Risk assessment in pulmonary hypertension

A thesis submitted by

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Abstract

Pulmonary hypertension (PH) is a disease of the pulmonary circulation that, if untreated, can progress to right ventricular failure and death. Assessment of the risk of mortality guides treatment strategies, such as the selection and modification of targeted pulmonary vasodilator therapy and consideration of lung transplantation. Risk stratification models employ multi-modality metrics which include an assessment of patient's functional disability, exercise capacity and right ventricular impairment.

Currently used models in clinical practice require face-to-face assessment to allow objective risk stratification. In addition, risk stratification is required at regular intervals which consequently results in frequent outpatient appointments. There has been increased interest in telehealth within PH, which was further accelerated by the 2019 coronavirus pandemic, however robust methods to acquire virtual risk metrics are lacking. The first work package in this thesis aimed to describe the current challenges to the implementation of the remote assessment of risk in PH and to develop exploratory knowledge into how exercise capacity and the measurement of biomarkers could be remotely obtained. The results demonstrate that remote risk assessment in PH is feasible, although there were important caveats to the validity of such testing.

The second work package focused on the refinement of risk assessment models in PH. The first study herein demonstrates the validity of the novel 4-strata risk assessment model in a cohort of patients with Chronic Thromboembolic Pulmonary Hypertension (CTEPH). The 4-strata model is limited by the inclusion of the World Health Organisation Functional Class and the MRC Dyspnoea Scale was studied an alternative as a measure of functional limitation, with results suggesting that incorporating this may allow further refinement of risk strata. Finally, two pre-test probability algorithms (the H2FPEF and OPTICS scores) were validated to assess whether patients with pre- and post-capillary PH can be differentiated non-invasively, without the need for invasive haemodynamic studies. The results demonstrated that these non-invasive scoring systems do not have sufficient specificity to recommend their routine clinical use.

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Preface

This thesis aims to further knowledge into the assessment of risk within the field of pulmonary hypertension (PH). Chapter 1 introduces Pulmonary Hypertension, outlining the diagnosis and treatment of the disease whilst concentrating on the topics that are most relevant to the work herein. A literature review is undertaken in Chapter 2, highlighting the current knowledge of remote assessment in PH and the existing evidence gaps. The knowledge gained from this review is used to compile the aims for Chapter 3, while the methods used to achieve these are provided in Chapter 4.

The first work package, "**Remote Risk Assessment in Pulmonary Hypertension**" includes the following chapters. Chapter 5 explores the potential challenges to implementing telehealth within the UK and Scottish population. A study regarding the provision of longitudinal remote exercise testing forms Chapter 6. Chapter 7 provides the results of a validation study of remote biomarker sampling.

The second work package, "**Risk Assessment Modelling in Pulmonary Hypertension**" includes chapters which focus on the current risk stratification models in the disease. Chapter 8 explores whether the novel 4-strata model is applicable to patients with medically managed Chronic Thromboembolic PH. Chapter 9 studies whether an alternative measure of functional disability could strengthen the 4-strata model. Chapter 10 aims to externally validate the use of two models which have been proposed as a non-invasive tool to differentiate between pre- and post-capillary PH.

The final chapter provides an overview of the results, strengths and limitations of these studies and contemplates their clinical applications. The appendices and references are then listed.

Acknowledgements

I would like to express my heartfelt gratitude to my supervisors. Dr Martin Johnson provided me with the opportunity to work with the Scottish Pulmonary Vascular Unit and has been my mentor for many years. Despite excessive hyphen-use and my persistence in split infinitives, he has continued to approach my work with patience and kindness. I am equally as indebted to my University of Glasgow supervisor, Dr Bhautesh Jani whose gentle persuasion and expertise has guided me throughout this process. Their enthusiasm and commitment have ensured the success of this thesis. Furthermore, the encouragement, guidance, and friendship of the SPVU consultants Dr Colin Church and Dr Melanie Brewis have been invaluable.

This work would not have been possible without the support from my colleagues within the Scottish Pulmonary Vascular Unit. The outdoor supervision of six-minute walk tests, as described in Chapter 6, were performed alongside Fiona Thompson. I am indebted to Louise Cowan and Joanna Ford for their enthusiasm in collecting capillary and venous samples, as described in Chapter 7. I wish to thank the whole nursing team at SPVU for assisting with many aspects of these studies; Rachel Thompson, Karon Carson, James Mearns, Agnes Crozier and Val Irvine. Kirsty Menzies and Veronica Ferry, the SPVU secretaries, have spent many hours helping me send questionnaires and mailshots, a job I know they relished. Dr Michael McGettrick, Dr Alexander MacLellan, Dr Stephanie Lua and Dr Jamie Ingram were all fellows at SPVU during my time with the unit and each assisted with approaching participants for the study described in Chapter 6. The head of research at the Golden Jubilee Hospital, Dr Catherine Sinclair, enabled the rapid local approval of each study.

My thanks go to Dr Fola Arogundade for her assistance with the data collection for the work described in Chapter 9. I wish to thank all the healthcare professionals, research nurses and team from Thriva for their contribution to the work in Chapter 7; this was a complex study and wouldn’t have been possible without their dedication.

Finally, I would like the thank all the patients with pulmonary hypertension. In late 2024, I was climbing a Scottish mountain when I met a patient with PH whom I recognised. She was using pulsed ambulatory oxygen and had started the hill at dawn, ensuring she had time to walk up and down at her own pace. The optimism, stoicism and fortitude of the patients I have met at SPVU has never ceased to amaze me. This thesis is dedicated to them.

Declaration

The work presented in this thesis was undertaken during my post as a Clinical Research Fellow at the Scottish Pulmonary Vascular Unit at the Golden Jubilee National Hospital, Glasgow and as a MD student at the School of Health and Wellbeing at the University of Glasgow. I was supervised by Dr Martin Johnson and Dr Bhautesh Jani. The work reported in this thesis was undertaken by me, although with the assistance of colleagues as described below.

The work described in Chapter 7 is the culmination of the collaboration between seven of the UK pulmonary hypertension centres. Professor Alex McConnachie provided advice and review of the statistical methods and power calculation for this work. My role in this study was to write the protocol, apply for ethical approval, apply for funding, co-ordinate the study including acting as data manager, analyse the results and write the related abstract and manuscript.

I supervised Dr Fola Arogundade in the data collection for the work described in Chapter 9. Aside from this, all work relating to this chapter is my own.

Work relating to this thesis has been published or submitted to peer-reviewed journals and/or presented at conferences. It has not previously been submitted for consideration of a higher degree.

Signed,

Dr Harrison Douglas Stubbs

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Abbreviations

1MSTS	1-Minute Sit to Stand
6MWD	Six-Minute Walk Distance
6MWT	Six-Minute Walk Test
ABG	Arterial blood gas
AF	Atrial fibrillation
AIC	Akaike Information Criteria
AT	Anaerobic Threshold
AUC	Area Under the Curve
BMI	Body Mass Index
BNP	B-type natriuretic peptide
BPA	Balloon Pulmonary Angioplasty
CBG	Capillary Blood Gas
CE	Cardiac Effort
CHD	Congenital Heart Disease
CI	Cardiac Index
CLD	Chronic Lung Disease
CMRI	Cardiac Magnetic Resonance Imaging
CO	Cardiac Output
COMPERA	Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CpC-PH	Combined Pre- and Post- Capillary Pulmonary Hypertension
CPET	Cardiopulmonary Exercise Test
CT	Computerised Tomography
CTD	Connective Tissue Disease associated Pulmonary Arterial Hypertension
CTEPD	Chronic Thromboembolic Pulmonary Disease
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
CTPA	Computerised Tomography Pulmonary Angiogram
CV	Coefficient of Variation
DLCO	Diffusion factor for carbon monoxide
DPAH	Drug Induced Pulmonary Arterial Hypertension
DPAP	Diastolic Pulmonary Arterial Pressure
DPG	Diastolic Pressure Gradient
E-10	EmPHasis-10
ECG	Electrocardiogram
E/e’	Ratio between early mitral inflow velocity and mitral annular early diastolic velocity
EF	Ejection Fraction
ERA	Endothelin Receptor Antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
FAC	Fractional Area Change
FC	Functional Class
FN	False Negative
FP	False Positive
GJNH	Golden Jubilee National Hospital

