



ORIGINAL ARTICLE

Seroconversion in patients with cancer and oncology health care workers infected by SARS-CoV-2

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Background: Patients with cancer have high risk for severe complications and poor outcome to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related disease [coronavirus disease 2019 (COVID-19)]. Almost all subjects with COVID-19 develop anti-SARS-CoV-2 immunoglobulin G (IgG) within 3 weeks after infection. No data are available on the seroconversion rates of cancer patients and COVID-19.

Patients and methods: We conducted a multicenter, observational, prospective study that enrolled (i) patients and oncology health professionals with SARS-CoV-2 infection confirmed by real-time RT-PCR assays on nasal/pharyngeal swab specimens; (ii) patients and oncology health professionals with clinical or radiological suspicious of infection by SARS-CoV-2; and (iii) patients with cancer who are considered at high risk for infection and eligible for active therapy and/or major surgery. All enrolled subjects were tested with the 2019-nCoV IgG/IgM Rapid Test Cassette, which is a qualitative membrane-based immunoassay for the detection of IgG and IgM antibodies to SARS-CoV-2. The aim of the study was to evaluate anti-SARS-CoV-2 seroconversion rate in patients with cancer and oncology health care professionals with confirmed or clinically suspected COVID-19.

Results: From 30 March 2020 to 11 May 2020, 166 subjects were enrolled in the study. Among them, cancer patients and health workers were 61 (36.7%) and 105 (63.3%), respectively. Overall, 86 subjects (51.8%) had confirmed SARS-CoV-2 diagnosis by RT-PCR testing on nasopharyngeal swab specimen, and 60 (36.2%) had a clinical suspicious of COVID-19. Median time from symptom onset (for cases not confirmed by RT-PCR) or RT-PCR confirmation to serum antibody test was 17 days (interquartile range 26). In the population with confirmed RT-PCR, 83.8% of cases were IgG positive. No difference in IgG positivity was observed between cancer patients and health workers (87.9% versus 80.5%; P = 0.39).

Conclusions: Our data indicate that SARS-CoV-2-specific IgG antibody detection do not differ between cancer patients and healthy subjects.

Key words: cancer, COVID-19, SARS-CoV-2, coronavirus, antibody response, seroconversion

INTRODUCTION

Since its first reported case in late December of 2019, the outbreak of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—related disease [coronavirus

disease 2019 (COVID-19)] has rapidly spread around the world. As of 29 July 2020, >16 million confirmed cases and 650 000 deaths related to COVID-19 have been reported worldwide. Since the beginning of the epidemic, subjects with chronic diseases such as cancer have been shown to have an increased risk of severe complications and poor outcomes with COVID-19. Patients with cancer are more susceptible to infection than general population because of their systemic immunosuppressive state. Accordingly, some studies reported that patients with cancer have a higher risk of severe outcomes related to COVID-19, including death,

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intensive care unit admission, development of severe/critical symptoms, and utilization of invasive mechanical ventilation, compared with patients without cancer. ^{7,8} Several factors, including increased age, male sex, active or former smoking, poor performance status, and active cancer, have been associated with high 30-day mortality rate in patients with cancer and COVID-19. ⁹ Moreover, patients with cancer who underwent chemotherapy or surgery seem to be at high risk of clinically severe events, ^{7,8,10} although other studies did not confirm this observation. ^{9,11} By contrast, patients with cancer and COVID-19 can also experience a spectrum of asymptomatic or *paucisymptomatic* infections with subclinical courses, ¹² being managed at home and referred to the telemedicine systems or primary health care network. ¹³

RT-PCR has demonstrated to be a sensitive methodology and can effectively confirm SARS-CoV-2 infection. ¹⁴ Studies on SARS and Middle East respiratory syndrome (MERS) showed that virus-specific antibodies were detectable in 80%-100% of patients at 2 weeks after symptom onset. ¹⁵⁻¹⁷ Similarly, almost all patients with COVID-19 are tested as positive for anti-SARS-CoV-2 immunoglobulin G (IgG) within 19 days after symptom development. ¹⁸ Furthermore, combining viral RNA by RT-PCR and antibody detections significantly improves the sensitivity of pathogenic diagnosis for COVID-19. ¹⁹ However, very limited information on the antibody responses against SARS-CoV-2 in patients with cancer is currently available, with two retrospective analyses on small populations of cancer patients that reported lower detection rates of SARS-CoV-2 antibodies. ^{20,21}

This article reports the first analysis of a prospective observational study aimed to evaluate the antibody response in cancer patients and oncology health care workers presenting with confirmed or clinically suspected COVID-19.

