Patterns of seroconversion for SARS-CoV2-IgG in patients with malignant disease and association with anti-cancer therapy

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Article

Keywords: SARS-CoV-2 IgG, cancer, seroconversion

Posted Date: December 29th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-127470/v1

Version of Record: A version of this preprint was published at Nature Cancer on March 22nd, 2021. See the published version at https://doi.org/10.1038/s43018-021-00191-y.

Abstract

Patients with cancer have been identified in several studies to be at high risk of developing severe COVID-19; however, rates of SARS-CoV-2 IgG seroconversion and its association with cancer types and anti-cancer therapy remain obscure. We conducted a retrospective cohort study in patients with cancer that underwent SARS-CoV-2 IgG testing. Two hundred and sixty-one cancer patients underwent SARS-CoV-2 IgG testing and demonstrated a high rate of seroconversion (92%). However, significantly lower seroconversion was observed in patients with hematologic malignancies (82%), patients that received anti-CD-20 antibody therapy (59%), CAR-T/cellular therapy (33%) and stem cell transplant (60%). Interestingly, all 17 patients that received immunotherapy, including 16 that received anti-PD-1/PD-L1 monoclonal antibodies, developed SARS-Cov-2 IgG antibodies (100% seroconversion). These data show differential rates of seroconversion in specific patient groups and bear importance for clinical monitoring and vaccination strategies that are being developed to mitigate the COVID-19 pandemic

Introduction

The coronavirus pandemic that started in December 2019 in Wuhan, China continues to send waves of COVID-19 disease throughout the world[1, 2]. Several observational studies have identified patients with cancer as being at higher risk of contracting the virus and higher rates of manifesting a severe form of COVID-19 disease [3-5]. We have previously reported a higher case fatality rate in patients with hematologic malignancies compared to solid malignancies in patients with cancer[6]. A pooled meta-analysis of 52 studies involving patients with cancer and COVID-19 reported a mortality rate of 25.6%[7]. While the mortality rates of patients with cancer are higher than the general population, it appears that about 70-80% of patients with cancer survive COVID-19 and therefore, it is important to understand the natural history of COVID-19 in this high-risk patient population. Of particular importance, is the fact that this patient population often receives immunosuppressive cancer-directed therapy which may impact their ability to mount a humoral immune response to the virus. It is therefore prudent to study the rate of formation of such antibodies to SARS-CoV-2 in patients with cancer who survived the illness to properly inform and develop treatment, surveillance and monitoring strategies in this vulnerable patient population.

Methods

Study Objectives

The primary objectives were to study the rate of seroconversion for SARS-CoV-2 IgG for patients with cancer and its association with type of malignancy and type of anti-cancer therapy. Additionally, we also aimed to study patterns in the natural history of COVID-19 and patients with cancer. Specifically, we studied the rate of symptomatic and asymptomatic infection in patients with cancer and COVID-19 and its association with type of malignancy and treatment received.

Study Design

This was an observational retrospective cohort study. We collected data on demographic variables (age, sex, cancer diagnosis), comorbidities (excluding cancer itself), SARS-CoV-2 IgG result, SARS-CoV-2 RT-PCR result, cancer treatment history, onset of symptoms of COVID-19, subsequent disease course, treatment setting, complications and outcomes. The data were extracted through a retrospective medical record review using Montefiore Medical Center's EPIC electronic health record system. All patient information was de-identified. The study was approved by the Institutional Review Board of Albert Einstein College of Medicine/MHS.

Definitions

Asymptomatic infection

Patients were classified as having an asymptomatic infection if a) there was clear documentation at the time of a positive SARS-CoV-2 test that patient had no symptoms b) if there was documentation at the time of a SARS-CoV-2 IgG test that patient had no symptoms or c) a test result of SARS-CoV-2 PCR or IgG was present in the patient's chart and documentation was unable to confirm that patient had any symptoms.

Active cancer

Patients were classified as having active cancer if they were actively being treated with either surgery, radiation or medical cancer therapy. Patient who were previously treated and on surveillance at time of SARS-CoV-2 testing or had a diagnosis that did not warrant therapy (example, monoclonal gammopathy of unknown significance) were classified as cancer that was not active.