HHT	Hereditary Haemorrhagic Telangiectasia
HIV	Human Immunodeficiency Virus
HPAH	Hereditary Pulmonary Arterial Hypertension
HR	Hazard Ratio
HRCT	High Resolution Computerised Tomography
HRQoL	Health-care Related Quality of Life
ICC	Intraclass Correlation Coefficient
IHM	Implantable Haemodynamic Monitor
IPAH	Idiopathic Pulmonary Arterial Hypertension
IpC-PH	Isolated postcapillary pulmonary hypertension
IQR	Interquartile Range
ISWT	Incremental Shuttle Walk Test
IVC	Inferior Vena Cava
JVP	Jugular Venous Pressure
LA	Left Atrium
LFT	Liver Function Test
LHD	Left Heart Disease
MPAP	Mean Pulmonary Arterial Pressure
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NO	Nitrous Oxide
NPV	Negative Predicative Value
NT-proBNP	N-terminal prohormone of B-type natriuretic peptide
NS	Non-significant
NYHA	New York Health Association
PAH	Pulmonary Arterial Hypertension
PAP	Pulmonary Arterial Pressure
PAWP	Pulmonary Arterial Wedge Pressure
PDE	Phosphodiesterase
PE	Pulmonary Embolism
PEA	Pulmonary Endarterectomy
PETCO2	Partial Pressure of End Tidal Carbon Dioxide
PFT	Pulmonary Function Test
PH	Pulmonary Hypertension
PHA	Pulmonary Hypertension Association
PHRET	Remote Exercise in Pulmonary Hypertension
PICOS	Population, Intervention, Comparison, Outcomes and Study
POCT	Point-of-care Test
PPH	Primary Pulmonary Hypertension
PPV	Positive Predictive Value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PVOD	Pulmonary Veno-occlusive disease
PVR	Pulmonary Vascular Resistance
QEUH	Queen Elizabeth University Hospital
RA	Right Atrium
RAP	Right Atrial Pressure
RBH	Royal Brompton Hospital
REC	Research Ethics Committee

REVEAL	Registry to Evaluate Early and Long-term PAH Disease Management
RHC	Right Heart Catheterisation
ROC	Receiver Operator Curve
RV	Right Ventricle
RVEDP	Right Ventricular End Diastolic Pressure
RVF	Right Ventricular Failure
RVP	Right Ventricular Pressure
SV1+RV6	Sum of the s wave in v1 and r wave in v6 on an electrocardiogram
SIMD	Scottish Index of Multiple Deprivation
SPAHR	Swedish Pulmonary Arterial Hypertension Registry
SPAP	Systolic Pulmonary Artery Pressure
SPVU	Scottish Pulmonary Vascular Unit
ST	Step Test
STARD	Standard for Reporting Diagnostic Accuracy
STS	Sit to Stand Test
SV	Stroke Volume
SVI	Stroke Volume Index
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TAPSE	Tricuspid annular plane systolic excursion
TN	True Negative
TP	True Positive
TPR	Total Pulmonary Resistance
TR	Tricuspid Regurgitation
TRPG	Tricuspid Regurgitation Peak Gradient
TRV	Tricuspid Regurgitation Velocity
TTE	Transthoracic Echocardiogram
TUG	Timed Up and Go Test
VCO2	Ventilatory Equivalent for Carbon Dioxide
VO2	Ventilatory Equivalent for Oxygen
WHO	World Health Organisation
WSPH	World Symposium on Pulmonary Hypertension
WU	Woods Units

Publications

The following publications relate to work undertaken between 2020 to 2023, during this Doctor of Medicine degree. They have been structured in relation to the chapters within this thesis.

Chapter 5. Patient Paradigms in Telehealth for Pulmonary Hypertension

Publication: **Stubbs H**, Brewis M, Church C, *et al*. Towards telemedicine in pulmonary hypertension: Assessing the Feasibility of Remote Quality of Life and Exercise Capacity Assessment. Pulmonary Circulation. 2022; 12(4).

Abstract: **Stubbs H**, Johnson M. Patients' opinions of remote exercise capacity testing in pulmonary hypertension. European Respiratory Journal. 2021; 58(Suppl 65): PA414.

Chapter 6. Remote Exercise Testing in Pulmonary Hypertension

Publication: **Stubbs H**, Lua S, Ingram J, *et al*. Remote exercise testing in pulmonary hypertension (PHRET). Pulmonary Circulation. 2023; 13(4).

Abstracts:
Stubbs H, Jani B, Brewis M, *et al*. Remote exercise testing can detect clinical change in pulmonary hypertension. Thorax. 2022; 77: A98.

Stubbs H, A MacLellan A, McGettrick M, *et al*. Validity of alternative exercise tests in pulmonary hypertension. European Respiratory Journal. 2022; 60(Suppl 66): 121.

Chapter 7. Capillary NT-proBNP in Pulmonary Hypertension

Publication: **Stubbs H**, Cannon J, Knightsbridge E, *et al*. Sendaway capillary NT-proBNP in pulmonary hypertension. BMJ Open Respiratory Research. 2024;11(1).

Abstract: **Stubbs H**, Cannon J, Durrington C, *et al*. Capillary NT-proBNP is a valid tool for remote risk assessment in pulmonary hypertension. European Respiratory Journal. 2023; 62(Suppl 67): 3956.

Chapter 8. COMEPRA 2.0 risk stratification in medically-managed Pulmonary Hypertension

Publication: **Stubbs H**, Lua S, Brewis M, *et al*. COMPERA 2.0 risk stratification in medically-managed chronic thromboembolic pulmonary hypertension. European Respiratory Journal. 2022; 60(2).

Abstract: **Stubbs H**, Lua S, Brewis M *et al*. COMPERA 2.0 risk stratification in medically managed chronic thromboembolic pulmonary hypertension. Pulmonary Circulation. 2022; 12(4): A149.

Chapter 9. Risk Stratification using the MRC Dyspnoea Scale in Pulmonary Arterial Hypertension

Publication: Arogundade F, Jani B, Church C, Brewis M, Johnson M, **Stubbs H**. The MRC Dyspnoea Scale and mortality risk prediction in pulmonary arterial hypertension: a retrospective longitudinal cohort study. Pulmonary Circulation. 2023; 13(3).

Abstract: Arogundade F, Jani B, Church C, Brewis M, Johnson M, **Stubbs H**. The MRC Dyspnoea scale may predict survival in pulmonary arterial hypertension. European Respiratory Journal. 2023; 62(Suppl 67): 3962.

Chapter 10. Non-invasive prediction of postcapillary pulmonary hypertension

Publication: **Stubbs H,** MacLellan A, McGettrick M, *et al*. Predicting Group II pulmonary hypertension: diagnostic accuracy of the H2FPEF and OPTICS scores in Scotland. BMJ Open Heart. 2022;9(1).

Abstract: **Stubbs H**, Johnson M. Predicting postcapillary pulmonary hypertension: validation of the H2FPEF and OPTICS scores. Thorax. 2021; 76: A50.

