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Original Research Article

Differential antibody response to COVID-19 disease and COVID-19 vaccines

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ABSTRACT

Background: In our study, antibody positivity was evaluated by two methods in vaccinated and unvaccinated people according to their demographic characteristics and history of COVID-19.
Methods: In this study, venous blood samples were taken from patients who were requested to have COVID-19 antibodies from our hospital's outpatient clinics between February 2022 and March 2022.
Results: There was no statistically significant difference when IgG antibody positivity was compared according to the age ranges in chemiluminescence and immunochromatographic methods. When patients were evaluated according to antibody titers, it was found that 81% of the seronegative patients were unvaccinated and had not had Covid-19, and it was found that this group was statistically significant compared to other groups.
Conclusions: It has been concluded that it will be of great importance for every country, even every region, to have a test and vaccine policy for diagnosis and follow-up in the fight against COVID-19.

Keywords: Antibody, COVID-19, Chemiluminescence immunoassay, Immunochromatography, Vaccine

INTRODUCTION

SARS-CoV-2, from the coronavirus family, is an RNA virus. Coronaviruses are divided into four groups, alpha, beta, gamma, and delta, which are a group of 20 different virus types. The SARS-CoV-2 virus is in the beta coronavirus family and it is called corona due to its round shape and crown-like projections on electron microscopy.[1,2] The genome sequencing of SARS-CoV-2 was first made available to all researchers in the world on January 12, 2020, by Chinese scientists [3]. SARS-CoV-2 is a single-stranded, spherical-enveloped, positive polarity virus.[2]

The virus contains four structural proteins: membrane protein (M), spike glycoprotein (S), an envelope protein (E envelope), and nucleocapsid protein (N). The RNA genome of the virus forms a complex with the nucleocapsid protein.[1,4] It has been stated that the genome structure of SARS-CoV2 and SARS-CoV is 79% similar, and approximately 50% similar to MERS-CoV.[5] SARS-CoV-2 is transmitted through droplets, and the virus attaches to the ACE-2 (angiotensin converting enzyme) receptors on the outer part of the host cell membrane through the S protein during viral entry and multiplies rapidly.[6] Apart from the lung, ACE-2 receptors are also found in the gastrointestinal tract, kidney, and heart cells.

During lung infection, symptoms of hyperinflammation and COVID-19 appear. As the disease progresses, redox homeostasis deteriorates and free radical production increases, and cell destruction begins.[7]

In the diagnosis of COVID-19, it is very important to combine the tests and epidemiological data. Antibody tests support the diagnosis of COVID-19 disease, indirectly. It is also important in cases where viral nucleic acid cannot be detected, contact tracing, investigating humoral immunity in patients and recipients of vaccine candidates, serological surveillance at the local, regional, state, and national levels, and identifying people who have previously been infected and may therefore be immune.[8–10] There are different serological tests to determine the antigenic regions of the structural S and N proteins of SARS-CoV-2 or the antibody response against these antigenic structures. The N protein of SARS-CoV-2 is responsible for virus replication. N protein, which is seen at the highest level in urine and serum in the first 14 days of COVID-19 patients, is an important antigen for early diagnosis.[11,12] The S protein enables the virus to bind to the corresponding receptor on the host cell. Antibodies against the S protein are used for neutralizing antibodies and vaccine studies rather than the diagnosis of the disease.[13,14] In SARS-CoV-2 infections, after a certain period, IgM, IgG, and IgA appear in the serum depending on the immune response. IgG indicates exposure to the virus, begins to form on the 7th day of the incubation period after exposure to the virus, and its amount in the serum increases in the 2nd and 3rd weeks. Although it is not known exactly how long the antibodies remain stable and how long the decline begins, publications are stating that it is 4-8 months. WHO recommends that patients' serum be sampled at least three weeks after the onset of complaints for single-sample studies.[15]