Statistical Analysis

Associations between pairs of variables were assessed with standard statistical procedures. In the case of two-level categorical variables, a Fisher's exact test was used. For a two-level categorical and one numerical variable, we used a two-sample t-test. For a multi-level categorical and one numerical variable, an Anova. Pairings between a two-level and a multi-level categorical variable were summarized in a table where each row tests the association of a single multi-level category to the remaining, split by the two-level categories. All analyses were run in R software version 3.6.2.

Covid-19 test methods (assay)

1. SARS-CoV-2 RT-PCR

    - Real time RT-PCR for SARS-CoV-2 was performed on nasopharyngeal swabs collected in viral transport media using one of three testing platforms. These include the Hologic Panther Fusion, Abbott m2000 and Cepheid GenXpert SARS-COV-2 assays. All testing was performed in accordance with manufacturer or laboratory EUA instructions. Each assay is designed to

amplify two separate regions within the SARS-CoV-2 viral genome and one amplification control in a single multiplex reaction. The target regions of amplification differ by platform with Hologic amplifying 2 separate regions of ORF1a, Abbott amplifying RdRp and N genes and Cepheid amplifying portions of the N and E genes.

2. SARS-CoV-2 IgG test

- IgG testing was performed using the Abbott SARS-COV-2 IgG assay which has received emergency authorization form the FDA. The assay is a high throughput chemiluminescent microparticle immunoassay (CMIA) designed to detect IgG antibodies to the nucleocapsid of SARS-CoV-2. Recombinant SARS-CoV-2 antigen is incubated with a patient serum or plasma sample. The presence of patient IgG in a sample reacts with anti-human IgG acridinium-labeled conjugate to produce a chemiluminescent reaction measured as relative light units (RLU). The greater the IgG present the higher the RLU value. This relationship is reflected in the calculated signal-to-cutoff index (S/C) produced upon comparing patient RLU to the assay calibrator. Positive results for IgG antibodies is determined when the S/C is >=1.4

Results

Patient selection

We collected data for all cancer patients cared for at the Montefiore Health System (MHS) starting March 1, 2020 (first observed COVID-19 infection at MHS) until September 15, 2020. Figure 1 represents cohort selection for this study. A total of 4302 patients were identified, of which 3561 were excluded as they did not have a SARS-CoV-2 RT-PCR in our system leaving 741 patients. Of the 741 patients 461 were excluded as 9 patient records were duplicates and 452 did not have a SARS-CoV-2 IgG test. After excluding the aforementioned patients, 280 patients were identified of which, 15 were excluded as they did not have a confirmed diagnosis of malignancy. Three more patients were excluded as they had a negative SARS-CoV-2 PCR and a negative SARS-CoV-2 IgG and one patient was excluded as negative SARS-CoV-2 IgG test preceded a positive SARS-CoV-2 PCR. Finally, 261 patients with a confirmed diagnosis of malignancy and at least one SARS-CoV-2 IgG test performed during their care at MHS were included for analysis

Baseline Characteristics

A total of 261 patients with a confirmed diagnosis of malignancy were included in this study. The median age of the cohort was 64 years (range 20-90 years). Seventy-seven percent (201/261) had a diagnosis of solid malignancy and 23% (60/261) had hematologic malignancy. Fifty-one percent (134/261) of patients were female and 49% (127/261) were male. Forty-one percent (106/261) of patients were African-American, 37% (98/261) were Hispanic, 13% (33/261) were Caucasian, 3% (8/261) were Asian and 6% (16/261) belonged to other ethnicities.

Among the solid malignancy patients, 22% (58/261) had breast cancer, 17% (44/261) had gastrointestinal cancer, 9% (24/261) had thoracic and head and neck cancer, 2% (5/261) had central nervous system cancer, 1% (3/261) cancer of skin and musculoskeletal system, 22%(57/261) had genitourinary cancer and 4% (10/261) had gynecologic cancer. Among the hematologic malignancy patients, 10% (26/261) had lymphoid disorders, 5% (14/261) had myeloid disorders and 8% (20/261) had plasma cell disorders.

