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IgG Neutralizing Antibodies to SARS-CoV-2 Among Healthcare Workers Who Frequently Encountered Patients with COVID-19

Hastanemizde COVID-19 Hastalarıyla Sıklıkla Karşılaşan Sağlık Çalışanlarında SARS-CoV-2'ye Karşı IgG Nötralize Edici Antikorların Değerlendirilmesi

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Abstract

Introduction: Since the Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2) first emerged in Wuhan, on 12 December 2019, it has spread rapidly across the world and developed into a pandemic. As healthcare workers are frequently in contact with Coronavirus disease-2019 (COVID-19) patients, they can be affected more often than the general population. In this study we aimed to investigate the SARS-CoV-2 seroprevalence and the IgG antibody levels among healthcare workers who frequently encountered COVID-19 patients in our hospital.

Materials and Methods: In total, 182 healthcare workers were identified from database and their data was retrospectively analyzed. Participants with previous PCR positivity, pregnant, autoimmune disease history or immunosuppressive treatment history were excluded. Participants were grouped depending on their frequency of contact with COVID-19 patients (high and medium risk). All the samples were tested simultaneously for anti-SARS-CoV-2-IgG antibodies by the ELISA method. A chi-square test was used to compare categorical variables. A t-test and an ANOVA test were carried out to where appropriate.

Results: Serological testing of 182 HCWs exposed to SARS-CoV-2 patients illustrated that 13.2% of them (24 out of 182) might have experienced an asymptomatic or subclinical SARS-CoV-2 infection. High risk participants, anosmia, and ageusia were statistically significant risk factors. The rate of detection of antibody positivity among doctors (p=0.030) and patients with anosmia, and ageusia (p=0.047) were found significantly higher than the others. In addition, SARS-CoV-2 antibody ratio results were found significantly higher in the groups of high risk participants (p=0.046), patients with clinical signs (p=0.008), myalgia (p=0.039), anosmia, and ageusia (p=0.025), respectively.

Conclusion: Our study showed that serological testing is useful for determining asymptomatic or subclinical infections prevelance of SARS-CoV-2 among those with close contact with COVID-19 patients. Serological tests can be helpful determining the prevelance COVID-19 infection, especially among the HCWs.

Keywords: COVID-19, healthcare workers, pandemic, SARS-CoV-2, seroprevalance

Öz

Giriş: Şiddetli akut solunum yolu sendromu-Koronavirüs-2 (SARS-CoV-2) ilk olarak 12 Aralık 2019'da Wuhan'da ortaya çıktığından beri, dünya çapında hızla yayıldı ve bir pandemi haline geldi. Sağlık çalışanlarının Koronavirüs hastalığı-2019 (COVID-19) hastalarıyla sıklıkla temas halinde olmalarından dolayı, genel popülasyona göre daha sık etkilenebilirler. Bu çalışmada hastanemizde COVID-19 hastalarıyla sıklıkla karşılaşan sağlık çalışanları arasında, SARS-CoV-2 seroprevalansını ve virüse karşı gelişen IgG antikor düzeylerini araştırmayı amaçladık.

Gereç ve Yöntem: Veri tabanından 182 sağlık çalışanı belirlendi ve verileri geriye dönük olarak analiz edildi. Daha önce polimeraz zincir reaksiyonu pozitifliği olan, hamile, otoimmün hastalık öyküsü veya immünosüpresif tedavi öyküsü olan katılımcılar çalışma dışı bırakıldı. Katılımcılar, COVID-19

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Öz

hastalarıyla temas sıklıklarına göre (yüksek ve orta riskli) gruplandırıldı. Tüm numuneler, ELISA yöntemiyle anti-SARS-CoV-2-IgG antikorları için aynı anda test edildi. Kategorik değişkenleri karşılaştırmak için ki-kare testi kullanıldı. Uygun olanlarda t-testi ve bir ANOVA testi yapılmıştır.