MATERIAL AND METHODS

Study design

This was a multicenter, observational, prospective study conducted at five Italian Institutions. At time of this interim analysis, a total of 166 subjects were enrolled in this study from one general hospital and one comprehensive cancer center in the Lombardy region, which was the epicenter of the COVID-19 epidemic in Italy. 22,23 Study population included three different categories: (i) patients or health professionals already confirmed to be positive for SARS-CoV-2 by RT-PCR assays on nasal/pharyngeal swab specimens; (ii) patients or health professionals who are suspected of being infected with SARS-CoV-2, defined as a history of contact with confirmed cases before the onset of illness or subjects with at least one clinical manifestation or imaging characteristics of COVID-19 in the last week before accrual in the trial; (iii) patients with cancer who are considered at high risk for infection and eligible for active therapy and/or major surgery. Subjects diagnosed with bacterial or viral pneumonia in previous 3 months were excluded from the study. Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2020.10.473 graphically presents a flowchart with the enrolled subjects.

Ethics approval and consent to participate

Institutional Review Board and Ethics Committee approval was obtained from all participating institutions. The study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before any study-related procedure.

Detection of SARS-CoV-2 RNA by RT-PCR

Presence of SARS-CoV-2 on nasopharyngeal swab specimens was determined by real-time RT-PCR. GeneFinder COVID-19 Plus RealAmp Kit (EliTech, Milan, Italy) or Allplex 2019 n-CoV Assay (Seegene Inc, Seoul, South Korea) were used to detect SARS-CoV-2 by amplification of *RdRp* gene, *E* gene, and *N* gene according to the World Health Organization (WHO) recommendations and as previously described.²⁴

Overall, 836 specimens obtained from nasopharyngeal swab were tested by RT-PCR.

Detection of IgG and IgM against SARS-CoV-2

To evaluate the presence of IgG and IgM against SARS-CoV-2, all enrolled subjects were tested with the 2019-nCoV IgG/IgM Rapid Test Cassette (PRIMA Lab SA, Balerna, Switzerland), which is a qualitative membrane-based immunoassay for the detection of IgG and IgM antibodies to SARS-CoV-2 in whole blood, serum, or plasma specimen. For this purpose, capillary blood was obtained from each subject by fingerstick. After a droplet was formed, capillary blood was captured in a capillary tube until filled to approximately 20 μ l. The whole blood was then dispensed to the specimen well of the test cassette. Lastly, two drops of diluent were added to the specimen well of the test cassette

The 2019-nCoV IgG/IgM Rapid Test Cassette consists of two components, an IgG component and an IgM component. In the IgG component, anti-human IgG is coated in the IgG test line region. During testing, the specimen reacts with 2019-nCoV antigen-coated particles in the test cassette. The mixture then migrates upward on the membrane chromatographically by capillary action and reacts with the anti-human IgG in the IgG test line region if the specimen contains IgG antibodies to 2019-nCoV. Antihuman IgM is coated in the IgM test line region and if the specimen contains IgM antibodies to 2019-nCoV, the conjugate-specimen complex reacts with anti-human IgM. If the specimen contains 2019-nCoV IgG antibodies, a colored line appears in the IgG test line region as a result of this. Similarly, a colored line appears in the IgM test line region if the specimen contains 2019-nCoV IgM antibodies. If the specimen does not contain 2019-nCoV antibodies, no colored line appears in either of the test line regions, indicating a negative result. To serve as a procedural control, a colored line always appears in the control line region, indicating that the proper volume of specimen has been

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added and membrane wicking has occurred. Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2020. 10.473 displays the three possible results and interpretation of the rapid test. Overall, 166 (one for each enrolled subject) serological rapid tests were performed.

Aim of the study

The primary end point of the study was to evaluate anti-SARS-CoV-2 seroconversion rates in cancer patients and cancer health professionals with confirmed or clinically suspected COVID-19.