Enzyme-linked immunosorbent assay (ELISA), chemiluminescence immunoassay (CLIA), electrochemiluminescence immunoassay (ECLIA), immunofluorescent antibody test, "western blot", protein micro-sequencing and neutralization tests are used to detect virus-specific antibodies. ELISA and CLIA methods are mostly preferred due to their high efficiency, and short and simple test procedures.[16] Antigens with high specificity should be preferred because of cross-reactions due to similar genetic characteristics of coronaviruses. For the measurement of antibodies against SARS-CoV-2 N protein, it should be taken into account which may cause cross-reaction, due to ~the 92% similarity of N proteins of SARS-CoV-2 and SARS-CoV.[17,18] Preferring different test methods targeting different antigens can prevent false positive results caused by cross-reaction.[15] Immunochromatographic card tests, which are another diagnostic test used in the diagnosis of SARS-CoV-2, have many advantages despite a few disadvantages. These advantages are ease of production, low cost, high sensitivity and specificity, individual testing, easy analysis, long shelf life, visible and reliable results, and no requirement for equipment, training requirements, and specialists. It can be used for examining whole cell and nucleic acid structures apart from other bio compounds.[18,19] The disadvantages are being not quantitative, differences in the interpretation of results, insufficient analysis for small volumes, only one analyte measurement per strip, and is compatible with samples in the liquid state.[18,19]

This study aims to evaluate the antibody levels of COVID-19 vaccinated and unvaccinated individuals with different methods according to demographic characteristics and COVID-19 history and to provide a basis for countries to create their own COVID-19 vaccination and testing policies.

METHODS

This study is a retrospective study using previously obtained serum materials from patients. In this study, the demographic characteristics of the patients, whether they had COVID-19, which COVID-19 vaccine they had, and the number of doses were evaluated retrospectively. The current study included 14-80 years 400 patients (256 (64%) female and 144 (36%) male) who were tested for COVID-19 antibodies from Elazig Fethi Sekin State Hospital polyclinics between February 2022 and March 2022. Pregnant women and patients taking immunosuppressive therapy were excluded from the study. In this study, venous blood samples taken from patients were studied quantitatively by chemiluminescence test with paramagnetic beads targeting the receptor binding site (RBD) of Spike (S) protein with ACCESS SARS-CoV-2 IgG assay (Beckman Coulter, Inc., Brea, CA, USA). A titer of >30IU/ml was considered positive. The immunochromatographic method was used with the ECOTEST (COVID-19 IgG/IgM Rapid Test Device, China) rapid test kit in line with the company's instructions and IgG positivity was investigated.

Statistical analysis

Descriptive statistics for the features; are expressed as numbers and percentages. For the difference between the ratios in terms of these features, the ratio compared with the Z test and the Fisher Exact test was performed. The statistical significance level was taken as 5% in the calculations and the MINITAB (ver: 14) statistical package program was applied for the calculations.

RESULTS

In this study, 256 (64%) of 400 patients were female and 144 (36%) were male. Their age ranged from 14 to 80 years. It was determined that 46 (11.5%) of the patients were not vaccinated and 354 (88.5%) of them had at least one dose of vaccine. It was determined that as the vaccine dose increased, the rates of vaccination in both genders decreased statistically significantly ($p<0.05$). While there

was no statistically significant difference between the genders of the 1st, 2nd, and 3rd dose vaccines in terms of vaccination doses, the difference was statistically significant between men and women who received the 4th dose (p=0.030) and men had a higher rate of 4th dose vaccine (Table 1).

Table 1: Vaccine doses and distribution according to gender in vaccinated people.

Gender	Total N	1st dose N (%)	2nd dose N (%)	3rd dose N (%)	4th dose N (%)
Male	134	134 (100)	130 (97.01)	68 (50.74)	24 (17.91)[d]
Female	220	220 (100)	206 (93.63)	114 (51.81)	21 (9.54)[d]
Total	354	354 (100)	336 (94.91) [a]	182 (51.41) [b]	45 (12.71) [c]

[A]*P*=0.042; between to 1st dose and 2nd dose, [b]*p*=0.010; between to 1st dose 3rd dose, [c]*p*=0.012; between to 1st dose and 4th dose, [d]*p*=0.030; between to male and female at 4th dose.

Table 2: Comparison of antibody positivity by age range according to chemiluminescence and immunochromatographic assays.

