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Humoral Immune Response of SARS-CoV-2–Infected Patients with Cancer: Influencing Factors and Mechanisms

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Disclosures of potential conflicts of interest may be found at the end of this article.

ABSTRACT

Background. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–infected patients with cancer show worse outcomes compared with patients without cancer. The humoral immune response (HIR) of patients with cancer against SARS-CoV-2 is not well characterized. To better understand it, we conducted a serological study of hospitalized patients with cancer infected with SARS-CoV-2.

Materials and Methods. This was a unicentric, retrospective study enrolling adult patients with SARS-CoV-2 admitted to a central hospital from March 15 to June 17, 2020, whose serum samples were quantified for anti–SARS-CoV-2 receptor-binding domain or spike protein IgM, IgG, and IgA antibodies. The aims of the study were to assess the HIR to SARS-CoV-2; correlate it with different cancer types, stages, and treatments; clarify the interplay between the HIR and clinical outcomes of patients with cancer; and compare the HIR of SARS-CoV-2–infected patients with and without cancer.

Results. We included 72 SARS-CoV-2–positive subjects (19 with cancer, 53 controls). About 90% of controls revealed a robust serological response. Among patients with cancer, a strong response was verified in 57.9%, with 42.1% showing a persistently weak response. Treatment with chemotherapy within 14 days before positivity was the only factor statistically shown to be associated with persistently weak serological responses among patients with cancer. No significant differences in outcomes were observed between patients with strong and weak responses. All IgG, IgM, IgA, and total Ig antibody titers were significantly lower in patients with cancer compared with those without.

Conclusion. A significant portion of patients with cancer develop a proper HIR. Recent chemotherapy treatment may be associated with weak serological responses among patients with cancer. Patients with cancer have a weaker SARS-CoV-2 antibody response compared with those without cancer. *The Oncologist* 2021;26:e1619–e1632

Implications for Practice: These results place the spotlight on patients with cancer, particularly those actively treated with chemotherapy. These patients may potentially be more vulnerable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, so it is important to provide oncologists further theoretical support (with concrete examples and respective mechanistic correlations) for the decision of starting, maintaining, or stopping antineoplastic treatments (particularly chemotherapy) not only on noninfected but also on infected patients with cancer in accordance with cancer type, stage and prognosis, treatment agents, treatment setting, and SARS-CoV-2 infection risks.

INTRODUCTION

The new beta coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the causative agent of a cluster of pneumonias originally reported during December 2019 in Wuhan, China [1, 2]. The fast spread of this new virus around the world led to the declaration of the coronavirus disease 2019 (COVID-19) pandemic by the World Health Organization on March 11, 2020 [3]. As of December 2020, this virus has affected more than 200 countries, infecting 66,300,000 individuals and causing more than 1,500,000 deaths (https://coronavirus.jhu.edu).

Patients with cancer are more susceptible to SARS-CoV-2 infection and have worse associated outcomes, as measured by higher mortality, higher rates of intensive care unit (ICU) admission, higher chances of needing invasive mechanical ventilation (IMV), and higher rates of having at least one severe or critical symptom [4–11]. The increased susceptibility to SARS-CoV-2 infection of patients with cancer is mainly due to their immunosuppressive state, which is both a product of the intrinsic biological activity of cancer cells and a consequence of the use of different antineoplastic therapeutic agents and coexisting medical conditions [12, 13].

The interplay between cancer and the immune system is complex. The influence of tumor burden on systemic immunity is not well described. Allen et al. characterized the immune landscape over time in response to tumor development across different cancer tissues in mouse tumor models and demonstrated that tumor growth dynamically molds systemic immunity, which can be restored by the surgical removal of the tumor [14]. The immune remodeling during tumor growth comprises progressive changes in systemic T-cell composition, dysfunction of systemic T cells leading to an impairment of de novo T-cell responses, reduced antigen presentation capacity of dendritic cells, dysfunction of antigen-presenting cells, and subsequent weakening of immune responses to bacterial and viral infections [14]. The worst outcomes amid SARS-CoV-2–infected patients with cancer have been reported in cases of higher tumor burden, specifically, among cancer stages, metastatic malignancies, and also, among cancer types, hematologic malignancies and lung tumors [4].

Antineoplastic therapies, like cytotoxic agents, immune checkpoint inhibitors (ICIs), and radiation, also have the power of influencing immune responses [15–18]. There is evidence showing that in SARS-CoV-2–infected patients with cancer, those who received antitumor treatment within 14 days before COVID-19 diagnosis, including chemotherapy, radiotherapy, targeted therapy, and immunotherapy, had a higher risk of ICU admission, IMV need, and death [12]; other studies have shown that among patients with cancer who received antitumor treatment within 40 days before the onset of COVID-19 symptoms, those who received immunotherapy and underwent surgery had worse outcomes [4].

A growing body of evidence points to significant inflammation and cytokine-associated different organ injury as crucial contributors to the development of severe events in SARS-CoV-2–positive patients. Nonetheless, the development of cancer is usually associated with a blunted immune status, which is contradictory to the events believed to result in severe outcomes in patients with COVID-19 [5]. This conceptual divergence needs clarification with studies characterizing the immune response of SARS-CoV-2–positive patients with cancer, exploring the influence of different factors on its nature and correlating it with clinical outcomes.

Moreover, patients with cancer can have inherent or iatrogenic disruption of host immunity (having defects in B-cell, T-cell, and myeloid cell maturation by themselves and undergoing treatment with agents that affect individual immune cell subpopulations [19]). The study of their immune response subsequent to SARS-CoV-2 infection may help to clarify specific regulators of SARS-CoV-2 immune response.

To better understand the antiviral immune response in context of cancer, we conducted a serological study of hospitalized patients with cancer infected with SARS-CoV-2.

MATERIALS AND METHODS

Study Design

We extracted data from a retrospective cohort of oncological (hematologic or solid malignancy confirmed diagnosis) and nononcological adult patients with SARS-CoV-2 confirmed infection, defined by a positive reverse transcription polymerase chain reaction (RT-PCR) assay, who were admitted to Hospital de Santa Maria/Centro Hospitalar Universitário Lisboa Norte between March 15 and June 17, 2020, and whose serum samples were obtained during hospitalization for quantification of IgM, IgG, and IgA antibodies recognizing the SARS-CoV-2 receptor-binding domain (RBD) or the spike protein. The cancer cases were matched with SARS-CoV-2–positive non-cancer controls. Matching was performed in terms of age, sex, and time since symptom onset.

