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Original Article

Immune response against the SARS-CoV-2 spike protein in cancer patients after COVID-19 vaccination during the Omicron wave: a prospective study

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ABSTRACT

Background: Cancer patients often have weakened immune systems, resulting in a lower response to vaccines, especially those receiving immunosuppressive oncological treatment (OT). We aimed to assess the impact of OT on the humoral and T-cell response to the B.1 lineage and Omicron variant following COVID-19 vaccination in patients with solid and hematological neoplasms.

Methods: We conducted a prospective study on cancer patients, stratified into OT and non-OT groups, who received a two-dose series of the COVID-19 mRNA vaccine and a booster six months later. The outcomes measured were the humoral (anti-SARS-CoV-2 S IgG titers and ACE2-S interaction inhibition capacity) and cellular (SARS-CoV-2 S-specific T-cell spots per million PBMCs) responses against the B.1 lineage and Omicron variant. These responses were evaluated four weeks after the second dose (n = 98) and eight weeks after the booster dose (n = 71).

Results: The humoral response after the second vaccine dose against the B.1 lineage and Omicron variant was significantly weaker in the OT group compared to the non-OT group (q-value < 0.05). A booster dose of the mRNA-1273 vaccine significantly improved the humoral response in the OT group, making it comparable to the non-OT group. The mRNA-1273 vaccine, designed for the original Wuhan strain, elicited a weaker humoral response against the Omicron variant compared to the B.1 lineage, regardless of oncological treatment or vaccine dose. In contrast, T-cell responses against SARS-CoV-2, including the Omicron variant, were already present after the second vaccine dose and were not significantly affected by oncological treatments.

Conclusions: Cancer patients, particularly those receiving immunosuppressive oncological treatments, should require booster doses and adapted COVID-19 vaccines for new SARS-CoV-2 variants like Omicron.

Abbreviations: COVID-19, Coronavirus Disease 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; S, Spike glycoprotein; HUIL, Hospital Universitario Infanta Leonor; PBMC, Peripheral blood mononuclear cell; ELISA, Enzyme-linked immunosorbent assay; IgG, Immunoglobulin G; IgM, Immunoglobulin M; IgA, Immunoglobulin A; N, Nucleocapsid protein; AUC, Area under the curve; ACE2, Angiotensin-converting enzyme 2; IL-2, Interleukin 2; IFN-γ, Interferon-gamma; mAb, Monoclonal antibody; OT, Oncological treatment; OR, Odds ratio; 95 % CI, 95 % confidence interval; GLMM, Generalized Linear Mixed Models; GMR, Geometric mean ratio; GMFR, Geometric mean fold rise

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Future studies should evaluate the durability of the immune response and the efficacy of individualized regimens.

Introduction

Since the emergence of Coronavirus Disease 2019 (COVID-19) in December 2019 in Wuhan, China, the disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) rapidly became a global pandemic, constituting a significant public health threat [1,2]. As of May 2024, SARS-CoV-2 has caused over 775 million infections and nearly seven million deaths worldwide [3].

SARS-CoV-2 mainly targets the respiratory system but also affects the cardiovascular, central nervous, and gastrointestinal systems [4]. The infection causes significant changes in the gut and airway microbiota, influencing disease progression and outcome [5]. Elderly patients and those with comorbidities, impaired organ function, and preexisting polypharmacy tend to experience more severe COVID-19 complications [5].

The mRNA vaccines, including mRNA-1273 (Moderna), prevent symptomatic COVID-19 infections in the general population. They elicit robust humoral immune responses by activating B cells, leading to the production of specific neutralizing antibodies against the SARS-CoV-2 "spike" or S glycoprotein [6]. These vaccines also induce antigen-specific T cells, contributing to long-term protective immunity [7]. However, SARS-CoV-2 continually evolves, with new variants emerging that carry mutations in the spike protein, a crucial component of the COVID-19 vaccines, reducing their effectiveness [8]. The Omicron variant is particularly concerning due to its numerous mutations, high transmissibility, and ability to evade immunity [9]. Omicron's increased transmissibility has made it the dominant variant worldwide [10].

Approximately 75 % of hospitalized COVID-19 patients have at least one comorbidity, such as hypertension, neurological disorders, diabetes, endothelial dysfunction, cardiovascular diseases, or cancer [11]. Cancer patients often have weakened immune systems due to the disease or its treatments. This significantly impacts the body's ability to respond effectively to infections or vaccinations. Evidence indicates that cancer patients are more susceptible to viral infections, including COVID-19, and face higher risks of severe complications and mortality compared to the general population [12–15]. Clinical factors like age or specific oncological therapies are linked to worse outcomes in cancer patients with COVID-19 [14,16,17]. Consequently, immunocompromised cancer patients were prioritized for receiving COVID-19 vaccines. However, cancer patients were initially excluded from COVID-19 vaccine clinical trials, leading to low vaccination rates in this group [18,19]. Therefore, data on the immune response to the COVID-19 vaccine in cancer patients are more limited than in the general population.

COVID-19 vaccines can induce an immune response in cancer patients. However, this response is often lower in patients with hematological and solid malignancies, resulting in higher rates of low or absent serological responses than in the general population, especially in those receiving immunosuppressive oncological treatment [20–22]. Therefore, it is necessary to gather comprehensive information to establish vaccination guidelines for cancer patients due to the impact of oncological treatments on the immune response [18,19]. Furthermore, with the emergence of variants like Omicron, which exhibits heightened immune evasion, it is crucial to gather information on the efficacy of COVID-19 vaccines in vulnerable groups [23].

Objective

This study assessed how oncological treatments with immunosuppressive effects impact humoral and T-cell responses to the B.1 lineage and Omicron variant after COVID-19 vaccination in a cohort of patients with solid and hematological neoplasms.

Materials and methods

Study design

We conducted a prospective study on oncology patients who received their first COVID-19 vaccination between February 2021 and January 2022 at the Hospital Universitario Infanta Leonor (HUIL) in Madrid, Spain. The vaccination regimen included two doses of mRNA-1273 (Moderna) administered 28 days apart and a booster dose 6 months later, following international guidelines [24]. Inclusion criteria included: (i) cancer patients over 18 years old; (ii) life expectancy of over 6 months; (iii) confirmed diagnosis of solid or hematological cancer. We collected biological samples from cancer patients to evaluate their immune response to the COVID-19 vaccine about four weeks after the second dose (N = 98) and eight weeks after the booster dose (N = 71).

