The PanSurg-PREDICT Study

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STUDY COORDINATION CENTRE: Imperial College London
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Protocol authorised by:

Name & Role	Date	Signature

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This protocol describes the PanSurg-PREDICT study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the UK Policy Framework for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and all other regulatory requirements as appropriate.

Study Management Group

Chief Investigator: James Kinross

Co-investigators: PanSurg Collaborative Study Group - Sheraz Markar, Jonathan Clarke, Guy Martin, Leigh Warren, Jasmine Winter Beatty, Viknesh Sounderajah, Amish Acharya.

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Endocrine subcommittee chair: Aimee di Marco

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Clinical Queries

Clinical queries should be directed to Sheraz Markar (Co-Investigator) who will direct the query to the appropriate member of the research team.

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

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Funder

This study is internally funded by the Department of Surgery and Cancer, Imperial College London

GLOSSARY OF ABBREVIATIONS

COVID-19	COronaVIrus Disease 2019
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
WHO	World Health Organisation
APACHE	Acute Physiology and Chronic Health Evaluation
P-POSSUM	Portsmouth Physiological and Operative Severity Score
NELA	National Emergency Laparotomy Audit
NVR	National Vascular Registry
NHFS	Nottingham Hip Frailty Score
Rockwood CFS	Rockwood Clinical Frailty Score
SORT	Surgical Outcome Risk Tool
EUROSCORE II	European System for Cardiac Operative Risk Evaluation
THORACOSCORE	Thoracic surgery scoring system (Thoracoscore) risk model
EuroLUNG1&2 Models	European risk models for morbidity (EuroLung1) and mortality (EuroLung2) to predict outcome following anatomic lung resections

KEYWORDS

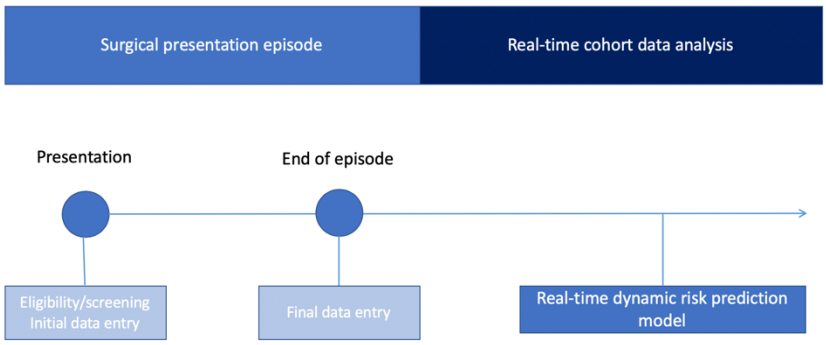
COVID-19, SARS-CoV-2, coronavirus, pandemic, risk prediction model, surgical outcomes

STUDY SUMMARY

TITLE	PanSurg-PREDICT Study
DESIGN	Observational cohort study (retrospective and prospective)
AIMS	1. To quantify the additional risk of mortality and morbidity associated with patients who suffer from surgical pathology that present to hospital during COVID-19 pandemic. 2. To create a dynamic risk prediction model that would provide individualised risk estimates for morbidity and mortality in patients who present to hospital with a surgical pathology during COVID-19 pandemic.
OUTCOME MEASURES	Data related to the following fields: (1) hospital and status of surgical department, (2) patient details (such as comorbidities), (3) COVID-19 status, (4) investigation data (physiological parameters, biochemical parameters, radiology reports) (5) surgical details and (6) outcomes.
POPULATION	Patients presenting to hospital with any surgical pathology during COVID-19 pandemic including patients admitted, or planned for admission and cancelled.
ELIGIBILITY	Global
DURATION	Duration of COVID-19 pandemic as defined by World Health Organisation (11th March 2020 onwards)

REFERENCE DIAGRAM

Simplified flow diagram demonstrating study conduct



1. INTRODUCTION

1.1 BACKGROUND

The COVID-19 pandemic is placing unprecedented stressors upon healthcare services internationally. At the time of writing, the World Health Organisation (WHO) (1) has stated that COVID-19 is in a period of exponential growth globally, with over 4,628,903 cases confirmed and over 312,009 deaths directly attributed to infection (2).

