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Research Article

Antibody responses of COVID-19 patients according to symptoms and the presence of pneumonia

COVID-19 hastalarının semptomlarına ve pnömoni varlığına göre antikor tepkileri

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Abstract

Introduction: The aim of the study was to examine the 30-day total SARS-CoV-2 antibody positivity in patients across a clinical spectrum ranging from asymptomatic to pneumonia.

Methods: This prospective cohort study consisted of 51 consecutive patients who were RT-PCR positive and diagnosed COVID-19 pneumonia (Group 1) and 58 consecutive patients who were also RT-PCR positive but were asymptomatic or had mild symptoms (Group 2). On the 30th day from the date of symptom onset, the patients were called for examination and blood samples were taken for the detection of SARS-CoV-2 antibodies.

Results: Patients with pneumonia, fever, muscle pain, and loss of taste and smell had significantly higher rates of antibody positivity (p= 0.001, 0.003, 0.030, and 0.018, respectively). Antibody positivity was found to be significantly higher in patients with at least one symptom on admission compared to asymptomatic patients (p = 0.001). While the antibody positivity rate was 96.1% in Group 1 (patients with pneumonia), it was 50% in Group 2 (patients without pneumonia), and 77.7% in patients with at least one symptom on admission compared to 33.3% in asymptomatic patients (p=0.001).

Conclusions: Patients with COVID-19 pneumonia have significantly higher disease-specific total antibody positivity rates than patients without pneumonia. Considering the 50% antibody positivity in patients who had COVID-19 infection who were asymptomatic or had symptoms other than pneumonia, the issue of COVID-19 re-infection and immunity is much more important than it appears.

Keywords: COVID-19, pneumonia, antibody, SARS-CoV-2

Öz

Giriş: Klinik spektrumu asemptomatik hastalardan pnömonili hastalara kadar değişen hastalarda 30. gün total SARS-CoV-2 antikor pozitifliğini incelemeyi amaçladık.

Yöntem: Bu prospektif kohort çalışması, RT-PCR pozitif olan ve COVID-19 pnömonisi teşhisi konan 51 hastadan(Grup 1) ve aynı zamanda RT-PCR pozitif olan ancak asemptomatik veya hafif semptomları olan 58 hastadan (Grup 2) oluşmaktadır. Semptomların başladığı tarihten itibaren 30. günde hastalar kontrole çağrılarak SARS-CoV-2 antikorlarının tespiti için kan örnekleri alındı.

Bulgular: Pnömoni, ateş, kas ağrısı, tat ve koku kaybı olan hastalarda antikor pozitiflik oranları anlamlı olarak daha yüksekti (sırasıyla p= 0.001, 0.003, 0.030 ve 0.018). Başvuru anında en az bir semptomu olan hastalarda antikor pozitifliği asemptomatik hastalara göre anlamlı derecede yüksek bulundu (p=0.001). Antikor pozitiflik oranı Grup 1'de (pnömonili hastalar) %96.1, Grup 2'de (pnömonisi olmayan hastalar) %50 ve başvuru anında en az bir semptomu olan hastalarda %77.7 iken asemptomatik hastalarda %33.3 idi(p=0.001).

Sonuç: COVID-19 pnömonisi olan hastalar pnömonisi olmayan hastalardan önemli ölçüde daha yüksek total antikor pozitiflik oranlarına sahiptir. Asemptomatik veya pnömoni dışında semptomları olan COVID-19 enfeksiyonu olan hastalarda %50 antikor pozitifliği göz önüne alındığında, COVID-19'un re-enfeksiyonu ve immunitesi göründüğünden çok daha önemlidir.

Anahtar Kelimeler: COVID-19, pnömoni, antikor, SARS-CoV-2

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Introduction

The rapid spread of novel coronavirus disease 2019 (COVID-19) caused widespread concern around the world, and it was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 [1]. SARS-CoV-2 , the agent responsible for COVID-19, is a typical coronavirus of the beta coronavirus 2b family, which includes severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) coronavirus. As the infection became a worldwide pandemic, markers were needed to diagnose the disease and predict the course of the pandemic. In this way, the right approach to the patient would be the determinant of the current health policy. The detection of IgG and IgM type specific antibodies that form against SARS-CoV-2 in the blood serum of the patient is also critical in diagnosis. Studies on SARS-CoV and MERS-CoV have shown that virus-specific antibodies are detectable in 80–100% of patients two weeks after symptom onset [2-7]. Currently, the protective role of antibodies against SARS-CoV-2 is unknown, and the antibody responses against SARS-CoV-2 remain poorly understood. However, previous studies have shown that the decrease in antibody titers after viral antigenic exposure is approximately exponential [8] and antibody loss was quicker than that reported for SARS-CoV [9, 10]. Some studies have shown that during the first three weeks after symptom onset, there were increases in SARS-CoV-2-specific IgG and IgM antibody titers. Approximately 17–19 days after symptom onset, SARS-CoV-2 IgG antibody was detected in 100% of the patients, and at 20–22 days after symptom onset, SARS-CoV-2 IgM antibody was detected in 94.1% of the patients [11, 12].

