Efficacy and safety profile of COVID-19 vaccine in cancer patients: a prospective, multicenter cohort study

Ayse Irem Yasin*,1, Sabin Göktaş Aydin2, Bilge Sümbül3, Lokman Koral4, Melih Şimşek5, Çağlayan Geredeli6, Akin Öztürk7, Perihan Perkin8, Derya Demirtaş9, Engin Erdemoglu10, İlahan Hazibe Karoğlu10, Emre Çaks10, Eda Tanrıku11, Ezgi Çoban1, Melike Ozçelik12, Sinemis Çelik13, Fatih Teker14, Asude Aksoy15, Sedat T Frat16, Ömer Tekin17, Ziya Kalkan18, Orhan Türken19, Bala Boven20, Faysal Dane21, Ahmet Bilici2, Abdurrahman Isikogan18, Mesut Seker1, Haci M Türk1 & Mahmut Gümüş9

1Bezmialem Vakif University, Department of Medical Oncology, Istanbul 34093, Turkey
2Medipol University, Department of Medical Oncology, Istanbul 34214, Turkey
3Bezmialem Vakif University, Department of Microbiology, Istanbul 34093, Turkey
4Canakkale 18 March University, Department of Medical Oncology, Canakkale 17020, Turkey
5Okmeydani Training and Research Hospital, Department of Medical Oncology, Istanbul 34384, Turkey
6Sureyyapasa Chest Diseases And Thoracic Surgery Training And Research Hospital, Department of Medical Oncology, Istanbul 34844, Turkey
7Yıldırım Beyazıt University Yenimahalle Training and Research Hospital, Department of Medical Oncology, Ankara 06330, Turkey
8Ankara City Hospital, Department of Medical Oncology, Ankara 06800, Turkey
9Göztepe Medeniyet University, Department of Medical Oncology, Istanbul 34000, Turkey
10Sakarya University Medicine Faculty, Department of Medical Oncology, Sakarya 54050, Turkey
11Haydarpaşa Training and Research Hospital, University of Health Sciences, Istanbul 34668, Turkey
12Marmara University School of Medicine, Department of Medical Oncology, Istanbul 34722, Turkey
13Istanbul Oncology Hospital, Department of Medical Oncology, Istanbul 34846, Turkey
14Gaziantep University, Department of Medical Oncology, Gaziantep 27470, Turkey
15İzmir University Faculty of Medicine, Department of Medical Oncology, Elazığ 23119, Turkey
16İzmir University of Economics, Department of Medical Oncology, Kaseyir 38039, Turkey
17İnönü University, Department of Medical Oncology, Malatya 44280, Turkey
18Dicle University, Department of Medical Oncology, Diyarbakır 21200, Turkey
19Maltepe University, Department of Medical Oncology, Istanbul 34844, Turkey
20Bahcesehir University School of Medicine, Department of Medical Oncology, Istanbul 34349, Turkey
21Acıbadem University, Department of Medical Oncology, Istanbul 34758, Turkey

*Author for correspondence: Tel.: +90 212 453 1700; ayseiremyasin@gmail.com

Aim: To compare the seropositivity rate of cancer patients with non-cancer controls after inactive SARS-CoV-2 vaccination (CoronaVac) and evaluate the factors affecting seropositivity. Method: Spike IgG antibodies against SARS-CoV-2 were measured in blood samples of 776 cancer patients and 715 non-cancer volunteers. An IgG level $\geq 50$ AU/ml is accepted as seropositive. Results: The seropositivity rate was 85.2% in the patient group and 97.5% in the control group. The seropositivity rate and antibody levels were significantly lower in the patient group ($p < 0.001$). Age and chemotherapy were associated with lower seropositivity in cancer patients ($p < 0.001$). Conclusion: This study highlighted the efficacy and safety of the inactivated vaccine in cancer patients.

Clinical Trials Registration: NCT04771559 (ClinicalTrials.gov)

Plain language summary: Cancer patients are at high risk for infection with SARS-CoV-2 and of developing the associated disease, COVID-19, which therefore puts them in the priority group for vaccination. This study evaluated the efficacy and safety of CoronaVac, an inactivated virus vaccine, in cancer patients. The immune response rate, defined as seropositivity, was 85.2% in the cancer patient group and 97.5% in the control group. The levels of antibodies, which are blood markers of immune response to the vaccine, were also significantly lower in the patient group, especially in those older than 60 years and receiving chemotherapy. These results highlight the importance of determining the effective vaccine type and dose in cancer patients to protect them from COVID-19 without disrupting their cancer treatment.
COVID-19, which emerged in China in 2019 and spread all over the world in a short time, caused many deaths around the world [1]. In many countries, including Turkey, measures are continuing to prevent the spread of the virus, which has many negative effects on social and economic life. Since the beginning of the pandemic, many countries have carried out studies to develop a vaccine against COVID-19. Today there are more than ten different vaccines currently in use worldwide [2]. Turkey’s national immunization program continues by prioritizing high-risk groups such as elderly adults and cancer patients. Approximately 70% of the population has been vaccinated with at least two doses [3].