Patients were divided into three categories based on their comorbidities, 0-1, 2-3, and >3 comorbidities. Cancer diagnosis itself was not included as a comorbidity. The distribution of patients in the comorbidity categories was 26% (68/261), 30% (78/261) and 44% (115/261) respectively. Seventy percent (183/261) patients had active malignancy whereas 30% (78/261) did not. Overall, 92% patients (239/261) had a positive SARS-CoV-2 IgG test and 8% (22/261) patients had a negative SARS-CoV-2 IgG test.

Fifty six percent (147/261) had symptomatic SARS-CoV-2 infection while 44% (114/261) patients had an asymptomatic infection. Of the patients with solid malignancies, 53% (106/201) had symptoms, whereas 47% (95/201) did not. Among the patients with hematologic malignancies, 68% (41/60) had a symptomatic infection, whereas 32% (19/60) did not. There was a significant association seen between patients with hematologic malignancy and symptomatic infection compared to overall cohort (p=0.04)

The baseline characteristics and frequencies of asymptomatic infection of the cohort are summarized in Tables 1 and 2.

Cancer Treatment History

We collected data for all cancer treatment that was received by each patient. We classified the treatments into the following categories, chemotherapy, immunotherapy, tyrosine-kinase inhibitors, anti-HER therapy, antibody-drug conjugate, anti-CD20 antibody, anti-CD38 antibody, proteasome inhibitors, immunomodulator, BTK inhibitor, IDH1 inhibitor, BCL2 inhibitor, mTOR inhibitors, PARP inhibitor, TGF-β inhibitor, AR-targeted therapy, bispecific T-cell engager therapy, anti-EGFR monoclonal antibody, anti-VEGF monoclonal antibody therapy and history of stem cell transplant and CAR-T and cellular therapy. Each treatment was classified only once. CAR-T and cellular therapy included two patients who received CAR-T cell therapy and one patient who received sipuleucel-T for prostate cancer. The most common treatment modality was cytotoxic chemotherapy in 46% (119/261) patients followed by endocrine therapy in 27% (71/261) patients. The frequencies of all treatments have been summarized in Table 3.

Clinical course of patients with absent seroconversion

All 22 patients who had a negative SARS-CoV-2 IgG had a preceding SARS-CoV-2 PCR that was positive. Sixteen of 22 patients had symptomatic infection whereas 6 were asymptomatic. Fourteen patients needed hospitalization with 2 patients needing ICU level of care. Twelve patients were treated on the general medical floor. Four patients were quarantined at home of which 2 were asymptomatic. Details of course of infection for four asymptomatic patients is not available to us. Five other patients were

asymptomatic. Overall, in the seronegative cohort of patients, we observed high symptomatic infection rate, high rates of hospitalization with some needing ICU level of care.

Eleven of 22 patients had a hematologic malignancy and eleven had solid malignancy. In the seronegative group, 14 patients had chemotherapy, 7 had received anti-CD-20 antibody, 4 had received stem cell transplant, 3 had received a tyrosine kinase inhibitor, 2 patients each had received BiTE and CAR-T and one patient each had received immunomodulator, proteasome inhibitor, antibody-drug conjugate, PARP inhibitor and BTK inhibitor. These treatments are summarized in Table 4.

Association between seroconversion and cancer type

Given that patients with hematologic malignancies tend to be more immunosuppressed, and as several series have suggested, carry higher morbidity with COVID-19, we wanted to investigate differences in seroconversion in patients with hematologic versus solid malignancies. Among the 60 patients with hematologic malignancies, 49 manifested SARS-CoV-2 IgG positivity while 11 did not. In the solid malignancy cohort, 190 of the 201 patients manifested SARS-CoV-2 IgG positivity while 11 did not. (Fisher exact test OR 3.8, p value =0.005). As noted previously, a statistically significant association was seen between patients with hematologic malignancies and symptomatic COVID-19 infection. Hence, in our cohort, patients with hematologic malignancies had a higher frequency of manifesting symptomatic COVID-19 and significantly lesser likelihood of seroconversion.