Little is known about the relationship between clinical symptoms and disease severity and virus-specific antibody positivity in patients infected with SARS-CoV-2. It is not known whether the rate of antibody positivity differs between asymptomatic and mild COVID-19 patients, which constitute the majority of cases, and patients with COVID-19 pneumonia. Antibody levels could provide an insight into the reinfection of COVID-19 and herd immunity. The aim of this study was to examine the 30th day total SARS-CoV-2 antibody positivity in patients across a clinical spectrum ranging from asymptomatic patients to patients with pneumonia and to reveal the relationship between symptoms, disease severity, and antibody positivity.

Methods

This cross-sectional study consisted of 109 COVID-19 patients confirmed with reverse transcription polymerase chain reaction (RT-PCR) who were admitted to the outpatient clinics of Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, in Istanbul, Turkey on October 11 and 12, 2020. Lung computed tomography (CT) was performed on all patients on admission. Patients demographic information, comorbidities, symptoms, and duration of symptoms (admission and 30th day) data were from outpatient records. On the 30th day from the date of symptoms onset, blood samples were taken for the detection of SARS-CoV-2 antibodies. Group 1-PCR and CT positive group included 51 consecutive patients who were RT-PCR positive and had pneumonic infiltration on lung CT, and 58 consecutive patients who were also RT-PCR positive but had no pneumonic infiltration on lung CT were named Group 2-PCR positive and CT negative group, with asymptomatic or mild symptoms. Patients under the age of 18 years, or who were receiving immunosuppressive therapy for any reason or had received immunosuppressive therapy due to COVID-19 infection were excluded from the study.

To determine the sample size for this study comparing total antibody levels in Group 1 (with pneumonia-study group) and Group 2 (without pneumonia- study group), power analysis was performed with Clinical software [13]. The primary outcome in the study was binomial, with a power of 0.5 based on clinical experience. Considering that the antibody positivity rate was around 90% in similar studies [14] conducted in patients who were previously diagnosed with COVID-19 pneumonia at 80% power and a 0.05 type 1 error level, it was determined that a minimum of 92 cases should be included and to account for data loss greater than 20%, 110 cases should be included in the study.

Nasopharyngeal and oropharyngeal specimens were collected once from patients, and specimens were evaluated for SARS-CoV-2 using real-time RT-PCR (Bioeksen, Turkey) at our hospital. SARS-CoV-2 antibodies were quantified in human plasma using a fully automated Cobas e801 analyzer (Roche Diagnostics, Switzerland) and the novel Elecsys Anti-SARS-CoV-2 EIA diagnostic kits for the qualitative detection of SARS-CoV-2 IgM, IgG, and IgA antibodies. The Elecsys Anti-SARS-CoV-2 EIA diagnostic kit detects total SARS-CoV-2 antibodies, including IgA, IgM, and predominantly IgG. The measurement of Anti-SARS-CoV-2 was performed following the manufacturer's instructions. The results were reported as numerical values in the form of a cutoff index (COI) as well as qualitative results of non-reactive (COI <1.0; negative) and reactive (COI ≥1.0; positive). According to the product information provided by the manufacturer, Elecsys® anti-SARS-CoV-2 assay sensitivity is 99.5% (95% CI: 97.0–100%) for ≥ 14 days and overall specificity is 99.80% (95% CI: 99.69–99.88%). At least one radiologist evaluated and reported whole-lung CT scans of the patients (Somatom 64 Slice, Siemens Healthcare, Forchheim, Germany).

Ethical approval, informed consent and permissions

Informed consent was obtained from each subject prior to the study. The study was approved by the Medical Research Ethics Committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital (Approval number: 07.09.2020/2020-380). All procedures were in compliance with the Helsinki Declaration, and patient confidentiality was protected at all times.

Statistical Analysis

The SPSS version 25 software (IBM Corp., Armonk, NY, USA) was used to analyze the study data statistically. Descriptive statistical methods were used in the evaluations (mean±standard deviation (SD), median, minimum, maximum, and percentage). The Kolmogorov-Smirnov test, the Shapiro-Wilk test, and graphic methods were used to determine whether quantitative data conformed to a normal distribution. The Student's t-test was applied in the comparison of two groups of quantitative data showing normal distribution. In the comparison of qualitative data, the Pearson chi-square test was used. A statistically significant value of p 0.05 was accepted.

