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Comparison of Interleukin 15 gene Expression in Vaccinated Individuals (Pfizer – AstraZeneca- Sinopharm) Vaccines and Critical COVID-19 Iraqi patients

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ABSTRACT

Objective: The cytokine interleukin-15 is widely known for helping natural killer cells and CD8 T cells development and maintain homeostasis, but recent research reveals that IL-15 also mediates the antiviral responses of both cell types during an active immune response.

Aim of the study: study Interleukin-15 gene expression in vaccinated individuals (Pfizer Sinopharm and AstraZeneca vaccines) and critical cases infected with COVID-19 in Iraqi individuals, for the purpose of investigating the role of IL -15 gene in determining the immune response in vaccinated individuals (Pfizer – AstraZeneca- Sinopharm vaccines) and COVID-19 patients.

Study design: This study was conducted between the period from January and March 2022. A total number of 179 (male and female) blood samples were collected from Ibn AI-Khatib Hospital and health centers (AL-Sindibad health center, AL Rasheed health center and other places). Immunological assay for evaluation of anti-COVID-19 IgG and IgM was accomplished by ELISA technique. Molecular analysis was achieved by real time PCR to confirm our results by detecting of IL-15 gene levels.

Results: Showed that the Sinopharm, BioNTech and AstraZeneca vaccines groups exhibited the highest neutralization potential compared to the unvaccinated controls. The results indicated that Sinopharm vaccines generally induced the highest amounts of SARS-CoV-2 reactive IgM and IgG compared to other vaccines (7.31 ± 1.52) IgM and (38.84 ± 26.35) IgG P -value (0.001). The critical patient showed a highly significant difference between males and females of IgM P- value (0.002). The patients had the highest IgM production in males. The Sinopharm vaccine had the highest productivity of IgG in the two groups compared to Pfizer and AstraZeneca vaccine. The critical patient, Sinopharm vaccine and AstraZeneca vaccine showed significant difference between (41-70) (21-40) groups of IgM. The critical patient showed a highly significant difference between males and females of IgG P- value (0.006). The patients had the highest IgG production in males. The critical patient and Pfizer vaccine showed significant difference between (41-70) (21-40) groups of IgG. The IL-15 gene showed no effect with COVID-19.

Conclusion: The study showed that Pfizer, Sinopharm and AstraZeneca vaccines produced IgM and IgG against COVID-19 in terms of age and gender compared to the unvaccinated individuals, with no effect of the booster dose compared to the second dose.

Keyword: SARS-CoV-2, IgG, IgM, Real-Time PCR, IL-15 gene.

INTRODUCTION

The pandemic has swiftly expanded after the first COVID-19 cases were found in China in December 2019. By February 22, 2022, there had been more than 426 million cases of COVID-19, which was brought on by the SARS-CoV-2 virus, and more than 5.8 million fatalities [(1)]. Virion-like organisms with viral envelopes are coronaviruses (CoVs). These virion particles have a 120 nm diameter. The virus's surface is covered in glycoproteins and proteins that form cloverleaf structures, which give the virus a crown-like appearance. Because of their crown-like form, these viruses are also referred to as coronaviruses. These viruses contain genetic material inside a region known as the nucleocapsid, which is formed of capsid-coated proteins [(2)]. RNA genomics belongs to the genus coronavirus. In the virus's nucleocapsid, this genetic material appears as a spiral or circular structure [(3)]. The four structural proteins of the SARS-CoV-2 virus are nucleocapsid (N), spike (S), membrane (M), and envelope (E). When a virus enters the body and forms envelopes, protein M is essential [(3)].

The virus reproduces, germination, forms an envelope, and disseminates due to protein E [(4)]. Increased viral transcription and assembly are caused by the multifunctional N protein [(5)]. The virus attaches to host cells thanks to the spike (S) protein as well. It thus occupies a unique place in the study of medications and vaccinations. It is important to note that because proteins N, M, and E do not respond to neutralizing or immunological antibodies, they are not considered to be therapeutic targets [(6)].