Age range	Number of patients N	Chemiluminescence assay N (%)	Immunochromatographic assay N (%)
14-30	96	76 (79.16)	79 (82.29)[a]
30-50	184	157 (85.32)	158 (85.86)[b]
>50	120	107(89.16)	107 (89.16)[c]

[a]*p*=0.780; between to Chemiluminescence assay and Immunochromatographic assay at 14-30 years, bp=0.935; between to chemiluminescence assay and immunochromatographic assay at 30-50 years, cp=0.999; between to chemiluminescence assay and Immunochromatographic assay at >50 years.

Table 3: Distribution of antibody titers by chemiluminescence method according to their history of COVID-19 and vaccination.

COVID-19 Status	Number of patients	Chemiluminescence Assay			
		Negative N (%)	Antibody Titers		
			30-100 IU/ml N (%)	100-200 IU/ml N (%)	200> IU/ml N (%)
COVID-19 infected + unvaccinated	14	4 (28.57)[a,b,**]	8 (57.14)[a,*]	2 (14.28)[b,**]	-
COVID-19 infected + vaccinated	138	8 (5.79)[c,***]	84 (60.86)[a,*]	34 (24.63)[b,*]	12 (8.69)[c,*]
COVID-19 non-infected + unvaccinated	32	26 (81.25)[a,*]	4 (12.5)[b,**]	2 (6.25)[b,***]	-
COVID-19 non-infected + vaccinated	216	22 (10.18)[c,**,***]	120 (55.55)[a,*]	44 (20.37)[b,*,**]	30 (13.88)[b,c,*]
Total	400	60 (%15)[b,c,**]	216 (54)[a,*]	82 (20.5)[a,*,**]	42(10.5)[c,*]

a, b, c: the difference between the rates that take different lowercase letters in the same line is significant (p<0.05). *,**,***: the difference between the rates with different capital letters in the same column is significant (p<0.05).

The blood samples of all patients who were vaccinated and not hospitalized against COVID-19 were studied by chemiluminescence and immunochromatographic methods for antibody screening. In the chemiluminescence assay, antibodies were detected in 121 (84%) of 144 male patients and 219 (86%) of 256 female patients. In the immunochromatographic method, antibodies were detected in 124 (86%) of 144 male patients and 220 (86%) of 256 female patients. There was no statistically significant difference between genders in terms of antibody formation rate according to both methods.

It was determined that 152 (38%) of 400 patients had COVID-19, of these 152 patients 14 (9.21%) were unvaccinated, 45 (29.60%) had COVID-19 before vaccination, 93 (61.18%) had COVID-19 in the post-vaccine period. Considering the antibody positivity of 400 patients; while IgG antibody was not detected positive by chemiluminescence method in 60 (15%) patients, IgG antibody positivity was detected in 6 of these 60 patients who were not found to be positive for IgG antibodies by the immunochromatographic method. IgG positivity was detected by the chemiluminescence method in two patients who were found to be IgG negative by the immunochromatographic method. When IgG antibody positivity was compared according to age ranges of chemiluminescence and immunochromatographic methods, no statistically significant difference was found between the two methods (Table 2).

The people whose antibody titers were checked with the chemiluminescence method were evaluated according to

their history of COVID-19 and vaccination, it was found that the majority of those who did not have a titer was found in 25 (81.25%) people who did not have COVID-19 and unvaccinated, and it was statistically significant when compared to other people with negative titers ($p<0.05$). A titer in the range of 30-100 IU/ml was detected in more people compared to other titers with a rate of 54%. Titers in the range of 30-100 IU/ml were found to be less common (12.5%) and statistically significant ($p<0.05$) in unvaccinated patients who do not have a history of COVID-19. The number of people with a titer in the range of 30-100 IU/ml was found to be statistically significantly higher in all groups, except for those who did not have COVID-19 and were unvaccinated, compared to those in other titers ($p<0.05$) (Table 3). Persons with a titer of >200 IU/ml were identified only in the vaccinated group. There was no statistically significant difference between these groups of people who had and did not have COVID-19 (Table 3).

Table 4: Distribution of people with a titer of 200 IU/ml according to the number of doses and types of vaccine.