The HUIL Ethics Committee authorized the study (Ref.: 030-21). The research adhered to the Declaration of Helsinki. All participants gave informed consent before enrollment.

Clinical samples

A peripheral blood sample was collected via venous puncture using ethylene diamine tetra-acetic acid tubes. Samples were taken at three points: baseline (first COVID-19 vaccine dose), about four weeks after the second dose, and eight weeks after the booster dose. Plasma and peripheral blood mononuclear cells (PBMC) were isolated using a Ficoll gradient. PBMCs were stored in liquid nitrogen, and plasma samples were stored at −80 °C.

Clinical data

Patient characteristics were collected from the hospital's electronic medical records and stored using the Research Electronic Data Capture system (REDCap, Vanderbilt University, Nashville, TN, USA). Cancer diagnosis and oncological treatments followed international guidelines [25].

Test for SARS-CoV-2 infection

We determined the presence of SARS-CoV-2 antibodies in plasma samples both before vaccination and after receiving the second and booster doses of the vaccine. The detection method used was a commercial enzyme-linked immunosorbent assay (ELISA) (Platelia SARS-CoV-2 Total Ab, Bio-Rad Laboratories Inc., Hercules, California, USA). This ELISA test identified IgG, IgA, and IgM antibodies against the SARS-CoV-2 nucleocapsid protein (N). The optical density ratio ≥ 1.0 of the test sample to the control sample provided in the kit was considered positive. This cut-off point was chosen based on the test's sensitivity and specificity, which are 94.7 % and 97.5 %, respectively [26].

Immunoassays for COVID-19 vaccine humoral response

A detailed description of the materials and protocols for antibody quantification is provided in Martin-Vicente et al. [27]. Briefly, Dr. Jason McLellan (University of Texas at Austin-USA) kindly provided the plasmid pH encoding the S protein ectodomain (residues 1–1208) of SARS-CoV-2 2019-nCOV (GenBank: MN908947) stabilized in the prefusion conformation [28]. Mutagenesis was used to create a HexaPro construct that produces a high yield of the stabilized prefusion spike protein [29]. The ectodomain was modified with the following substitutions: glycine at residue 614 (D614G), a "GSAS" substitution at the furin cleavage site (residues 682–685), and proline at residues 817, 892, 899, 942, 986, and 987. This protein is referred to as B.1 throughout the text. The SARS-CoV-2 S Omicron (B.1.1.529) HexaPro construct contains the natural cleavage site "RRAR" (residues 682–685) and the following Omicron-specific mutations: A67V, Δ69–70, T95I, G142D/Δ143–145, Δ211/L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, and L981F. A plasmid containing the ACE2 SARS-CoV-2 cell receptor (residues 1–165) was also constructed and linked to a StrepTag.

Antibody titers to the S protein were measured in ELISA assays by incubating serial 1:3 dilutions of serum samples, starting at 1:50 and ending at 1:36450, with 0.2 μg of the S protein ectodomain. One-phase exponential decay, least-squares fit curves, and the area under the curve (AUC) were calculated using GraphPad Prism 9.0.

Antibody inhibition of the ACE2-S protein interaction was tested by ELISA. Serum samples were diluted serially (1:2 dilutions) from 1:10 to 1:320. These dilutions were incubated with the S protein, followed by the addition of ACE2 complexed with StrepTactin-peroxidase [27]. A pool of sera collected in 2016 from individuals negative for anti-S antibodies served as a control. After subtracting the background, the percentage of inhibition was calculated as [1 - (OD_{493} test serum / OD_{493} control serum)] x 100 %.

Immunoassays for COVID-19 vaccine cellular response

The FluoroSpot Plus Human IFN-γ/IL-2 Kit (Mabtech Inc., Cincinnati, Ohio, USA) was used to detect interleukin 2 (IL-2) and interferon-gamma (IFN-γ) secretion in T-cells. PBMC samples were stimulated with protein S peptides and an anti-CD28 monoclonal antibody (mAb) as co-stimulus. As a positive control, PBMC samples were stimulated with anti-CD3 mAb and anti-CD28 mAb. As a negative control, PBMC samples were incubated only with anti-CD28 mAb. For specific stimulation, two distinct peptide pools were employed. The first pool contained 166 peptides covering the S1 domain of the spike protein from the ancestral (Wuhan) strain of SARS-CoV-2 (Mabtech Inc., Cincinnati, Ohio, USA). The second pool contained 168 peptides from the S1 domain of the SARS-CoV-2 Omicron (B.1.1.529) variant, lineage BA.1, with the following mutations: A67V, _D_69–70, T95I, G142D, _D_143–145, _D_211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H (Mabtech Inc, Cincinnati, Ohio, USA).

Briefly, 96-well microplates precoated with monoclonal capture antibodies against IFN-γ and IL-2 were used. The base medium was RPMI with penicillin/streptomycin, L-glutamine, fetal bovine serum, non-essential amino acids, and anti-CD28 mAb (1 μg/ml). For the negative control, 20 μl of this base medium was added per well. Additionally, 20 μl of the base medium was added to wells with anti-CD3 mAb (0.2 μg/ml, positive control) or peptide pools (final concentration of 0.2 μg/ml for each peptide), diluted in the base medium. Then, 300.000 PBMCs were added per well in 80 μl of the base medium, and the plates were incubated at 37 °C and 5 % CO_2 for 18 h.

After the incubation, the plates were washed with sterile phosphate-buffered saline with Ca^{2+} and Mg^{2+}. Biotin-conjugated antibodies against IL-2 and BAM-labeled antibodies against IFN-γ were added. Following a two-hour incubation and subsequent washing, Cy3-conjugated streptavidin and FITC-conjugated anti-BAM were added for another hour. After further washing, a fluorescence enhancer was applied for 5 min.

The plates were dried, and readings were taken using an AID iSpot ELISpot FluoroSpot Reader (AID GmbH, Strassberg, Germany) with two specific filters. The calculations were done by subtracting the number of spots in the negative control wells, and the results were expressed as the number of spots per million PBMCs.

Main factors and outcomes

This study examined the immune response of cancer patients to the COVID-19 vaccine, stratifying them based on whether they received concurrent or recent oncological treatment (OT) with immunosuppressive effects. The study compared the OT group to the non-OT group. At the second dose of the COVID-19 vaccine (n = 98), the OT group had 61 patients (38 chemotherapy, 11 radiotherapy, 11 immunotherapy, 18 targeted therapy, and 1 other oncological treatment). The non-OT group had 37 patients (23 never received oncological treatments, and 14 completed the oncological treatments 6 months before vaccination). At the booster dose, only 71 individuals were analyzed, as 27 patients were lost to follow-up. The OT group had 51 patients (23 chemotherapy, 6 radiotherapy, 10 immunotherapy, 14 targeted therapy, and 2 other oncological treatments). The non-OT group had 20 patients (13 never received oncological treatment, and 7 completed the oncological treatments 6 months before vaccination).