Statistical analyses

Descriptive statistics were used to analyze and report patients' characteristics. Clinical and biological variables were stratified into categories whenever reasonable, to preserve statistical power and feasibility of data collection. Continuous variables are expressed as the median [interquartile range (IQR)] and were compared with the Mann—Whitney U test. Categorical variables are expressed as numbers and proportions (%) and were compared by Fisher's exact test or chi-square test, as appropriate. All tests were performed two-sided at a significance level of $\alpha=0.05$. Statistical analyses were performed using SAS (version 9.4) and R Studio (version 1.1.463).

RESULTS

From 30 March 2020 to 11 May 2020, 166 subjects were enrolled in the study. Among them, cancer patients and health workers were 61 (36.7%) and 105 (63.3%), respectively. Median age was 46 years (IQR 21) and 118 (71.1%) were females. Health workers were younger than patients with cancer (median age 41 versus 62 years; P < 0.001). Patients with cancer were more frequently diagnosed with hypertension (26.2% versus 2.9%; P < 0.001) and type 2 diabetes (8.2% versus 1.0%; P = 0.01) as compared with health care workers. Conversely, health care workers were more frequently carriers of autoimmune diseases (12.4% versus 3.3%; P = 0.04), mainly chronic autoimmune thyroiditis and rheumatoid arthritis (data not shown). Patients' characteristics are reported in Table 1.

Among 61 cancer patients, breast carcinoma was the most frequent diagnosed tumor (55.7%), followed by lung cancer (13.1%). Thirty-three (54.1%) had metastatic disease. Forty-one (67.2%) patients were receiving active antitumoral therapies, that included systemic chemotherapy (14.8%), immunotherapy (8.2%), targeted therapy (9.8%), and hormonal therapy with or without targeted therapy (6.6% or 29.5%, respectively). Main characteristics of enrolled patients with cancer are described in supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.10.473.

Overall, 86 patients (51.8%) had confirmed SARS-CoV-2 diagnosis by prior RT-PCR testing on nasopharyngeal swab specimen, whereas 60 (36.2%) and 20 (12.0%) were clinically suspected or at high risk for SARS-CoV-2 infection, respectively. The majority (79.2%) were diagnosed with mild COVID-19 condition, according to the *Italian Society for*

Table 1. Patients' characteristics							
Characteristics	Health care workers (N = 105)	Cancer patients (N = 61)	Total (N = 166)	<i>P</i> -value			
Age, years, median (IQR)	41 (14)	62 (21)	46 (21)	<0.001			
Sex				0.629			
Female, n (%)	76 (72.4)	42 (68.9)	118 (71.1)				
Male, n (%) Seasonal flu vaccine	29 (27.6)	19 (31.1)	48 (28.9)	0.548			
No, n (%)	85 (81.0)	47 (77.0)	132 (79.5)	0.540			
Yes, n (%)	20 (19.0)	14 (23.0)	34 (20.5)				
Comorbidities							
Cardiovascular, n (%)	3 (2.9)	2 (3.3)	5 (3.0)	0.878			
Pulmonary, n (%)	0 (0.0)	2 (3.3)	2 (1.2)	0.062 0.353			
Asthma, n (%) Diabetes, n (%)	7 (6.7) 1 (1.0)	2 (3.3) 5 (8.2)	9 (5.4) 6 (3.6)	0.333			
Autoimmunity, n (%)	13 (12.4)	2 (3.3)	15 (9.0)	0.049			
Hypertension, n (%)	3 (2.9)	16 (26.2)	19 (11.4)	<0.001			
Concomitant drugs							
ARB, n (%)	1 (1.0)	3 (4.9)	4 (2.4)	0.108			
ACE inhibitor, n (%)	2 (1.9)	4 (6.6)	6 (3.6)	0.122			
Inclusion criteria Confirmed, n (%)	56 (53.3)	30 (49.2)	86 (51.8)	<0.001			
High risk, n (%)	0 (0.0)	20 (32.8)	20 (12.0)				
Suspected, n (%)	49 (46.7)	11 (18.0)	60 (36.2)				
Contact with infected	· · · · ·	, ,		<0.001			
individual							
NA, n	39	27	66				
No, n (%)	16 (15.2)	22 (36.1)	38 (22.9)				
Yes, n (%) Presentation	50 (47.6)	12 (19.7)	62 (37.3)	0.226			
NA, n	60	29	89	0.220			
Mild, n (%)	38 (84.4)	23 (71.9)	61 (79.2)				
Moderate, n (%)	5 (11.1)	4 (12.5)	9 (11.7)				
Severe, n (%)	2 (4.4)	5 (15.6)	7 (9.1)				
Setting of care	50	20	00	0.084			
NA <i>, n</i> Home <i>, n</i> (%)	59 45 (97.8)	29 27 (84.4)	88 72 (92.3)				
Hospital, n (%)	1 (2.2)	4 (12.5)	5 (6.4)				
ICU, n (%)	0 (0.0)	1 (3.1)	1 (1.3)				
Ventilation		. ,	. ,	0.273			
No, n (%)	103 (98.1)	58 (95.1)	161 (97.0)				
Yes, n (%)	2 (1.9)	3 (4.9)	5 (3.0)				
Complications None, n (%)	101 (96.2)	47 (77.0)	148 (89.2)	<0.001			
Pneumonitis, <i>n</i> (%)	4 (3.8)	14 (23.0)	18 (10.8)				
Outcome	4 (5.0)	14 (23.0)	10 (10.0)	0.229			
Ongoing, n (%)	4 (3.8)	5 (8.2)	9 (5.4)				
Recovered, n (%)	101 (96.2)	56 (91.8)	157 (94.6)				
lgG				0.030			
Negative, n (%)	68 (64.8)	29 (47.5)	97 (58.4)				
Positive, n (%)	37 (35.2)	32 (52.5)	69 (41.6)	0.003			
IgM Negative, n (%)	103 (98.1)	60 (98.4)	163 (98.2)	0.902			
Positive, n (%)	2 (1.9)	1 (1.6)	3 (1.8)				
RT-PCR testing	\ ,	` "-/	- \=/	<0.001			
No, n (%)	21 (20.0)	0 (0.0)	21 (12.7)				
Yes, n (%)	84 (80.0)	61 (100.0)	145 (87.3)				
RT-PCR result	24		24	0.529			
NA, n	21	0	21				
Negative, n (%)	43 (51.2) 41 (48.8)	28 (45.9) 33 (54.1)	71 (49.0) 74 (51.0)				
Positive, n (%)	41 (40.0)	JJ (J4.1)	/4 (31.0)				

