance of contracting COVID-19. Some studies have shown that the elderly and males are more likely to acquire the disease than others [4]. Furthermore, research from different regions of the world demonstrated a relationship between ABO blood types and susceptibility to COVID-19.

Many papers discussed the relationship between the sars-cov2 and blood groups. They mentioned that people with blood group O were associated with a lower risk of COVID-19 than blood groups A, B, and AB [5]. Despite inconsistencies, these studies found a general tendency for People with Type A and B to be more susceptible to this viral infection, while people with blood type O and AB are less likely to be infected [5-13]

Other researchers investigated the antibody levels of these blood groups and their relationship with the risk of SARS-CoV-2 infection. The outcomes showed low serum levels of ABO antibodies in infected patients compared to healthy individuals, indicating that it may be a factor that increases the chance of getting the disease [14]. This result contradicted the findings of a Bahraini study that presented no association between these variables and the susceptibility to the infection [7].

It is impressive that in less than a year since the identification of the SARS-CoV-2 DNA sequence, the scientific community has demonstrated an exceptional effort to develop over 150 vaccine projects against the emerging Coronavirus. Each project has unique characteristics that distinguish it from others regarding effectiveness, the time required to stimulate the immune response, and vaccine safety [15-16]. Ten vaccine candidates have entered clinical trial phase 3: two of which are mRNA-1273 (US) by Moderna and BNT162b2 (US-Germany) by Pfizer-BioNTech, using mRNA coding for the spike protein encapsulated in lipid nanoparticles. Four products employ adenoviruses as delivery vectors for the spike protein: ChAdOx1 nCoV-19 for AstraZeneca in collaboration with the University of Oxford (US-UK), Ad26.COV2.S (US) by Johnson & Johnson, Ad5 by CanSino Biologics (China), and Gam-COVID-Vac

(Sputnik V) by the Gamaleya Research Institute of Epidemiology and Microbiology (Russia). The latter utilizes a vector containing two recombinant adenoviruses, types 26 and 5, to deliver the gene coding for the spike protein. Many Chinese pharmaceutical companies, such as SinoVac BioTech and SinoPharm, developed traditional vaccines using inactivated SARS-CoV-2 [17]. As of April 17, 2023, a total of 5,090,630 vaccine doses have been administered to Syrian individuals, according to WHO [17].

This work attempted to determine whether there is a relationship between the immunogenicity of COVID-19 vaccines and the essential ABO blood groups and their subtypes $Rh^+$ and $Rh^-$ in a group of Syrian individuals.

## Materials and methods

### Study population

Overall, 243 participants, 153 vaccinated and 90 unvaccinated, were enrolled in this study. The vaccinated group included 72 females and 81 males aged between 20 and 70 years. The control group involved 45 females and 45 males between 20 and 65 years old who had negative PCR tests for SARS-CoV-2 on the day of collecting blood samples.

The Directorate of Health in Homs, Syria, immunized the subjects, using AstraZeneca, Sinopharm, and Sputnik V. This work was in collaboration between Homs University, Faculty of Sciences at the Department of Biology, and Al Wataniya Private University, Faculty of Pharmacy at the Department of Biochemistry. It was conducted following the guidelines of the Declaration of Helsinki. Ethical approval was obtained from the Human Research Ethics Committee.

**Blood specimen collection and processing**

Samples were collected randomly from June 2022 to August 2022. 5 ml of blood samples were collected from participants in lithium heparin tubes. Determination of the essential blood groups and their subtypes in all subjects was achieved by utilizing ABO &Rh. Blood Grouping Kit (InTec, China). Serum was obtained by centrifugation for 10 min at 3.000 rpm at 4°C. To measure the immune response against the vaccine (ichroma™ COVID-19), Ab (antibody) from (Boditech) was used for qualitative determination of IgG/IgM, 10 days after receiving the first and the second doses of the vaccine. The ichroma$^{TM}$ COVID-19Ab test result indicates the 'positive' or 'negative' of a sample defined by the algorithm of the ichroma$^{TM}$ reader based on COI (cut-off index). The result is considered positive for IgG/IgM if the titer is $\geq 1.1$. IgM titer was used as a suitable

indicator of the body response after 10 days of the first vaccination, while IgG titer was a suitable reference after 10 days of the second dose.

