RESEARCH ARTICLE

F.U. Med.J.Health.Sci.
2022; 36 (1): 19 - 24
http://www.fusabil.org

Evaluation of Antibody Levels and Certain Biochemical Parameters in the Patients Infected with SARS-COV-2 *

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Objective: In cases with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease clinical usefulness of serological tests remains uncertain. The study aimed to evaluate anti-SARS-CoV-2 antibody and some biochemical parameters such as leukocyte (WBC), neutrophil (NEU), lymphocyte (LYM), thrombocyte (PLT), erythrocyte (RBC), hemoglobin (Hb), ferritin, procalcitonin (PCT), C-reactive protein (CRP) and D-dimer in the patient specimens sent from the polyclinic and service/intensive care unit.

Materials and Methods: A total of 110 patients' specimens sent from the polyclinic and from the service/intensive care unit were used. SARS-CoV-2 RT PCR, immunoassay SARS-CoV-2 antibody and other biochemical tests were assessed.

Results: Anti-SARS-CoV-2 antibody was positive in 11 (5 polyclinic, 6 service/intensive care) of 24 patients with negative RT-PCR test. Significant difference was determined between the two groups from the polyclinic and service/intensive care unit in terms of WBC, NEU, RBC and Hb, ferritin, CRP, PCT and D-dimer levels (p= 0.001, 0.007, 0.002, 0.006, 0.001, <0.001, 0.012 and 0.001, respectively), whereas other parameters (lymphocyte, platelet) showed no significant difference.

Conclusions: Because of gradually increasing rate of exposure to SARS-CoV-2**,** we suggest that seroprevalence needs to be determined, antibody levels should be identified before vaccination**,** and antibody should be studied in the symptomatic patients with negative RT-PCR.

Key Words: *SARS-COV-2,Covid-19, immunoassay, serologic test, antibodies*

SARS-COV-2 Enfekte Hastalarda Antikor Düzeyleri ve Bazı Biyokimyasal Parametrelerin Değerlendirilmesi

Amaç: Ağır akut solunum sendromu korona virus 2 (SARS-CoV-2) hastalığına karşı serolojik testlerin klinik yararlarının belirsizliği devam etmektedir. Çalışmada poliklinik ve servis/yoğun bakımdan gelen hasta numunelerinde SARS-CoV-2 antikor ve WBC, NEU, LYM, PLT, RBC sayısı, Hb miktarı, ferritin, PCT, CRP ve D-dimer gibi bazı biyokimyasal parametrelerin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmada poliklinik ve servis/yoğun bakımdan gelen toplam 110 hasta numunesi kullanılmıştır. Hastaların SARS-CoV-2 RT-PCR, immunoassay SARS-CoV-2 antikor ve diğer biyokimyasal testleri çalışılmıştır.

Bulgular: RT-PCR testi negatif 24 hastanın 11'inde (5 poliklinik, 6 servis/yoğun bakım) Anti-SARS-CoV-2 antikorları pozitif saptanmıştır. WBC, NEU, RBC sayısı, Hb, ferritin, CRP, PCT, D dimer düzeyleri için poliklinik ve servis/yoğun bakımdan gelen iki grup arasında anlamlı farklılık (sırasıyla p= 0.001, 0.007, 0.002, 0.006, 0.001, <0.001, 0.012, 0.001) saptanmış olup diğer testler (LYM, PLT) için anlamlı farklılık saptanmamıştır.

Sonuç: Giderek artan sayıda SARS-CoV-2 maruziyeti nedeniyle seroprevalansın belirlenmesi, aşı öncesi antikor düzeylerinin varlığı, semptomu olup RT-PCR negatif olan kişilere antikor bakılması gerektiği ileri sürülebilir.

Anahtar Kelimeler*: SARS-COV-2,Covid-19, immunoassay, serolojik test, antikorlar*

Received : 24.06.2021
Accepted : 15.12.2021

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) disease (COVID-19) is still a major problem all over the world. Substantial number of SARS-CoV-2-related patients and deaths has been reached worldwide and, unfortunately, this increase is still continuing (1-3). Accurate and prompt diagnosis of SARS-CoV-2 is important to isolate the patients in time, to terminate the outbreak and to save human life. Detection of viral nucleic acid using reverse-transcription real time polymerase chain reaction (RT-PCR) test, which was developed for rapid detection of SARS-CoV-2, is used as the standard test for the diagnosis of disease. The facts that RT-PCR test is time consuming, laborious and requires special equipment have restricted its usage particularly in the areas with limited laboratory facilities (2, 4).

