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Exercise testing in the acute setting – the utility of exercise testing to predict safe discharge in acute cardiopulmonary disease including validation of the 40 steps desaturation test in the assessment of acute or suspected COVID-19

Rhys, Gwenllian

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Exercise testing in the acute setting – the utility of exercise testing to predict safe discharge in acute cardiopulmonary disease including validation of the 40 steps desaturation test in the assessment of acute or suspected COVID-19

Dr Gwenllian Haf Rhys BSc MBBCh

Thesis for the degree of Masters by Research (MSc Res)

School of Human and Behavioural Sciences

Bangor University, Wales

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Statements

Statement of Originality

The work presented in this thesis is entirely from the studies of the individual student Gwenllian Rhys, except where otherwise stated. Where derivations are presented and the origin of the work is either wholly or in part from other sources, then full reference is given to the original author. This work has not been presented previously for any degree, nor is it at present under consideration by any other degree awarding body. I confirm that I am submitting this work with the agreement of my supervisors.

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Abstract

The COVID-19 pandemic has led to marked changes in the assessment of dyspnoea in the acute care setting. The role of silent hypoxaemia as a feature of COVID-19 has gathered prominent attention among clinicians, and desaturation on exertion has been proposed as a possible predictive feature for clinical deterioration in COVID-19. Consequently, exercise testing in the acute setting has become a prominent component of the assessment of suspected COVID-19 cases.

The opening chapter of this thesis outlines the pathophysiology of exercise-induced hypoxaemia and explores the proposed mechanisms for the phenomenon in COVID-19. In the second chapter, the evidence base for exercise testing within the acute setting is explored, with focus on the assessment of acute cardiopulmonary disease. It reports on the exercise tests used in the context of COVID-19 and finds that both the 6-minute walk test and a novel, and very brief 10 feet desaturation test have been used, with some proposed links to adverse outcomes. Furthermore, post-exertion oxygen saturation has been linked to clinical deterioration in patients with COVID-19 who had normal oxygen saturation at rest in one multicentre study.

In other acute cardiopulmonary disease, varying exercise tests including walk tests, step tests, sit to stand tests, bicycle and treadmill tests have been utilised with varying success to demonstrate exertional desaturation. Many small studies have shown that exertional desaturation between 2-4% can give insight into safe discharge through links to adverse outcomes including clinical deterioration, rehospitalisation, length of hospital stay, and mortality. However, shorter tests, which are more practical for the acute and space-limited setting are less commonplace, including the 40 steps desaturation test, which features prominently in national and local NHS guidance for triage in suspected COVID-19, but is not validated.

The third chapter aims to establish the validity and feasibility of the 40-steps desaturation test in the acute setting. In a prospective observational cohort study conducted between November 2020 and February 2021, 152 patients were screened and 64 recruited to perform 40 steps on the spot at discharge. Those recruited and able to complete the test were on average younger and less frail than those excluded. Evaluation of the maximum heart rate

achieved during the test suggests this a is a sub-maximal test of exertion, with moderate or above levels of exertion achieved by over 75% of patients.

Four patients were re-hospitalised within 30 days of their discharge, one clinically deteriorated, and no participants died. Most patients showed little change in oxygen saturations during the test, including those with pre-existing respiratory disease. Of the 13 patients with desaturation of 3% or more, none were readmitted within 30 days. Changes in oxygen saturation, heart rate, respiratory rate and patient-reported dyspnoea were not predictive of death or rehospitalisation within 30 days. There were insufficient numbers of COVID-19 patients recruited in this study to conclude the safety and utility of the test in this group.

The 40 steps desaturation test requires further evaluation in a larger study, including in higher numbers of COVID-19 patients to establish its clinical utility. Clinical practicalities favour the use of a shorter exercise test in the acute setting. However, the existing evidence base to support one suitable test is lacking. Desaturation on exertion may have clinical implications for disease progression and prognosis in a range of respiratory conditions including COVID-19. However, some observations in this cohort study that other physiological parameters particularly respiratory rate and dyspnoea may also have an important role, warrants further exploration in COVID-19.

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Abbreviations

Δ – delta

%HR – percentage heart rate

10MeWT – 10 metre walk test

30s-STS – 30-second sit to stand test

3MWT – 3-minute walk test

5-STS – 5 repetitions sit to stand test

6MWD – 6-minute walk distance

6MWT – 6-minute walk test

95% CI – 95% confidence interval

A-a gradient – Alveolar-arterial gradient

$AaDO_2$ – Alveolar-arterial oxygen gradient

ACE2 – angiotensin converting enzyme 2

AECOPD – acute exacerbation of chronic obstructive pulmonary disease

AIDS – acute immunodeficiency syndrome

ARDS – acute respiratory distress syndrome

BCUHB – Betsi Cadwaladr University Health Board

BiPAP – bilevel positive airway pressure

Breaths/min – breaths per minute

Bpm – beats per minute

BP – blood pressure

CCF – congestive cardiac failure

Chi^2 – Chi square coefficient

COPD – chronic obstructive pulmonary disease

COVID-19 – coronavirus disease

CPAP – continuous positive airway pressure

CST – Chester step test

CT – computerised tomography

ECG – electrocardiogram

ED – emergency department

EIAH – exercise-induced arterial hypoxaemia

EWS – early warning score

EU – European Union

FiO_2 – fraction of inspired oxygen

HIV – human immunodeficiency virus

HR – heart rate

HRa – hazard ratio

HRR2 – heart rate recovery within 2-minutes,

P – p-value

HRmax – maximum predicted heart rate

ICU – intensive care unit

IBM SPSS – International business machines statistical package for the social sciences

IPF – idiopathic pulmonary fibrosis

IRAS – integrated research application system

km/h – kilometres per hour

kPa – kilopascal

m – metres

min – minutes

MAU – medical admissions unit

MIST – modified incremental step test

mmHg – millimetre of mercury

NEWS – National early warning score

NHS – National health service

NYHA – New York heart association

OR – odds ratio

$PaCO_2$ – partial pressure of carbon dioxide

PaO_2 – partial pressure of oxygen

PCP – pneumocystis pneumonia

PCR – polymerase chain reaction

PE – pulmonary embolism

PICO – population, intervention, comparator, outcome

PRISMA-ScR – preferred reporting items for systematic reviews and meta-analysis extension for scoping reviews

QS1 – qanadli score 1

QS2 – qanadli score 2

r – pearson correlation coefficient

ROC – receiver operating characteristics

RR – respiratory rate

SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2

SD – standard deviation

SE – standard error

SpO_2 – peripheral saturation of oxygen

V/Q mismatch – ventilatory-perfusion mismatch

VO_2 – maximal aerobic capacity, oxygen consumption or uptake

UK – United Kingdom

USA – United States of America

CHAPTER 1

The pathophysiology of silent hypoxaemia in COVID-19 and its relevance to rapid exercise testing in suspected SARS-CoV-2 infection

Silent hypoxaemia

Since the emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the features of its causative disease, COVID-19 have been extensively studied and described (1). When the virus was declared a pandemic in early 2020, health services worldwide sought to quickly and accurately calculate how to assess and manage increasing case numbers based on emerging evidence from the early affected countries. One puzzling feature of the disease that gained prominence is the phenomenon colloquially referred to as "silent" or "happy" hypoxia; based on observations that critically ill patients with COVID-19 appeared to display minimal features of respiratory distress despite profoundly low oxygen saturation (2). It is important to make the distinction between hypoxia, which refers to insufficient oxygen to support the normal cellular function, and hypoxaemia – a low arterial oxygen concentration, which can lead to hypoxia (3). The term "happy hypoxia" despite its popularity is more in truth referring to low arterial oxygen saturation in the absence of significant symptoms of respiratory distress, making silent hypoxaemia a more accurate description of the phenomenon. However, despite the widespread attention the phenomenon has received, some clinicians have proposed that silent hypoxaemia in COVID-19 may be explained by known mechanisms (4,5).

The early recognition of silent hypoxaemia quickly led to intense focus on identifying hypoxaemia in suspected COVID-19, which was compounded by preliminary findings that hypoxaemia in the context of COVID-19 could be an early indicator of clinical deterioration (6–8). Oximetry has therefore emerged as integral to the assessment of suspected COVID-19 (9), with research suggesting that a higher oxygen saturation threshold for initiating oxygen therapy may have contributed to lower mortality rates during the first waves of the disease in some countries (10).

The pathophysiology of silent hypoxaemia

Peripheral oxygen saturation (SpO_2) is one of the key components of the national early warning score (NEWS), and alongside respiratory rate, heart rate, blood pressure and temperature forms a key clinical tool in healthcare settings designed to give early indication of clinical deterioration (11). Partial pressure of oxygen (PaO_2) measured via arterial blood sampling can offer more accurate measurement of oxygen saturations and is used to characterise respiratory failure. COVID-19 related respiratory failure is more commonly associated with type 1 (hypoxaemic) failure (12), which is characterised by a PaO_2 of less than

8.0 kPa (60mmHg) with a normal or low $PaCO_2$. Hypoxaemic respiratory failure usually arises due to impaired gas exchange. The efficiency of gas exchange within the alveolo-capillary unit can be calculated using the Alveolar-arterial gradient (A-a gradient). An increased A-a gradient is indicative of impaired diffusion, ventilation/perfusion mismatch or intrapulmonary shunting (13). In COVID-19 the A-a gradient is predominantly increased, with ventilation-perfusion (V/Q) mismatch and intrapulmonary shunting proposed as the most likely causes for this observed change (14).

Silent hypoxaemia is not unique to COVID-19, and has been observed in patients experiencing intrapulmonary shunt, and atelectasis. In early COVID-19 infection, arterial hypoxaemia is thought to arise due to ventilation-perfusion (V/Q) mismatch, due to adequately perfused, non-ventilated alveoli (15). As the disease progresses, increased interstitial lung oedema is thought to increase the transpulmonary pressure required to inflate alveoli, which results in reduced lung compliance and increased work of breathing (15,16). Interstitial lung oedema gives rise to the characteristic ground-glass appearance and consolidation on chest radiography typically seen in patients presenting acutely to hospital with COVID-19 (17). The normal physiological response to hypoxaemia is an increase in minute ventilation through an increase in tidal volume and respiratory rate. This could suggest that tachypnoea (increase in respiratory rate) and hyperpnea (increase in tidal volume) could be sensitive clinical signs of hypoxaemic respiratory failure in COVID-19 (18).

Exacerbating factors in COVID-19 are SARS-CoV-2's interaction to upregulate ACE2 (19) and the resulting pro-coagulable state induced (20) which has been noted to lead to intravascular microthrombi, which, if present, will worsen existing V/Q mismatch through reduced blood flow and increasing physiological dead space. One suggested mechanism for the lack of dyspnoea seen in the early stages of COVID-19 disease, includes a direct viral-mediated effect on peripheral oxygen sensing either at the level of the carotid bodies or central nervous system (21,22). Notably, silent hypoxaemia is a feature of early COVID-19 disease, and patients who later deteriorate or require mechanical ventilation have been observed to exhibit dyspnoea (23). Intrapulmonary shunt is thought to be a prominent feature in severe COVID-19, characterised by features of acute respiratory distress syndrome (ARDS), including hypoxemia, bilateral infiltrates on CT, and a decrease in lung compliance (16). Kotwica *et al.* retrospectively calculated the degree of intrapulmonary shunt in COVID-19 patients and their findings suggest a

higher degree of intrapulmonary shunt may also be linked to mortality in COVID-19 (24). Whilst insights into the mechanisms of this process remain incomplete, anxiety surrounding the diagnosis of COVID-19 given the extraordinary public attention given to the mortality from SARS-CoV-2 virus could also impact the perceived dyspnoea caused by the virus, through cortical feedback on central respiratory receptors (25), which must be considered by any researcher wishing to measure dyspnoea in COVID-19 .

Exertional hypoxaemia

In addition to tachypnoea and silent hypoxaemia, it has been suggested that exercise-induced desaturation may also be a prominent early feature to imply future clinical deterioration in COVID-19 (26–28). However, the mechanism by which exertional hypoxaemia arises is not fully understood. The PaO_2 during maximal exertion can vary considerably even in individuals with similar levels of aerobic fitness, as well as with exercise type. Exercise-induced arterial hypoxaemia (EIAH) may happen in the normal physiological response to exertion in healthy individuals, due to an increase in the Alveolar-arterial difference for oxygen ($AaDO_2$), a measure of the efficiency of oxygen exchange at the alveolar-capillary interface (29). When there is an inadequate compensatory hyperventilation response to rises in $AaDO_2$, arterial hypoxaemia can occur (30). However, inadequate hyperventilation is unlikely to play a major role in short or sub-maximal exertion. One of the main contributions to increased $AaDO_2$ during exercise is V/Q mismatch. A prominent physiological hypothesis for V/Q inequality during exercise includes induction of interstitial pulmonary oedema, which has been demonstrated in some studies of maximal exertion (31). It can be hypothesised therefore that the existing interstitial pulmonary oedema in COVID-19 may exacerbate exertional desaturation at lower exercise intensities.

Arterial hypoxaemia may also arise due to the influence of acidity and temperature to cause a rightward shift in the oxygen dissociation curve (27, Figure 1). During hypoxaemic conditions, blood acidity rises due to anaerobic metabolism producing lactic acid. This causes a rightward shift in the oxygen dissociation curve, which increases oxygen release to tissues (27). This temporarily maintained oxygenation could explain silent hypoxia. However, the metabolic contribution to acidosis, through lactic acid production, may be more explanatory. To compensate for metabolic acidosis, carbon dioxide is removed, through increased respiratory rate. However, dyspnoea is not a common reported symptoms to accompany this process,

which may explain lack of dyspnoea in "silent" hypoxia. Increasing the tissue's metabolic demands for oxygen through exercise would worsen existing hypoxaemia as the increased release of oxygen tissues may be insufficient to meet demands. High exercise intensity will also exacerbate lactic acid production and raise temperature exaggerating rightward shift of the curve.

Diffusion capacity for carbon monoxide has also been shown to be decreased in COVID-19 patients, particularly those with more severe disease (32), leading some to suggest that pulmonary diffusion impairment could be a mechanism for EIAH in COVID-19. In maximal exercise this could be explained by a severely reduced capillary transit time not allowing an adequate duration for gas exchange to occur. However, at submaximal exercise, capillary recruitment is not likely to be maximal, and therefore reduction in capillary transit time is unlikely to be raised significantly enough to impact PaO_2 (29). The alternative explanation for a diffusion impairment leading to EIAH includes a damaged alveolar epithelial membrane secondary to the immune response to SARS-CoV-2 (33), which coupled with a diminished vasoconstriction response could give rise to an increased Alveolar-arterial gradient and induce hypoxaemia with minimal exertion (30).

In a patient with normal oxygen saturation at rest, the primary mode for developing EIAH in COVID-19 is likely to be exacerbation of existing V-P mismatch by increased oxygen demand. This could be coupled with a diffusion impairment from alveolar-capillary membrane disruption by inflammation. Exacerbation of rightward shift in the oxygen curve is likely to be a factor in producing EIAH in patients with hypoxaemia at rest, or a secondary factor exacerbating hypoxaemia in patients with V-P mismatch attempting prolonged exercise.

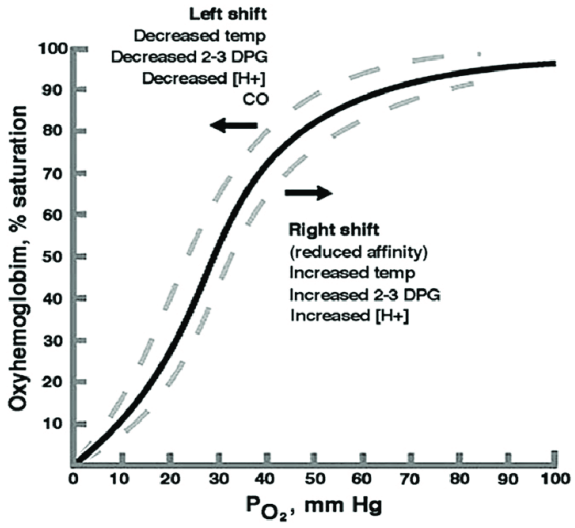

Figure 1 – Oxygen dissociation curve

During hypoxaemia, shifts in the oxygen dissociation curve can have significant effects on PaO_2. In SARS-CoV-2, the inflammatory response gives rise to fever, with impaired gas exchange and thrombosis contributing to hypoxaemia. This in turn leads to lactic acid production increasing blood acidity. Hypoxaemia also leads to an increase in the blood concentration of 2,3-DPG. These mechanisms combine to reduce haemoglobin's (Hb) affinity to oxygen, leading in the short term to increased release of oxygen to tissue, but also reduced binding of Hb oxygen in the lungs, exacerbating hypoxaemia (27).

Image obtained from: *Alvertson, B. et al. 2014. Clinical practice guideline: the diagnosis and management and prevention of Bronchiolitis. Paediatrics. 134(5).*

Thesis Aims

Understanding the mechanisms that underline the presentation and progression of COVID-19 to severe acute respiratory distress syndrome is key to developing strategies to recognise and ultimately prevent clinical deterioration and death from SARS-CoV-2 infection.

In the early pandemic when treatments for COVID-19 were supportive, with randomised control trails for medicinal treatments including convalescent plasma, steroids, and various antivirals still in their infancy, healthcare systems across the world were preparing their emergency guidelines for frontline clinicians on how to assess and manage COVID-19. Case reports detailing the clinical feature of silent hypoxaemia in COVID-19, led to a focus on assessing a patient's oxygenation. This led many healthcare systems to adopt the use of a short exercise test within their triage guidelines for suspected COVID-19.

This approach mirrors some of the approaches used during the HIV pandemic in the 1980s, which initially came to the attention of clinicians via an increase in the respiratory disease pneumocystis pneumonia (PCP). PCP is similarly characterised by exertional hypoxaemia and was tested for by using tests of exertion, in the absence of rapid diagnostic testing for the condition.

The rapid exercise test introduced for COVID-19 in the UK was the 40 steps desaturation test, a short walking test involving 40 steps of walking. The test was proposed for use in the acute setting on patients with normal oxygen saturation and other physiological parameters at rest, as a way of verifying that a patient otherwise being considered for discharge was safe to go home. The test was also used in primary care settings as a decision tool for whether to admit patients with respiratory symptoms including COVID-19 to hospital for assessment. Two years later, this test which prior to its introduction had never been described within the literature remains in use in the acute medical setting to discharge COVID-19 patients with mild symptoms.

Whilst it must be acknowledged that the creation of the 40 steps test, and its implementation was done in a crisis setting, where pressure on hospital beds were expected to be insurmountable, and resources stretched to breaking point, it is also imperative that this now widely used tool is validated for this purpose. Additionally, it must be considered whether other short exercise tests are currently in use or validated, that may be more suitable for adaptation to the context of the COVID-19 pandemic.

The second chapter of this thesis comprises a scoping review into the use of exercise testing in the acute clinical setting, which explores the use of short exercise tests to aid with safe discharge or ensure safe ongoing care. Specific research within the assessment of COVID-19 is presented, as well as exercise tests used in other acute cardiopulmonary to aid with safe discharge or predict rehospitalisation or clinical deterioration. This is followed by a discussion on the most suitable exercise tests for use within the acute setting, both for COVID-19 and other acute cardiopulmonary disease.

The third chapter will present the findings of original research aiming to provide validation to the 40 steps on the spot test, in the acute hospital setting. The test was completed by patients at discharge from hospital, with oxygen saturation, heart rate, respiratory rate and dyspnoea monitored before and after the test. We assessed the outcome for these patients at 30 days, including rehospitalisation, clinical deterioration, and death. The results will be used to discuss the suitability of the 40 steps test as a discharge decision tool in COVID-19 and other acute illness. The thesis will conclude with a general discussion and summary from both chapters and propose relevant future directions for research and clinical practice.

CHAPTER 2

Exercise testing in the acute setting to guide safe discharge – a scoping review

2.1 Introduction

The role of oximetry in acute breathlessness

Dyspnoea or breathlessness is one of the most prevalent symptoms reported in patients presenting to emergency and ambulance services (34). The assessment of any patient presenting with acute breathlessness routinely includes measurement of oximetry as part of the Early Warning Score (EWS), a tool instrumental in identifying the physiological deterioration that frequently precedes clinical deterioration in patients (11). In clinical practice the measurement of oximetry can prompt early initiation of oxygen therapy as well as indicate underlying lung disease, whether acute or chronic.

Silent hypoxaemia in COVID-19

The phenomenon of silent hypoxaemia, although not unique to COVID-19, has received much clinical attention. It has been recognised that having lower oxygen saturations, in the absence of a co-morbid chronic lung disease, could be an indicator of future respiratory failure in COVID-19 (6–8), which has led to the integral role of oximetry in the assessment of suspected COVID-19 (8). Goyal *et al.* (10) report a higher rate of mortality in countries where a lower value of oxygen saturation was recommended prior to initiation of oxygen therapy. Whilst this highlights a potentially important link between supplemental oxygen and mortality, other factors including high case load and resource availability in these countries may have also influenced these outcomes (35).

Exertional hypoxaemia as an indicator of clinical deterioration

As well as the phenomenon of silent hypoxia, there have been reports of patients presenting with COVID-19, who have normal oxygen saturation at rest, and develop hypoxaemia on exertion (36). Consequently, exercise testing has formed a key part of national guidance for the assessment of suspected COVID-19, within primary care and emergency departments (37-39). The recommendation for using exercise tests appears to be limited to circumstances where hypoxia is not present at rest. Emerging evidence of exertional hypoxaemia in COVID-19 as a potential indicator of future deterioration (40), has increased interest in an appropriate exercise test within the acute setting to detect exertional desaturation.

To date, exercise testing for the purpose of identifying exertional hypoxaemia appears to be primarily focused on the long term monitoring and prognostication of chronic respiratory disease patients in the outpatient setting (41). Literature on exercise testing for detection of exertional hypoxaemia in the acute setting was, prior to the COVID-19 pandemic, less commonplace. Possibly the most relevant research to the current medical context are studies from the AIDS epidemic aiming to differentiate the respiratory disease Pneumocystis pneumonia (PCP) from other pneumoniae in HIV positive patients. PCP shares clinical, radiological and pathophysiological features with COVID-19, including, most notably, exertional desaturation (42). Previous studies have demonstrated that lack of desaturation during an exercise test could rule out PCP as a diagnosis (43), a finding which has interesting implications for exercise testing within COVID-19.

Exercise testing in COVID-19

The "40 steps" desaturation test initially appeared on NHS England guidance for Emergency Department assessment during the first wave of the pandemic in the UK (38). Greenhalgh *et al.* used a panel of front line clinicians to gather consensus on a risk score for suspected COVID-19 in primary care, which includes a suggestion to use this test in patients with oxygen saturations above 96% (44). A drop of oxygen saturation of 3% was proposed as a threshold to prompt transfer to hospital, which corresponds with the definition of exertional hypoxaemia outlined in the British Thoracic Society guidance on oxygen prescription (45). The 40 steps test does not appear to have been validated in existing literature but may more closely resemble the non-standardised walking tests (e.g., walking the length of a ward) used commonly in clinical practice. Such non-standardised tests may occasionally inform a clinician's decision to discharge a patient from hospital. Whilst a pre-defined length of test attempts to bring consistency to decision making after exercise testing, exertional hypoxaemia noted during a test that has not been validated must be interpreted with caution.

Other exercise tests that have been proposed for use in assessing COVID-19 patients with normal oxygen saturations at rest and no resting dyspnoea include the 6-minute walk test (46,47); a test which involves walking for 6-minutes on a course of 30 metres in length. With this test, desaturation as well as 6-minute walk distance are measurements that could be assessed in relation to COVID-19 outcomes. A shorter 3-minute walk test could also be feasible in frail patients, who may struggle to complete 6 minutes of walking (48). The 1-minute sit to stand test

has also been proposed as a potential short test suitable for the acute or remote setting (36) although the exertion and lower limb strength this requires may make this challenging in in frailer adults.

Rationale for scoping review

There are a wide range of exercise tests in general use with differing capabilities to assess lung function, exercise capacity, muscle strength, and frailty. Some require equipment or stairs (49), while others such as the 6-minute walk test may be too time-consuming, or impractical in the acute setting (50). Factors such as poor mobility, or unsteady gait may also influence how achievable various exercise tests are within the general patient population. Furthermore, in the era of the COVID-19 pandemic, where patients may also need to be assessed virtually, space in their own homes as well as access to a pulse oximeter may be requirements of a suitable test.

There is an urgent need to identify an appropriate rapid exercise test that can be used in the acute setting to assess exertional desaturation in the unwell patient, particularly those suspected of having COVID-19. Furthermore, the pressure presented by high numbers of COVID-19 cases attending primary and secondary care settings during each new wave of the virus, makes it essential that such a test adequately distinguishes patients most at risk of deterioration, who would most benefit from further investigation and hospitalisation. It is desirable that patients who do not exhibit exertional desaturation during the test are also safe to recover from their illness at home, which could ease pressures on hospital capacity during periods of high demand.

Objectives

This chapter consist of a scoping review, which aims to describe the existing use of exercise testing in the context of suspected Covid-19. It will assess the utility of standardised exercise tests in the acute setting, and whether there is evidence of these being applied to promote safe discharge from hospital, or identify patients at increased risk of clinical deterioration, with focus on tests used to assess lung function. The review will be used to form recommendations of appropriate exercise tests for the acute setting, and to propose future research for suitable exercise tests that could be used to identify exercise-induced hypoxaemia in the context of COVID-19, and other causes of acute breathlessness.

Review questions

This review aims to identify where exercise tests have previously been used in the clinical setting as a discharge decision aid, or way of escalating more rapid definitive diagnosis and management.

The review questions for the purpose of this study include:

- Which existing exercise tests have been used as part of patient assessments in the acute setting to promote safe discharge?
- Which exercise tests have been validated for this use in the context of COVID-19?
- Which exercise tests have been shown to effectively demonstrate exertional desaturation, and can they be safely applied to an acute setting?
- Does existing evidence support the use of an exercise test be used to promote safe discharge, or reduce length of stay, rate of readmissions, or mortality in the acute setting?
- What degree of desaturation during an exercise test is significant for outcomes including safe discharge, hospitalisation, mortality, or length of stay?

2.2 Methods

Scoping review

The literature review follows a scoping review format to gain insights into the relevant existing research in this area and identify key areas where further study is most needed in the context of the COVID-19 pandemic. Arksey and O'Malley's framework (51) was applied to undertake the review, which broadly includes the following five steps:

1. Defining the research question(s)
2. Searching the literature for relevant studies
3. Selecting studies meeting the pre-defined research question
4. Presenting the data
5. Collating the findings and summarising the results

A protocol for the scoping review was designed with reference to the Preferred Reporting Items for Systematic Reviews and Meta-analysis extension for Scoping Reviews (PRISMA-ScR) (52) guidelines. This was written prospectively, although it was not formally registered (Appendix A).

Eligibility criteria

The review aims to collate the literature on exercise testing performed in the acute setting with the intention to inform safe discharge and/or provide safe ongoing care, with particular focus on tests that assess exertional desaturation. PICO (Population, Intervention, Comparator and Outcome) criteria were used to select eligible studies (53). The PICO question for this review is: "Which exercise tests (I) can be used in the assessment of adults in acute setting (P), in addition to usual care (C), to promote safe discharge from hospital (O)?"

Inclusion criteria

Population

The population included in the review are adults aged 18 years or older. Studies specifically in suspected and confirmed COVID-19, other lung diseases and other medical conditions that may present with acute dyspnoea or exertional desaturation, including

exacerbation of chronic lung disease, pulmonary embolism, pneumonia, and decompensated congestive cardiac failure are included. Patients assessed in any of the following acute care settings are included:

- Emergency Department
- Acute Medical Unit
- Inpatient wards
- Intensive Care Unit
- Ambulance Service
- Primary Care

Intervention

Included interventions are any exercise test used in the assessment of patients as part of the admission or discharge decision making process. “Exercise test” is defined as any of the following:

- Walking test of any distance or duration
- Step test involving stair climbing, step or on the spot stepping for any duration
- Sit to Stand test of any duration or repetition
- Exercise involving equipment e.g., treadmill or bicycle ergometer
- A combination of the above e.g., Get up and go test

Comparator

Comparison to usual care is included whether this involves no exercise intervention or comparison to a different type of exercise test.