Bold text indicates a statistically significant difference with a P value less than 0.05. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; ICU, intensive care unit; IgG, immunoglobulin G; IgM, immunoglobulin M; IQR, interquartile range; NA, not applicable.

Anesthesia, Analgesia, Resuscitation and Intensive Care (SIAARTI) clinical classification, whereas 11.7% and 9.1% were diagnosed with moderate and severe COVID-19 condition, respectively.

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Table 2. IgM and IgG seroconversion in the overall population, cancer patients, and health care workers							
	RT-PCR- negative (N = 71)	•	Total (<i>N</i> = 145)	<i>P</i> -value			
Overall							
IgG				<0.001			
Negative, n (%)	65 (91.5)	12 (16.2)	77 (53.1)				
Positive, n (%)	6 (8.5)	62 (83.8)	68 (46.9)				
IgM				0.535			
Negative, n (%)	69 (97.2)	73 (98.6)	142 (97.9)				
Positive, n (%)	2 (2.8)	1 (1.4)	3 (2.1)				
Cancer patients							
IgG							
Negative, n (%)	25 (89)	4 (12)	29 (20)	<0.001			
Positive, n (%)	3 (11)	29 (88)	32 (22)				
Health workers							
IgG							
Negative, n (%)	40 (93)	8 (20)	48 (33)	<0.001			
Positive, n (%)	3 (7)	33 (80)	36 (25)				

Bold text indicates a statistically significant difference with a P value less than 0.05. IgG, immunoglobulin G; IgM, immunoglobulin M.

The median time from symptom onset (for cases not confirmed by RT-PCR) or RT-PCR confirmation to serum antibody test was 17 days (IQR 26), whereas the median time to symptom resolution or viral RT-PCR negativization was 22 days (IQR 33). Of note, nine subjects (5.4%) still had RNA viral detection by RT-PCR on swab specimen at time of this analysis.