Studies have shown that the morbidity and mortality of COVID-19 in cancer patients are higher than in non-cancer individuals [4–6]. COVID-19 progresses more severely in cancer patients due to the natural course of the cancer and the oncological treatments [7,8].

Cancer patients were also negatively affected by disruptions in cancer diagnosis and treatment during the pandemic. A European survey showed an average reduction of 29.3% in all types of oncological surgeries [9]. Riera et al. reviewed delays and disruptions in cancer management due to the pandemic; they reported up to 77.5% interruption in any stage of cancer treatment [10]. As a result of interruptions in oncological diagnosis and treatment processes, the increase in cancer-related deaths in England over the past year was estimated to be 20% [11].

The COVID-19 seroprevalence in cancer patients was evaluated in recent studies. Fillmore et al. screened the results of 22,914 cancer patients tested for COVID-19 and reported 7.8% positivity [12]. In another study, 928 cancer patients with a COVID-19 diagnosis were evaluated, and 4% were reported as asymptomatic [13].

The leading oncological societies, such as the American Society of Clinical Oncology, European Society of Medical Oncology and National Comprehensive Cancer Network (NCCN), have developed guidelines to minimize the negative effects of the COVID-19 pandemic on cancer patients. However, there is no consensus for SARS-CoV-2 testing of asymptomatic patients before initiation of immunosuppressive therapies [14]. An individual risk–benefit assessment for each patient appears to be the most reliable method yet [14].

Because there is no standard treatment for COVID-19, vaccination is considered to be the cornerstone for mitigation of the pandemic. The severe course of COVID-19 in cancer patients puts them among the priority groups for vaccination. The NCCN recommends that people with active cancer undergoing treatment, those about to be treated for cancer and those who have been treated for cancer in the past 6 months should be prioritized to receive vaccinations as soon as possible [15].

Different types of COVID-19 vaccines are currently available around the world. CoronaVac, an inactivated vaccine, is one of the most applied vaccines. Solodky et al. reported that the antibody level in cancer patients after COVID-19 was lower than that in healthy individuals [16]. A similar situation is expected to be seen in the post-vaccine antibody response. Although the seroconversion rate in healthy adults after two doses of inactivated vaccine was reported as 100% in the CoronaVac study, seroconversion in cancer patients was not assessed [17]. In another study evaluating the efficacy of CoronaVac, the seropositivity rate was 89.7% [18]. Furthermore, the seroconversion rate of the BNT162b2 mRNA vaccine was found to be 95% in healthy adults [19]. Currently, limited data are available showing the efficacy and safety of COVID-19 vaccines in cancer patients. Ariamanesh et al. recently demonstrated 86.9% seropositivity after administration of inactivated vaccine in patients with malignancy [20]. Massarweh et al. reported 90% seropositivity in 102 cancer patients vaccinated with the BNT162b2 mRNA vaccine [21]. However, the role of COVID-19 vaccination remains a challenging issue in cancer patients.

In this study we aimed to compare cancer patients with non-cancer controls in terms of the efficacy and safety of inactive SARS-CoV-2 (CoronaVac) vaccination. In addition, factors affecting seropositivity in cancer patients were evaluated.

This trial is registered with ClinicalTrials.gov (NCT047771559) and is closed to accrual.

**Patients & methods**

**Study design**

This study is a prospective, multicenter cohort study evaluating the efficacy and safety of the CoronaVac in cancer patients. Initially, 2154 adult patients with histologically diagnosed solid tumors who were admitted to medical
Efficacy & safety profile of COVID-19 vaccine in cancer patients

Research Article

Oncology clinics between 1 March and 1 July 2021 were informed about the study; the control group consisted of healthcare workers and volunteers accompanying the patients. From this initial group, 776 cancer patients and 715 non-cancer volunteers who received a second dose of inactivated vaccine in 4–6 weeks were included in the study. Vaccination information and the COVID-19 history of the participants were checked from the national health record database. Patients and controls who had a documented COVID-19 infection (positive PCR test result) at any time before enrollment and patients who received an mRNA vaccine were excluded. In addition, controls who were pregnant or had an immunosuppressive disease or were receiving immunosuppressive therapy for any reason were excluded from the study. The study was carried out with permission of the Turkish Ministry of Health and approved by the local ethics committee (02/28). All participants signed a written informed consent form.