The resulting data was analyzed to investigate the relationship between the essential ABO blood groups and their subtypes with the levels of antibodies after immunization.

**Statistical analysis**

Statistical tests were performed with GraphPad Prism 5.0 and SPSS version 10. The data was presented as standard deviation SD, minimum, maximum, and mean values. The "*t*" test was applied for independent samples to examine the significant differences between dichotomous variables, and one-way ANOVA to examine the significant differences between dummy variables. A confidence level of 95 (% $p < 0.05$) was considered to be statistically significant.

**Results**

This study included 243 randomly collected individuals, of whom 153 were vaccinated and 90 were not. Three brands of COVID-19 vaccines were used in this study: AstraZeneca for 105 participants, Sinopharm for 21, and Sputnik V for 27 subjects (Figure 1).

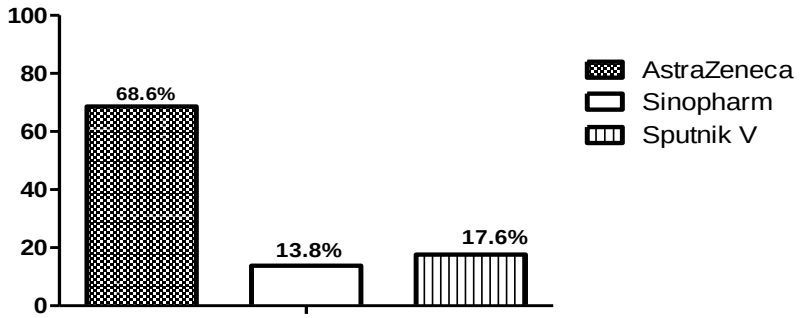


**Figure 1. Prevalence of used vaccines**

The vaccinated group consisted of 72 (≈47%) females and 81 (≈53%) males between 20 and 70 years old, whilst the control group (unvaccinated) involved 45(50%) females and 45 (50%) males between 20 and 68 years old (Figure 2).

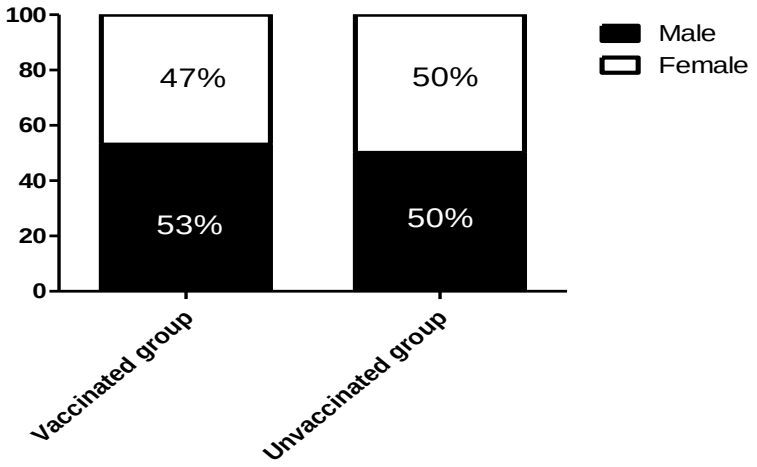


**Figure 2. Prevalence of participants of each sex in both groups**

Demographic, experimental, and clinical findings of participants are summarized in Table 1.

