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Supplementary information

Patterns of seroconversion for SARS-CoV-2 IgG in patients with malignant disease and association with anticancer therapy

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BACKGROUND

The COVID-19 pandemic has posed a tremendous health risk to the global population. Per the World Health Organization, the virus has been attributed to over 350,000 deaths worldwide in the setting of 5.7 million confirmed infections through May 27. Estimates of the true case fatality rate in the general population vary widely, often ranging from 0.5% to 6% depending on the model and methodology[1]. Mortality amongst the immunosuppressed population stands to be even higher. To date, the largest cohort study of patients with a known malignancy and COVID-19 infection in the United States from our institution revealed a 28% case fatality rate among 218 patients studied[2].

A combination of immunosuppressive therapy, medical comorbidities and underlying malignancy increase the mortality risk associated with COVID-19 infection in the cancer population. These factors may also affect the trajectory of the infection in terms of duration, severity, and the body's ability to mount an immune response. How baseline immune suppression might impact potential re-infection rates is also unclear. In addition, how the pulmonary and other organ involvement by Covid-19 might impact outcome and toxicity of treatment response/tolerance to needed cancer treatments- such as radiation, chemo/immunotherapy are ill-defined. The true duration of viral shedding and seroconversion of the COVID-19 virus in the general population remains unclear. Some studies suggest the post-infection antibody response and timeline of viral shedding correlates with the severity of the illness[3]. However, it is not well-understood why some members of the general population have demonstrated seroconversion (with successful detection of antibodies to COVID-19 following a confirmed COVID infection via polymerase chain reaction), while others have not[4-5]. To date, there have not been confirmed, credible reports of COVID-19 reinfection. While there have been reported incidences of positive COVID-19 PCR following clinical recovery from a prior infection, these have been widely attributed to persistence of inactive RNA debris in respiratory samples[6].

Given the elevated risk of COVID-19 mortality in the cancer population and potential major impact of impaired clearance and organ dysfunction on future treatments/outcome, it will be important to better understand the patterns of viral shedding and seroconversion of the virus amongst patients with a known malignancy. Factors that may impact the host's ability to mount an immune response include type of malignancy, past treatment course and stage of disease. Studies to this point have reinforced the importance of infection control protocols in the cancer population. Expanding on our knowledge of viral shedding, seroconversion and possibly even re-infection patterns can help inform policy and enhance efforts to safely manage cancer patients amidst a pandemic.

STUDY DESIGN & POPULATION

Aims:

Our proposed study is an observational prospective and retrospective cohort study which will aim in an exploratory/pilot fashion to assess the following variables in a population of cancer patients with known prior or current COVID-19 infection:

- Rates of detection of antibodies to SARS-CoV-2
- Correlation of SARS-CoV-2 serologies to factors including history of positive COVID PCR testing, type of malignancy, prior chemotherapy and prior immunotherapy
- Signal strength of SARS-CoV-2 antibodies on laboratory assay and its correlation to cancer therapies the patients have received

- Duration of persistent viral shedding amongst patients who received multiple COVID PCR tests during the study period
- Comparison of seropositivity rates to those amongst the general population

We hypothesize that patients with immunosuppression in the setting of malignancy and prior medical cancer treatments will have lower rates of seroconversion compared to the general population. This may indicate continued infectious risk in a more constrained window than we would expect amongst the general population, who may produce and retain COVID-19 antibodies more effectively.

Inclusion Criteria:

Our target population consists of patients with a known diagnosis of cancer who were seen at Montefiore Medical Center after March 1, 2020. Our study will employ the following inclusion criteria:

- Above the age of 18
- Known diagnosis of any malignancy- either active or completed therapy within last 12 months
- Underwent an in-person encounter at a Montefiore Medical Center facility during the study period
- Had a COVID-19 PCR swab test and/or a COVID-19 antibody test performed during the study period at Montefiore Medical Center
- Established diagnosis of COVID-19 infection

Outcomes:

We will be studying the following primary outcome:

- Rates of seroconversion amongst patients with known malignancy and known history of COVID-19 infection as compared to the general population of COVID-19 patients seen at Montefiore Medical Center

We will be studying the following secondary outcomes:

- Duration of viral shedding, as defined by time until repeat COVID-19 swab result is negative
- Correlation between malignancy type and seroconversion
- Correlation between timing of most recent cancer-directed treatment and seroconversion
- Correlation between the total number of cancer-directed treatments received and seroconversion
- Comparison of seroconversion rates between cancer population and a sample general adult population without cancer
- Correlation of COVID infection with adverse treatment outcomes such as pneumonitis and incidence of thrombosis during subsequent therapy

Methods:

Using the EPIC electronic health record and records from the Cancer Center's Quality 360 Team, we will identify patients from our cancer database that have had a positive COVID-19 PCR test starting March 1, 2020.