Assessments

Blood samples were taken from the patients and centrifuged at 2500 rpm for 10 min. The separated serum samples were backed up in two Eppendorf tubes and stored at -80 or -20°C. All serum samples were delivered by cold chain and collected in a single center. A US FDA-approved chemiluminescent microparticle immunoassay, the Abbott Architect i1000sr SARS-CoV-2 IgG II Quant assay (Abbott Laboratories, IL, USA), was used to quantify IgG antibodies against the SARS-CoV-2 spike receptor-binding domain following the manufacturer’s instructions [22]. This assay has 98.1% sensitivity and 99.6% specificity at least 15 days after first symptom onset or documented COVID-19 infection [23]. An IgG level ≥50 AU/ml is accepted as seropositive.

Patient characteristics were collected and included age, sex, BMI, smoking status, comorbidities and receipt of any other vaccination (influenza or pneumococci) within 2 years. All participants were asked about local and systemic side effects of vaccination. Additionally, all clinical information about the cancer diagnosis (tumor type, disease stage and treatment status) were recorded. Treatment groups were: chemotherapy group (including taxane, platin, fluorouracil, gemcitabine, anthracycline, cyclophosphamide, pemetrexed); immunotherapy group (including nivolumab, pembrolizumab and atezolizumab); targeted therapies group (tyrosine kinase inhibitors, anti-VEGF agents, trastuzumab, pertuzumab, CDK4/6 inhibitors); and hormonal therapies group (tamoxifen, aromatase inhibitors, LHRH analogs). We evaluated each treatment group for seropositivity. Additionally, we created another group for those receiving active targeted or immunotherapies and compared the seropositivity rates of this group with those of the active chemotherapy group.

Statistical analysis

Descriptive statistics are shown as mean ± standard deviation for variables with normal distribution, median (minimum to maximum) for non-normal distributions, and the number of cases and percentage (%) for nominal variables. The Mann–Whitney U-test was used for comparison of the groups. Pearson’s χ²-square or Fisher’s exact tests were performed for nominal variables. Multivariate analysis was applied with a logistic regression test. A p-value < 0.05 was considered to be statistically significant. SPSS for Windows (v. 22; IBM Corp., NY, USA) was used to analyze the data.

Results

Our study group consisted of 776 cancer patients and 715 non-cancer controls. The median age in the patient group was 64 years (range: 20–88), and the median age in the control group was 50 years (range: 21–94). The characteristics of the study participants are shown in Table 1.

The seropositivity rate was 85.2% and the median antibody titer was 363.9 AU/ml in the patient group. The seropositivity rate was 97.5% and the median antibody titer was 656.5 AU/ml in the control group. When the two groups were compared, the seropositivity rate and antibody levels were significantly lower in the patient group than in the non-cancer controls (p < 0.001). Additionally, administration of influenza and pneumococcal vaccine prevalence was higher in the patient group (p < 0.001). Vaccine features and antibody levels are shown in Table 2.

While the incidence of side effects after the first dose of vaccine was 15.9% in the patient group, this rate was 22.5% in the control group. The rate of side effects reported after the first dose was significantly higher in the controls than the patients (p = 0.001). While the most common side effect in the control group was local pain (9.7%), the most common side effect in the patient group was fatigue (6.4%). When the prevalence of side effects after the second dose was compared, there was no significant difference between the two groups (Table 3).

The most common tumor types were breast cancer (32.3%), lung cancer (23.6%), gastrointestinal cancer (22.4%) and genitourinary cancer (13.8%). Of the patients, 51.3% (n = 398) had metastatic disease; 39.8% (n = 309) were...
Table 1. Characteristics of study participants.