Bulgular: SARS-CoV-2 hastalarına maruz kalan 182 sağlık çalışanının serolojik testleri, bu kişilerin %13,2'sinin (182 kişiden 24'ü) asemptomatik veya subklinik SARS-CoV-2 enfeksiyonu geçirmiş olabileceğini gösterdi. Yüksek riskli katılımcılar arasında koku ve tat alamama, istatistiksel olarak anlamlı risk faktörleriydi. Antikor pozitiflik oranı doktorlar (p=0,030) ve koku ile tat alamama şikayeti bulunan olgularda (p=0,047) diğer olgulardan anlamlı şekilde daha yüksek saptandı. Ek olarak, SARS-CoV-2 antikor düzeyleri ise sırasıyla, yüksek riskli olgularda (p=0,046), klinik belirtileri (p=0,008), miyalji (p=0,039) ve koku ile tat alamama şikayetleri (p=0,025) olan hastalarda anlamlı şekilde daha yüksek saptandı.

Sonuç: Çalışmamız, COVID-19 hastalarıyla yakın teması olanlar arasında SARS-CoV-2'nin asemptomatik veya subklinik enfeksiyon prevalansını belirlemek için, serolojik testlerin yararlı olduğunu göstermiştir. Serolojik testler, özellikle sağlık çalışanları arasında COVID-19 enfeksiyonu prevalansının belirlenmesine yardımcı olabilir düşüncesindeyiz.

Anahtar Kelimeler: COVID-19, sağlık çalışanları, pandemi, SARS-CoV-2, seroprevalans

Introduction

Since the Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) first emerged in Wuhan, China, on December 12, 2019, it has spread rapidly worldwide. The pandemic has affected over 100 countries and regions, with over 290 million confirmed cases of COVID-19. The rapid spread of SARS-CoV-2 has caused considerable harm to public health and economy. Clinical manifestations of COVID-19 include fever, dry cough, and fatigue. Approximately half of the patients with COVID-19 developed severe pneumonia, and nearly one-third developed acute respiratory distress syndrome[1-3]. To date, 9.1 million people in Turkey have been affected by COVID-19[4]. As healthcare workers (HCWs) are frequently in contact with patients with COVID-19, they can be affected more often than the general population. Thus, HCWs and their family members are especially at risk for the infection.

Alongside other laboratory tests and clinical findings of COVID-19, serological testing may be beneficial for epidemiological monitoring and outbreak control. The determination of antibodies enables confirmation of the SARS-CoV-2 infection in patients without symptoms in addition to those with typical symptoms[5]. The immunoassay method, which is currently available, targets antigens that include the spike protein (S) or the nucleocapsid (N) of SARS-CoV-2[6]. Determining antibody levels and seroprevalence of healthy HCWs will be useful in controlling the COVID-19 pandemic.

In this study, we aimed to determine the SARS-CoV-2 seroprevalence and IgG antibody index levels among HCWs who frequently encountered patients with COVID-19 in our hospital.

Materials and Methods

Sera were obtained from individuals exposed to patients with COVID-19 during the pandemic. All of them tested negative for SARS-CoV-2 using polymerase chain reaction (PCR) tests. A total of 182 samples were collected in November 2020 from HCWs with negative results in the PCR test for SARS-CoV-2. Participants who tested positive using the same method and had COVID-19 were excluded. Participants who were pregnant, had autoimmune diseases, and received immunosuppressive therapy were also excluded.

Participants were grouped depending on their frequency of contact with patients with COVID-19. A total of 182 HCWs participated in this study. Group A (high-risk group) had daily contact with patients with COVID-19 on intensive care units and other care rooms. Group B (medium-risk group) consisted of people working in laboratories and surgical units and all other staff who had to wear a surgical mask since April 14, 2020. Risk groups A and B were made based on a previous study[7]. The sampling period was conducted in November 2020 through a cross-sectional study.

All samples were tested simultaneously for anti-SARS-CoV-2-IgG antibodies by the enzyme-linked immunosorbent assay (ELISA). They were detected in the sera using a semiquantitative ELISA (Euroimmun Medizinische Labordiagnostika, Lübeck, Germany) according to the manufacturer's instructions[8].

Multiple manufacturers offer serological assays, but few have received emergency use authorization (EUA). The Euroimmun IgG assay has received EUA from the U.S. Food and Drug Administration. Of the immunoassays currently available, SARS-CoV-2 target antigens include the spike protein (S) or nucleocapsid (N).