Ancillary work relating to Pulmonary Hypertension but outside the scope of this thesis

Publications

Stubbs H, MacLellan, A, Lua, S, *et al*. The right ventricle under pressure: Anatomy and imaging in sickness and health. Journal of Anatomy. 2022;1-12.

Stubbs H, Johnson M. Pulmonary hypertension for the non-specialist. Journal of the Royal College of Physicians of Edinburgh. 2021; 51(4).

Stubbs H, Church C, Johnson M, Thomson, S. Impairment of skeletal muscle oxygen extraction and cardiac output are matched in precapillary pulmonary hypertension. European Respiratory Journal Open Research. 2021; 7(3).

Abstracts

Thomas J, **Stubbs H**, Johnson M, Church C, Brewis M. Pulmonary arterial hypertension with comorbidities – does dual therapy have a role? European Respiratory Journal. 2023; 62(Suppl 67): 1201.

Harley E, **Stubbs H**, Brewis M, *et al*. The distance saturation product as an outcome predictor in idiopathic pulmonary arterial hypertension. Thorax. 2022; 77: A102.

Lua S, **Stubbs H**, MacLellan A, *et al*. Genetics in pulmonary arterial hypertension. European Respiratory Journal. 2022; 60(Suppl 66): 1225.

1. Clinical Assessment of Pulmonary Hypertension

1.1 Background

Pulmonary hypertension (PH) is the term used to describe a disease of the pulmonary circulation that encompasses a broad range of heterogenous conditions(1). PH can be characterized by an increased pulmonary vascular resistance (PVR) and remodelling and obstruction of the pulmonary vasculature. As the right ventricle (RV) afterload increases, right heart strain develops with pressure overload causing the RV to remodel from a low to a high-pressure system. In response to the subsequent volume overload, the RV dilates in an attempt to maintain stroke volume, leading to eventual decompensation and right heart failure. This often leads to non-specific symptoms such as exertional dyspnoea, peripheral oedema, exertional presyncope and syncope. If PH is undiagnosed and untreated, the disease may ultimately result in death.

The risk of mortality is a key concept in clinical decision making in PH and forms the basis of risk stratification in the disease. Clinical observations and investigations are combined into multi-modality tools to enable clinicians to assign risk and predict the likelihood of clinical deterioration and death. In conventional clinical practice, risk assessment investigations are performed face-to-face within a clinic or hospital environment. There has been an increasing recognition for the need for enhanced telehealth strategies for risk assessment for PH patients due to the reduced need for patient travel and the reduced risk of nosocomial infections. This need was spurred on by the 2019 coronavirus pandemic, where such objective data was unavailable as patients were unable to travel. Furthermore, recent guidelines and studies have enhanced the rigor and utility of such risk stratification tools. This thesis aims to further investigate methods of remote risk assessment and the application of different risk assessment models.

This chapter will discuss how pulmonary hypertension is classified and go on to discuss the history, epidemiology and pathobiology of the disease. It will then describe the diagnosis and treatment of PH. Focus is placed on the mechanism of exercise limitation, the role of risk stratification, and the current use of telemedicine in pulmonary hypertension as these concepts are critical to the work described in this thesis.

1.2 Clinical Classification of Pulmonary Hypertension

Pulmonary hypertension encompasses a range of conditions where the pulmonary artery pressure is raised, with the unifying threshold of a mean pulmonary artery pressure of ≥20mmHg. The mPAP cut-off value was first defined at the 1973 1st World Symposium on Pulmonary Hypertension (WSPH) as ≥25mmHg(2), however this was a relatively arbitrary cut off, used to facilitate differentiating more severe forms of PH and with the aim of preventing overdiagnosis and treatment. A report of the World Health Organization (WHO) Expert Committee on Cor Pulmonale commented in 1961 that mPAP doesn't exceed 15mmHg in healthy subjects(3) and a subsequent systemic review has demonstrated an mPAP of >20 mmHg is greater than two standard deviations above the healthy population mean(4). The ≥25mmHg threshold was retained in the 2015 European Respiratory Society / European Society of Cardiology (ERS / ESC) guidelines but lowering the diagnostic threshold to ≥20mmHg was proposed at the 2019 19th WSPH(5) and this definition was adopted for the 2022 ERS/ESC guidelines(1). In conjunction with this, the diagnostic threshold for pulmonary vascular resistance (PVR) was lowered from ≥3 to ≥2.

A classification system of Primary and Secondary PH was proposed at the 1973 first WSPH(2) and revised at the 1998 second WSPH(6) as the "Evian classification", whereby PH was categorized into five groups with similar clinical attributes, pathophysiology, haemodynamics and response to treatment. This has subsequently undergone several revisions but has retained its overall structure, undergoing further refinement in the ERS/ESC 2022 Guidelines(1), as described in Table 1.

A further distinction can be made as to the presence of the disease process in relation to the pulmonary vascular capillary bed. Pre-capillary pulmonary hypertension occurs prior to the capillary bed and consists of Pulmonary Arterial Hypertension (PAH, Group 1), PH due to lung disease and/or hypoxia (Group 3), Pulmonary artery obstruction (Group 4) and several conditions within Group 5. Postcapillary PH (Group 2 and a selection of Group 5) occur as a result of backpressure arising from left-heart disease, defined as PH in the presence of a raised pulmonary artery wedge pressure (PAWP) of ≥ 15 mmHg. In isolated postcapillary PH (IpcPH) there is no discernible pulmonary vasculopathy (pulmonary vascular resistance (PVR) ≤ 2 woods units) and hence there is no pressure gradient between the diastolic pulmonary artery pressure (DPAP) and the PAWP (hence a diastolic pressure gradient (DPG) <7 mmHg)(7). In combined pre- and postcapillary PH (CpcPH) there is evidence of pulmonary vasculopathy (PVR ≥ 2 woods units) and hence a DPG ≥ 7 mmHg(7).

Group	Subgroup		PVR (woods units, WU)	PAWP (mmHg)
Group 1. Pulmonary Arterial Hypertension (PAH)	1.1 Idiopathic (IPAH) 1.1.1 Non-responders at vasoreactivity testing 1.1.2 Acute responders at vasoreactivity testing 1.2 Heritable (HPAH) 1.3 Associated with drugs and toxins (DPAH) 1.4 PAH associated with: 1.4.1 Connective tissue disease (CTD-PAH) 1.4.2 HIV infection 1.4.3 Portal hypertension (PoPAH) 1.4.4 Congenital heart disease (CHD-PAH) 1.4.5 Schistosomiasis 1.5 PAH with features of venous / capillary involvement (PVOD) 1.6 Persistent PH of the newborn		>2	≤15
Group 2. Left Heart Disease (PH-LHD)	2.1 PH due to Heart failure: 2.1.1 with preserved LV ejection fraction (HFpEF) 2.1.2 with reduced or mildly reduced LV ejection fraction (HFrEF) 2.2 Valvular heart disease 2.3 Congenital/acquired cardiovascular conditions leading to post-capillary PH	Isolated postcapillary (IpcPH)	≤2	>15
		Combined pre- and postcapillary (CpcPH)	>2	>15
Group 3. Chronic lung disease and/or hypoxia (PH-CLD)	3.1 Obstructive lung disease or emphysema 3.2 Restrictive lung disease 3.3 Lung disease with mixed obstructive/restrictive pattern 3.4 Hypoventilation syndromes 3.5 Hypoxia without lung disease 3.6 Developmental lung disorders		>2	≤15
Group 4. Pulmonary arterial obstruction	4.1 Chronic thromboembolic pulmonary hypertension (CTEPH) 4.2 Other pulmonary artery obstructions		>2	≤15
Group 5. Multifactorial and/or unclear mechanisms	5.1 Haematological disorders 5.2 Systemic disorder 5.3 Metabolic disorders 5.4 Chronic renal failure with or without haemodialysis 5.5 Pulmonary tumour microangiopathy 5.6 Fibrosing mediastinitis		>2	≤15

Table 1. 2022 Clinical and haemodynamic classification of pulmonary hypertension.