Human antibody response against virus infection has been widely used to help with the diagnosis of viral infections. Comparing with RT-PCR tests, detection of

* Bu çalışmanın bir bölümü 6. Uluslararası Sağlık Bilimleri ve Aile Hekimliği Kongresi (6. IHSFM) 16-18 Nisan 2021'de sunulmuştur.

antibody levels is generally faster, cheaper, user friendly and it is also easier to access as it requires less laboratory professionalism (2).

Antibody response to SARS-CoV-2 is still unclear, and clinical benefits of serological tests remain uncertain (5).

Coronaviruses are among the most common causes of human respiratory tract infections with six main types other than SARS-CoV-2 including highly pathogenic SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), NL63, 229E, OC43 and HKU1 (6). In many patients, SARS-CoV-2 infection manifests itself primarily with fever, cough or dyspnea as well as the symptoms such as muscle pain, headache, confusion, chest pain and diarrhea. In addition, many patients presents to the hospitals with organ dysfunctions including acute respiratory distress syndrome (ARDS), acute respiratory injury, acute renal injury, septic shock and ventilator-associated pneumonia (7). The definite diagnosis of SARS-CoV-2 infection is made by reverse transcription polymerase chain reaction (RT-PCR) and in some articles, however, it was reported that antibody tests are still not suitable enough either for diagnosis or for case management (8).

Changes in the amount of blood cells and the distribution of shape including white blood cell (leukocytes,WBC) count, white blood cell classification count [neutrophils (NEU), lymphocytes (LYM) etc.)], red blood cell (RBC) count, hemoglobin (Hb) concentration and platelet (PLT) count, as well as routine blood test parameters including C-reactive protein (CRP), procalcitonin (PCT), D-dimer and ferritin are used in many situations such as assessment of disease course, efficacy of drug therapy, and healing and relapses (9-11).

Data from severe acute respiratory syndrome epidemic indicate that serologic responses containing virus-specific IgM and IgG are adequate for serological diagnosis (12, 13). Woo et al. (13) stated that enzyme-linked immunosorbent assay (ELISA) test is accurate and economic for the serological diagnosis of SARS-CoV pneumonia and that it provides an advantage because it is laborsaving and does not require viral cultivation.

Long et al. (5) obtained serum samples from 164 subjects for antibody testing nearly 30 days after exposure to virus. All of the 16 subjects with positive RT-PCR test result were also positive for virus-specific IgG and/or IgM, whereas 7 of the 148 subjects with negative RT-PCR were positive for virus-specific IgG and/or IgM; they concluded that 4.3% (7/164) of the close contacts have been missed by RT-PCR test (5). Seroconversion was observed 5 days after symptom onset for IgM and within 5-7 days after symptom onset for IgG (14, 15). Some researchers reported that maximum seroconversion occurs in 2-3 weeks for IgM and in 3-6 weeks for IgG (5, 14, 15). It is known that studies on antibody tests are limited in number because immunoassay test is new.

The present study aimed to evaluate the antibody test results studied using immunoassay system, as well as some biochemical parameters (ferritin, PCT, D-dimer, CRP) and the components of complete blood count (WBC, NEU, LYM, RBC, PLT count and Hb concentration) in the SARS-CoV-2 patient specimens, which have been sent from the polyclinic and from the service/intensive care unit.

Materials and Methods

Research and Publication Ethics: The present study was carried out with the approval of Training and Research Hospital Ethics Committee (Date: 16.10.2020 and Decision no: 600).

In this study, specimens from 110 patients (A total of 54 polyclinic; 28 female and 26 male and a total of 56 service/intensive care patients; 26 female and 30 male) that applied to the hospital between April and May 2020 were used. All patients underwent SARS-CoV-2 RT-PCR testing using nasopharyngeal smear specimens and Roche SARS-CoV-2 antibody testing using blood samples were at least once. For biochemical analyses, blood samples were drawn into the tubes containing gel serum for ferritin, PCT and CRP and containing sodium citrate for D-dimer, whereas the blood sample for complete blood count parameters such as WBC, NEU, LYM, RBC, PLT and Hb was drawn into the tubes containing e*thylene-diamine-tetraacetic acid dipotassium salt*. In order to obtain serum, blood samples were centrifuged at 1500 g for 10 minutes after coagulation at room temperature, and then the serum samples were separated and stored at -70 ^{0}C until used for antibody detection.

