Imperial College London

RESEARCH STUDY PROTOCOL

Title:	**OnCovid: natural history and outcomes of cancer patients during the COVID19 epidemic.**
Protocol Version:	**Version 3.0 dated 1st June 2020**
Chief Investigator:	**Dr David James Pinato**
Sponsor:	**Imperial College London**
IRAS Project ID:	**282140**

SYNOPSIS

Study title:	OnCovid19: natural history and outcomes of cancer patients during the COVID19 epidemic.
Objectives:	To describe the natural history and clinical outcomes of patients with cancer and Covid19 infection.
Study design & methodology:	Retrospective observational study. Research will be limited to secondary use of information previously collected in the course of normal care (without an intention to use it for research at the time of collection). Every aspect of this research will be undertaken by staff within a care team using information previously collected in the course of care for their own patients. Routinely collected clinical data including patients' demographics, prior medical history, cancer history including prior and current anti-cancer therapy, co-morbidities will be collected in a data collection proforma. Results of routinely collected blood tests, radiologic assessment and therapies received by the patient will also be entered onto the database. Clinical outcomes including response to treatment and patients' survival will be evaluated in relationship to baseline clinico-pathologic profile.
Duration of Research:	2 years
Planned sample size:	Due to the descriptive and retrospective nature of this study, no sample size is required for hypothesis testing. We aim to describe clinical outcomes of consecutively presenting patients with a diagnosis of cancer and SARS-CoV-2 infection and aim to retrieve data on up to 5000 fulfilling eligibility criteria.

Summary of eligibility criteria:	Inclusion criteria: 1. Be ≥18 years of age. 2. Have a confirmed diagnosis of malignancy of any type. 3. Have a confirmed diagnosis of SARS-CoV-2 infection.
Number of study centres:	1
Endpoints:	To retrospectively describe the survival of cancer patients affected by SARS-CoV-2 infection.

General Study Information

Name of sponsor:	**Imperial College London** Joint Research Compliance Office Room 221 Medical School Building St Mary's Campus Norfolk Place London, W2 1PG Contact: Becky Ward Research Governance Manager Email: becky.ward@imperial.ac.uk Tel: +44 (0) 207 594 9459
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1.0 BACKGROUND AND RATIONALE

1.1 Introduction

Coronaviruses are a large family of viruses that are common in people and many different species of animals. Rarely, animal coronaviruses can infect people and then spread between people such as with MERS-CoV, SARS-CoV, and now with this new virus (named SARS-CoV-2).

The World Health Organisation (WHO) declared the coronavirus outbreak a pandemic on 11th March 2020, and it has now been officially recognised that the spread of COVID-19 is expected to affect most countries in the world.

The complete clinical picture with regards to COVID-19 is not fully known. Reported illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, a report out of China suggests serious illness occurs in 16% of cases. Older people and people of all ages with severe chronic medical conditions — like heart disease, lung disease and diabetes, for example — seem to be at higher risk of developing serious COVID-19 illness. A CDC Morbidity & Mortality Weekly Report that looked at severity of disease among COVID-19 cases in the United States by age group found that 80% of deaths were among adults 65 years and older with the highest percentage of severe outcomes occurring in people 85 years and older.

The morbidity and mortality stemming from COVID-19 infection in cancer patients is not fully appreciated. Patients with cancer often have multiple co-morbid conditions and are often immune-suppressed as a result of their malignancy or systemic anti-cancer treatment.

2.0 STUDY OBJECTIVES

The overarching purpose of this retrospective, non-interventional study is to describe the features of COVID-19 infection in cancer patients, investigate its severity in this population and evaluate long-term outcomes by means of medical charts review of consecutive patients co-diagnosed with SARS-CoV-2 infection and malignancy.

3.0 STUDY DESIGN AND METHODS

3.1 Endpoints

1. Describe presenting characteristics and severity of SARS-CoV-2 infection in patients with cancer.
2. Evaluate prognostic factors for survival in patients with SARS-CoV-2 infection and cancer.

3.2 Methods

Patients with a diagnosis of malignancy and SARS-CoV-2 infection will be identified from electronic medical records and entered into a pre-designed database.

Methodologically, this project will be limited to secondary use of information previously collected in the course of normal care (without an intention to use it for research at the time of collection). Every aspect of this project will be undertaken by staff within a care team using information previously collected in the course of care for their own patients.

Routinely collected clinical information including patients' demographics, prior medical history, cancer history including prior and current anti-cancer therapy, co-morbidities will be collected in a data collection proforma. Results of routinely collected blood tests, radiologic assessments and therapies received by the patient will also be entered onto the database. Clinical outcomes including response to treatment and patients' survival will be evaluated in relationship to baseline clinico-pathologic profile. Clinico-pathologic will be correlated to patient's outcome, in particular overall survival (OS) as derived from electronic medical records.

The database consists of a Microsoft Excel spreadsheet including the following variables: age, gender, smoking status, prior comorbidities (cardiovascular, diabetes, dementia, pulmonary and kidney disease, liver disease, hypertension, immunesuppression), histotype of malignancy, date of first cancer diagnosis and stage of cancer at the time of SARS-CoV-2 infection, prior and current anti-cancer therapy, presenting symptoms at SARS-CoV-2 diagnosis and severity, routine blood tests at SARS-CoV-2 diagnosis (routine biochemistry, full blood count), radiologic data at diagnosis and follow up data (admission to intensive care, anti SARS-CoV-2-specific therapy, complications from SARS-CoV-2 infection).