Detection of IgG against SARS-CoV-2 in subjects with positive RT-PCR

In the overall population, 69 (41.6%) and 3 (1.8%) participants were IgG and IgM positive, respectively. Considering the population with confirmation by RT-PCR, 62 (83.8%) was IgG positive (Table 2). No difference in terms of IgG positivity was observed between cancer patients and health workers (87.9% versus 80.5%; P=0.39; Figure 1). Furthermore, no differences were observed in time from SARS-CoV-2 diagnosis to IgG detection between cancer

Table 3. Median time to IgG positivization						
	Median (IQR)	Q1	Q3	<i>P</i> -value		
Category						
Health care workers	23.0 (13.0)	17	29	0.208		
Patients	28.0 (19.2)	16	35			
Sex						
Female	25.0 (16.5)	16	34	0.761		
Male	27.0 (17.7)	16	34			

IQR, interquartile range; Q1, first quartile; Q3, third quartile.

patients and health workers (23.0 versus 28.0 days; P=0.21; Table 3; Figures 2 and 3). Age, sex, comorbidities, and symptom intensity did not significantly influence rate and time of IgG antibody response.

DISCUSSION

According to the European Commission recommendations, 25 timely and accurate SARS-CoV-2 laboratory testing is an essential part of the management of COVID-19 for slowing down the pandemic, supporting decisions on infection control strategies and patient management at health care facilities, and detecting asymptomatic cases that could spread the virus further if not isolated.

Rapid tests are nonautomated procedures and have been designed to give a fast result. For COVID-19, rapid tests may take $\sim\!10\text{-}15$ min until giving a result compared with $\sim\!4$ h for molecular tests. 26 These rapid tests are relatively simple to perform and interpret and therefore require limited test operator training. They may be intended either for use in hospital for particular situations or in other social needs, allowing rapid screening of symptomatic and asymptomatic SARS-CoV-2 carriers.

Our findings suggest that patients with cancer infected with SARS-CoV-2 tend to have an antibody response comparable with healthy subjects, who in our population were represented by health care workers. Understanding the duration of potential infectiousness and the time to IgG antibody response are critical to the containment of

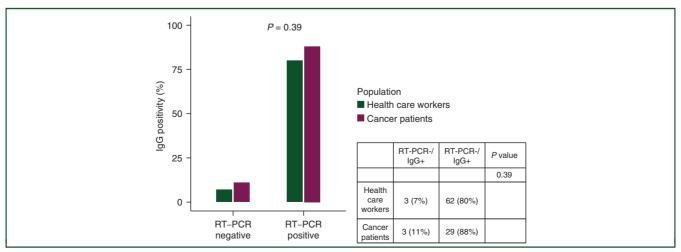


Figure 1. Comparison of immunoglobulin G positivity rate between health care workers and cancer patients according to the RT-PCR test result for SARS-CoV-2. P value refers to Fisher's exact test.

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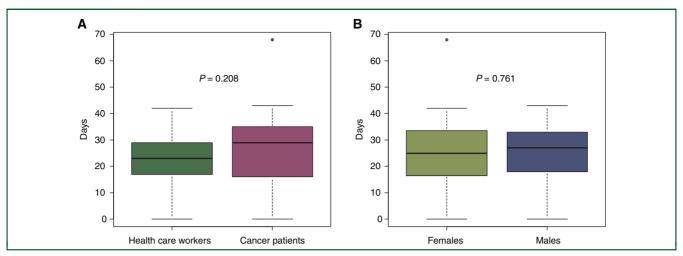


Figure 2. Comparison between time to immunoglobulin G seroconversion and (A) participant category (health care workers versus cancer patients) and (B) sex (female versus male).

On each box, the central mark is the median, the edges of the box are the 25th and 75th percentiles, the whiskers extend to the most extreme data points not considered outliers, and outliers are plotted individually. P value refers to the Mann—Whitney U test.

SARS-CoV-2 spread, especially in cancer patients and health care workers who are in constant exposure to high-risk populations. Moreover, monitoring previously infected subjects is essential to optimize the adequate personal protective equipment, the clinical management and the administration of oncological treatments.