Vaccine brand			Number of vaccinated people			>200 IU/ml titer N (%)	
4 doses CoronaVac[1]			25			4 (16.00)	
4 doses BioNTech[2]			20			7 (35.00)	
3 doses CoronaVac [3]			60			6 (10.00)	
3 doses BioNTech [4]			30			6 (20.00)	
2 CoronaVac +1 BioNTech [5]			47			7 (14.89)	
2 doses CoronaVac [6]			110			5 (4.54)	
2 doses BioNTech [7]			89			7 (7.86)	
P values	[1]	[2]	[3]	[4]	[5]	[6]	[7]
[1]	1						
[2]	0.176	1					
[3]	0.471	0.028	1				
[4]	0.741	0.246	0.123	1			
[5]	0.902	0.090	0.450	0.569	1		
[6]	0.061	0.005	0.210	0.041	0.063	1	
[7]	0.254	0.014	0.657	0.122	0.236	0.340	1

Antibody titer above 200 IU/ml was not detected in all unvaccinated patients with or without COVID-19. Antibody titer above 200 IU/ml was detected in individuals with the highest 35% rate of 4 doses of BioNTech (Pfizer-USA). In the comparison of the doses, it was determined that the titer in 4 doses of BioNTech was statistically significantly higher than in 3 doses of CoronaVac (Sinovac-China), 2 doses of CoronaVac, and 2 doses of BioNTech ($p=0.028$, $p=0.005$, $p=0.014$). It was determined that 3 doses of BioNTech were significant compared to 2 doses of BioNTech (Table 4).

DISCUSSION

In the fight against the COVID-19 pandemic, rapid diagnosis and detection of viral antibodies in the infected person are important.[15] Situations such as exceeding test capacities for diagnosis due to the rapidly increasing number of patients, difficulties in providing rapid results following intensive laboratory processes, and secondary viral infections in patients infected with SARS-CoV-2 make it difficult to diagnose COVID-19.[20,21] COVID-19 antibody levels against SARS-CoV-2 can be used to assess acquired protective immunity in COVID-19 patients or vaccinated people.[22] In studies conducted with all age groups in the world, it was found that protection against COVID-19 decreased significantly 6 months after mRNA vaccination, but there was a decrease in the rates of serious illness and hospitalization.[23–26]

According to epidemiological studies, 6 months after 2-dose mRNA vaccination, the efficacy of the vaccine decreased from 88% to 47%.[26] However, it is effective at protecting against serious diseases compared to unvaccinated people.[25] Detection of virus-specific antibodies indicates that the virus has been encountered. With serological methods, it can be investigated whether there are specific antibodies such as IgM, IgG, IgA, or total antibodies against SARS-CoV-2 in serum or plasma.

The presence of an antibody response to the infection is directly related to the host immune system and may be affected by factors such as the patient's age, use of immunosuppressive drugs, the severity of the disease, and comorbidities. Although it is observed that the first antibody response generally occurs 7-11 days after the onset of complaints, this period may vary.[27] It has been reported that the diagnostic sensitivity of antibodies for COVID-19 will increase, and may even be a complementary diagnostic test (28,29).[9] ELISA is used as a diagnostic test for SARS-CoV-2. It is used to detect

IgM and IgG antibody responses against recombinant viral N protein and recombinant viral S protein.[28]

The properties of the antigen to be used are important when producing antibody tests, and the analytical sensitivity and specificity of the tests are significantly affected by the selected target antigen. There is a possibility of cross-reactions due to the similar genetic makeup of coronaviruses. Therefore, more specific and more immunogenic antigens (purified recombinant antigens) should be preferred to ensure their reliability and standardization.[16] Immunochromatographic methods also called rapid antibody or card tests, are reported to have lower sensitivity, accuracy, and specificity than CLIA and ELISA methods. Working with serological methods, especially with standardized procedures and auto analyzers, is important in obtaining more reliable results. Due to the differences in test formats and designs, verification studies should be carried out by the laboratories before antibody tests are routinely put into practice, and it should be specially considered that false positive results may be seen due to the low seroprevalence in the population while evaluating the results.[29] Candel et al reported that rapid serological tests (mainly IgG detection) may be useful in the diagnosis and treatment of COVID-19 patients 15 days after the onset of symptoms (32).[30]