Data collection will be completely solely by members of the patients' team. Resulting clinical data will be fully anonymised and stored in a password-protected NHS computer.

4.0 SUBJECT POPULATION

4.1 Subject number and selection

We plan to collect descriptive data in all consecutive patients with confirmed diagnosis of SARS-CoV-2 infection and cancer. Due to the descriptive and retrospective nature of this study, no sample size is required for hypothesis testing. We aim to describe clinical outcomes of consecutively presenting patients with a diagnosis of cancer and SARS-CoV-2 infection and aim to retrieve data on up to 5000 fulfilling eligibility criteria.

4.1.1 Inclusion criteria

The investigators will evaluate and include consecutive patients observed in the outpatients and inpatients facility of the study centre meeting all the following CRITERIA:

Inclusion criteria:

1. Be ≥18 years of age.
2. Have a confirmed diagnosis of malignancy of any type.
3. Have a confirmed diagnosis of SARS-CoV-2 infection.

4.1.2 Exclusion criteria

Patients will not be entered in the study database when one or more of the following CRITERIA are present:

1. Unconfirmed diagnosis of SARS-CoV-2 infection
2. Insufficient clinical/follow up data.

5.0 STATISTICAL ANALYSIS

5.1 Subject numbers.

5.1.1 Sample size.

For this observational, retrospective study, we propose a sample size of 5000 patients. Given the descriptive nature of this study no formal hypothesis testing is required. We will be retrospectively including patients fulfilling eligibility criteria between 1st January 2020 and 1st of April 2020.

5.2 Statistical methods.

Analysis of overall survival (OS) will validate the prognostic value of each clinico-pathologic trait collected at treatment initiation. Univariable analysis of survival will be used to derive median OS and associated 95% CI by using Kaplan-Meier methods and Log-rank tests.

The HRs and their associated CIs for OS will be computed using unadjusted and adjusted Cox proportional hazards models. We will employ a backward stepwise conditional model where each variable with an entry threshold of $p<0.05$ and an exit threshold of $p<0.10$ at each iteration. Proportional hazards will be adjusted for factors including active anticancer treatment type and features reflective of SARS-CoV-2 infection. Receiver-operating characteristics curve (ROC) will be used to test each variable for the accuracy of prediction of mortality at landmark survival endpoints (ie. 8, 12 weeks).

To test the predictive accuracy of each candidate prognostic variable we will use Harrell's rms packages to identify a subset of predictors by backward elimination, estimating the confidence intervals of the c-index statistics via bootstrapping (150 iterations).

6.0 DATA MANAGEMENT

Data will be collected and retained in accordance with the Data Protection Act 2018. The data collected from the study will be entered in a study specific database by designated staff. The database will be kept on a secure NHS computer. Access to the database will be given to authorised personnel only and log of access will be kept in the study file by the Principal Investigator.

7.0 REGULATORY ISSUES

7.1 Ethics Approval

In view of the retrospective nature of this study, approval from a Research Ethics Committee within the UK Health Departments Research Ethics Service is not necessary. and Health Research Authority (HRA). The criteria for REC review exemption is:

Research involving previously collected, non-identifiable information

Research limited to secondary use of information previously collected in the course of normal care (without an intention to use it for research at the time of collection) is generally excluded from REC review, provided that the patients or service users are not identifiable to the research team in carrying out the research. This exception also applies to research undertaken by staff within a care team using information previously collected in the course of care for their own patients or clients, provided that data is anonymised or pseudonymised in conducting the research.

The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

7.3 Confidentiality

A unique reference number will be used to anonymize the details of all participants. The investigator must ensure that the patient's privacy is maintained at all times. On the Case Report Form (CRF) or other documents, patients will be identified by a study ID number only. The investigator shall permit direct access to study source document for the purposes of monitoring, auditing, or inspection by the Sponsor, authorised representatives of the Sponsor and Regulatory Authorities.

7.4 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

7.5 Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

7.6 Audits

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the UK Policy Frame Work for Health and Social Care Research.

7.8 Publication Policy

A whole or part of the study results will be communicated, orally presented, and/or published in appropriate scientific journals. Full anonymity of subject's details will be maintained throughout. Subjects wanting to see the results of the trial can request a copy of the article from the investigators once it has been published.

8.0 STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through the Cancer Research office at Hammersmith Hospital.

10.0 REFERENCES

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6: Wang T, Du Z, Zhu F, Cao Z, An Y, Gao Y, Jiang B. Comorbidities and multi-organ injuries in the treatment of COVID-19. Lancet. 2020 Mar 21;395(10228):e52. doi: 10.1016/S0140-6736(20)30558-4. Epub 2020 Mar 11. PubMed PMID: 32171074.

11. PROTOCOL SIGNATURE PAGE

I agree to conduct the Study in accordance with the approved protocol.

I agree to comply with the procedures for data recording/reporting

Name of Principal Investigator:

Signature:

Date: