

Low Serological Prevalence of SARS-CoV-2 Antibodies in Cancer Patients at a German University Oncology Center

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Keywords

Coronavirus disease-19 seroprevalence · Severe acute respiratory syndrome coronavirus type 2 · Antibody testing · Epidemiology · German oncology center

Abstract

Background: Coronavirus disease 2019 (COVID-19) cases in Germany, as in most other places in Europe or worldwide, are still highly prevalent. Vaccination rates currently remain low, putting cancer patients at a continued risk of infection with SARS-CoV-2, while prevalence of SARS-CoV-2 antibodies among cancer patients in Germany remains essentially unknown. **Methods:** Between August 2020 and February 2021, patients admitted to our hospital were prospectively enrolled in our COVID-19 biobank. Collected sera were analyzed for SARS-CoV-2-IgM/IgG using Elecsys Anti-SARS-CoV-2 assay. **Results:** One hundred and ten patients with cancer were included in this study. With 71 (65%) patients, most had active cancer treatment, mainly chemotherapy (56%). The most frequent diagnosis was gastrointestinal cancer (54%) with pancreatic cancer being the most common cancer type (24%). Hematologic malignancies were present in 21 patients (17%). Among the cancer patients first diagnosed during the pandemic, the rate of palliative treatment situations tended to be higher (76% vs. 67%, $p = 0.17$). A history of SARS-CoV-2 infection was documented in 15 (14%) patients; however, SARS-CoV-2 antibodies were de-

tected in 10 (67%) patients only. Of the patients without a history of SARS-CoV-2 infection, none displayed SARS-CoV-2 antibodies. **Conclusion:** In the present single-center experience, a low serological prevalence of SARS-CoV-2 antibodies among cancer patients even after SARS-CoV-2 infection was found. The results support continued strict preventive measures as well as efforts toward faster vaccination, due to a low immunity level in the population. © 2021 S. Karger AG, Basel

Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) remains a worldwide public health concern [1, 2]. Previous studies suggested presence of a cancer diagnosis to be a risk factor for a more serious course of COVID-19 [3]. Especially patients with a pulmonary manifestation or a hemato-oncological disease appeared to be at a higher risk for severe COVID-19 disease [4, 5]. A study by Williamson et al. [6] lately found that an increased risk for COVID-19-related death is associated with a recent cancer diagnosis. However, the cohort of cancer patients is heterogeneous, and data on the rate of asymptomatic carriers among these patients are scarce. Additionally, risk of nosocomial transmission of COVID-19 is a serious concern for patients that rely on regular in- or outpatient visits. While rigorous infection

control measures help prevent nosocomial infection [7], data on their effectiveness for the above-mentioned collective in Germany are limited.

SARS-CoV-2 PCR testing following a nasopharyngeal swab is the current standard for detection of SARS-CoV-2 infection [8]. SARS-CoV-2 IgG and/or IgM antibody testing may complement PCR testing [9]. Only half of the patients show positive results of SARS-CoV-2 IgG and IgM antibodies within the first week, and seroconversion usually occurs 2 weeks after symptom onset [10–12]. Thus, antibody testing is not essential for the acute detection of SARS-CoV-2 infection, but may be utilized in detecting previous and potentially asymptomatic infections as well as subsequent immunity following a SARS-CoV-2 infection [13, 14].

Data concerning the prevalence of SARS-CoV-2 antibodies are ambiguous and highly dependent from the local pandemic status [15]. Thus, while an Austrian study reported a prevalence of 3.6% among oncological patients [16], prevalence among outpatient cancer patients in high prevalence areas like Madrid (Spain) was reported to be around 30% [17]. However, these results represent the status quo after the pandemic's "first wave" and do not respect the worldwide surge in SARS-CoV-2 infections in fall/winter of 2020/21 [18]. Therefore, the present study aims to report the current prevalence of SARS-CoV-2 antibodies among cancer patients in a German university hospital after 1 year of COVID-19 pandemic.

Methods

Patients in this study were prospectively enrolled into our COVID-19 biobanking study between August 2020 and February 2021. To be eligible for enrollment, patients had to have suspected or proven infection with SARS-CoV-2 and/or belonged to 1 or more specified risk groups, including cancer patients. This study incorporated a subanalysis of all registered patients with an oncological or hemato-oncological diagnosis, who presented at our department.

