AI-COV-19

Artificial intelligence-assisted diagnosis and prognostication in COVID-19 using electrocardiograms and imaging (AI-COV-19)

V1.2 05-05-2020

MAIN SPONSOR: Imperial College London
FUNDERS: N/A
STUDY COORDINATION CENTRE: xxx

IRAS Project ID: 283210
REC reference: xxx

Protocol authorised by:

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Sponsor

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Funder

This study is not funded from a specific research grant, and the researchers involved are funded through Imperial College London and Chelsea & Westminster Hospital NHS Foundation Trust.

This protocol describes the Artificial intelligence-assisted diagnosis and prognostication in COVID-19 using electrocardiograms and imaging (AI-COV-19) 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 Frame Work for Health and Social Care Research. It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ECG	Electrocardiogram
AI	Artificial intelligence
CXR	Chest x ray
CT	Computed Tomography
ML	Machine learning
MDT	Multi-Disciplinary Team
NHS	National Health Service
ROI	Region of Interest
CMIH	Centre for Mathematical Imaging in Healthcare

KEYWORDS
ECG, COVID-19, CT, chest x-ray, deep learning, artificial intelligence

STUDY SUMMARY

TITLE	**AI-assisted diagnosis and prognostication in COVID-19**
DESIGN	Retrospective data study on patients with suspicious and confirmed COVID-19.
AIMS	To investigate whether computer-based analysis (machine learning) enable the diagnosis of Covid-19 primarily on ECGs, but also from CXR and CT images
OUTCOME MEASURES	Accuracy with which computer based analysis (machine learning) can diagnose and/or prognosticate Covid-19 infection primarily from ECG, but also from chest xray and CT images
POPULATION	The study aims to collect data from up to 2000 patients at Chelsea and Westminster Hospital NHS Foundation Trust, Imperial College Healthcare NHS Trust and London North West London University Healthcare NHS Trust, from 15 May 2020.
ELIGIBILITY	To be included in this study the patient must: - have ECGs, Chest x-ray and/or chest CT imaging (with or without contrast) - laboratory Covid-19 virus nucleic acid test (RTPCR assay with throat swab samples) or clinical suspicion for Covid-19 infection - be aged >18 years
DURATION	2 years

1. INTRODUCTION

1.1 BACKGROUND

Coronavirus Disease 2019 (COVID-19) has been widespread worldwide since December 2019 [1] [2]. It is highly contagious, and severe cases can lead to acute respiratory distress or multiple organ failure [3]. On 11 March 2020, the WHO made the assessment that COVID-19 can be characterised as a pandemic. As of 25 March 2020, in total, 416, 916 cases of COVID-19 have been recorded, and the death toll has reached 18,565 with a rapid increase of cases in Europe and North America.

The disease can be confirmed by using the reverse-transcription polymerase chain reaction (RT-PCR) test [4]. While being the gold standard for diagnosis, confirming COVID-19 patients using RT-PCR is time-consuming, and both high false-negative rates and low sensitivities (60-95%) may put hurdles for the presumptive patients to be identified and treated early [3][5][6]. With infected patients and tested individuals steadily increasing, health care systems are overwhelmed by the unprecedented testing frequencies and massive patient loads. Thus, the situation presents a diagnostic dilemma with patients showing non-specific symptoms, as well as RT-PCR assays often being unavailable and known for high false negative rates.

As non-invasive electrocardiographic (ECG) recordings and imaging techniques, such as computed tomography (CT) and chest X-ray (CXR) can detect those characteristics, e.g., myocarditis, bilateral patchy shadows or ground glass opacity (GGO), manifested in the COVID-19 [7][8]. Hence ECG, CT and CXR may serve as an important tool for COVID-19 to be screened, diagnosed and prognosticated early.

1.2 RATIONALE FOR CURRENT STUDY

Coronavirus Disease 2019 (COVID-19) has been widespread worldwide since December 2019. It is highly contagious, and severe cases can lead to acute respiratory distress or multiple organ failure and ultimately death. The disease can be confirmed by using the reverse-transcription polymerase chain reaction (RT-PCR) test. ECGs, Chest x-rays and CT scans are rich sources of data that provide insight to disease that otherwise would not be available. Knowing who to admit to the hospital or intensive care saves lives as it helps to mitigate resource shortages. Novel Artificial Intelligence tools such as Deep learning will allow a complex assessment of the Imaging and clinical data that could potentially help clinicians to make a faster and more accurate diagnosis, better triage patients and assess treatment response and ultimately better prediction of outcome.

Our group has significant experience implementing machine learning algorithms on vast quantities of ECGs, such as from the UK Biobank, and propose to extend our techniques to data from patients with Covid-19.