The Euroimmun anti-SARS-CoV-2 assay is an ELISA that provides semiquantitative *in vitro* determination of human antibodies of immunoglobulin classes IgG against SARS-CoV-2 in the serum or ethylenediaminetetraacetic acid plasma. Each kit contains microplate strips with eight break-off reagent wells coated with a recombinant structural protein of SARS-CoV-2. In the first reaction step, diluted patient samples were incubated in the wells. In positive samples, specific antibodies will bind

to the antigens. A second incubation was conducted to detect the bound antibodies, using an enzyme-labeled antihuman IgG (enzyme conjugate) catalyzing a color reaction. The Euroimmun anti-SARS-CoV-2 assay detects SARS-CoV-2 antibodies against S1 (spike) proteins.

Results were evaluated semiquantitatively by calculating a ratio of the extinction of the control or patient sample over the extinction of the calibrator. This ratio is interpreted as follows: <0.8, negative; ≥0.8-<1.0, borderline; and ≥1.1, positive. Borderline results were considered positive for this analysis.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) Statistics for Windows, version 17.0 (SPSS Inc., Chicago, Ill., USA). A chi-square test was used to compare categorical variables. A t-test was applied to compare the means groups of two that fit the normal distribution, and an analysis of variance (ANOVA) test was conducted to compare the mean of multiple groups. Nonparametric tests were used to compare group averages that were abnormally distributed; $p<0.05$ was considered significant.

Results

A total of 182 samples were collected in November 2020 from HCWs with negative PCR results for SARS-CoV-2. These HCWs had a high or medium risk for COVID-19 at the University of Baskent Hospital from March 2020 to November 2020. The average age of the 182 HCWs was 34 years old, which ranged from 20 to 60 years old. Standard deviations were ±10,443 for women and ±8,011 for men. Of the 182 participants, 102 (54.9%) were women and 80 (45.1%) were men. Participants were analyzed according to their relative risk of exposure to patients with symptomatic COVID-19: high risk (group A) and medium risk (group B). Group A comprised 108 participants who were doctors, nurses, dentists, or assistive personnel. They worked in the intensive care units, anesthesiology and reanimation units, otorhinolaryngology, infectious diseases, emergency, and respiratory science departments. Group B was composed of participants working in the laboratory and other surgical departments. All nasopharyngeal swab samples collected tested negative for SARS-CoV-2 using PCR tests during the pandemic period. The clinical and serological characteristics of the participants are shown in Table 1. Of the total number of samples, 24 (13.2%) were positive and 158 (86.8%) were negative for the anti-SARS-CoV-2 antibody.

Seventy-two participants had clinical signs, namely, fever, 17 (9.3%); no fever, 165 (90.7%); headache, 49 (26.9%); no headache, 133 (73.1%); myalgia, 38 (20.9%); no myalgia, 144 (79.1%); cough, 43 (23.6%); no cough, 139 (76.4%); anosmia and ageusia, 8 (4.4%); no anosmia and ageusia, 174 (95.6%); diarrhea, 15 (8.2%); no diarrhea, 167 (91.8%); dyspnea, 10 (5.5%); no dyspnea, 172 (94.5%).

When antibody positivity status (positive or negative) was compared with the profession (doctors, nurses and the others), anosmia, and ageusia by the chi-square test, the result was significant (Table 2), showing differences of p=0.030 and p=0.047, respectively. It was observed that the rate of detection of antibody positivity among doctors was higher than the others. Results for other variables were interpreted as non-significant. In addition, when clinical symptoms were compared according to risk levels by the chi-square test, only a cough was found to be significant (p=0.026), whereas other symptoms were non-

Table 1. Participant clinical and serological characteristics

	Group A (High risk) n=109 (59.9%)	Group B (Medium risk) n=73 (40.1%)	Total n=182 (100%)
Sex			
Female	59	43	102 (56.1%)
Men	50	30	80 (43.9%)
Profession			
Doctor	48	32	80 (44%)
Nurse	31	17	48 (26.6%)
Other	30	24	54 (29.7%)
Clinical signs			
Positive	49	23	72 (60.4%)
Negative	60	50	110 (29.5%)
SARS-CoV-2 antibody status			
Positive	18	6	24 (13.2)
Negative	92	67	158 (86.8)