The Bio-Speedy Direct RT-qPCR SARS-CoV-2 nucleic acid detection kit, which is used for PCR (Bioeksen, Turkey) test, was designed for qualitative identification of nucleic acid in SARS-CoV-2. The kit is a single-step reverse transcription and real time (RT) PCR test targeting SARS-CoV-2-specific N and Orf1ab gene regions. Nasopharyngeal smear specimens, which have been put into viral nucleic acid buffered tubes for SARS-CoV-2 RT-PCR, were studied using Bio-Rad CFX96 Touch Thermal Cycler device (Bio-Rad Laboratories, USA). The phases of RT-PCR tests were as following: at 52 ^{0}C for 5 min (1 cycle), at 95 ^{0}C for 10 sec (1 cycle) and subsequently at 95 ^{0}C for 1 sec, at 55 ^{0}C for 30 sec (40 cycles) (16). Negative and positive controls for each analysis and internal controls for each specimen were evaluated and the result of PCR test was interpreted as negative or positive if the controls were suitable.

Among the biochemical parameters, ferritin was studied using PCT *Cobas e601* (Roche diagnostics, Germany), D-Dimer was studied using IL ACL TOP 500 (Instrumentation Laboratory, Werfen Company, Spain) and CRP *was studied using ARCHITECT c16000* (Abbott Laboratories, USA) devices. Complete blood count parameters (WBC, NEU, LYM, RBC, PLT and Hb) were studied using Mindray BC 6800 device (Mindray Building, High-Tech Industrial Park, China).

Antibody levels were studied with the original kits after performing bi-level quality control in the Roche *Cobas e601* device (Roche Diagnostics, Germany). Roche SARS-CoV-2 antibody test is based on chemiluminescent immunoassay method. The results were obtained automatically by the software comparing the electrochemiluminescent signal obtained from the reaction product with the threshold signal obtained previously by calibration (17).

The results of the samples obtained by Roche *Cobas e601* were interpreted as reactive or non-reactive together with *cut-off index* (COI). In the samples, COI <1.0 non-reactive was interpreted as negative for Anti-SARS-CoV-2 antibodies, COI ≥ 1.0 reactive was interpreted as positive for Anti-SARS-CoV-2 antibodies.

The statistical analysis of the study data was done using SPSS 22.0 package program. Shapiro-Wilk test was used to analyse whether the data were distributed normally. Since the data didn't normally distributed**,** the difference between the patients from polyclinic vs. service/intensive care unit was evaluated by Mann-Whitney U test. A p value of <0.05 was considered statistically significant. The sample number was calculated with the G-Power 3.1.9.4 program, taking into account the significance level and effect size of the established hypothesis. The effect size was found to be 0.65 (moderate effect level) based on the averages of WBC levels in the polyclinic group (5.94±1.86) and WBC levels in the service/intensive care group (9.10±6.35), which we obtained at the end of our study. In order to find a significant difference between the groups, while α=0.05, 1-β=0.95, that is, the error amount was 0.005 and the power of the test was 95%, the sample size was calculated as at least 52 patients in each group. According to these results, the sample size of our study seems sufficient.

Results

The 110 patient specimens studied in the present study were selected randomly. Of these specimens, 54 were sent from the polyclinics and 56 were sent from the service/intensive care unit. Polyclinic patients consisted of those who have been either isolated or admitted to the service after their treatment was set. Service/intensive care patients consisted of those who have been staying in hospital and the time between PCR test and blood test was 2 - 34 days.

For overall specimens, there were 86 positive and 24 negative results for SARS-CoV-2 RT-PCR test, and 43 positive and 67 negative results for Roche Anti-SARS-CoV-2 antibody (Table 1).

Roche Anti-SARS-CoV-2 antibodies were positive in 11 (11/54=20.37%) and RT-PCR test was positive in 42 (42/54=77.78%) of the 54 patient specimens sent from the polyclinic. Roche Anti-SARS-CoV-2 antibodies were positive in 32 (32/56=57.14%) and RT-PCR test was positive in 44 (44/56=78.57%) of the 56 patient specimens sent from the service/intensive care unit.

SARS-CoV-2 RT-PCR test was negative in 11 of the 43 patients with positive Roche Anti-SARS-CoV-2 antibody.