| Characteristic                  | Patient group (n = 776) | Control group (n = 715) | p-value |
|---------------------------------|-------------------------|-------------------------|---------|
| Age, median (range)             | 64 (20–88)              | 50 (21–94)              | <0.001† |
| Age (years)                     |                         |                         |         |
| <60                             | 291 (37.5)              | 614 (85.9)              |         |
| ≥60                             | 485 (62.5)              | 101 (14.1)              |         |
| Sex                             |                         |                         | 0.958   |
| Female                          | 433 (55.8)              | 398 (55.7)              |         |
| Male                            | 343 (44.2)              | 317 (44.3)              |         |
| BMI, median (range)             | 27.1 (16–48)            | 26.1 (18–40)            | 0.943   |
| Smoking                         |                         |                         | <0.001† |
| No                              | 436 (59.3)              | 422 (69.3)              |         |
| Ex-smoker                       | 165 (22.4)              | 16 (2.7)                |         |
| Yes                             | 135 (18.3)              | 149 (25.1)              |         |
| Diabetes mellitus               |                         |                         | <0.001† |
| No                              | 635 (81.8)              | 666 (93.1)              |         |
| Yes                             | 141 (18.2)              | 49 (6.9)                |         |
| Hypertension                    |                         |                         | <0.001† |
| No                              | 513 (66.1)              | 616 (86.2)              |         |
| Yes                             | 263 (33.9)              | 99 (13.8)               |         |
| Coronary disease                |                         |                         | <0.001† |
| No                              | 710 (91.5)              | 698 (97.6)              |         |
| Yes                             | 66 (8.5)                | 17 (2.4)                |         |
| Chronic renal failure           |                         |                         | <0.001† |
| No                              | 759 (97.8)              | 714 (99.9)              |         |
| Yes                             | 17 (2.2)                | 1 (0.1)                 |         |
| Chronic liver disease           |                         |                         | 0.081   |
| No                              | 761 (98.1)              | 709 (99.2)              |         |
| Yes                             | 15 (1.9)                | 6 (0.8)                 |         |
| Rheumatological disease         |                         |                         | 0.816   |
| No                              | 766 (98.7)              | 707 (98.9)              |         |
| Yes                             | 10 (1.3)                | 8 (1.1)                 |         |
| Psychiatric disease             |                         |                         | 0.004†  |
| No                              | 762 (98.2)              | 713 (99.7)              |         |
| Yes                             | 14 (1.8)                | 2 (0.3)                 |         |
| Respiratory disease             |                         |                         | 0.002†  |
| No                              | 741 (95.5)              | 703 (98.3)              |         |
| Yes                             | 35 (4.5)                | 12 (1.7)                |         |
| Other                           |                         |                         | 0.152   |
| No                              | 731 (94.2)              | 686 (95.9)              |         |
| Yes                             | 45 (5.8)                | 29 (4.1)                |         |

† Statistically significant results.

Table 2. Vaccine features and antibody levels of the study population.

| Characteristic                  | Patient group (n = 776) | Control group (n = 715) | p-value |
|---------------------------------|-------------------------|-------------------------|---------|
| Antibody level, median (range)  | 363.9 AU/ml (0–40,000)  | 656.5 AU/ml (0.2–10,615.3) | <0.001† |
| Seropositivity                  |                         |                         |         |
| Positive (≥50)                  | 661 (85.2)              | 697 (97.5)              |         |
| Negative (<50)                  | 115 (14.8)              | 18 (2.5)                |         |
| Other vaccines                  |                         |                         | <0.001† |
| Yes                             | 217 (28.0)              | 117 (16.4)              |         |
| No                              | 559 (72.0)              | 598 (83.6)              |         |
| Type of vaccine                 |                         |                         | 0.236   |
| Influenza                       | 71 (32.7)               | 48 (41.0)               |         |
| Pneumococcal                    | 59 (27.2)               | 24 (20.5)               |         |
| Influenza + pneumococcal        | 87 (40.1)               | 45 (38.5)               |         |

† Statistically significant results.
Table 3. Side effects after the first and the second doses of the vaccine.

| Characteristics | Patient group (n = 776) | Control group (n = 715) | p-value |
|-----------------|-------------------------|-------------------------|---------|
|                 | Total (%) | Gr 1 (%) | Gr 2 (%) | Gr 3–4 (%) | Total (%) | Gr 1 (%) | Gr 2 (%) | Gr 3–4 (%) |
| First dose      | 15.9       | 22.5      |          |           | .001†      |          |           |           |
| Local pain      | 5.7        | 5.3       | 0.4      | –         | 9.7        | 8.3       | 1.1       | 0.3       | .005†      |
| Erythema        | 0.5        | 0.4       | 0.1      | –         | 2.1        | 1.8       | 0.3       | –         | .009†      |
| Fever           | 2.1        | 1.2       | 0.8      | 0.1       | 1.8        | 1.7       | –         | 0.1       | .852       |          |
| Fatigue         | 6.4        | 5.0       | 1.3      | 0.1       | 8.4        | 6.7       | 1.4       | 0.3       | .165       |          |
| Headache        | 4.6        | 3.6       | 0.9      | 0.1       | 7.8        | 6.2       | 1.1       | 0.6       | .013†      |          |
| Myalgia         | 4.5        | 3.2       | 0.9      | 0.4       | 6.7        | 4.4       | 2.2       | 0.1       | .071       |          |
| Nausea          | 1.8        | 1.7       | –        | 0.1       | 1.4        | 1.4       | –         | –         | .681       |          |
| Diarrhea        | 0.8        | 0.4       | 0.4      | –         | 1.0        | 0.8       | 0.2       | –         | .783       |          |
| Other           | 0.9        | 0.9       | –        | –         | 2.6        | 2.6       | –         | –         | .269       |          |
| Second dose     | 15.2       |          |          |           | 16.8       |          |          |           | .436       |          |
| Local pain      | 5.0        | 4.6       | 0.4      | –         | 7.7        | 6.2       | 1.3       | 0.3       | .042†      |          |
| Fever           | 1.3        | 1.0       | 0.3      | –         | 2.1        | 2.0       | 0.1       | –         | .234       |          |
| Fatigue         | 6.7        | 4.9       | 1.5      | 0.3       | 6.4        | 5.1       | 1.0       | 0.3       | .917       |          |
| Headache        | 4.5        | 3.7       | 0.8      | –         | 4.8        | 3.5       | 0.7       | 0.6       | .902       |          |
| Myalgia         | 4.9        | 3.4       | 1.0      | 0.5       | 5.9        | 4.3       | 1.0       | 0.6       | .422       |          |
| Nausea          | 1.2        | 0.8       | 0.4      | –         | 0.7        | 0.7       | –         | –         | .427       |          |
| Diarrhea        | 0.9        | 0.7       | 0.1      | 0.1       | 0.3        | 0.3       | –         | –         | .182       |          |
| Other           | 1.1        | 1.1       | –        | –         | 1.3        | 1.3       | –         | –         | .647       |          |