The primary outcome was the humoral response to the COVID-19 vaccine (anti-SARS-CoV-2 S IgG titers and ACE2-S interaction inhibition capacity) against the B.1 lineage and Omicron variant after the second and booster doses. The secondary outcome was the cellular response (SARS-CoV-2 S-specific T-cell spots per million PBMCs) against the B.1 lineage and Omicron variant after the second dose.

Statistical analysis

IBM SPSS Statistics 25.0 (SPSS INC, Armonk, NY, USA) and Stata 15.0 (StataCorp, Texas, USA) were used for statistical analysis. GraphPad Prism 9.0 (GraphPad Software, Inc., San Diego, CA, USA) was used to generate figures. Significance was set at $p < 0.05$ (two-tailed).

Descriptive analysis included absolute counts (percentages) and median (P25th; P75th). The Chi-squared test compared categorical variables, and the Mann-Whitney U test compared continuous variables.

COVID-19 vaccine immune response data were log10-transformed. The impact of oncological treatment with immunosuppressive effect on the COVID-19 vaccine immune response (OT vs. non-OT groups) was evaluated using logistic regressions. These regressions were adjusted for clinical variables (age, sex, previous SARS-CoV-2 infection, tumor type (solid or hematological), and COVID-19 vaccination timing) selected by a stepwise forward selection method (pin < 0.15 and pout < 0.20). This test provided the odds ratio (OR) and the 95 % confidence interval (95 %CI). Differences between dependent measures in the COVID-19 vaccine immune response were also evaluated using generalized linear mixed models (GLMM), a repeated measures test where each patient serves as their control. This test provided the geometric mean ratio (GMR) for differences between the Omicron variant and the B.1 lineage and the geometric mean fold rise (GMFR) for the differences between post-

and pre-vaccination, along with their 95 %CI. P-values were adjusted by the False Discovery Rate (q-value).

Results

Patient characteristics

At the second dose of the COVID-19 vaccine (n = 98, Table 1), the median age was 60. Among participants, 41.8 % were male, and 24.5 % had a previous SARS-CoV-2 infection. In addition, 45.9 % had solid neoplasms, with breast cancer being the most common (40 %). Meanwhile, 54.1 % had hematological neoplasms, with lymphoproliferative neoplasia being the most frequent (34 %). Participant characteristics at the booster dose (n = 71) were similar to those at the second dose (Supplementary Table **(ST) 1**).

Patients were stratified by the primary outcome variable (OT or non-OT) and the timing of vaccine response assessment (after the second dose or booster dose). We found 37 patients in the non-OT group and 61 patients in the OT group after the second dose (Table 1). After the booster dose, there were 20 patients in the non-OT group and 51 in the OT group (**ST1**). The OT group had lower lymphocyte counts and fewer hematological neoplasms than the non-OT group, both after the second dose and after the booster dose (Table 1 **& ST1**).

Additionally, eight patients in the non-OT group and 16 in the OT group tested positive for SARS-CoV-2 infection after the second dose (Table 1). After the booster dose, three patients in the non-OT group and 14 in the OT group tested positive (**ST1**). However, there were no statistically significant differences in infection rates between the groups (Table 1 **& ST1**).

Humoral immune response to the COVID-19 vaccine

Table 2 shows the GMFR in humoral response, measured by IgG antibody levels against SARS-CoV-2 S protein and ACE2-S inhibition titers, after the second and booster doses of the COVID-19 vaccine. Notably, the GMFR values were higher after the second dose compared to the booster dose.

Impact of oncological treatment with immunosuppressive effect

After the second dose of the COVID-19 vaccine, the OT group exhibited lower humoral response (measured by anti-SARS-CoV-2 S IgG titers and ACE2-S interaction inhibition capacity) against the B.1 lineage and Omicron variant compared to the non-OT group (q-value < 0.05; Fig. 1**A**; full description in **ST2**). However, after the booster dose, the humoral response against both the B.1 lineage and the Omicron variant was similar between OT and non-OT groups (Fig. 1**B**; full description in **ST2**). Therefore, the booster dose improved the humoral response in the OT group to levels comparable to the non-OT group.

Response against the Omicron variant

The humoral response, characterized by anti-SARS-CoV-2 S IgG levels and ACE2-S interaction inhibition, was consistently lower against the Omicron variant compared to the B.1 lineage after both the second and booster COVID-19 vaccine doses in OT and non-OT groups (q-value < 0.05; Fig. 2; full description in **ST3**). Notably, the rate of non-responders (AUC = 0) for ACE2-S interaction inhibition against Omicron was significantly higher than against B.1 after the

Table 1
Characteristics of the patients at the second dose of COVID-19 vaccine.