Roche Anti-SARS-CoV-2 antibodies were positive in 11 (5 from the polyclinic and 6 from the service/intensive care unit) of the 24 patients with negative SARS-CoV-2 RT-PCR test. There were 13 patients with both

Table 1. RT-PCR and antibody tests results of the patients

Tests	Result	Polyclinic (*N*= 54)	Service/Intensive care (*N*= 56)	Total
Roche Anti-SARS-CoV-2	Positive	11	32	43 (%39.09)
	Negative	43	24	67 (%60.91)
SARS-CoV-2 RT- PCR	Positive	42	44	86 (%78.18)
	Negative	12	12	24 (%21.82)

Table 2. Biochemical test results of the patients from the polyclinic and service/intensive care unit

	Polyclinic					Service/Intensive care					
Features†	*N*	Median	IQR	Min	Max	*N*	Median	IQR	Min	Max	p
Age	54	54	25	17	83	56	55.5	26	19	86	0.174
Ferritin	54	184.5	299	13	1469	56	443	815	15	2000	0.001*
CRP	54	15.8	36.72	2	187.8	56	62.85	83.30	2	346.9	<0.001*
D dimer	54	173	128	37	1468	56	269	309	27	2973	0.001*
WBC	54	5.48	2.70	3.24	10.23	56	7.24	5.06	2.21	40.78	0.001*
NEU	54	3.6	2.13	1.38	7.56	56	5.04	4.86	1.56	38.4	0.007*
LYM	54	1.15	0.78	0.5	5.12	56	1.36	1.18	0.33	3.06	0.783
RBC	54	4.83	0.41	3.56	5.68	56	4.55	0.98	2.25	56	0.002*
Hb	54	13.7	2.22	10.6	15.6	56	12.6	9.80	6.2	16	0.006*
PLT	54	181.5	91	87	376	56	208.5	157	106	546	0.054
PCT	12	0.04	0.035	0.02	0.07	47	0.887	0.190	0.02	27.4	0.012*

**p<0.05 significiant, Mann Whitney U* test. IQR: Interquartile Range,†: WBC, NEU, LYM, PLT= $x10^3$µL, RBC= $x10^6$µL, Hb= g/dL, CRP= mg/L, D dimer= µg/L, PCT= µg/L.

Discussion

The study was conducted using the specimens obtained from 110 patients that have applied to *Training and Research Hospital*. Rapid detection of SARS-CoV-2 was performed using RT-PCR test. Articles about antibody response after SARS-CoV-2 infection are limited in number. There are scarcely any studies because the antibodies in immunoassay systems have become available very recently. Roche SARS-CoV-2 antibody test identifies total antibody levels but does not differentiate virus-specific IgM and IgG.

Zhao et al. (18) conducted a study in 173 patients and detected overall seroconversion rate to be 93.1%, whereas seroconversion rate was 82.7% for IgM and 64.7% for IgG. They reported that not analyzing the specimens in the late phases of the disease might be the reason for antibody negativity in 12 patients. In the present study, antibody positivity rate was 20.37% (11/54) in the patient specimens sent from the polyclinic and 57.14% (32/56) in the patient specimens sent from the service/intensive care unit.

Wang et al. (19) detected a positivity rate of 63% for SARS-CoV-2 RNA in the nasopharyngeal smear specimens and 32% in the oropharyngeal smear specimens. RT-PCR was found positive in 86 (78.18%) of the 110 patient specimens sent both from the polyclinic and from the service/intensive care unit. All of the specimens in the present study were obtained by nasopharyngeal smear, and the positivity rate was quite high.

SARS-CoV-2 RT-PCR test was negative in 11 of the 43 patients with positive Roche Anti-SARS-CoV-2 antibody; 4 of these 11 specimens were from the service, 2 were from the intensive care unit and 5 were from the polyclinic. Antibody seropositivity and PCR negativity in the service/intensive care patients can be attributed to the specimen-associated positivity rates or time of sampling. Accordingly, using antibody test in symptomatic patients with negative RT-PCR can be beneficial in identifying the ill subjects.

Long et al. (5) detected RT–PCR positivity and virus-specific IgM and/or IgG seropositivity in 16 specimens (of which three were asymptomatic) obtained from 164 close contacts; however, they detected RT-PCR negativity and virus-specific IgM and/or IgG seropositivity in the specimens of the 7 of 148 asymptomatic subjects. The fact that the antibody was positive in PCR-negative 5 subjects from the polyclinic indicates that antibody testing can be used during pandemic for not missing the cases and taking necessary isolation measures. Furthermore, antibody tests may help with diagnosis since the RT-PCR-negative symptomatic patients with low viral burden might be overlooked.