Results

Evaluation was made of a total of 109 RT-PCR confirmed patients, 58 with asymptomatic or mild COVID-19 infection and 51 with COVID-19 mild to severe pneumonia. The mean age of all the patients was 35.66 ± 8.61 years; 37.35 ± 9.54 years in Group 1; and 34.17 ± 7.47 years in Group 2 (p = 0.054). While 29.4% (n = 32) of the total patient group was male, 70.6% (n =77) were female; in Group 1, 33.3% (n =17) were male and 66.7% (n =34) were female, and in Group 2, 25.9% (n =15) were male and 74.1% (n =43) were female (p = 0.392).At least one symptom was present at the time of presentation in 86.2% of the patients, the most common symptom being diarrhea (80.7%). A total of 15 patients (13.8%) were asymptomatic. The demographic data of the patients is summarized in Table 1 and 2.

Table 1. Demographic data of the patients

Demographic data	Overall	Patients with pneumonia	Patients without pneumonia
n	109	51 (46.8%)	58 (53.2%)
Gender			
Male	32 (29.4%)	17 (33.3%)	15 (25.9%)
Female	77 (70.6%)	34 (66.7%)	43 (74.1%)
Age (years) (Mean ± SD)	35.66 ± 8,61	37.35 ± 9.54	34.17 ± 7.47
# of patients with positive total antibody	78 (71.6%)	49 (96.1%)	29 (50%)

SD: Standard Deviation

Table 2. Distribution of symptoms in patients participating in the study

Symptoms	Absent	Present
Fever	74 (67.9%)	35 (32.1%)
Throat ache	82 (75.2%)	27 (24.8%)
Cough	57 (52.3%)	52 (47.7%)
Dyspnea	79 (72.5%)	30 (27.5%)
Headache	68 (62.4%)	41 (37.6%)
Loss of taste and smell	75 (68.8%)	34 (31.2%)
Diarrhea	88 (80.7%)	21 (19.3%)
Myalgia	65 (59.6%)	44 (40.4%)

On the 30th day after symptoms onset, the overall SARS-CoV-2 total antibody positivity rate was 71.6% (n = 78). The relationship was examined between total antibody positivity and gender, presence of pneumonia, and symptoms on admission, and it was determined that patients with pneumonia, fever, muscle pain, and loss of taste and smell had significantly higher antibody positivity (p = 0.001, 0.003, 0.030, and 0.018, respectively). Antibody positivity was found to be significantly higher in patients with at least one symptom on admission compared to asymptomatic patients (p = 0.001). The antibody positivity rate was 96.1% in Group 1, 50% in Group 2, 77.7% in patients with at least one symptom on admission, and 33.3% in asymptomatic patients (Table 3).

Table 3. Relationships between the presence of antibody and the presence of pneumonia and other symptoms

		Antibody			
Symptoms		**Negative (%)**	**Positive (%)**	**Total (%)**	p
Pneumonia	Absent	29 (50%)	29 (50%)	58 (100%)	<0.001*
	Present	2 (3.9%)	49 (96.1%)	51 (100%)	
Gender	Female	25 (32.5%)	52 (67.5%)	77 (100%)	0.225
	Male	6 (18.8%)	26 (81.3%)	32 (100%)	
Fever	Absent	28 (37.8%)	46 (62.2%)	74 (100%)	0.002*
	Present	3 (8.6%)	32 (91.4%)	35 (100%)	
Throat ache	Absent	23 (28%)	59 (72%)	82 (100%)	0.875
	Present	8 (29.6%)	19 (70.4%)	27 (100%)	
Cough	Absent	20 (35.1%)	37 (64.9%)	57 (100%)	0.107
	Present	11 (21.2%)	41 (78.8%)	52 (100%)	
Dyspnea	Absent	24 (30.4%)	55 (69.6%)	79 (100%)	0.466
	Present	7 (23.3%)	23 (76.7%)	30 (100%)	
Headache	Absent	21 (30.9%)	47 (69.1%)	68 (100%)	0.467
	Present	10 (24.4%)	31 (75.6%)	41 (100%)	
Loss of taste and smell	Absent	27 (36%)	48 (64%)	75 (100%)	0.009*
	Present	4 (11.8%)	30 (88.2%)	34 (100%)	
Diarrhea	Absent	26 (29.5%)	62 (70.5%)	88 (100%)	0.601
	Present	5 (23.8%)	16 (76.2%)	21 (100%)	
Myalgia	Absent	24 (36.9%)	41 (63.1%)	65 (100%)	0.017*
	Present	7 (15.9%)	37 (84.1%)	44 (100%)	
Asymptomatic	Yes	10 (66.7%)	5 (33.3%)	15 (100%)	<0.001*
	No	21 (22.3%)	73 (77.7%)	94 (100%)	

Pearson Chi-square Test *Significant P value <0.05

There was no relationship between antibody levels and comorbidity or age (p = 0.565 and 0.639, respectively) (Table 4)

Table 4. Relationships between the presence of antibodies and age, and between the presence of antibodies and comorbidities

Antibody	**Age (Years)(Mean±SD)**		**p**
Negative	34.90 ± 7.30		0.565[b]
Positive	35.96 ± 9.11		
	Antibody Positive n, %	**Antibody Negative n, %**	**p**
Comorbidity Present	21(75%)	7(25%)	0.639[a]
Comorbidity Absent	57(70.4%)	24(29.6%)	

[a] Pearson Chi-square Test, [b] Student t Test , Significant P value <0.05.

Discussion

Previous research has shown that both IgM and IgG antibodies against SARS-CoV-2 can be detected as early as the fourth to tenth day after symptom onset, with virus-specific IgG peaking at 17–19 days after symptom onset and virus-specific IgM peaking at approximately 20–22 days [11,12,14,15].Recent studies have shown that anti-SARS-CoV-2 receptor-binding domain IgG antibodies persist for at least six weeks in patient sera and have a half-life of 26 to 60 days [9, 16]. Another study conducted by Hou et al. [17] showed that IgM levels can be detected one week after symptom onset and reach a peak level in 2–3 weeks, and IgG levels can be detected a little later and remain at a high level for two months. There are gradual and notable increases in virus-specific IgM and IgG antibody titers during the first three weeks after symptom onset, and the maximum rate of cumulative seroconversion of the antibodies against SARS-CoV-2 is around the 30th day after symptom onset [11]. Another study conducted to determine the kinetics of serological antibodies in COVID-19 patients showed that both IgM and IgG antibodies were seropositive in nearly all the patients within the disease course for ≥ 30 days [14].

The most recent studies regarding antibody levels in patients are kinetic studies, and there is no study of COVID-19 patients showing the relationship between antibody levels and COVID-19 pneumonia. In these few kinetic studies, there are conflicting results between the severity of the disease and the antibody levels. Kai-Wang To et al [12], Hou et al [17] and Phipps et al [18], there was no correlation between serum antibody levels and clinical severity, whereas in studies by Wang et al [15] and Chen et al [19], mildly ill patients were seen to have lower IgM responses to SARS-CoV-2 compared to severely ill patients. The current study results showed a relationship between total antibody positivity on the 30th day after symptoms onset and the presence of pneumonia, fever, muscle pain, and loss of taste and smell in patients. In addition, antibody positivity rates were found to be significantly higher in patients with at least one symptom on admission compared to asymptomatic patients (77.7% vs 33.3%). Likewise, antibody positivity rates were significantly different in patients with and without pneumonia (96.1% vs 50%).

In a previous study, no association was shown between comorbidity and disease specific IgG or IgM antibody levels, or between age and disease-specific IgM or IgG antibody levels [12]. Similarly, in the current study, no relationship was found between antibody positivity and age or between antibody positivity and comorbidities. In the current study, 25.7% of patients had comorbidities, which is a similar proportion to the rate reported in a large clinical series (24%) [20].

The results of this study suggest that severe cases are more likely to elicit IgG antibody responses. This provides an idea of the interaction between the virus and the host immune system and the relationship between the presence of SARS-CoV-2 antibodies and clinical symptoms. Despite the clear correlation between COVID-19 severity and the development of humoral immunity, the cause-effect relationship is unclear. One possibility is that severe disease caused by hyperinflammation and/or uncontrolled viral replication causes overproduction of antibodies which function as "biomarkers" of severity. This is supported by the fact that the most severely affected patients with the highest levels of anti-RBD and anti-spike antibodies also have the highest inflammatory and pro-inflammatory cytokine markers [21]. In a study supporting this possibility, immune activation and high antibody production from extrafollicular B cells in critically ill patients were seen to have a pathogenic role in the process [22].

Limitations

The limitations of this study were that it was conducted in a single center, the number of patients was relatively low, and neutralization antibody levels were not checked.

Conclusion

Patients with COVID-19 pneumonia have significantly higher disease-specific total antibody positivity rates than patients without pneumonia. In addition, patients with at least one symptom on admission and patients who have fever, myalgia, or loss of taste and smell on admission have significantly higher disease-specific total antibody positivity rates than those without. Considering the 50% antibody positivity rate in COVID-19 patients who are asymptomatic or without pneumonia, the issue of COVID-19 re-infection and immunity is much more important than it appears. This low seroconversion rate could cause the pandemic to last much longer than previously thought, and it is obvious that there is an emergent and desperate need for effective therapies and vaccines for SARS-CoV-2.

Conflict of Interests: None.

Author Contributions		Author Initials
SCD	Study Conception and Design	RK, FK
AD	Acquisition of Data	RK, FK
AID	Analysis and Interpretation of Data	RK, FK
DM	Drafting of Manuscript	RK, FK
CR	Critical Revision	RK

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