1.2.0.1 2022 Clinical Classification of PH

In September 2022, the ERS/ESC published updated guidelines for the diagnosis and management of pulmonary hypertension(1), replacing the 2015 ERS/ESC guidelines and 2019 WSPH recommendations. These heralded significant changes which are relevant to the works incorporated into this thesis, including revised haemodynamic criteria for the confirmation of pulmonary hypertension and changes to the risk stratification system at follow up. Of note, prior to 2019, the MPAP threshold for diagnosing PH was ≥25 mmHg and the PVR threshold was ≥3 WU. A significant proportion of the work included within this thesis commenced between 2020 and 2021. Furthermore, this thesis contains three retrospective data studies, with start dates of 2010. Hence, the 2015 haemodynamic criteria were used for all studies within this thesis.

1.2.1 History and Epidemiology of Pulmonary Hypertension

1.2.1.1 History of the Clinical Classification and Pulmonary Hypertension

Dr Ernst von Romberg first described “pulmonary vascular sclerosis” following observations made during an autopsy in 1891(8) yet the recognition of pulmonary vascular medicine did not truly begin until the mid-20th century with the advent of right heart catheterisation (RHC), pioneered by Werner Forssmann who performed the first procedure upon himself, aged 24(9). Andre Cournand and Dickinson Richards developed this technique in the 1940s(10) with further refinement by William Swan and Jeremy Ganz in the 1960s(11), confirming the safety of right heart catheterisation and demonstrating its ability to directly measure the haemodynamics of the right ventricle and of the pulmonary vascular system. The World Health Organisation (WHO) hosted an expert committee on “chronic cor pulmonale” in Geneva in 1960, leading to the subsequent understanding and classification of a range of conditions known at the time as primary pulmonary hypertension (PPH) (3). In 1965 numerous cases were reported in central Europe, which were subsequently found to be attributable to the novel anorexigenic Aminorex(12). This epidemic led to the first WSPH meeting in Geneva, 1973(2) and the formation of the first national pulmonary hypertension registry(13).

1.2.1.2 Pulmonary Hypertension Registries

The PH registries depict the real-life practice and outcomes of PH across broad geographical areas, providing epidemiological data and data for retrospective research, including risk stratification(14). Notable registries mentioned in this thesis include the USA Registry to Evaluate Early and Long-term PAH disease management (REVEAL), the pan-European Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), the French Registry and the Swedish Pulmonary Arterial Hypertension Registry (SPAHR)(15).

1.2.1.3 Epidemiology of Pulmonary Hypertension

96% of pulmonary hypertension in Europe is due to left heart or chronic lung disease(16). In the UK, PAH affects approximately 48-55 people per million (ppm) with an incidence of 7.6 ppm per year(14). The incidence of CTEPH is acknowledged to be under-reported at 3-6 ppm per year with a prevalence of 26-38 ppm(17, 18). Globally, the causes of PH can differ significantly, with cases of PH related to sickle cell disease and infectious diseases (HIV, schistosomiasis, post-streptococcus rheumatic heart disease) being more prevalent in countries where these remain endemic(16). In the UK, the mean age at diagnosis of IPAH is 60 years and around one third of IPAH patients are male(19).

The incidence of PAH has risen over the last 20 years, likely due to a combination of increased availability of baseline investigations and enhanced awareness of PH amongst general physicians(14). Newly diagnosed patients with PAH are more likely to be older than in the past; the mean age of diagnosis with IPAH in 1981 was 36 years, as opposed to 65 years in 2020(15). This reflects the increased recognition and onward referral of older patients with PH(20, 21). Furthermore, the number of patients diagnosed with PAH with cardio-pulmonary co-morbidities is increasing and subsequently there is increased complexity in how to refine the diagnosis and manage side effects and interactions when commencing on treatment.

Whilst PH remains a progressive and life-limiting condition, prognosis significantly varies depending on aetiology. Prior to the advent of targeted pulmonary vasodilator therapy survival for PAH was uniformly poor; 5 year survival in the United States during the 1980s for patients who had precapillary PH was 34%, with a median survival of 2.8 years(22). The development of Epoprostenol in the 1990s(23), subsequently followed by other pulmonary vasodilators, has led to improved survival rates in younger patients, yet morbidity and mortality remain significant(14, 24). In the UK, younger patients (18-53 years old) now have a 5 year survival of 83-85% and patients with chronic thromboembolic PH (CTEPH) who undergo surgical treatment have a five year survival of 85%(19). In patients who demonstrate a response to inhaled nitric oxide and have a long-term response to calcium channel blockers, PH may not limit their life expectancy(25).

1.3 Development of Pulmonary Hypertension

1.3.1 PAH Pathobiology

In PAH, the development of an obstructive pulmonary vascular system is mediated though the dysregulation of key cell signalling cascades (the nitric oxide (NO), endothelial-1 (ET-1), prostacyclin (PGI2) and thromboxane A2 (TXA2) pathways) which affect multiple cell types (endothelial cells, smooth muscle cells, fibroblasts and inflammatory cells)(26). Under normal conditions, NO synthase (eNOS) produces NO in endothelial cells, where it diffuses to pulmonary vascular smooth muscle and binds to soluble guanylate cyclase (cGC) to facilitate the production of cyclic guanosine monophosphate (cGMP). PGI2 is produced in the endothelium via cyclooxygenase (COX) and prostacyclin synthase, binding to smooth muscle cells to activate cyclic adenosine monophosphate (cAMP). cAMP and cGMP subsequently lead to the activation of protein kinases which result in pulmonary vascular smooth muscle vasodilation. ET-1 activates the G-protein coupled receptors ETA and ETB which lead to vasoconstriction when found on smooth muscle, however ET-1 activation of endothelial ETB results in NO and PGI2 production resulting in vasodilation(26).

In PAH there is a decreased bioavailability of eNOS, a reduction in NO, upregulation of smooth muscle ETA and ETB receptors and reduced ET-1 activation of endothelial ETB. Furthermore, there is imbalance in the COX pathway, resulting in reduced availability of PGI2 and overproduction of TXA2, resulting in vascular proliferation and platelet aggregation(27). The summative effect of these changes is pathological smooth muscle remodelling, in situ thrombosis and vasoconstriction. In PAH, these pathways contribute to progressive increases in PVR with similar mechanisms regardless of contributing factors(28).

1.3.2 CTEPH Pathology

CTEPH occurs as the result of persistent pulmonary vascular occlusion by organized thrombi with subsequent vascular remodelling*(29)*. Following an acute pulmonary embolism (PE), the persistence of pulmonary arterial filling defects (referred to here as chronic thromboembolic pulmonary disease, CTEPD) is common, with studies suggesting ~22-50% of patients will have some form of radiographic evidence following PE(30, 31). Despite the prevalence of CTEPD, only ~0.5-4% of patients will go on to develop CTEPH following an acute PE, although this is likely to be an underestimate(31, 32).

The mechanism underlying the failure of thrombi to resolve is incompletely understood but likely as a result of an interplay between inadequate fibrinolysis, abnormal

coagulation cascades and immune dysregulation(30). Microvascular small vessel disease is increasingly recognized as a contributing factor to pathology and symptoms, although may not be detected on conventional computerised tomography. Redistributed pulmonary blood flow from disease areas to non-occluded pulmonary arterioles, leads to an increase in RV pressure and wall stress, with similar histological features to the changes seen in PAH(30). The distribution of CTEPD is described in relation to its proximity to the main pulmonary artery, as shown in Table 2; this is clinically relevant as more central disease is more likely to be suitable to surgical intervention and result in beneficial outcomes(33).