Guo et al. (6) conducted a study using 208 plasma specimens (a total of 140 subjects; 82 confirmed and 58 PCR-negative but symptomatic) and they reported that the efficacy of IgM ELISA was higher than that of the PCR after 5.5 days of symptom onset and that combination of IgM ELISA with PCR significantly increased the rate of detecting positivity (98.6%) as compared to PCR alone (51.9%). In addition, many studies have emphasized that serological tests may enhance the rate of positivity and they need to be used in subclinical patients and in the future epidemiologic studies (20-22). In the present study, there were 11 antibody-positive patient specimens (RT-PCR negative) and 86 RT-PCR-positive patient specimens. The rate of detecting Covid-19 positivity was 88.18% (97/110) with combination of antibody and PCR tests.

Rapid viral replication and release of strong proinflammatory cytokines in the early phases of COVID-19 infection may later result in extensive endothelial inflammation and further release of various inflammatory cytokines due to viral infection of the endothelial cell in addition to pulmonary infiltration and extensive alveolar injury (23, 24). Neutrophils and leukocytes may strengthen extra-lymphocyte cytokine storm in COVID-19 (25). Güçlü et al. found that leukocyte and neutrophil counts were higher but lymphocyte count was lower in severe cases vs. mild cases at hospital admission and that leukocyte and neutrophil counts increase more in severe cases but decrease in mild cases on the third day of hospital stay. However, although lymphocyte count decreased much more in severe cases vs. mild cases on the third day, they reported that the difference is not significant (23). In the present study, leukocyte, neutrophil and erythrocyte counts, hemoglobin, ferritin, CRP, PCT and D- dimer levels were statistically significantly different between the patient specimens sent from the polyclinic and those sent from the service/intensive care unit ($p= 0.001$, 0.007, 0.002, 0.001, <0.001, 0.012, 0.006 and 0.001, respectively). However, lymphocyte and thrombocyte counts were not statistically significantly different between the patient specimens sent from the polyclinic and sent from the service/intensive care unit ($p>0.05$).

Some studies detected a relationship between thrombocytopenia and the severity of COVID-19 and related deaths, and it was reported that mortality rate increases as the thrombocyte count decreases (26, 27). In the present study, thrombocyte count was significantly low in two (89 and 94, respectively) of the 11 male patients died of COVID-19. Mechanisms associated with the thrombocytes in SARS-CoV-2 and the relation with gender could be the subjects of investigation.

Many laboratory parameters make it possible to assess the severity of the disease due to Covid 19 and to predict the risk of progression to serious diseases. In COVID-19 patients, recommendations have been made to establish certain threshold-values for Ferritin, PCT, CRP, D dimer, WBC, NEU, LYM and some other parameters and to evaluate accordingly (28-30). It was found that higher PCT values were associated with disease severity in COVID-19 patients (30) and higher D-dimer values at hospital admission were significantly associated with in-hospital mortality (31). A significant decrease was found in WBC and also other leukocyte formula parameters (neutrophils, eosinophils, basophils, lymphocytes and monocytes) in Covid 19 patients (28).

In another study, lymphopenia (83.2%), thrombocytopenia (36.2%) and an increase in D dimer (43.2%) values were observed in COVID-19 patients (32).

It is demonstrated that Covid 19 patients have neutrophilia, leukocytosis and increased procalcitonin due to bacterial (super) infection, thrombocytopenia due to consumption (disseminated) coagulopathy, lymphopenia due to decreased immunological response to the virus, increased CRP levels due to severe viral infection/viremia/viral sepsis, blood coagulation activation and/or severe coagulopathy due to increased D-dimer levels (29). It has been reported that high ferritin levels are associated with acute respiratory distress syndrome (ARDS) and a high risk of death (33). Similar to the studies, it can be said that the significant increase in WBC, NEU PCT, CRP, D dimer, ferritin levels in our study, especially in service/intensive care patients, is due to the increase in the severity of the disease and the occurrence of secondary infections.

In conclusion, it can be suggested that seroprevalence needs to be detected, antibody levels should be determined before vaccination, and antibody should be studied in RT-PCR-negative symptomatic patients because of increasing number of exposure to SARS-CoV-2.

Acknowledgments

The authors thank to Diyar-Med Health Products Ind. and Com. Ltd. Co. for supplying *Roche* SARS-CoV2 antibody test kit.

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