Outcome

The primary outcome of interest is safety of discharge from the use of the test defined by any of the following:

- Readmission to hospital rate

- Mortality rate
- Length of stay in hospital during the primary admission
- Results of further investigations and/or interventions, prompted by an abnormal result during the exercise test

Secondary outcomes include:

- Feasibility of the exercise test in an acute or resource/space limited setting
- Safety of the exercise test in an acute or resource/space limited setting i.e., rate of complications, and false negative assessments
- Reliability, and validity of the test to detect exertional desaturation

Exclusion criteria

Population

The following populations specifically are excluded:

- Preoperative and postoperative patients
- Acute coronary syndrome
- Non-healthcare settings e.g., armed forces personnel, athletes

Intervention

Exercise not meeting the pre-defined criteria for “exercise test” include:

- Cardiopulmonary resuscitation
- Level of physical activity (e.g., number of steps walked per day) or general mobility
- Exercise testing as part of measuring the efficacy of a rehabilitation programme rather than an assessment in an acute care setting
- Exercise testing combined with the use of specialised equipment, not usable by a clinician without specialised expertise (e.g., echocardiography, and CT imaging modalities)

Comparison

Where the exercise testing is used to compare the response to different environmental conditions e.g., altitude, or presence or absence of supplemental oxygen this is excluded.

Outcome

Excluded outcomes are cost effectiveness of an exercise test as part of specific clinical pathway, and rehabilitation outcomes such as gait speed and balance.

Study types

Randomised control trials, cohort studies, case-control studies, and observational studies (prospective and retrospective) are included. Descriptive papers, case series and case reports are excluded, along with response letters, guidelines, and position statements. Systematic reviews or other literature reviews have been screened for references of any relevant studies that met the inclusion criteria outlined. References of identified papers have then been screened for further relevant studies ("snowballing"). The search criteria has not been limited based on study publication date, language, or location.

Search strategy

The databases used in the search are PubMed, AMED, Embase, CINAHL and LitCovid for published studies, and the ClinicalTrials.gov and Clinical Trials registry (EU) databases for ongoing studies. The search terms used can be seen in full in Appendix B.

Study selection

The Rayyan (54) platform was used to screen abstracts, with two reviewers independently deciding on inclusion and exclusion using the above outlined criteria. Discrepancies between reviewers' decisions were referred to a third independent reviewer, as required, to decide on inclusion. A full text review of all included papers was used confirm eligibility. The study selection is reported using the standards outlined in the PRISMA-ScR guideline (52).

Data extraction

From the selected studies, the following data was extracted by a single author.

- Study methods (title, date of study, study design)
- Setting (country, location of recruitment i.e., emergency department, primary care etc., person undertaking the testing, resource utilisation)
- Participants (age, diagnosis, COVID-19 status, sex, ethnicity, inclusion, and exclusion criteria)
- Intervention (Type of exercise test, location and physiological monitoring recorded e.g., oxygen saturation)
- Comparator (where applicable)
- Outcomes including rehospitalisation, length of stay and mortality
- Conclusions including safety and feasibility of the test in the acute setting

Critical appraisal

Assessment of the quality of research including risk of bias was not assessed formally within the scope of this review.

Data handling and analysis

A pre-designed schematic diagram was used to report on the selection process. The main findings of the papers included are reported and discussed, starting with exercise testing in COVID-19 and then within other acute cardiopulmonary disease, followed by a discussion of the main findings and implications for research and clinical practice.

2.3 Results

Selection

The search yielded 1,944 records of which 339 were duplicates. Of 1,612 original records screened, one abstract could not be sourced, and 1,582 were excluded. A further seven were excluded following full text review and discussion between the two screening authors. One additional study was identified through screening relevant review citations (snowballing). Seventeen completed studies and two ongoing studies were included in the analysis stage (Figure 2).

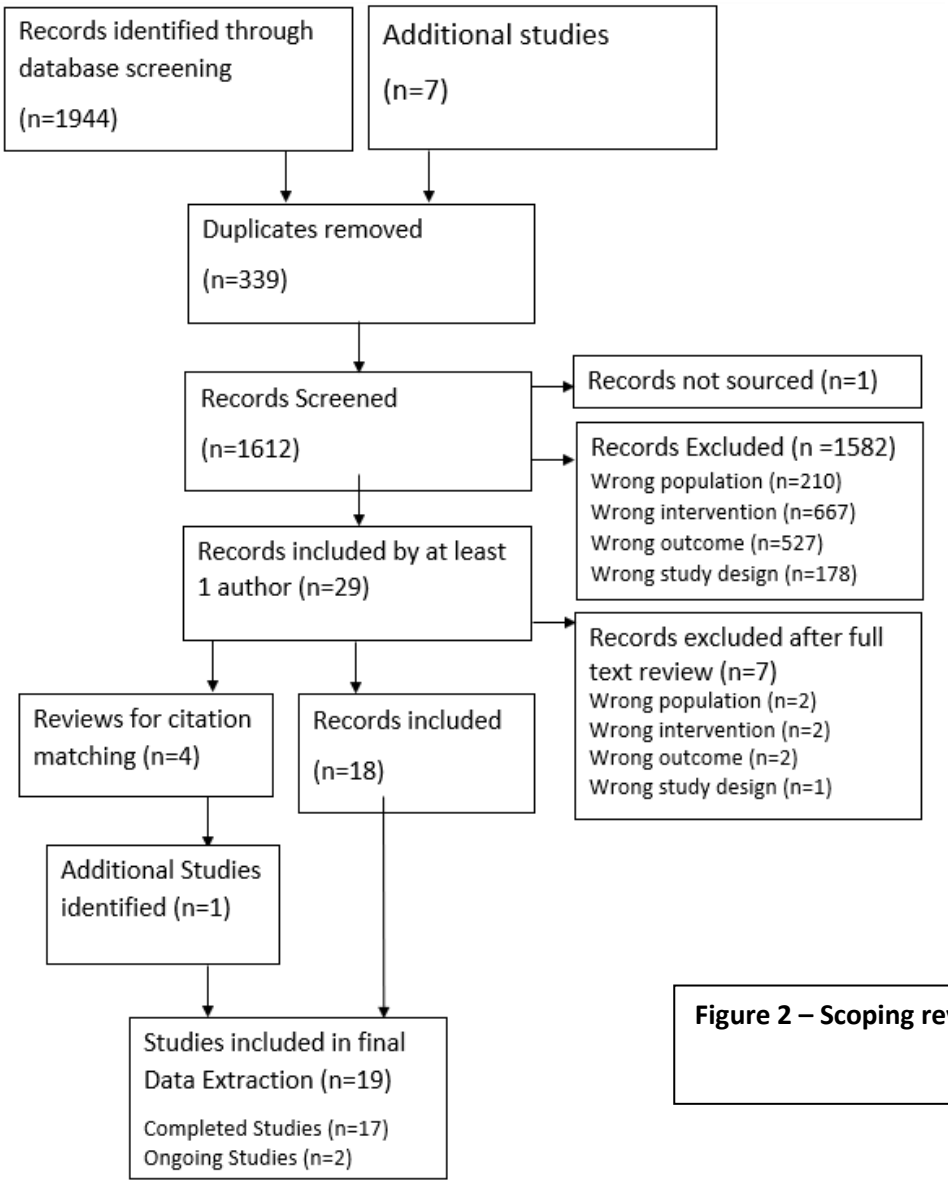

Figure 2 – Scoping review study selection

Reference	Study type	Setting	Diagnosis	Sample	Demographics
Kamran *et al.* 2020. (55)	Single-centre cross-sectional study	Hospital, Pakistan	COVID-19	252	Age, median (range): 63 (29–85) Sex, %: Male 61.5
Fuglebjerg *et al.* 2020. (56)	Prospective cohort study, retrospective control group	Hospital, Denmark	Cases: COVID-19 Controls: IPF	Cases: 26 Controls: 204	Age, median (IQR): 59 (50-70) Sex, %: Male 86.5
Banzi *et al.* 2020. (57)	Pilot feasibility study	Primary care, Italy	Suspected or confirmed COVID-19	37	Age, median (range): 53.9 (23-83) Sex, %: Male 27%
Goodacre *et al.* 2021. (40)	Observational Cohort study (mixed prospective and retrospective methodology)	Multicentre, ED, UK	Suspected or confirmed COVID-19	817	Age, mean (SD): 58.4 (24.2) Sex, %: Male, 49.2, Female, 49.9, NR 0.9 Ethnicity, %: White 58.1, Asian 8.2, Black 5.8, Mixed/Multiple 2.2, Other 5.8, Not recorded 20.0
Chouaid *et al.* 1993. (58)	Prospective cohort study	Respiratory Unit, France	HIV positive, suspected PCP	85	Age, median (range): 35 (25-60) Sex, %: Male 90.5
Sauleda *et al.* 1994.(59)	Case-control study	ED, Spain	HIV positive, Cases: PCP Controls: non-PCP	Cases: 22 Controls: 23	Age, mean (SE): cases 31(1), controls 28(1)
Amin *et al.* 2015. (60)	Prospective cohort study	ED and rapid access clinic, Canada	Suspected PE	114	Age, mean: 52.9 Sex, %: Male 36.8
Danielsbacka *et al.* 2018. (61)	Cross-sectional study	Medical Admissions Unit, Sweden	PE, subdivided to 2 groups based on vessel occlusion	50	Age, mean (SD): 54.7 (9.9) Sex, %: Male, 39
Sakai *et al.* 2019. (62)	Prospective cohort study	Hospital, Japan	Interstitial pneumonia	73	Age, mean: 68.5 Sex, %: Male 63
José and Dal Corso. 2016. (63)	Case-control study	Hospital, Brazil	Cases: acute lung disease Controls: healthy volunteers	Cases: 77 Controls: 20	Age, mean: 56 (36-68) case, 52 (41-66) control Sex, %: Male 59.7

Reference	Study type	Setting	Diagnosis	Sample	Demographics
Kakavas *et al.* 2020. (64)	Observational cohort study	Pulmonary Unit, Greece	AECOPD	22	Age, mean (SD): 67.2 (7.2) Sex, %: Male, 63.
Pan *et al.* 2009. (65)	Prospective cohort study	ED, Canada	CCF, COPD, and stable chest pain	40	Age, mean (range): 69 (53–91) Sex, %: Male, 60.
Kichura *et al.* 2020. (66)	Prospective cohort study	ED, USA	Heart Failure	50	Age, median (SD): 66.2 (±12.5) Sex, %: Male 42
La Rovere *et al.* 2015. (67)	Retrospective cohort study	Cardiology Unit, Italy	Heart Failure	466	Age, mean (SD): 61.3 (±11.0) Sex, %: Male 35.0
Howie-Esquivel and Dracup. 2008. (68)	Prospective pilot Study	Hospital, USA	Heart Failure	44	Age, mean (range): 59.6 (27-100) Sex, %: Male 65.9 Ethnicity, %: Caucasian/White: 50 African American/Black: 29.5, Hispanic/Latino: 11.4 Asian/Pacific Islands: 9.1
McCabe *et al.* 2017. (69)	Observational cohort study	Hospital, USA	Heart Failure	71	Age, mean (SD): 52.6 (12.3) Sex, %: Female, 42.3 Ethnicity, %
Denehy *et al.* 2013. (70)	Nested cohort study	ICU, Australia	ICU inpatients	144 at admission, 116 at discharge	Age, mean (SD): 60.4 (15.8) Sex, %: Male, 63

Table 1 – Demographics of included studies

Abbreviations: AECOPD; Acute exacerbation of chronic obstructive pulmonary disease, CCF; Congestive cardiac failure, COPD; Chronic obstructive pulmonary disease, COVID-19; Coronavirus disease, ED; Emergency department, HIV; Human immunodeficiency virus, ICU; Intensive Care Unit, IPF; Idiopathic pulmonary fibrosis, PCP; Pneumocystis pneumonia, PE; Pulmonary embolism, SD; Standard deviation, SE; Standard error, UK; United Kingdom, USA; United States of America.

Scope of exercise testing in the acute setting

Six studies - four completed and two ongoing - in COVID-19 met the eligibility criteria. In addition, twelve studies conducted in a range of acute lung and cardiac conditions were included. The demographics of the studies included are summarised in Table 1.

A general overview of all included exercise tests is provided in Appendix C. Seven studies included a 6-minute walk test (6MWT), either as a primary test or as a comparison to a prospective test (61,62,67-69). Two studies included a shorter version: the 3-minute walk test (60,65). Another describes a 10 feet desaturation test which involves walking a distance of 10 feet (55). Two other studies used a non-standardised or non-specified rapid walk test. One ongoing study aiming to validate the 40 steps desaturation test was also identified (71).

Step tests included the Chester step test (72) and Modified incremental step tests (73) Two versions of a sit to stand test were also identified; a five repetition sit to stand test, and 30-second sit to stand (74,75). Two-minute and 3-minute variations of a Bicycle Ergometry test were used in two studies involving fixed speed increments (59,66), and another study used fixed increasing increments of a treadmill test over a total duration of 8 minutes (58).

Exercise testing in suspected or confirmed COVID-19

Studies involving exercise testing in confirmed or suspected COVID-19 are summarised in Table 2. Kamran *et al.* assessed 252 COVID-19 positive patients upon admission to hospital, using a 10-feet desaturation test, with the intention of detecting minimal exertional desaturation (55). Sixteen patients were classified as mild, 99 moderate, 115 severe and 22 critical disease at admission, and monitored for clinical deterioration defined as moving up a severity rating. After the exercise test, oxygen saturation decreased by 3% from pre-exercise SpO_2 in the 128 stable patients, compared to 9% in the 124 patients who clinically deteriorated ($p<0.001$), and 15% in 49 patients who died ($p<0.001$). More than half (51.6%) of the patients who remained stable desaturated ≥3%, compared to 83.6% of the clinically deteriorating group and 95.9% of the mortality group (Chi square test, $p<0.001$). However, on multivariate Cox regression analysis, desaturation during the 10 feet test was not found to be a significant predictor of disease progression (HR 0.99, CI 0.95-1.04, p=0.706).

Reference	Intervention	Monitoring	Outcome
Kamran *et al.* 2020. (55)	10 feet walk O_2 desaturation test at hospital admission	SpO_2 using pulse oximeter, supported by ABG - ≥3% desaturation defined as notable	**128 Stable**, n(%): • < 3%: 62 (48.4) • ≥3%: 66 (51.6) **124 Clinical deterioration**, n(%): • < 3%: 17 (13.7) • ≥3%: 107 (86.3) (Chi^2 p<0.001) **49 Mortality,** n(%): • < 3%: 2 (4.1) • ≥3%: 47 (96.0) (Chi^2 p<0.001) Univariate HR: 3.89 (2.33-6.49) p< 0.001 Multivariate HR: 1.44 (0.78 – 2.62) p= 0.227
Fuglebjerg *et al.* 2020. (56)	6MWT at hospital discharge	SpO_2 using pulse oximeter – terminated early if below 90%	SpO_2 <90%: • 13 (50%) • 6 (46.2%) **investigated further**. • 4 (66.7%) PE confirmed
Banzi *et al.* 2020. (57)	Daily rapid walk test as admission decision tool	SpO_2 using pulse oximeter - ≥5% desaturation or <90% on exertion used as trigger for hospitalisation	0% patients desaturated ≥5%, 4 (11%) recorded SpO_2 <95% during study period. 1 (3%) patient a**dmitted to hospital** • SpO_2 on arrival 89% • Escalated to CPAP Insufficient sample size for feasibility conclusions
Goodacre *et al.* 2021. (40)	Exertional test (not standardised)	SpO_2 following exertion – method of obtaining not specified - ≥3% desaturation considered significant	Baseline SpO_2: • **30-day adverse outcome**: 94.5% • No adverse outcome: 97.1% Mean desaturation: • **30-day adverse outcome**: -2.9% • No adverse outcome: -1.9% Primary analysis: • c-statistic - 0.59 (95% CI 0.465-0.713) • PPV of ≥3% desaturation 1.78 (95% CI 1.25-2.53) • 0.67 of ≥3% desaturation (95% CI 0.46-0.98) Secondary* analysis: • c-statistic - 0.67 (0.46 to 0.98) • PPV of ≥3% desaturation – 1.98 (95% CI 1.26-3.10) • NPV of ≥3% desaturation – 0.61 (95% CI 0.35-1.07)

Table 2 – Exercise testing in COVID-19

Abbreviations: 6MWT; 6-minute walk test, 95% CI; 95% confidence interval, ABG; Arterial blood gas, Chi2; Chi square, CPAP; Continuous positive airway pressure, c-stat; concordance statistic, CXR; Chest X-Ray, ITU; Intensive treatment unit, O_2;; Oxygen, HR; Hazard ratio, n; number, NPV; negative predictive value, p; p-value, PE; Pulmonary embolism, PPV; positive predictive value, SpO_2; peripheral oxygen saturation.

*Excluded ages <16, SpO_2 <94%, National early warning score >3 (76).

A small study by Fuglebjerg *et al.* (56) screened 47 inpatients with COVID-19, who displayed SpO_2 >94% and absence of fever, and recruited 26 participants without pre-existing lung or cardiac disease. A six-minute walk test (6MWT) was performed at discharge, and compared to a retrospective cohort with idiopathic pulmonary fibrosis. Thirteen participants terminated the 6MWT due to desaturation below SpO_2 90%, of whom six had been admitted to ITU, two received mechanical ventilation, and all had bilateral infiltrates reported on chest radiography. Only six of the thirteen cases were investigated further for Pulmonary embolism (PE) following an earlyterminated 6MWT, but of those investigated four (66%) tested positive for PE.

Banzi *et al.* conducted a study in primary care (57) to assess the feasibility of a daily rapid walk test as an admission decision tool. Desaturation of more than or equal to 5%, or a fall in SpO_2 below 90%, was used to prompt admission to hospital. None of the 37 participants desaturated more than 5%, and only one patient was admitted to hospital due to SpO_2 <90% at rest; SpO_2 on arrival was 89% and the patient required continuous positive airway pressure ventilation (CPAP). Due to the small sample obtained conclusions about feasibility were not reached.

Goodacre *et al.* in a multicentre study involving 70 sites (40) analysed 22,000 records retrospectively, identifying 817 suspected or confirmed COVID-19 cases presenting to emergency departments who had post-exertional oxygen saturations recorded as part of routine care. The exertional test used was not standardised and could include asking the participant to exercise in a specific way or opportunistically recording oxygen saturation after the patient had exerted themselves. Adverse events were recorded including death or need for respiratory, cardiovascular, or renal support.

Those with no adverse event had a baseline SpO_2 of 97.1% and a mean desaturation of 1.9% on exertion. The mean oxygen saturation at baseline was lower in the adverse outcome group at 94.5%., with mean desaturation on exertion also greater at 2.9%. A post-exertion reduction in SpO_2 of 3% or more was found to be optimal at predicting adverse outcome, giving a positive likelihood ratio for an adverse outcome of 1.78, and a negative likelihood ratio of 0.67. Exertional desaturation was not found to be predictive of adverse outcomes in the primary analysis cohort (model coefficient p=0.368, likelihood ratio with and without post-exertional SpO_2 0.78, p=0.376). A secondary analysis cohort which excluded participants with baseline

SpO_2 <94%, NEWS score (76) of three or more, age below 16 years, and limited ability to self-care, gave a model coefficient p value of 0.019, but a likelihood ratio with and without post-exertional SpO_2 of 4.82 (p=0.078), giving a tentative indication that post-oxygen saturations could be predictive of adverse outcomes in this group.

Two registered clinical trials, each assessing exertional desaturation in COVID-19 were identified as being in the recruitment phase (see Appendix D). Preliminary data from one of these is presented in the following chapter. The other, by Artaud-Macari *et al.* aims to examine the efficacy of the 1-minute sit-to-stand test to guide decision to discharge COVID-19 patients (77).

Exercise testing in other acute illness

Six-minute walk test

Studies using a six-minute walk test (6MWT) are summarized in Table 4. Danielsbacka *et al.* (61) used a 6MWT performed at discharge in 50 patients with Pulmonary embolism (PE), and found 17% of the cohort desaturated below 90% by the end of the test. Heart rate recovery at 2 minutes was not significantly different depending on degree of vessel occlusion by the PE, calculated using a Qanadli score assigned by a qualified radiologist (78). However, there were significant differences in the 6-minute walk distance (6MWD) depending on degree of vessel occlusion, with Qanadli score 1 (QS1) group (i.e., those with lesser degree of vessel occlusion) walking further (mean 516 ± SD 98.4) than the Qanadli score 2 (QS2) group (more severe vessel occlusion); mean 446m ± SD 137.4, p = 0.05. The dyspnoea score using the Borg scale post-6MWT was also significantly higher in the QS2 group compared to QS1 (p= 0.01).

Sakai *et al.* (62) conducted a 6MWT at time of discharge from hospital in 73 patients with interstitial pneumonia. Using receiver operator characteristic (ROC) curves of the SpO2 recovery index, 4% desaturation during the 6MWT was optimal to predict rehospitalisation within 12 months from respiratory-related events (71.4% sensitivity, 79.2% specificity, positive likelihood ratio 3.43). SpO_2 recovery index was calculated using the difference between a subject's SpO_2 measured 1 minute after the 6MWT, and the lowest recorded SpO_2 at the end of the 6MWT (measured at the point the study was terminated or completed), divided by the resting SpO_2 and multiplied by 100 [(SpO_2 1 min into recovery – lowest SpO_2)/Resting SpO_2 x 100]. Kaplan-Meier analyses compared ≥4% with <4% and demonstrated a significant association with

rehospitalisation (p <0.001). On Cox regression univariate analysis SpO_2 recovery index, SpO_2 at 1 min, Heart rate recovery in 1 minute, were all significantly associated with respiratory-related rehospitalisation (p<0.05). SpO_2 recovery index was significantly associated with rehospitalisation on multivariate analysis (HR 0.30 (95% CI 0.10-0.90), p=0.03).

La Rovere *et al.* (67) assessed the value of a 6MWT at discharge in addition to two clinical risk scores, the 3C-HF (79) and MAGGIC scores (80), to predict 12-month mortality in 466 heart failure patients. 6MWD was significantly lower in participants who died within 12-months at 311.1 metres versus 408.9 metres in those who were alive (p<0.0001). The 6MWT alone predicted risk of death within 12-months (HR 1.007 (95% CI 1.005-1.010, p<0.0001), and provided additional prognostic information when combined with the 3C-HF and MAGGIC scores. A prospective pilot study by Howie-Esquivel and Dracup (68) conducted the 6MWT in 44 patients with heart failure 24-48 hours prior to discharge, with lowest SpO_2 recorded. On univariate analysis, no association was found between the lowest SpO_2 value and 90-day cardiac-related rehospitalisation (HR 1.01, 95% CI 0.94-1.08, p= 0.78). However, 6MWD was significantly associated with rehospitalisation (HR 0.99, 95% CI 0.99-1.00, p=0.06).

Seventy seven patients hospitalised with acute decompensation of heart failure completed a 6MWT at discharge in the final study by McCabe *et al.* (69). Mean 6MWD was significantly lower in patients hospitalised within 30-days (536 m, SD 434) compared to those who did not require readmission (811 m, SD 380, p<0.02). A higher 6MWD was associated with reduced odds of readmission on univariate (OR 0.85, 95% CI 0.73-0.98), and multivariate analysis (OR 0.84, 95% CI 0.71-0.99). 25% of patients had an interruption in the 6MWT and patient's readmitted to hospital were more than twice as likely to stop during the 6MWT (42.9% compared to 21.1%), although this finding was not statistically significant (p=0.09).

Reference	Intervention	Monitoring	Outcome
Danielsbacka *et al.* 2018. (61)	6MWT on day of discharge	Masimo Rad 5 pulse oximeter finger probe Significant desaturation defined as end-test SpO_2 <90%, or HRR2 <22 bpm	6MWD, distance m(SD): • QS1 516 (98.4) • QS2 446 (137.4) (p =0.050) 17% Desaturation below 90%: • 38% QS1 • 62% QS2 • 100% SpO_2 ≥ 94% at 2 mins
Sakai *et al.* 2019. (62)	6MWT at discharge	Pulsox-M pulse oximeter 4% determined as optimal cut off	**12-month rehospitalisation** 4% desaturation • 71.4% sensitivity for interstitial pneumonia • 79.2% specificity for interstitial pneumonia Univariable analysis • HR 0.45 (0.29-0.72), (p= 0.001) Multivariate analysis • HR 0.30 (0.10-0.90) (p=0.032) • Kaplan-Meier analysis of ≥4% vs <4%, (p <0.001)
La Rovere *et al.* 2015. (67)	6MWT at discharge	Distance walked (6MWD) measured (m)	**12-month mortality:** 6MWD (m), mean ±SD; • Alive 408.9±95.9 • Deceased 311.1 ±102.2 (p<0.0001) • Chi square 32.86 (p<0.0001) • HR 1.007 (CI 1.005–1.010)
Howie-Esquivel and Dracup. 2008. (68)	6MWT, inpatients	6MWD and lowest O_2 recorded with Writox (Nonin Medical) pulse oximeter	**90-day cardiac rehospitalisation:** Lowest O_2 value: HRa (95% CI): 1.01 (0.94-1.08), p= 0.78 6MWD: HR (95% CI): 0.99 (0.99-1.00), p=0.06
McCabe *et al.* 2017. (69)	6MWT prior to discharge	6MWD	**Rehospitalisation (within 30 days):** • 6MWD, mean (SD) 536 (434) **No rehospitalisation:** • 6MWD, mean (SD) 811 (380), p =0.02 Higher 6MWD and readmission, Univariate analysis: OR (95% CI); 0.85 (0.73 -0.98) Multivariate analysis: OR (95% CI); 0.84 (0.71 - 0.99)

Table 3 – Studies using the six-minute walk test in the acute setting

Abbreviations: 6MWD; 6-minute walk distance, 6MWT; 6-minute walk test, 95% CI; 95% confidence interval, bpm; beats per minute, HRa; hazard ratio, HRR2; heart rate recovery within 2-minutes, m; metres, p; p-value, QS1; qanadli score group 1, QS2; qanadli score group 2, SpO_2; peripheral oxygen saturation, r; Pearson correlation coefficient.

Three-minute walk test

A shorter modified 6MWT, the three-minute walk test (3MWT) was used in two studies (Table 4). Amin *et al.* (60) used the 3-minute walk test as part of the diagnostic workup for 114 suspected cases of Pulmonary embolism (PE), with criteria for stopping the test set as; SpO_2 <86% for 30 seconds, a decrease in oxygen saturation of ≥2%, or HR > 110 bpm. A total of 65.8% of participants met at least one of these criteria, of whom 32% tested positive for PE. The stopping criteria was met by 10% of the PE group compared to 2% of the non-PE group. An SpO_2 decrease of more than or equal to 2% with a heart rate increase of more than 10bpm was 100% sensitive for PE, but only 11.9% specific.

A prospective study by Pan *et al.* (65) assessed the feasibility of a 3-minute walk test as a clinical decision tool for patients presenting to emergency departments with acute dyspnoea. A sample of 40 participants were recruited, including 16 with congestive cardiac failure (CCF), 9 with COPD and 15 with stable chest pain. 85% of participants completed the test in full, and 30% of the sample had a poor outcome defined by an admission to hospital, need for respiratory support (Bilevel positive airway pressure (BiPAP) or intubation), relapse in their condition or death. There was a statistically significant difference of 38% (95% CI 11.7-64.6, $p<0.01$) in the percentage of those unable to complete the test fully, and outcome, with 42% of those with a poor outcome not completing the 3MWT, compared to 4% of those with a good outcome. Patients with an SpO_2 below 90% at test completion made up 25% of those with a poor outcome, and none who had a good outcome ($p<0.01$).

Step tests

Three steps tests were comapred in 77 inpatients hospitalised with acute lung disease in José and Dal Corso's study (63). Participants perfromed the Chester step test (CST) and modified incremental step test (MIST) on the same day, followed by a 6MWT the following day (Table 5). Both the CST and MIST performance were significantly correlated with increased length of hospital stay (CST; r—0.23, p=0.049, MIST; r= -0.23, p=0.042). Exercise-induced desaturation was induced by all three tests with a mean desaturation of 2% with each test. 6MWD was found to correlate with CST (r=0.590) and MIST (r=0.64), and no adverse events were recorded with any of the three tests.