The BNT162b2 vaccine from Pfizer-BioNTech is an mRNA vaccine included in a lipid nanoparticle formulation. The prefusion S glycoprotein of SARS-CoV-2, the virus that causes COVID-19, can be encoded by the Pfizer vaccine [(7)]. The ideal temperature for this vaccine to be kept at with a high level of efficiency is -70 °C, although creating such an environment is difficult [(8)]. A collaboration between the German Biotechnology

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Company BioNTech and the American business Pfizer handled the clinical research, logistics, and manufacturing for its development [9, 10]. Intramuscular injection is used to provide the vaccination. It consists of lipid nanoparticles encapsulated in nucleoside-modified mRNA (modRNA), which produces a mutant form of the full-length spike protein of SARS-CoV-2 [11].

The Oxford-AstraZeneca COVID-19 vaccine, also known by the codename AZD1222 [12], is a viral vector vaccine for COVID-19 protection. Chimpanzee adenovirus ChAdOx1 modified was used as a vector [13]. In order to prevent COVID-19 in individuals 18 years of age and older, the Oxford-AstraZeneca COVID 19 vaccine offers defense against infection by the SARS-CoV-2 virus. The medication is injected intramuscularly into the deltoid muscle in two dosages of 0.5 ml [14].

One of two inactivated viral COVID-19 vaccines created by Sinopharm's Beijing Institute of Biological Products is the COVID-19 vaccine, also known as BBIBP-CorV. The deltoid muscle receives the intramuscular injection of the vaccination. There is no evidence to support the necessity for a third booster dosage after the first course of two doses. Between dosages, the World Health Organization (WHO) suggests a 3–4 weeks gap [15].

Based on its capacity to promote the growth of the murine T cell line CTLL-2, IL-15 is a γc (gamma chain) cytokine that was independently discovered by two groups in 1994. IL-15 has now been cloned from a variety of animals, showing structural homology in 70–80% of human, murine, bovine, porcine, feline, and rabbit samples. Of the four cytokines that contain α -helix bundle, IL-15 is a 14–15 kDa glycoprotein, similar to IL-2. Along with IL-2, IL-4, IL-7, IL-9, and IL-21 [16], IL-15 is a member of the cytokine family with four α –helixes [17].

IL-15 is produced by muscles, epithelium, and monocytes. Both T cells and activated B cells are impacted by it. Both B and T cells multiply as a result of it. It promotes the growth of CD8+ T cells and NK cell memory [18]. In 1994, IL-15, a soluble factor generated by HTLV-1-transformed T-cell leukemia cells and a simian epithelial kidney cell line, was independently cloned by two labs (HuT-102) [19, 20]. Under steady-state conditions, it is simple to find high quantities of IL-15 transcripts in the placenta, skeletal muscles, kidney, and LPS-activated monocytes, but less so in the lungs, liver, heart, and pancreas [21].

SUBJECTS AND METHODS

This study was conducted in the period from January 2022 to March 2022. 179 individuals (129 males and 50 females) were subjected to test in this study and then divided into two age groups 21-40 and 41-70 years. We analyzed BioNTech vaccine, Sinopharm vaccine and AstraZeneca vaccine specific IgM and IgG in the sera of vaccinated individuals from 7 -14 days into seven months after full vaccination of the second and third doses. All vaccinated individuals from AstraZeneca, their samples were withdrawn from 4 months to 7 months due to the lack of availability in health centers by the government.

Study groups:

Critical patients group: The study included 36 blood specimens that were collected from Ibn AI-Khatib Hospital in intensive care and lobbies.

Control group: The study included 36 blood specimens that were collected from different places. Depending on the absence of symptoms of infection COVID-19 and negative PCR.

Vaccinated group: The study included 104 blood specimens that were collected from health centers (AL Sindibad health center, AL Rasheed health center and other places) from vaccinated individuals (who received Pfizer, Sinopharm and AstraZeneca vaccine). The samples were collected at different intervals and from two dose and three dose after two weeks and between month to seven months.

Ethical consideration: The Iraqi Ministry of Health, the Department of Biology, and the College of Science at the University of Baghdad, Baghdad, Iraq approved this work (Ref.: CSEC/0122/0048). The consent of each participant was taken. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Assay Procedure: According to manufactures instructions. MyBioSource.com company [www.abcam.com/ab277287/use www.abcam.cn/ab27728for China or www.abcam.co.jp /ab277287 for Japan for ELISA kit. Macrogen Company, Korea for RT.PCR].

Statistical Analysis

SPSS version 26 for Windows® was used to collect, code, and analyse the data. To evaluate if the data had a normal distribution. The t-test was used to compare the differences between two or more sets of qualitative variables. The mean ± SD of quantitative data was used. To compare two independent groups of regularly distributed variables (parametric data), the independent samples t-test was utilised. $P \leq 0.05$ was considered significant.