Level	Location
I	Disease involving one of the main pulmonary arteries
II	Disease starting at the lobar branches of the pulmonary arteries
III	Disease starting at the segmental branches of the pulmonary arteries
IV	Disease starting at the subsegmental branches of the pulmonary arteries

Table 2. San Diego classification of pulmonary endarterectomy disease levels.

1.3.3 Mechanisms of RV Failure

In both CTEPH and PAH, the occlusion of the pulmonary arterial system leads to an increased RV afterload. In response to the increased stretch during RV diastole and systole, cardiomyocytes increase in size and structure, culminating in RV concentric hypertrophy(29). This leads to a compensatory phase as the resting cardiac output is maintained, yet if unchecked this progresses to RV dilation(28). As the RV dilates, annular dilation occurs causing functional tricuspid valve regurgitation, leading to further RV volume overload. RV dilation increases the RV wall tension, increasing myocardial oxygen demand and reducing perfusion, leading to RV wall ischaemia(34, 35). Furthermore, prolongation of RV systole results in a rise in RV end-diastolic pressure, altering the pressure-volume relationship curve and leading to interventricular asynchrony. This causes the intraventricular septum to bow towards the left ventricle during diastole, and later in the disease during systole, causing a decrease in LV end-diastolic volume which contributes toward a decrease in stroke volume and hence cardiac output (CO)(28). CO is determined by;

$$CO = HR \cdot SV$$

and thus neurohormonal activation leads to increases in the heart rate (HR) to augment a reduced CO, leading to the baseline tachycardia seen in PH patients. If untreated the disease will progress and the RV will undergo fibrosis and further strain and will eventually decompensate, leading to decreased inotropy, RV failure (reduction of the

cardiac output at rest) and death(28) (Figure 1). The process of RV adaptation to an increased afterload is determined by a myriad of factors including the cause of PH, the rapidity of onset and the age at which it occurs. Together, these factors predict outcomes in patients with PH.

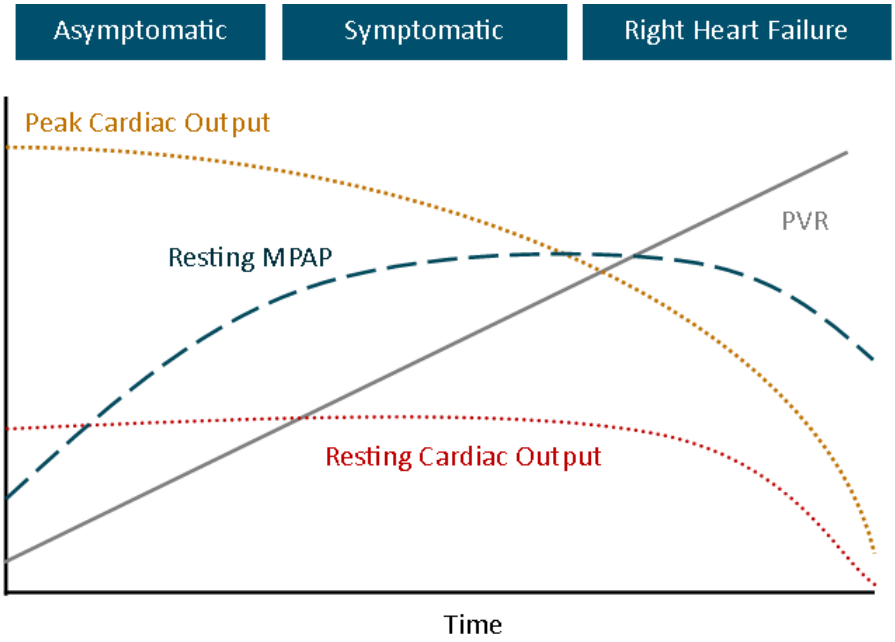


Figure 1. Representation of the progression of pulmonary haemodynamics in pulmonary hypertension over time. Adapted from Howard, European Respiratory Review 2011(36) and reproduced with permission of the © ERS 2022.

1.4 Exercise Limitation in Pulmonary Hypertension

1.4.1 Mechanism of Exercise Limitation

Exercise is a process whereby oxygen is transferred from the atmosphere to the mitochondria in skeletal muscles, via the lungs and circulatory system(37). The Fick equation quantifies this process;

$$VO_2 = CO \cdot (CaO_2 - CvO_2)$$

Where VO_2 is the consumption of oxygen by skeletal muscle mitochondria, CO is the cardiac output and CaO_2-CvO_2 is the arterial oxygen content minus the venous oxygen content, i.e., the arteriovenous oxygen content difference(38).

Pulmonary hypertension affects all determinants of the equation. As demonstrated in 1.3.3 Mechanisms of RV Failure, in PH there is a decrease in SV and hence CO. During exercise, this limitation leads to a steeper rise in the heart rate than is seen in health i.e., an elevated chronotropic index (ΔHR/ΔVO2). The decrease in SV is augmented by an increase in oxygen extraction by muscle from the blood, resulting in a widened CaO_2-CvO_2 and a fall in mixed venous oxygen saturation (SvO_2), further limiting VO_2(39).

CaO2 is determined by;

$$CaO2 \propto (SaO2 \cdot Hb) + PaO2$$

Where SaO2 is the arterial oxygen saturation, Hb is haemoglobin and PaO2 is the arterial oxygen tension. All three components are reduced in PH due to ineffective lung mechanics and ventilatory control, respiratory muscle weakness, pulmonary vascular bed obliteration with V/Q mismatching and the possibility of disease-attributable iron deficiency anaemia. Ventilation is inefficient, with an increased ratio between minute ventilation (V_E) and carbon dioxide production (VCO_2) due to an increase in the physiological dead space resulting from obstructed pulmonary arterioles. The SvO2 may be reduced due to impaired oxygen extraction due to a skeletal muscle myopathy in PH, with systemic endothelial dysfunction and a proinflammatory state.

A pulmonary haemodynamic response to exercise in a healthy population would be an increase in mPAP of 0.5-3 mmHg per litre increase of CO with a smaller increase in the PAWP. In PH However, the ability of the heart to augment CO by increased SV is blunted and thus the mPAP/CO slope is steeper than in health.

1.4.2 Exercise Capacity Assessment

As discussed above, exercise limitation is a hallmark feature of pulmonary hypertension and hence assessment of exercise capacity allows a measure of the disease severity and response to treatment.

1.4.2.1 Cardiopulmonary Exercise Test (CPET)

The cardiopulmonary exercise test (CPET) is a maximal test, used as the gold standard for a comprehensive assessment of exercise limitation that allows for quantification of peak oxygen consumption ($VO2_{PEAK}$), an independent predictor of prognosis in PH(40). Furthermore, CPET allows discrimination between factors contributing toward decreased exercise tolerance and can quantify their severity. The test is performed on a treadmill or cycle ergometer, supervised by a physiologist with software used to collate the output data, whilst expertise is required in order to analysis the results(41).

A characteristic CPET profile is seen in patients with PH. There are abnormalities of oxygen transport and delivery including a reduced $VO2_{PEAK}$, a reduced VO_2 at the anaerobic threshold, reduced work efficiency (a reduced VO2 to work rate slope), a high chronotropic index, and a reduction in O2 pulse (VO2/HR), a surrogate marker of stroke volume. Unless a primary lung abnormality is present, there is often a preserved breathing reserve. Gas exchange abnormalities are evidenced by raised ventilatory equivalents, reduction in end-tidal CO2 (PETCO2), high dead space, a wide arterial-alveolar gradient, oxygen desaturation and a high VE/CO2 slope.