Reference	Intervention	Monitoring	Outcome
Amin *et al.* 2015. (60)	3MWT during diagnostic workup	Criticare 504-DXP pulse oximeter Stopping criteria: SpO_2 <86% for 30 sec, ≥2% desaturation, HR > 110 (CCF), >120 (COPD) for 60 sec or new chest pain	65.8% of tests met stopping criteria: • 32% positive for PE • 10% of PE, vs 2% non-PE group met criteria SpO_2 drop ≥2% and HR increase >10 bpm • 100% sensitivity (CI 88.7-100) • 11.9% specificity (6.6-21.0)
Pan *et al.* 2009. (65)	3MWT prior to discharge	Nellcor Puritan Bennett (NPB-40) pulse oximeter Terminated if Borg dyspnoea score >7, chest pain, SpO2 <86% for 30 sec or HR > 120 for 60 sec, or patient's request	85% completed walk test 30% **poor outcome* within 14-days** **Walk test completed**: Poor outcome 58%, Good outcome 96%, Difference 38% (95% CI 11.7-64.6), p<0.01 **SaO_2 <90% at 3 minute (end-test):** Poor outcome 25%, Good outcome 0%, Difference 25% (95% CI 4.9 - 53.2), p<0.01

Table 4 – Studies using a three-minute walk test in the acute setting

Abbreviations: 3MWT; 3-minute walk test, 95% CI; 95% confidence interval, CCF; congestive cardiac failure, COPD; chronic obstructive pulmonary disease, HR; Heart rate, p; p-value, PE; pulmonary embolism, sec; seconds, SpO_2; peripheral oxygen saturation.

*Admission to hospital, the need for BiPAP, intubation, relapse, or death.

Reference	Intervention	Monitoring	Outcome
José and Dal Corso. 2016. (63)	CST, MIST and next day 6MWT in inpatients	9500 Nonin pulse oximeter	**Length of Stay**: CST (r = −0.23, p= 0.049) MIST (r = −0.23, p = 0.042) 6MWD – no correlation with length of stay Exercise-induced desaturation: Mean; 95% CI CST (−2%; −6 to 0) MIST (−2%; −6 to −1) 6MWT (−2%; −5 to 0) 6MWD correlated with CST (r = 0.590) and MIST (r = 0.64) No adverse events recorded in all three tests

Table 5 – Studies using a step test in the acute setting

Abbreviations: 6MWD; 6-minute walk distance, 6MWT; 6-minute walk test, CST; Chester step test, MIST; modified incremental step test, r; Pearson correlation coefficient.

Sit to stand tests

In an observational study by Kakavas *et al.* (64), 22 patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), completed a 30-second sit to stand (30s-STS) and five repetition sit to stand test (5-STS) at discharge at least two hours apart. Mean repetitions of the 30s-STS were significantly lower in patients who had a further exacerbation of COPD within 12 months at 11, compared to 18 in those who did not have an exacerbation (p=0.05). Mean time to complete the 5-STS was significantly longer at 14.2 seconds in those who had a repeat exacerbation, compared to 10.2 seconds hose who did not (p=0.05). Heart rate and SpO_2 change during the test were not found to be correlated with future exacerbations. Significant correlation between the 30s-STS and 5-STS was found (r= -0.036, p=0.01). On univariate logistic regression both 30s-STS and 5-STS were significantly correlated to future exacerbations (30s-STS; OR 0.782 (95% CI 0.586-0.964), p=0.05, 5-STS; OR 0.782 (95% CI 0.586–0.964), p=0.05). However, on multivariate regression, the correlation was not statistically significant (30s-STS; OR 0.65 (95% CI 0.16–2.58) p= 0.54, 5-STS; OR 0.60 (0.03–13.94), p= 0.75).

Reference	Intervention	Monitoring	Outcome
Kakavas *et al.* 2020. (64)	30-second and five-repetition sit-to-stand tests at discharge	Number of repetitions in 30-seconds and duration to five repetitions	30s-STS, mean (SD): **12-month Exacerbation*** 11 (3) No exacerbation 18 (8), p=0.05 5-STS, mean (SD): **Exacerbation** 14.2 ± 3.3 No exacerbation 10.1 ± 3.1, p=0.05 30s-STS and 5-STS correlation: r = -0.836, p=0.001 Univariate regression: • 30s-STS p =0.05, OR 0.782 (95% CI 0.586–0.964) • 5-STS p=0.05, OR 0.782 (95% CI 0.586–0.964) Multivariate analysis: • 30s-STS p= 0.539, OR 0.649 (CI 0.163–2.578) • 5-STS, p= 0.749, OR 0.598 (CI 0.026–13.943)

Table 6 – Studies using a sit to stand tests in the acute setting

Abbreviations: 30s-STS; 30-second sit to stand test, 5-STS; 5 repetitions sit to stand test, 95% CI; 95% Confidence interval, OR; odds ratio, p; p-value, r; Pearson correlation coefficient, SD; Standard deviation.

*Acute exacerbation of chronic obstructive pulmonary disease requiring outpatient or inpatient assessment > 14 days after previous exacerbation. Defined by as at least 2 respiratory symptoms and need for treatment with antibiotics or steroids.

Bicycle ergometry

Sauleda *et al.* conducted an exercise test involving pedalling on a stretcher bed at a rate of 40 cycles per minute in a study of 45 HIV patients presenting with symptoms of pneumonia (59). Twenty-two cases had confirmed Pneumocystis pneumonia (PCP) while 23 controls were diagnosed with other non-Pneumocystis pneumonia. Desaturation of ≥3% occurred in 77% of PCP cases, compared to 9% of non-PCP pneumonias. SaO_2 decreased by 4%, from 88% to 84% in the PCP group ($p<0.01$), compared to increasing from 91 to 93% in the non-PCP group ($p<0.05$). Mortality was 18% in the PCP group of whom 100% desaturated more than 3%, with mortality 9% in the non-PCP group. The exercise test had a sensitivity of 77% for PCP, and a specificity of 91%.

Reference	Intervention	Monitoring	Outcome
Sauleda *et al.* 1994. (59)	2-minute pedalling on stretcher bed (40 cycles/min)	Ohmeda 3740 pulse oximeter Positive if desaturation ≥3%	Desaturation ≥3%: • 77% of PCP • 9% non-PCP Pre and post exercise SaO_2, mean % (SE): • PCP 88(4) → 84(3), $p < 0.01$ • Non-PCP 91(1) → 93(3), $p < 0.05$ Sensitivity 77%, Specificity 91% **Mortality:** • 18% PCP (100% desaturated) • 9% non-PCP
Kichura *et al.* 2020. (66)	3-minute Bike ergometry distance at admission and discharge	DeskCycleTM Exercise Bike Pedal Exerciser (3D Innovations) Distance biked recorded in metres	**Length of stay:** Admission; r= -0.11, p=0.46 Discharge; r=-0.03, p=0.85 Difference; r= 0.08, p=0.56 **30-day readmission:** Admission; r= -0.03, p=0.85 Discharge; r= 0.02, p= 0.91 Difference; r= 0.04, p=0.78

Table 7 – Studies using bicycle ergometry in the acute setting

Abbreviations: min; minutes, SaO_2; oxygen saturation of arterial oxygen, p; p-value, PCP; pneumocystis pneumonia, r; Pearson correlation coefficient, SE; standard error.

Kichura *et al.* asked 55 heart failure patients presenting to the emergency department with symptoms relating to their heart failure to complete a 3-minute bicycle ergometry at hospital admission and discharge (66). The distance cycled in the test improved in 74% of patients between admission and discharge. However, no significant correlation was identified between bike distance at admission or discharge and length of hospital stay. 20% of patients in the study were readmitted within 30-days of discharge, including one death. Bike distance at admission and discharge were not correlated with readmission or mortality risk.

Treadmill exercise tests

A treadmill exercise test with fixed speeds increased at 2-minute intervals was used to aid with diagnosis in 85 HIV positive patients with suspected Pneumocystis pneumonia (PCP) in a study by Chouaid *et al.* (58). A 3% decrease in saturation during the test had a 100% sensitivity for detecting PCP, and 70-80% specificity. Compared to the use of a cut-off of less than 96% baseline oxygen saturation (sensitivity 100%, specificity 31%), exertional desaturation was more specific for PCP, than resting hypoxia. The test was terminated early in 2% of cases due to exhaustion – both participants desaturated more than 4%.

Reference	Intervention	Monitoring	Outcome
Chouaid *et al.* 1993. (58)	Treadmill exercise test with increasing 2-min constant-speed steps (2, 4, 6, and 8 km/h) as part of diagnostic workup	SpO_2 measured using finger pulse oximetry	22% confirmed PCP on diagnostic testing. 3% desaturation: • 100% sensitivity • 70%-80%* specificity (*with or without prophylactic pentamidine) SpO_2 <96% at rest: • 100% sensitivity • 31% specificity Terminated early in 2/85 due to exhaustion: both desaturation ≥4%

Table 8 – Studies using treadmill exercise tests in the acute setting
Abbreviations: km/h; kilometres per hour, min; minutes, PCP; pneumocystis pneumonia, SpO_2; peripheral oxygen saturation.

Other exercise tests

The final included study was not carried out in any specific disease or condition. Denehy *et al.* (70) assessed 144 inpatients at an intensive care unit, who completed a Physical function ITU test (PFIT) which included a marching on the spot test, and compared to the Timed up and go test and 6MWT. Correlation between the PFIT and the TUG (r= -0.60, 95% CI -0.70 to -0.46, p<0.001) and the 6MWT (r=0.41, 95% CI 0.24-0.55, p<0.001). Higher PFIT scores (i.e., better function) was found to be significantly associated with discharge home (OR 1.20, p=0.01), and reduced length of hospital stay (B coefficient -2.13, p<0.001). However, admission PFIT was not significantly associated with 28-day readmission.

Reference	Intervention	Monitoring	Outcome
Denehy *et al.* 2013. (70)	Physical function ITU test* at admission and discharge, compared to TUG and 6MWT	Sit to stand assistance, marching on the spot (steps/min), shoulder flexion and knee extension strength	Discharge PFIT correlated with: • TUG (r= -0.60, 95% CI -0.70 to -0.46, p<0.001) • 6MWT (r=0.41, 95% CI 0.24 – 0.55, p<0.001) Discharge home: • PFIT, OR 1.20, p=0.01 **Length of stay:** • Admission PFIT, B coefficient -2.13, p<0.001 **28-day Readmission** • Admission PFIT not correlated (data not presented)

Table 9 – Studies using other exercise tests in the acute setting
Abbreviations: 6MWT; 6-minute walk test; 95% CI; 95% confidence interval, B; beta, ITU; Intensive treatment unit, p; p-value, PFIT; Physical function ITU test, r; Pearson correlation coefficient, TUG; Timed up and go test.

2.4 Discussion

Summary of main findings in COVID-19

This scoping review is the first to describe the use of different exercise tests in the assessment of confirmed or suspected COVID-19. Additionally, a summary of the different types of exercise tests used within acute settings to assess exertional dyspnoea is presented, encompassing diagnostics and prognostication in a wide range of acute lung diseases that may present with exertional dyspnoea. In suspected COVID-19, the well-established 6-minute walk test and a novel but extremely brief 10 feet desaturation test are described, as well as two studies where a non-standardised test of exertion was used. Of note is the absence of published studied using the 40 steps desaturation test, which features prominently in national and local NHS guidance for triage in suspected COVID-19.

Findings by Fuglebjerg and colleagues (56), using a 6MWT completed at discharge, confirms widely reported observations of exercise-induced hypoxaemia as a feature of COVID-19. Furthermore, this study suggests that exercise-induced hypoxaemia may be prevalent at the point of early recovery from the disease. The study also reports findings of pulmonary embolism in some desaturating patients, although definitive conclusions cannot be made as not all participants were investigated for this condition. Kamran *et al.* (2020) used a 10-feet walking test in a moderate sized population of COVID-19 patients (55). There is no previous evidence of this test being used in the clinical or research setting. Associations between desaturating during the test with clinical deterioration and death were identified, including some evidence to support 3% desaturation during the test as a sensitive marker of adverse outcome. This suggests a possible utility for very brief exercise tests as a clinical decision tool in COVID-19, although a larger study is required to validate the appropriate cut-offs to use, and its validity to predict clinical deterioration or death. The study itself has also not been subject to the peer review process so findings should be interpreted with caution. Banzi *et al*. (57) use a similarly short walking test in the community setting as a decision tool to trigger hospital admission, although the duration or distance of this test is not specified within the paper. No patients met the desaturation criteria selected of 5%, leading to insufficient data to comment on the utility of brief exercise tests as an admission decision tool.

Goodacre *et al*. (40) did not find that exertional desaturation sufficiently predicts adverse outcomes in COVID-19 and there are several key limitations to this study. Firstly, the nature of the exertional test is not standardised making it difficult to recommend predictive thresholds. Secondly, the significant findings in the study are limited to participants with normal observations at rest, including SpO_2.This suggests that the utility of an exercise test in COVID-19 to predict early deterioration, using post-exertional desaturation, may be limited to mobile, high-functioning patients with stable observations at rest i.e., those who would not otherwise be typically considered for admission. Additional caution must be applied in interpreting these results given that only 3% of the screened cohort had post-exertional saturations recorded, and the indication for prompting an exercise test were not described.

Findings in other acute lung disease

In other acute lung disease, the 6MWT arises as the most prominent test used in the acute setting, with findings by Danielsbacka *et al*. that desaturation below 90% is a sensitive, but poorly specific indicator of pulmonary embolism (61). The use of a 6MWT at discharge in interstitial pneumonia inpatient cases by Sakai *et al.* calculated that desaturation of more than 4% was most predictive of rehospitalisation within 12 months (62). Studies in heart failure found that mean 6MWD could predict 12-month mortality (67), 30-day (69) and 90-day rehospitalisation (68). However, a link between 90-day rehospitalisation and lowest recorded SpO2 value during the 6MWT was not identified in the study by Howie-Esquivel and colleagues (68).

The combination of desaturation ≥2% with a heart rate increase of more than 10 bpm during the shorter 3-minute walk test had 100% sensitivity for Pulmonary embolism but had low specificity in the study by Amin *et al.* (60). The 3MWT was also trialled in the triage of patients presenting to the emergency department with acute dyspnoea by Pan *et al.*, with inability to complete the test fully as well as desaturation below 90% linked to adverse outcomes within 14 days (65). These findings are promising as the 3MWT being shorter than the more-widely validated 6MWT offers some practical benefits in the acute setting, coupled with an adverse outcome time-frame that is applicable to COVID-19.

Other studies identified by the search, include José and Dal Corso correlating the Chester step test (CST), modified incremental step test (MIST) and the 6MWT with performance linked

to length of hospital stay (63). Exercise-induced desaturation during the step tests averaged at 2%, with no adverse events recorded. However, correlation with the 6MWT does not validate the test for use in a clinical setting, as one would most exercise tests to broadly correlate. Kakavas *et al.* assessed two variations of a sit-to-stand tests (30 seconds duration, and 5 repetitions) in a small sample of acute exacerbations of COPD patients, and did not identify a significant correlation between changes in either oxygen saturation, or heart rate during the tests with frequency of future exacerbations (64). Their study describes two very short exercise tests which could be easily deliverable in the acute setting. However, the lack of significant findings highlights that exercise tests that are too brief may be insufficiently vigorous to induce exertional desaturation.

Three identified studies used exercise involving equipment – two bicycle and one treadmill test. Sauleda *et al*.'s study involving a pedalling exercise (59), and Chouaid *et al.*'s involving a treadmill exercise test (58) showed that desaturation had good sensitivity and specificity for diagnosing PCP, with exertional hypoxaemia offering additional diagnostic insight compared to resting hypoxia. A 3% desaturation on exertion was also linked to mortality by Sauleda *et al.* (59). Whether similar findings would arise if the same test was used in COVID-19 requires further exploration. Bike distance was also not found to aid with safe discharge in Kichura *et al.*'s cohort of heart failure patients, with outcomes not predictive of length of hospital stay or readmission within 30-days (66).

Strengths and limitations of scoping review process

A scoping review format was used with consideration for the likely breadth of relevant research that would be identified. The search included both COVID-19 and other acute cardiopulmonary disease, recognising the need to gain insights on current practice in COVID-19, whilst also drawing experience from previous application of exercise testing in the acute setting, which until the COVID-19 pandemic was less commonplace. The search was comprehensive in the terms used, and databases searched, and the screening process aimed to minimise bias by pre-defining the inclusion and exclusion criteria and using two independent authors to screen abstracts. The double screening method yielded strong agreement regarding inclusion, and on full text review discrepancies were resolved on full text review in all except two papers where a third independent reviewer was consulted.

The search found few results matching the inclusion criteria. In the scoping review protocol, it was decided to exclude tests carried out in the outpatient setting, which limited the scope of literature assessed. Whilst the range of tests identified covered a broad range of the available exercise tests, this approach may have led to overlooking some studies where a brief exercise test, which could be applied in assessing suspected COVID-19. However, selecting only studies within the acute setting aimed to identify research looking at shorter-term outcomes so that the results were more useful to guide the ongoing debate about how best to assess and predict deterioration in patients presenting with acute COVID-19.

The identified literature is methodologically diverse, consisting mainly of small-scale studies, with significant variation in the exercise test performed, condition studied, and outcomes assessed. This makes drawing definitive conclusions more challenging. In addition to physiological monitoring using oxygen saturation, parameters such as the 6MWD, repetitions performed within a specified time frame, or time taken to complete a pre-defined test were used in several studies. These likely measure frailty and co-morbidity as well as respiratory disease so may be less useful in acute setting to predict short term outcomes, particularly in COVID-19. Many of the studies identified also used longer term outcomes such as 12 months, which are not as relevant to the assessment of acute presentation with COVID-19.

A risk of bias assessment of the studies included was not formally evaluated within the scope of this review. While some commentary on the choice of methodology has been discussed, critically appraisal of the validity of the findings has not been formally attempted.

Limitations of the research identified

There were several methodological limitations to the studies included. Kamran *et al.* and Goodacre *et al.* had the two largest studies in COVID-19 (40,55), but both excluded a high proportion of the screened population. This high exclusion rate may suggest that the exercise tests used may not be safe to perform in the normal hospitalised population. Fuglebjerg *et al*. used the 6MWT at discharge, therefore it's utility and safety as part of the admission decision process has not been established, with COVID-19 patients possibly displaying more pronounced hypoxia at time of presentation to hospital, compared to at the point of recovery or discharge (56,81). Additionally, despite 50% of the sample desaturating below 90%, less than half of these were investigated further for pulmonary embolism. The authors do not describe the reasons

some patients were investigated further whilst others were not, and therefore caution should be applied when interpreting the sensitivity and specificity of the 6MWT to detect PE in COVID-19. The low specificity of exertional desaturation to detect PE seen in multiple studies (67,75) within this review also highlight the potential issue of over-investigating patients with desaturation on exertion.

The significant findings in the study by Goodacre *et al.* were in a select sample of the included participants with suspected COVID-19 who did not have resting hypoxia or other abnormalities in their NEWS score (40). This provides important insight that the utility of exercise testing in acute presentation of COVID-19 may be limited to patients who would otherwise be considered for discharge, as opposed to performed routinely even in clearly severe illness. This corresponds to the use to exercise testing in the feasibility trial by Pan *et al.* using the 3-minute walk test in patients with acute dyspnoea who were being considered for discharge (65).

The 40 steps desaturation step test is also currently recommended for use in patients with otherwise normal clinical observation being considered for discharge. This review did not find literature to support the safety, feasibility, or utility of the 40 steps desaturation test in clinical practice in either COVID-19, or other acute lung disease. Both Goodacre *et al* and Banzi *et al.* did not use a standardised exercise test, although as Goodacre's study was based in the UK it is reasonable to assume that a proportion of the patients exercised using the 40 steps desaturation test (40,57). However, due to the lack of standardisation it is challenging to generate clinical assessment recommendations based on their findings alone.

Kamran *et al.* (55), used a different extremely brief exercise test that has not been previously described in the literature prior to the COVID-19 pandemic; the 10 feet desaturation test. Its benefits include that the time and space required to deliver it are low, which is desirable in the acute setting, as it could potentially be delivered to patients needing to be isolated in a cubicle or at home due to COVID-19. Due to its shortness, a desaturation of 3% would likely represent severe clinical illness. However, with such a short test if desaturation can be provoked, it is also reasonable to speculate that other physiological abnormalities in the NEWS score would be present at rest, which may be safer to record in order prediction of clinical deterioration. Within the paper, no commentary on whether the studied participants had other features that would indicate need for admission is provided. The definition of an adverse

outcome within the study may have also been overly selective for the sickest patients, as other indications for hospitalisation such as a supplemental oxygen requirement were not included, making the findings less generalisable. The definition of clinical deterioration used also makes the results harder to interpret as this includes mild patients who became moderately unwell, whilst critically ill patients who remained in a critical state would be classified as stable. Therefore, the utility of the 10 feet desaturation test in identifying the well patient who is likely to deteriorate cannot be concluded from this study.

Despite some evidence to suggest utility in the setting of acute lung and cardiac disease, the 6MWT has some practical limitations in the acute setting. Both the time and space required to conduct the test could be impractical in the acute setting for example in emergency departments where corridors may be busy and need to be kept clear for emergencies. A 10 metre variation of the 6MWT course has been reported (82), but this method is not extensively validated, and could lead to a lower 6MWD, due to increased need for turning (83,84). Additionally, many of the outcomes studied within this review focus on longer term outcomes than is clinically relevant in COVID-19.

There is promising evidence for the shorter 3-minute walk test, which similarly involves walking on a flat surface at a self-paced speed for a duration of 3 minutes. Correlation with distance walked in 6 minutes was found in a trial of the 3MWT along a 60 metre hospital corridor (85). The time required to perform the test is more suitable to an acute setting, as evidenced by Pan *et al.*'s feasibility trial (65), and it may be achievable by patients unable to complete a longer test. Correlation to the 6MWT is expected, and does not in itself validate the test, with few small studies outside of the acute setting. Therefore, further larger studies are required before it can be recommended for widespread use. In the context of COVID-19, adaptations to the distance walked to comply with infection prevention standards would also be required.

There was limited evidence identified regarding the previous use of the sit to stand test in the acute setting, although it is deliverable in a cubicle, which is beneficial in COVID-19 patients who require care in isolated cubicles to minimise spread of the virus. The extremely brief 30 second and 5 repetition versions may be too brief to elicit desaturation, however the 1-minute sit to stand test may warrant further exploration, with some evidence to support its practicality in COVID-19 in the post-discharge setting (86). However, the exertion required to

achieve a sit to stand test is likely to be more challenging than short walk tests and therefore it may be difficult for many patients to achieve than the 40 steps test (35).

Tests involving cycle ergometry, or other exercise equipment are less practical in the acute setting where lack of space for large equipment can be a challenge. Exercise testing during the AIDS pandemic may have offered timely risk stratification while confirmatory tests for PCP were sought, aiding prompt treatment to be initiated. While using desaturation to predict a diagnosis of COVID-19 may have been useful in the earliest stages of the pandemic, biochemical diagnostic testing for COVID-19 is now far more widely available, making this use of exercise testing less necessary as a diagnostic tool. These findings also highlight the need to consider wider differential diagnoses if desaturation is present, other than COVID-19, raised by the multiple case reports of missed PCP diagnoses during the COVID-19 pandemic (42).

Implications of previous research to scoping review findings

As alluded to previously, there is a wide evidence base for the use of exercise testing in chronic lung disease. Often, this has focused on markers of fitness including VO2 (maximal aerobic capacity), distance walked or cycled, or number of repetitions completed, with less focus on exertional desaturation. When exertional hypoxaemia has been assessed, this has been linked to longer term prognostication than is relevant in COVID-19, where mortality is primarily linked to the acute presentation. This research may be relevant in the long-term follow-up of severe COVID-19 patients in the outpatient setting as well as those experiencing ongoing symptoms of the condition widely termed “long COVID-19”.

However, the most suitable exercise test for the acute setting, particularly in terms of aiding with safe discharge remains up for debate. Clinical practicalities favour a shorter test, although the evidence base for the longer 6MWT is more widely established. This contrasts to new additions to the field of exercise testing with the 10 feet desaturation test and 40 steps desaturation test being used in COVID-19 without prior validation. The shortest comparable test identified within the literature is the 10-metre walk test (10MeWT), which involves walking as quickly as possible between two points on a flat surface measuring 10 metres, with the time taken to complete the test recorded. Excellent inter-test and test-retest reliability was found between the 10MeWt, and 6MWT in a cohort of dementia patients (87), and the 15 and 30 metre variations of the 6MWT in stroke patients (88). Furthermore, the shorter 4 metre test

which most closely resembles the distance of the 10 feet desaturation was found to correlated with the 10MeWT in terms of gait speed. However, the 4-metre gait speed was not sufficiently concurrently valid as an interchangeable test to the 10-metre walk test. Both tests differ from the 10 feet desaturation test in that gait speed is measured not desaturation (89). No evidence of a similarly short walk test which linked desaturation to clinical deterioration or mortality has been identified. Therefore, the national recommendation to use these tests as tools for uncovering exertional desaturation is concerning.

The 3MWT may offer a compromise to deliver a timely yet valid test. Observations in paediatric studies indicate a quicker walking speed during the first minute of the six-minute walk test, as well as moderate reliability from 3 minute onwards, a finding that warrants further investigation in adult patients with a range of mobility ability, before recommendation about a shorter walking test can made (90).

There was lack of data to support the use of sit to stand tests in the acute setting. Kalin *et al.* produced a rapid systematic review (35) on the safety and efficacy of rapid exercise tests for exertional desaturation in COVID-19 and concluded the 1-minute sit to stand test is a potential test that merits further research. This review has identified that a prospective study aims to explore its use in the assessment of COVID-19 patients to predict hospitalisation and adverse events. This slightly longer version of the test is more extensively validated in a range of settings (91), including in the pre-operative assessment for lung transplantation (92), and may be more benficial in demonstrating exertional desaturation. However, it has been noted to induce high cardiopulmonary stress, as well as requiring muscular strength to stand from sitting without support. This may make it unsuitable for use in a remote setting, and not easy to achieve by many hospitalised patients, including the most frail.

Implications for clinical practice

This review's findings substantiates the recommendation by Greenhalgh *et al.* (36) that a desaturation of 3% or more on exertion is a significant threshold to indicate serious underlying disease, and, if present in a patient, warrants further investigation. Five or more percent desaturation appears to be too high a threshold in a cohort of COVID-19 patients (57), whilst a threshold of 2% has only been used in combination with a change in heart rate to predict PE (60), and not found to correlate with hospital length of stay in COPD exacerbations (64).

Meanwhile, a desaturation between 3% or 4% appears to be the most useful in balancing sensitivity and specificity in many of the studies discussed (55,56,59). A cut off SpO_2 below 90% (representing 4% desaturation as these studies also specified a baseline saturation of 94%) has also been used with some success both in patients with (39) and without (65) COVID 19. However, given high variability in exercise test length and intensity, the most appropriate threshold would need to be decided on a test-by-test basis, and may vary.

It is also important to speculate whether exercise testing may be inappropriate in a proportion of COVID-19 patients with severe disease who may have resting hypoxia or dyspnoea. Furthermore, the predictive value of exertional desaturation may be most relevant in patients who have normal baseline oxygen saturations at rest and may otherwise be felt suitable to discharge. Therefore, defining the eligibility of a patient for exercise testing is crucial in any study wishing to establish the utility or feasibility of an exercise test to the acute setting.

A range of tests used within the acute setting were identified. All tests discussed were found to be safe with none or few adverse events reported. Commentary on which tests are most feasible for the acute setting have been proposed, with the broad conclusion that brief tests of exertion, requiring no equipment, and limited space are most feasible to deliver in the current clinical context. Additionally, applying current insights into the pathophysiology of acute COVID-19, a cautious and risk-reducing approach to exertional testing in COVID-19 is advisable, as desaturation in the acute phase of the COVID-19 pneumonitis could be more marked when compared to chronic lung disease. The drawback is that there is an identified a lack of validation for the shorter exertional tests used commonly in clinical practice including the 40 steps desaturation test. A shorter test may be less sensitive to detect desaturation but could have high specificity to detect COVID-19, or its complications, and a validation study to assess this is urgently indicated.