According to the study protocol of our COVID-19 biobank, patients had their blood drawn and medical data documented at time of enrollment and/or specified dates afterward during clinical routine. Written informed consent was obtained from all included patients. Blood serum samples were centrifuged and stored locally at -80°C . The study was approved by the Ethics Committee of the Medical Faculty, Ruhr-University Bochum (Approval No. 20-6953-bio).

All laboratory analyses were performed at the Central Laboratory of St. Josef-Hospital Bochum, Hospital of the Ruhr-University Bochum. SARS-CoV-2-IgM/IgG were analyzed using the Elecsys Anti-SARS-CoV-2 assay. This test utilizes a recombinant protein representing the nucleocapsid (N)-antigen for qualitative detection of high-affinity antibodies against SARS-CoV-2. Results are given as a numeric cutoff index (COI) with results ≥ 1.0 representing reactivity and positivity, respectively, for SARS-CoV-2 antibodies. This assay proved to be highly sensitive with a sensitivity up to 99.5% >14 days after positive PCR testing for SARS-CoV-2 infection. From day 0–6, it has a sensitivity of 60.2% and from day

7–13 85.3%. All tests were performed according to the manufacturer's manual.

Descriptive data are presented as n (%) or median (range of values). All own percentual results are rounded to the nearest full number. Data were analyzed using Fisher's exact test or Student's t test. Results were considered significant at $\alpha = 0.05$.

Results

Patient Characteristics

One hundred and ten patients with a total of 123 diagnosed cancers were included in this study. Baseline characteristics are presented in Table 1. Forty-six percent of the patients were female, and median age was 67.5 years. Most patients (65%) were undergoing active cancer treatment. The most frequent diagnosis was gastrointestinal cancer in general (54%) with pancreatic cancer being the most common cancer type (24%). Hemato-oncological diseases (leukemia, lymphoma, myeloma, and myelodysplastic syndrome) accounted for 17% and lung cancer for 8% of the cases. Median time since initial diagnosis was 3 months (0–192 months).

Most patients were treated with chemotherapy (62, 56%) and about a third (35, 32%) received immunotherapy (10, 9%) or targeted therapy (25, 23%). Only one of these patients was solely treated with immunotherapy, whereas the others got combinations with either chemotherapy (3), chemotherapy and radiation (5), or a targeted therapy (1). Among those on a targeted therapy, 18 patients received additional chemotherapy and 1 the forementioned immunotherapy. Nineteen (12%) patients were in follow-up, while 7 (4%) received best supportive care. Eighty-five (69%) treatments were palliative and 39 (32%) were curatively intended. Fifty-four percent of the patients received inpatient treatment or diagnostics. Twenty-four patients (22%) did not receive any active cancer treatment because they presented with the initial diagnosis of a malignant disease. The rate of palliative treatment situations among those first diagnosed during the pandemic was higher than in the whole population (76% vs. 67%), although not statistically significant ($p = 0.17$). Sixty-nine patients (63%) suffered from metastatic disease (if applicable) and 26 had pulmonary metastasis (24%).

SARS-CoV-2 Antibody Prevalence

Fifteen patients had a positive history of SARS-CoV-2 infection (14%, see Table 2). Positive results for SARS-CoV-2 antibodies were detected in 10 of these patients (66%), and the median cutoff index (COI) was 113.5. There was no statistically significant difference in COI between patients on antitumor treatment and pretreatment ($p = 0.33$). Five patients with a history of SARS-CoV-2 infection had a negative test for SARS-CoV-2 an-

Table 1. Patient characteristics

Median age, years	67.5 (18–88)
Sex, <i>n</i> (%)	
Female	51 (46)
Male	59 (54)
Cancer type, <i>n</i> (%)	
Colorectal	17 (14)
Pancreas	29 (24)
Esophageal	7 (6)
Gastric	1 (1)
Anal	3 (2)
Hepatobiliary	7 (6)
Lung	10 (8)
Lymphoma	7 (6)
Leukemia	8 (7)
Myeloma	5 (4)
Urogenital	5 (4)
Gynecological	1 (1)
Breast	7 (6)
Prostate	1 (1)
Others	15 (12)
Intent of treatment, <i>n</i> (%)	
Curative	39 (32)
Palliative	84 (68)
Outpatient	56 (46)
Inpatient	67 (54)
UICC I* (*if applicable)	8 (7)
II	8 (7)
III	14 (13)
IV	69 (63)
M1 (PUL)	26 (24)
Patients on active cancer treatment, <i>n</i> (%)	71 (65)
Chemotherapy	62 (56)
Radiation	8 (7)
Immunotherapy	10 (9)
Targeted therapy	25 (23)
Hormonal therapy	2 (2)
Patients without active treatment, <i>n</i> (%)	39 (36)
Best supportive care	7 (6)
Aftercare	8 (7)
Initial diagnosis/pretreatment	24 (22)
Median time since initial diagnosis, months	3 (0–192)