ECGs are routinely performed on unwell patients presented to hospital and often have serial recordings during their inpatient stay. This provides a unique method by which disease progression can be tracked using a simple, non-invasive and inexpensive method throughout the course of the illness. Furthermore, whether COVID-19 causes specific ECG changes is not known. Identifying and understanding ECG changes related to COVID-19, particularly those features that may predict clinical outcomes, would be especially useful. The non-invasive, quick and easy nature of recording ECGs in unwell patients makes it an ideal modality to investigate and predict COVID-19 related outcomes.

As the manifestation of COVID-19 and related complications on ECG is currently unknown, we hypothesise that beyond routine radiographic imaging, ECG can provide an insight into clinical outcomes related to COVID-19 that can be helpful for prognostication.

Imaging of COVID-19 is performed with CXR and CT. Chest radiograph is the initial screening imaging tool in patients with suspicious clinical symptoms of COVID-19 (including fever and lymphopenia). Radiographic appearances are of symmetric patchy or diffuse airspace opacities. Typical CT appearances include peripheral, bilateral ground glass opacity (GGO) which may have a rounded morphology, with or without consolidation. A crazy-paving pattern can be seen with ground glass opacity and intralobular lines. Imaging features depend on when infected patients are imaged. Up to approximately 50% of patients with COVID-19 infection may have normal CT scans 0–2 days after onset of flu-like symptoms [18]. GGO opacity usually develops between day 0 and 4 after symptom onset. The frequency of consolidation increases later in the course of the disease, peaking at 6-13 days with higher rates of bilateral and multilobar involvement. An organising pneumonia pattern is observed with reverse halo or atoll sign and perilobular opacities. About 2–3 weeks after the onset, CT may show varying degrees of clearing of the patchy consolidative opacities, reticular opacities, bronchial wall thickening, and interlobular septal thickening [9]. Imaging (CXR & CT) may be used as an aid in diagnosing COVID-19, guide individual patient management decisions, deal with complications or look for an alternative diagnosis.

With the development of machine learning, deep learning based artificial intelligence (AI) technology has demonstrated tremendous success in the field of medical data analysis due to its capacity of extracting rich features from imaging and complex clinical datasets [10]. Recently, deep learning has been used for diagnosing and distinguishing bacterial and viral pneumonia from thoracic imaging data [11]. In addition, attempts have been made to detect various ECG and chest CT imaging features [12]. In the current COVID-19 pandemic, some preliminary studies have shown promising results for the ECG, chest CT and CXR data analysis and classification [2][3][13]. Besides, small scale initial studies have been done for COVID-19 monitoring [14], screening [15] and prediction of the hospital stay [16].

Exploring the added value of artificial intelligence-assisted disease detection and characterisation may potentially help clinicians to make a prompt correct diagnosis, guide treatment and predict prognosis.

We hypothesise ECGs, CXR and CT scans from patients with confirmed or suspected COVID-19 infection can be used to develop machine learning algorithms that will subsequently diagnose and predict the clinical course of the infection in other patients as well. Furthermore, we believe machine learning and artificial intelligence when applied to ECG, CXR and CT can evaluate the effect of COVID-19 on heart function and more accurately diagnose and prognosticate infection than doctors.

2. STUDY OBJECTIVES

Primary objectives

- We will investigate if the standard electrocardiogram (ECG), which is a conventional clinical tool used record the electrical activity of the heart, a chest X-ray and/or a CT scan, can be used to predict the course and severity of disease in patients with Coronavirus Disease 2019 (COVID-19).

Secondary objectives

- We will also investigate if the standard electrocardiogram (ECG), which is a conventional clinical tool used record the electrical activity of the heart, a chest X-ray or a CT scan, can be used in patients with Coronavirus Disease 2019 (COVID-19) to predict subsequent heart involvement due to the infection.

- We will assess if computer-based analyses are better than doctors at diagnosing features of COVID-19 infection.

3. STUDY DESIGN

This is a retrospective observational study on patients with suspicious and confirmed COVID-19.

The study aims to recruit up to 2000 patients who will be referred to have ECGs, chest X-rays or CT scans at Chelsea and Westminster Hospital NHS Foundation Trust, Imperial College Healthcare NHS Trust and London North West London University Healthcare NHS Trust, since 1 February 2020.

Patients with suboptimal ECGs, chest radiograph and CT studies due to artefacts will be excluded.

The study will gather data retrospective and therefore data collection will cease once the prespecified number of participants is reached.

3.1 STUDY OUTCOME MEASURES

The accuracy with which computer based analysis (machine learning) can diagnose and/or prognosticate Covid-19 infection primarily from ECG, but also from chest xray and CT images.

To determine if computer based analysis (deep learning) enables assessment of the effect of COVID-19 on heart function.

To determine if AI system is superior to cardiology/medical team and/or radiologist assessment.