Implications for research

The studies identified to date in COVID-19 are varied in their approach, including two of the studies not using a standardised test. Where a standardised test was used, one was the 10 feet desaturation which is not previously validated. The other used a 6-minute walk test performed at discharge rather than as an assessment tool during initial presentation. Whilst these studies offer some insight into the role of exertional desaturation within COVID-19, and how it may be

linked to clinical deterioration, they are not sufficient to propose a valid exercise test to be used within the acute setting to ensure safe discharge.

Several exercise tests ranging from the six and three-minute walk tests, step tests, sit to stand tests, bicycle and treadmill tests have been utilised with varying success to demonstrate exertional desaturation in a range of acute cardiopulmonary disorders. Many have been shown in small studies that exertional desaturation between 2-4% can give insight into safe discharge through link to adverse outcomes including clinical deterioration, rehospitalisation, length of hospital stay, and mortality.

Shorter tests are more practical in the acute setting but are less validated in relation to facilitating safe discharge. One of these in widespread use in the assessment of suspected COVID-19 is the 40 steps desaturation test, which is not yet validated in the literature. A protocol for this test is urgently required, with both 40 steps around the room and on the spot variations proposed, and in clinical use. The benefits of this test include being short and therefore quick and easy to deliver without expert equipment. With regards to COVID-19, the 40 steps on the spot test may be the most useful as these patients need to be assessed remotely or in isolation, where space is a limiting factor for completing exercise.

Establishing the utility of the 40 steps test to detect exertional desaturation and its validity in ensuring safe discharge is key and has urgent implications to current clinical practice and guidance within the acute assessment of COVID-19. In the following chapter, the preliminary data from a validation study into the 40 steps desaturation test as a tool to facilitate safe discharge in acute hospitalised patients will be presented, using an on-the-spot variation of the test.

CHAPTER 3

40 steps to safety? Feasibility and validity of the 40 steps on the spot desaturation test to promote safe discharge in patients presenting to hospital with and without COVID-19

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Rhys G.H, Wakeling T, Moosavi S.H, Moore J.P, Dawes H, Knight, M Inada-Kim M, Frischknecht-Johansen E, and Subbe C.P. Feasibility and accuracy of the 40-steps desaturation test to determine outcomes in a cohort of patients presenting to hospital with and without COVID-19. *Clinical Medicine*. 2022:22(4). (93)

3.1 Abstract

Desaturation on exercise has been proposed as an early predictive feature for clinical deterioration in COVID-19. This study aimed to ascertain the feasibility and validity for the 40-steps desaturation test. A prospective observational cohort study was undertaken in patients assessed in hospital prior to discharge. One-hundred and fifty-two participants were screened between November 2020 and February 2021, and 64 were recruited to perform a 40-steps on the spot desaturation test. Patients who were able to perform the test were younger and less frail. Four patients were readmitted to hospital and one patient deteriorated within 30 days, but no patient died. Most patients showed little change in oxygen saturations during the test, even with pre-existing respiratory pathology. Change in saturations, respiratory rate, heart rate and breathlessness were not predictive of death or readmission to hospital within 30 days. Of 13 patients who had a desaturation of 3% or more during exercise, none was readmitted to hospital within 30 days. Not enough patients with COVID-19 could be recruited to the study to provide evidence for the safety of the test in this patient group. The 40-steps desaturation test requires further evaluation to assess clinical utility.

3.2 Introduction

Silent and exertional hypoxaemia in COVID-19

In the introductory chapter, the hypothesised mechanisms by which silent hypoxaemia in COVID-19 may arise are outlined. Prominent theories include V/Q mismatch (15), secondary to increased interstitial lung oedema (12) or microthrombi (20), as well as direct viral-medicated modification of peripheral oxygen sensing in the central nervous system (21,22).

The phenomenon of silent hypoxaemia in COVID-19, characterised by low arterial oxygen saturation in the absence of the typical features of respiratory distress including tachypnoea and dyspnoea, may be a precursor to clinical deterioration (2,7,8). Consequently, significant focus has been placed on the early identification of hypoxaemia in suspected COVID-19 cases, and later exercise-induced desaturation which has also been proposed as an early indicator of clinical deterioration in COVID-19 (26–28). Unsurprisingly therefore, pulse oximetry, particularly following an exertional test, forms a key part of the assessment of suspected COVID-19 (11).

Notably, exercise-induced arterial hypoxaemia (EIAH) can be present in the normal physiological response to exertion in healthy persons (15,29,30), but is unlikely during sub-maximal exertion. Exacerbation of existing V/Q mismatch during exertion (29), as well as decrease diffusion capacity for carbon monoxide in severe COVID-19 patients (32), are both proposed as possible mechanisms for EIAH in COVID-19.

The use of exercise testing in COVID-19

Chapter 2 presents the evidence base for use of exertional tests in the acute setting, and where this has been linked to outcomes relevant to safe discharge. In COVID-19, only a 6-minute walk test at discharge and 10-feet walk test at admission are described. The former is likely to be impractical in the acute and infectious setting due to the time needed to deliver it, and the need for COVID-19 patients to be isolated, meaning a suitable exercise test for assessing COVID-19 cases needs to be deliverable in a small space. The 10-feet desaturation test has none of these drawbacks, but its use is not previously documented outside of the one published study by Kamran *et al*. (55). Another study in COVID-19 provided modest evidence of a link between clinical deterioration and exertional hypoxaemia but did not use a standardised exercise test (39). In other acute cardiopulmonary conditions, several small studies using a range of different exercise tests provide some evidence to support that exertional desaturation in the range of 2-

4% may be used to predict adverse outcomes. However, a prominent exercise test which is both highly validated, and practical to use in the acute setting, particularly in COVID-19, is lacking.

The question of which exercise test should be used to identify exertional desaturation in suspected COVID-19 was faced clinicians worldwide in early 2020 when the feature of exertional hypoxaemia in COVID-19 was identified. The test proposed by the UK's National Health Service (NHS) for both emergency departments and primary care settings (37-39,-) is the 40 steps desaturation test; a short exercise test involving 40 steps of walking on a flat surface, with peripheral oxygen saturations being measured before and after the test. A drop in saturation of 3% or more has been proposed as significant to trigger further investigation, and/or consideration of admission to hospital (35). The guidance suggests that a negative test, where a patient does not desaturate, can be used as an indication that the patient is suitable to discharge. Changes in heart rate, respiratory rate or dyspnoea following the 40 steps test that should trigger hospitalisation or further investigation are not currently specified. Despite its simplicity, and ease of delivery in a potentially small space, the 40 steps desaturation has not been previously validated. Given its widespread adoption in UK hospitals following its recommendation by NHS England and continued use by UK clinicians as part clinical assessment of COVID-19 patients, validating the test for use in ensuring safe discharge is essential.

Study aim

The emergency context under which the 40 steps desaturation test was introduced into clinical guidance has long passed. However, the test continues to have an important and influential role in informing clinical decisions to discharge COVID-19 patients and is still relied upon as an indicator of likely progression of COVID-19 in many clinical settings.

The widespread use of the 40 steps test as a discharge decision tool could bring structure to the common clinical practice of requiring a patient with mild symptoms and minimal derangement in vital signs to complete a short walking test prior to discharge. It offers a potential triage tool to safely discharge low-risk patients, whilst aiming to identify those at risk of later deterioration.

This study aims to establish the safety and feasibility of the 40 steps test, using a novel variation where the patient is asked to perform 40 steps of walking on the spot, which is more suitable for a space-limited setting. The main objective is to establish the normal response to 40 steps on the spot in a population of emergency medical admissions, and to explore relationships between some key physiological measurements and clinical outcomes in a range of age groups

with and without COVID-19. The findings may inform understanding of the utility of the test suspected cases of COVID-19 and be used to amend current clinical guidance as necessary.

3.3 Methods

Registration and Ethics

The study protocol was designed in collaboration with clinicians and scientists at Oxford Brookes University, Betsi Cadwaladr University Health Board (BCUHB), and Bangor University. The study was registered with IRAS, reference 283998. Ethical approval was obtained prior to recruiting for the study (REC 20/WA/0286). This chapter reports the results from recruiting at one site: Ysbyty Gwynedd, a district general hospital serving a rural area in North-West Wales.

Population and Screening

Whilst this chapter reports on the participants recruited at one study site, the study forms part of a larger multi-centre trial across the UK and EU. Recruitment was done from the emergency department (ED), medical admissions unit (MAU), and adult inpatient wards. Participants were screened on five medical wards and recruited by two members of the research team, during weekdays between the hours of 9am to 5pm.

Eligibility

Inclusion criteria

The inclusion criteria for the study were as follows. The patient or participant:

- was being considered for discharge to independent care.
- was willing and able to take part in the study and able to give informed consent.
- had an independent, stable gait.
- was alert, attentive, coherent, and calm.

Exclusion criteria

Patients admitted for the following reasons were excluded from the study.

- Minor injury or injuries.
- Elective surgery or investigation.

Patients meeting any of the following criteria were also excluded.

- Post-operative patients at discharge.
- Requirement for supplemental oxygen.
- On long term oxygen therapy prior to admission.
- Current diagnosis of unstable angina.

- Patient reporting feeling too short of breath at rest to attempt exertion.
- Patient pregnant as stated by them.
- Resting oxygen saturations <95% on room air (or <92% in COPD patients).
- Resting heart rate >100 bpm.
- Resting respiratory rate >25 breath per minute.
- National Early Warning Score of 5 or more.
- ECG with signs of acute ischemia in patients where an ECG had been requested by the treating clinician.
- Nursing home residents, or those being transferred to a nursing home or similar facility, including residential home, hospice, or rehabilitation hospital.

Informed Consent

Eligible participants were asked to provide written informed consent to take part in the study, including consent to accessing their medical records for follow-up purposes (Appendix E). A patient information leaflet was provided with the details of the intervention and follow-up (Appendix F).

Baseline characteristics

During the index visit the following data was collected for each participant:

- Age by date of birth
- Gender
- Ethnicity
- Working diagnosis and/or presenting complaint
- Past medical history of heart failure and/or COPD, asthma, or interstitial lung disease If the patient was confirmed COVID-19 positive, negative, suspected or not suspected to have COVID-19.

Physiological monitoring

Each participant was asked to wear a pulse oximeter attached to the end of the finger. Standard medical equipment used in NHS hospitals was used, as in other routine physiological monitoring of inpatients, and calibrated as per the hospital's requirements and policy. Baseline observations of oxygen saturation (SpO_2), heart rate (HR), respiratory rate (RR), blood pressure

(BP), and temperature were recorded from the patient's vital signs chart, with readings performed within four hours accepted. If no valid observations were available, the baseline observations were recorded by the researcher (using the same medical equipment used routinely for vital signs) prior to the exercise test. In addition, the patient was asked to give a dyspnoea score from 0 to 10 using the word-anchored, pictural numerical rating scale provided (Appendix G). Dyspnoea score, RR (counted manually by observing breathing for one minute), SpO_2 and HR (©Mindray VS-900, ©Edan iM50 and General Electronics, Carespace^{TM} V100) were re-recorded immediately at completion of the 40 steps test and at 2 minutes after the test.

Intervention

The initial NHS England guidelines (37,38) on the 40 steps test did not give specifications for carrying out the test. During this study, the intervention was standardised to involve asking the participant to walk 40 steps on the spot at a self-paced walking pace, to enable reproducibility in a limited space.

The test was discontinued if the participant expressed that they could not continue for reasons including breathlessness, light-headedness, or chest pain during the test. Any concerns from the researcher about the safety of the participant to complete the intervention safely also led to early termination, for example unsteadiness or an adverse event. An adverse event was defined as a significant event that:

- resulted in death
- is deemed to be life-threatening
- resulted in persistent or significant disability/incapacity
- resulted in hospitalisation and/or prolongation of hospitalisation

Adverse events may include falls, loss of consciousness or persistent tachyarrhythmia, which was prompted by the 40 steps test. A routine cut off for early termination due to exertional hypoxia, tachycardia or tachypnoea was not specified, however both researchers were qualified medical professionals who applied clinical judgement as to whether the test needed to be terminated early for patient safety.

Safety and Feasibility

The safety of the test was determined by the recorded number of adverse events. Feasibility was estimated by the number of eligible patients. Test usability was determined using the number of patients able to complete the test in full, compared to the number of patients invited to complete the test.

Follow-up/Outcome

Participant medical records were accessed at completion of the recruiting phase of the study to assess 30-day outcome. The primary outcome for this study was to validate the 40 steps on the spot as a marker for safe discharge from hospital. The primary outcome measured used to assess this were as follows:

- Rehospitalisation within 30-days
- Mortality within 30-days
- Subsequent COVID-19 diagnosis within 7 days of taking part of the test
- Clinical deterioration within 7 days
- Change in decision to discharge assessed by further investigations prompted by the test or continued hospital admission

The secondary outcome for the study was to establish normal values for the 40 steps test in a range of age groups. This was measured by changes in oxygen saturation, heart rate, respiratory rate and breathlessness precipitated by the exercise test.

Data Collection

Data was collected directly onto a Case report from (Appendix H), with each participant given a unique anonymised identifier. Study files were kept in a locked room on the hospital site, and participant names and details were kept in a separate locked drawer.

Data Analysis

Data was uploaded to Microsoft Excel and IBM SPSS version 27 for data analysis purposes and stored securely at the study site. Demographics are presented in terms of percentage except age which is reported as mean ± Standard deviation (SD). The exercise intensity achieved by participants during the 40 steps test, was calculated using percentage of

predicted maximum heart rate equation (220-age) and presented as mean ±SD (94). The data was assessed for normal distribution, and the relevant test used for comparison of means for baseline observations and change in physiological parameter after the 40 steps test for all the outcomes measures studied. Values are presented in dot plots as mean and 95% confidence intervals, or when quoted in text as mean ± SD. Adjustment for type 1 error was done using the family wise error rate adjustment, and the Šidák inequality equation; $P'_s = 1- (1-P)^m$, where "m" refers to the number of comparisons in a group. For the differences in physiological values following the 40 steps test a significance level of $p<0.05$ is used.

Receiver operating characteristics (ROC) analysis was used to assess the most appropriate physiological variable cut-offs to characterise COVID-19 and predict adverse outcomes as defined by any of the primary outcome criteria being met, with sensitivity and specificity calculated. A Chi-square test was then applied to these identified cut-offs to assess their utility to predict an adverse outcome in the collected sample.

3.4 Results

Screening

154 participants were screened between November 2020 and February 2021 of whom 2 were duplicates and 64 were recruited to the study. One patient was found to have been excluded in error (RR 24, exclusion criteria >25 breaths per minute). The attrition of patients screened, including reasons for exclusion and outcome are summarised in Figure 3. The mean age of included participant was significantly younger at 63 years (range 19-90) versus 71 years (range 24-98) in excluded participants (p=0.008), with participants in older age groups more likely to meet criteria for exclusion (Figure 4 and Table 10).

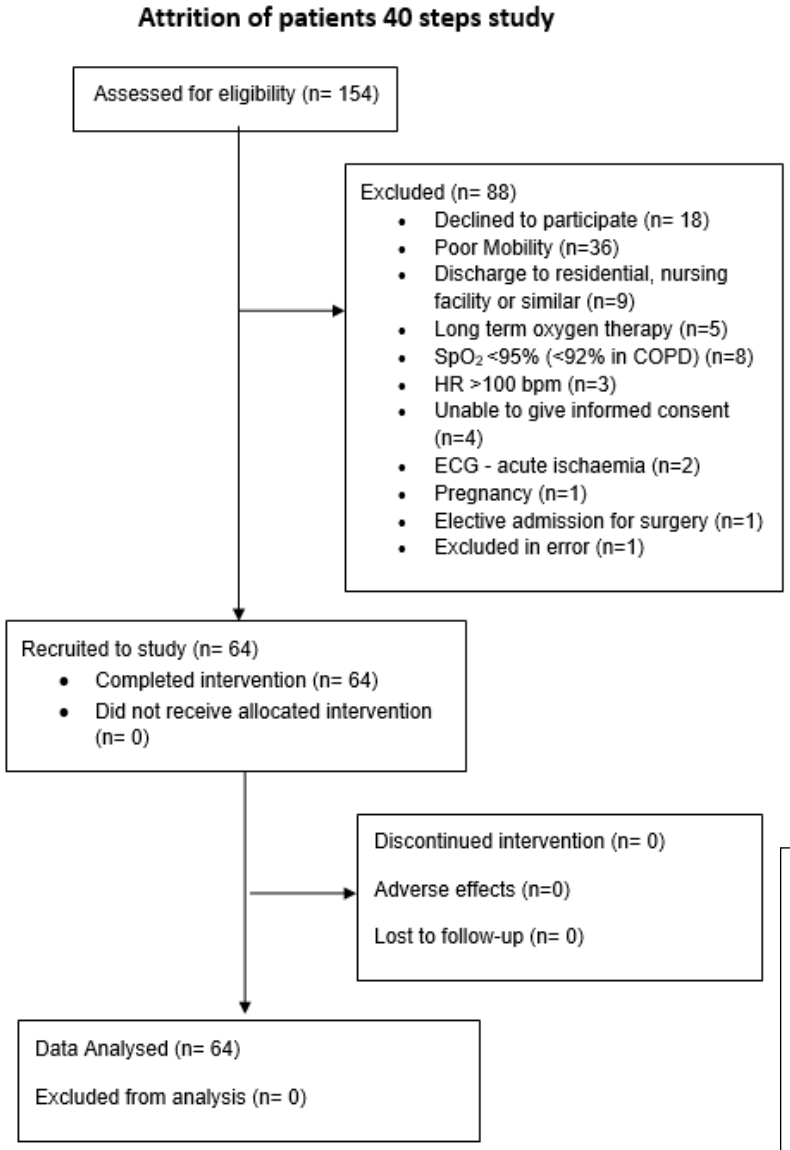


Figure 3 – CONSORT flow diagram 2010 for the 40 steps study at one site.

Details the number of participants screened, excluded/recruited, completed the intervention, and followed up.

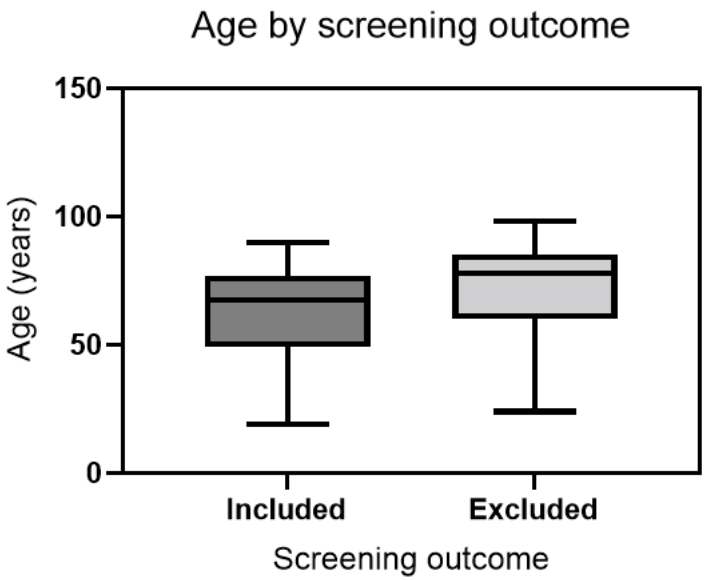


Figure 4 – Box plot of included and excluded participants by age
Mean is indicated by the horizontal line within the box, the interquartile range by the box length, and range (highest to lowest value) by the bars/whiskers.

Age	Included (n=64)	Excluded (n=90)	p-value
18-30	5	7	
31-45	7	6	
46-60	16	10	
61-75	14	14	
76-90	22	43	
91+	0	7	
Mean ±SD	63 ±19	71 ±19	0.008
Range	19-90	24-98	

Table 10– Included and excluded participants by age
Excluded participants were more highly represented in older age groups, with a statistically significant difference in mean age of included and excluded participants
Abbreviations: SD; Standard deviation.

Demographics

Demographic data for the study participants are presented in Table 11. The sample included 45% male and 55% female participants. All readmitted patients and those who clinically deteriorated were female, as well as a third of patients investigated further. The ethnicity of 93% participants was White, with 2% Asian, 2% Black/African-Caribbean and 2% Arabic participants. Fifty percent of participants were recruited from inpatient wards, 36% from the medical admissions unit, and 14% from the emergency department. A third of participants recruited from an emergency department or medical admissions unit were hospitalised further, with those assessed in ED accounting for two thirds of participants investigated further, and two thirds of those readmitted within 30-days. The prevalence of other pre-existing co-morbid

conditions affecting cardiopulmonary exercise in the cohort was 34% (16% COPD, 19% asthma, 2% pulmonary fibrosis, and 3% heart failure). Those with co-morbidities were not more highly represented in the adverse outcome groups studied.

Eleven COVID-19 positive patients were included in this study (17%), of whom two had pre-existing asthma and one COPD. 49 participants (77%) were confirmed negative, and 4 participants were not suspected to have COVID-19 but were not tested for the presence of the virus. A third of COVID-19 positive patients required further inpatient hospital stay after the 40 steps test was completed, 9% were readmitted, 27% were investigated further, and 18% clinically deteriorated. COVID-19 positive patients represented 25% of all readmissions, and 100% of those investigated further but none of the participants clinically deteriorated within 7 days.

Follow-up

All participant electronic records were accessed successfully to assess 30-day outcome, using the patient consent obtained at the primary visit. Same day discharge occurred in 49 (76.6%) participants. Fifteen (23.4%) participants required further inpatient hospital stay; 5 were discharged the following day (7.8%), 9 within 7 days (14.1%), and 1 (1.6%) within 14 days of the 40 steps test. The reason for prolonged hospitalisation was not clearly recorded in the follow-up sources used. Where a reason was given, these included need for further physiotherapy, awaiting COVID-19 PCR result, unresolved symptoms (including anaemia, diarrhoea and vomiting, visual disturbance, headache, and rash), and new unanticipated information from a pending investigations (e.g., electrolyte abnormality).

Three participants (5%) had further investigations done as an inpatient: one had a D-dimer test to assess for Pulmonary embolism following marked desaturation of 10% on the 40 steps test, one had repeat chest imaging which confirmed a hospital-acquired pneumonia, and another had a COVID-19 test which confirmed COVID-19. Only one patient (2%) experienced clinical deterioration while still in hospital who was also diagnosed with a hospital-acquired pneumonia.

Four participants were re-hospitalised (6%) within 30-days of taking part in the study, including one who presented to the ED and was then discharged. The reasons for readmission

included worsening symptoms of metastatic cancer, COVID-19 related diarrhoea and vomiting, and back pain. There were no participant deaths within 30-days (0% mortality).

	N=64	Readmission (n=4)	No readmission (n=60)	Same day discharge (n=49)	Further hospitalisation (n=15)	Further investigation (n=3)	Clinical deterioration (n=1)
Gender: n(%)							
Male	29 (45.3)	0 (0.0)	29 (48.3)	23 (46.9)	6 (40.0)	2 (66.7)	1 (100.0)
Female	35 (54.7)	4 (100.0)	31 (52.7)	26 (53.1)	9 (60.0)	1 (33.3)	0
Age:							
Mean ±SD	62.5 ±18.7	76.3 ±19.6	61.7 ±18.5	60.1 ±18.4	70.9 ±16.5	54 ±21.4	85 ±0
Ethnicity: n(%)							
White	61 (95.3)	4 (100.0)	57 (95.0)	48 (98.0)	13 (86.7)	3 (100.0)	1 (100.0)
African-Caribbean	1 (1.6)	0	1 (1.7)	1 (2.0)	0	0	0
Asian	1 (1.6)	0	1 (1.7)	0	1 (6.7)	0	0
Arab	1 (1.6)	0	1 (1.7)	0	1 (6.7)	0	0
Other	0 (0.0)	0	0	0	0	0	0
Location: n(%)							
ED	9 (14.1)	2 (50.0)	7 (11.7)	6 (12.2)	3 (20.0)	2 (66.7)	0
MAU	23 (35.9)	1 (25.0)	22 (36.7)	16 (32.7)	7 (46.7)	0	0
Ward	32 (50)	1 (25.0)	31 (51.7)	27 (55.1)	5 (33.3)	1 (33.3)	1 (100.0)
Ambulance	0 (0.0)	0	0	0	0	0	0
Primary care	0 (0.0)	0	0	0	0	0	0
Co-morbidity: n(%)							
COPD	7 (10.9)	0	7 (11.7)	6 (12.2)	1 (6.7)	0	0
Asthma	9 (14.1)	0	9 (15.0)	9 (18.4)	0	0	0
COPD+asthma	3 (4.7)	0	3 (5.0)	2 (4.1)	1 (6.7)	0	0
P.fibrosis	1 (1.6)	0	1 (1.7)	1 (2.0)	0	0	0
Heart Failure	2 (3.1)	0	2 (3.3)	2 (4.1)	0	0	0
COVID-19: n(%)							
Positive	11 (17.2)	1 (25.0)	10 (16.7)	7 (14.3)	4 (26.7)	3 (100.0)	0
Negative	49 (76.6)	3 (75.0)	46 (76.7)	39 (79.6)	10 (66.7)	0	1 (100.0)
Not tested	4 (6.2)	0	4 (6.7)	3 (6.1)	1 (6.7)	0	0

Table 11 – Demographic data for the 40 steps study
Data for age, gender, and ethnicity was collected, as well as patient location, cardio-pulmonary co-morbidity, and COVID-19 status. The distribution of these participants is displayed according to all outcome measures studied. Abbreviations: COPD; Chronic obstructive pulmonary disease, COVID-19; Coronavirus disease, ED; Emergency department, MAU; Medical admissions unit, P.fibrosis; pulmonary fibrosis, SD; Standard deviation.

Safety

Of the 64 participants recruited, 100% completed the 40 steps test in full. There were no adverse events or early terminations of the test recorded. One participant was identified as requiring physiotherapy after appearing unsteady during the exercise test. Several participants were noted to need to hold a surface to stabilise themselves during or immediately after the test, however the number was not recorded formally.

Exercise intensity of the 40 steps test

Using the standard calculation for maximum predicted heart rate (Hrmax), 220-age (94), 17% of the cohort achieved a HR less than 50% their predicted maximum during the 40 steps test. Most participants (66%) exercised to a moderate intensity during the 40 steps test (HR 50-70% of maximum predicted HR), and a further 17% were vigorously exercising during the test (>70%). Mean percentage of maximum predicted HR during the test was 60% ±11.51 (Figure 5). Exercise intensity was not noted to be higher in most of the adverse outcome groups studied, although the participant who later clinically deteriorated was exercising vigorously (Hrmax 83% predicted), compared to a mean Hrmax of 53% in the comparison group.

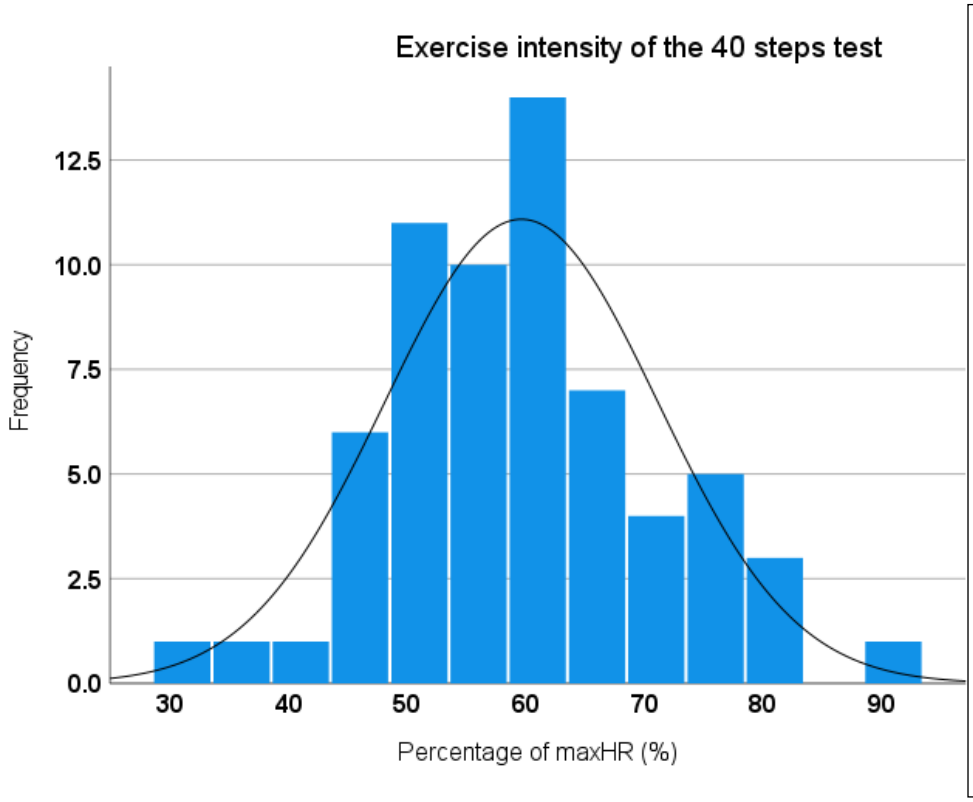


Figure 5 – Distribution of the percentage of the maximum predicted heart rate elicited by the 40 steps test. Histogram showing the percentage of the maximum predicated heart rate reached by participants during the 40 steps test. The majority achieved moderate exercise intensity (50-70%).