Prospective multivariate survival analysis by WENSEL in 2002 demonstrated that a reduced VO2PEAK, reduced systolic and diastolic blood pressure at peak exercise, exercise duration, resting PETCO2 and a raised VE/VCO2 gradient were all independent predictors of survival in patients with PH(42). Subsequently, the VO2PEAK and VE/VCO2 gradient have been included in PH risk models(1, 41).

A proportion of patients will be unable to perform a CPET or achieve a maximal test for reasons such as motivation, mobility issues or disease severity. Together with the staffing, equipment and expertise requirements for testing, these factors limit the widespread use of CPET.

1.4.2.2 Six-Minute Walk Test (6MWT)

The six-minute walk test (6MWT) is a submaximal test that comprises of a participant walking along a fixed-length corridor for six minutes, the primary outcome being the total distance walked in metres (6MWD) with recorded secondary measures of HR and peripheral oxygen saturations (SpO_2). The 6MWT has been well validated in PH as a measure of prognosis and for risk stratification(40, 43) and has been shown to correlate

with $VO2_{PEAK}$, O2 pulse and the VE/VCO2 slope. The 6MWT is low cost, simple, reproducible, easily-standardized and easily interpretable and hence is the most common exercise test used in PH. A minimally important distance (MID) has not been agreed for the 6MWT in PH but has been reported between 33-41m in PAH(43). Amongst patients with chronic obstructive pulmonary disease (COPD) the intra-test reliability has been demonstrated to be excellent with an intraclass correlation coefficient of 0.98 and a mean difference (standard deviation) of 7.9m (15.8m)(44).

However, the 6MWT requires a technician to administer the test, a corridor of sufficient length and for patients to travel to a healthcare facility for assessment and supervision(43, 45, 46). Confounding factors, other than cardiac function, will determine the outcome of a 6MWT, including motivation, frailty, sarcopenia and other co-morbidities affecting mobility and biometrics. A “ceiling effect” is described with the 6MWT, as it is harder to detect a positive response to therapy in patients with a good baseline result. Furthermore, a proportion of patients with PH will be unable to undertake a 6MWT due to disease severity. Current risk stratification uses defined cut offs for 6MWD which are not corrected for age, sex, height and other factors. Although normal ranges and lower limits of normal have been proposed, these are not in common use(47). Lastly, Both the 6MWT and CPETs are snapshots of activity in a clinical environment, prone to fluctuations depending on other transient factors.

1.5 Diagnosis of Pulmonary Hypertension

In the UK, patients are generally referred from Respiratory, Rheumatology and Cardiology specialties to specialist PH centres. Referrals undergo a vetting process within the multi-disciplinary team (MDT) meeting as to whether further investigations, including RHC, are warranted.

1.5.1 Clinical Presentation

Early symptoms of pulmonary hypertension are non-specific, subtle and hence are often missed, with a subsequent delay in diagnosis. It remains the case that patients are diagnosed late into their disease course, with an average time from symptom onset to diagnosis of ≥1 year(48). Symptoms in the earlier stages of disease are related to RV dysfunction and include dyspnoea, fatigue, chest pain, exertional presyncope and reduced exercise tolerance. Abnormalities of the pulmonary vasculature and/or bronchial artery hypertrophy may lead to haemoptysis whilst compressive pathology due to enlargement of the pulmonary artery may cause coronary ischaemia or left vocal cord palsy and thus voice hoarseness. Clinical signs of right heart strain may be absent, but when present include an accentuated component of the second heart sound over the pulmonary valve (loud P2), the pansystolic murmur of tricuspid regurgitation, the diastolic murmur of pulmonary regurgitation and an RV heave. Signs of right heart failure occur later in the disease and include dependent peripheral oedema, ascites, hepatomegaly and a raised jugular venous pulse (JVP). Clinical examination should thus aim to detect these signs and further focus on potential underlying causes of pulmonary hypertension.

A thorough clinical history is used to assess possible underlying aetiologies and the disease severity. This should include past medical conditions that predispose to pulmonary hypertension (e.g., connective tissue disease, previous pulmonary embolism or liver disease), a family history (relevant for conditions such as HHT, PVOD, HPAH and CTDPAH), and risk features for underlying cardiorespiratory disease.

1.5.2 Initial Investigations and Referral

Transthoracic echocardiography (TTE) remains the cornerstone initial investigation for diagnosing PH. Whilst not sufficiently accurate to confirm PH, TTE should assign a probability of PH in order to assess the need for onward referral and further investigation. The maximum velocity of blood through a regurgitant tricuspid valve (TRV_{MAX}) is measured using doppler, from which the peak tricuspid valve pressure gradient (TRPG) can be calculated using the simplified Bernoulli equation;

$$TRPG = 4 \cdot (TRVmax)^2$$

An estimation of right atrial pressure (RAP) is added to the TRPG to estimate the right ventricular systolic pressure, which in the absence of right ventricular outflow obstruction is equal to the systolic pulmonary artery pressure (SPAP);

$$SPAP \sim RVSP = TRPG + RAP$$

And therefore, theoretically, the estimated mPAP can be calculated as thus;

$$mPAP = 0.61 \cdot (SPAP + 2)$$

A TRPG ≤31 mmHg suggests a low probability of PH, whilst ≥46 mmHg suggests a high probability. TRPG estimates of 32-45 give an intermediate probability and patients in this category, or where a TR is not measurable, should be assessed in conjunction with other echocardiographic parameters. These include abnormalities of the right ventricle (RV:LV basal diameter >1, flattening of the intraventricular septum), the pulmonary artery (reduced pulmonary valve acceleration time <105ms, pulmonary artery diameter >25mm) and the inferior vena cava (IVC) or right atrium (RA) (decreased inspiratory collapse of the IVC, enlargement of the RA). Patients with a high probability, or intermediate probability with the presence of signs from two of the above categories, should be referred to a tertiary PH centre for consideration of further assessment(49). Patients with Group II and Group III disease should be considered for referral if the extent of pulmonary hypertension is disproportionate to the underlying disease(7, 50). Patients with severe symptoms (presyncope or syncope) or presenting with right heart failure should be seen urgently(49).

1.5.3 Group II and Group III Pulmonary Hypertension

The diagnosis of PH-LHD, especially in the context of heart failure with preserved ejection fraction, can be challenging. It is important to differentiate this group as further investigations may help to refine the diagnosis and thus significantly alter management. PH-LHD patients tend to be older (>70 years), have comorbidities of increasing cardiovascular risk (diabetes, systemic hypertension, dyslipidaemia, atrial fibrillation) and may have undergone previous cardiac intervention such as valve replacement or coronary angiography(51). Studies have proposed using transthoracic echocardiogram indices to estimate the PAWP(52).

Patients with PH-LHD should be managed according to the underlying disease(7). Patients with PH due to lung disease and/or hypoxia may still be considered for tertiary referral if the extent of pulmonary hypertension is felt disproportionate to the disease process, as these patients may benefit from a trial of pulmonary vasodilator

therapy(53). Patients with PH-ILD can be entered into clinical trials. Features favouring proportional PH include moderate or severe impairment on pulmonary function testing, characteristic lung disease features on CT imaging, mild to moderate PH at RHC and ventilatory limitation on CPET(50).

1.5.4 UK and Ireland Pulmonary Hypertension Centres

The Scottish Pulmonary Vascular Unit (SPVU) is based at the Golden Jubilee National Hospital in Glasgow and acts as the tertiary diagnostic and management centre for adults with pulmonary hypertension for all of Scotland (population ~5.5 million in 2021). It was founded in 1990 by Professor Andrew Peacock and is funded under the National Services Division (NSD) of the Scottish Executive.