**Table 1.** Demographic, Experimental, and Clinical Findings of Participants

| **Variable** | **Mean ± SD*** | **Min.** | **Max.** |
|---|---|---|---|
| Age, yr vac** | 39.8±15 | 20 | 70 |
| IgM vac 1st dose | 1.6±0.5 | 0.6 | 3.1 |
| IgG vac 1st dose | 2.5±0.7 | 1.4 | 4.2 |
| IgM vac 2nd dose | 2.3± 1.7 | 0.6 | 14 |
| IgG vac 2nd dose | 16.2 ±10.8 | 2.6 | 43.4 |

| | | | |
|---|---|---|---|
| Age, yr unvac** | 36±13.5 | 20 | 68 |
| IgM unvac | 0.09±0.07 | 0 | 0.1 |
| IgG unvac | 0.1±0.06 | 0 | 0.09 |

Note: *SD=standard of deviation, **vac=vaccinated group,

***unvac=unvaccinated group

Vaccinated and unvaccinated subjects were further divided into 4 groups according to age as follows: 20-33 years, 33-46 years, 46-59 years, and 59 ≥ years. The outcomes for each group are represented in (Figures) and (Figure 4).

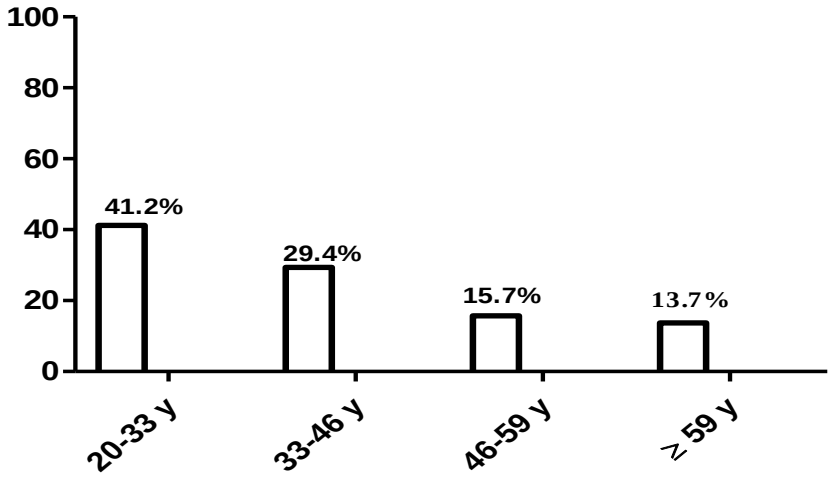


**Figure 3. Prevalence of vaccinated subgroups according to age**

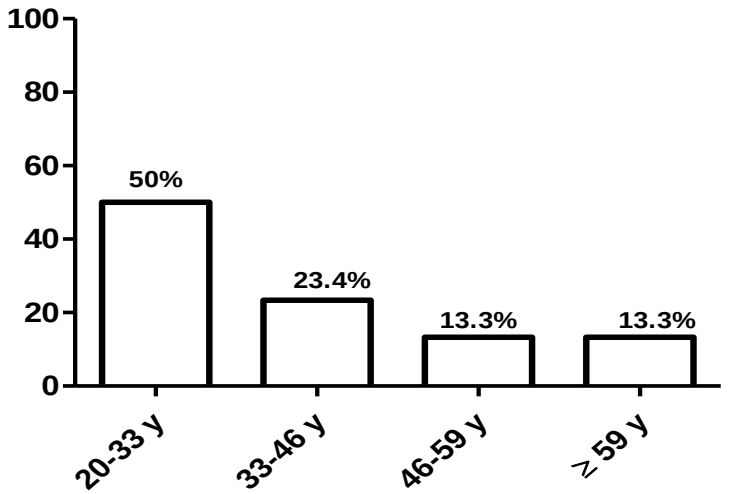


**Figure 4. Prevalence of unvaccinated subgroups according to age**

No significant difference was found between males and females regarding the average age in both groups (P=0.29). Significant p-values were obtained from IgM and IgG titers between the vaccinated and unvaccinated groups, favoring the vaccinated group ($p<0.0001$).