In the midst of this crisis, patients with or without COVID-19 will continue to present to the hospital with surgical pathologies that necessitate careful consideration regarding intervention. Currently, allocation to surgical intervention in elective and emergency settings is a considered balance between the benefit of intervention against the risk of adverse outcomes; all within the dynamic context of resource availability and health context.

In addition to using their own judgement and best empirical evidence clinicians routinely seek objective guidance from the use of risk prediction models, such as the P-POSSUM, NELA, APACHE, NHFS, Rockwood CFS, SORT, EUROSCORE, THORACOSCORE, EUROLUNGS scores (3). These are able to provide estimations of perioperative morbidity and mortality based upon physiological, biochemical and operative parameters. However, such traditional modelling of operative risk may under-estimate the current risk due to two new modifying factors; (1) concurrent infection with a COVID-19 and (2) a working environment short of normal resources where alternative clinical decisions are made.

Therefore, as clinicians continue to work in these uniquely difficult conditions, there is an urgent need for dynamic risk prediction tools which are specific to this particular context in order to guide optimal decision making for all patients.

1.2 RATIONALE FOR CURRENT STUDY

In the absence of observational data regarding the effect of COVID-19 in patients with surgical pathologies, let alone the presence of COVID-19 specific risk prediction models, this study aims to achieve the following:

Research question:

How can we build on existing data and knowledge of risk to support evidence-based real-time decision-making for patients with surgical pathology in the current climate?

2. STUDY AIMS AND OBJECTIVES

Primary outcomes:

1. To quantify the additional risk of mortality and mortality associated in patients who suffer from surgical pathology warranting presentation to hospital during COVID-19 pandemic.

2. To create a dynamic risk prediction model that will provide individualised patient-level estimates for morbidity and mortality for the cohort of patients who present to hospital with surgical pathology during COVID-19 pandemic.

3. STUDY DESIGN

This will be an observational cohort study, consisting of retrospective and prospective data collection, starting from 11/03/20, to identify patients of all ages presenting to hospital with a surgical pathology during the COVID-19 pandemic. It follows established processes for multi-centre quality audits such as NELA (National Emergency Laparotomy Audit) and NVR (National Vascular Registry). This will be a global study with data entry undertaken at secondary care settings. As we will be collecting routinely collected data that is anonymised, we do not intend to attain patient level consent. As such, patient level withdrawal is not anticipated either.

We aim to collect anonymised patient level outcome data for the duration of the COVID-19 pandemic; a timeframe controlled by the WHO. Data will be collected at each site from the medical notes (electronic or paper based). A local Principal Investigator will ensure that data entry is completed as per local best practice protocol. Data will be collated, anonymised and submitted by members of the direct clinical team in each participating centre. The local Principal Investigator subsequently reports back to the Chief Investigator of the study.

Eligible patients will be identified by the direct clinical care team and data collected subject to all relevant approval processes as per existing mechanisms for national quality audit data collection. The identification of patients will be the same for all hospitals (though direct clinical care) whether they are based in the United Kingdom or abroad.

The principle inclusion criteria are the presence of a surgical pathology in patients of all ages presenting to hospital during the COVID-19 pandemic as defined by the WHO. This also includes children who present with surgical pathologies. This subgroup will most consist of patients between the ages of 4 and 16. There are no exclusion criteria.

There are currently in the region of 600,000 acute surgical admissions per annum (4) in the UK, although this number has significantly dropped by an unknown amount as a result

of the COVID-19 pandemic. In addition, participating clinical teams are likely to be working in high stressed environments. We will seek to recruit as many patients as possible to improve the accuracy of the risk-prediction model, however, for the two reasons outlined we have no minimum or maximum recruitment target. Recruitment of 100 patients per week is likely to be a realistic goal for large secondary care facilities.

Data will be collected for all patients presenting to hospital with any surgical pathology, across specialties, irrespective of admission, COVID status, or urgency of presentation. We aim to collect the following data points regarding (1) hospital and status of surgical department, (2) patient details (such as co-morbidities), (3) COVID-19 status, (4) investigation data (physiological parameters, biochemical parameters, radiology reports) (5) surgical details and (6) outcomes. All analyses will be conducted on a cohort basis and no patient level analyses will be undertaken.