		Oncological treatment (OT)		
	All	Non-OT group	OT group	*p*
No.	98	37	61	
Sex (male), N (%)	41 (41.8)	16 (43.2)	25 (41)	0.826
Age (years). median (IQR)	60 (52 - 66)	61 (52 - 66)	60 (51 - 66)	0.814
Spanish. N (%)	83 (84.7)	32 (86.5)	51 (83.6)	0.701
Comorbidities. N (%)				
Hypertension	28 (28.6)	6 (16.2)	22 (36.1)	**0.035**
Dyslipidemia	21 (21.4)	6 (16.2)	15 (24.6)	0.327
Diabetes	16 (16.3)	7 (18.9)	9 (14.8)	0.589
Obesity	12 (12.2)	2 (5.4)	10 (16.4)	0.108
Smoker	23 (23.5)	9 (24.3)	14 (23)	0.876
HPSCT. N (%)	5 (9.4)	3 (11.1)	2 (7.7)	0.670
SARS-CoV-2 Infection. N (%)	24 (24.5)	8 (21.6)	16 (26.2)	0.607
Lymphocytes (10^3/μl). median (IQR)	1.7 (1.1 - 2.3)	1.85 (1.4 - 2.95)	1.5 (1.1 - 1.9)	**0.006**
Solid neoplasms. N (%)	45 (45.9)	10 (27)	35 (57.4)	**0.003**
Lung	5 (11.1)	1 (10)	4 (11.4)	0.657
Breast	18 (40)	4 (40)	14 (40)	0.714
Prostate	1 (2.2)	1 (10)	0 (0)	0.499
Colorectal	7 (15.6)	1 (10)	6 (17.1)	0.956
Stomach	2 (4.4)	0 (0)	2 (5.7)	0.923
Esophagus	3 (6.7)	0 (0)	3 (8.6)	0.811
Pancreas	1 (2.2)	0 (0)	1 (2.9)	0.499
Uterus	1 (2.2)	0 (0)	1 (2.9)	0.499
Head and neck	1 (2.2)	1 (10)	0 (0)	0.499
Bladder	2 (4.4)	1 (10)	1 (2.9)	0.923
Others	4 (8.9)	1 (10)	3 (8.6)	0.624
Hematologic neoplasms. N (%)	53 (54.1)	27 (73)	26 (42.6)	**0.003**
Acute Lymphocytic Leukemia	1 (1.9)	0 (0)	1 (3.8)	0.999
Chronic Lymphocytic Leukemia	7 (13.2)	5 (18.5)	2 (7.7)	0.448
Multiple Myeloma and Gammopathy	4 (7.5)	1 (3.7)	3 (11.5)	0.576
Myelodysplastic syndrome	4 (7.5)	3 (11.1)	1 (3.8)	0.603
Lymphoproliferative neoplasm	18 (34)	12 (44.4)	6 (23.1)	0.101
Myeloproliferative neoplasm	13 (24.5)	5 (18.5)	8 (30.8)	0.302
Chronic Myeloid Leukemia	6 (11.3)	1 (3.7)	5 (19.2)	0.177

Statistics: Values are expressed as the median (P25; P75) and absolute count (percentage). P-values were calculated using the Chi-square test for categorical variables and the Mann-Whitney U-test for continuous variables.
Abbreviations: COVID-19, coronavirus disease 2019; HPSCT, Hematopoietic stem cell transplant; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2
Summary of geometric mean fold rises from baseline stratified by the oncological treatment with immunosuppressive effect during follow-up.

	After the second dose GMFR (95 %CI)	After the booster dose GMFR (95 %CI)
All patients		
Wuhan (B.1)		
IgG antibody titers	39.4 (29.4; 52.7)	5.9 (5; 7)
Inhibition ACE2-S titer	34.6 (22.5; 53.2)	8.1 (6.7; 9.9)
Omicron		
IgG antibody titers	27.2 (21.2; 34.9)	5.7 (5; 6.6)
Inhibition ACE2-S titer	7.1 (4.8; 10.6)	6 (4.9; 7.4)
Non-OT group		
Wuhan (B.1)		
IgG antibody titers	54.3 (35.1; 84.1)	7.1 (5.4; 9.3)
Inhibition ACE2-S titer	75.3 (45.6; 124.3)	10.1 (7.9; 12.9)
Omicron		
IgG antibody titers	39.6 (28.2; 55.6)	6.9 (5.5; 8.5)
Inhibition ACE2-S titer	15.1 (8; 28.4)	6.4 (4.5; 9.1)
OT group		
Wuhan (B.1)		
IgG antibody titers	32.4 (22.2; 47.1)	5.5 (4.5; 6.8)
Inhibition ACE2-S titer	21.5 (12; 38.6)	7.9 (6.2; 9.9)
Omicron		
IgG antibody titers	21.7 (15.7; 30.2)	5.3 (4.4; 6.3)
Inhibition ACE2-S titer	4.5 (2.8; 7.3)	5.9 (4.6; 7.6)

Statistics: Values are expressed as median (95 % confidence interval). Data were calculated using generalized linear mixed models adjusted (GLMM, see Statistical analysis section). **Abbreviations**: GMFR, geometric mean fold rise (GMFR) from baseline, 95 % CI, 95 % confidence interval; OT, oncological treatment; Area under the Curve; IgG, immunoglobulin G; ACE2, angiotensin-converting enzyme 2; S, Spike glycoprotein.

second dose in both groups (q-value < 0.05; Supplementary Fig. 1). However, these differences were not statistically significant after the booster dose. Therefore, the COVID-19 vaccine elicited a weaker humoral response against Omicron than B.1, regardless of oncological treatment. However, this response improved after the booster dose.

T-cell immune response to the COVID-19 vaccine

The T-cell response to the B.1 lineage and Omicron variant was similar between the OT and non-OT groups after the second COVID-19 vaccine dose (Fig. 3**A**; full description in **ST4**). Additionally, the T-cell response to the Omicron variant was similar to that of the B.1 lineage in both groups (Fig. 3**B**; full description in **ST5**). Therefore, after the second vaccine dose, the T-cell response reached comparable levels in both OT and non-OT groups for both the B.1 lineage and the Omicron variant.

Discussion

Cancer patients have an elevated risk of SARS-CoV-2 infection and related complications due to systemic immunodeficiency, primarily induced by oncological therapy [30]. This study investigated the immune response after COVID-19 vaccination in cancer patients, with or without immunosuppressive oncological treatments, who received the monovalent Moderna mRNA-1273 vaccine based on the Wuhan-Hu-1 strain. The main findings were: i) The humoral immune response, after the second vaccine dose, against the B.1 lineage and Omicron variant was significantly weaker in cancer patients undergoing oncological treatment (OT group) compared to those not receiving treatment (non-OT group). ii) A booster dose of the mRNA-1273 vaccine significantly improved the humoral immune response in the OT group, bringing it to a level comparable to the non-OT group. iii) The mRNA-1273 vaccine, designed for the original Wuhan strain, elicited a weaker humoral response against the Omicron variant compared to the B.1 lineage, regardless of oncological treatment or vaccine dose. iv) In contrast, T-cell responses against SARS-CoV-2, including the Omicron variant, were already present after the second vaccine dose and were not significantly affected by oncological treatments. Overall, our data offers valuable insights into the immune response of cancer patients to COVID-19 vaccination. It