**Distribution of blood group:** The distribution of essential and subtypes of blood groups in vaccinated and unvaccinated subjects has been shown in Figures 5a, 5b, 6a, and 6b as follows:

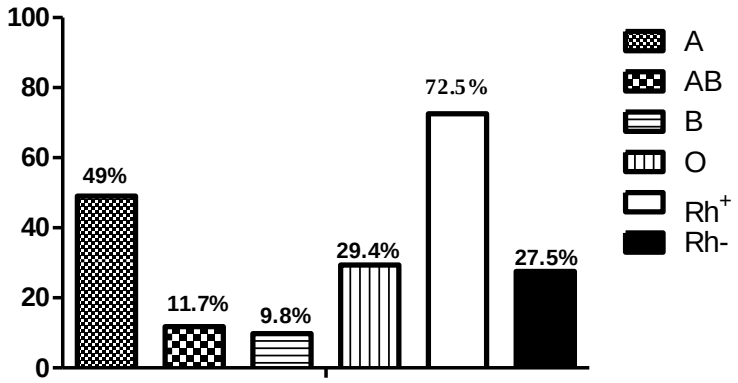


**Figure 5a. Distribution of blood groups in vaccinated subjects**

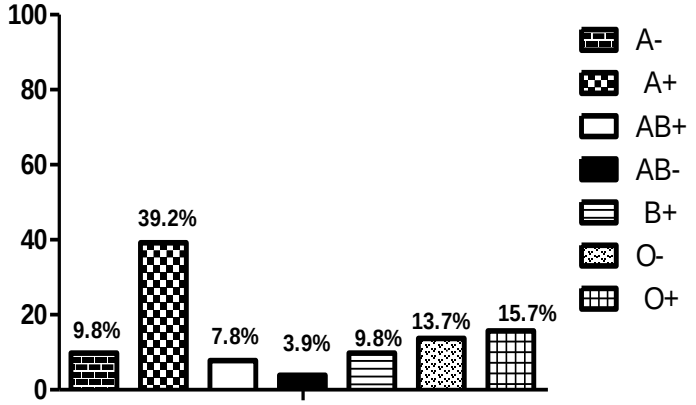


**Figure 5b. Distribution of essential ABO blood groups and its subtypes in vaccinated group**

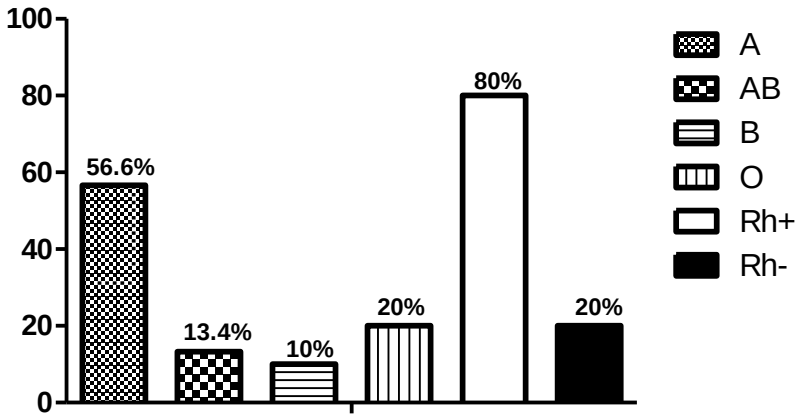


**Figure 6a. Distribution of blood groups in unvaccinated subjects**

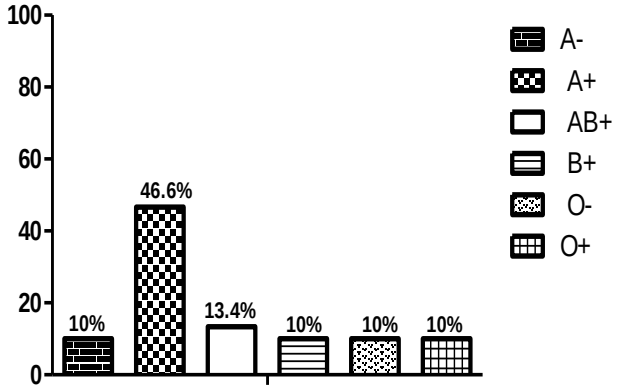


**Figure 6b. Distribution of essential ABO blood groups and its subtypes in unvaccinated group**

**Immune response against immunization:**

Two independent samples test was used to examine the significant differences between dichotomous variables (dose and gender), and one-way ANOVA was used to examine the significant differences between

dummy variables (types of vaccine, blood groups, and age groups) in terms of IgM and IgG titers:

**1- Tow-independent samples test (IgM):**

There was a significant difference in IgM titers between the (IgM first dose) and the (IgM second dose) of vaccine in favor of the 2nd dose, IgM second dose (average ± SD) > IgM first dose (average ± SD) IgM second dose (2.3±1.7) > IgM first dose (1.6±0.5), $p = 0.007$. However, no significant difference was detected between IgM first dose and IgM second dose in terms of sex, type of vaccine, ABO blood groups, or age.