Association between seroconversion and cancer-directed therapy

Furthermore, we aimed to investigate if seroconversion was associated with type of cancer therapy received by a patient. In our analysis, we observed a significant association between prior use of anti-CD20 antibody therapy and SARS-CoV-2 IgG. A total of seventeen patients had received anti-CD20 therapy, of which 7 patients had a negative SARS-CoV2 IgG. (Fisher exact test OR 0.09, p=0.00013). A similar finding was observed in the cohorts of patients who had a history of stem cell transplant or received prior chimeric antigen receptor T cellular (CAR-T cell) therapy. Ten patients had received a stem cell transplant in our cohort of which, 4 remained negative for SARS-CoV-2 IgG (Fisher exact test OR 0.1, p=0.0057). Three patients had received CAR-T/cellular therapy of which 2 were negative for SARS-CoV-2 IgG (Fisher exact OR 0.043, p=0.019). Two patients received bi-specific T-cell engager therapy and both stayed negative for SARS-CoV-2 IgG (OR 0, p=0.0068). All the above odds ratios compare with the entire cohort of cancer patients.

In contrast, we observed significantly higher seroconversion rates in patients who received immunotherapy or endocrine therapy. Seventeen patients received prior immunotherapy for their cancer and all seventeen of them manifested a positive SARS-CoV-2 antibody response (p=0.38). Of 71 patients who received endocrine therapy for their cancer, 70 manifested a positive SARS-CoV-2 IgG (Fisher exact test OR 8.6=0.01). The above odds ratios represent comparison with entire cohort of cancer patients. While the notable finding of 100% seroconversion amongst patients whom had received immunotherapy

was not statistically significant this is likely due to baseline high frequency of seroconversion for the entire patient population. These results have been summarized in Table 5.

The above results indicate that hematologic malignancies, anti-CD-20 antibody therapy, CAR-T cell therapy and stem cell transplant are predictors of reduced seroconversion in patients with SARS-CoV-2. On the other hand, endocrine therapy is a predictor of a positive antibody response in patients with SARS-CoV-2. While association between immunotherapy and seroconversion was not statistically significant, there is a strong trend toward antibody positivity with 100% seroconversion observed in our cohort.

Persistent SARS-CoV-2 PCR positivity

Eighteen percent (47/261) of patients underwent serial SARS-CoV-2 PCR testing per institutional policies. Shedding time was calculated as the time between first and last positive SARS-CoV-2 PCR for these patients and we observed that in patients with hematologic malignancies, mean shedding time was significantly higher than in patients with solid malignancies (61 days vs 33 days, p = 0.007, table 6). This observation again stresses the importance of close follow-up and monitoring of patients with hematologic malignancies and may be impactful in designing quarantine strategies for these patients after clinical improvement from acute COVID-19 illness.

Discussion

COVID-19 disease caused by SARS-CoV-2 has now affected more than 68 million humans worldwide, including 14.9 million patients and caused more than 283,000 deaths in the United States alone (Johns Hopkins Coronavirus Resource Center as of December 8, 2020). Older age and having multiple comorbid conditions have been identified as predictors of mortality in this disease[8]. Several observational cohorts have identified patients with cancer have a longer, protracted course with COVID-19 necessitating hospitalization and intensive care. Patients with hematologic malignancies have been reported in many series, including our own, to have higher mortality compared to solid malignancies[6, 9]. While it was hypothesized in many cohorts that a diagnosis of cancer predicts mortality, data on this particular aspect is still evolving as recent matched-studies report similar mortality in patients with cancer compared to age-matched controls without a diagnosis of cancer[10]. Nevertheless, concern about seroconversion in this patient population, which often receives immunosuppressive treatments, has been raised as mounting a humoral immunity is crucial in not only recovery from the infection, but to also establish and maintain herd immunity.

In an observational study from Spain involving 43 cancer patients, seroconversion was noted in 83% patients and was absent in 17% (6) patients. Four of the 6 patients were on immunosuppressive therapy, of which 2 received rituximab and 2 received cisplatin-based therapy[11].Studies comparing seroconversion in patients with cancer versus controls, report seroconversion rates ranging from 72.5% [12] (retrospective) to 87.9 % (prospective) [13].