This study was approved by the Centro Académico de Medicina de Lisboa (CAML) ethics committee. Signed informed consent was waived.

Variables

Data were collected from the hospital electronic health record regarding date of first symptoms, date of hospital admission, presence of specific symptoms previously or during hospital stay (fever, dyspnea, dry cough, sputum production, sore throat, fatigue, myalgia, arthralgia, nausea, vomiting, diarrhea, headache, chest distress, anosmia, ageusia), laboratory test results upon admission and before clinical discharge/death, period of hospitalization (time between hospital admission date and clinical discharge/death date), ICU admission, ICU length of stay, need for IMV, IMV length, presence of acute respiratory distress syndrome (ARDS), severity of ARDS (moderate defined by a ratio of partial pressure of oxygen to fraction of inspired oxygen [P/F] of 100–200 and severe defined by a P/F < 100), presence of a P/F < 200, and time between hospital admission date and documentation of a P/F < 200

date. In parallel, cancer-specific data were also obtained, including cancer type, stage, metastases sites, and antineoplastic treatment details—therapeutic intent, number of previous lines of treatment (a new line of treatment was considered as any regimen started after discontinuation of a previous regimen administered with the same therapeutic intent, and as the unplanned addition or substitution of one or more drugs in an existing regimen), types of antineoplastic treatment, and dates of each antineoplastic treatment (patients were considered to have been recently treated if they had been exposed to any kind of regimen within 14 days before admission and previously treated if they had been exposed to any kind of regimen exclusively more than 14 days before admission).

Serological Assay

Serum samples were obtained upon admission (in the first 48 hours of hospitalization) and, when possible, 7 days after. Blood was collected by vein puncture, and two BD Vacutainer CPT (Becton Dickinson, San Diego, CA) tubes of blood and one serum tube were obtained per patient. For serum collection, tubes were centrifuged at 2200 rpm, 10 minutes at 4°C, and the upper 6×0.25 mL of serum was placed into six cryotubes. Samples were stored in a $-80°C$ ultralow freezer at the Instituto de Medicina Molecular (IMM) Biobank. Serum samples were obtained from the IMM Biobank COVID-19 collection. The COVID-19 collection and scientific use were approved by the CAML ethics committee.

Sera were analyzed as previously described in detail [20]. Serum samples were analyzed for anti–SARS-CoV-2 antibodies using SARS-CoV-2 RBD or spike protein, followed by titer determination on RBD. Flat bottom 96-well plates (Immulon 4 HBX; Thermo Fisher Scientific, Waltham, MA) were coated with 2 μg/mL recombinant protein in phosphate-buffered saline (PBS) at 4°C. Coated plates were washed with PBS + 0.05% Tween three times and blocked with 3% nonfat milk powder in PBS + 0.1% Tween for 1 hour at room temperature. Patient serum samples were diluted 1:50 in PBS + 0.1% Tween +1% nonfat milk powder, added (100 μl/well) and incubated for 1 hour at room temperature, and washed with PBS + 0.05% Tween three times. Hereafter, horseradish peroxidase–labeled anti-human total Ig, IgG, IgM, or IgA (Abcam, ab102420, ab97225, ab97205, ab97215) was diluted in PBS + 0.1% Tween and 1% nonfat milk powder (50 μl/well) (added for 1 hour at room temperature), washed with PBS + 0.05% Tween three times, and developed with TMB substrate solution (TMB Substrate Reagent Set, BD OptEIA, 555214; BD Biosciences, San Jose, CA), 100 μl/well, for 10 minutes. The reaction was stopped with 2 M sulfuric acid (50 μl/well), and optical density at 450 nm was measured via Infinite M200 (TECAN) plate reader (Tecan, Männedorf, Switzerland). Levels of anti-RBD IgM, IgG, IgA, and total Ig antibodies were quantified by twofold serial dilutions.

We considered an IgG titer of 200 as a cutoff value for the differentiation between weak and strong serological responses.

Aims of the Study

The primary outcome was the assessment of the humoral immune response to SARS-CoV-2. The secondary outcomes were the correlation between the humoral immune response of SARS-CoV-2–positive patients with cancer and different cancer types, stages, and treatments; the clarification of the interplay between humoral immune response of SARS-CoV-2–positive patients with cancer and clinical course and outcomes; and, finally, the comparison between humoral immune responses of SARS-CoV-2–positive patients with and without cancer.

Statistical Analysis

Patients' different characteristics were analyzed and reported using descriptive statistics. Categorical variables are expressed as proportions.

Statistical analysis was conducted using GraphPad Prism (version 8; GraphPad Software, La Jolla, CA) and STATA (version 16; StataCorp LLC, College Station, TX).

The association of persistently weak serological responses with different factors was analyzed using univariable logistic regression models. We compared groups using Fisher's exact test and Mann-Whitney U test for categorical and continuous variables, respectively. The tests were performed two-sided with a significance level of $\alpha = .05$.

RESULTS

The present study included 72 adult SARS-CoV-2–positive patients. Among these, 19 patients had a confirmed cancer diagnosis, 4 of which were hematologic and the remaining 15 different solid organ malignancies (Table 1). Fifty-three patients without a cancer diagnosis were matched by age, sex, and time since COVID-19 symptom onset (supplemental online Table 1).

Characteristics of Patients Without Cancer

The median age was 58.0 years, with a preponderance of female sex (60.0%), as shown in supplemental online Table 1. The great majority of these patients were symptomatic (92.0%), with cough (64.0%), and fever (62.0%) being the most frequent symptoms. Most patients had underlying conditions (54.7%), with hypertension (28.3%) and diabetes mellitus (17.0%) being the most frequent ones. Most patients were not under any medication with immunomodulating properties (92.5%).

Cancer-Specific Characteristics

Prostate cancer (21.1%) was the most frequent cancer type, followed by breast cancer and acute myeloid leukemia (AML; 15.8%) (Table 1).

Early stage (stage I or II) cancers were more frequent (52.6%) (regarding the AML cases, only the French-American-British classification was available). Three cancers were metastatic (15.8%), and lung metastases were referred in two cases (10.5%).

Seven patients were under active surveillance (36.8%), 11 were being actively treated (57.9%), and one had palliative radiotherapy planned for the week after admission

Table 1. Cancer-specific characteristics and systemic antineoplastic treatments

Patient	Cancer type	Cancer stage	Metastatic cancer	Sites of metastasis	Time MA	CT	CT agents	Last session within 14 days	RT	Dose	Last session within 14 days	ICI	ICI agents	Last session within 14 days	HT	HT agents	Last session within 14 days
1	Uterus	IV	Yes	Lung Ganglionic	2.5 months	No	—	—	No	—	—	No	—	—	No	—	—
2	Breast	I	No	—	—	Yes	PCTX	Yes	No	—	—	No	—	—	No	—	—
3	Prostate	I	No	—	—	No	—	—	Yes	M	No	No	—	—	No	—	—
4	NPharynx	IV	No	—	—	Yes	CPT	Yes	Yes	69.96 Gy	Yes	No	—	—	No	—	—
5	Breast	III	No	—	—	No	—	—	No	—	—	No	—	—	Yes	EXM	Yes
6	Lung	III	No	—	—	Yes	PMTD	No	Yes	54 Gy	No	No	—	—	No	—	—
7	Prostate	I	No	—	—	No	—	—	Yes	66 Gy	No	No	—	—	No	—	—
8	Rectum	IV	Yes	Brain	10 days	Yes	CPB OXP	Yes	Yes	M	No	No	—	—	No	—	—
9	Prostate	I	No	—	—	No	—	—	Yes	25 Gy	Yes	No	—	—	Yes	TPT BCLT	Yes
10	Breast	I	No	—	—	Yes	CYP 5-FU	No	Yes	60 Gy	No	No	—	—	Yes	TMF	Yes
11	Prostate	II	No	—	—	No	—	—	Yes	70 Gy	No	No	—	—	Yes	LPR	Yes
12	Kidney	I	No	—	—	No	—	—	No	—	—	No	—	—	No	—	—
13	CSarcoma	I	No	—	—	No	—	—	No	—	—	No	—	—	No	—	—
14	AML	M5	No	—	—	Yes	ARA-C	Yes	No	—	—	No	—	—	No	—	—
15	BCC	I	No	—	—	No	—	—	No	—	—	No	—	—	No	—	—
16	SDLBL	FLIPI I	No	—	—	Yes	R-CHOP	No	No	—	—	No	—	—	No	—	—
17	Rectum	IV	Yes	Lung Liver	12 months	Yes	CPB	Yes	Yes	M	No	No	—	—	No	—	—
18	AML	M7	No	—	—	Yes	ARA-C FLD	Yes	No	—	—	No	—	—	No	—	—
19	AML	M1	No	—	—	Yes	ARA-C SFB	Yes	No	—	—	No	—	—	No	—	—

Abbreviations: 5-FU, 5-fluorouracil; AML, acute myeloid leukemia; ARA-C, cytosine arabinoside; BCC, basal cell carcinoma; BCLT, bicalutamide; CPB, capecitabine; CPT, carboplatin; CSarcoma, chondrosarcoma; CT, chemotherapy; CYP, cyclophosphamide; EXM, exemestane; FLD, fludarabine; HT, hormone therapy; ICI, immune checkpoint inhibitor; LPR, leuprorelin; M, missing; NPharynx, nasopharynx; OXP, oxaliplatin; PCTX, paclitaxel; PMTD, pemetrexed; R-CHOP, rituximab, cyclophosphamide, doxorubicin hydrochloride, and prednisone; RT, radiotherapy; SDLBL, splenic diffuse large B-cell lymphoma; SFB, sorafenib; Time MA, time between documentation of metastasis and admission; TMF, Tamoxifen; TPT, triptorelin.

(5.3%) (Table 2). One patient was under neoadjuvant treatment (5.3%), four were under adjuvant treatment (21.1%), three were under induction treatment (15.8%), two were under definitive treatment (10.5%), and two were under palliative treatment or had it programmed (10.5%). One patient had been treated with more than one previous line of treatment (5.2%). Nine patients had undergone surgery previously (47.4%), none in the 14 days before positivity for SARS-CoV-2.

Three patients had been previously treated with chemotherapy (15.8%), and seven had their last chemotherapy session in the 14 days before positivity (36.8%). Seven patients had been previously treated with radiotherapy (36.8%), and two had their last radiotherapy session in the 14 days before positivity (10.5%). Four patients were under hormone therapy (21.1%); no patients were treated with ICIs or any other targeted therapy.

Symptom Characterization of Patients with Cancer

The great majority of patients with cancer were symptomatic (94.7%) as summarized in supplemental online Table 2, with 55.6% developing symptoms prior to admission. The median time, among patients who developed symptoms prior to admission, between onset of symptoms and hospital admission was 8.7 days. The most commonly presenting symptoms were fever and dyspnea (55.6%). Constitutional (fever [55.6%] and fatigue [38.9%]) and respiratory (dyspnea [55.6%], dry cough [44.4%], chest distress [27.8%], and sputum production [22.2%]) symptoms were the most frequent ones.

Laboratory Findings of Patients with Cancer

As listed in supplemental online Table 3, the most frequent laboratory findings upon admission were lymphopenia (lymphocyte count <1,000/mm^3) (68.4%) and value of C-reactive protein (CRP) >5 mg/dL (68.4%). Elevated values of lactate dehydrogenase (LDH) >250 U/L (52.6%) and of ferritin >250 ng/mL (47.4%) were also frequent. Before discharge/death, LDH >250 U/L (47.4%) and CRP >5 mg/dL (47.4%) were the most consistent findings.

Clinical Outcomes of Patients with Cancer

Among patients with cancer, two fatal events occurred (10.5%) (supplemental online Table 4). The median length of stay was 15.9 days. One patient was admitted to ICU (5.3%), no patients were subjected to IMV, two had documentation of ARDS (10.5%), and two had P/F < 200 (10.5%) with a median time between admission and P/F < 200 documentation of 1.5 days.

Serological Responses

Around 90% of patients without cancer showed a strong serological response (89% for spike protein, 91% for RBD) (supplemental online Table 1). Among these patients, the median time between symptom onset and first blood sample collection was 19.7 days, whereas the median time between RT-PCR positivity for SARS-CoV-2 and blood sample collection was 17.5 days. Eleven patients (20.8%) had other comorbid conditions (diabetes mellitus, hepatitis B virus infection, and human immunodeficiency virus

infection) that could potentially impair immune response, and four (7.5%) were under medication (prednisolone, methotrexate, and darunavir/cobicistat) with possible immune modulating effects.

Among patients with cancer, 57.9% displayed a strong serological response (Table 3; Fig. 1), whereas 42.1% showed a persistently weak serological response (Table 3; Fig. 2).

Within the group of patients with cancer who had a strong serological response, prostate (27.3%) and breast (18.2%) were the most frequent cancers. The majority had early stage (stage I or II) cancers (63.6%). Five patients were under active surveillance (45.5%), three were under adjuvant treatment (27.3%), two were under definitive treatment (18.2%), and one had palliative radiotherapy planned (9.0%). None of the patients was treated with more than one line of treatment. The majority of the patients had undergone surgery (54.5%), none within 14 days before positivity. Regarding chemotherapy treatment, 72.7% of these patients had not been treated with chemotherapy, whereas 18.2% had undergone chemotherapy previously and 9.1% had their last chemotherapy session within 14 days before positivity. More than half of these patients (54.5%) had been treated with radiotherapy, 18.2% had their last radiotherapy session within 14 days before positivity, and 36.4% were actively under hormone therapy. None was under ICI or any other targeted therapy. All of the patients within this group were symptomatic, 9.1% developed moderate ARDS, 9.1% had a P/F < 200, 9.1% were admitted to the ICU, 9.1 % died, and the median period of hospitalization in this group was 14.9 days (supplemental online Table 5).

Within the group of patients with cancer who showed a persistently weak serological response, the distribution between solid organ malignancies (50%) and hematologic malignancies (50%) was similar, with AML being the most frequent (37.5%) cancer type, followed by rectum cancer (25%). In patients with solid organ malignancies, an equal percentage of early (50%) and late (50%) stage cancers was reported. Half of the patients had rectum cancer (50%), 25% had breast cancer, 25% had prostate cancer, and 50% had documented metastases (brain—patient 8; lung and liver—patient 17). Two patients were under active surveillance (25.0%), one was under neoadjuvant treatment (12.5%), one was under adjuvant treatment (12.5%), three were under induction treatment (37.5%), and one was under palliative treatment (12.5%). One patient was treated with more than one line of treatment (12.5%) (patient 17). Only 37.5% of patients underwent surgery, none within 14 days before positivity.

The great majority (87.5%) of patients with cancer with a persistently weak serological response had been treated with chemotherapy. Most patients with a persistently weak serological response had their last chemotherapy session within 14 days before positivity (75%), with only 12.5% having had a chemotherapy session previously. Around 37.5% of patients within this group had been previously treated with radiotherapy. None was or had been under hormone, ICI, or any other targeted therapy.

The majority of patients within this group were symptomatic (87.5%), 12.5% developed severe ARDS, 12.5% had

Table 2. Antineoplastic treatment characterization

Patient	Cancer type	Cancer stage	Present therapeutic intent	Number of previous lines	NAdj treatment	Date	Surgery	Date	Adj treatment	Date	Palliative treatment	Date	Previous lines	Notes
1	Uterus	IV	Palliative	0	No	—	No	—	No	—	No	—	—	Palliative RT was intended to be started on the week after admission
2	Breast	I	Neoadjuvant (under PCTX)	0	ddAC PCTX	04/2020	No	—	No	—	No	—	—	—
3	Prostate	I	Active surveillance	0	No	—	Prostatectomy	05/2009	ERT	07/2009	No	—	—	—
4	NPharynx	IV	Definitive (under definitive CRT)	0	CIS 5-FU	02/2020	No	—	No	—	CPT + ERT (definitive CRT)	04/2020	—	Previous induction with CIS + 5-FU. Under definitive CRT when admitted
5	Breast	III	Adjuvant (under EXM)	0	No	—	Radical mastectomy	03/2019	TMF EXM	TMX (03/2019 03/2020) EXM (03/2020)	No	—	—	Previously treated with TMF, which was switched to EXM after 1 year as planned
6	Lung	III	Active surveillance	0	No	—	Superior left lobectomy	03/2014	PMTD ERT	04/2014 06/2014	No	—	—	—
7	Prostate	I	Active surveillance	0	No	—	Prostatectomy	10/2017	ERT	04/2018 05/2018	No	—	—	—
8	Rectum	IV	Adjuvant (under CPB + OXP)	0	CPB ERT	06–07/2019	Rectum anterior resection	08/2019	CPB OXP	10/2019 03/2020	No	—	—	Brain metastasis were detected 5 days before admission when the patient was under adjuvant treatment with CPB and OXP
9	Prostate	I	Definitive (under TPT + BCLT + definitive ERT)	0	No	—	No	—	No	—	No	—	—	—
10	Breast	I	Adjuvant (under TMF)	0	No	—	Quadrantectomy	09/2013	CYP 5-FU ERT TMF	10/2013 03/2014	No	—	—	Previously treated with CYP + 5-FU + ERT from 10/2013 to 03/2014. Since then, as planned, under TMF
11	Prostate	II	Adjuvant (under LPR)	0	No	—	Prostatectomy	07/2018	ERT LPR	07/2019 08/2019	No	—	—	—

(continued)

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Table 2. (continued)

Patient	Cancer type	Cancer stage	Present therapeutic intent	Number of previous lines	NAdj treatment	Date	Surgery	Date	Adj treatment	Date	Palliative treatment	Date	Previous lines	Notes
12	Kidney	I	Active surveillance	0	No	—	Radical left nephrectomy	08/2010	No	—	No	—	—	Previously treated with ERT from 07 to 08/2019. Under LPR since 08/2018
13	CSarcoma	I	Active surveillance	0	No	—	No	—	No	—	No	—	—	Recently diagnosed chondrosarcoma awaiting multidisciplinary decision
14	AML	M5	Induction (under ARA-C)	0	—	—	—	—	—	—	—	—	—	Under ARA-C when admitted
15	BCC	I	Active surveillance	0	No	—	No	—	No	—	No	—	—	—
16	SDLBL	FLIPI I	Active surveillance	0	No	—	No	—	No	—	No	—	—	Previously treated with R-CHOP in 2008. Under active surveillance since then
17	Rectum	IV	Palliative (Under CPB)	2	CT (M) ERT	01–03/2016	Rectum Anterior Resection	03/2016	FOLFIRI + CXM FOLFOX CPB	04/2016–03/2019 03–09/2019 05/2020	—	No	First adjuvant line with FOLFIRI +CXM with posterior progression. Second line with FOLFOX with posterior progression. Under CPB when admitted.	—
18	AML	M7	Induction (Under ARA-C and FLD)	0	No	—	No	—	No	—	No	—	—	Under ARA-C and FLD when admitted
19	AML	M1	Induction (Under ARA-C and SFB)	0	No	—	No	—	No	—	No	—	—	Under ARA-C and SFB when admitted

Abbreviations: 5-FU, 5-fluorouracil; Adj, adjuvant; AML, acute myeloid leukemia; ARA-C, cytosine arabinoside; BCC, basal cell carcinoma; BCLT, bicalutamide; CIS, cisplatin; CPB, capecitabine; CPT, carboplatin; CRT, chemoradiotherapy; CSarcoma, chondrosarcoma; CT, chemotherapy; CXM, cetuximab; CYP, cyclophosphamide; ddAC, dose-dense doxorubicin and cyclophosphamide; ERT, external radiotherapy; EXM, exemestane; FLD, fludarabine; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; LPR, leuprorelin; M, missing; NAdj, neoadjuvant; NPharynx, nasopharynx; OXP, oxaliplatin; PCTX, paclitaxel; PMTD, pemetrexed; R-CHOP, rituximab, cyclophosphamide, doxorubicin hydrochloride, and prednisone; RT, radiotherapy; SDLBL, splenic diffuse large B-cell lymphoma; SFB, sorafenib; TMF, tamoxifen; TPT, triptorelin.

Table 3. Immunoglobulin titers and strength of serological response of patients with cancer

Patient / Days after symptom onset at time of sample collection	Total Ig	IgM	IgG	IgA	Seroconversion	Grade of serological response
1 / AS	0	0	0	0	Negative	Weak
1 / D4	200	800	200	800	Positive	Strong
2 / AS	0	50	50	50	Negative	Weak
2 / AS +7	0	50	50	50	Negative	Weak
3 / D17	1,600	800	6,400	6,400	Positive	Strong
4 / D2	400	400	800	800	Positive	Strong
4 / D9	400	400	800	1,600	Positive	Strong
5 / D16	0	0	0	100	Negative	Weak
5 / D23	3,200	100	12,800	25,600	Positive	Strong
6 / D18	100	400	200	400	Positive	Strong
6 / D23	3,200	6,400	6,400	1,600	Positive	Strong
7 / D6	0	0	0	0	Negative	Weak
7 / D13	0	100	100	50	Negative	Weak
8 / AS	50	50	0	100	Negative	Weak
9 / D4	100	100	200	3,200	Positive	Strong
10 / D7	200	800	400	400	Positive	Strong
10 / D14	3,200	1,600	6,400	3,200	Positive	Strong
11 / D9	400	100	1,600	400	Positive	Strong
11 / D16	3,200	800	1,2800	1,600	Positive	Strong
12 / D23	400	400	800	400	Positive	Strong
13 / D2	400	400	400	1,600	Positive	Strong
14 / D37	0	0	0	0	Negative	Weak
15 / AS	400	100	100	3,200	Negative	Weak
15 / D4	1,600	400	800	12,800	Positive	Strong
16 / D3	100	200	100	800	Negative	Weak
17 / D3	0	0	0	100	Negative	Weak
18 / D9	0	0	0	0	Negative	Weak
19 / D1	0	0	0	0	Negative	Weak

Abbreviations: AS, asymptomatic at the time of blood sample collection; AS +7, patient who was asymptomatic at the time of first blood sample collection and who remained asymptomatic 7 days later when the second blood sample was collected; D, days after symptom onset when the blood sample collection took place.

a P/F < 200, none was admitted to the ICU, 12.5% died, and the median period of hospitalization in this group was 17.4 days (supplemental online Table 5).

Association of Persistently Weak Serological Responses and Different Factors Among Patients with Cancer

Patients with cancer who were treated with chemotherapy within the 14 days before admission had increased risk of displaying a persistently weak serological response (odds ratio, 30; 95% confidence interval, 2.22–405.98; $p = .011$) (Table 4). Having a metastatic or a late-stage disease was not associated with the risk of developing a weak serological response.

Comprehensive cancer characteristics, treatment factors, and outcome profile comparison between patients with cancer with strong and persistently weak serological responses are displayed in supplemental online Table 6.

Clinical Outcomes Differences Between Patients with Cancer with Strong and Persistently Weak Serological Responses

Regarding the strength of the serological response among patients with cancer, we observed no difference in mortality rate (12.5% vs. 9.1%, $p = .999$), development of ARDS (12.5% vs. 9.1%, $p = 1.000$), and acquiring a P/F < 200 (12.5% vs. 9.1%, $p = .999$) (supplemental online Table 5).

Antibody Titer Comparison Between Patients with and Without Cancer

Comparing antibody titers between patients with and without cancer, it is clear that IgG ($p < .001$), IgM ($p = .0042$), IgA ($p = .0237$), and total Ig ($p = .0016$) levels were all significantly lower in patients with cancer (Fig. 3A). It is also possible to see a trend toward a delayed serological response in patients with cancer (when comparing with
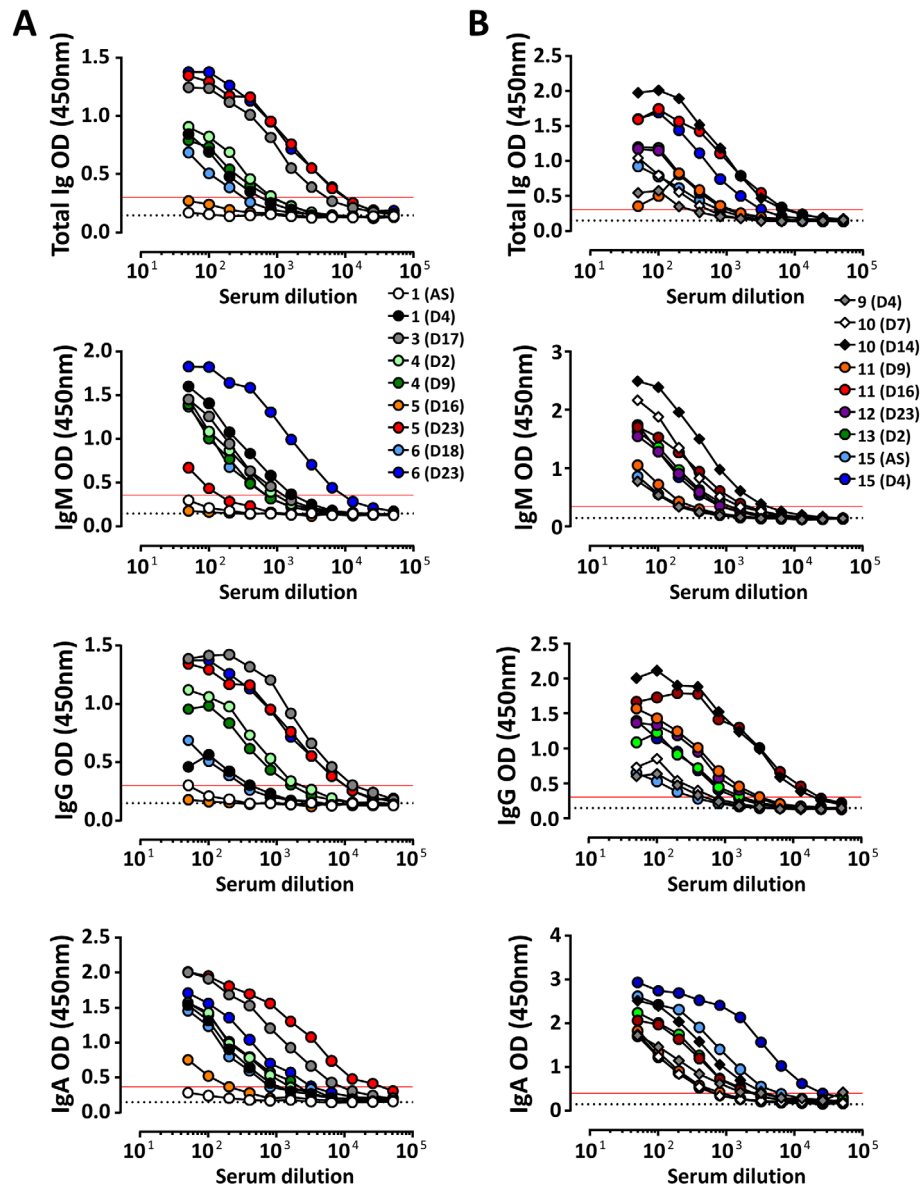
Figure 1. Immunoglobulin titer trend of patients with cancer with a strong serological response (panel A - patients 1,3,4,5 and 6; panel B - patients 9,10,11,12,13 and 15). Blood samples were obtained upon admission (in the first 48 hours of hospitalization) and, when possible, 7 days after, and sera were analyzed as described in the serological assay subsection (Materials and Methods). The corresponding day of symptoms, or asymptomatic (AS), of each time point of immunoglobulin titer determination is indicated between brackets; if the patient was asymptomatic when the sample was collected the abbreviation AS is placed between brackets. Abbreviations: AS, asymptomatic at the time of blood sample collection; D, days after symptom onset when the blood sample collection took place; OD, optical density.

patients without cancer) (Fig. 3B), even though it is difficult to rigorously ascertain this.

Discussion

Our study provides additional clarification on the nature of the immune response of SARS-CoV-2–infected patients with cancer, emphasizing the capability of a significant portion of them to build up an appropriate humoral response, identifying chemotherapeutic agents as the main modulators of antibody production in patients with cancer, and pointing

to significantly reduced levels of IgG, IgM, IgA, and total Ig in patients with cancer when compared with those without.

The immune response of SARS-CoV-2–infected patients with cancer is poorly characterized, with only two retrospective analysis reporting lower detection rates of antibodies in patients with cancer (compared with those without cancer) [21, 22] and one prospective study describing similar detection rates of antibodies in patients with and without cancer [23].

In the present study, seroconversion was documented in 57.9% of patients with cancer, a value that is higher than the value of 30% described by Solodky et al. [21] and lower
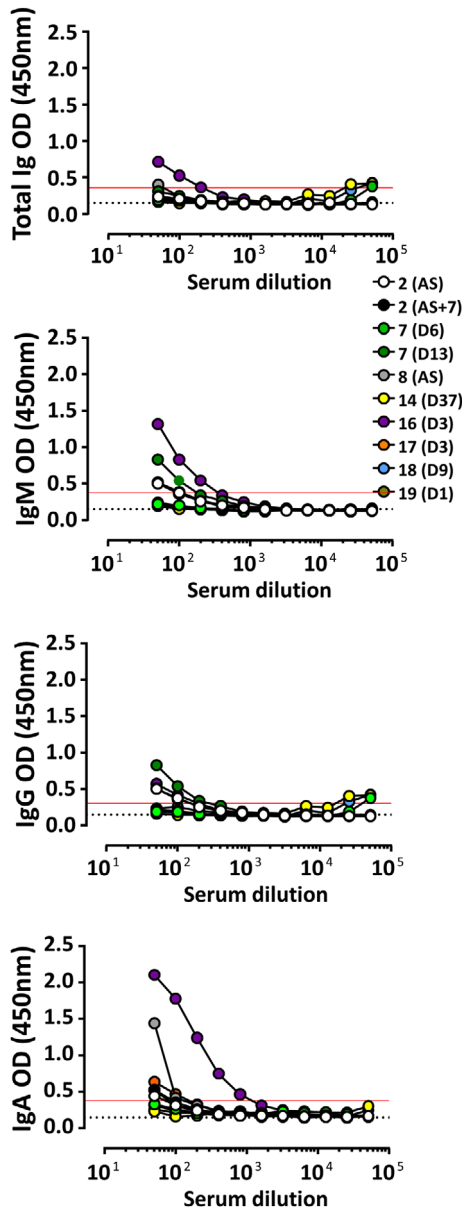
Figure 2. Immunoglobulin titer trend of patients with cancer with a persistently weak serological response. Blood samples were obtained upon admission (in the first 48 hours of hospitalization) and, when possible, seven days after and sera were analyzed as described in the serological assay subsection (Materials and Methods). The corresponding day of symptoms, or asymptomatic (AS), of each time point of immunoglobulin titer determination is indicated between brackets; if the patient remained asymptomatic when the second sample was collected the abbreviation AS + number of days after first sample collection is indicated.

Abbreviations: AS, asymptomatic at the time of blood sample collection; AS +7, patient who was asymptomatic at the time of first blood sample collection and who remained asymptomatic 7 days later when the second blood sample was collected; D, days after symptom onset when the blood sample collection took place; OD, optical density.

than the values of 72.5% reported by Liu et al. [22] and 85% mentioned by Marra et al. [23]. This disparity may be partly justified by the distinct study designs (particularly

regarding the size of the samples). Foremost, it stresses the need for further exploration of this topic.

A persistently weak serological response was documented in 42.1% of patients with cancer.

The most striking contributive factor for the development of a weak response among oncological patients was the treatment with chemotherapy within the 14 days before positivity for SARS-CoV-2.

Indeed, the great majority of patients with cancer with a persistently weak response have had a chemotherapy session in that period (patients 2, 8, 14, 17, 18, and 19). Chemotherapy agents may have played a role in the attenuation of the humoral immune responses.

For instance, paclitaxel has antimitotic and immunomodulatory (inhibiting B-cell differentiation and proliferation [24]) properties; capecitabine has antimetabolite (by inhibition of thymidylate synthase, and subsequent inhibition of DNA synthesis and repair [25, 26]) activity that may cause depletion of both diving and resting lymphocytes, including B cells [15]; oxaliplatin has alkylating-like activity and generates DNA lesions, inhibits DNA synthesis, and triggers immunologic reactions [27], directly affecting progenitor cells in the bone marrow (BM) and peripheral blood cells and leading to the development of type II hypersensitivity reactions [27–29], possibly impairing B-cell proliferation and activity (moreover, its combined administration with capecitabine boosts the antimetabolite effect of capecitabine since oxaliplatin slows down its catabolism [27]); cytosine arabinoside (ARA-C) can cause DNA damage in proliferating cells by its incorporation into elongating DNA strands with posterior blockage of replication forks and generation of DNA double-stranded breaks [30, 31]; the dramatic long-lasting effect of chemotherapy (the great majority of regimens include ARA-C) applied for the treatment of AML on B-cell compartment (increased frequencies of transitional B cells, a lack of affinity-matured, class-switched B cells and an antigen-inexperienced B-cell repertoire) is well documented, with inability to produce protective antibody titers several weeks or months after the last chemotherapy session [32]; fludarabine modulates the intracellular metabolism of ARA-C (enhances the formation of ARA-C triphosphate by inhibiting ribonucleotide reductase [33, 34]), potentiating its cytotoxic effect, and has itself a cytotoxic profile by repressing DNA polymerization and inhibiting DNA ligase and DNA primase [33], exerting an unfavorable effect on B-cell proliferation; and sorafenib has the ability to inhibit FMS-related tyrosine kinase-3 (a kinase that promotes recruitment of hematopoietic stem cells into cell cycle and, being expressed in early myeloid and lymphoid precursors, stimulates its differentiation and proliferation [35]), having deleterious effects on B-cell development.

Even though AML was the most frequent cancer type found among oncological patients with a weak serological response, and, regarding cases of solid organ malignancies within the same group, half of the patients had late-stage disease, no significant statistical association was found between having a hematologic, metastatic, or late-stage malignancy and the development of a weak response. This finding is interesting since in AML, within BM (where B cells essentially differentiate in a process dependent on an

Table 4. Odds ratio for persistently weak serological responses as a function of neoplastic disease characteristics and treatment regimens and timings of patients with cancer

Variables	Coef.	OR (95% CI)	*p* value
Metastatic disease	2.30	10 (0.58–171.20)	.112
Late-stage cancer (III and IV)	0.56	1.75 (0.17–17.69)	.635
Surgical procedure more than 14 days before positivity	−0.69	0.50 (0.08–3.21)	.465
Radiotherapy session more than 14 days before positivity	0.05	1.05 (0.16–6.92)	.960
Chemotherapy session more than 14 days before positivity	−0.44	0.64 (0.05–8.62)	.739
Chemotherapy session within 14 days before positivity	3.40	30 (2.22–405.98)	.011

A significant number of neoplastic disease characteristics and treatment regimens and timings were tested; only variables whose analysis provided valid results were included in this table.

Abbreviations: Coef., coefficient; CI, confidence interval; OR, odds ratio.

intact microenvironment [36]), the B-cell population is decreased when compared with what is seen in the BM of healthy subjects [37]. Concomitantly, as previously mentioned, tumor growth dynamically shapes the systemic immune landscape, with tumor burden driving distinct changes in peripheral immune organization [14]. The strength of these associations must be reassessed in larger causal studies.

Radiotherapy treatment was not associated with persistently weak serological responses. It is noteworthy that patients (patient 4 and patient 9) who had had a radiotherapy session in the 14 days before positivity had shown seroconversion. The effect of radiation of tumor cells derives from its direct action on DNA and indirect action on other intracellular atoms and molecules [38]. Radiation also has nontargeted effects in nonirradiated cells (like lymphocytes) that are in the vicinity of irradiated cells—bystander effect—and in nonirradiated tissues located outside the radiation field—abscopal effect [39]. Interestingly, the two patients who received radiotherapy in the 14 days before positivity had prostate and pharynx cancer, having received radiation beams directed to these organs. Receptor of angiotensin-converting enzyme 2 (ACE2) and transmembrane protease serine 2 are critical for SARS-CoV-2 cell entry and are highly expressed on prostate cancer cells [13], making these cells vulnerable to SARS-CoV-2 infection. It is possible that radiation triggered immunogenic cell death of the prostate cancer cells (potentially infected with SARS-CoV-2), leading to release of damage- or pathogen-associated molecular patterns [40] related to SARS-CoV-2 and allowing the development of both an early innate (based on monocytes and macrophages, that are more radioresistant than other immune cells [38], proliferation) and adaptive immune response. Evidence of increased antibody production in patients with head and neck cancer subjected to definitive radiation (with lysis of tumor cells and exposure of intracellular content to antigen-presenting cells) has been described [41]. It is possible that this effect might also be verified on surrounding noncancer cells, a fact of major importance, since the cells of the nasal mucosae and pharyngeal epithelium express ACE2 [42] and therefore may be infected by SARS-CoV-2. Nevertheless, it is crucial to underline that B-cell–mediated modulation due to conventional or high-dose fractionated radiation therapy is largely unknown [43].

Although no patients in the present study had been under therapy with ICIs, it is important to mention that ICIs may enhance humoral immunity by blocking the interaction between PD-1 and B-cell PD-L1, inducing increased clonality of circulating B cells, proliferation of plasmablasts, and notable immunoglobulin production [44]. PD-L1 inhibition may also enhance humoral immunity by modulating the function of T regulatory cells [44]. The maintenance of ICI programmed therapy in patients with cancer during the pandemic is still controversial, although ICIs may be pivotal for cancer eradication and also a game changer as they can restore these patients' T-cell anticancer (and possibly antiviral) immune response [45].

Although we did not observe significant differences in clinical outcomes between patients with cancer with weak and strong serological responses, these data should be interpreted with caution given the small size of our sample.

The lower antibody titer levels in patients with cancer, when compared with patients without cancer, are more likely attributable to the malignancy-related contributing factors for a systemic immunosuppressive state, as stated earlier.

Our study has several limitations. The small size of our cohort, the absence of access to data, specifically of patients with hematologic cancer, that has important prognostic value, the absence of patients under ICIs among the group treated with antineoplastic therapies, the absence of uniformity of the plasma samples collection method (there were patients whose first samples were not collected in the first 48 hours of hospitalization and patients whose second samples were not collected even though they still were hospitalized 7 days after the first sample collection), and the absence of collection of additional samples during hospital stay and after discharge are certainly some of them.

Conclusion

Our study suggests that a significant portion of SARS-CoV-2–infected patients with cancer are able to develop a
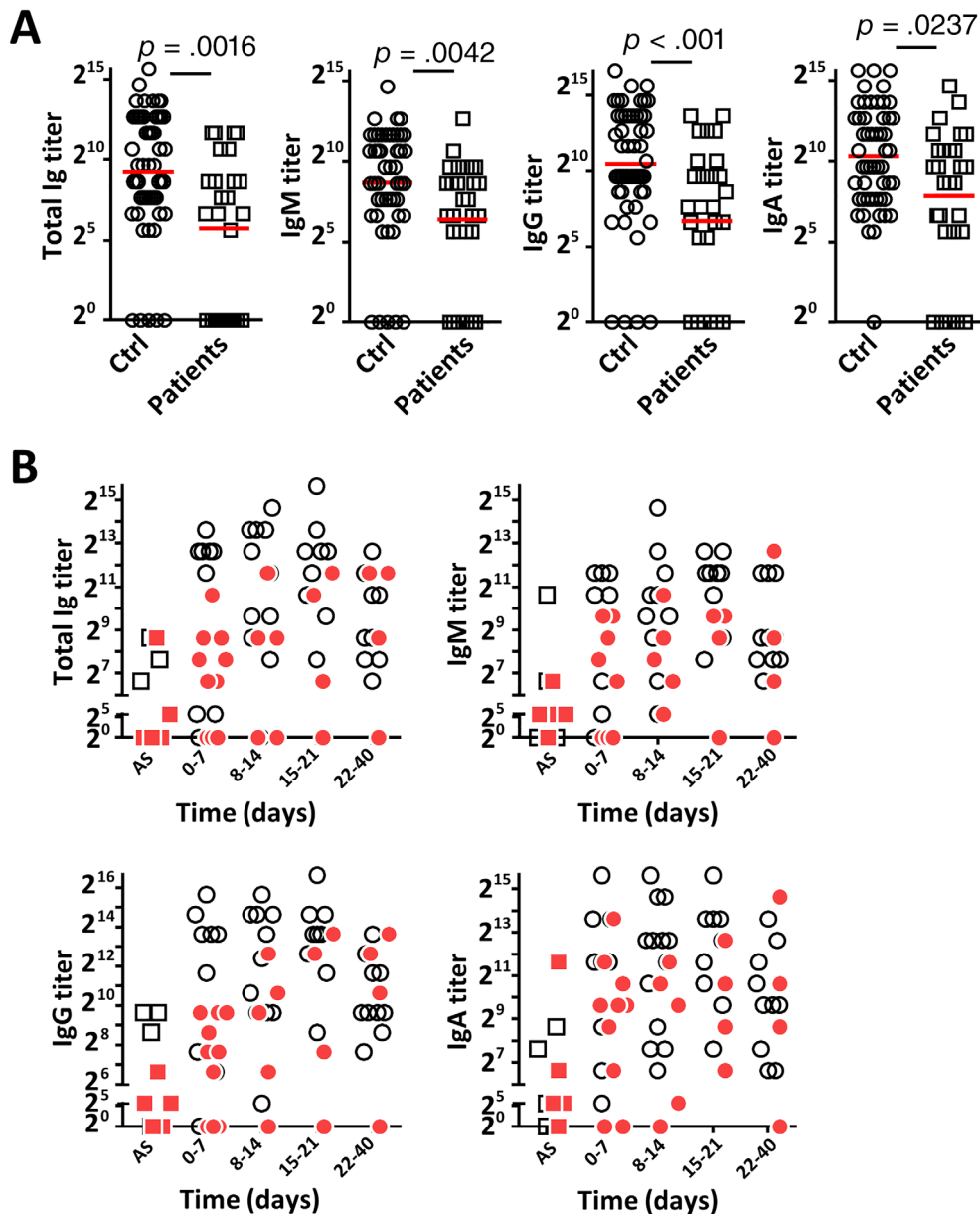
Figure 3. Comparison of immunoglobulin titers between patients with and without cancer. A Mann-Whitney *U* test (two-sided with a significance level of α = .05) was performed showing significantly lower levels of IgG ($p < .001$), IgM ($p = .0042$), IgA ($p = .0237$), and total Ig ($p = .0016$) in patients with cancer. **(A):** Dashed lines indicate blank values; continuous red lines indicate titer cutoffs. **(B):** Red symbols correspond to patients with cancer; non-colored symbols correspond to controls. Abbreviations: AS, asymptomatic at the time of blood sample collection; ctrl; control.

proper humoral immune response. Antibody production in SARS-CoV-2–infected patients with cancer seems to be negatively influenced by recent treatment with agents, in close relation with their antiproliferative and immunomodulant properties. The clinical outcomes of patients with cancer do not seem to differ according to the strength of their serological response. Patients with cancer, when compared with those without cancer, generally produce lower levels of antibodies in response to viral infection.

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