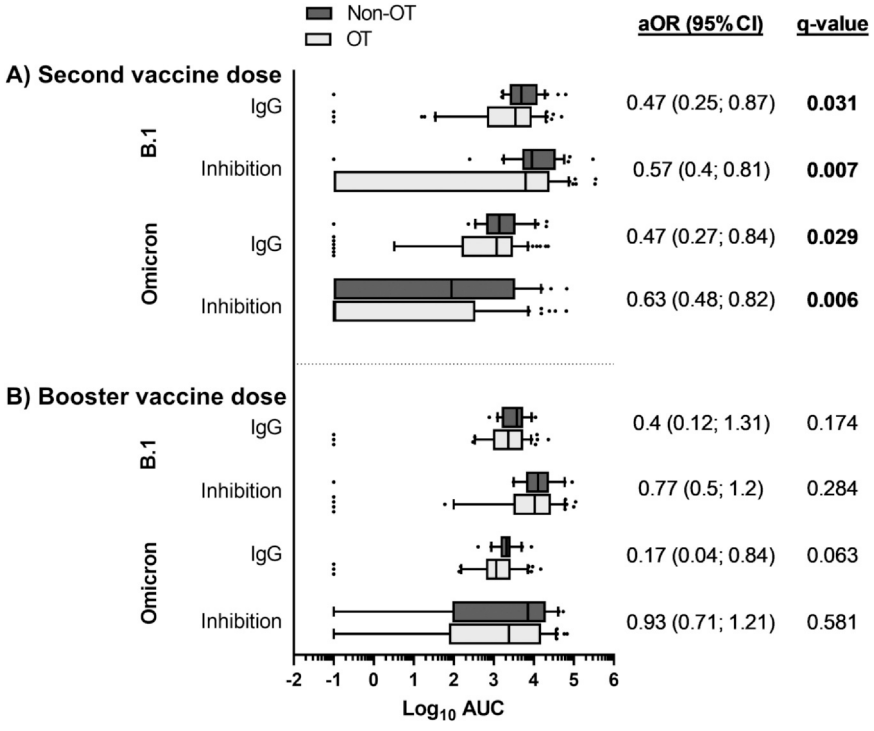

Fig. 1. Plasma IgG antibody levels against the SARS-CoV-2 S protein and ACE2-S inhibition titers, stratified by oncological treatment and SARS-CoV-2 variants, weeks after the administration of the second (A) and booster dose (B) of the COVID-19 vaccine. **Statistics**: Data were calculated by logistic regression analysis adjusted for the most relevant clinical and epidemiological characteristics. Significant differences are shown in bold. **Abbreviations**: aOR, adjusted odds ratio; 95 % CI, 95 % confidence interval; AUC, the area under the Curve; IgG, immunoglobulin G.

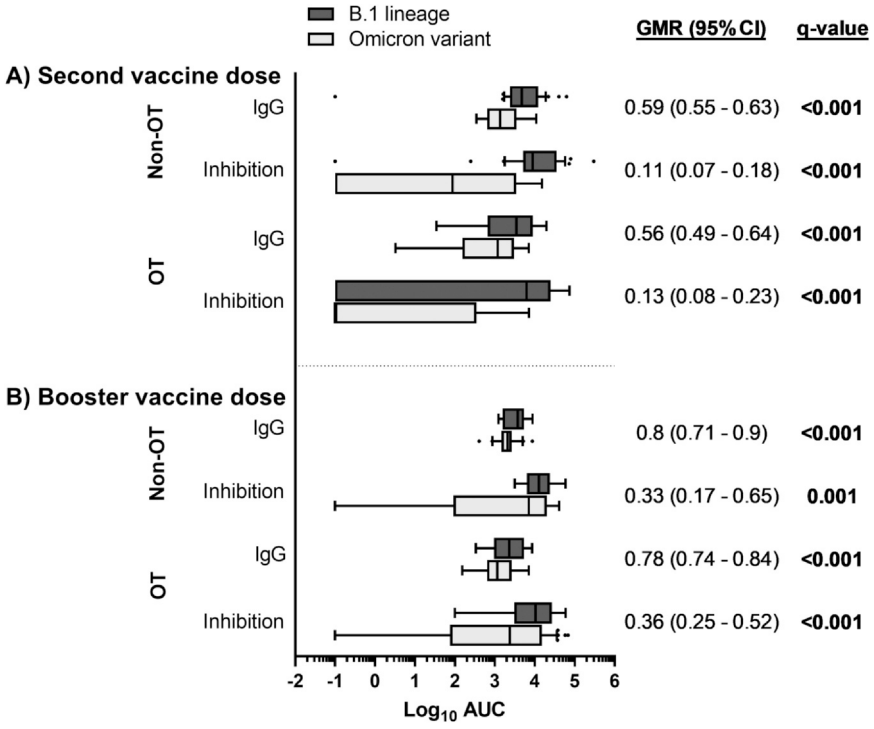

Fig. 2. Plasma IgG antibody levels against the SARS-CoV-2 S protein and ACE2-S inhibition titers, stratified by SARS-CoV-2 variants and oncological treatment, several weeks after the administration of the second (A) and booster dose (B) of the COVID-19 vaccine. **Statistics**: Data were calculated using generalized linear mixed models. Significant differences are shown in bold. **Abbreviations**: GMR, geometric mean ratio; 95 % CI, 95 % confidence interval; AUC, the area under the Curve; IgG, immunoglobulin G.

highlights the need for personalized vaccination approaches and the potential benefits of booster doses in enhancing humoral immunity, especially against challenging variants like Omicron.

An important finding is the improved humoral immune response after the booster vaccine dose in the OT group, aligning it with the non-OT group. Our findings are consistent with prior studies that reported a reduced humoral response in patients undergoing oncological treatment after two doses of the COVID-19 vaccine [22,31–34]. This response improves with a booster dose [35–41] and lasts at least 6 months [41]. Therefore, for cancer patients on immunosuppressive oncological treatment, a booster dose is crucial for adequate immunization. These findings suggest the need to revise vaccination strategies to include additional doses for this vulnerable population.

Oncological treatments with an immunosuppressive effect alter the intestinal microbiota, causing dysbiosis and modifying the immune response [42]. This has been linked to the modulation of the immune response against SARS-CoV-2 [43]. Gut-lung axis dysbiosis worsens COVID-19 symptoms, increases systemic inflammation, and causes greater tissue damage, leading to long-term complications and death [5]. However, this dysbiosis and the translocation of bacterial components (lipopolysaccharides, flagellin, peptidoglycan, and short-chain fatty acids) appear to enhance COVID-19 vaccine efficacy by improving the production of antibodies by plasma B cells [43]. Although we lack data on bacterial translocation in the analyzed patients, we should not rule out the possible impact of cancer treatments on gut microbiota and humoral response to the COVID-19 vaccine, which recovered after the booster dose.