†Statistically significant results.
Gr: Grade.

Figure 1. Seropositivity rates of cancer patients after SARS-CoV-2 vaccination according to the treatment status and stage of the disease.

on active chemotherapy; 15.1% (n = 117) were on immunotherapy or targeted therapies; and 45.1% (n = 350) had not received any of these treatment modalities within the previous 3 months. The seropositivity rates were 78.6% in the active chemotherapy group, 85.7% in the immunotherapy group, 86.0% in the targeted therapies group and 87.1% in the hormone therapy group. For the patients not receiving any active treatment including chemotherapy, immunotherapy or targeted therapies, the seropositivity rate was 91.1% (Table 4). Additionally, 90.7% of the nonmetastatic patients and 79.9% of the metastatic patients were seropositive (Figure 1).

In univariate analysis of the patient group, chemotherapy, metastatic disease, age and male gender were negatively correlated with seropositivity (p < 0.001). The seropositivity rate in the active chemotherapy group was significantly lower than in the group of patients not receiving active chemotherapy (p < 0.001). Tumor type, BMI, smoking and comorbidities were not associated with seropositivity (Table 4). In univariate analysis of the control group, age was found to be the only factor negatively correlated with seropositivity (p < 0.001; Table 4). When the multivariate analysis was performed, age and chemotherapy were defined as the factors significantly associated with lower seropositivity in cancer patients (p < 0.001 and p = 0.038, respectively; Tables 5 & 6).
Table 4. The factors affecting seropositivity in the study population.

| Factors affecting seropositivity in the patient group (univariate analysis) | Characteristics | n (%) | Seropositivity (%) | p-value |
|---|---|---|---|---|
| **Age (years)** | <60 | 291 (37.5) | 93.5 | <0.001† |
| | ≥60 | 485 (62.5) | 80.2 | 0.015† |
| **Gender** | Female | 433 (55.8) | 88.0 | 0.435 |
| | Male | 343 (44.2) | 81.6 | 0.577 |
| **BMI** | <25 kg/m² | 187 (30.7) | 88.8 | 0.335 |
| | ≥25 kg/m² | 422 (69.3) | 86.3 | 0.920 |
| **Smoking** | No | 436 (59.2) | 85.3 | 0.811 |
| | Ex-smoker | 165 (22.4) | 87.3 | 0.426 |
| | Yes | 112 (17.8) | 83.0 | |
| **Tumor type** | Breast | 251 (32.3) | 88.0 | 0.225 |
| | Gastrointestinal | 174 (22.4) | 86.2 | |
| | Genitourinary | 107 (13.8) | 84.1 | |
| | Lung | 183 (23.6) | 80.9 | |
| | Other | 61 (7.9) | 85.2 | |
| **Treatment type (active)** | No treatment | 350 (45.1) | 91.1 | <0.001† |
| | Chemotherapy | 309 (39.8) | 78.6 | |
| | Targeted or IO | 117 (15.1) | 84.6 | |
| **Chemotherapy** | Never | 152 (19.6) | 87.5 | <0.001† |
| | Not in the last 3 months | 315 (40.6) | 90.5 | |
| | Active | 309 (39.8) | 78.6 | |
| **Immunotherapy (IO)** | Yes | 42 (5.4) | 85.7 | 0.920 |
| | No | 734 (94.6) | 85.1 | |
| **Targeted therapies** | Yes | 178 (22.9) | 86.0 | 0.711 |
| | No | 598 (77.1) | 84.9 | |
| **Hormone therapy** | Yes | 209 (26.9) | 87.1 | 0.426 |
| | No | 567 (73.1) | 84.5 | |
| **Comorbidities** | No | 373 (48.1) | 86.9 | |
| | Yes | 403 (51.9) | 83.6 | |
| **Stage** | Nonmetastatic | 378 (48.7) | 90.7 | <0.001† |
| | Metastatic | 398 (51.3) | 79.9 | |