RESULTS

Detection the effectiveness of IgM in patients and vaccinated groups according to age and gender by ELISA technique.

This study was conducted through the period from January 2022 to March 2022. A total number of 179 individuals (129 males and 50 females) were subjected to test in this study and were divided into 2 groups according to the age factor 21-40 years and 41-70 years. Pfizer vaccine, Sinopharm vaccine and AstraZeneca vaccine specific IgM and IgG were analyzed in the sera of vaccinated individuals from 7 -14 days up to seven months after full vaccination of second and third doses. All vaccinated individuals from AstraZeneca, their samples were withdrawn from 4 months to 7 months due to the lack of availability in health centers by the government. The immune response varied from person to person (age, gender and from vaccine to another). The results showed that the two age groups of vaccinated individuals produced IgM compared to the unvaccinated, while the Sinopharm vaccine had highest IgM production compared to Pfizer and AstraZeneca vaccines in the two age groups. The statistical analysis of these results showed significant difference between the patient, Sinopharm vaccine and AstraZeneca vaccine groups. There was no significant difference between the control, and Pfizer vaccine groups for age categories (21-40 years) and (41-70 years). The Sinopharm vaccine showed a highly significant difference (Table 1 & figure 1).

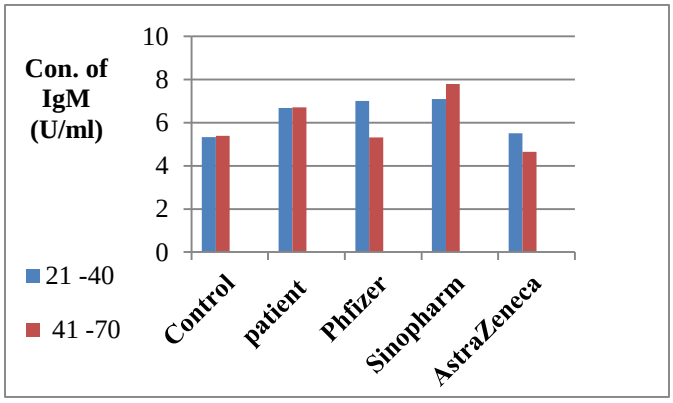

Figure (1): Distribution of IgM in studied group according to the age factor.

Table (1): Relationship between age groups and IgM with difference vaccination of COVID-19.

IgM(u/ml)							
Study groups	21-40 years			41 – 70 years			P-value
	Mean	±	SD	Mean	±	SD	
Control	5.33	±	1.38	5.38	±	1.35	0.914 N.S
Critical Patient	6.68	±	0.00	7.15	±	1.04	0.013*
Sino-pharm	7.07	±	1.57	8.39	±	0.456	0.001**
Pfizer	6.73	±	1.96	5.64	±	2.20	0.193 N.S
Astra-Zeneca	5.50	±	1.65	4.65	±	0.579	0.039*

Data presented as Mean ± SD, ¥: Independent t-test was used to test between age groups, N.S not significant (P > 0.05), *, ** Significant (P < 0.05) highly significant at (P < 0.01) respectively.

The males had a higher production of IgM, while the females had lower than males. The patients had the highest IgM production in males, while the Sinopharm vaccine had the highest IgM production compared to Pfizer and AstraZeneca vaccines. (Table 2 & figure 2).

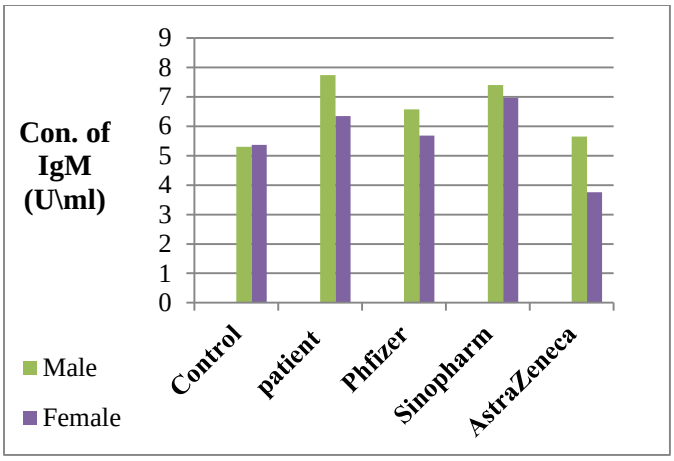

Figure (2): Distribution of IgM in studied group according to the gender factor

Table (2): Relationship between Gender and IgM with difference

IgM(u/ml)							
Study groups	Female			Male			P-value¥
	Mean	±	SD	Mean	±	SD	
Control	5.37	±	1.34	5.33	±	1.40	0.935 N.S
Critical Patient	6.50	±	0.68	7.52	±	1.00	0.002**
Sino-pharm	6.97	±	2.07	7.40	±	1.40	0.646 N.S
Pfizer	5.68	±	2.12	6.57	±	2.05	0.380 N.S
Astra-Zeneca	4.09	±	1.33	5.57	±	1.41	0.043*

Data presented as Mean ± SD, ¥: Independent t-test was used to test between age groups, N.S not significant (P > 0.05), *, ** Significant (P < 0.05) highly significant at (P < 0.01) respectively.

The statistical analysis of these results showed significant difference between the patients and the AstraZeneca vaccine group. There was no significant difference between the control, Sinopharm vaccine and Pfizer vaccine groups for the males and females groups. The patient showed a highly significant difference between males and females (Table 2 & figure 2).

Detection of effectiveness the IgG in patients and vaccinated groups according to age and gender by ELISA technique.

Both groups produced IgG against SARS-CoV-2, while the 41-70 group had the highest productivity of IgG than the 21-40 group. On the other hand, the Sinopharm vaccine had the highest productivity of IgG in the two groups compared to the Pfizer and AstraZeneca vaccine. In general the male group had the higher productivity of IgG than the female group but we noted that Pfizer vaccine had highest in female group. Sinopharm vaccine had the highest productivity of IgG in the male groups compared to Pfizer and AstraZeneca vaccine. Pfizer vaccine was highest in female group figure (3).

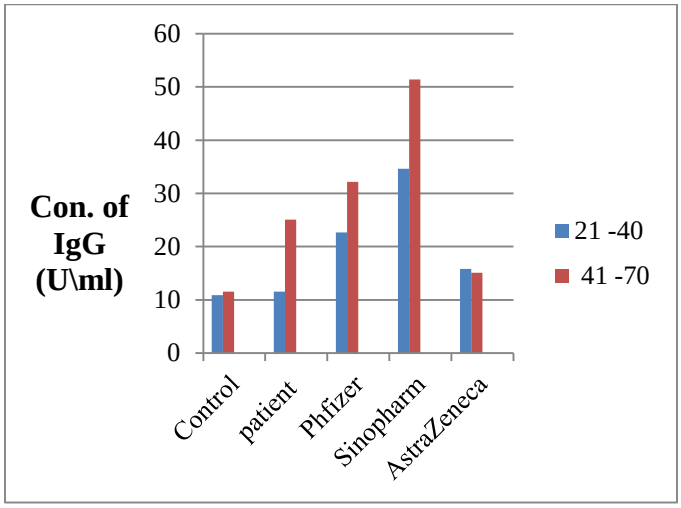

Figure (1-3): Results of immune response by IgG in studied group according to the age factor.

As shown in the above figure, Sinopharm vaccine had the highest productivity of IgG in the two age groups compared to Pfizer and AstraZeneca vaccine. Both groups produced IgG against SARS-CoV-2, while the 41-70 group had higher productivity of IgG than the 21-40 group. The statistical analysis of these results showed significant difference between the patients and Pfizer vaccine groups.

There was no significant difference between the control, AstraZeneca vaccine and Sinopharm vaccine groups for age categories (21-40years) and (41-70years). The patient showed a highly significant difference between (21-40years) and (41-70years) (Table 3).

Table (3): Relationship between age groups and IgG with difference vaccination of COVID-19.

IgG(u/ml)							
Study groups	**21-40 years**			**41 – 70 years**			**P-value**
	Mean	**±**	**SD**	**Mean**	**±**	**SD**	
Control	**10.81**	**±**	**2.88**	**11.70**	**±**	**4.11**	**0.510** N.S
Critical Patient	**11.53**	**±**	**0.00**	**25.07**	**±**	**16.02**	**0.001****
Sino-pharm	**33.30**	**±**	**22.68**	**62.85**	**±**	**29.68**	**0.059** N.S
Pfizer	**21.61**	**±**	**8.88**	**36.57**	**±**	**25.40**	**0.015***
Astra-Zeneca	**15.79**	**±**	**4.34**	**15.08**	**±**	**2.75**	**0.599** N.S

Data presented as Mean ± SD, ¥: Independent t-test was used to test between age groups, N.S not significant (P > 0.05), *, ** Significant (P < 0.05) highly significant at (P < 0.01) respectively.