Both OT and non-OT groups showed weaker responses against the Omicron variant compared to the B.1 lineage after the second and booster vaccine doses. Monovalent vaccines, based on the Wuhan strain, are less effective against Omicron in both the general population and cancer patients [44,45]. This is due to many amino acid changes in Omicron's S protein, which helps it evade the humoral response and reduces vaccine protection [44]. Previous data highlighted the need for booster doses to achieve adequate neutralizing antibody levels against Omicron [46]. Our findings support this, showing no significant differences in non-responder rates for the ACE2-S interaction inhibition between the B.1 lineage and Omicron after the booster dose in both the OT and non-OT groups. However, the bivalent COVID-19 vaccine, introduced after our study's enrollment period had closed, has shown improved neutralization against Omicron sub-variants [47]. This underscores the importance of monitoring variants and developing adapted vaccines to control SARS-CoV-2 effectively.

The cellular immune response may play a crucial role in preventing severe COVID-19 [48]. Previous reports show that vaccinated individuals generate T-cell responses against epitopes conserved across many variants [49]. In our study, the antigen-specific T-cell responses after the second dose of the COVID-19 vaccine showed no significant differences between the OT and non-OT groups. These results align with previous studies indicating that systemic oncological therapy impairs antibody responses but does not significantly affect cellular responses [40,50]. Despite this T-cell response, patients undergoing cancer treatment have higher morbidity and mortality than the general population [18]. Our results also showed a T-cell response against the Omicron variant similar in magnitude to the response against the Wuhan lineage. This underscores the significant benefits of vaccination, particularly for patients with compromised humoral immunity.

Our article uniquely combines a comparative analysis of oncological treatment effects, an evaluation of variant-specific immune responses, and the impact of multiple vaccine doses. Overall, the study significantly enhances the understanding of COVID-19 vaccine efficacy in cancer patients and informs future vaccination strategies to ensure adequate protection for this high-risk group.

Promoting vaccination is crucial for oncology patients with compromised immune systems [18]. Our findings, along with other studies, underscore the need for personalized vaccination strategies for those undergoing oncological treatments. These strategies should

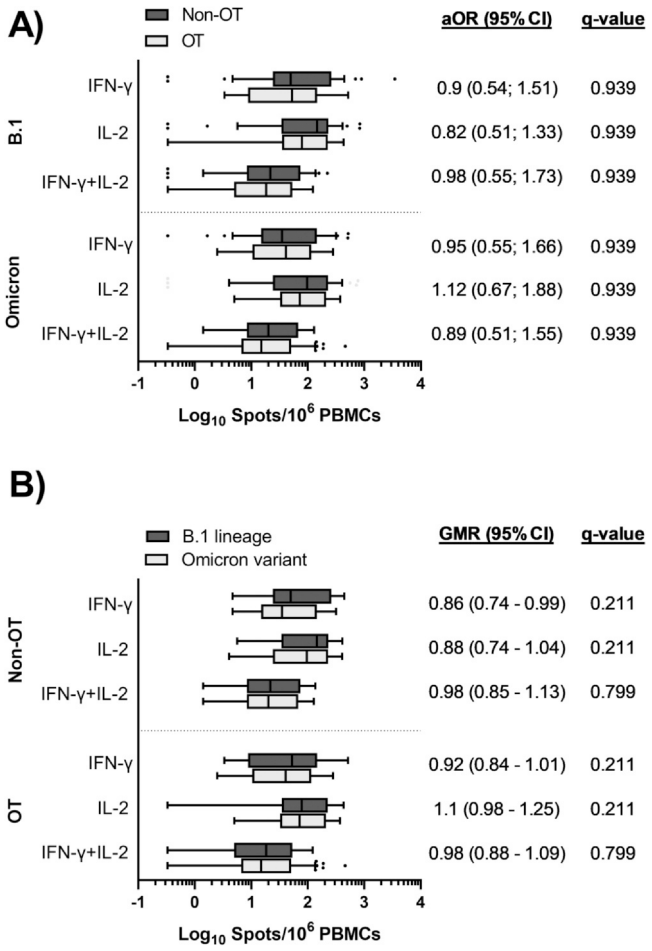

Fig. 3. SARS-CoV-2 S-specific T-cell response against the B.1 lineage and Omicron variant, stratified by oncological treatment (A) or SARS-CoV-2 variants (B), several weeks after the second dose of the COVID-19 vaccine. **Statistics**: Data were calculated using logistic regression analysis adjusted for the most relevant clinical and epidemiological characteristics, as well as generalized linear mixed models. **Abbreviations**: aOR, adjusted odds ratio; 95 % CI, 95 % confidence interval; GMR, geometric mean ratio; IFN, interferon; IL-2, interleukin 2; AUC, Area under the Curve; PBMCs, peripheral blood mononuclear cells.

include personalized vaccination schedules and booster doses to ensure optimal protection against COVID-19, especially with the emergence of new variants. Emphasizing the benefits of vaccination can encourage higher vaccination rates among oncology patients, providing broader protection against COVID-19 and reducing the risk of severe disease in this high-risk group.

Limitations

This study has several limitations. First, the small sample size reduces statistical power and increases the risk of false positives. In this regard, hybrid immunity was not analyzed in detail due to the low number of patients with SARS-CoV-2 infection in the non-OT group. However, prior infection status was included in multivariate regression analyses to account for the potential protective effects of this hybrid immunity. A larger sample size could provide a more accurate depiction of the immune response in oncology patients. Second, the prospective design of this study introduced biases, including patient and sample loss to follow-up. Third, conclusions could not be reached for certain subgroups, such as those with different tumors or specific anti-cancer regimens. Fourth, patient follow-up was limited to four weeks after the second dose and eight weeks after the booster dose. A longer follow-up could provide valuable information on the durability and effectiveness of the long-term immune response. Fifth, some cancer patients showed no immune response to the COVID-19 vaccine, possibly due to test sensitivity issues. Sixth, there was no healthy control group. Differences between cancer patients and healthy subjects are well documented, so this was not a priority for our study. Finally, no significant differences were found in the immune response against COVID-19 vaccination between solid and hematological cancer patients, possibly due to treatment heterogeneity and combined treatment regimens.

Conclusions

Cancer patients, particularly those on immunosuppressive oncological treatments, need booster doses and updated COVID-19 vaccines for new variants like Omicron. Future studies should evaluate the durability of the vaccine-induced immune response and the efficacy of personalized vaccine regimens.

Ethics approval and consent to participate

The HUIL Ethics Committee authorized the study (Ref.: 030–21), which was conducted following the Declaration of Helsinki. All participants gave their informed consent before enrollment.