To our knowledge, this is the first large cancer cohort reporting seroconversion rates for SARS-CoV-2. Ninety-two percent patients manifested a positive antibody response in our study. With the same SARS-CoV-2 IgG assay, seroconversion rates in the general population have been reported as 90-100%[14-16]. Indeed, in an unselected cohort of 1008 patients with SARS-CoV-2 PCR positivity in our health system who had subsequent antibody testing, seroconversion rate was 91%, nearly identical with the overall seroconversion rate of our overall cohort providing reassurance that most cancer patients are able to mount an antibody response to SARS-CoV-2 similar to the general population. .In our study, we observed highly significant and clinically meaningful differences in seroconversion rates in patients who had received anti-CD20 antibody therapy, CAR-T cell therapy and stem cell transplants. The biologic basis of this can be explained by the fact that anti-CD-20 antibody therapy, such as rituximab, does deplete native B-cells not only in lymphoid tissue but also in the bone marrow[17]. CAR-T cells directed toward CD-19 also deplete native B cells leading to hypogammaglobulinemia, often needing intravenous immunoglobulin replacement[18]. Patients who are recipients of stem cell transplantation are often subject to myeloablative doses of chemotherapy and total body irradiation which contributes to profound immunosuppression in these patients. Our study in conjunction with existing literature highlights that in patients with hematologic malignancies who have received the aforementioned therapies, need close follow-up and monitoring is necessary to document clearance of infection and seroconversion might not take place, possibly raising the concern of recurrent infections. As vaccines against SARS-CoV-2 are planned to be distributed on a large scale, monitoring SARS-CoV-2 IgG, immunoglobulin levels and lymphocyte subsets may be warranted in this patient population. Booster dosing may need to be studied in future trials and considered for this patient population should initial antibody responses be blunted.

In contrast, our study demonstrated high rates of seroconversion in patients who received immunotherapy and endocrine therapy for cancer treatment. Immunotherapy continuation, specifically raised concern for patients with COVID-19 as immune-mediated pneumonitis is a significant side effect and immunotherapy, specifically for patients who received it for lung cancer, was associated with increased risk of ICU admission in one series of 275 patients[19] . However, there is an ongoing debate on continuation of immunotherapy through the COVID-19 pandemic as two large cohorts, the UK Coronavirus Cancer Monitoring Project (UKCCMP) and the COVID-19 and Cancer Consortium (CCC 19) reported mortality was not affected in patients with cancer and COVID-19 by type of anti-cancer therapy, including immunotherapy[4, 20]. It is also hypothesized that immune-checkpoint inhibitors may induce immunocompetence in patients infected SARS-CoV-2 [21] based on prior data from human immunodeficiency virus and immunotherapy and ongoing trials with nivolumab in patients with sepsis[22, 23]. Our 100% seroconversion rate provides supportive evidence that immunotherapy is not deleterious and may support the hypothesis of restoring immunocompetence in patients with COVID-19.

Asymptomatic infection has been identified as a significant factor in the community spread of SARS-CoV-2, which in turn, continues to propagate the pandemic[24]. As discussed previously, patients with cancer are prone to more symptomatic and serious illness. However, in our cohort, we found a surprisingly high rate of asymptomatic infections in these patients. Many patients tested positive as part of routine screening prior to procedures, or during admission for unrelated acute problems. In some

cases, patients who had contact with family members who were symptomatic with COVID-19 remained asymptomatic themselves. In a recent study, seroconversion was noted in patients with cancer only if they had a symptomatic infection [25] In our cohort 41% patients who were asymptomatic had positive SARS-CoV-2 IgG (Table 7). This finding suggests that asymptomatic infection may be protective for patients with cancer and possibly contributes to herd immunity.

Another significant finding noted in our study is the persistent shedding of SARS-CoV-2 in patients with hematologic malignancies with a mean of 61 days despite clinical improvement in many cases. While we are unable to confirm if virus was live in each patient our findings appear concordant with a recent study that reported patients who had received stem cell transplant and CAR-T cell therapy, shed viable virus for up to 2 months from onset of symptoms[26].