Data capture and trial management will be conducted through REDCap - a widely used and secure online platform. The REDCap system is available for use internationally and without charge. Data input will be coordinated and conducted by each of the local Principal Investigators at their respective hospitals and will not include any identifiable data fields. Data will be encrypted, password- protected and stored on a secure data environment fully compliant with the Health Insurance Portability and Accountability Act (HIPAA) and General Data Protection Regulations (GDPR). Only members of the research teams will be able to access the data though password protected gateways. The data will be kept on the secure Imperial College London Department of Surgery and Cancer Big Data Analytical Unit (BDAU) server for 10 years following completion of the study, as per college guidelines. A data monitoring lead and safety lead have been appointed as part of this study and will ensure that the data is analysed at regular intervals. The collected data will not be used for further analyses outside the scope of this project.

Following our data analysis, we intend to disseminate our research findings. As we are in the midst of a pandemic, we are looking to expand upon traditional publication strategies. Our website, www.pansurg.org, will provide dynamic interactive and real-time learning and dissemination of knowledge that is crucial to optimise care for our patients in these extreme times. We will also employ non-traditional routes, such as social media platforms (e.g. Twitter, Facebook, LinkedIn), in order to ensure that there is rapid dissemination of the pertinent study findings. We will ensure that the PanSurg-PREDICT tool, the primary research output from this study, will be available on multiple platforms; website and app based (on iOS and Android).

Upon the recruitment of each site from NHS hospitals, as well as those from oversees, we will seek to amend our application to reflect these changes.

3.1 STUDY OUTCOME MEASURES

The principal outcome measure will be the creation of a dynamic risk prediction model for patients presenting with a surgical pathology during the COVID-19 pandemic . This will

provide estimates of outcomes, mortality and morbidity for patients receiving treatment for surgical pathology during the COVID-19 pandemic.

In the longer-term we may seek to examine the impact of concurrent COVID-19 infection in the medium- and long-term through interrogation of linked routinely collected data. This will be subject to a future regulatory application and approval.

4. PARTICIPANT ENTRY

4.1 INCLUSION CRITERIA

The principle inclusion criteria are:

1. Surgical pathology in patients of all ages presenting to hospital during the COVID19 pandemic with any surgical pathology, across specialties, irrespective of admission, COVID status, or urgency of presentation.. The surgical specialties include, but are not limited to, the following: general surgery (consisting of colorectal surgery, upper gastrointestinal surgery, hepato-pancreato-biliary surgery, breast surgery), vascular surgery, cardiac and thoracic surgery, neurosurgery, plastic surgery, orthopaedic surgery, trauma surgery, endocrine surgery, sarcoma and soft tissue cancer surgery, obstetrics and gynaecology, paediatric surgery, maxillofacial surgery and ENT (ears, nose and throat) surgery.
2. Hospital episode commencing during the COVID-19 pandemic as defined by the WHO.

4.2 EXCLUSION CRITERIA

1. Nil

4.3 WITHDRAWAL CRITERIA

As the risk prediction model is reliant upon large scale data collection, we do not foresee any circumstances by which we would end the data collection phase earlier than intended.

5. ASSESSMENT AND FOLLOW-UP

There are no active assessments associated with the patients whose data will be used in the creation of this database. As previously noted, routinely collected episode-specific health outcome data will be collected for this cohort of patients. In the future we may seek to acquire long term outcome data following the completion of this distinct project and subject to a future application and necessary approvals.

Data collection will be collected locally as per local guidelines, to the end of that particular presentation episode, whether it be discharge or death.