Data are presented as *n* (%) or median (range of values).

tibodies. None of them had a relevant comorbidity that would lead to an impaired immune response. Characteristics of all patients with a history of SARS-CoV-2 infection are presented in Table 3. None of the patients without a known history of SARS-CoV-2 infection were tested positive for SARS-CoV-2 antibodies, exhibiting a nonexistent serological prevalence of SARS-CoV-2 antibodies among the majority of our collective. SARS-CoV-2 infection of 8 (54%) patients occurred nosocomial.

It is worth noting that except one, those patients with a history of SARS-CoV-2 infection and negative serological testing had their blood drawn within up to 2 weeks after their first positive PCR testing (2–10 days), where antibody response is usually still low and the sensitivity

Table 2. Results of SARS-CoV-2 antigen testing

Patients with history of COVID-19	15	13.6%
Positive SARS-CoV-2 IgG/IgM	10	9%
Negative SARS-CoV-2 IgG/IgM	100	91%
Median SARS-CoV-2 COI	113.5	(17.9–187)

Data are presented as *n* (%) or median (range of values). COI, cutoff index.

of the test assay is limited [11, 19]. Due to various reasons, including early discharge because of mild or asymptomatic disease, no follow-up samples were possible. The remaining patient (#10) had mild symptoms and a positive PCR test in October 2020 before his diagnosis with pancreatic cancer. The possibility of a false-positive PCR test should be taken into consideration in this case.

None of our cancer patients who suffered from COVID-19 had a lethal course of the infection or required any kind of mechanical ventilation. Nonetheless, 4 patients (27%) had a severe course, requiring prolonged hospitalization and intensified treatment with oxygen. The minority of our patients with a nosocomial infection had a severe course (38%). Additionally, none of the patients reported signs of a long COVID syndrome, yet.

Discussion

COVID-19 cases in Germany, as in most other places in Europe or worldwide, are still highly prevalent [18], although incidence rates recently declined slowly in May 2021. Vaccination rates currently remain low, putting oncological patients at a continued risk of infection with SARS-CoV-2. Our results with a low serological prevalence of SARS-CoV-2 antibodies among cancer patients even after SARS-CoV-2 infection and no prevalence among those without a history of COVID-19 support continued strict preventive measures as well as efforts toward faster vaccination, due to low immunity in the population.

At the time of initiation of this study, serological prevalence among asymptomatic ambulatory patients in the North Rhine-Westphalia region in Germany was reported to be 1.2% [20]. A nearby tertiary hospital reported an incidence of 1.6% among health care workers [21]. This is consistent with our findings among asymptomatic patients, as well as with 2 studies from Austria that reported COVID-19 prevalence among cancer patients of 0.4% and 2.4%, respectively, and a French study describing a seroprevalence of SARS-CoV-2 antibodies of 1.7% in a cohort of oncological patients [16, 22, 23]. From the original pandemic epicenter in Wuhan, an incidence of 2.9% of asymptomatic infections among cancer patients was

Table 3. Characteristics of patients with a history of COVID-19

#	SARS-CoV-2 IgG/IgM	COI	Age, years	Origin of infection	Cancer type	Therapy	Severity	Days since first positive PCR test	Days since first symptoms
1	Negative		73	Nosocomial	Urogenital	Follow-up	Asymptomatic	2	n/a
2	Positive	21.3	62	Unknown	Lung	Carboplatin, pemtrexed, pembrolizumab, radiation	Severe	4	n/a
3	Negative		65	Nosocomial	Esophageal	Paclitaxel, ramucirumab	Severe	9	15
4	Positive	39.3	46	Nosocomial	Lymphoma	Pretreatment	Severe	>1 mo	n/a
5	Positive	92.3	78	Nosocomial	MDS	Pretreatment	Severe	24	24
6	Negative		71	Nosocomial	Pancreas	Pretreatment	Mild	10	n/a
7	Positive	132	71	Unknown	Rectum	FOLFOX, panitumumab	Mild	>1 mo	>1 mo
8	Positive	160	68	Community	Breast	Pretreatment	Mild	>1 mo	>1 mo
9	Positive	137	49	Nosocomial	Pancreas	FOLFIRINOX, experimental drug within phase 3 clinical trial	Mild	>1 mo	>1 mo
10	Negative		60	Community	Pancreas	Pretreatment	Mild	>1 mo	>1 mo
11	Positive	125	62	Nosocomial	Pancreas	FOLFIRINOX, experimental drug within phase 3 clinical trial	Mild	>1 mo	>1 mo
12	Positive	187	63	Nosocomial	Urogenital	FOLFIRINOX, experimental drug within phase 3 clinical trial	Mild	>1 mo	>1 mo
13	Negative		81	Community	Leukemia	Atezolizumab	Moderate	>1 mo	>1 mo
14	Positive	17.9	58	Community	Rectum	Follow-up	Mild	2	4
15	Positive	102	80	Unknown	Colon	Pretreatment	Mild	>1 mo	>1 mo

