

Determination of SARS-CoV-2 IgG antibody levels in hematology-oncology patients after COVID-19 vaccination

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Abstract. – OBJECTIVE: Cancer patients are among the high-risk groups where COVID-19 infection tends to be severe and can lead to increased mortality. Therefore, they are included in the priority groups for COVID-19 vaccination. This study aimed to compare the levels of SARS-CoV-2 immunoglobulin G (IgG) antibodies following two different COVID-19 vaccinations between hematology-oncology patients and healthcare personnel and to identify factors associated with these antibody levels.

PATIENTS AND METHODS: A prospective study was conducted with 91 hematology-oncology patients (cancer group) and 75 healthcare personnel (control group) from January 2020 to June 2023. The cancer and control groups comprised adults who had received a booster dose, with either a single dose of BNT162b2 or two doses of CoronaVac™ spaced one month apart, following their primary vaccination with two doses of either CoronaVac™ or BNT162b2. Four weeks after the administration of the booster dose, levels of SARS-CoV-2 IgG antibodies were assessed using an ELISA kit. Antibody levels above 50 AU/mL were accepted as signifying seropositivity.

RESULTS: The median SARS-CoV-2 IgG antibody level was lower in the cancer group compared to the control group (4,509 vs. 7,268, $p = 0.004$), while the rate of seroconversion was similar between the groups (97.8% vs. 100%, $p = 0.564$). In the cancer group, no association was found between SARS-CoV-2 IgG antibody levels and age, sex, comorbidity, type of malignancy, stage and duration, or type of vaccine.

CONCLUSIONS: In cancer patients, the seroconversion positivity rate was about 98%. However, antibody responses were still lower compared to the control group. No difference was detected in antibody levels among cancer patients based on the type of vaccine.

Key Words:

Antibodies, Cancer, COVID-19, Pandemics, Vaccination.

Introduction

The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), has been a significant public health issue both worldwide and in Turkey. In the span of just one year during the COVID-19 pandemic, COVID-19 vaccines were developed and began to be used worldwide with emergency use authorization¹.

Among the COVID-19 vaccines, 21 have received emergency use authorization, and various COVID-19 vaccines have been introduced in many countries. According to data from the World Health Organization², between January 2020 and August 2023, there were 17,004,677 confirmed cases of COVID-19 in Turkey and 101,419 reported deaths due to COVID-19. As of January 28, 2023, a total of 139,694,693 vaccine doses had been administered in the country. In Turkey, the COVID-19 vaccines CoronaVac™ (Sinovac, China), which is an inactivated virus vaccine, and BNT162b2 (Pfizer-BioNTech, USA/Germany), which is an mRNA vaccine, have received approval for clinical use and were widely used in mass vaccination campaigns³. However, there are limited studies in Turkey investigating the IgG antibody response to the COVID-19 vaccine in hematology-oncology patients.

In cancer patients, the factors influencing the SARS-CoV-2 immunoglobulin G (IgG) response, which is an indicator of the humoral immune response triggered by the vaccine, have yet to be adequately defined⁴. This study aimed to compare SARS-CoV-2 IgG antibody levels in hematology-oncology patients and healthy individuals and to determine the factors associated with these antibody levels.

Patients and Methods

Following the principles set forth in the Declaration of Helsinki, this retrospective study was conducted at the Kırıkkale University Faculty of Medicine, Department of Internal Medicine, Division of Oncology, and Health Sciences University Ankara Training and Research Hospital from January 2020 to June 2023. The study received approval from the Kırıkkale University Clinical Research Ethics Committee (Approval Date: 3 August 2022, Decision No. 11/01).

Study Population

In this study, 91 hematology-oncology patients (cancer group) who visited the Oncology Clinic

during the study period were included, along with 75 healthcare personnel (control group) from the same hospital. Cancer and control groups comprised adults who had received a booster dose, with either a single dose of BNT162b2 or two doses of CoronaVac™ spaced one month apart, following primary vaccination with two doses of either CoronaVac™ or BNT162b2. Inclusion criteria for the study were as follows: being 18 years of age or older, consenting to sign the informed consent form, being under outpatient monitoring and treatment as a hematological-oncological malignancy patient for the cancer group, not having any underlying immunosuppressive diseases for the control group, and having received the COVID-19 vaccine (Figure 1).

Study Protocol

The demographic and clinical data of the participants were recorded on follow-up forms. These data included age, sex, additional diseases, type of COVID-19 vaccine received (inactivated and/or mRNA), history of COVID-19, and the type of malignancy, stage, and duration of the disease. Four weeks after the administration of the booster dose, the levels of SARS-CoV-2 IgG antibodies were assessed as described below.

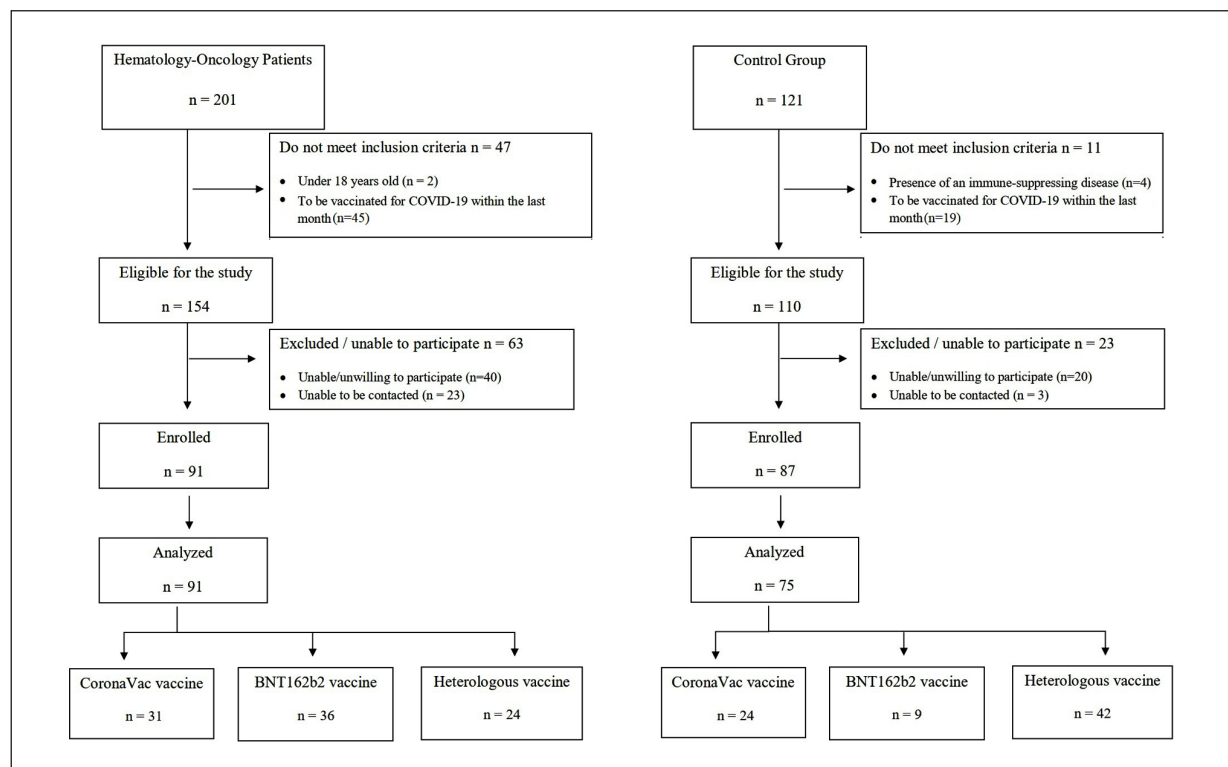


Figure 1. Study flowchart.

Analysis of SARS-CoV-2 IgG Antibody Titers

SARS-CoV-2 IgG antibody levels were assessed in the Microbiology Laboratory using the commercial SARS-CoV-2 IgG II Quant Reagent Kit 6S60 (Abbott, Chicago, IL, USA) in accordance with the manufacturer's recommendations, employing the ELISA method. This test, an automated two-step immunoassay, was utilized for both qualitative and quantitative assessment of IgG antibodies targeting SARS-CoV-2 in human serum and plasma, employing chemiluminescent microparticle immunoassay (CMIA) technology. The sample was combined with paramagnetic microparticles coated with the SARS-CoV-2 antigen and the assay diluent and then incubated. The SARS-CoV-2 IgG antibodies in the sample bind to the microparticles coated with the SARS-CoV-2 antigen. After washing the mixture, an acridinium-labeled anti-human IgG conjugate was added to form a reaction mixture, which was then incubated. After a cycle of washing, Pre-Trigger and Trigger solutions were administered. The resulting chemiluminescent reaction was measured as a relative light unit (RLU). A direct correlation exists between the quantity of SARS-CoV-2 IgG antibodies in the sample and the RLUs measured by the optical system. A threshold of 50 AU/mL was established as the cut-off value. Antibody levels above this value were considered to indicate seropositivity⁵.

Statistical Analysis

All data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean $\pm$ standard deviation (SD) values while non-normally distributed variables are given as median (25th-75th quartile) values. Differences between two groups for numerical variables were assessed with Student's *t*-test or the Mann-Whitney U test. For three or more groups, the ANOVA test (post hoc: Bonferroni test) or Kruskal-Wallis H test (post hoc: Dunn test) was used. Categorical variables are given as numbers and percentages, and inter-group comparisons were conducted with Chi-square and Fisher exact tests. Spearman correlation analyses were applied to evaluate the relationships between numerical variables. Spear-

man correlation coefficients of < 0.10 were evaluated as negligible correlations, 0.10-0.39 as weak correlations, 0.40-0.69 as moderate correlations, 0.70-0.89 as strong correlations, and 0.90-1.00 as almost perfect, very strong correlations⁶. Significance was accepted at $p < 0.05$ (*) for all statistical analyses.

Results

The study population included 91 cancer patients with a median malignancy duration of 9 months and 75 healthcare personnel. The distribution of cancers included predominantly lung (17.6%), breast (17.6%), and colon cancer (16.5%). Other cancer types included stomach cancer in 7 cases; bladder, ovarian, and endometrial cancers in 5 cases each; renal cell carcinomas in 4 cases; lymphoma, prostate, pancreas, and rectal cancers in 3 cases each; melanoma in 2 cases; and adrenal, brain, nasopharynx, and thymus cancers in 1 case each. The distributions of age, sex, and comorbidities were similar across the cancer and control groups. Demographic findings are presented in Table I.

The rate of patients with a history of COVID-19 was lower in the cancer group compared to the control group (33% vs. 56%, $p = 0.004$), while the median time elapsed since the history of COVID-19 was similar (12 vs. 14 months, $p = 0.462$). The rate of heterologous booster vaccination was lower in the cancer group compared to the control group (56.0% vs. 26.4%, $p < 0.001$). In the cancer group, the SARS-CoV-2 IgG antibody levels were found to be lower compared to the control group (4,509 vs. 7,268, $p = 0.004$), while the seroconversion rate was similar between the groups (97.8% vs. 100%, $p = 0.564$) (Table I). The SARS-CoV-2 IgG antibody levels were below the threshold value of 50 AU/mL for two patients with malignant melanoma and colon cancer. One of these patients had received the BNT162b2 vaccine, while the other had received the CoronaVacTM vaccine.