6. STATISTICS AND DATA ANALYSIS

Existing validated risk prediction tools (P-POSSUM, CR-POSSUM, Vascular-POSSUM, NHFS, Rockwood CFS, SORT, EuroSCORE, Thoracoscore, Eurolungs I & Eurolungs II etc) will be used to quantify risk for surgical patients based on information collected at the time of presentation. Additionally, data relating to the COVID-19 status of the patient and the wider clinical burden of the surgical team in terms of staffing, redeployment and critical care capacity will be recorded. Data will be recorded until the end of each surgical patient episode. In hospital mortality (+/- discharge for palliation) will be estimated using binary logistic regression modelling incorporating the available clinical data and features relating to surgical team burden. Data will be trained on 75% of the available cases using five-fold cross validation and will be tested on the remaining 25% of cases which are retained as a hold-out validation sample. This analysis will be conducted on a real-time basis in order to provide an updated model as to the current risk associated with surgical management during a COVID pandemic.

7. REGULATORY ISSUES

7.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the Imperial College Research Ethics Committee (REC) and Health Regulator Authority (HRA). The study must also receive confirmation of capacity and capability from each participating NHS Trust before accepting participants into the study or any research activity is carried out. 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.

7.2 CONSENT

As the data recorded is anonymised and routinely collected. The acquired data will be used to create a risk prediction model that will in no way allow for the identification of individual patients. As such individual patient consent is not required and will not be obtained for this project as per standard practice.

7.3 CONFIDENTIALITY

No identifiable data will be required for the registration process. The Study Coordination Centre will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act

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 FUNDING

This study is funded internally by the Department of Surgery and Cancer and Institute of Global Health Innovation at Imperial College London.

7.7 AUDITS

The study may be subject to inspection and audit by Imperial College London under their remit as Sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to Good Clinical Practice.

8. STUDY MANAGEMENT

The day-to-day management of the study will be coordinated through the PanSurg-PREDICT Study Management Committee (SMC).

The SMC will be convened including the Chief Investigator, co-investigators, key collaborators and the study statistician. The committee will be responsible for day-to-day conduct of the trial and operational issues. Specialty-specific sub-studies may be run on a day to day basis by a dedicated sub-committee.

Quality Control will be performed according to Imperial College London internal procedures. The study may be audited by a Quality Assurance representative of the Joint Research Compliance Office (JRCO) at Imperial College London. All necessary data and documents will be made available for inspection. The study may be subject to inspection and audit by regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care.

There will not be a formal data monitoring committee, however, a data monitoring and safety lead will be appointed who will independently analyse data at regular intervals.

9. PUBLICATION POLICY

As we are in the midst of a pandemic, we are looking to expand upon traditional publication strategies. Our website, www.pansurg.org, will provide dynamic interactive and real-time learning and dissemination of knowledge that is crucial to optimise care for our patients in these extreme times. We will also employ non-traditional routes, such as social media platforms (e.g. Twitter, Facebook, LinkedIn), in order to ensure that there is rapid dissemination of the pertinent study findings. We will ensure that the PanSurg-PREDICT

tool, the primary research output from this study, will be available on multiple platforms; website and app based (on iOS and Android). Only anonymised data will be published.

In addition to leveraging online dissemination strategies, we will also target the following groups in a more specific fashion:

Policymakers:
Upon completion, we will produce an executive summary of our findings, which is to be distributed to relevant policy makers so that the relevant results may be rapidly disseminated globally through official and well-respected sources.

Clinicians and Health Managers:
The main findings will be submitted for publication in peer-reviewed scientific journals and presented in national and international conferences. We will provide updated information concerning the publication of study results to all stakeholders. The study results will also be presented to healthcare commissioners and policy makers at appropriate meetings and in publications.

Patients and the Public:
We will produce a short, easy to understand summary of our research findings that will be available from our website or that can be sent to interested stakeholders.

Academics:
We will make our intervention methodology and results available through presentations, workshops, conferences, the website, working papers and journal articles. We will provide an interactive framework on a web-based platform to facilitate the adoption of our model and methodology in clinical practice. We will publish our results in high impact peer-reviewed journal. In addition, we will present our findings at conferences and in clinical settings.
Publications using subspecialty- specific data, eg endocrine, T&O, cardiac and thoracic data will be published as full collaborative authorship with designated representative organisation where possible eg CIRN (Cardiothoracic Interdisciplinary Research Network).

10. REFERENCES

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services/acute-surgical

11. APPENDIX

eCRF outlining all data fields to be captured