The sensitivity and specificity of the ELISA and CLIA-based assays are better than rapid card tests. IgG or total antibodies tests provide more accurate results.[31] Anti-Spike IgG and neutralizing antibodies are higher in vaccinated persons and patients with pneumonia than in mild COVID-19 patients and decline in vaccinated persons but persist at higher levels in pneumonia patients, however, initial antibody levels returned after the booster dose. Anti-S IgG persisted from two to seven months after infection in patients with pneumonia, whereas it was reported to decrease after six months in mild-COVID-19 patients and vaccinated people ($p<0.001$).[32] Another study reported no difference between mild and severe COVID-19 patients.[33] The higher protection from SARS-CoV-2 infection observed in vaccinated individuals may be due to natural immunity in most patients developing mild COVID-19 or asymptomatic SARS-CoV-2 infection.[34] In this study, when the antibody positivity of 400 patients was examined, IgG antibody positivity was not detected in 60 (15%) patients by the chemiluminescence method, while IgG antibody positivity was detected in 6 of 60 patients by the immunochromatographic method. IgG positivity was detected by the chemiluminescence method in 2 patients who were found to be IgG negative by the immunochromatographic method. When IgG antibody positivity was compared according to age ranges of chemiluminescence and immunochromatographic methods, no statistically significant difference was found. When the people whose antibody titers were detected with the chemiluminescent method were evaluated according to whether they had COVID-19 or not, and whether they were vaccinated, it was found that the people without titers were mostly unvaccinated people who did not have COVID-19 (81.25%), and it was statistically significant when compared to people with other negative titers ($p<0.05$). A titer in the range of 30-100 IU/ml was detected in more people compared to other titers with a rate of 54%. The titer in the range of 30-100 IU/ml was found to be less common (12.5%) and statistically significant ($p<0.05$) in unvaccinated people who did not have COVID-19. The number of people with a titer in the range of 30-100 IU/ml was found to be statistically significantly higher in all groups, except for those who did not have COVID-19 and were unvaccinated, compared to those in other titers ($p<0.05$).

Goldberg Y et al analyzed the association of age, gender, and co-existing conditions with immunogenicity, after the second dose vaccination and at 6 months; low IgG titers were associated with advanced age, male gender, and the presence of two or more co-existing conditions (i.e. hypertension, diabetes, dyslipidemia or heart, lung, kidney or liver), autoimmune disease and immunosuppression.[24] In two different studies, they found that antibody levels were higher in women than men and that antibody levels decreased with age, both after the first and second dose of the vaccine.[35,36] They found that individuals under the age of 40 had higher antibody titers than people over 40 with all methods. Some of their patients had COVID-19 before vaccination and had negative antibody titers despite receiving their first dose of vaccination.[37] Hörber et al found similar results in the SARS-CoV-2 antibody measurement study using fully automated systems with Roche Diagnostics, Siemens Healthineers, and Euroimmun companies.[38] Mazzoni et al reported that after mRNA vaccination, memory cells were still detectable 8 months after vaccination, and antibody levels were significantly lowered, that revaccination was effective in re-activating immunological memory in naive individuals, whereas it was ineffective in individuals previously infected with SARS-CoV-2. Finally, in a cohort of unvaccinated individuals, they observed similar kinetics of impaired humoral and cellular immunity against SARS-CoV-2 up to 1 year following natural infection.[39] In this study, however, we did not detect significant differences according to age. Antibody titer above 200 IU/ml was not detected in any unvaccinated people with or without COVID-19, and we detected antibody titers over 200 IU/ml in people who were vaccinated with 4 doses of BioNTech, with the highest rate of 35%.

This study has some limitations. First of all, it has a relatively small sample size. It also included patients in a single center. Most importantly, the time elapsed after recovering from the disease or being vaccinated was unknown. This may have affected the antibody titer. Future studies involving larger and homogeneous sample sizes with many centers are needed. These future studies may help determine the frequency and number of vaccinations.

CONCLUSION

With the COVID-19 epidemic, it has been seen that over a hundred million people have been infected with this virus all over the world and it has caused the death of more than one million people. Thus, the importance of rapid and accurate diagnostic methods in the early stages of infection has been revealed. In the fight against all infectious diseases and COVID-19, optimizing existing microbiological diagnostic methods such as ELISA, CLIA, and rapid card test, and developing new molecular diagnostic methods would be beneficial as well as vaccination programs which have been shown the parallelism between vaccine dose and antibody level in the present study.

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