Neither the control group nor the cancer group showed any relationship between SARS-CoV-2 IgG antibody levels and demographic findings (Table II). Among cancer patients, SARS-CoV-2 IgG antibody levels did not vary according to the type of vaccination. The distribution of SARS-CoV-2 IgG antibody levels based on vaccine types in the control and cancer groups is shown in Figure 2.

Table 1. Demographic and clinical characteristics of the study population.

Variables	Control group n = 75	Cancer group n = 91	p
Age, years	57.0 ± 10.2	58.8 ± 11.4	0.290
Sex, n (%)			
Female	42 (56.0)	41 (45.1)	0.160
Male	33 (44.0)	50 (54.9)	
Comorbidities, n (%)	32 (42.7)	48 (52.7)	0.196
Diabetes mellitus	14 (18.7)	25 (27.5)	0.202
Hypertension	17 (22.7)	29 (31.9)	0.187
Coronary artery disease	5 (6.7)	11 (12.1)	0.239
Chronic kidney disease	1 (1.3)	4 (4.4)	0.251
Thyroid disease	5 (6.7)	7 (7.7)	0.800
Type of malignancy, n (%)			
Lung	-	16 (17.6)	-
Colon	-	15 (16.5)	
Breast	-	16 (17.6)	
Other	-	44 (48.4)	
Cancer stage, n (%)			
I	-	2 (2.2)	-
II	-	24 (26.4)	
III	-	20 (22.0)	
IV	-	45 (49.5)	
Duration of malignancy, months	-	9 (5-19)	-
History of COVID-19, n (%)	42 (56.0)	30 (33.0)	0.004*
Duration of COVID-19, months	14 (10-16)	12 (10-14)	0.462
Type of booster vaccine, n (%)			
CoronaVac™	24 (32.0)	31 (34.1)	< 0.001*
BNT162b2	9 (12.0)	36 (39.6)	
Heterologous	42 (56.0)	24 (26.4)	
SARS-CoV-2 IgG antibody, AU/mL	7,268 (3,158-14,310)	4,509 (1,891-9,336)	0.004*
Seroconversion, n (%)	75 (100.0)	89 (97.8)	0.564

Categorical variables are shown as numbers and percentages. Numerical variables are shown as mean ± SD or median (IQR).

*: Values of $p < 0.05$ reflect statistical significance. COVID-19: Coronavirus disease 2019; IgG: immunoglobulin G; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SD: standard deviation; IQR: interquartile range.

Discussion

Cancer patients have an increased risk of COVID-19 infection caused by SARS-CoV-2 compared to healthy populations without cancer⁷. This also leads to an elevated risk of mortality and morbidity. While the 30-day mortality rate associated with COVID-19 is reported^{8,9} to be approximately 20-25% in cancer patients, this rate is reported to be 3-4% in the general population. Therefore, cancer patients have been prioritized in the COVID-19 vaccination schedules of many countries, including Turkey.

Despite the effective vaccination schedules for hematological and oncological patients, many studies^{8,10-12} have reported that the SARS-CoV-2 IgG antibody response, as the humoral immune response indicator, was lower in cancer patients compared to healthy individuals. Similarly, in this study, which included patients with various types of cancer, the SARS-CoV-2 IgG antibody

titers of cancer patients were lower than those of the control group after vaccination. A recent study¹³, which involved cancer patients on active therapy, compared the immunogenicity of the CoronaVac™ vaccine to natural COVID-19 infection. The results demonstrated that natural COVID-19 infection is associated with a higher immunogenic response than vaccination. The response to vaccines in cancer patients can be influenced by various factors, including advanced age, the presence of any comorbidities, disease activity, treatment regimen or response to treatment, and the dose of the vaccination and types of SARS-CoV-2 variants¹⁴.

Cancer has an incidence that increases with advanced age, and advanced age is associated with a weaker immune response^{15,16}. A meta-analysis study¹⁷ conducted on cancer patients showed that advanced age is an independent predictor of weak serological response to the COVID-19 vaccine. On the other hand, comorbid conditions with an

Table II. Relationships between SARS-CoV-2 IgG antibody levels and demographic and clinical findings in control and cancer groups.