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CRediT authorship contribution statement

Data curation: MJMG, PR, GC, JV, EJ, NBL, MALA, JAHR, GR, and JTM. Investigation: MJMG, MMV, MQD, VM, DSC, MV, PR, SR, and IM. Data analysis and interpretation: MJMG, SR, and IM. Supervision and visualization: SR, IM, and PR. Funding acquisition: SR, IM, and PR. Drafting the article: MJMG, SR, and IM. Critical revision of the article: PR. All authors have read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2024.102473.

References

[1] Muralidar S, Ambi SV, Sekaran S, Krishnan UM. The emergence of COVID-19 as a global pandemic: understanding the epidemiology, immune response and potential therapeutic targets of SARS-CoV-2. Biochimie 2020;179:85–100.

[2] Farooqi T, Malik JA, Mulla AH, Al Hagbani T, Almansour K, Ubaid MA, et al. An overview of SARS-COV-2 epidemiology, mutant variants, vaccines, and management strategies. J Infect Public Health 2021;14(10):1299–312.

[3] **WHO Coronavirus (COVID-19) dashboard**. ⟨https://data.who.int/dashboards/covid19⟩. Accessed 15 May 2024.

[4] Duloquin G, Pommier T, Georges M, Giroud M, Guenancia C, Bejot Y, et al. Is COVID-19 Infection a Multiorganic Disease? Focus on Extrapulmonary Involvement of SARS-CoV-2. J Clin Med 2024;13(5).

[5] Malik JA, Ahmed S, Yaseen Z, Alanazi M, Alharby TN, Alshammari HA, et al. Association of SARS-CoV-2 and polypharmacy with gut-lung axis: from pathogenesis to treatment. ACS Omega 2022;7(38):33651–65.

[6] Park JW, Lagniton PNP, Liu Y, Xu RH. mRNA vaccines for COVID-19: what, why and how. Int J Biol Sci 2021;17(6):1446–60.

[7] Painter MM, Mathew D, Goel RR, Apostolidis SA, Pattekar A, Kuthuru O, et al. **Rapid induction of antigen-specific CD4(+) T cells is associated with coordinated humoral and cellular immunity to SARS-CoV-2 mRNA vaccination**. Immunity 2021;54(9):2133–42. e2133.

[8] Malik JA, Ahmed S, Mir A, Shinde M, Bender O, Alshammari F, et al. The SARS-CoV-2 mutations versus vaccine effectiveness: New opportunities to new challenges. J Infect Public Health 2022;15(2):228–40.

[9] Fan Y, Li X, Zhang L, Wan S, Zhang L, Zhou F. SARS-CoV-2 Omicron variant: recent progress and future perspectives. Signal Transduct Target Ther 2022;7(1):141.

[10] Coronavirus Pandemic (COVID-19). Published online at OurWorldInData.org. Retrieved from: '⟨https://ourworldindata.org/coronavirus⟩ [Online Resource].

[11] Ahmad Malik J, Ahmed S, Shinde M, Almermesh MHS, Alghamdi S, Hussain A, et al. The Impact of COVID-19 on comorbidities: a review of recent updates for combating It. Saudi J Biol Sci 2022;29(5):3586–99.

[12] Cook G, John Ashcroft A, Pratt G, Popat R, Ramasamy K, Kaiser M, et al. Real-world assessment of the clinical impact of symptomatic infection with severe acute respiratory syndrome coronavirus (COVID-19 disease) in patients with multiple myeloma receiving systemic anti-cancer therapy. Br J Haematol 2020;190(2):e83–6.

[13] Mato AR, Roeker LE, Lamanna N, Allan JN, Leslie L, Pagel JM, et al. Outcomes of COVID-19 in patients with CLL: a multicenter international experience. Blood 2020;136(10):1134–43.

[14] Pinato DJ, Scotti L, Gennari A, Colomba-Blameble E, Dolly S, Loizidou A, et al. Determinants of enhanced vulnerability to coronavirus disease 2019 in UK patients with cancer: a European study. Eur J Cancer 2021;150:190–202.

[15] Desai A, Gupta R, Advani S, Ouellette L, Kuderer NM, Lyman GH, et al. Mortality in hospitalized patients with cancer and coronavirus disease 2019: A systematic review and meta-analysis of cohort studies. Cancer 2021;127(9):1459–68.

[16] Grivas P, Khaki AR, Wise-Draper TM, French B, Hennessy C, Hsu CY, et al. Association of clinical factors and recent anticancer therapy with COVID-19 severity among patients with cancer: a report from the COVID-19 and Cancer Consortium. Ann Oncol 2021;32(6):787–800.

[17] Robilotti EV, Babady NE, Mead PA, Rolling T, Perez-Johnston R, Bernardes M, et al. Determinants of COVID-19 disease severity in patients with cancer. Nat Med 2020;26(8):1218–23.

[18] Fendler A, de Vries EGE, GeurtsvanKessel CH, Haanen JB, Wormann B, Turajlic S, et al. COVID-19 vaccines in patients with cancer: immunogenicity, efficacy and safety. Nat Rev Clin Oncol 2022;19(6):385–401.

[19] Negahdaripour M, Shafiekhani M, Moezzi SMI, Amiri S, Rasekh S, Bagheri A, et al. Administration of COVID-19 vaccines in immunocompromised patients. Int Immunopharmacol 2021;99:108021.

[20] Corti C, Antonarelli G, Scotte F, Spano JP, Barriere J, Michot JM, et al. Seroconversion rate after vaccination against COVID-19 in patients with cancer-a systematic review. Ann Oncol 2022;33(2):158–68.

[21] Becerril-Gaitan A, Vaca-Cartagena BF, Ferrigno AS, Mesa-Chavez F, Barrientos-Gutierrez T, Tagliamento M, et al. Immunogenicity and risk of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection after Coronavirus Disease 2019 (COVID-19) vaccination in patients with cancer: a systematic review and meta-analysis. Eur J Cancer 2022;160:243–60.

[22] Tang K, Wei Z, Wu X. Impaired serological response to COVID-19 vaccination following anticancer therapy: a systematic review and meta-analysis. J Med Virol 2022;94(10):4860–8.

[23] Chen J, Wang R, Gilby NB, Wei GW. Omicron variant (B.1.1.529): infectivity, vaccine breakthrough, and antibody resistance. J Chem Inf Model 2022;62(2):412–22.