Abbreviations: HR; heart rate, HRmax; maximum heart rate calculated as end-test HR/(220-age)x100

Physiological variables by outcome

Mean changes in the physiological variables recorded (percentage SpO_2, heart beats per minute, breaths per minute and patient-selected numerical dyspnoea score) are summarised in Figure 6.

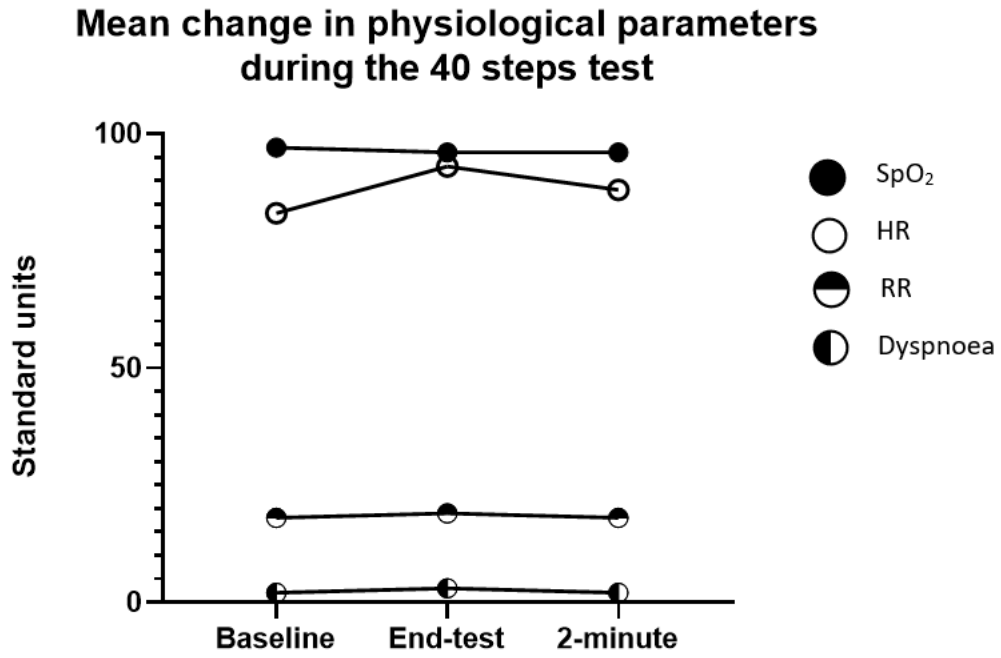


Figure 6 – Mean change in physiological parameters during the 40 steps test

- Mean SpO_2 (%) at baseline was 97% (±2.0), with a mean decrease of 1% to 96% at end-test (±2.9) and 2-minutes (±.
- Mean HR (bpm) at baseline was 83 bpm (±12.3) rising by a mean of 11 bpm to 93bpm (±18.0), before decreasing to a mean of 88 bpm (±17.0) by 2-minutes
- Mean RR (breaths/min) was 18 (±2.0) at baseline, increasing by 1 breath/minute by end-test (±3.5) before returning to a mean of 18 breaths/min (±2.1) by 2-minutes
- Mean dyspnoea score (on a scale from 0-10) was 2 at baseline (±2.5), which increased by a mean of 1 by end test to 3 (±2.9). Mean dyspnoea score at 2-minutes was also 2 (±2.6).

Abbreviations: HR; heart rate, RR; respiratory rate, SpO_2; oxygen saturation

COVID-19

In the COVID-19 cohort (n=11), pre-exercise saturation was 96% (±2.3), and this fell to 94% immediately post-exertion (±3.6). There was, however, wide clinical variability (Figure 7a). Two minutes after completing the test SpO_2 was 97% (±2.0). The difference in SpO_2 at baseline between COVID-19 and non-COVID-19 patients was <1%, and the mean difference in change in

SpO_2 from baseline to test completion in the COVID-19 positive and negative cohort was also <1%. Neither finding was statistically significant (p=0.837, p=0.959). COVID-19 positive and COVID-19 negative patients had a similar mean baseline heart rate at 83bpm (±14) and 82bpm (±12), but COVID-19 positive patients had a mean increase in HR of 16 bpm by test completion compared to 10bpm in non-COVID-19 participants (end test HR 92 bpm (±18) in COVID-19 negative vs 99bpm (±22) in COVID-19 positive patients). Heart rate recovered by 5 bpm by 2-minutes after the test in both groups, leaving COVID-19 positive patients with a HR a mean of 11bpm higher than their baseline HR at 94bpm (±19), compared 87bpm (±17) in COVID-19 negative patients. The mean change in Heart Rate from baseline was 13% in the cohort (Figure 7b). Patients positive for SARS-CoV-2 represented 31% of those whose HR increased by more than 20% during the 40 steps test, despite accounting for 17% of the overall cohort taking part in the study, indicating that patients exhibiting a higher chronotropic index during the 40 steps test may be more likely to have COVID-19.

The mean baseline RR in COVID-19 positive patients was higher by a mean of 2 breaths/min than the COVID-19 negative group (19 breaths/min ±3 versus 18 breaths/min ±1, p=0.707). The difference in respiratory rate change observed following the 40 steps test was less than 1 breath/min between COVID-19 and non-COVID-19 cases (p=0.825). COVID-19 positive patients reported dyspnoea scores on average twice as high as non-COVID-19 patients at baseline (2 ±2 versus 4 ±3) and end test (Figure 8). The mean difference in baseline dyspnoea score between the groups was however not statistically significant after adjusting for multiple comparisons (p=0.837). Additionally, the difference in change of dyspnoea score prompted by the 40 steps test in the two groups was <1, which was not statistically significant (p=0.970).

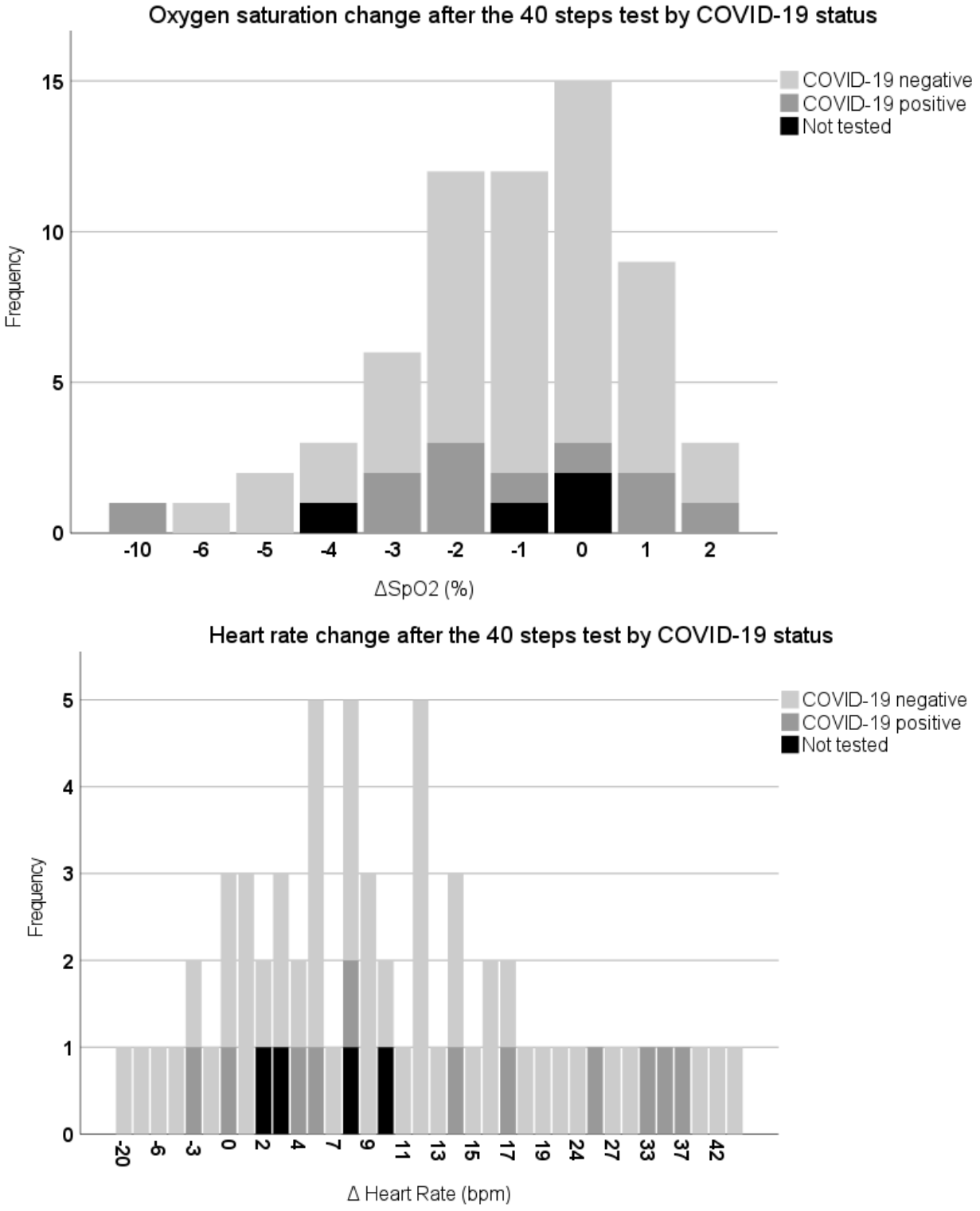


Figure 7 – Post exertion change in oxygen saturation and heart rate according to COVID-19 status

a) Stacked histogram showing the change in oxygen saturation from baseline to immediately after completion of the 40 steps on the spot test in coronavirus disease (COVID-19) positive, negative, and untested participants

b) Stacked histogram shows the distribution of the percentage change in heart rate from baseline to immediately after completing the 40 steps on the spot test in COVID-19 positive, negative, and untested participants.

Abbreviations: Bpm; beats per minute, COVID-19; Coronavirus disease

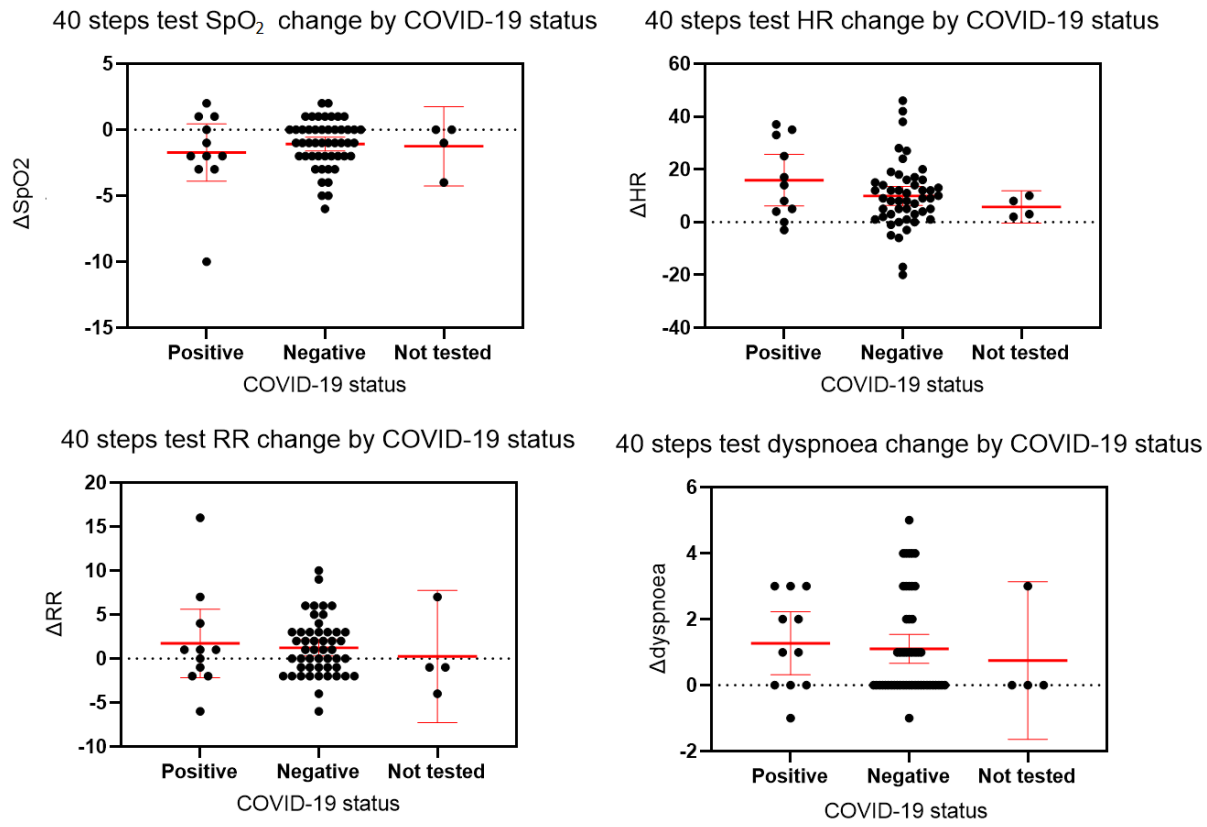


Figure 8 – Dot plots showing changes in SpO2, HR, RR, and dyspnoea according to COVID-19 status
Each participant is represented by a single dot, with a thick red central horizontal line to indicate the mean. The bars/whiskers show the 95% confidence interval for the mean calculated.
Abbreviations: Δ; delta, COVID-19; Coronavirus disease, HR; heart rate, RR; respiratory rate, SpO_2; oxygen saturation

Rehospitalisation

The one participant with COVID-19 who was readmitted within 30 days of the 40 steps test, had resting SpO_2 of 100% and did not desaturate during the test. Three readmitted patients without COVID-19 had SpO_2 change between -1% and +1%., with a mean desaturation of 0%. None of the physiological parameters measured during the 40 steps test showed a significant association with readmission to hospital at baseline, as well as for change in HR, RR, SpO_2 and dyspnoea (Figure 9).

Mortality

No deaths were recorded in the cohort therefore no conclusions on the link between physiological parameters during the test and mortality can be drawn.

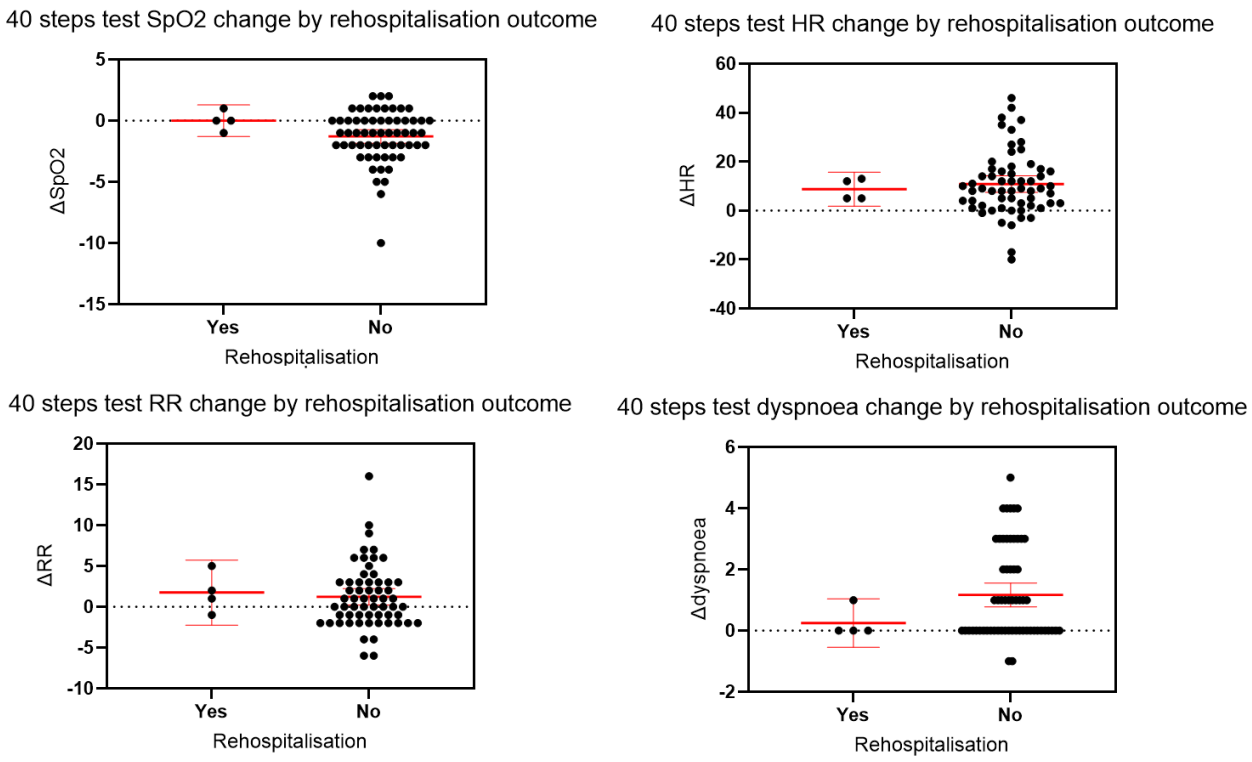


Figure 9 – Dot plots showing changes in SpO2, HR, RR and dyspnoea and rehospitalisation outcome
Each participant is represented by a single dot, with a thick red central horizontal line to indicate the mean. The bars/whiskers show the 95% confidence interval for the mean calculated.
Δ SpO_2 - mean change in SpO_2 was 0% ±1 in rehospitalised versus -1% ±2 in non-rehospitalised patients
Δ HR – mean change in HR was +8 bpm ±4 in rehospitalised versus +10 bpm ±13 in non-rehospitalised patients
Δ RR - mean change in RR was +2 breaths/min ±3 in rehospitalised versus +1 breath/min ±4 in non-rehospitalised patients
Δ dyspnoea - mean change in dyspnoea was 0 ±1 in rehospitalised versus 1±2 in non-rehospitalised patients
Abbreviations: Δ; delta, HR; heart rate, RR; respiratory rate, SpO_2; oxygen saturation.

Same day discharge

All patients were planned for discharge on the day the 40 steps test was conducted, of whom 23% patients were hospitalised further. Of the COVID-19 patients, the oxygen saturation changes from baseline to test completion ranged from -10% to +2% in those hospitalised further, and in the COVID-19 negative cohort SpO_2 change ranged from -5% to +1%. The mean differences in SpO_2 at baseline, test completion and 2-minute, between those hospitalised further and those discharged on the day of the test were less than 1%. The mean change between SpO_2 at the end of the test from baseline was -2% (±3) in those further hospitalised, compared to -1% (±2) in those discharged on the same day, and was not statistically significant (Figure 10).

The baseline HR values for those hospitalised further were on average lower than those discharged on the same day (78 ±12 bpm versus 84 ±12 bpm), and both groups increased HR by a mean of 11 bpm (± 9bpm same day discharge, ±13 bpm continued hospitalisation) during the 40 steps test. End-test RR was 2 breath/minute ±4 lower in the same day discharge group, but the difference in change to RR during the test between the groups was <1 breath/min and not statistically significant (p=0.902). Dyspnoea scores did not differ significantly from baseline or increase significantly after 40 steps between the groups (p=0.922, p=0.916).

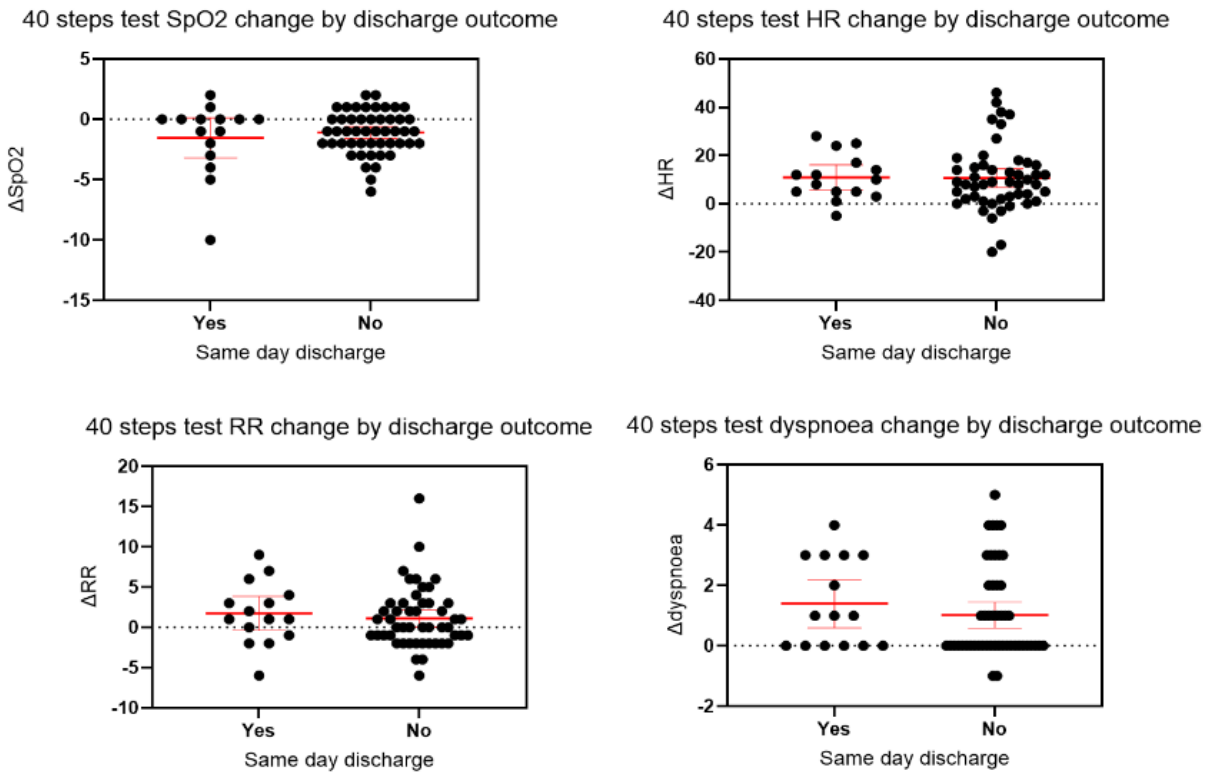


Figure 10 – Dot plots showing changes in SpO2, HR, RR and dyspnoea and discharge outcome
Each participant is represented by a single dot, with a thick red central horizontal line to indicate the mean. The bars/whiskers show the 95% confidence interval for the mean calculated.
Abbreviations: Δ; delta, HR; heart rate, RR; respiratory rate, SpO_2; oxygen saturation.

Further investigation

Of the three participants investigated further, mean decrease in SpO_2 was higher at -4% (±5) compared to a mean desaturation of -1% (±2) in the non-investigated group (Figure 11). All

three participants were either already or subsequently diagnosed with COVID-19. HR increased marginally less on average in investigated (9bpm ±5) versus non-investigated (11bpm ±13) individuals. Baseline RR was higher in the investigated cohort at 21 (±5) breaths/min compared to 18 (±2) breath/min in the non-investigated cohort. End test RR was 4 breaths/min higher in the investigated group compared to non-investigated. However, the change in RR from baseline prompted by the 40 steps test was less than 1 breath per minute higher in the investigated group, and not statistically significant (p=0.809).

Dyspnoea scores were on average 3 points higher in participants investigated further (end-test dyspnoea 6 ±3 versus 3 ±3). However, the change in dyspnoea score following the 40 steps was minimally different between the two groups (p=0884). A subgroup analysis comparing covid-19 patients who were investigated further with those who were not did also not show any statistically significant findings (data not shown).

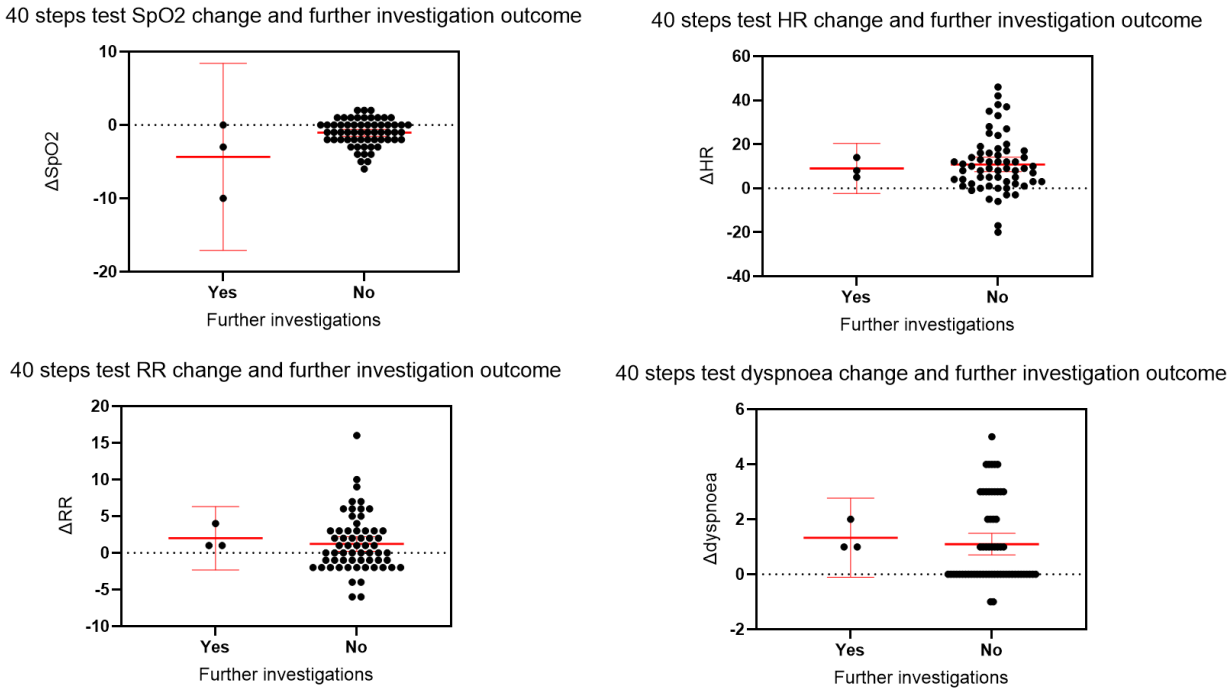


Figure 11 – Dot plots showing changes in SpO2, HR, RR and dyspnoea and investigation outcome
Each participant is represented by a single dot, with a thick red central horizontal line to indicate the mean. The bars/whiskers show the 95% confidence interval for the mean calculated.
Abbreviations: Δ; delta, HR; heart rate, RR; respiratory rate, SpO_2; oxygen saturation.

Clinical deterioration

Only one patient within the recruited cohort clinically deteriorated within 7 days of undertaking the test, who was diagnosed with a hospital-acquired pneumonia two days after the 40 steps test. They had not desaturated on exertion during the 40 steps test and tested negative for COVID-19. The HR in this individual increased by 24 bpm compared to a mean of 11 bpm in the non-deteriorating cohort, and RR increased by 9 breath/min compared to an average of 1 breaths/min in the non-deteriorating group. The change in dyspnoea score prompted by the 40 steps test was 4 in the patient who later clinically deteriorated compared to a mean change of 1 in the group who did not deteriorate (Figure 12).