Sinopharm vaccine had the highest productivity of IgG in the male groups compared to the Pfizer and AstraZeneca vaccine, while the Pfizer vaccine was highest in female group (tables 3 and 4). The statistical analysis of these results showed significant difference between the patients. There was no significant difference between the control, Sinopharm, Pfizer and AstraZeneca vaccines groups for males and females. The patient showed a highly significant difference between males and females (table 4 & figure 4).

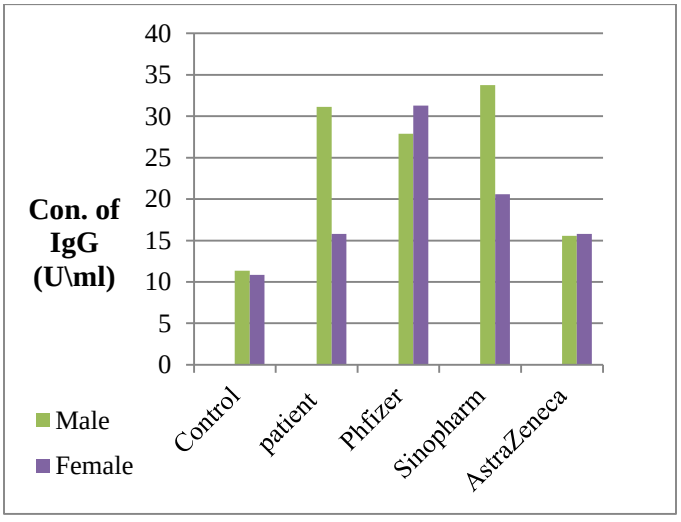

Figure (4): Results of immune response by IgG in studied group according to the gender factor.

Table (4): Relationship between gender and IgG with difference vaccination of COVID-19

IgG(u/ml)							
Study groups	Female			Male			P-value
	Mean	±	SD	Mean	±	SD	
Control	10.85	±	3.25	11.37	±	3.45	0.644
Critical Patient	16.79	±	4.70	29.11	±	18.55	0.006**
Sino-pharm	40.61	±	31.25	38.43	±	25.77	0.878 N.S
Pfizer	31.27	±	30.04	24.88	±	12.89	0.630 N.S
Astra-Zeneca	16.43	±	3.47	15.42	±	4.12	0.553 N.S

Data presented as Mean ± SD, ¥: Independent t-test was used to test between age groups, N.S not significant (P > 0.05), *, ** Significant (P < 0.05) highly significant at (P < 0.01) respectively.

Detection the effectiveness of IgM and IgG in patients and vaccinated groups by ELISA technique.

The results indicated that Sinopharm vaccinated patients showed higher expression of SARS-CoV-2-specific IgM and IgG compared to other vaccinated groups. The patient and Sinopharm, Pfizer and AstraZeneca vaccinated individuals generally induced amounts of SARS-CoV-2-reactive IgM and IgG compared to control. The results showed that patient induced amounts of SARS-CoV-2-reactive IgM and IgG. Sinopharm, Pfizer and AstraZeneca vaccines generally induced amounts of SARS-CoV-2-reactive IgM and IgG, higher expression of SARS-CoV-2-specific IgM and IgG in Sinopharm vaccinated individuals compared to other vaccines table. The statistical analysis of these results showed a highly significant difference between all study groups of IgM and IgG (table 5 & figure 5).

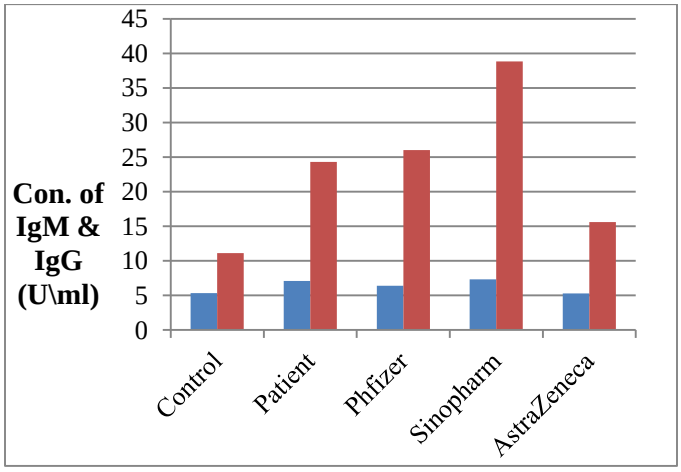

Figure (5): Detection of the immune response (IgM) and (IgG) to SARS-CoV-2 by ELISA in the studied group.