| Factors affecting seropositivity in the control group (univariate analysis) | Characteristics | n (%) | Seropositivity (%) | p-value |
|---|---|---|---|---|
| **Age (years)** | <60 | 614 (85.9) | 98.4 | <0.001† |
| | ≥60 | 101 (14.1) | 92.1 | 0.347 |
| **Gender** | Female | 398 (55.7) | 98.0 | |
| | Male | 317 (44.3) | 96.8 | 0.435 |
| **BMI** | <25 kg/m² | 118 (30.5) | 97.5 | 0.711 |
| | ≥25 kg/m² | 269 (69.5) | 97.0 | |
| **Smoking** | No | 428 (72.2) | 97.2 | |
| | Ex-smoker | 16 (2.7) | 93.8 | 0.399 |
| | Yes | 149 (25.1) | 97.3 | |
| **Comorbidities** | No | 544 (76.1) | 97.8 | |
| | Yes | 171 (23.9) | 96.5 | |

†Statistically significant results.
IO: Immunotherapy.
Table 5. The factors affecting seropositivity in the study population (multivariate analysis).

| Characteristics       | SE   | RR   | 95% CI       | p-value |
|-----------------------|------|------|--------------|---------|
| Noncancer vs cancer   | 0.286| 3.519| 2.009–6.162  | <0.001† |
| Age (<60 vs ≥60)      | 0.246| 3.545| 2.190–5.737  | <0.001† |
| Gender (female vs male)| 0.194| 1.271| 0.868–1.859  | 0.218   |
| Comorbidities (yes vs no) | 0.195| 1.129| 0.771–1.655  | 0.533   |

†Statistically significant results.
RR: Relative risk; SE: Standard error.

Table 6. The factors affecting seropositivity in the patient group (multivariate analysis).

| Characteristics       | SE   | RR   | 95% CI       | p-value |
|-----------------------|------|------|--------------|---------|
| Age (<60 vs ≥60)      | 0.276| 3.016| 1.758–5.176  | <0.001† |
| Gender (female vs male)| 0.221| 1.154| 0.701–1.667  | 0.724   |
| Chemotherapy (yes vs no) | 0.358| 1.396| 0.692–2.818  | 0.038†  |
| Targeted therapy or IO (yes vs no) | 0.300| 0.709| 0.393–1.277  | 0.351   |
| Comorbidities (yes vs no) | 0.213| 1.116| 0.736–1.692  | 0.606   |
| Stage (metastatic vs nonmetastatic) | 0.304| 1.458| 0.804–2.645  | 0.214   |

†Statistically significant results.
IO: Immunotherapy; RR: Relative risk; SE: Standard error.

Discussion

This study showed 85.2% seropositivity in cancer patients, whereas this rate was 97.5% in non-cancer controls. Additionally, IgG antibody titers in cancer patients were significantly lower than in the controls. The factors significantly associated with low seropositivity rates in the patient group were age and active chemotherapy. When the side effects in both groups were compared, the control group reported significantly more side effects after the first dose. Nevertheless, there was no significant difference between the groups in side effects after the second dose. Our findings confirmed the efficacy and safety of CoronaVac in cancer patients.

The COVID-19 pandemic negatively affected cancer patients. In addition to the severe course of COVID-19 in cancer patients, covidophobia, delays in cancer diagnosis and disruptions to oncological treatments increased the mortality of cancer patients during the pandemic [4–11]. NCCN and other oncological societies recommended that all cancer patients, especially those receiving active treatment, should be vaccinated as a priority [15]. The high seropositivity rate of cancer patients in our study also supports these recommendations, even though the seropositivity rate was relatively lower than in non-cancer adults.

The low seropositivity rate in cancer patients compared with the non-cancer controls found in this study was expected, as immunosuppression negatively affects the immune response. Similar to our results, Ariamanesh et al. found that older age, chemotherapy and hematological malignancies were related to lower seropositivity rates after administration of inactivated vaccine [20]. Massarweh et al. reported that chemotherapy plus immunotherapy treatment was associated with lower IgG titers in cancer patients vaccinated with the BNT162b2 mRNA vaccine [21]. Furthermore, studies evaluating the response to pneumococcal and influenza vaccines in patients with malignancy showed a decreased response in patients with hematological malignancies [24]. In another study, influenza vaccine response was low in breast cancer patients receiving active chemotherapy [25]. Our findings also highlight the negative effect of active treatment on immune response.

Although a clear relationship has not yet been established between antibody levels and prevention of the disease, the main target of the vaccines is to trigger the formation of neutralizing antibodies against the SARS-CoV-2 spike protein [26]. Harvey et al. reported an approximately tenfold increase in positive nucleic acid amplification test results among patients with positive antibody tests compared with those who had negative antibody tests, suggesting a protective effect of antibodies [27]. Another study demonstrated that the antibody titers were correlated with protection against COVID-19 [28]. Considering that the cellular immune response is suppressed in cancer patients, even adequate antibody levels may not effectively protect from the infection. Based on this, the application of additional doses, especially in cancer patients, may come to the fore in light of future studies. Patients receiving active chemotherapy and those in older age groups might be among the priority groups.
Another finding of our study was that the control group reported side effects more frequently, especially after the first dose. The reason might be that cancer patients experience such side effects due to the disease itself and their treatment processes, even before vaccination. The frequency of side effects reported after the second dose was found to be similar in both groups; this can be explained by the decrease in the perception of the side effects following the second dose.

Finally, when we created two groups by matching the patient and control groups by age and gender, the significant difference in seropositivity rates between the groups persisted.

This study had some limitations. First, we measured only spike IgG antibody levels of the participants but did not assess neutralizing antibody levels. However, studies have shown that neutralizing antibody levels are correlated with spike IgG antibody levels [29]. Second, we did not evaluate the pre-vaccination antibody levels of the participants. Nevertheless, we excluded patients who had a documented COVID-19 infection at any time before enrollment.

The median follow-up period after vaccination was 3 months, and eight patients were infected with COVID-19 during this period. The patient group will be followed up for long-term results to evaluate the effect of vaccination and antibody levels on disease prevention.

**Conclusion**

This study highlighted the efficacy and safety of CoronaVac in cancer patients. The seropositivity rate was lower in cancer patients than in non-cancer controls, especially in patients aged over 60 years and those receiving active chemotherapy. Further studies with larger sample sizes are needed to determine the effective vaccine type and vaccine dose for cancer patients so that cancer patients might be protected from COVID-19-related morbidity and mortality without disrupting their oncological treatments.

### Summary points

- COVID-19 is associated with high morbidity and mortality in cancer patients, but there are limited data on the efficacy and safety of currently used COVID-19 vaccines in cancer patients.
- We compared the seropositivity rate of cancer patients with non-cancer controls after CoronaVac administration and evaluated the factors affecting seropositivity in cancer patients.
- 776 cancer patients and 715 non-cancer volunteers who received a second dose of inactivated vaccine in 4–6 weeks were included in the study.
- The seropositivity rate and antibody levels were significantly lower in the patient group than in the non-cancer controls (p < 0.001). Age and chemotherapy were associated with lower seropositivity in cancer patients (p < 0.001).
- Side effects reported after the first dose were significantly higher in the control group (p < 0.001). There was no significant difference between the two groups after the second dose.
- The high seropositivity rate of cancer patients indicates that these patients benefit from the vaccine as protection from COVID-19 infection.
- It should be kept in mind that patients over the age of 60 and receiving chemotherapy have lower seropositivity rates and are in a higher risk group for COVID-19.

### Financial & competing interests disclosure

This study was funded by the Oncological Clinical Research Association (ONKAD). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

### Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval (02/28) and have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

### References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

1. Zhu N, Zhang D, Wang W et al. A novel coronavirus from patients with pneumonia in China, 2019. *N. Engl. J. Med.* 382(8), 727–733 (2020).
2. Sun L, Warner JL, Purikh RB. Immune responses to SARS-CoV-2 among patients with cancer: what can seropositivity tell us? JAMA Oncol. 7(8), 1123–1125 (2021).

• Comment about seropositivity in cancer patients.

3. WHO. WHO coronavirus (COVID-19) dashboard. https://covid19.who.int/region/euro/country/tr

4. Liang W, Guan W, Chen R et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 21(3), 335–337 (2020).

5. Robilotti EV, Bahady NE, Mead PA et al. Determinants of COVID-19 disease severity in patients with cancer. Nat. Med. 26(8), 1218–1223 (2020).

6. Rugge M, Zorzi M, Guzzinati S. SARS-CoV-2 infection in the Italian Veneto region: adverse outcomes in patients with cancer. Nature Cancer 1(8), 784–788 (2020).

7. Saini KS, Tagliamento M, Lamberti M et al. Mortality in patients with cancer and coronavirus disease 2019: a systematic review and pooled analysis of 52 studies. Eur. J. Cancer 139, 43–50 (2020).

8. Bakouny Z, Hawley JE, Choueiri TK et al. COVID-19 and cancer: current challenges and perspectives. Cancer Cell 38(5), 629–646 (2020).