The National Pulmonary Hypertension Audit is published each annum by National Health Service (NHS) Digital and reports data on the care patients receive at PH centres. In 2019-2020 the SPVU had 648 PH patients under its care of whom 513 patients were diagnosed with PAH or CTEPH. Given the adult population (>16 years) in Scotland in 2020 was 4.53 million, this gives a point prevalence of 143 cases of PH per million(54).

There are eight further tertiary pulmonary hypertension centres in England and Ireland. These are based at the Freeman Hospital in Newcastle, the Royal Papworth Hospital in Cambridge, the Royal Hallamshire Hospital in Sheffield, Mater Hospital in Dublin and the Hammersmith Hospital, the Royal Brompton Hospital and the Royal Free Hospital in London. Great Ormond Street Hospital in London provides paediatric PH care for the UK. The PH centres are connected through the PH network and collaborate on research. SPVU has particularly close links to the Royal Papworth Hospital, as they are the UK centre for CTEPH and CTEPD and receive all of the SPVU referrals for potentially operable patients with these diagnoses, and the Freeman Hospital, due to its role as the Lung Transplant Unit for Scotland.

1.5.5 Further Investigations

Once the probability of PH has been established, further investigations at specialist centres should aim to discern the possible aetiologies, assess prognosis and confirm the diagnosis through direct haemodynamic measurement. Following these investigations, all incident patients at SPVU are discussed within a multidisciplinary team setting, comprised of a specialised PH pharmacist, clinical nurse specialists and consultants in respiratory medicine and pulmonary hypertension, cardiac imaging and thoracic radiology. It is within this setting that a final diagnosis is formed and an initial treatment plan outlined.

1.5.5.1 Blood tests

Routine biochemical and haematological assay includes renal function, liver function, thyroid function, inflammatory markers and full blood count, which are used to detect possible causes of dyspnoea and/or PH and in helping to discern the suitability of certain PH-specific medications. Thrombophilia screening is performed in cases of suspected CTEPH, when off anticoagulation for 48 hours, as patients with triple-positive antiphospholipid syndrome require different anticoagulation strategies(55). Screening tests for blood-borne viruses and connective tissue disease are performed. Arterial blood gas (ABG) or capillary blood gas (CBG) sampling is used to assess for the presence of acute or chronic type two respiratory failure.

Natriuretic peptides are hormones that cause vasodilation and natriuresis. B-type natriuretic peptide (BNP) is secreted by myocardiocytes in response to increased ventricular wall stress and is cleaved in the blood to N-terminal prohormone of BNP (NT-proBNP)(56). Originally used for the diagnosis and management of left heart failure, NT-proBNP has become established for use in pulmonary hypertension as a surrogate marker for ventricular wall stress and has been shown to correlate well with multiple pulmonary haemodynamics including RAP, mPAP, PVR and CI(57, 58). Therefore, NT-proBNP is used to risk-stratify patients at the point of diagnosis and serial monitoring allows an assessment of disease activity and response to treatment(40). NT-proBNP has a longer half-life than BNP leading to increased stability and preference for use in clinical practice and at SPVU. However, NT-proBNP can be affected by volume status in addition to pulmonary haemodynamics, is prone to the specific effects of sex and obesity and is not specific to RV dysfunction as it is also raised in left ventricular failure(59). NT-proBNP levels have been shown to demonstrate diurnal variation(60).

1.5.5.2 Respiratory Function

Pulmonary function testing (PFT) is used to assess the probability of obstructive and restrictive lung disease which may indicate Group 3 PH(50). Gas exchange measurement should be undertaken as this can underpin the severity of chronic lung disease yet the diffusion factor for carbon monoxide (DLCO) may also be reduced in cases of severe PAH, CTD-PAH and PVOD.

A raised Epworth score, the presence of a type 2 respiratory failure or a raised BMI may lead to the suspicion of sleep-disordered breathing or obesity hypoventilation and hence further studies should be performed to confirm the diagnosis and assess the severity.

1.5.5.3 V/Q Scintigraphy

Nuclear medicine imaging of the thorax allows visualization of global thoracic perfusion. Mismatched perfusion defects raise the possibility of acute or chronic pulmonary

vascular occlusion. V/Q imaging has advantages over conventional CT pulmonary angiography in being able to detect cases of more distal chronic thromboembolic disease and has a greater sensitivity (97.4% vs 51%) with a comparable specificity (95% vs 99%) at detecting CTEPD(61).

1.5.5.4 Computerised Tomography

Acquisition of a computerised tomography (CT) pulmonary angiogram (CTPA) provides information on the probability of pulmonary hypertension, by assessing the shape and size of the main pulmonary artery and right-sided cardiac chambers. Furthermore, it is important for detecting evidence of CTEPD in which case arterial obstruction, webs, stenoses and chronic thrombus may be seen(62). High resolution CT (HRCT) provides a detailed assessment of the lung parenchyma, particularly useful in assessing for Group 3 PH, yet additionally allows detection of septal lines, which may be seen in PVOD(63).

1.5.5.5 Cardiac MRI

Cardiac magnetic resonance imaging (MRI) allows the non-invasive quantification of cardiac structure, size and function, providing prognostic data such as the stroke volume, cardiac output, right ventricular ejection fraction and a visual assessment of RV function(62). Furthermore, it provides data on congenital heart disease, allows quantification of shunts and provides an assessment of left-sided cardiac function which is pertinent in Group II disease. It is especially useful when the views obtained during TTE are suboptimal(62). CMRI is used at SPVU as a non-invasive technique to serially quantify the RV response to treatment and disease progression.

1.5.5.6 Exercise Capacity

Exercise intolerance is a hallmark feature of PH and is discussed in depth in Chapter 1.4. Maximal and submaximal exercise tests are used at diagnosis and follow-up to assess disease severity and inform risk stratification. CPET may provide information on the cause of reduced exercise capacity and may help to identify alternative causes of dyspnoea. The 6MWT is used at each face-to-face assessment at SPVU.

1.5.5.7 Genetics

In IPAH, HPAH, DPAH and PVOD, genetic screening should be undertaken. 53-86% of patients with a family history of PAH have monoallelic mutations in the *BMPR2* gene, i.e. Hereditary PAH (HPAH) and these patients present at a younger age with a worse prognosis when compared to non-carriers(64, 65).18-35% of sporadic IPAH patients prove to have a *BMPR2* mutation, which may prompt genetic screening of family members after appropriate counselling, therefore genetic screening should be considered in all patients with IPAH, even in the absence of a family history(64). Patients with

Hereditable PVOD have a biallelic mutation in the *EIF2AK4* gene, a therefore autosomal recessive condition(66, 67).

1.5.5.8 Right Heart Catheterisation

All patients investigated for Group 1, 2 and 5 PH should undergo right heart catheterisation (RHC) in order to confirm the diagnosis of PH, assess the disease severity and delineate aetiology. All the participants involved in the studies outlined in this thesis underwent RHC as part of their routine clinical care, usually at the initial diagnostic assessment, and thus patients were pulmonary vasodilator-naïve at the time. The procedure is performed in a catheterization laboratory with the patient lying supine. A balloon-tipped 7 French Swan-Ganz catheter is passed through the internal jugular or femoral vein to access the vena cava, right atrium, right ventricle and main pulmonary artery whilst directly observed with Xray fluoroscopy(11). The intracardiac and pulmonary artery pressures are measured in relation to a transducer which is set at the mid-thoracic level. Routine measurements include the right atrial pressure (RAP), right ventricular pressure (RVP), right ventricle end-diastolic pressure (RVEDP), systolic/diastolic/mean pulmonary artery pressure (SPAP/DPAP/mPAP)(68). The tip of the catheter, with the balloon inflated, is wedged into a pulmonary artery branch to measure the pulmonary artery wedge pressure (PAWP), allowing an estimation of left atrial pressure and thus left ventricular end diastolic pressure(69). Thermodilution is used to calculate the cardiac output (CO), where saline at 10 degrees Celsius is injected into the right atrium, with the transit time to the main pulmonary artery measured(70). Mixed venous saturations (SvO_2) are measured by withdrawing blood from the main pulmonary artery. The pulmonary vascular resistance (PVR) is calculated as;

$$PVR = \frac{MPAP - PAWP}{CO}$$

Further provocatory testing may be performed to refine the diagnosis, including fluid challenge and exercise testing. Vasoreactivity testing with inhaled nitric oxide at 40 parts per million for five minutes is performed in patients with IPAH, DPAH and HPAH to assess for a vasodilator response, which may identify them as patients who can be treated successfully with calcium channel blockers. In cases of a suspected left to right shunting, which may be indicated by a SvO_2 above 75%, a saturation run is performed, where the oxygen saturation of blood is measured in the inferior and superior vena cava, right heart and pulmonary artery to isolate the source of the shunt.