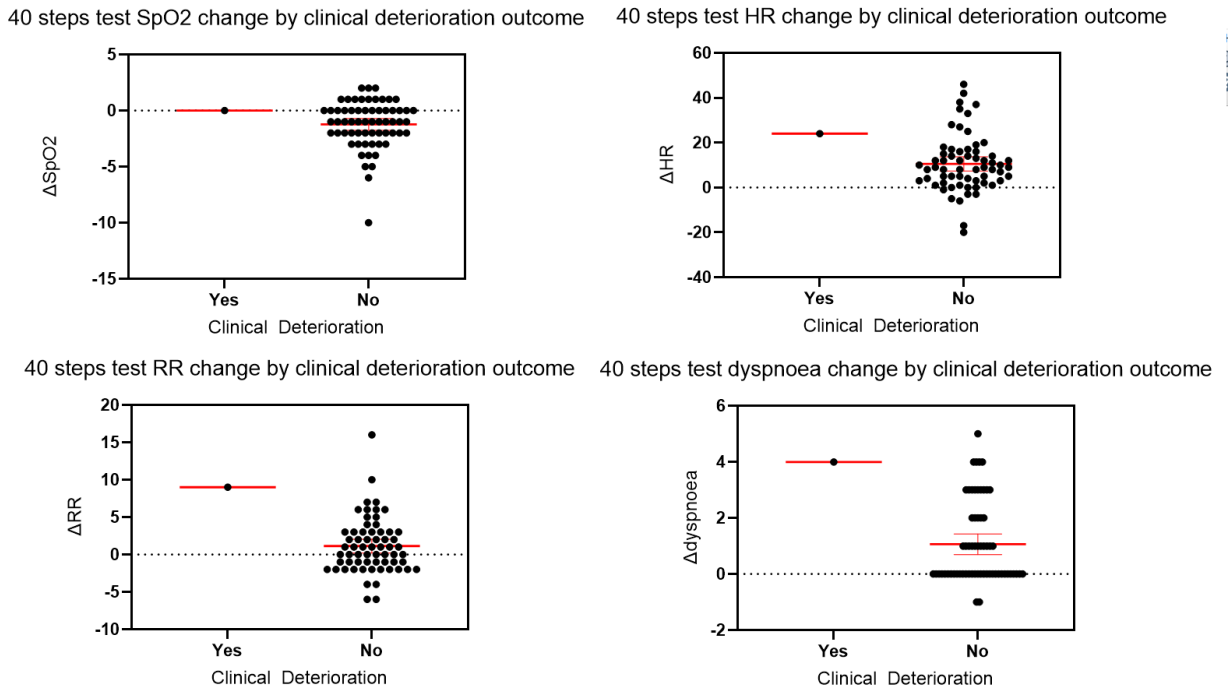


Figure 12 – Dot plots showing changes in SpO2, HR, RR and dyspnoea and clinical deterioration
Each participant is represented by a single dot, with a red dark central horizontal line to indicate the mean. The bars/whiskers show the 95% confidence interval for the mean calculated.
Abbreviations: Δ; delta, HR; heart rate, RR; respiratory rate, SpO_2; oxygen saturation.

ROC curve analysis of oxygen saturation and adverse outcome gave an area under the curve of 0.493, indicating that desaturation during the 40 steps test is poorly predictive of adverse outcome. A cut-off value of ≥3% desaturation was found to be the most suitable to

balance sensitivity with specificity, the latter of which decreases steeply at lower desaturation thresholds.

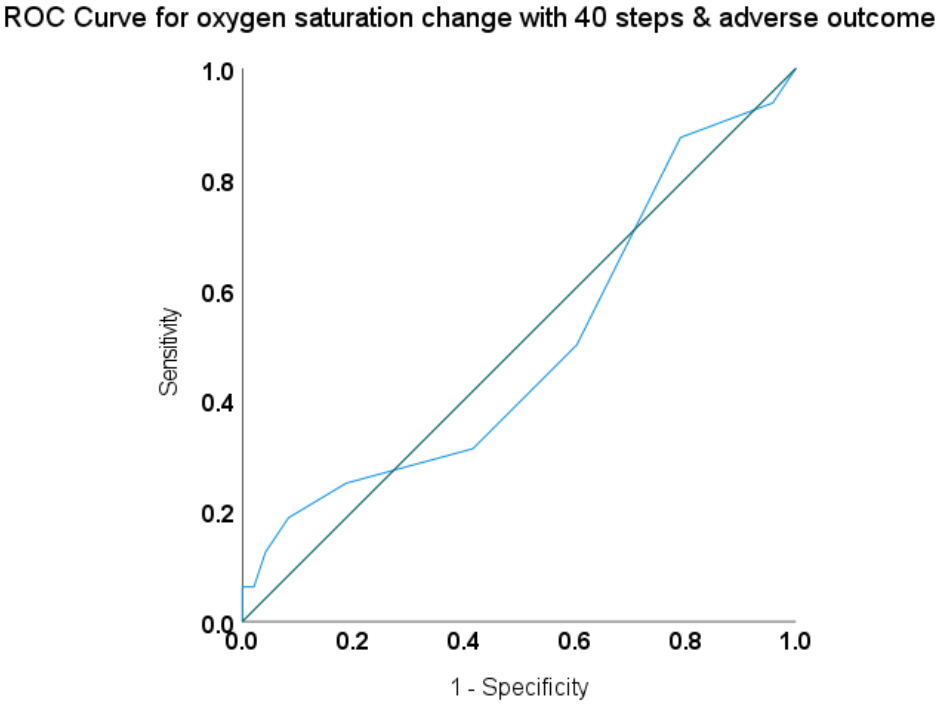


Figure 13 – Receiver operating characteristic (ROC) curve for oxygen saturation changes during the 40 steps test and adverse outcome
Outcome measures combined were rehospitalisation, prolonged hospitalisation (i.e. no same day discharge), further investigations and clinical deterioration.

Area under the curve (AUC); 0.493, indicating the 40 steps test was poorly predictive of adverse outcome in the study cohort.

Using an SpO_2 threshold of ≥3% desaturation during the 40 steps test, as currently recommended for admission to be considered (37,39), a 27% sensitivity, and 81% specificity for COVID-19 was calculated. The Positive predictive value (PPV) of the test for identifying COVID-19 was 23% with a negative predictive value (NPV) of 84%.

As a tool for safe discharge, ≥3% desaturation during the 40 steps test has a sensitivity of 25%, specificity of 81%, PPV of 31% and NPV of 76% for adverse outcome including rehospitalisation, continued hospitalisation, further investigations, and clinical deterioration. The Area under the ROC curves (AUC) were low for all physiological parameters in predicting both COIVD-19 status and adverse outcome (Table 12 and 13). For all parameters, an optimal cut off was identified; when both high sensitivity and specificity was not achievable a higher specificity was favoured, given that the 40 steps test is currently recommended as a test where

a negative test is used to guide a decision to discharge. A HR change of more than 15bpm or %HR change of more than 20% from baseline gave the highest combination of sensitivity and specificity of all the physiological parameters for predicting COVID-19. However, for predicting adverse outcome a RR increase of 3 or more breaths/min was one of the most useful parameters with a sensitivity of 44%, and specificity of 73%, whilst a dyspnoea score increase of 3 or more points (on the scale from 1 to 10) had a sensitivity of 31%, and specificity of 73% to predict adverse outcome.

	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Optimal cut off
Δ SpO2	0.46 (0.25-0.67)	27%	86%	30%	84%	≥3%
Δ HR	0.60 (0.39-0.80)	45%	73%	28%	86%	≥15 bpm
%Hrchange	0.52 (0.32-0.72)	45%	78%	31%	86%	≥20%
Δ RR	0.48 (0.27-0.68)	27%	82%	25%	83%	≥4 breath/min
Δ dyspnoea	0.55 (0.36-0.74)	27%	78%	25%	83%	≥3 increase score

Table 12 – Sensitivity, specificity, and optimal cut-offs for changes in physiological parameters during the 40 steps test to predict COVID-19 status

AUC was low for all physiological parameters indicating poor ability of the 40 steps test to predict COVID-19 status. Sensitivity, specificity, PPV and NPV are given according to the optimal cut off identified by the analysis.

Abbreviations: Δ; delta, 95%CI; 95 percent confidence interval, AUC; area under ROC curve, bpm; beats per minute, COVID-19; coronavirus disease, HR; heart rate, NPV; negative predictive value, PPV; positive predictive value, ROC; receiver operating characteristics, RR; respiratory rate.

	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Optimal cut off
Δ SpO2	0.51 (0.34-0.68)	25%	83%	33%	77%	≥3%
Δ HR	0.54 (0.39-0.70)	38%	67%	18%	76%	≥13 bpm
%Hrchange	0.56 (0.40-0.71)	25%	75%	25%	75%	≥20%
Δ RR	0.60 (0.44-0.77)	44%	73%	35%	80%	≥3 breath/min
Δ dyspnoea	0.56 (0.40-0.71)	31%	79%	33%	78%	≥3 increase score

Table 13 – Sensitivity, specificity, and optimal cut-offs for changes in physiological parameters during the 40 steps test to predict adverse outcome

AUC was low for all physiological parameters indicating poor ability of the 40 steps test to predict COVID-19 status. Sensitivity, specificity, PPV and NPV are given according to the optimal cut off identified by the analysis.

Abbreviations: Δ; delta, 95%CI; 95 percent confidence interval, AUC; area under ROC curve, bpm; beats per minute, COVID-19; coronavirus disease, HR; heart rate, NPV; negative predictive value, PPV; positive predictive value, ROC; receiver operating characteristics, RR; respiratory rate.

By applying a Chi square test (Table 14) to the optimal cut offs identified, there was a significant association between desaturating ≥3% on the 40 steps test and further investigation (p=0.041). Two of the three patients investigated further had desaturated ≥3% during the 40 steps test, both of whom the decision to investigate was prompted by the result of the 40 steps test (d-dimer to exclude PE and rapid COVID-19 PCR to confirm COVID-19 diagnosis).

Of the COVID-19 positive patients, 45% had a HR increase of ≥15 bpm versus 26% of COVID-19 negative patients. There wasn't a statistically significant difference in adverse outcome and HR increase ≥15bpm. Using a threshold of 4 or more breath/min increase following the 40 steps test, 27% of COVID-19 positive cases met this criterion versus 18% of COVID-19 negative participants, although the Chi square test was not statistically significant (Chi^2 0.498, p=0.780). For predicting adverse outcomes, a threshold of ≥3 breaths/min was optimal based on the ROC analysis, which was not significantly associated with any of the adverse outcome groups. There was no significant difference in the proportion of COVID-19 positive or negative patients reporting a dyspnoea score increase of 3 points or more, and no statistically significant association was noted with any of the adverse outcome groups.

	Covid-19		**Readmission**		**Same day discharge**		**Further Investigation**		**Clinical Deterioration**	
	Y	**N**	**Y**	**N**	**Y**	**N**	**Y**	**N**	**Y**	**N**
desat ≥3%	3	9	0	13	9	4	2	11	0	13
desat <3%	8	40	4	47	40	11	1	50	1	50
Chi^2 (p-value)	0.498	(0.780)	1.088	(0.297)	0.489	(0.485)	4.178	(0.041)	0.259	(0.611)
HR ≥15 bpm	5	13	0	18	14	4	0	18	1	17
HR <15 bpm	6	36	4	42	35	11	3	43	0	46
Chi^2 (p-value)	3.261	(0.196)	1.670	(0.196)	0.021	(0.886)	1.232	(0.267)	2.596	(0.107)
RR ≥3/min	3	16	1	19	14	6	1	19	1	12
RR <3/min	8	33	3	41	35	9	2	42	0	51
Chi^2 (p-value)	0.199	(0.905)	0.078	(0.781)	0.698	(0.403)	0.006	(0.936)	2.235	(0.135)
Dyspnoea ≥3	3	11	0	15	10	5	0	15	1	14
Dyspnoea <3	8	38	4	45	39	10	3	46	0	49
Chi^2 (p-value)	0.122	(0.941)	1.306	(0.253)	1.069	(0.301)	0.964	(0.326)	3.319	(0.069)

Table 14 – Using physiological thresholds during the 40 steps test to predict outcome
Thresholds refer to the change in SpO2, HR, RR, and dyspnoea from the baseline measurement to the measurement immediately after completing the 40 steps test. Frequency of participants by outcome measure are displayed, with Chi square statistic and p-value presented for each outcome and physiological variable
Abbreviations: Bpm; beats per minute, Chi^2; Chi square statistic, COVID-19; Coronavirus disease, desat; desaturation, HR; heart rate, RR; respiratory rate

3.5 Discussion

Summary of main findings

This study indicates that the 40 steps test is feasible and safe in mobile patients within the acute setting and could potentially be applied in a pathway as a pre-discharge tool. The findings presented demonstrate that it is a sub-maximal test of exertion, with moderate or above levels of exertion achieved by over 75% of patients. The study sample collected was small, and a high number of hospitalised patients were excluded, raising the possibility that the 40 steps desaturation test, is potentially unsuitable in older patients, potentially limiting its utility.

Predictive modelling is challenging with the small numbers included in the study, but no association between desaturation during the test and COVID-19 or any other outcomes, including readmission and clinical deterioration were identified. The mean observed difference in oxygen saturation was marginally higher in COVID-19 positive patients, those not discharged on the day of the test and those investigated further. These observed differences are often <1% which is not clinically meaningful and makes establishing a valid desaturation cut-off for considering admission difficult. Desaturation of 3% or more was observed in 50% of the cohort who were not discharged on the same day as the test as planned, and in 67% of participants investigated further. However, given that NHS guidance at the time of the data collection advised admission if desaturation is more than 3% is present during the test, it is necessary to question whether the admission and investigations link identified is guidance-driven or based on other clinical judgement, particularly as desaturation of 3% was not linked to clinical deterioration or mortality in this study. As such it must be considered that the 40 steps might not be sufficiently challenging to elicit exertional desaturation in a patient at risk of becoming more unwell, and its role in uncovering silent hypoxaemia to aid safe discharge has not been established by this study.

Heart rate change was higher in COVID-19 positive at the end of the 40 steps test and at 2-minutes post exercise. A HR increase of 15 bpm, or more was seen more commonly in COVID-19 positive patients and was a feature in the COVID-19 negative patient who clinically deteriorated. This is a potentially intriguing finding linking COVID-19 and an exaggerated increase in HR during exercise, although due to the small sample size in this study, could also be a spurious finding. There was no observed link between an exaggerated HR response to exercise

and prolonged hospitalisation, rehospitalisation, or further investigation. Measuring the percentage change in heart rate from baseline is a potentially useful marker, with an increase of 20% found to be optimal with a 44% sensitivity and 78% specificity for COVID-19. However, this appears less useful as a marker for adverse outcome within 30 days of the test, with a lower sensitivity of 25%.

Respiratory rate was noted to be 2-4 breaths/minute higher in all the adverse outcomes studied. However, the mean change in RR following the test was less than 1 breath per minute for all outcomes studied, which is neither statistically nor clinically significant. An increase in respiratory rate following the 40 steps test of 3 breath/minute was more common in all the outcome groups studied. Higher dyspnoea scores were observed in participants with a COVID-19 diagnosis, and those who were further investigated, continued to be hospitalised, or clinically deteriorated. However, the change in dyspnoea was not significantly higher following 40 steps in the adverse outcome groups studied, with a mean increase of 1 difference in score from baseline to test completion.

Notably, the hospitalised cohort included in this study did not all have respiratory symptoms (COVID-19 related or otherwise), and therefore larger studies of COVID-19 patients to incorporate those who were hospitalised or clinically deteriorated for cardio-pulmonary compromise are desirable to validate these findings. The study findings indicate that a short test of exertion may induce some physiological changes of prognostic significance, and which may aid in ensuring safe discharge. However, many of the changes seen within this cohort were minimal and not clinically significant.

Previously recommended thresholds for desaturation were not found to be predictive of clinical deterioration, and although a 3% threshold was most optimal, desaturation during the 40 steps test was a poorly sensitive indicator or COVID-19 and adverse outcome, with moderate specificity. The optimal thresholds for HR, RR and dyspnoea identified by this study were also not statistically significant within this limited sample.

Previous research in COVID-19

As per the findings outlined in the previous chapter, this research is the first to assess the 40 steps desaturation test, which is nevertheless in widespread clinical use, with multiple literature reviews proposing the urgent need to validate this test (35,36).

Limited evidence for using desaturation as a clinical decision tool in the acute care setting has been outlined, including in COVID-19. In a COVID-19 study measuring post-exertion desaturation following a non-standardised period of exertion, 3% desaturation was linked to adverse outcome at 30-days in a select group of patients with oxygen saturations above 94% at rest (39). Similarly mixed results were seen using the extremely brief 10 feet desaturation test, in COVID-19 (55); a higher proportion of patients who deteriorated clinically or died desaturated more than 3%, however 51% of the stable cohort also met this criterion. This appears to correspond to this study's findings that the 40 steps test is a poorly sensitive test for COVID-19, but high levels of desaturation are relatively specific for COVID-19 and other adverse outcomes.

The most stark differences in physiological response in this study cohort was higher respiratory rate and clinical deterioration, which is corroborated by other research indicating that respiratory rate is a key factor in predicting clinical deterioration (95,96). A link between respiratory rate and clinical deterioration has also been identified in other observational studies in COVID-19 (97,98), although this physiological parameter has not formally been linked to risk of rehospitalisation.

Dyspnoea scoring using an extended Medical Research Council dyspnoea scale has been linked to 28-day mortality in acute exacerbations of COPD. Dyspnoea as a symptom in COVID-19 at admission has also been linked to deterioration from the disease (99,100). These are intriguing findings given the widespread focus on silent hypoxaemia and its consequential incorporation into COVID-19 assessment and suggests that clinicians should perhaps focus on quantifying a patient's breathlessness instead of performing a test of exertion.

Limitations

Despite being one of the shortest, less vigorous exercise tests within the literature many patients were excluded from participating in the 40 steps test using the exclusion criteria for this study, mainly due to poor mobility. This limits the potential wider applicability of the 40 steps as a screening tool. Assessment of whether the 40 steps on the spot test can be safely used in patients who use a stick or frame has not been evaluated within the scope of this study. Even in independently mobile patients, some required a surface (e.g., bedside table) to stabilise themselves at test completion. The specified exclusion criteria led to participants included in the study who were younger on average. However, COVID-19 patients who require hospitalisation

and with higher rates of clinical deterioration and mortality tend to be older in age (101). If the 40 steps test is not achievable in older individuals, its potential utility may be limited to distinguishing younger patients who are more likely to clinically deteriorate, which limits its potential usefulness.

The study sample includes relatively few patients with COVID-19, mainly due to the comparatively low number of COVID-19 patients admitted to the recruiting hospital site. Other barriers to recruiting patients included that data collection was done by two masters students working 2 days per week in daytime hours. This limited ability to recruit patients admitted in the evening and overnight when more medical admissions tend to occur. Patients were also more often recruited from inpatient wards. Within this study, the difference between COVID-19 patients recruited on admission (where the 40 steps test was used to decide if discharge could be considered) versus those recruited at discharge following recovery from acute COVID-19 was not assessed. Due to the novel nature of SARS-CoV-2 it is difficult to conclude whether this has impacted the findings.

Due to the small sample size obtained, it was not possible to assess one of the primary outcomes of mortality, with also low numbers of patients clinically deteriorating, readmitted to hospital, and investigated further. Consequently, to substantiate these findings, further studies with a larger sample size is desirable, especially in COVID-19 patients.

As non-COVID-19 patients were included in this feasibility study some of the reasons for readmission and/or delayed discharge were unrelated to an acute respiratory illness therefore disturbance in oxygen saturation, heart rate, and respiratory rate might not be expected. Factors such as test completion, stopping, or needing to stabilise oneself, may provide surrogate markers for frailty, and be beneficial in predicting readmission in the general hospital setting. Such factors were not collected as part of the data collection, and therefore do not form part of the analysis. Limiting the study to patients with cardiopulmonary symptoms may have improved the application of the study's findings to suspected COVID-19.

The associations between the parameters studied and further investigation may be linked to the guidance being followed by the participating hospital which included a recommended cut-off of 3% for further investigating or considering hospitalisation of a patient

(37-39), therefore observations linked to this outcome in itself are not sufficient to conclude that the 40 steps test aids in safe discharge.

The equipment used was the standard equipment available within the NHS making these findings generalisable to the standard clinical setting. Race adjustments to the peripheral oxygen saturation values recorded were not conducted as part of this study, in line with current routine clinical practice, although is a key consideration if national recommendation are to be made (102). The lack of ethnic diversity within this study sample also precludes recommendations regarding different physiological cut offs according to racial background.

Implications for clinical practice

As one of the shortest tests ever recommended in the clinical setting, it is likely that the 40 steps is not sufficiently challenging to elicit exertional desaturation. If significant desaturation is prompted by the test therefore, one should consider that the individual may be quite unwell, and further investigation may be indicated to rule out serious pathology. More importantly, for clinicians perhaps, is that not desaturating during the test does not rule out future clinical deterioration or readmission, and therefore other clinical features should be considered alongside the presence or absence of desaturation during 40 steps test when deciding to discharge a patient.

Given that the 40 steps test is currently in widespread use as a clinical pathway to discharge mild cases of suspected COVID-19 (102), this should urgently be reconsidered and may over-rely on peripheral oxygen saturation. The findings outlined in this chapter indicate that other physiological parameters including heart rate response, respiratory rate and subjective dyspnoea may be of relevance and should also be considered as part of the discharge decision process. Importantly as an “on the spot” walking test was used in this study; the findings may not be generalisable to walking around a room or a fixed distance.

The COVID-19 patients included in this study reported dyspnoea scores on average twice their negative counterparts. Some of this effect may be due to the subjective impact of a COVID-19 diagnosis on dyspnoea rating in patients already known to have COVID-19 prior to undertaking the 40 steps test. However, it highlights the importance of quantifying dyspnoea in suspected COVID-19. More evidence linking dyspnoea scoring and outcomes is required to assess whether there is a link between perceived dyspnoea and COVID-19 outcomes.

Implications for research and policy

The recommendation to test for exertional desaturation as part of COVID-19 assessment remains present in most the recent NHS England guidance, although explicit reference to the 40 steps desaturation test has been removed (103). However, due to its widespread use in the early stages of the pandemic the 40 steps test remains a routine part of many clinicians' practice in the assessment of mild COVID-19 patients for discharge and still features in some current guidelines (39). Within this validation study oxygen saturation has not been found to be predictive of clinical deterioration, suggesting that the 40 steps test should not be used to detect desaturation as a pre-discharge decision tool in COVID-19. However, the use of other physiological parameters including respiratory rate and dyspnoea should be explored further, and a larger sample incorporating a higher number of COVID-19 patients, including more who clinically deteriorate is required to conclude on the utility of exercise testing in ensuring a safe discharge. Policymakers should also reflect on the impact of the other significant developments in the COVID-19 landscape including widespread vaccination, preventative treatments and availability of rapid-testing which all contribute to less severe disease and may impact the relevance of a pre-discharge exercise test to predict clinical deterioration.

This study has established some of the normal responses to the 40 steps test in a range of hospitalised individuals, including in those without COVID-19. Future studies may wish to limit recruitment to patients with acute dyspnoea including COVID-19 to avoid the statistical impact of patients hospitalised or continuing hospitalisation for reasons other than respiratory or physiological decline.

The numerical dyspnoea scale used in this study attempted to quantify dyspnoea in a simple way. However, the visual aid used was confusing to some users, and an alternative is suggested for future research. This could include simplifying the scale used to remove any words and images (i.e., "How breathless do you feel? Please give a number from 0-10"). If a high score is given, a more comprehensive assessment e.g. the Borg dyspnoea score or the Dyspnoea-12 (104,105) could be used, to quantify in more detail the aspects contributing to the subjective symptom of dyspnoea. An original proposal criterion of including only participants with a dyspnoea score below 2 was modified during the early stages of recruitment and the researchers simply asked the participant if they felt able to attempt 40 steps of walking.

A further recommendation is that future studies consider pacing the 40 steps test to ensure a consistent exercise intensity and minimise the effect that a lower exercise intensity may have on physiological parameters. Further exploration of the finding of a higher increase in heart rate in COVID-19 by the 40 steps test may also be indicated, with the potential that COVID-19 patients exercise more intensively due to inability to perceive hypoxia an area of particular interest.

In summary, these findings demonstrate that the 40 steps on the spot test can be safe and feasible sub-maximal test for use in the acute setting, in mobile patients. However, it may not be achievable for a significant proportion of hospitalised patients. Therefore, the evidence to support the use of very-short exertional tests to predict outcomes and facilitate safe discharge from hospital remains limited. An association between exertional desaturation and COVID-19, clinical deterioration, or rehospitalisation was not identified. Larger studies are desirable to further validate the findings potentially linking dyspnoea score with COVID-19 diagnosis, and respiratory rate post-exertion with clinical deterioration. Consideration of using other exertional tests that have been linked to adverse outcome predictions is warranted if further evidence does not support the use of the 40 steps test to promote safe discharge in the acute setting.

CHAPTER 4

Summary and Conclusion

This thesis has outlined how the practice of using a structured exercise test as part of the admission or discharge process to aid with estimating disease cause or prognosis has historically been limited to small studies. A prominent exercise test which is highly validated in acute cardiopulmonary disease has not been identified. This does not, however, mean that there is no role for exercise testing in the acute setting to aid with safe discharge. Indeed, outside of formal studies it is not uncommon for clinicians to use a non-standardised test of exertion to aid with decision to discharge a hospitalised patient. A short walk can give insight into mobility, frailty, physiological reserve, and symptomatology in patients with co-morbid lung disease, or recovering from an acute pulmonary event such as pneumonia or pulmonary embolism. Additionally, the recognition of exertional hypoxaemia as an indicator for clinical deterioration in COVID-19 provides a compelling reason for the increased interest in exercise testing within the acute setting in recent years. Two of the studies discussed in the scoping review chapter of this thesis provide additional evidence of exertional hypoxaemia in COVID-19 with tentative links to predicting clinical deterioration made (39,63), which justifies the continued inclusion of exercise testing within COVID-19 assessment guidelines nationally and globally (103,106). In a range of acute cardiopulmonary disease, it was summarised that desaturation in the range of 2-4% had been linked to various adverse outcomes including rehospitalisation, clinical deterioration, and death. However, in the validation study of the 40 steps test presented in chapter 3, no association between exertional desaturation and adverse outcomes of clinical deterioration or rehospitalisation was identified.

In chapter 1, the normal physiological response to hypoxaemia to increase minute ventilation was described, which may manifest as an increase in respiratory rate or tidal volume (18). Furthermore, silent hypoxaemia appears to be an early feature of coronavirus disease, with those with severe COVID-19 requiring mechanical ventilation noted to report breathlessness (23). Intriguingly, the COVID-19 patients included in the study in chapter 2 reported breathlessness twice as high as those without a COVID-19 diagnosis, which could suggest that efforts to quantify dyspnoea more comprehensively in COVID-19 may be more beneficial than seeking to identify exertional desaturation. However, given the small number of COVID-19 patient included in this study, larger studies are required to substantiate any links between dyspnoea and tachypnoea in COVID-19 and clinical deterioration.

The patient who clinically deteriorated in the experimental study presented had increases in their heart rate, respiratory rate and reported dyspnoea that were markedly higher than those observed in the patients who remained clinically stable or recovered. This provides an insight that changes in respiratory rate, heart rate and breathlessness on exercise may be as relevant to exertional desaturation in cardiopulmonary disease.

I have outlined the reasons that the acute setting favours a brief exertional test in the assessment of acute cardiopulmonary disease. However, the findings of the scoping review in chapter 2 demonstrates that the most used test in the acute setting is the 6-minute walk test, which would be challenging to deliver routinely in the average overcrowded NHS Emergency department, despite being widely validated in the outpatient setting. A feasibility study of the 3-minute walk test shows promise (65), and may produce the most appropriate compromise between a sufficiently short test, and one sufficient to elicit exertional desaturation. A sit to stand test, may be suitable for a small space and quick to deliver, however concerns about how challenging it is to complete for the average hospitalised patient warrants consideration (91), particularly in light of the feasibility conclusions regarding the less challenging 40 steps test.

In suspected COVID-19, only two structured exercise tests were identified as having been previously trialled within the acute setting. One of these is an unvalidated extremely short test; the 10 feet desaturation test. Like the 40 steps desaturation test, it appears to have been created specifically for the COVID-19 setting. Such emergency measures may have been necessary in the early pandemic, and a risk-averse approach by using a brief test of exertion (to avoid risk of collapse from more challenging tests) could be deemed sensible. However, there are concerning consequences of the incorporation of unvalidated tests in national guidance, such as the case with the 40 steps desaturation test. The widespread adaptation of the test in the early pandemic response has potentially led to an assumption amongst clinicians that is it a valid way of identifying low-risk COVID-19 patients suitable for discharge. This is reflected in my current clinical practice where I continue to encounter colleagues using the test as a pre-discharge tool. This is potentially unsafe, and the importance of not overlooking other factors requires urgent highlighting. Furthermore, the absence of significant desaturation in the small number of COVID-19 patient included in the experimental study presented in this thesis, suggests that a very short test such as the 40 steps test may not sufficiently challenging to elicit exertional desaturation.