[24] World Health Organization. Interim recommendations for use of the Moderna mRNA-1273 vaccine against COVID-19: interim guidance, **25 January 2021** (In). Geneva: World Health Organization,; 2021.

[25] NCCN Clinical Practice Guidelines in Oncology. ⟨https://www.nccn.org/guidelines/category_1⟩. Accessed 15 Dec 2023.

[26] Tre-Hardy M, Wilmet A, Beukinga I, Favresse J, Dogne JM, Douxfils J, et al. Analytical and clinical validation of an ELISA for specific SARS-CoV-2 IgG, IgA, and IgM antibodies. J Med Virol 2021;93(2):803–11.

[27] Martin-Vicente M, Carrasco I, Munoz-Gomez MJ, Lobo AH, Mas V, Vigil-Vazquez S, et al. Antibody levels to SARS-CoV-2 spike protein in mothers and children from delivery to six months later. Birth 2022.

[28] Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020;367(6483):1260–3.

[29] Hsieh CL, Goldsmith JA, Schaub JM, DiVenere AM, Kuo HC, Javanmardi K, et al. Structure-based design of prefusion-stabilized SARS-CoV-2 spikes. Science 2020;369(6510):1501–5.

[30] Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020;21(3):335–7.

[31] Greenberger LM, Saltzman LA, Senefeld JW, Johnson PW, DeGennaro LJ, Nichols GL. Antibody response to SARS-CoV-2 vaccines in patients with hematologic malignancies. Cancer Cell 2021;39(8):1031–3.

[32] Perry C, Luttwak E, Balaban R, Shefer G, Morales MM, Aharon A, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with B-cell non-Hodgkin lymphoma. Blood Adv 2021;5(16):3053–61.

[33] Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic lymphocytic leukemia. Blood 2021;137(23):3165–73.

[34] Ghione P, Gu JJ, Attwood K, Torka P, Goel S, Sundaram S, et al. Impaired humoral responses to COVID-19 vaccination in patients with lymphoma receiving B-cell-directed therapies. Blood 2021;138(9):811–4.

[35] Shroff RT, Chalasani P, Wei R, Pennington D, Quirk G, Schoenle MV, et al. Immune responses to two and three doses of the BNT162b2 mRNA vaccine in adults with solid tumors. Nat Med 2021;27(11):2002–11.

[36] Rottenberg Y, Grinshpun A, Ben-Dov IZ, Oiknine Djian E, Wolf DG, Kadouri L. Assessment of Response to a Third Dose of the SARS-CoV-2 BNT162b2 mRNA vaccine in patients with solid tumors undergoing active treatment. JAMA Oncol 2022;8(2):300–1.

[37] Fenioux C, Teixeira L, Fourati S, Melica G, Lelievre JD, Gallien S, et al. SARS-CoV-2 antibody response to 2 or 3 doses of the BNT162b2 vaccine in patients treated with anticancer agents. JAMA Oncol 2022;8(4):612–7.

[38] Shapiro LC, Thakkar A, Campbell ST, Forest SK, Pradhan K, Gonzalez-Lugo JD, et al. Efficacy of booster doses in augmenting waning immune responses to COVID-19 vaccine in patients with cancer. Cancer Cell 2022;40(1):3–5.

[39] Munro APS, Janani L, Cornelius V, Aley PK, Babbage G, Baxter D, et al. Safety and immunogenicity of seven COVID-19 vaccines as a third dose (booster) following two doses of ChAdOx1 nCov-19 or BNT162b2 in the UK (COV-BOOST): a blinded, multicentre, randomised, controlled, phase 2 trial. Lancet 2021;398(10318):2258–76.

[40] Lim SH, Stuart B, Joseph-Pietras D, Johnson M, Campbell N, Kelly A, et al. Immune responses against SARS-CoV-2 variants after two and three doses of vaccine in B-cell malignancies: UK PROSECO study. Nat Cancer 2022;3(5):552–64.

[41] Thakkar A, Pradhan K, Duva B, Carreno JM, Sahu S, Thiruthuvanathan V, et al. Study of efficacy and longevity of immune response to third and fourth doses of COVID-19 vaccines in patients with cancer: A single arm clinical trial. Elife 2023;12.

[42] Lu Y, Yuan X, Wang M, He Z, Li H, Wang J, et al. Gut microbiota influence immunotherapy responses: mechanisms and therapeutic strategies. J Hematol Oncol 2022;15(1):47.

[43] Ng HY, Leung WK, Cheung KS. Association between gut microbiota and SARS-CoV-2 infection and vaccine immunogenicity. Microorganisms 2023;11(2).

[44] Araf Y, Akter F, Tang YD, Fatemi R, Parvez MSA, Zheng C, et al. Omicron variant of SARS-CoV-2: genomics, transmissibility, and responses to current COVID-19 vaccines. J Med Virol 2022;94(5):1825–32.

[45] Debie Y, Van Audenaerde JRM, Vandamme T, Croes L, Teuwen LA, Verbruggen L, et al. Humoral and cellular immune responses against SARS-CoV-2 after third dose BNT162b2 following double-dose vaccination with BNT162b2 versus ChAdOx1 in patients with cancer. Clin Cancer Res 2023;29(3):635–46.

[46] Muik A, Lui BG, Wallisch AK, Bacher M, Muhl J, Reinholz J, et al. Neutralization of SARS-CoV-2 Omicron by BNT162b2 mRNA vaccine-elicited human sera. Science 2022;375(6581):678–80.

[47] Davis-Gardner ME, Lai L, Wali B, Samaha H, Solis D, Lee M, et al. Neutralization against BA.2.75.2, BQ.1.1, and XBB from mRNA Bivalent Booster. N Engl J Med 2023;388(2):183–5.

[48] Tan AT, Linster M, Tan CW, Le Bert N, Chia WN, Kunasegaran K, et al. Early induction of functional SARS-CoV-2-specific T cells associates with rapid viral clearance and mild disease in COVID-19 patients. Cell Rep 2021;34(6):108728.

[49] Tarke A, Coelho CH, Zhang Z, Dan JM, Yu ED, Methot N, et al. SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from Alpha to Omicron. Cell 2022;185(5):847–59. e811.

[50] Oosting SF, van der Veldt AAM, GeurtsvanKessel CH, Fehrmann RSN, van Binnendijk RS, Dingemans AC, et al. mRNA-1273 COVID-19 vaccination in patients receiving chemotherapy, immunotherapy, or chemoimmunotherapy for solid tumours: a prospective, multicentre, non-inferiority trial. Lancet Oncol 2021;22(12):1681–91.