**2- Tow-independent samples test (IgG):**

There was a significant difference in IgG titers between the 1st (IgG first dose) and the 2nd (IgG second dose) doses of the vaccine, to the advantage of the 2nd dose, IgG second dose (16.3±10.8) > IgG first dose (2.5±0.7), $p < 0.0001$. No significant difference was detected between the IgG first dose and the IgG second dose in terms of gender. Concerning blood groups, a difference was seen between IgG first dose and IgG second dose titers in favor of the (A) blood group IgG second dose(A) (16.9±11.6) > IgG first dose(A) (2.5±0.7),

$p < 0.0001$.

**3- Statistical analysis after the 1st dose of IgM:**

After the first dose, the IgM titer was used for statistical analysis. No significant difference was noticed between males and females for IgM titers. There were no effects of age groups, ABO blood groups, $Rh^+$ and $Rh^-$ or type of vaccine on IgM concentration.

**4- Statistical analysis after the 2nd dose of IgG:**

After the second dose, the IgG titer was utilized for statistical analysis. No significant difference was noticed between males and females for IgG titers. Significant differences were detected in terms of vaccine type and blood group in favor of AstraZeneca vaccine [IgG second dose AstraZ (18.2±11.6), IgG second dose SinoPh (12.7±0.8), IgG second dose Sputk (7.3±0.3), $P<0.0001$] and blood group A as compared to blood type O [ IgG second dose A (16.9±11.6) vs. IgG second dose O (10.6±5.5), $p<0.0001$]. Furthermore, males with A-blood type showed higher IgG titers (19.8±13) than females with A-blood type (16.4±11.7), $p<0.0001$. Concerning age groups, the only significant difference was seen for participants in the 33-46 age group, with blood type O who received the AstraZeneca vaccine (constitute ≈ 33% of the age group) compared to those with similar blood type who received other vaccines in the same age

group (constitute 20% of the age-group), (14.4±6.9) vs. (8.6±2.4) $p<0.0001$ respectively.

No significant difference was attained between $Rh^-$ and $Rh^+$ subgroups as to IgG titers according to type of vaccine or gender.

Significant differences were obtained between $Rh^+$ subjects who received the AstraZeneca vaccine compared to those vaccinated with Sinopharm and Sputnik V, (17.3±11.7) vs. (11.6±8) $p<0.0001$respectively. No such difference was seen with the Rh-subgroup.

**Discussion**

The World Health Organization declared COVID-19 a pandemic in March 2020. To manage this problem, numerous doses of vaccine against SARS-CoV-2 have been offered globally. The correlation between the ABO blood group and the immunogenicity or reactogenicity of COVID-19 vaccine is still unclear.

In this study, we aimed to evaluate the relationship between the immunogenicity of COVID-19 vaccines and the essential ABO blood groups and their subtypes $Rh^+$ and $Rh^-$ in a group of Syrian society. For that, 153 participants who received COVID-19 vaccines were enrolled in this

work. IgM and IgG titers were measured after 10 days of the 1st and the 2nd doses of the vaccine.