Data are presented as n. Severity is reported as defined by the NIH COVID-19 Treatment Guidelines [55]. COI, cutoff index.

reported [24]. A large, prospective Belgian study came to similar results [25]. However, the seroprevalence in our cohort (9%) is still higher than the forementioned numbers. This might be due to selection bias, as this is an analysis of a subgroup of patients included in our COVID-19 biobank. As such, patients with an active or known history of COVID-19 were preferably included. Nonetheless, these results are still lower than those in regions with severe outbreaks of COVID-19, like a study reporting a prevalence of 30% among cancer outpatients in Madrid [17]. The German Robert Koch-Institute estimated the seroprevalence of COVID-19 in Germany at 7.8% in March 2021.

The ambiguous results of antibody testing among patients with an active infection with SARS-CoV-2 highlight a demand for longitudinal testing to avoid false-negative results. A COI below median in these patients might be due to hematological disease (#4, #5), antigen test shortly after COVID-19 diagnosis (#2), long time since SARS-CoV-2 infection (#14), or immunosenescence (#15). This also underlines the fact that antibody tests should not be used for frontline detection of an active SARS-CoV-2 infection due to low sensitivity [26, 27]. PCR testing remains the gold standard in this case. However, regular measurement of antibody titers might also prove useful among cancer patients who have already received their COVID-19 vaccination to identify nonresponders or patients with declining antibody levels. Patients with an increased risk of low or no response to a SARS-CoV-2 vaccination naturally include such with a hematological disease or on certain types of treatment (e.g., anti-CD20 antibodies and CAR T-cell therapy) [28–32]. While durability of immune response in general remains high, Eliakim-Raz et al. [33] already reported a decline of antibody titers in cancer patients after 4 months. Seropositivity has been shown to be a useful correlate with protection from infection [34], although the degree of contribution of cellular immunity toward a durable immune response remains unclear and requires further evaluation [35].

None of our patients with COVID-19 had a lethal course, and severe courses were scarce even among those with a nosocomial infection. While previous data suggested a lower mortality among nosocomial-acquired SARS-CoV-2 infections in general [36], an increased mortality among cancer patients with hospital-acquired COVID-19 has been reported by Elkrief et al. [37].

Given the association of increased risk of mortality due to COVID-19 and a cancer diagnosis, especially for lung cancer and hematological malignancies [6, 38–40], as well as scarce resources in the context of the pandemic, various recommendations regarding the management of cancer care were issued last year [41–43]. Continuation of cancer treatment was generally recommended [5, 44–46]. Additionally, the COVID-19 pandemic led to a signifi-

cant decrease in cancer screenings [47–49]. A subsequent increase in cancer-related deaths due to delayed diagnosis is expected [50]. In this context, our data suggest that oncological diagnostics as well as treatments can and should safely be continued during a pandemic, when and while strict safety measures are in place.

As our data suggest a generally low immunity against SARS-CoV-2 among oncological patients in Germany, vaccination remains highly recommended [51, 52]. Especially as SARS-CoV-2 vaccine appears to be a scarce resource, the present results highlight the need for further studies to identify whether there are groups of patients that do not benefit from vaccination (e.g., patients with a B-cell depletion or severe combined B-/T-cell impairment or deficiencies) [53, 54].

Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of the Medical Faculty, Ruhr-University Bochum, Approval No. 20-6953-bio, and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion.

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Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

O.O. collected and analyzed the data and drafted and revised the manuscript. T. S.-G. was responsible for the laboratory analyses. All authors contributed to the conceptional design of the study. All authors read and approved the final manuscript.

Data Availability Statement

The data used and analyzed during this study are available from the corresponding author upon request.

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