Patients with cancer are at a higher risk of developing infections for several factors that include advanced age, underlying immunosuppressive status, and treatment-related factors such as chemotherapy, radiation, and surgical procedures. Accordingly, several works reported that patients with cancer have a higher risk of severe outcomes related to COVID-19. 7-11

In contrast to prior literature, ^{20,21} our experience showed that >85% of the cancer patients who had laboratory-documented SARS-CoV-2 infection or high clinical suspicious developed IgG antibodies using our rapid assay. Notably, no differences in terms of antibody formation and time to seroconversion were observed in cancer patients as

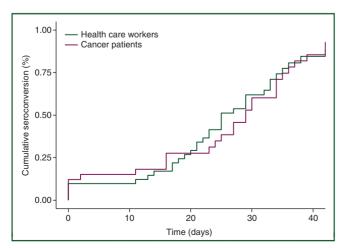


Figure 3. Cumulative incidence of seroconversion of immunoglobulin G antibodies against severe acute respiratory syndrome coronavirus 2 among coronavirus disease 2019 health care workers and cancer patients.

compared with health care workers. Given that cytotoxic agents are able to dampen immune response and interfere with antibody formation, 28 it could be expected that patients on chemotherapy have lower rates of antibody positivity. 20 Of note, $>\!60\%$ of our patients were receiving active treatments, but only a minority ($\sim\!10\%$) chemotherapy. Accordingly, such association needs to be confirmed in larger cohorts of patients with cancer and COVID-19.

Additionally, our findings suggest that IgG antibodies develop over a median period of 17 days from symptom onset or RT-PCR confirmation. This suggests that the ideal time frame for antibody testing is at least two weeks after symptom onset and no >3 or 4 weeks after symptom resolution or RT-PCR negativization. As reported by Long et al., 18 antibody testing should be performed as early as possible, because ~12% of the patients had already plateaued in IgG titer within 7 days of symptom onset. For patients who were not sampled during the ideal window or are tested at later stages, repeated serological tests would be needed to confirm an antibody response against SARS-CoV-2 infection. Comparable data were recently reported in a preprint paper summarizing the results of a study conducted in the New York region (United States).²⁹ Moreover, considering that many infected patients remain asymptomatic and fully capable of transmitting SARS-CoV-2, 30,31 combining antibody testing and RT-PCR on swab specimen can potentially increase COVID-19 diagnosis.

Although scant information is available on the immunity conferred by IgG and its duration, previous experiences in other viral infections, such as SARS and MERS, suggest that IgG may confer some level of immunity^{32,33}; however, it seems to wane over the time. Similar data have been reported for other coronaviruses where immunity can confer limited protection.³⁴ In order to study the duration of IgG antibody response to SARS-CoV-2, we planned to prospectively follow our patient population and retest for IgG by both quantitative and qualitative assays after 3 and 6

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months in order to measure time and level of immunization. Moreover, blood samples from each enrolled subject will be analyzed to evaluate quantitative IgG and IgM levels in the peripheral blood. At time of this analysis, data on antibody titer were available only for 16.9% of the overall population (data not shown).

Among subjects for whom infection was not confirmed by RT-PCR, but were considered as clinically suspected or high risk, including those with symptoms consistent with COVID-19, highly suggestive radiological imaging results, or close contact with patients with confirmed SARS-CoV-2 infection, we found that only 8.8% of this population had IgG antibodies. This finding suggests that a majority of participants suspected for COVID-19 actually were not infected with SARS-CoV-2. In addition, recent evidence suggests weaker immune responses and a more rapid reduction in the IgG titer for asymptomatic individuals infected by SARS-CoV-2 as compared with symptomatic cases.³⁵ By contrast, the low rates of IgG positivity in subjects without a confirmed diagnosis of SARS-CoV-2 infection by RT-PCR may be related to a false-negative rate of our assay or insufficient time for participants to mount an IgG antibody response detectable by rapid test. This stresses the importance of harmonizing and validating proper methodologies for SARS-CoV-2 detection to improve diagnosis and reduce false-negative rates.

Notably, nine subjects (5.4%) remained RT-PCR positive despite full resolution of symptoms and IgG seroconversion. This had relevant implications regarding the real duration of viral transmission. Although other viral genomes can be detected even months after resolution of clinical infection,³⁶ additional research on SARS-CoV-2 is needed to determine whether nasopharyngeal RT-PCR positivity is related to transmission and the duration of viral shedding.³⁷

We are aware that our study presents some limitations. About 90% of participants had mild disease, and thus these data may not reflect antibody response in moderate or severe COVID-19. Furthermore, we did not collect rigorous data regarding symptom severity which could potentially be related to the timeline and strength of IgG antibody response to SARS-CoV-2. As mentioned earlier, further studies are needed to understand the magnitude and duration of the IgG response in patients recovered from SARS-CoV-2. In addition, the antibody titer that is necessary to protect individuals from reinfection is currently unknown. Lastly, the clinical significance of prolonged positive SARS-CoV-2 nasopharyngeal PCR in the absence of clinical evidence requires additional clarification.