A retrospective chart review will be conducted for patients who have had a positive SARS-CoV-2 PCR test between March 1 2020 and IRB approval date. For patients being actively followed at Montefiore-Einstein Center for Cancer Care, an informed consent would be obtained at follow-up visit for continued monitoring of their clinical course and outcomes beginning IRB approval date. The informed consent

would include obtaining one investigational blood sample for patients who have tested positive for SARS-CoV-2 at a follow-up lab visit and consent to run future serologic tests on the sample. The investigational sample would be stored in the lab for the possibility that if in the future, a more sensitive or specific serologic test is available for SARS-CoV-2 IgG, samples would be available to run them.

Furthermore, to study the duration of viral shedding, we will simply be conducting retrospective chart review on patients after they are discharged or deceased to assess the timeline between initial positive COVID-19 PCR and a negative COVID-19 PCR result.

Sample Size:

Based on a study previously performed at Montefiore Medical Center looking at cancer patients at our institution with PCR-confirmed COVID-19 infection, we project approximately 500 cancer patients as part of our cohort during the study period.

Statistical Analysis:

To assess our goals as outlined above, statistical analysis will be done in the R software environment. The significance of associations between certain malignancies and the rates of seroconversion in the retrospective cohort and general population will be measured by a Cochran-Mantel-Haenszel test. The more complicated relationship between patients' seroconversion rates, their recent receival of medical treatment, and additional factors such as history of malignancy will be examined through a multivariate logistic regression model. After addressing the appropriateness of interaction terms, a Wald test will be used to consider the statistical significance of all included variables at the $p < 0.05$ level. Given the pilot/exploratory nature of the study and the practical limitations as to sample size- our study plans to encompass all cancer patients diagnosed with Covid-19, a power calculation was not performed.

Duration:

Our study will follow patients from March 1, 2020 through May 31, 2021, which will allow for sufficient time to assess follow-up serologies after PCR-confirmed COVID-19 infection in cancer patients.

Matching:

Cancer patients will be matched to a control group of the general population on the basis of their age, sex, BMI, and Charlson Comorbidity Index (the latter of which will control for disease severity as a confounder, which may affect patients' ability to effectively clear the virus and/or seroconvert). This cohort will be obtained from a Pathology Department database without any patient identifiers to preserve the privacy of our non-cancer group.

Planned Intervention

The planned intervention will simply be chart review of PCR and antibody testing related to COVID-19, as well as general patient demographic information to assess the characteristics of our cohort. The study will not involve extraneous blood draws, nasal swabbing, or other testing beyond the standard of care at Montefiore Medical Center with the exception of a collection of a one-time biospecimen collection (2 tubes of blood) for future research in consenting patients. Patients will be able to opt out of the biospecimen collection.

PARTICIPANT RECRUITMENT

The study will utilize data from the electronic health record to identify patients meeting the above inclusion criteria. Patients who qualify for COVID-19 antibody testing on the basis of previously positive COVID-19 PCR will be recruited to participate in our study if they have an admission to Montefiore Medical Center or a primary care/oncology appointment during the study period. If a patient has not had COVID-19 antibody test already from their care provider, one will be run on the biospecimen collected.

INFORMED CONSENT

For all patients that will be prospectively studied following the initiation of the study, we will obtain informed consent to gain permission to use their serologic data. Consent will be obtained by members of the research group. We will flag patients with histories of positive COVID-19 swabs in our database and contact them in advance of their appointment to explain our study objectives and how they can contribute to our goal of understanding the natural history of COVID-19 in patients with cancer. Alternatively, if patients are admitted to the hospital at Montefiore Medical Center, a member of the research team will consent the patient for use of their antibody data. Patients will not be offered compensation for participating in our study.

RISK/BENEFIT

The main foreseeable risk is that of inadvertent disclosure of HIPAA protected information. As a measure to minimize such risks the collected data will be accessed only by approved individuals, will be collected onto the Excel Data Collection Sheet, and stored on encrypted Montefiore Secure Drive, MonteBox. All patient identifiers will be destroyed one year after final publication. Other than this, there will be no immediate direct risks to the patients whose medical charts will be reviewed. For patients who will consent to the additional biospecimen collection, there will be added minimal risk of phlebotomy.

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