9. Steiss C, Steffani M, Pergolini I et al. Impact of the COVID-19 pandemic on surgical oncology in Europe: results of a European survey. Dig. Surg. 38(4), 259–265 (2021).

10. Riera R, Bagattini AM, Pacheco RL, Pachito DV, Roitberg F, Ilbawi A. Delays and disruptions in cancer health care due to COVID-19 pandemic: a systematic review. JCO Glob. Oncol. 7, 311–323 (2021).

11. Lai AG, Pasea L, Banerjee A et al. Estimated impact of the COVID-19 pandemic on cancer services and excess 1-year mortality in people with cancer and multimorbidity: a near real-time data on cancer care, cancer deaths and a population-based cohort study. BMJ Open 10(11), e043828 (2020).

12. Fillmore NR, La J, Szalat RE et al. Prevalence and outcome of COVID-19 infection in cancer patients: a National Veterans Affairs study. J. Natl Cancer Inst. 113(6), 691–698 (2021).

13. Kuderer NM, Choueiri TK, Shah DP et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. Lancet 395(10241), 1907–1918 (2020).

14. Haradaa G, Antonacio FF, Gongora AB et al. SARS-CoV-2 testing for asymptomatic adult cancer patients before initiating systemic treatments: a systematic review. Eancermedicalsience 14, 1100 (2020).

15. National Comprehensive Cancer Network. Recommendations of the NCCN COVID-19 vaccination advisory committee. www.nccn.org/docs/default-source/covid-19/2021_covid-19_vaccination_guidance_v3-0.pdf?sfvrsn=b483da2b

16. Solodky ML, Galvez C, Rusiñas B et al. Lower detection rates of SARS-COV2 antibodies in cancer patients versus health care workers after symptomatic COVID-19. Ann. Oncol. 31(8), 1087–1088 (2020).

• Study which evaluated antibody development in cancer patients after COVID-19 infection.

17. Xia S, Zhang Y, Wang Y et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomized, double-blind, placebo-controlled, Phase 1/2 trial. Lancet Infect. Dis. 21(1), 39–51 (2021).

18. Tanriover MD, Doğanay HL, Akova M et al. Efficacy and safety of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac): interim results of a double-blind, randomized, placebo-controlled, Phase 3 trial in Turkey. Lancet 398(10296), 213–222 (2021).

• Study which evaluated the efficacy and safety profile of CoronaVac.

19. Polack FP, Thomas SJ, Kitchin N et al. Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N. Engl. J. Med. 383(27), 2603–2615 (2020).

20. Ariamanesh M, Porouhan P, Peyroshabany B et al. Immunogenicity and safety of the inactivated SARS-CoV-2 vaccine (BBIBP-CorV) in patients with malignancy. Cancer Invest. doi:10.1080/07357907.2021.1992420 1–9 (2021) (Epub ahead of print).

• Study which evaluated the efficacy and safety profile of CoronaVac in cancer patients.

21. Massarweh A, Eliakim-Raz N, Stemmer A et al. Evaluation of seropositivity following BNT162b2 messenger RNA vaccination for SARS-CoV-2 in patients undergoing treatment for cancer. JAMA Oncol. 7(8), 1133–1140 (2021).

• Study which evaluated the mRNA vaccine BNT162b2 in cancer patients.

22. Abbott. SARS-CoV-2 Immunoassays. www.corelaboratory.abbott/int/en/offerings/segments/infectious-disease/sars-cov-2-

23. Abbott Laboratories. AdviseDx SARS-CoV-2 IgG II package insert (2021). www.fda.gov/media/146371/download

24. Siber GR, Weintraub SA, Aisenberg AC, Weinstein HJ, Schiffman G. Impaired antibody response to pneumococcal vaccine after treatment for Hodgkin’s disease. N. Engl. J. Med. 299(9), 442–448 (1978).

25. Vilar-Compte D, Cornejo P, Valle-Salinas A et al. Influenza vaccination in patients with breast cancer: a case–series analysis. Med. Sci. Monit. 12(8), CR332–CR336 (2006).

26. Krammer F. SARS-CoV-2 vaccines in development. Nature 586(7830), 516–527 (2020).
27. Harvey RA, Rassen JA, Kabelac CA et al. Association of SARS-CoV-2 seropositive antibody test with risk of future infection. *JAMA Intern. Med.* 181(5), 672–679 (2021).

28. Jin P, Li J, Pan H, Wu Y, Zhu F. Immunological surrogate endpoints of COVID-2019 vaccines: the evidence we have versus the evidence we need. *Signal Transduct. Target. Ther.* 6(1), 48 (2021).

29. Sahin U, Muik A, Derhovanessian E et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. *Nature* 586(7830), 594–599 (2020).