Our study has a few limitations including retrospective design and small cohorts among patients who received therapies which predicted seroconversion. Another limitation of the study may be a slight overestimation of the asymptomatic infection rate given the manner asymptomatic infection needed to be defined in a retrospective design. Our cohort also represents standard of care practice wherein testing was done at provider discretion, however as PCR negativity was required for patients to be able to resume cancer management in our practices, testing was frequent in the majority of patients.

In summary, we present a large cohort of patients with malignancy who underwent SARS-CoV-2 IgG testing. In our cohort, statistically significant absent seroconversion was observed in patients with hematologic malignancies, patients receiving anti-CD-20 antibody therapy, CAR-T cell therapy and stem cell transplant. These findings may be impactful not only for clinical monitoring and surveillance, but also in designing and tailoring vaccination for this high-risk patient population. These findings should be investigated in larger, prospective studies for further validation but should provide immediate guidance for clinicians and researcher.

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Tables

Table 1		
Baseline Characteristics		
Total number of patients	261	
Median Age (Range)	64 years (20-90 years)	
Sex	**n**	**%**
Male	127	49%
Female	134	51%
Comorbidities	**n**	**%**
0-1	68	26%
2-3	78	30%
>3	115	44%
Ethnicity	**n**	**%**
African-American	106	41%
Hispanic	98	37%
Caucasian	33	13%
Asian	8	3%
Other	16	6%
Type of Cancer	**n**	**%**
Solid	201	77%
Breast cancer	58	22%
Gastrointestinal cancer	44	17%
Thoracic & Head and Neck Cancers	24	9%
Central Nervous System Cancers	5	2%
Genitourinary cancer	57	22%
Gynecologic cancer	10	4%
Skin/Musculoskeletal cancer	3	1%
Hematologic	60	23%
Lymphoid malignancy	26	10%
Myeloid malignancy	14	5%

Plasma cell malignancy	20	8%
SARS CoV-2 IgG	**n**	**%**
SARS CoV-2 IgG positive	239	92%
SARS CoV-2 IgG negative	22	8%
Active Cancer	**n**	**%**
Yes	183	70%
No	78	30%

Table 2			
Type of Malignancy	**Symptomatic**	**Asymptomatic**	**p value**
Hematologic malignancy	41 (68%)	19 (32%)	0.04
Solid malignancy	106 (53%)	95 (47%)	
Total (%)	147 (56%)	114 (44%)	

Table 3		
Cancer Directed Therapy	**261**	**%**
Chemotherapy	119	46%
Immunotherapy	17	7%
Anti-CD-20 antibody therapy	17	7%
Anti-CD-38 antibody therapy	2	1%
Immunomodulator	6	2%
Proteasome inhibitor	6	2%
Anti-VEGF antibody therapy	5	2%
Anti-EGFR antibody therapy	2	1%
Antibody-drug conjugate	2	1%
Anti-HER antibody	10	4%
Tyrosine-kinase inhibitor	13	5%
Bispecific T-cell engager	2	1%
Androgen receptor-targeted therapy	11	4%
PARP-inhibitor	1	0%
TGF-β therapy	1	0%
BTK inhibitor	3	1%
BCL2 inhibitor	1	0%
IDH1 inhibitor	1	0%
CDK 4/6 inhibitors	3	1%
mTOR inhibitor	1	0%
Endocrine therapy	71	27%
Stem cell transplant	10	4%
CAR-T/Cellular therapy	3	1%

Table 4	
Treatment summary in seronegative cohort	
Chemotherapy	14
Anti-CD-20 antibody	7
Stem Cell Transplant	4
Tyrosine-kinase inhibitor	3
CAR-T	2
BiTE	2
Immunomodulator	1
Proteasome inhibitor	1
Antibody-drug conjugate	1
PARP inhibitor	1
BTK Inhibitor	1
Endocrine therapy	1

Table 5				
Results				
Type of Cancer	**SARS-CoV-2-IgG positive**	**SARS-CoV-2 IgG negative**	**Odds Ratio**	**p value**
Hematologic malignancies	49	11	3.8	0.005
Solid malignancies	190	11		
Type of Cancer-directed therapy				
Anti-CD-20 antibody therapy	10	7	0.09	0.00013
Stem cell transplant	6	4	0.1	0.0057
BiTE	0	2	0	0.0068
CAR-T/cellular therapy	1	2	0.043	0.019
Endocrine therapy	70	1	8.6	0.01
Immunotherapy	17	0		0.38

Table 6			
Type of malignancy	**Hematologic malignancy**	**Solid malignancy**	**p value**
SARS-CoV-2 PCR shedding time (mean)	61 days	33 days	0.007

Table 7		
	SARS-CoV-2 IgG negative	**SARS-CoV-2 IgG positive**
Symptomatic n, %	16 (6%)	131 (50%)
Asymptomatic n, %	6 (2%)	108 (41%)

Figures

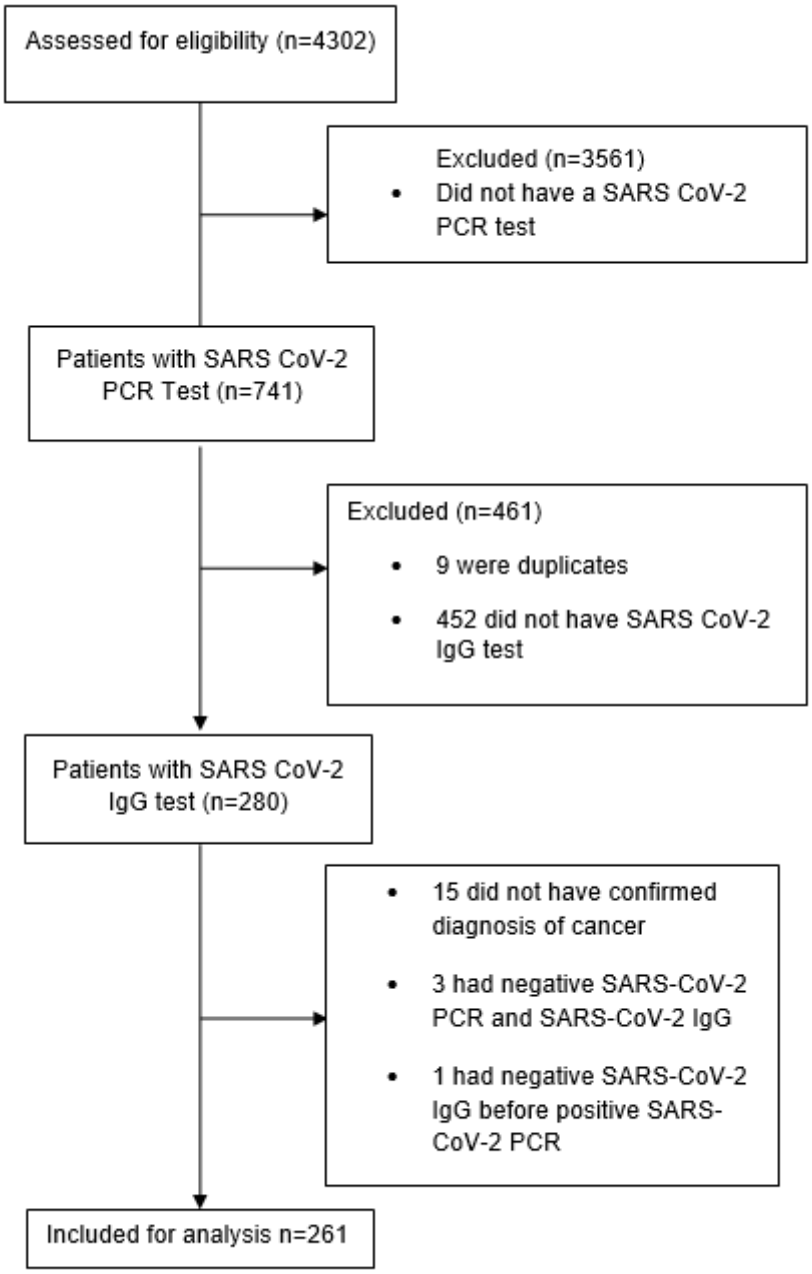

Figure 1

Consort Diagram