*Laboratory technologist and auxiliary staff of intensive care units and emergency rooms.
SARS-CoV-2: Severe acute respiratory syndrome-Coronavirus-2

Table 2. Results of the statistical analyses

	SARS-CoV-2 antibody status p* Chi-square test	Level of risk p* Chi-square test	Ratio p* Mann-Whitney test
Profession	**0.030**	0.650	0.773
Sex	0.240	0.448	–
Levels of risks	0.144	–	**0.046**
Clinical signs	0.496	0.089	**0.008**
Clinical signs			
Fever	0.808	0.143	0.145
Headache	0.455	0.054	0.514
Cough	0.772	**0.026**	0.402
Myalgia	0.549	0.114	**0.039**
Anosmia and ageusia	**0.047**	0.100	**0.025**
Diarrhea	0.437	0.576	0.366
Dyspnea	0.132	0.158	0.095

SARS-CoV-2: Severe acute respiratory syndrome-Coronavirus-2

significant. A significant difference was found between levels of risk (p=0.046), clinical signs (p=0.008), myalgia (p=0.039) anosmia, and ageusia (p=0.025) when comparing antibody results ratio values using the t-test (in groups of two) and ANOVA test in multiple groups (Table 2).

SARS-CoV-2 antibody ratio results were found significantly higher in the groups of high risk participants, patients with clinical signs, myalgia, anosmia and ageusia, respectively.

Among the total 182 participants, 12 of 24 HCWs with positive antibody tests had clinical signs, whereas the others did not have clinical signs. The clinical signs were fever (n=2), headache (n=6), myalgia (n=7), cough (n=7), anosmia and ageusia (n=7), and diarrhea and dyspnea (n=3) in the antibody-positive participants.

Discussion

A wide spectrum of disease severity in laboratory-confirmed COVID-19 has been depicted, including asymptomatic or minimally symptomatic cases[9]. Efficient human-to-human transmission of SARS-CoV-2 mostly occurs among close contacts[1]. The proportion of patients with asymptomatic COVID-19 is still unknown, which remains a critical epidemiological puzzle, and whether it is possible to seroconvert to SARS-CoV-2 with minimal or no symptoms still needs to be answered.

HCWs have been on the frontline of the fight against the COVID-19 pandemic. Accordingly, they have been at an increased risk of contracting COVID-19 since the pandemic started. More understanding of the risk factors of the SARS-CoV2 infection in clinical settings is urgently needed, as it will provide HCWs with essential guidance of self-protection. It will also help policymakers formulate appropriate measures for infection control in hospital settings.

Serological testing of those who have close contact with patients with COVID-19 helps define both the local transmission rate and risk factors for infection, which can be especially helpful, as it leads to identifying asymptomatic or subclinical infections in HCWs[9].

The anti-SARS-CoV-2 ELISA demonstrated good sensitivity for the detection of IgA and excellent sensitivity for IgG antibodies in samples collected within 4 days after COVID-19 diagnosis by PCR. It did not show any cross-reaction with common human coronaviruses[8]. Accordingly, Van Elslande et al.[5] stated that commercial automated assays and ELISA, which detected antibodies against S1 proteins, are suitable for the detection of IgG antibodies against SARS-CoV-2. The Euroimmun IgG assay detects S1 proteins, with a specificity of 96.5% (91.0-98.9%), and has no false positives[5].

In the present study, anti-SARS-CoV-2 antibodies in HCWs were detected using the Euroimmun assay. Nasopharyngeal swab samples collected from all HCWs were negative for SARS-CoV-2 RNA. However, our serological analysis indicated a 13.1% asymptomatic or subclinical SARS-CoV-2 infection rate in the hospital setting. The seropositivity rate was 16.5% in the high-risk group, whereas it was 8.2% in the medium-risk group. By contrast, the results of a study conducted in Germany revealed that the seroprevalence rate was higher in the medium-risk group (5.4%) than in the high-risk group (1.2%) of HCWs[10].