Table (1- 5): Relationship between IgM and IgG with difference vaccination of COVID-19

Study groups	IgM				IgG			
	Mean	±	SD		Mean	±	SD	
Control	5.35	±	1.35		11.11	±	3.31	
Critical Patient	7.12	±	1.01		24.32	±	15.87	
Sino-pharm	7.31	±	1.52		38.84	±	26.35	
Pfizer	6.41	±	2.06		26.01	±	16.70	
Astra-Zeneca	5.29	±	1.49		15.61	±	3.98	
P-value¥	0.001**				0.001**			

Data presented as Mean ± SD, ¥: Oneway ANOVA was used to test between groups, ** highly significant at (P < 0.01), means followed by different letter vertically are significantly different (P < 0.05).

Detection the effectiveness of the booster dose in vaccinated groups by ELISA technique:

Three samples were taken of the booster dose that represented two doses of Sinopharm and a booster dose of Pfizer taken after twenty one (21) days of full vaccination, two doses of Pfizer and a booster dose Pfizer, samples were taken after one month of full vaccination and two doses of AstraZeneca and a booster dose of Pfizer where the samples were taken after two months and fifteen (15) days of full vaccination. The results showed that booster dose had no effect compared to vaccinated individuals two doses. The Cut-off IgM > 6 was positive and < 6 was negative. The Cut-off IgG >11 was positive and <11 was negative. The results showed higher expression of SARS-CoV-2-specific IgM and IgG in Sinopharm vaccinated individuals compared to other vaccines. In some results, we noted a difference between the Pfizer vaccine and Sinopharm vaccine, for example individuals vaccinated with the Pfizer vaccine (E9 females 45 y, F6 31y and F5 26 y males).

On the other hand , individuals vaccinated with Sinopharm vaccine (D8 females 45y, D4 31y and D3 26 y males) where the samples were withdrawn from them 7-14 days after the second dose, the results were (E9 IgM (6.244U/ml) IgG (69.968 U/ml), F6 IgM (8.242 U/ml) IgG (22.157 U/ml) and F5 IgM (8.155 U/ml) IgG (20.075U/ml)), while were (D8 IgM (8.743 U/ml)IgG (80.696 U/ml), D4 IgM (6.356 U/ml) IgG (36.671U/ml) and D3 IgM (8.044 U/ml) IgG (27.122 U/ml). On the other hand, individuals vaccinated with Pfizer vaccine (F2 males 40 y). Individuals vaccinated with Sinopharm vaccine (D10 males 36y) where the sample D10 was withdrawn after a month, while the F2 after two month from the second dose. The results were (D10 IgM (8.243U/ml) IgG (29.223U/ml) and (F2 IgM (3.672U/ml) IgG (10.201U/ml) (appendix).

The possible reasons firstly, the reasons are still unknown Secondly, Sinopharm vaccine all parts of the virus were used to reverse Pfizer vaccine only spike protein. Thirdly, the nature of the surrounding environment and the physiology of the body. Concerning Pfizer vaccine, there were differences in gender for example, (F9 female 32y , F6 male 31y) and(F1 female 48y ,E9 female 45y and E7 male 53y) the results were (F9 IgM (7.721 U/ml) IgG (14.282 U/ml), F6 IgM (8.242 U/ml) IgG (22.157), (F1 IgM (3.077 U/ml) lgG (9.562 U/ml), E9 lgM (6.244 U/ml) IgG (69.968 U/ml), and E7 IgM (7.748 U/ml) IgG (45.438 U/ml). We noted in the results that there was a difference in the same gender, for instance Pfizer vaccinated (E9 45y and F1 48y female). Knowing that E9 was not previously infected and F1 was infected more than once previously, all the samples were withdrawn from them within 7-14 days.