In summary, this work has established a lack of consensus about the most appropriate exercise test for use in the clinical setting, with many unanswered and unexplored avenues. Evidence of an association between exertional desaturation and clinical deterioration in acute cardiopulmonary disease including COVID-19 has been suggested, with 2-4% desaturation potentially indicative of a need for further investigation or observation. However, the evidence provided in chapter 3 is insufficient to recommend the 40 steps desaturation test for use as part of the discharge process for COVID-19, with lack of desaturation on the test not proven sufficiently to aid or ensure a safe discharge. Whilst the 40 steps test can be broadly concluded as safe to deliver, it's feasibility may be limited to young, mobile patients who are not considered to be frail. As one of the least challenging exertional tests in clinical use, this has wider implications on feasibility of other more strenuous exercise tests in the acute setting.

Due to the low number of COVID-19 patients recruited and only one participant within the study sample clinically deteriorating larger studies in COVID-19 patients are required to validate the use of the 40 steps desaturation test with these early findings indicating a lack of relevance between oxygen saturation change and clinical outcome., I relevance of changes in other physiological parameters merits greater consideration. Other exercise tests may also require further exploration, with the challenge remaining of balancing rapid assessment with accurate disease progression prediction. Alternative solutions such as using longer term monitoring, with the potential to use at-home monitoring, such as with home pulse oximeters currently being explored in the context of COVID-19 to detect silent hypoxia (107). While this work is conducted, clinicians should interpret the outcome of the 40 steps test with caution, and its result should not be relied upon, in isolation, to indicate a safe discharge.

5. Appendices

Appendix A - Protocol for scoping review into the use of exercise tests for exertional desaturation in the acute setting, and outcomes for safer discharge

Author: **Rhys, G.H.**

Background

Dyspnoea and breathlessness make up one of the most prevalent symptoms reported in patients presenting to emergency and ambulance services. The assessment of any patient presenting with acute breathlessness routinely includes measurement of oximetry. Oxygen saturations is one of the parameters that make up the Early Warning Score (EWS), a tool instrumental in identifying the physiological deterioration that frequently precedes clinical deterioration in patients. In clinical practice the measurement of oximetry can prompt early initiation of oxygen as well as indicate underlying lung disease, whether acute or chronic.

Silent hypoxaemia and COVID-19

Since the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) emerged in late 2019, scientists and clinicians globally have sought to describe the clinical characteristics of its causative disease, COVID-19. One surprising and potentially alarming phenomenon observed in some COVID-19 patients is “silent hypoxaemia”; patients with severely low oxygen levels, who do not exhibit corresponding features of respiratory distress. Having lower oxygen saturations, in the absence of a co-morbid chronic lung disease, could be an indicator of future clinical deterioration.

Understanding that patients at risk of deterioration from COVID-19 could exhibit hypoxaemia as an early indicator of respiratory failure, has led to focus on oximetry in the assessment of COVID-19 patients.

Exertional Hypoxaemia

Tests of exertion in the assessment of suspected COVID-19 patients aims to detect exertional hypoxaemia. There is increasing interest in whether exertional hypoxaemia is an indicator of future deterioration in lung function, need for hospitalisation and mortality.

There are a wide range of potential exercise tests in use to assess exertional hypoxaemia. Most commonly, these are used in the outpatient setting and primary care in the management of chronic respiratory conditions. For example, in Chronic Obstructive Pulmonary Disease (COPD), the presence of exertional hypoxaemia has been linked to more frequent exacerbations and hospitalisations and reduced mortality.

Less literature has focused on testing for exertional hypoxaemia in acute disease. However, one study of patients with HIV presenting with acute lung disease, found that those with pneumocystis pneumonia (PCP), exhibited exertional desaturation, whilst those with other acute lung disease did not. Clinical, radiological and pathophysiological similarities between COVID-19 and PCP have been noted, making the study of exertional desaturation in COVID-19 of great clinical interest.

In the acute setting a clinician may ask a patient to perform a non-standardised exercise test (e.g. walking the length of a ward) to determine whether exertional hypoxaemia is present, which may form part of their clinical decision to discharge. However, without a standardised test, the degree of desaturation which could be classed as acceptable cannot be ascertained.

In early 2020, NHS England recommended the 40 steps desaturation test in the assessment of the acutely breathless patient with suspected COVID-19. A drop in pulse oximetry reading of more than 3% following the test has been recommended as a decision tool to NHS trusts across England for prompting

further investigations as an inpatient. Whilst a 40-step test is brief, and potentially easy to conduct in a wide variety of settings, it has not been formally validated to our knowledge. Therefore, further assessment is indicated before it can be formally recommended to clinicians for widespread use.

1.4 Exercise testing in the acute setting

There is a wealth of available exercise tests with differing capabilities to assess lung function, exercise capacity, muscle strength, or frailty. Some require equipment or stairs, or else are time-consuming, therefore may be impractical in the acute setting. Others are not achievable by many patients due to poor mobility, or unsteady gait. In the era of the COVID-19 pandemic, patients may also need to be assessed virtually, therefore space in their own homes as well as access to a pulse oximeter may be required.

There is an urgent need to identify an appropriate rapid exercise test that can be used in the acute setting to assess exertional desaturation in the unwell patient. Furthermore, with the pressure that high numbers of COVID-19 cases presenting to hospital and primary care settings, it is essential that such a test adequately distinguishes patients most at risk of deterioration, who would most benefit from further investigation and hospitalisation. Additionally, it is desirable that patients who do not exhibit exertional desaturation during the test are safe to recover from their illness at home, which could ease pressures on hospital capacity at a time of high demand.

Objectives

We aim to conduct a scoping review aim to describe the existing use of exercise testing in the contexts of suspected Covid-19. It also aims to identify the utility of standardised exercise tests in the acute setting, and whether there is evidence of these being applied to promote safe discharge from hospital or identify patients at increased risk of clinical deterioration, particularly those assessing lung function. The review of the literature will be used to form recommendations of appropriate exercise tests for the acute setting, and to propose future research for suitable exercise tests that could be used to identify exertion-induced hypoxaemia in the context of COVID-19, and or other causes of acute breathlessness.

1.6 Review Question

The review aims to identify where exercise tests have previously been used in the clinical as a discharge decision aid, or way of escalating more rapid definitive diagnosis and management.

The review questions for the purpose of this study include:

- Which exercise tests have already been used in the context of COVID-19?
- Which existing exercise tests have been used as part of patient assessment in the acute setting to promote safe discharge?
- Which exercise tests have been shown to effectively demonstrate exertional desaturation?
- Which exercise tests are safe and appropriate to use in the acute setting?
- Does existing evidence support the use of an exercise test be used to promote safe discharge, or reduce length of stay, rate of readmissions, or mortality in the acute setting?

Methods

2.1 Scoping Review format

A scoping review will be used to gain insights into the relevant existing research in this area and identify key areas where further study is most needed in the context of the COVID-19 pandemic. Arksey and O'Malley's framework (51) will be applied to undertake the review, to broadly include the following five steps:

1. Defining the research question(s)
2. Searching the literature for relevant studies
3. Selecting studies meeting the pre-defined research question
4. Presenting the data
5. Collating the findings and summarising the results

The protocol for the scoping review has been designed with reference to the Preferred Reporting Items for Systematic Reviews and Meta-analysis extension for Scoping Reviews (PRISMA-ScR) (52) guidelines. A protocol for the scoping review outlining the eligibility criteria was written prior to undertaking the review, and although it was not formally registered, its contents is replicated in the method section below.

2.2 Eligibility Criteria

The selection of eligible studies for inclusion in the review will use PICO (Population, Intervention, Comparator and Outcome) criteria.

2.2.1 Clinical Domain

Exercise testing in the acute setting to inform safe discharge or safe ongoing care, particular focus on tests that assess exertional desaturation.

2.2.2 PICO Question

The PICO question for this review is as follows: "Which exercise tests (I) can be used in the assessment of adults in acute setting (P), in addition to usual caI(C), to promote safe discharge from hospital (O)?"

2.3 Inclusion Criteria

2.3.1 Population

The review will include adults aged 18 years or older.

We will conduct searches specifically in suspected and confirmed COVID-19 as well as other lung diseases and other medical conditions that may present with **acute** dyspnoea or exertional desaturation.

We will include studies of patient's assessed in any of the following acute care settings:

- Emergency Department
- Acute Medical Unit
- Inpatient wards
- Intensive Care Unit
- Ambulance Service

- Primary Care

We will also report descriptively on other exercise tests that have been used outside of the acute setting if the test assesses exertional desaturation. This will be used to inform recommendations on exercise tests with suitable clinical properties to detect exertional desaturation, for potential use in the in the acute setting. However, these papers will not be included in the evaluation.

2.3.2 Intervention

Any exercise used in the assessment of patients as part of the admission or discharge decision making process.

"Exercise test" will include the following:

- Walking test of any distance or duration.
- Step test involving stair climbing, step or on the spot stepping for any duration.
- Sit to Stand test of any duration or repetition.
- Exercise involving equipment e.g. treadmill or bicycle ergometer.
- A combination of the above e.g. Get up and go test.

2.2.3 Comparator

Comparison to usual care whether this includes no exercise intervention or comparison to a different type of exercise test.

2.2.4 Outcomes

Primary Outcome:

Safety of discharge from the use of the test defined by the following:

- Readmission to hospital rate
- Mortality rate
- Length of stay in hospital for the primary admission
- Results of further investigations and/or interventions, prompted by an abnormal result during the exercise test.

Secondary outcomes:

- Feasibility of the exercise test in an acute or resource/space limited setting
- Safety of the exercise test in an acute or resource/space limited setting i.e. rate of complications, and false negative assessments
- Reliability, and validity of the test to detect exertional desaturation

2.3 Exclusion Criteria

2.3.1 Population

Specific exclusions include the following populations:

- Preoperative and postoperative patients
- Acute coronary syndrome
- Non-healthcare settings e.g. armed forces, athletes

2.3.2 Intervention

Exercise not meeting our criteria for “exercise test” include:

- Cardiopulmonary resuscitation
- Level of physical activity (e.g. number of steps walked per day) or general mobility
- Exercise testing as part of measuring efficacy of a rehabilitation programme rather than an assessment in an acute care setting
- Exercise testing combined the use of specialised equipment, not usable by a clinician without specialised expertise (e.g. echocardiography, CT imaging modalities)

Exercise testing performed following patient discharge will also be excluded.

2.3.3 Comparison

Where the exercise testing is used to compare response to different environmental conditions e.g. altitude, this will be excluded

2.3.4 Outcomes

Outcomes that will be excluded include cost effectiveness of a exercise test as part of specific clinical pathway, and rehabilitation outcomes such as gait speed and balance.

2.4 Study Types

We will include Randomised control trials, cohort studies, case-control studies and observational studies (prospective and retrospective).

Descriptive papers, case series and case reports will be excluded. Response letter, guidelines and position statements will also be excluded. Systematic Reviews or other literature reviews will be screened for references of any relevant studies that meet the inclusion criteria outlined. References of identified papers will be screened for further studies (snowballing).

We will not limit the search criteria based on study publication date, language or location.

2.5 Search Strategy

We will search the databases Medline, PubMed, AMED Embase, CINAHL and LitCovid for studies meeting the inclusion and exclusion criteria. In addition, we will search databases for ongoing clinical trials at ClinicalTrials.gov and Clinical Trials registry (EU). The search terms used can be seen in Supplement 2.

2.6 Study Selection

The titles and abstracts of the studies identified using the search parameters will be screened independently by two review authors using the eligibility criteria outlined. The Rayyan platform will be used to screen abstracts, detect and remove duplicates. Once all abstracts have been screened, blinding will be removed to see papers included and excluded by both authors. Any discrepancy between author decision will be discussed between the two reviewer and, where necessary, a third independent reviewer will be used to decide on its inclusion. A full text review of all included paper will be done to confirm eligibility.

The study selection will be reported using standards outlined in the PRISMA-ScR (52).

2.7 Data Extraction

From the selected studies, the following data will be extracted by a single author.

- Study methods (Title, Date of study, study design)

- Setting (Country, location of recruitment i.e. Emergency Department, primary care etc, person undertaking the testing, resource utilisation)
- Participants (age, diagnosis, COVID-status, sex, ethnicity, inclusion, and exclusion criteria)
- Intervention (Type of exercise test, location and physiological monitoring recorded (oxygen saturations etc)
- Comparator (if used)
- Outcomes including rehospitalisation, length of stay and mortality
- Conclusions including safety and feasibility of the test in the acute setting

2.8 Critical Appraisal

Assessment of the quality of research including risk of bias will not be assessed formally within the scope of this review.

2.9 Data Reporting and Analysis

A summary of the number of abstracts screened for eligibility, and those included including reasons for exclusion at each stage will be reported by means of a pre-designed schematic flow diagram.

We will first comment on the scope of exercise tests identified within the literature during the screening process, including those performed in an outpatient setting.

The data for the included evidence will then be presented in relation to the review questions and objectives of the scoping review. We will address the review questions including whether the exercise tests used are sufficiently in the validated for use in the discharge decision making process. We will additionally assess feasibility, and safety of the tests described within the evidence collated.

From the literature collated an analysis of the existing use of exercise tests in acute settings will be completed. Their appropriateness for use in the assessment of COVID-19 will be discussed, as well as their broader applicability and suitability for the acute setting.

A discussion on the limitations of our review will also be outlined.

Our conclusions will be used to propose relevant research avenues on the use of exercise testing in the acute or resource-limited setting, to inform safe patient discharge, and may guide ongoing clinical guidance in assessment of COVID-19.

Appendix B – Scoping review searches

PubMed searches (16/02/2021):

- (exercise test[MeSH Terms]) AND (covid-19[MeSH Terms])
- ((exercise test[MeSH Terms]) AND (oxygen saturation[MeSH Terms]) AND (respiratory disease[MeSH Terms])) limit to Adults 19+
- ((exercise test[MeSH Terms]) AND (oxygen saturation[MeSH Terms])) AND (hospitalisation[MeSH Terms])
- ((exercise test[MeSH Terms]) AND (emergency care[MeSH Terms], limit to Adult 19+
- ((exercise test[MeSH Terms]) AND (emergency care, prehospital[MeSH Terms]), limit to Adult 19+
- (exercise test[MeSH Terms]) AND (discharge, patient[MeSH Terms]) limit to Adult 19+
- ((desaturation) OR (saturation)) AND (exercise test[MeSH Terms]) AND (emergency care[MeSH Terms])) limit to Adult 19+
- (exertional desaturation)

Medline searches (16/02/2021):

Search 1:

- 1 exp Exercise Test/ (42539)
- 2 exp Walk Test/ (1571)
- 3 step test.mp. (1059)
- 4 sit to stand.mp. (2191)
- 5 sit to stand test.mp. (560)
- 6 1 or 2 or 3 or 4 or 5 (45096)
- 7 exp Hypoxia/ (34238)
- 8 exp Oximetry/ (9780)
- 9 oxygen saturation.mp. (18231)
- 10 oxygen desaturation.mp. (2695)
- 11 desaturation.mp. (7284)
- 12 exertional hypoxaemia.mp. (4)
- 13 exertional hypoxia.mp. (4)
- 14 exertional desaturation.mp. (26)
- 15 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (61467)
- 16 6 and 15 (1288)
- 17 exp Respiratory Tract Diseases/ (794867)
- 18 exp Pulmonary Disease, Chronic Obstructive/ (44044)
- 19 exp Lung Diseases, Interstitial/ (28658)
- 20 exp Pneumonia/ (75702)
- 21 pneumonitis.mp. (7883)
- 22 exp Pulmonary Embolism/ (22345)
- 23 exp Respiratory Insufficiency/ (33709)
- 24 exp Acute Lung Injury/ (6083)

- 25 (covid 19 or covid-19).mp. (41761)
- 26 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 (812175)
- 27 16 and 26 (635)
- 28 limit “7 to "all adult (19 plus ”ears)" (540)

Search 2:

- exp Exercise Test/ (42539)
- exp Walk Test/ (1571)
- step test.mp. (1059)
- sit to stand.mp. (2191)
- sit to stand test.mp. (560)
- 1 or 2 or 3 or 4 or 5 (45096)
- exp Hypoxia/ (34238)
- exp Oximetry/ (9780)
- oxygen saturation.mp. (18231)
- oxygen desaturation.mp. (2695)
- desaturation.mp. (7284)
- exertional hypoxaemia.mp. (4)
- exertional hypoxia.mp. (4)
- exertional desaturation.mp. (26)
- 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (61467)
- 6 and 15 (1288)
- exp Emergency Medical Services/ (111944)
- exp Emergency Service, Hospital/ (66446)
- acute care.mp. (16813)
- prehospital.mp. (9272)
- exp Hospitalization/ (190489)
- hospitalisation.mp. (12099)
- hospital discharge.mp. (21417)
- exp Patient Discharge/ (24105)
- 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (315024)
- 16 and 25 (32)

LitCovid (12/02/2021):

- Exercise AND Test

Embase (19/02/2021):

- (exertional desaturation) AND (emergency care)
- (exercise test) AND (emergency care) AND (discharge)

CINAHL (22/02/2021):

- exertional desaturation
- (exercise test) AND (discharge) Limit to all aduts, English language

AMED (16/02/2021):

- (exercise test) AND desaturation OR hypoxia
- (exercise test) AND coronavirus

Clinical Trials.gov (19/02/2021):

- Condition/Disease: Covid19
- Intervention: Exercise test
- Outcome: Discharge
- Age: Adult (18-64), Older Adult (65+)

EU Clinical trials registry (19/02/2021)

- Covid19 AND exercise test

Appendix C – Overview of exercise tests discussed within the thesis

Walk tests

The **6-minute walk test (6MWT)** is a walking test of 6-minutes duration along a 30-metre flat surface course. The patient should sit in a chair for at least 10 minutes before attempting the test. Measurement of pulse oximetry at baseline is optional, but if worn during the test should be lightweight, and secured so as not to interfere with walking. The patient should stand and state their baseline dyspnoea using the Borg scale (103). The patient is then informed to walk back and forth between the length of the course for 6 minutes and turn briskly at the corners without stopping. The examiner doesn't routinely follow the patient so as not to influence their walking speed. The participant is told they can slow down, stop or rest as necessary. After 6-minutes the participant should be asked to stop walking; the distance walked (6-minute walk test) is recorded, as well as Borg score, fatigue level (and oxygen saturation if required) (50).

A **3-minute walk test (3MWT)** is a shorter variation of the 6-minute walk test. Both Amin *et al.* and Pan *et al.* used a flat corridor and asked patients to walk continuously for 3-minutes (60,65). Both allowed walking aids is used at baseline, and Pan *et al.* allowed supplemental oxygen at the patient's baseline settings if the patient was on long term oxygen. Pan *et al.* recorded heart rate, oxygen saturation, respiratory rate and dyspnoea at baseline, 1,2 and 3 minutes during the test and 1-minute after the test (65). Amin *et al.* recorded heart rate, oxygen saturation, were recorded at baseline, monitored continuously for the peak as well as at 1-minute. Respiratory rate was recoded at baseline and 1-minute after the test (60).

The **10 metre walk test (10MeWT)** involves asking the participant to walk 10 metres at a self-paced walking speed. The time to complete the distance is measured. This is completed twice, and a third fast walking speed also recorded. Walking assistance can be offered but should be documented with the test. The examiner walks behind the patient so as not to influence their speed (108).

A **10 feet desaturation** test is described by Kamran *et al*. (55), which involves walking a distance of 10 feet on a flat surface, although the protocol for the test is not elaborated upon within the paper. A 3% desaturation was considered significant in this case and the test was carried out under supervised care.

The **40 steps desaturation test** was recommended by NHS England in the early COVID-19 pandemic. The test was recommended in patients with COVID-19 with normal oxygen saturation and who were being considered for discharge (37,38). Updates to the initial guidance now proposes the test in mild-moderate COVID-19 with SpO_2 ≥93% or <3-4% less than their baseline, RR <24 and HR <130 being considered for discharge (39,103).

The initial guidance used in NHS hospitals did not specify a protocol for the test with on the spot and around the room variations of completing 40 steps performed. However, in the experimental chapter of this thesis (chapter 2) an on-the-spot variation of the test is used as outlined in the methods section of the paper and study protocol (Appendix H).

Step tests

The **Chester step test (CST)** is a submaximal test of aerobic capacity, involving stepping onto a step 10-30cm in height, depending on the persons height, to the timing of a recorded beat. The stepping speed is increased at 2-minute intervals until the subject reaches 80% of their maximal heart rate or reports moderate to vigorous levels of perceived exertion (72).

The **modified incremental step test (MIST)** is modelled on the CST and adapted for use in COPD, and similarly involves a paced stepping test, with increasing increments. Number of steps completed during the test is recorded (73).

Sit-to-stand test

The Sit-to-stand test involves using a chair without armrests, with a patient sat upright on the chair with legs fexed to 90 degrees, and arms on their hips or folded across the chest. A patient is then asked to stand upright from sitting, then sit down again.

The **30-second sit to stand test (30s-STS)** involves repeating the sit to stand motion for a period of 30 seconds (64,75). The **one-minute sit to stand test (1MSTS)** similarly involves repeating the sit to stand motion but for a period of one-minute. In both cases number of repetitions is recorded (109).

The **5 repetitions sit to stand test (5-STS)** involves 5 cycles of sitting to standing and a retutn to sitting, with the time taken to complete the task recorded (74).

Bicycle tests

Bicycle Ergometry refers to a form of stationary exercise testing using any exercise bicycle equipment installed with an ergometer to measure the work achieved by the test participant. Within this paper 2-minute and 3-minute variations of a stationary cycling tests were used using fixed speeds, in the former 2-minute test a rate of 40 cycles/min was used (59). In the latter 3-minute test the speed of cycling was not pre-determined, and distance cycled within the 3-minute period were recorded and evaluated (66).

Treadmill tests

Treadmill exercise testing can refer to a range of submaximal exercise test involving walking or running on a treadmill exercise equipment. A common clinical use of a treadmill test is an exercise stress test in cardiology. In the only study that used a treadmill exercise test a constant speed was used for 2-minute intervals starting at 2km/h, and increasing to 4km/h, 6km/h and finally 8km/h (58).

Timed up and go test

The **timed up and go** (TUG) test is a simple test to measure functional mobility, sometimes used to measure the effectiveness of an intervention. It involves asking a patient to stand from a sitting position on a chair, without using the arms, and walking a distance of 5 metres before sitting down on a chair (110). The time to complete this task is recorded, with an average time to complete of 15 seconds.

Physical function outcome measure

The **physical function outcome measure (PFIT)** test was designed for use in critically ill patients who are unable to perform the six-minute walk test or equivalent submaximal exercise test. It comprised five items: the assistance required to transfer from sitting to standing, the strength of shoulder flexion and knee extension, marching in place (on the spot walk test) and arm elevation to 90 degrees of shoulder flexion (111,112). In the study discussed in chapter 2, the shoulder flexion component of the test was removed (70).

Appendix D - Ongoing studies of exercise in the acute setting

Reference	Study type and setting	Prospective sample	Intervention	Outcome
Subbe, C. 2020. (71)	Prospective observational cohort study Hospital, Wales	Status: Recruiting Estimated Sample: 1000 Diagnosis: acutely ill patients with mild symptoms including COVID-19 Age: 18+ years	The 40 steps test, 40 steps performed on the spot at discharge	Change in decision to discharge (within 24 hours) Rehospitalisation (30-day) Mortality (30-day)
Artaud-Macari, E. 2020. (77)	Randomised Clinical Trial Hospital, France	Status: Recruiting Estimated Sample: 146 Diagnosis: COVID-19 Age: 18+ years	1 minute Sit-to Stand test Discharge SpO2 ≥90% and no decrease in SpO2 ≥ 4% during the test or for 3 mins after	Late hospitalisations, within 48 hours of first discharge Immediate hospitalisation after the first admission Adverse events related to SARS-Cov2 infection (within 7 days) Correlation between adverse events and number STS chair rise, SpO_2, HR and dyspnoea. (within 7 days)

Appendix D - Ongoing studies of exercise testing in the acute setting
Abbreviations: COVID-19; Coronavirus disease, HR; Heart rate, SARS-CoV2; Severe acute respiratory syndrome coronavirus 2, SpO_2; peripheral saturation of oxygen, STS; Sit to stand

Appendix E – 40 steps study Patient informed consent leaflet

Authors: **Rhys G.H**, Wakeling T and Subbe C.P.

40 steps to safety – consent form

Exertional desaturation as a marker of risk – Validation study for the 40 steps test

ID: _____

	Please initial
I have read and understood the information sheet **40-steps Participant Information Leaflet V 1.5.** I have had the opportunity to ask questions and have had these answered satisfactorily.	
I understand that my participation is voluntary, and that I am free to withdraw my consent at any stage without giving any reason, or having my legal rights affected.	
I understand that relevant sections of my medical notes and the data collected during the study may be looked at by individuals from Betsi Cadwaladr University Health Board or by regulatory authorities, or by the NHS Trust or by students from Bangor University where relevant to my participation in the project. I give permission for these individuals to have access to my records.	
I agree that my anonymised data for the purpose of this study, and for my anonymised data to be shared with collaborating centres for the purpose of data analysis.	
I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers.	
I give my permission for my GP to be informed that I have taken part in this study.	
I agree to take part in the above project.	

Signed (Participant) _____

Print name _____ Date: _____

Signed (Name of person taking consent) _____

Print name _____ Date: _____

When completed : 1 for participant; 1 for researcher site file; 1 to be kept in medical notes

Appendix F – 40 steps study Participant information leaflet

Authors: **Rhys G.H**, Wakeling T and Subbe C.P.

40 steps 2 safety – participant information leaflet

Exertional desaturation as a marker of risk – Validation study for the 40 steps test

Many thanks for your interest in this research project, investigating the effect of a simple exercise test on blood oxygen levels.

Since the start of the COVID-19 pandemic we are considering this condition in any patient presenting to hospital. Some COVID-19 patients may have “silent hypoxia” which means that their blood oxygen concentration is low, despite feeling well. Your oxygen level is currently normal, but we would like to know if this changes following a short period of exercise.

Why am I being asked to take part?

We are interested in investigating the ability of a simple exercise test to detect low blood oxygen levels in patients who appear well. We want to know whether developing low oxygen levels with exercise can be used to identify patients who are at higher risk of becoming unwell in the future.

We are asking individuals who are being considered to go home on the day of the study to take part.

What does the study involve?

You will be asked to perform a simple walking test. This will involve taking 40 steps on the spot at your normal walking speed. Your heart rate and oxygen saturation (level of oxygen in the blood) will be measured using a pulse oximeter that clips onto the end of your finger. You will also be asked to rate your level of breathlessness before and after the test on a scale of 0 to 10.

This information will help us decide whether we recommend you stay in hospital for further assessment or are discharged home.

What are the benefits to taking part?

You will be contributing to important research which could help develop a better way to identify patients who can be safely discharged from hospital. You will also be helping us to better understand the normal response to exercise, and how this is different in a range of medical conditions, including in COVID-19.

What are the risks of taking part?

We anticipate that taking part in this study is generally very safe. However, there is a small possibility of a fall, which could result in injury to yourself, whilst doing the 40-step test.

Some participants may experience symptoms such as breathlessness, light-headedness, or chest pain whilst taking part in the study. If you start to feel unwell during the test, please tell one of the researchers immediately who will stop the test. If any concerns arise during the test about your ability to complete the exercise task safely, we may also end the study early.

What happens after I take part?

We will not need to contact you following your involvement in this study.

The research team will need to access your hospital record to document whether you stayed in hospital, were readmitted, or remained at home in the 30 days after the study.

All patient data used will be anonymised, and we will not access your medical record for reasons other than those outlined.

If my oxygen levels drop during the study – what does this mean?

One purpose of this study is to identify what happens to oxygen levels during the 40-step test. Therefore, we do not currently know what how much oxygen changes during this test.