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

Clinical data will be reviewed by a member of the clinical team and the following clinical and laboratory data will be recorded:

- Gender
- Age
- Height/Weight, body mass index
- Medical history (diabetes, hypertension, coronary heart disease, malignancy, structural lung disease, pulmonary heart disease, chronic liver disease, immunosuppressed population)
- The duration of symptoms at the first visit (days, could be inquired from the main complaint of the patient at the first visit, symptoms including fever, dry cough, headache, myalgia, weakness, etc.)

- Smoking status (Never = 0, Ex-smoker = 1, Current = 2, Unknown = 3)
- Pack Years History
- Current NSAID use
- Current ACEi use
- Current Angiotensin receptor blocker use
- Respiratory rate (breaths/min)
- Heart Rate
- Blood Pressure
- Temperature
- Clinical Classification
- oxygen saturation at a rest state (%)
- arterial partial pressure of oxygen (PaO2)/oxygen concentration (FiO2, mmHg)
- Recovery/Death
- Time/date of the CT scanning
- Time/date of the Chest x ray
- D-dimer
- White blood cell count
- Lymphocyte cell count
- platelet count
- C-reactive protein
- Troponin T
- ALT, AST, ALB, ESR, CD3, CD3 count, CD4, CD4 count, CD8, CD8 count, CD19, CD19 count, IL-6, IL-8, IL-10, TNF-γ
- RT-PCR results for SARS-Cov 2 (Date, results)
- Stay at ICU (days)
- Hospital Stay (days)
- Date or death
- Cause of death
- Intubation
- Date of Intubation
- Time mechanical Ventilation (days)
- NEWS score on arrival

4.2 INCLUSION CRITERIA

To be included in this study the patient must:

- have ECGs, Chest x-ray and/or chest CT imaging (with or without contrast)
- positive laboratory Covid-19 virus nucleic acid test (RTPCR assay with throat swab samples) or clinical suspicion for Covid-19 infection
- be aged >18 years

4.3 EXCLUSION CRITERIA

The presence of any of the following will preclude the patient from the study:

1. Suboptimal ECGs, chest radiographs or CT studies for deep learning methods due to artefacts including severe motion artefacts which causes blurring of the contours of or significant artefacts due to metallic prosthesis which causes image degradation
2. Time-interval between ECGs, chest CT and the RT-PCR assay was longer than 7 days

4.4 WITHDRAWAL CRITERIA

This is a retrospective study and therefore there are no withdrawal criteria, in addition to the inclusion and exclusion criteria.

5. ASSESSMENT AND FOLLOW-UP

This is a retrospective data study and therefore there will be no follow-up. Therefore, there will be no assessments.

As all clinical data will be anonymised, incidental findings will not be reviewed or reported back to individuals or their GP or clinical care teams.

The study will end when the last pseudo-anonymised image has been segmented and ECG feature extracted, and the deep learning algorithm has been trained and validated.

6. STATISTICS AND DATA ANALYSIS

Machine learning algorithms will be trained to differentiate between patient groups (e.g. based on diagnosis or prognosis). For example, for the ECG analyses, in addition to conventional morphological features of QRS, we propose to analyse both temporal and spectrum features of the 12-lead ECG. The spectrum features would include band-powers of different frequency bands, and coefficients of auto-regression (AR) models of different orders would be used as temporal features. Moreover, the temporal stability of features (i.e., how the features vary from beat to beat) and the spatial dispersion of these features (i.e., who the features vary across the 12 leads) will also be investigated.

Data will be analysed by the chief investigator and the research team at the National Heart and Lung Institute, Imperial College London. Anonymised data may be shared with collaborators, for example at University College London, for data processing subject to any required data sharing agreements/approval being in place before the data is transferred.

Data and all appropriate documentation will be stored for a minimum of 10 years after the completion of the study, including the follow-up period.

7. REGULATORY ISSUES

7.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from 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.

An approval from the National Research Ethics Committee (NRES) will be obtained before the start of any study related procedure and other relevant documents. All correspondence with the NRES will be retained in the Study Files.

7.2 CONFIDENTIALITY

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

7.3 INDEMNITY

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

7.4 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.

7.5 FUNDING

This study is not funded from a specific research grant, and the researchers involved are funded through Imperial College London and Chelsea & Westminster Hospital NHS Foundation Trust.

There will be no payments to research participants or researchers.

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.

8. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Imperial College London, Chelsea and Westminster Hospital NHS Foundation Trust and London North West London University Healthcare NHS Trust.

The investigator will make all study documentation and related records available should an auditor inspection occur. Should a monitoring visit or audit be requested, the investigator will make the study documentation and source data available to the Sponsor's representative. All patient data will be handled and treated confidentially

9. PUBLICATION POLICY

The investigators will publish the findings of the study as conference abstract(s) and in peer-reviewed journals.

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