Of note, only 19% of health care workers in our study population reported having received seasonal flu vaccine. Although WHO and national agencies identify health workers as a priority target group and recommend for vaccination, influenza vaccination coverage rates of health care workers are significantly variable in Europe, ranging from 15.6% to 63.2%. In Italy, the coverage rate is very low (<20%), as showed in a multicenter cross-sectional study conducted in 10 Italian cities. These observations have relevant implications related to the current COVID-19

pandemic, especially considering the overlapping between seasonal flu- and COVID-19-related symptoms. In order to plan organization and management of future COVID-19 waves, it might be helpful to guarantee influenza vaccination coverage for all health care workers.

CONCLUSIONS

Our data indicate that SARS-CoV-2-specific IgG antibody detection is not different between cancer patients and healthy individuals. As a result, rapid test for antibody detection can be a complement to RNA RT-PCR testing for the diagnosis of COVID-19, especially in those situations where the knowledge of the COVID-19 status is rapidly mandatory for specific clinical decisions. In vulnerable population such as cancer patients, confirming suspected COVID-19 cases as early as possible with the help of serological testing could reduce exposure risk and help optimizing diagnostic and therapeutic algorithms. The key for success in COVID-19 and cancer is to implement diagnostic and therapeutic methodologies, maybe with a high sensitivity/sensibility and rapidity of execution/resulting that allow to ensure a continuum of the health care during pandemic.

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DISCLOSURE

DG reports personal fees for consulting, advisory role and speakers' bureau from Novartis, Pfizer, Lilly; fees for travel and accommodations from Novartis, Pfizer, Lilly. GC reports personal fees for consulting, advisory role, and speakers' bureau from Roche/Genentech, Novartis, Pfizer, Lilly, Foundation Medicine, Samsung, and Daichii-Sankyo; honoraria from Ellipses Pharma; fees for travel and accommodations from Roche/Genentech, and Pfizer. The other authors have declared no conflicts of interest.

DATA SHARING

All data generated or analyzed during this study are included in the published article. Additional supporting data are available from the corresponding author on reasonable request. All requests for raw and analyzed data and materials will be reviewed by the corresponding author to verify whether the request is subject to any intellectual property or confidentiality obligations.

REFERENCES

- World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report 191. Available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200729-covid-19-sitrep-191.pdf?sfvrsn=2c327e9e
 Accessed July 29, 2020.
- Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382:1708-1720.
- Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395:507-513.
- Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180:934-943.
- Mehta V, Goel S, Kabarriti R, et al. Case fatality rate of cancer patients with COVID-19 in a New York Hospital System. *Cancer Discov.* 2020;10: 935-941.
- Kamboj M, Sepkowitz KA. Nosocomial infections in patients with cancer. Lancet Oncol. 2009;10:589-597.
- Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21:335-337
- Dai M, Liu D, Liu M, et al. Patients with cancer appear more vulnerable to SARS-COV-2: a multi-center study during the COVID-19 outbreak. Cancer Discov. 2020:10:783-791.
- Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet*. 2020;395: 1907-1918.
- Zhang L, Zhu F, Xie L, et al. Clinical characteristics of COVID-19-infected cancer patients: a retrospective case study in three hospitals within Wuhan, China. *Ann Oncol.* 2020;31:894-901.
- Pinato DJ, Zambelli A, Aguilar-Company J, et al. Clinical portrait of the SARS-CoV-2 epidemic in European cancer patients. *Cancer Discov*. 2020;10:1465-1474.
- Li R, Pei S, Chen B, et al. Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). Science. 2020;368:489-493.
- Trapani D, Marra A, Curigliano G. The experience on coronavirus disease 2019 and cancer from an oncology hub institution in Milan, Lombardy Region. Eur J Cancer. 2020;132:199-206.
- Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med. 2020;382:1177-1179.
- **15.** Li G, Chen X, Xu A. Profile of specific antibodies to the SARS-associated coronavirus. *N Engl J Med*. 2003;349:508-509.
- Drosten C, Meyer B, Muller MA, et al. Transmission of MERScoronavirus in household contacts. N Engl J Med. 2014;371:828-835.
- Meyer B, Drosten C, Muller MA. Serological assays for emerging coronaviruses: challenges and pitfalls. Virus Res. 2014;194:175-183.
- 18. Long QX, Liu BZ, Deng HJ, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nat Med*. 2020;26:845-848.
- Zhao J, Yuan Q, Wang H, et al. Antibody responses to SARS-CoV-2 in patients with novel coronavirus disease 2019. Clin Infect Dis. 2020;71(16):2027-2034.
- Solodky ML, Galvez C, Russias B, et al. Lower detection rates of SARS-COV2 antibodies in cancer patients vs healthcare workers after symptomatic COVID-19. Ann Oncol. 2020;31:1087-1088.
- Liu T, Zeng G, Tao H, et al. Low prevalence of IgG antibodies to SARS-CoV-2 in cancer patients with COVID-19. Int J Cancer. 2020;147:3267-3269.

- 22. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? *Lancet*. 2020;395:1225-1228.
- Spina S, Marrazzo F, Migliari M, et al. The response of Milan's emergency medical system to the COVID-19 outbreak in Italy. *Lancet*. 2020;395:e49-e50.
- Corman VM, Landt O, Kaiser M, et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2020;25: 2000045.
- European Commission. COVID-19—EU recommendations for testing strategies. Available at: https://ec.europa.eu/info/sites/info/files/covid19
 --eu_recommendations_on_testing_strategies_v2.pdf. Accessed May 14. 2020.
- Li Z, Yi Y, Luo X, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol. 2020;92:1518-1524.
- Rolston KV. Infections in cancer patients with solid tumors: a review. Infect Dis Ther. 2017;6:69-83.
- 28. Bracci L, Schiavoni G, Sistigu A, Belardelli F. Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer. *Cell Death Differ.* 2014;21:15-25.
- 29. Wajnberg A, Mansour M, Leven E, et al. Humoral immune response and prolonged PCR positivity in a cohort of 1343 SARS-CoV 2 patients in the New York City region. *medRxiv*; 2020, 2020.04.30.20085613. Available at: https://www.medrxiv.org/content/10.1101/2020.04.30.20085613v1. Accessed October 29, 2020.
- Bai Y, Yao L, Wei T, et al. Presumed asymptomatic carrier transmission of COVID-19. JAMA. 2020;323:1406-1407.
- Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. N Engl J Med. 2020;382:970-971.
- Cao WC, Liu W, Zhang PH, et al. Disappearance of antibodies to SARS-associated coronavirus after recovery. N Engl J Med. 2007;357: 1162-1163.
- Al-Abdely HM, Midgley CM, Alkhamis AM, et al. Middle East respiratory syndrome coronavirus infection dynamics and antibody responses among clinically diverse patients, Saudi Arabia. Emerg Infect Dis. 2019;25:753-766.
- 34. Huang AT, Garcia-Carreras B, Hitchings MDT, et al. A systematic review of antibody mediated immunity to coronaviruses: antibody kinetics, correlates of protection, and association of antibody responses with severity of disease. *medRxiv*; 2020, 2020.2004.2014.20065771. Available at: https://www.medrxiv.org/content/10.1101/2020.04.14. 20065771v1. Accessed October 29, 2020.
- Long QX, Tang XJ, Shi QL, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med. 2020;26:1200-1204.
- Lin WH, Kouyos RD, Adams RJ, et al. Prolonged persistence of measles virus RNA is characteristic of primary infection dynamics. *Proc Natl Acad Sci U S A*. 2012;109:14989-14994.
- **37.** He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med*. 2020;26:672-675.
- European Centre for Disease Prevention and Control (ECDC). Seasonal Influenza Vaccination and Antiviral Use in EU/EEA Member States: Overview of Vaccine Recommendations for 2017-2018 and Vaccination Coverage Rates for 2015-2016 and 2016-2017 Influenza Seasons.
 Stockholm: ECDC; 2018. Available at: https://ecdc.europa.eu/sites/portal/files/documents/seasonal-influenza-antiviral-use-2018.pdf. Accessed July 29, 2020.
- Genovese C, Picerno IAM, Trimarchi G, et al. Vaccination coverage in healthcare workers: a multicenter cross-sectional study in Italy. J Prev Med Hyg. 2019;60:E12-E17.