Similar research has been conducted in different contexts with varying results. Chinese researchers found that the seropositivity rate was 17.14% among HCWs with subclinical and asymptomatic infections[9]. In line with these results, a

study conducted in Sweden found a seropositivity rate of 19.1% in 2149 HCWs. No significant difference was noted in age or sex between seropositive and seronegative groups[11]. Some other studies have detected lower rates. For instance, in Greece and Norway, seropositivity rates were 1.42% and 5.3%, respectively[12,13]. As with our study, the PCR-positive results were excluded in both of these studies. It was assumed that mortality rates were low due to the lockdown that started on March 12, 2020[13].

In our study, seropositivity varied across job categories (doctors, nurses, and others). A significant difference was found between doctors and other groups when the positivity of antibodies among job categories was analyzed (p=0.030). Similarly, a review provided updated and comprehensive information about the seroprevalence of the SARS-CoV-2 antibody in different populations. A higher risk of seroconversion was found in doctors exposed to patients with COVID-19. However, a lower risk of seroconversion was closely related to direct exposure to patients with COVID-19 while wearing a face mask[14]. The seroprevalence of the anti-SARS-CoV-2 antibody can vary across regions, and it can increase over time during longitudinal follow-up. Although HCWs, especially those caring for patients with COVID-19, are considered a high-risk group, the seroprevalence in this group may not be higher than that in other groups if they wear adequate personal protective equipment (PPE)[14]. In our country, HCWs have been using PPE from April 14, 2020, until now.

Recognizing the risk factors of SARS-CoV-2 has important implications for mitigating the pandemic, controlling infection, and helping improve understanding of the associated epidemiology. In our study, no significant difference was found between high- and medium-risk levels and antibody positivity. However, the significant correlation between the level of risk (p=0.046), positive clinical signs (p=0.008), and ratios demonstrate that antibody responses are more frequent and higher in those who frequently encounter COVID-19. Among the people who were positive for antibodies, 50% showed clinical signs of the infection. Among the clinical symptoms, a significant relationship was noted between anosmia and ageusia and antibody positivity. Moreover, a significant relationship was found between ratio levels and myalgia, anosmia, and ageusia (Table 1).

Serological tests are necessary for the diagnosis of asymptomatic or subclinical cases, especially those who are in close contact with patients with COVID-19. In our study, the presence of antibody positivity in 12 participants (10.9%) indicates that those working in at-risk areas could be infected with COVID-19 and could transmit the virus to their contacts, despite showing no symptoms and wearing PPE. The finding of a significant relationship between the levels of ratios and risk groups demonstrates that frequent exposure to the virus and viral load affects the occurrence of infection.

The primary limitation of this study is the levels of anti-SARS-CoV-2-IgG antibody status were not determined by quantitative test but through a semiquantitative test.

Conclusion

In summary, serological testing of 182 HCWs exposed to patients with COVID-19 illustrated that 13.2% of them (24 of 182) might have experienced an asymptomatic or subclinical SARS-CoV-2 infection. Our study showed that serological testing is useful for determining the prevalence of asymptomatic or subclinical infections of SARS-CoV-2 among those with close contact with patients with COVID-19. Serological tests can help determine the prevalence of COVID-19 infection, especially among HCWs. However, whether these asymptomatic or subclinical infections play a role in transmission dynamics remains to be determined. Our findings have important implications for the implementation of pandemic mitigation strategies. This result could help clarify the epidemiology of COVID-19, and it could be useful in defining the correct diagnostic approach. Further research is necessary to determine the prevalence of COVID-19 among HCWs.

Ethics

Ethics Committee Approval: This study was approved by Başkent University Institutional Review Board and Ethics Committee (project no. KA20-449, date: 08.01.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.Y., İ.Ö., Z.E.Ü., Concept: H.Y., H.E.A., Design: H.Y., H.E.A., Data Collection or Processing: H.Y., H.E.A., H.H.G., Z.E.Ü., Analysis or Interpretation: H.Y., H.E.A., H.H.G., İ.Ö., Z.E.Ü., Literature Search: H.Y., H.E.A., H.H.G., İ.Ö., Z.E., Writing: H.Y., H.E.A.

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