There are many reasons that your oxygen level could drop during the test – this could be different according to several factors including age, and underlying medical condition(s).

If you are concerned following your participation in the study, our researchers will be happy to discuss the test with you. In some cases, the result of the test could prompt your medical team to request further investigations, either as a hospital patient or as an outpatient.

Expenses and payments

There are no payments for taking part in this study.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers or the hospital concerns team who will do their best to answer your questions (Concerns office, telephone 01248-384 194).

In case of accidental disclosure of confidential details, you will be informed, and the disclosure will be reported in line with Standard Operating Procedures of BCUHB.

Will my taking part in the study be kept confidential?

For the study we will ask you a few questions. One copy of the answers to those questions will be added to your hospital notes and might help your doctors and nurses to look after you. All information which is collected about you during the research will be kept strictly confidential. Any quotes from you will be anonymized.

Any information about you that is not in the hospital notes will have your name, address and any other personal details removed so that you cannot be recognized. Your confidentiality will be safeguarded during and after the study by the Caldicott principles and/or Data Protection Act 1998. All identifiable information will be deleted 3 months after the completion of the study.

How will my information be used as part of the study?

We are guided by the principles set out in the General Data Protection Regulation (GDPR) 2016.

We will need to use the information from you, and from your medical records for this research project.

- Name
- Age
- Ethnicity
- Whether you have a diagnosis of a heart or lung conditions
- Oxygen saturations, heart rate and level of breathlessness before and after the 40 steps test
- Whether the decision to discharge you from hospital changes following the test
- Whether you are readmitted to hospital in the 30 days after the test
- Whether any COVID-19 test(s) you have already returned a positive result

People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Some of your anonymous information will be shared with other NHS trusts in the UK They must follow our rules about keeping your information safe.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study

What will happen if I don't carry on with the study?

You can stop being part of the study at any time, without giving a reason, and can request that all the information and data collected from you, to date, be destroyed and your name removed from all the study files.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

If you agree to take part in this study, you will have the option to take part in future research using your anonymised data saved from this study. For more information about how your information will be used as part of this study you can contact our Data Protection Officer at **<insert email>**, contact our Information Governance Department on **<telephone number>**, or speak to one of the research team.

Further information can also be found at: **<website links**>

What will happen to the results of the research study?

The results of the study will be published in medical journals. The research will also form part of an educational qualification for students at Bangor University. You will not be identified in any report/publication.

Who is organizing or sponsoring the research?

The study is organized by a European group of specialists in Acute Care. The researchers have not received extra funding for undertaking the study.

Further information and contact details:

We hope that you are interested in working with us on this important project.

For more information please don't hesitate to e-mail us on **<insert email>**

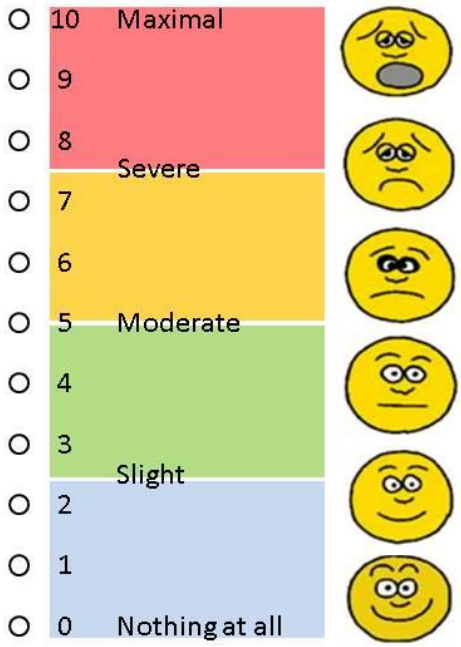
Consent

We ask you for your permission to participate in test and the review of your medical information.

You are free to stop participating at any time and without giving any reason to withdraw your permission. This has no negative consequences for your treatment.

If, after reading these notes questions remain unanswered, please send them directly to **<insert email>**

Appendix G – 40 steps study Numerical dyspnoea scale



Appendix H – 40 steps study Case report form

Authors: Subbe C.P, **Rhys G.H**, Wakeling T, Longshaw L.

Case Report Form V1.5 12 November 2020

Study Title: Physical Activity as a Vital Sign IRAS 283998

Protocol V1.0 24 September 2020

Site ID:			
Participant ID:			

1. Eligibility

1.1 Inclusion /Exclusion Criteria

INCLUSION	**YES**	**NO**
Adults patients (aged 18 years or above)		
Patients are being considered for discharge to independent care		
Participant is willing and able to give informed consent for participation in the study.		
Patient with independent, stable, gait		
Patient is alert, attentive, coherent, and calm		
EXCLUSION	**YES**	**NO**
Minor injuries		
Elective surgery patients		
Post-operative patients at discharge		
Requires supplemental oxygen		
Shortness of breath at rest (i.e. Borg or Numerical Rating Scale >=2)		
Unstable angina		
Patients on long-term-oxygen therapy		
Pregnancy as stated by patient		
Oxygen saturations < 95% on room air (or <92% for COPD)		
Resting heart rate > 100 bpm		
Resting respiratory rate > 25 bpm		
ECG with signs of acute ischemia in patients where an ECG has been requested by the treating clinician		
National Early Warning Score of 5 or more		
Nursing home residents, or those being transferred to a nursing home or similar care facility		

Inclusion/Exclusion assessed by:

PRINT Name:.....

Signature.....

Designation.....

Date.....

2. DAY 1 VISIT / BASELINE

2.1 Date of Informed Consent

D	D	/	M	M	/	Y	Y	Y	Y

2.2 Gender (Tick as appropriate)

Male	
Female	
Non-binary	
Unknown	

2.3 Ethnicity (Tick as appropriate)

White	
Mixed/Multiple ethnic groups	
Asian/Asian British	
Black/African/Caribbean/Black British	
Other ethnic group	

2.4 Date of Birth

D	D	/	M	M	/	Y	Y	Y	Y

2.5 Location (Tick as appropriate)

Emergency Department	
Medical admissions unit	
Inpatient ward	
Ambulance service	
Primary care	
Other (please specify)	

BASELINE

2.5 Date of Baseline Assessment:

D	D	/	M	M	/	Y	Y	Y	Y

2.6 Diagnosis

Condition

4.6 Medical History (include presence of heart failure, COPD, diabetes, inflammatory bowel disease)

Past-medical history	**YES**	**NO**
COPD		
Asthma		
Pulmonary Fibrosis		
Heart Failure		
COVID-status	**YES**	**NO**
Suspected		
Confirmed Positive		
Confirmed Negative		

4.7 40-Steps test

Guidance for researcher

- **Make sure a clock or timer is available before starting.**
- **Wait at least 1 minute before recording saturations at the beginning of the test.**
- **Keep the oxygen saturation probe on the patient for the duration of the test.**
- **Consider counting 40 steps aloud to help the patient.**
- **Please wipe all equipment clean after use.**

Baseline	**Value**	**Unavailable**
Rating Scale for Dyspnoea		
Respiratory Rate		
Oxygen Saturations		
Heart rate		
Blood pressure		
Temperature		
End-of test		
Rating Scale for Dyspnoea		
Respiratory Rate		
Oxygen Saturations		
Heart rate		
2-minutes follow-up		
Rating Scale for Dyspnoea		
Respiratory Rate		
Oxygen Saturations		
Heart rate		

2.8 Documentation

☐ **Documentation of vital signs in clinical notes**

☐ **Adverse Event Assessment : See Protocol, Safety SOP and complete adverse events forms of required – see section xx of Investigator Site File**

CRF completed by (PI or Delegate)

Note: signing the CRF certifies accuracy, completeness and legibility of the data collected.

PRINT Name:.....

Signature.....

Designation.....

Date.....

3. 30-day follow-up

3.1 Date of visit:

D	D	/	M	M	/	Y	Y	Y	Y

3.2 Outcome

Event	Yes	No	Date of event if applicable
Admitted to hospital (date of first admission after discharge)			
Death			
COVID-diagnosis confirmed			
Lost-to follow-up			

4. Withdrawal

Date of Withdrawal

D	D	/	M	M	/	Y	Y	Y	Y

Reason (If provided)

CRF completed by (PI or Delegate)

Note: signing the CRF certifies accuracy, completeness and legibility of the data collected.

PRINT Name:.....
Signature.....
Designation.....
Date.....

Appendix I – 40 steps study protocol

Authors: Subbe C.P, Moosavi S.P, Dawes H, Kelley J, Wakeling T, **Rhys G.H**.

Exertional desaturation as a marker of risk – Validation study for the 40 steps test
A multi-centre prospective observational cohort study

Study Title: Exertional desaturation as a marker of risk – Validation study for the 40 steps test

Internal Reference Number / Short title: 40 Steps 2 Safety

Ethics Ref:

Date and Version No: V4 August 2020

Chief Investigator:	Dr.Christian Subbe
Investigators:	Tbc
Sponsor:	Tbc
Funder:	n.a.
Chief Investigator Signature:	Tbc

Please declare any/no potential conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

TABLE OF CONTENTS

1. SYNOPSIS

Study Title	Exertional desaturation as a marker of risk – Validation study for the 40 steps test	
Internal ref. no. / short title	40 Steps to Safety	
Study Design	Observational cohort study	
Study Participants	Patients presenting to hospital or other acute services	
Planned Sample Size	1000	
Planned Study Period	12 months	
	Objectives	**Outcome Measures**
Primary	To validate the 40 steps on the spot test as a marker for safe discharge from hospital	Change in decision to discharge a) further investigations b) hospital admission c) 30-day hospital admission d) 30-day mortality
Secondary	To establish normal values for the 40 steps test in a range of age groups	Changes precipitated by test in: Oxygen saturation Heart rate Breathlessness

2. ABBREVIATIONS

CI	Chief Investigator
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
NHS	National Health Service
NRES	National Research Ethics Service
OXTREC	Oxford Tropical Research Ethics Committee
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SOP	Standard Operating Procedure

3. BACKGROUND AND RATIONALE

As deaths from covid-19 rise, it has become clear that people with different ethnic backgrounds have different outcomes (113). Silent hypoxia has also been identified as a harbinger of deterioration in COVID-19 (8). Oxygen desaturation during exertion is a feature of early interstitial lung disease. During the 1-minute sit-to-stand test (in which the patient goes from sit to stand as many times as they can in one minute) interstitial lung disease patients drop their oxygen saturation from 97% SD 1% to 92.5% SD 5%. There were also changes in heart rate increasing from 81 SD 14 beats per minute to 112 SD 17 beats per minute, and the Borg Exertion Scale (104) increasing from 0.8 SD 1.2 to 4.9 SD 2.2. (108).

The 40-step test (in which the patient takes 40 steps on a flat surface) has also been used to test for exertional desaturation. As it is less demanding it has been assumed to be safer and is in widespread use. However, it has not been validated (36). Moreover, it cannot be performed in a confined space, such as a crowded emergency department or in a patient's home. Therefore, it is proposed to modify the test by making it 40 steps while standing on one spot.

Many alert and mobile acutely ill patients with mild symptoms and little or not vital sign derangement are considered for early discharge. However, many serious illnesses often appear trivial in their early stages. This is particularly true of COVID-19, and oxygen desaturation on exertion has been highlighted as a possible feature of impending severe infection (28). The 40-steps test has been suggested for risk stratification of patients presenting to hospital, primary care, or testing-centres (37,38): oxygen desaturation in a patient with suspected COVID-19, or indeed any condition, prompting re-consideration of the decision to discharge without further immediate investigations and/or monitoring.

At the time of writing, it is unclear if COVID-19 is an illness that will be completely eradicated by a successful vaccination campaign, or a new infection that will remain endemic in the population indefinitely. It is irresponsible for the medical profession not to prepare for the latter possibility by accepting that from now on any patient may be in the early stages of SARS-CoV 2 infection, and it must be established if oxygen desaturation on exertion is or is not an early sign.

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To validate 40 steps on the spot test as a marker for safe discharge from hospital	1. Change in decision to discharge a) No change b) Further investigations c) Hospital admission 2. Hospital admission within 30 days 3. Death within 30 days	On test completion Within 30 days
Secondary Objectives To establish normal values for the 40 steps on the spot test in a range of ages, ethnic groups and lung or cardiac conditions. To establish whether the test is well received and accepted by patients. To find out if the test is easily carried out in a medical setting and whether it can be used in the care pathway.	Changes precipitated by the test in: Oxygen saturation Heart rate Breathlessness Patient debrief survey in sample of participants Survey of participating investigators	On test completion At completion of data collection period

5. STUDY DESIGN

Prospective, observational, multi-centre cohort study in xx distinct cohorts of interest.

Patients to be enrolled:

All alert and mobile acutely ill patients with mild symptoms and little or no vital sign derangement being considered for discharge to independent care

Outcomes to be recorded and/or measured:

Oxygen saturation, oximeter heart rate and Breathlessness (using numerical dyspnoea scale) at rest, after 40 steps and two-minute post-test.

Delay in discharge

Immediate hospital admission

Hospital admission within 30 days

Mortality within 30 days

Outcome of any pending COVID-19 swab(s) from date of study

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

All alert and mobile acutely ill patients with mild symptoms and little or no vital sign derangement being considered for discharge to independent care

6.2. Inclusion Criteria

- Patients are being considered for discharge to independent care
- Participant is willing and able to give informed consent for participation in the study.
- Patient with independent, stable, gait
- Patient is alert, attentive, coherent, and calm
- Male or Female, aged 18 years or above.

6.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Minor injuries
- Elective surgery patients
- Post-operative patients at discharge
- Requires supplemental oxygen
- Shortness of breath at rest (i.e. Borg or Numerical Rating Scale >=2)
- Unstable angina

- Patients on long-term-oxygen therapy
- Pregnancy as stated by patient
- Oxygen saturations < 95% on room air
- Resting heart rate > 100 bpm
- Resting respiratory rate > 25 bpm
- ECG with signs of acute ischemia in patients where an ECG has been requested by the treating clinician
- National Early Warning Score of 5 or more
- Nursing home residents, or those being transferred to a nursing home or similar care facility

7. STUDY PROCEDURES

Patients will be recruited in participating centres

7.1. Recruitment

Patients will be identified in the participating services during the 12-months recruitment period by the clinical investigators.

7.2 Screening and Eligibility Assessment

Patients will be screened by either nursing or medical staff. Recruitment is for same-day testing. A standardised proforma with inclusion and exclusion criteria will be used.

7.3 Informed Consent

This study is proposing to improve safe practice. What is being proposed is recommended by NHS England and has been adopted by some hospitals in Wales as part of routine practice. , It is self-evident that it is unsafe for a patient not able to perform the test to be discharged without further investigation. The results of the 40-step test will be communicated to the clinical team caring for the patient, for their consideration of whether discharge is considered safe.

We will, obtain informed consent from participants prior to their involvement in the study. As the research will form a part of an educational qualification for students at Bangor University consent will also be obtained for these students to access medical records for the patient's outcome at 30 days.

The person who obtains the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant and another placed in the patient's medical notes. The original signed form will be retained at the study site. In view of the test being offered in addition to usual care in some sites, we will allow the participant up to one hour to consider the information in the patient information sheet, and the opportunity to question the investigator, GP, clinical team or other independent parties to decide whether they will participate.

7.4 Randomisation, blinding and codebreaking

Centres will be stratified for country and teaching hospital status. Code breaking is not planned during the limited study period.

7.5 Baseline Assessments

During the index visit the following assessments will be undertaken:

- Collection of demographics: age by year of birth, gender
- Working diagnosis and/or complaint
- Past medical history of heart and/or COPD or interstitial lung disease
- Is COVID-19 confirmed, suspected, or not suspected?
- Ethnicity

The patient will then be asked to perform 40 steps up and down on the spot. Baseline Oxygen saturations, heart rate and breathlessness using a numerical rating scale () will be recorded prior to the test, immediately after and TWO minutes after ending the test.

The result of the 40 steps test will be communicated to the medical team looking after the patient for interpretation, and ongoing management decision(s). It should be recorded immediately after the test if its result changed the decision to discharge by either A) prompting further investigations or B) admission to hospital. The research team cannot recommend criteria for prompting further investigation or continued hospitalisation as the 40 steps test has not been validated for this purpose. We hope that the research will help to clarify such criteria.

A patient debrief survey will be conducted in a sample of 50 participants at one of the investigating sites to assess patient perception of the test.

All patient data will be deidentified before analysis.

7.6 30-day follow-up

It should be recorded if each participant has died, been admitted to hospital, COVID 19 diagnosis confirmed or lost to follow-up within 30 days of completing the test.

7.7 Care pathway assessment

Feasibility of implementing the testing in the care pathway will be addressed with a non-structured debriefing interview with a sample of participating investigators.

An informal focus groups will be held online given the context of the pandemic.

7.8 Discontinuation/Withdrawal of Participants from Study

Each participant has the right to withdraw from the study at any time. Withdrawal from the study will result in exclusion of the data for that participant from analysis.

7.9 Definition of End of Study

The end of study will be the date of the last visit of the last participant.

8. SAFETY REPORTING

8.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence during or after the 40-steps test that:

- results in death

- is life-threatening
- results in persistent or significant disability/incapacity
- results in hospitalisation and/or prolongation of hospitalisation

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

8.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant will be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form.

9. STATISTICS AND ANALYSIS

9.1. Description of Statistical Methods and Analysis of Outcomes

Descriptive statistics will express normal ranges for different age groups and the proportion of the primary outcome (change in discharge decision and need for admission to hospital and/or death within 30 days from undertaking the test) depending on the outcome of the test (drop in saturations, heart rate, and Borg score as a continuous or binary variable).

9.2. The Number of Participants

As many participants as possible should be recruited.

10. DATA MANAGEMENT

10.1. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

10.2. Data Recording and Record Keeping

Data will be collected using an electronic CRF. Compliance with the Sponsor organisation's policy will be assured.

11. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, Good Clinical Practice, relevant regulations and standard operating procedures.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

12.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

12.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

12.4. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

12.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database, except the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

12.6. Expenses and Benefits

No additional expenses will be incurred by participants in this study.

12.7. Other Ethical Considerations

No vulnerable participants, or participants who are unable to consent for themselves will be included in the study.

13. FINANCE AND INSURANCE

13.1. Funding

Local funding arrangements apply. It is anticipated that students might be reimbursed for their contribution where appropriate and that clinical investigators will not receive reimbursements for their contribution.

13.2. Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If patients or employees are harmed whilst taking part in a clinical research study as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University Hospitals NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances.

In exceptional circumstances an ex-gratia payment may be offered.

14. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

Appendix J - Ethical approval confirmation letters

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

Ariennir gan Lywodraeth Cymru
Funded by Welsh Government

Please note:

This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites until you receive HRA/HCRW Approval

Wales Research Ethics Committee 5
Bangor

Mailing address:
Health and Care Research Wales
Castlebridge 4
15-19 Cowbridge Road East
Cardiff, CF11 9AB
telephone: 07970 422139
email: Wales.REC5@wales.nhs.uk
website: ww.hra.nhs.uk

16 October 2020

Dr Christian Subbe
Ysbyty Gwynedd
Penrhosgarnedd
Bangor
LL572PW

Dear Dr Subbe

Study title:	**Exertional desaturation as a marker of risk – Validation study for the 40 steps test: A multi-centre prospective observational cohort study**
REC reference:	**20/WA/0286**
Protocol number:	**1.0**
IRAS project ID:	**283998**

The Research Ethics Committee reviewed the above application at the meeting held on 15 October 2020.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

This is a recommendation only and is not a condition of the ethical opinion.

Number	Recommendation
1	The Committee recommended that the Participant Information Sheet is tailored for use at research sites where the 40 steps procedures is part of routine care, to ensure that participants understand that they are given the test and participant in the study would solely involve their data being collected.

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

It is a condition of the REC favourable opinion that **all clinical trials are registered** on a publicly accessible database. For this purpose, 'clinical trials' are defined as the first four project categories in IRAS project filter question 2. Registration is a legal requirement for clinical trials of investigational medicinal products (CTIMPs), except for phase I trials in healthy volunteers (these must still register as a condition of the REC favourable opinion).

Registration should take place as early as possible and within six weeks of recruiting the first research participant at the latest. Failure to register is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/

As set out in the UK Policy Framework, research sponsors are responsible for making information about research publicly available before it starts e.g. by registering the research project on a publicly accessible register. Further guidance on registration is available at: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/transparency-responsibilities/

You should notify the REC of the registration details. We routinely audit applications for compliance with these conditions.

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter.

Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit: https://www.hra.nhs.uk/planning-and-improving-research/application-

summaries/research-summaries/

N.B. If your study is related to COVID-19 we will aim to publish your research summary within 3 days rather than three months.

During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you haven't already done so, please register your study on a public registry as soon as possible and provide the HRA with the registration detail, which will be posted alongside other information relating to your project. We are also asking sponsors not to request deferral of publication of research summary for any projects relating to COVID-19. In addition, to facilitate finding and extracting studies related to COVID-19 from public databases, please enter the WHO official acronym for the coronavirus disease (COVID-19) in the full title of your study. Approved COVID-19 studies can be found at: https://www.hra.nhs.uk/covid-19-research/approved-covid-19-research/

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

After ethical review: Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical review of research sites

NHS/HSC Sites

The favourable opinion applies to all NHS/HSC sites taking part in the study taking part in the study, subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland)being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS/HSC sites

I am pleased to confirm that the favourable opinion applies to any non NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Contract/Study Agreement template [mNCA_Version_2.1_Jul18_FINAL BCUHB]	1	07 October 2020
Contract/Study Agreement template [Tracked version of BCUHB model agreement]	1	07 October 2020
Copies of advertisement materials for research participants [40 Steps to Safety Flyer - local version v1.0 24Sept20]	1	24 September 2020
Covering letter on headed paper [Covering Letter]	1	24 September 2020
IRAS Application Form [IRAS_Form_29092020]		29 September 2020
Non-validated questionnaire [40 Steps to Safety Patient feedback survey V1.0 24Sept20]	1	24 September 2020
Non-validated questionnaire [40 Steps to Safety Patint feedback survey welsh versionV1.0 24Sept20]	1	24 September 2020
Other [NHS England Protocol for Usage of 40-Steps test]	1	27 September 2020
Other [Review Exercise Tests for Desaturations]	1	27 September 2020
Other [Email confirming no external funding]	-	07 October 2020
Participant consent form [40 Steps to Safety Consent Form v1.0 24Sept20]	1	24 September 2020
Participant consent form [40 Steps to Safety Consent Form Welsh version v1.0 24Sept20]	1	24 September 2020
Participant information sheet (PIS) [40 Steps to Safety Participant Information Leaflet V1.0 24Sept20]	V1	24 September 2020
Participant information sheet (PIS) [40 Steps to Safety Participant Information Leaflet welsh version V1.0 24Sept20]	1	24 September 2020
Research protocol or project proposal [40 Steps to Safety Protocol Version 1.0 24Sept20]	V1	24 September 2020
Summary CV for Chief Investigator (CI) [CV CP Subbe]	V1	16 March 2020
Summary CV for student [MRes Student CV - Gwenllian Rhys]	V1	24 September 2020
Summary CV for student [Tara Wakeling CV]	V1	24 September 2020
Summary CV for supervisor (student research) [CV Jonathan Moore]	V1	24 September 2020
Validated questionnaire [Numerical Rating Scale]	V1	24 September 2020

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

No declarations of interest have been made in relation to this application

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

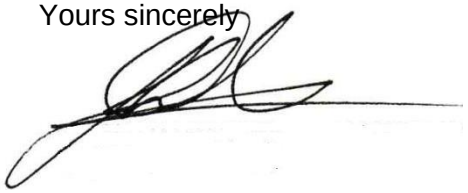
1. HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS project ID: 283998	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely



2. Dr Jason Donal Walker, MB BCh BAO, FRCA
Consultant Anaesthetist
Chairman Wales REC 5

E-mail: WalesREC5@wales.nhs.uk

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

3. Wales Research Ethics Committee 5

Attendance at Committee meeting on 15 October 2020

Committee Members

Name	*Profession*	*Capacity*	*Present*
Dr Swapna Alexander	Consultant Physician	Expert	Yes
Mr David Rhys Jones	Retired Teacher	Lay +	Yes
Mr Eliezer Lichtenstein	Manual Therapist	Lay +	No
Dr Pamela A Martin-Forbes	Clinical Studies Officer	Expert	Yes
Dr Paul G Mullins	Reader, Senior MRI Physicist (Vice-Chair)	Lay +	Yes
Mr Vishwanath Puranik	Consultant ENT Surgeon	Expert	Yes
Dr Judith L Roberts	Lecturer, Clinical Psychologist	Expert	Yes
Dr Giovanni d'Avossa	Consultant Neurologist	Expert	Yes
Dr Jason D Walker	Consultant Anaesthetist (Chairman)	Expert	Yes
Dr Sumayya Mushtaq	Clinical Pharmacist	Expert	No
Mrs Carolin Williams	Doctoral Candidate	Lay	Yes
Ms Rosie Spears	Senior Appraisal Scientist	Lay	Yes
Dr Rebecca Wallace	Research Lead for Radiology	Expert	Yes
Dr Gabriella Rossetti	Post-Doctoral Research Officer	Expert	Yes

In attendance

Name	*Position (or reason for attending)*
Mr Norbert Leon Ciumageanu	Research Approvals Officer
Ms Mair Davidson	Research Approvals Specialist
Mrs Zoe Morrison	Obeserver

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Christian Subbe
Ysbyty Gwynedd
Penrhosgarnedd
Bangor
LL572PW

Email: HCRW.approvals@wales.nhs.uk

22 October 2020

Dear Dr Subbe,

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Exertional desaturation as a marker of risk – Validation study for the 40 steps test: A multi-centre prospective observational cohort study**
IRAS project ID:	**283998**
Protocol number:	**1.0**
REC reference:	**20/WA/0286**
Sponsor	**BCUH**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **283998**. Please quote this on all correspondence.

Yours sincerely,

Mair Davidson

Email: HCRW.approvals@wales.nhs.uk

Copy to: Dr Lynne Grundy

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Contract/Study Agreement template [Tracked version of BCUHB model agreement]	1	07 October 2020
Copies of advertisement materials for research participants [40 Steps to Safety Flyer - local version v1.0 24Sept20]	1	
Covering letter on headed paper [Covering Letter]	V1	24 September 2020
IRAS Application Form [IRAS_Form_29092020]		29 September 2020
IRAS Application Form XML file [IRAS_Form_29092020]		29 September 2020
IRAS Checklist XML [Checklist_22102020]		22 October 2020
Non-validated questionnaire [40 Steps to Safety Patient feedback survey V1.0 24Sept20]	1	24 September 2020
Non-validated questionnaire [40 Steps to Safety Patient feedback survey welsh versionV1.0 24Sept20]	1	24 September 2020
Organisation Information Document [OID_Non-Commercial_v1-5 BCUHB IRAS283998]	1	07 October 2020
Other [Email confirming no external funding]		07 October 2020
Other [NHS England Protocol for Usage of 40-Steps test]	V1	27 September 2020
Other [Review Exercise Tests for Desaturations]	V1	27 September 2020
Participant consent form [40+Steps+to+Safety+Consent+Form+V1.1+22 October 2020]	1.1	22 October 2020
Participant information sheet (PIS) [40 Steps Participant Information Leaflet V1.1 22-10-2020 CLEAN]	1.1	22 October 2020
Research protocol or project proposal [40 Steps to Safety Protocol Version 1.0 24Sept20]	V1	24 September 2020
Schedule of Events or SoECAT [SoE Validated]	1	08 October 2020
Summary CV for Chief Investigator (CI) [CV CP Subbe]	V1	16 March 2020
Summary CV for student [MRes Student CV - Gwenllian Rhys]	V1	24 September 2020
Summary CV for student [Tara Wakeling CV]	V1	24 September 2020
Summary CV for supervisor (student research) [CV Jonathan Moore]	V1	24 September 2020
Validated questionnaire [Numerical Rating Scale]	V1	24 September 2020

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
sites will perform the same research activities therefore there is only one site type.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	An Organisation Information Document has been submitted and the sponsor is intending to use a model non-commercial agreement with sites.	No study funding will be provided to sites as per the Organisational Information Document. Email from applicant 07 Oct 2020 confirms that no funding has been secured.	A Principal Investigator should be appointed at study sites.	No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain a Letter of Access based on standard DBS checks and occupational health clearance.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

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