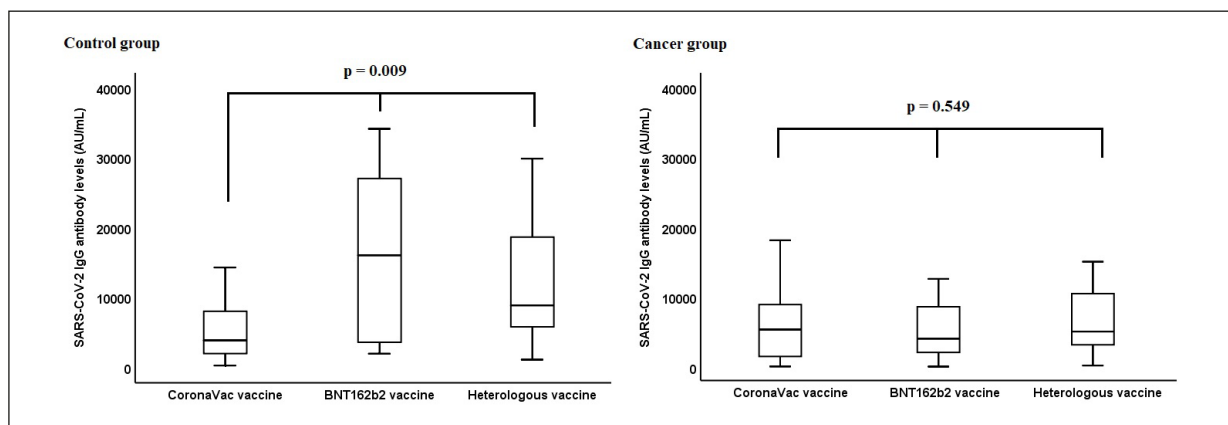
Variables	Control group SARS-CoV-2 IgG antibody titer	<i>p</i>	Cancer group SARS-CoV-2 IgG antibody titer	<i>p</i>
Age	$r = 0.042$	0.719	$r = 0.092$	0.385
Sex				
Female	6,317 (2,493-12,376)	0.212	5,352 (1,624-9,332)	0.323
Male	9,153 (3,523-16,189)		4,495 (2,676-9,337)	
Comorbidities				
No	7,713 (3,158-15,800)	0.563	4,438 (1,801-11,012)	0.805
Yes	6,317 (2,960-13,628)		5,425 (2,588-8,654)	
Type of malignancy				
Lung	-	-	3,298 (2,431-10,063)	0.628
Colon	-		4,082 (8,74-11,012)	
Breast	-		3,677 (1,786-7,176)	
Other	-		5,425 (2,895-9,844)	
Cancer stage				
I-II	-	-	5,897 (2,394-9,586)	0.325
III-IV	-		4,146 (1,880-9,641)	
Duration of malignancy	-		$r = 0.072$	0.500
History of COVID-19				
No	7,713 (2,868-18,669)	0.436	4,408 (1,801-7,544)	0.116
Yes	7,032 (3,422-12,392)		5,747 (2,676-11,403)	
Duration of COVID-19	$r = 0.011$	0.971	$r = -0.122$	0.690
Type of booster vaccine, n (%)				
CoronaVac™	3,866 (1,973-8,025)	0.009*	5,352 (1,437-9,946)	0.549
BNT162b2	16,062 (3,596-27,071) ^a		4,025 (2,056-8,631)	
Heterologous	8,875 (5,797-18,669) ^{a,b}		5,061 (3,147-10,530)	

SARS-CoV-2 IgG antibody levels are shown as median (IQR). *: Values of $p < 0.05$ reflect statistical significance. ^a: vs. CoronaVac™ vaccine; ^b: vs. BNT162b2 vaccine. COVID-19: Coronavirus disease 2019; IgG: immunoglobulin G; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; IQR: interquartile range.

incidence that increases with advanced age might have a negative impact on the serological response to COVID-19 vaccination¹⁸. In the current study, neither advanced age nor the presence of comorbidities was associated with SARS-CoV-2 IgG antibody titers. This finding could be associ-

ated with all patients being fully vaccinated and having received the booster dose.

No relationship was observed between cancer type and SARS-CoV-2 IgG antibody titers. A review¹⁰ encompassing 21 studies conducted on patients with hematological malignancies

**Figure 2.** SARS-CoV-2 IgG antibody levels according to vaccine types in the control and cancer groups.

and solid tumors reported that a single dose of the COVID-19 vaccine resulted in weaker and more heterogeneous serological responses in individuals with both hematological and solid-organ malignancies. However, compared to healthy controls, antibody titers were found to be lower. Additionally, a noteworthy decrease in seroconversion was observed in patients with hematological malignancies compared to those with solid-organ tumors. Similarly, the results of a meta-analysis study⁸ showed that the seroconversion rate was lower among patients with hematological malignancies. In a study¹⁹ involving patients with chronic lymphocytic leukemia (CLL) and non-Hodgkin's lymphoma, after two doses of vaccine targeting both the original SARS-CoV-2 and concerning variants such as B.1.167.2 (Delta) and B.1.1.529 (Omicron), a 67% seroconversion rate was observed. Additionally, that study indicated correlations between antibody responses, age, and specific SARS-CoV-2 variant types.

Approximately 98% of cancer patients exhibited positive seroconversion in the present study. In a study²⁰ on cancer patients infected with SARS-CoV-2, it was reported that the duration of anti-SARS-CoV-2 IgG was an average of 5.8 months in patients receiving chemotherapy and 5.6 months in those receiving radiotherapy. In the same study²⁰, it was observed that among patients receiving chemotherapy, CD8+ T cells, memory B cells, and plasma cells were continuously activated, and it was suggested that chemotherapy and radiotherapy might be beneficial in extending the duration of anti-SARS-CoV-2 IgG. On the other hand, it has been reported²¹ that the administration of chemotherapy within 14 days prior to seropositivity in cancer patients is associated with a persistently weak serological response. In another study¹¹ conducted with patients with CLL, it was reported that the response rate to BNT162b2 vaccination was higher in patients who achieved clinical remission after treatment. This was followed by those who had not previously received treatment, and then by those who were undergoing treatment at the time of vaccination. It was also reported²² that among prostate cancer patients who received two doses of the BNT162b2 vaccine, those concurrently undergoing steroid therapy had lower SARS-CoV-2 IgG antibody titers compared to patients not receiving steroid treatment. However, in cases of heterologous vaccination, higher rates of seropositivity have been reported²³⁻²⁵ after booster doses.

Limitations

To the best of our knowledge, this is the first study from Turkey to explore the relationship between SARS-CoV-2 IgG antibody response and various patient characteristics, in addition to the type of vaccine. However, this study had some significant limitations. First, SARS-CoV-2 IgG antibody titers were not measured at specific intervals after the COVID-19 vaccinations. Second, we could not access the treatment information of the cancer patients. Finally, the numbers of patients with certain types of cancer were quite low. This could limit the relationship between cancer types and SARS-CoV-2 IgG antibody titers.

Conclusions

In cancer patients, seroconversion positivity was found to be about 98%. However, antibody responses were still lower compared to the control group. In addition to demographic data, the type and stage of cancer were not related to antibody levels.

Conflict of Interest

The authors declare that they have no conflict of interests.

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Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author.

Ethics Approval

This study was performed in accordance with the Declaration of Helsinki and approved by the Kırıkkale University Clinical Research Ethics Committee (Approval Date: 3 August 2022, Decision No. 11/01).

Informed Consent

Written informed consent was obtained from all patients.

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Authors' Contributions

All authors read and approved the final manuscript.

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