There was a difference between Pfizer, AstraZeneca and Sinopharm vaccinated in IgG. For instance, one sample of vaccinated Pfizer the sample was taken before 7 months (E10 31y male IgM (7.333 U/ml) and IgG (21.145 U/ml)), Sinopharm vaccine sample was taken before 9 months (D9 35y male IgM (8.206 U/ml) and IgG (29.463 U/ml) and AstraZeneca vaccine sample was taken before 6 months (F10 36y male IgM (8.097 U/ml) and IgG (13.909 U/ml). All vaccinated individuals from AstraZeneca the sample was withdrawn from 4 months to 7 months due to the lack of availability in health centers by the government. The AstraZeneca vaccine induced slightly more IgM and IgG compared to Pfizer vaccine and Sinopharm vaccine.

Estimation of IL-15 gene expression in studied groups:

IL-15 gene levels were measured and compared in two groups, patient based on COVID -19 infection and vaccinated (Pfizer vaccine, Sinopharm vaccine and AstraZeneca vaccine). Based on taken vaccines two and three doses, and comparing their levels with those of uninfected controls. Whereas, D represents booster doses of vaccinated individuals of Pfizer vaccine, P represents infected individuals, F represents Pfizer vaccinated individuals, S represents Sinopharm vaccinated individuals and A represents AstraZeneca vaccinated individuals (Figure 6).

The results showed that Interleukin-15 had no effect with COVID-19. Where D represents the booster dose of the Pfizer vaccine. F represents two dose of Pfizer vaccinates, P represents critical cases is high because of sick history, A represents two dose of AstraZeneca vaccine, S represents two dose of Sinopharm vaccine, and C represents control. In the patient's group (P), IL-15 gene expression was high (23.75). This could be because they were suffering from ischemic heart disease, hypertension, heart failure and diabetes. The study showed the IL-15 usually rises in other viral infections, but with COVID-19 it had no effect. It did not reach the viral load that increases the gene expression of IL-15. There are studies that say depending on the viral load that determine the height of IL-15.

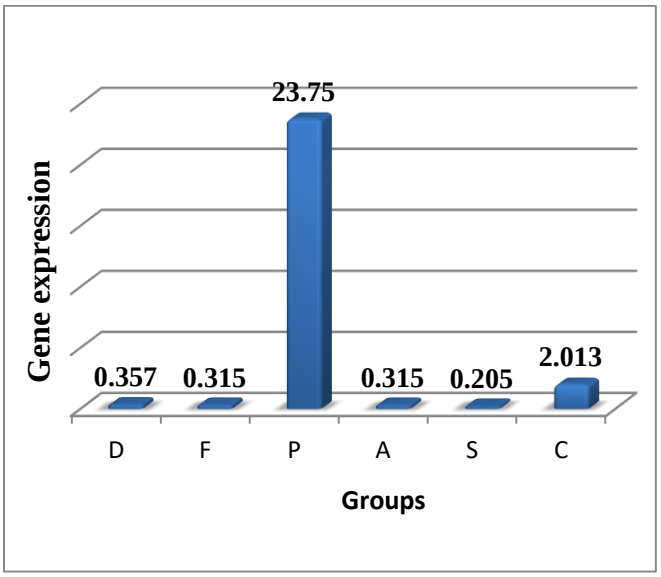

Figure (1-6): Results of IL-15 gene expression in studied groups.

DISCUSSION

The possible reasons for this observation can be explained as follow: Firstly, Sinopharm vaccine is whole genome attenuated vaccine so that it is more effective, unlike Pfizer vaccine is only spike protein coded by mRNA part from virus and loaded with nanoparticles. Secondly, Pfizer vaccine requires a certain degree of storage, where the effectiveness of the vaccine is reduced if the specified storage degree is not available for it by the vaccine manufacturers. The ideal temperature for this vaccine to be kept at with a high level of efficiency is -70 °C, although creating such an environment is difficult [8].

According to a study, Different infectious diseases have shown sex differences in prevalence, etiology, and consequences. In average, men are more prone to infection whereas women have stronger immune systems. A 2010 WHO study found that influenza outcomes are frequently worse for women, despite the fact that they routinely develop higher antibody titers in response to vaccination, therefore this does not necessarily translate to worse outcomes for men. Immune cell responses to sex hormones may explain sex disparities in immunity [23]. A growing body of research using COVID-19 has identified differences in cytokines between men and women [24].