Results have shown that there are significant differences in IgM and IgG titers after the 1st and the 2nd doses of vaccines, i.e., IgM second dose>IgM first dose, logically IgM after second dose must be close to the concentration of the first one, but the little increase in IgM titter after second dose may be caused by the compound material interred in vaccine which activated B-cell again to produced IgM, and IgG second dose>IgG first dose [18]. This is expected, as after the first dose of vaccine, an initial immune response is mounted and produces specific antibodies that mediate adaptive immunity. Then, after the second dose, the immunogenicity becomes stronger as the immune system has already encountered the vaccine antigen, and antibodies are more readily present [19]. Furthermore, IgG second dose titers for participants with type A blood were significantly higher than IgG first dose titers, i.e. IgG second dose A>IgG first dose A, and IgG second dose titers for those with blood type A were statistically different from type O blood titers, IgG second dose A>IgG second dose O. This finding concerning the high immunogenic property of the A blood group against the SARS-Cov-2 vaccine has been also demonstrated

elsewhere [20]. The study detected a strong relation between ABO blood types and seroconversion to the live, attenuated influenza vaccine as subjects with type A blood seroconverted after the administration of the 1st dose, and after the 2nd dose for the other blood types [20]. ABO blood groups are antigens found on the surface of erythrocytes. Different meta-analysis studies, observational research, and genome-wide association reports demonstrated a relationship between the ABO group and vulnerability to SARA-CoV-2 infection [21-24]. Despite the variability concerning the risk of severe outcomes, it seems that type A is the most associated with COVID-19 severity and mortality, whereas type O serves as a protective factor for the disease progression. It has also been demonstrated that patients with blood type A presented more severe reactogenicity to COVID-19 infection than others of blood type O [25,26]. Furthermore, the ABO locus has been genetically linked to both the likelihood of infection and the severity of disease. Preliminary experimental data have proposed some mechanisms to explain the potential implication of ABO groups with the severity of the infection. Such as the protective effect of ABO antibodies [27], the ABO(H)-like structure on the glycoprotein envelop of SARS-CoV-2, which may facilitate the viral entry into the host's cells, and the link between non-O blood types and

cardiovascular risk which probably gives COVID-19 patients with blood type O a lower risk of severe outcomes [28]. Hence, it is conceivable that there is an association between the immunogenicity or reactogenicity of the vaccine and ABO blood groups.

However, this contradicts the outcomes of a cross-sectional study conducted on 1180 participants from the Kingdom of Saudi Arabia to illustrate the relation between the severity of adverse effects of the COVID-19 vaccine and the associated predictors [29]. Findings reported an association between the severity of vaccine-adverse reactions and females receiving the AstraZeneca vaccine but did not detect any correlation with ABO blood types. It is worth noting that the same team repeated the methodological approach with a group of Taif University students [30]. Their results supported the correlation between females who received AstraZeneca and the severity of the effectiveness of the vaccine. Additionally, they presented blood type B and the young population as additional predictors of severity.

Regarding the type of vaccine, our work is by the previous study, as the level of immune response elicited by the AstraZeneca vaccine was significantly stronger than the other vaccines. In addition, participants with

$Rh^+$ who received the AstraZeneca vaccine showed a higher antibody response than those with $Rh^+$ who were vaccinated with Sputnik or Sinopharm. However, our results found that males with type A blood had higher IgG titers than females with type A. Concerning age, subjects in the age group 33-46 years of blood type O who received the AstraZeneca vaccine presented higher IgG titers compared to those with the same blood type receiving other vaccines in the same age group. The role of age as a mediator for the impact of other variables is widely examined and proven in research [31,32]. Generally, young individuals have stronger immunity, so the elicited immune response after the administration of the vaccine and the reported side effects would be higher.

**Conclusion:** Although it is challenging to evaluate the direct link of any individual demographic factor to the immunogenicity of a vaccine, this study assessed a link between the immunogenicity of SARS-CoV-2 vaccines and the ABO blood groups in a group of Syrians. Comparing the concentration of IgG titers after the first and second vaccination dose, so IgG titers may give an idea about the requirement of a booster dose of vaccine against SARS-CoV-2 in some individuals. Males with blood type A who received the AstraZeneca vaccine had higher IgG titers than females. Also, elevated IgG concentrations were found in young subjects

of blood type O who received the AstraZeneca vaccine. They could be considered positive predictors of vaccine effectiveness and full protection. Further study with a larger sample size is needed to confirm and find out more predictors of the immunogenicity of the COVID-19 vaccine.

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**Conflicts of interest**

The author declares no conflict of interest

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