According to a recent study, SARS-CoV-2-reactive IgG and IgA were most frequently produced by mRNA vaccinations. Comparing the Moderna and BioNTech vaccines, the Moderna vaccination generated somewhat more IgG and IgA. Similar levels of SARS-CoV-2 specific IgG were elicited by AstraZeneca and Sputnik-V. However, compared to the AstraZeneca group, IgA

expression was greater in the Sputnik-V group. The IgG expression in these two groups was reduced compared to both mRNA vaccines but significantly higher compared to the unvaccinated controls. As opposed to the unvaccinated control group, the Johnson & Johnson and Sinopharm groups had somewhat higher levels of SARS-CoV-2-specific IgG. Age and the expression of SARS-CoV-2-specific antibodies were not correlated in the Moderna, BioNTech, and AstraZeneca group. In Sinopharm group, there was a larger negative connection between the expression of SARS-CoV-2-specific IgG and age [(25)]. Possible reasons for this finding can be explained as follow: Firstly, Sinopharm vaccine is whole genome attenuated vaccine so that it is more effective, unlike Pfizer vaccine is only spike protein part from virus and loaded with nanoparticles. Secondly, Pfizer vaccine requires certain temperatures, and when the ideal temperature is not available, it loses its effectiveness. Thirdly, the small number of females in this study.

According to study, serum IgM and IgG levels in moderate and severe COVID-19 patients were significantly higher than mild cases, while no significant difference was observed between severe and moderate patients. In our study, we did not deal with moderate and severe COVID-19 patients only critical and from the point the IgM and IgG levels in critical COVID-19 patients were high [(26)]. One of the possible reasons firstly, Sinopharm vaccine is whole genome attenuated vaccine so that it is more effective, unlike the Pfizer vaccine includes only spike protein part from virus and loaded with nanoparticles. Secondly, Pfizer vaccine requires a certain degree of storage, where the effectiveness of the vaccine is reduced if the specified storage degree is not available for it by the vaccine manufacturers. The ideal temperature for this vaccine to be kept at with a high level of efficiency is -70 °C, although creating such an environment is difficult figure (1-5) [(8)].

The results showed that booster dose had no effect compared to vaccinated individuals two doses. According to recent studies, it is not completely reliable to evaluate the level of COVID-19 protection because patients are not checked for infection after receiving the vaccine [(27)]. However, the concept is starting to gain traction. Due to the lack of or limited information on the immunogenicity, safety, and reactogenicity of such schedules, they are not yet universally advised and are still unproven concept that should only be used when necessary to protect against supply shocks or shortages and to speed up vaccination [(28)]. With the heterologous vaccine regimens, the three cornerstones of any vaccine reactogenicity, safety, and immunogenicity remain under examination.

The study showed the Interleukin-15 usually rises in other viral infections, but with COVID-19 it had no effect. It did not reach the viral load that increases the gene expression of IL-15. There are studies that say depending on the viral load that determine the height of IL-15. IL-15 levels were significantly higher in patients with viral loads > 100,000 copies/ml (3.02 ± 1.53 pg/ml) compared to uninfected controls (1.69 ± 0.37 pg/ml, $p<0.001$). There was a significant correlation between HIV-1 viremia and IL-15 levels [(29)].

The IL-15 can be used as a treatment for people with COVID-19, as a study showed the effectiveness of IL-15 against COVID-19 when combined with IL-21. According to a study, combination of IL-15 and IL-21 has been shown to be more effective than IL-15 alone in promoting an effective immune response. The combination of IL-15 and IL-21 has been shown to be more effective than either interleukin alone in promoting an effective immune response. Therefore, a clinical trial that examines the use of the combination of IL-15 and IL-21 for COVID-19 patients is warranted. Previous studies of SARS-CoV-2 viral infection suggest that both the humoral and cytotoxic arms of the immune system are weak in patients with severe COVID-19 disease when compared to mild disease. A cytokine storm is also induced in severe disease. IL-15 has been shown to support the cytotoxic arm of the immune response. IL-21 has been shown to support both the cytotoxic and humoral arms of the immune response. In addition, in some settings, IL-21 has been shown to actually decrease IL-6 and TNF-alpha production, reducing the inflammatory proteins involved in the cytokine storm [(30)].

CONCLUSION

The study showed that Pfizer, Sinopharm and AstraZeneca vaccines produced IgM and IgG against COVID-19 in terms of age and gender compared to the unvaccinated individuals, with no effect of the booster dose compared to the second dose.

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