Whilst the gold standard test for pulmonary hypertension, RHC allows assessment only at one point in time, whilst the patient is supine and at rest and therefore is prone to intra-patient variability. Due to its invasive nature and need for skilled operators, clinicians and patients may wish to avoid repeat assessment.

1.5.5.9 Pulmonary Angiography

In cases of suspected CTEPH, conventional pulmonary angiography is performed at the time of right heart catheterisation. Contrast is injected through a pulmonary angiography catheter to the right and left pulmonary artery. The subsequent images are used to assess for perfusion abnormalities both distally and proximally which may include pulmonary arterial stenoses and cut-offs, webs and a lack of a distal perfusion pattern.

1.5.5.10 Patient Reported Outcome Measures

Health-related quality of life scores are used to quantify the impact of the disease on patients' lives. The emPHasis-10 questionnaire is employed in SPVU for measuring patient-reported outcomes, consisting of 10 questions asking patients how PH affects aspects of their routine life, with answers ranging from 0-5 where 0 represents no impact whilst 5 represents a maximum impact. The emPHasis-10 questionnaire has been shown to be an independent marker of prognosis in subcategories of PAH(71, 72).

1.6 Treatment of Pulmonary Hypertension

Treatment for pulmonary hypertension aims to reduce the mortality risk and reduce the impact of morbidity by improving symptoms and exercise capacity. Treatments are tailored to the individual, depending on the underlying pathology, risk-status and the appropriateness of intensifying treatment in cases where comorbidities, age and side effects may affect this decision. The risk strata influence clinical management decisions on the combination and type of treatment, which is discussed in detail in the section 1.7.3 Risk stratification.

1.6.1 Supportive Treatment

Treatment for all patients with PH should include appropriate vaccination as for any chronic respiratory disease. Long-term oxygen should be prescribed for a minimum of 16 hours a day if respiratory failure is present (partial pressure of oxygen ≤8 kPa at rest). Beta-blockers and cyclizine are relatively contraindicated due to their effects on cardiac output and heart rate response. Nitrates are contraindicated in combination with phosphodiesterase-5 inhibitors and cannot be used for anginal treatment in patients taking these. Patients with RV strain and failure are prone to fluid retention resulting in peripheral oedema, ascites and hepatic congestions, which should be managed with optimal diuresis(65). Female PH patients should be counselled about the high mortality associated with pregnancy, and given counselling on contraception and termination(73). Conditions that aggravate PH such as cardiac dysrhythmias, infection and acute PE, should be detected and treated promptly. Patients with acute RV failure may need to be treated in a high-dependency environment with inotropic and vasopressor support(74). Low-intensity aerobic exercise is safe and should be encouraged in patients with PH to reduce deconditioning and improve patients' quality of life(75).

All patients with CTEPH should have lifelong anticoagulation(76). There is no strong evidence for anticoagulation in other forms of precapillary PH; however, it is important to note that in CTD–PAH anticoagulation may be harmful due to an increased bleeding risk and should only be commenced when there is a clear indication(77).

1.6.2 Pulmonary Arterial Vasodilator Therapy

Current pharmacological therapies target three distinct biological pathways: the nitric oxide, endothelin and prostanoid pathways, which are further elaborated on in Table 3. These therapies lead to pulmonary arterial vasodilation and thus a reduction in RV afterload, improving RV function and reducing RV dilation(78).

Pathway	Examples of medication	Administration	Example Dose
Nitric Oxide and cGMP pathway	Phosphodiesterase-5 inhibitors (PDE5i)		
	Sildenafil	Oral, IV	Three times daily – Variable dosing*
	Tadalafil	Oral	Once daily – 20mg, 40mg
	Soluble Guanylate Cyclase (sGC) activators		
	Riociguat	Oral	1mg – 2.5mg three times a day
Endothelin Receptor Antagonists (ERA)	Bosentan	Oral	62.5mg-125mg twice daily
	Macitentan		10mg once daily
	Ambrisentan		5-10mg once daily
Prostanoids and cAMP pathway	Iloprost	Nebulised, IV	10-20 micrograms seven times a day Continuous infusion
	Selexipag	Oral	200-1600 micrograms twice daily
	Treprostinil	Subcutaneous, IV, Inhaled	
	Epoprostenol	IV	Continuous infusion – starting at 2ng/kg/min and increased in intervals.
IV; Intravenous, mg; milligram, LFT; liver function test, ng; nanogram, kg; kilogram *The licenced dose of Sildenafil is 20mg three times a day yet unlicensed doses may be used including 25mg, 50mg, 75mg and 100mg three times a day.			

Table 3. Pulmonary artery vasodilators

Pulmonary arterial vasodilators are not suitable for all patients with PH. Multiple studies have shown no benefit or deterioration amongst Group II patients treated with pulmonary artery vasodilators(7). Patients with Group III PH may be given a trial of therapy, especially if the extent of pulmonary vascular diseases appears disproportionate to the extent of underlying respiratory disease, yet this is unlikely to be escalated beyond monotherapy, with withdrawal considered if there is no objective improvement following treatment initiation(50).

Therapy is considered in patients with CTEPH to reduce the peri-operative risk of pulmonary endarterectomy and as a bridge to surgery. Alternatively, in cases where patients are inoperable due to a predominantly distal-disease pattern, medical co-morbidities or declination by the patients, medical therapy is the only available treatment modality.

1.6.3 Interventional treatment

Patients with CTEPH should be referred for consideration of interventional treatment which, in the UK, is performed at the Royal Papworth Hospital in Cambridge. Surgical options include pulmonary endarterectomy (PEA) for proximal disease and balloon pulmonary angioplasty (BPA) for more distal or isolated-proximal disease, whilst medical-management will be the only suitable option for very distal disease(76). Whilst response to PEA can be excellent, it involves hypothermic circulatory arrest and carries a significant perioperative mortality risk of 2–5%(79).

1.6.4 Novel and Emerging Therapies

At the time of writing, no novel agents have been licensed for PH treatment since Selexipag was approved as a pulmonary vasodilator agent in 2015. However, there are multiple novel agents in early production and clinical trials that are promising and target different pathways than the three outlined above. Sotatercept is an anti-remodelling agent with a novel therapeutic approach as it acts as a BMPR2 ligand trap. When used as an adjunct to PH targeted therapy, Sotatercept may allow modification of the disease process, rather than targeting the downstream consequences as is the mechanism of all current licensed treatments(80). There is also increasing interest in the use of inhaled Treprostinil for patients with chronic lung disease(81).

1.7 Risk Stratification and Monitoring

1.7.1 Risk Stratification Models

Judgement of clinical deterioration and requirement for escalation of therapy in PH is based on risk stratification, which employs multiple investigation modalities, including the underlying clinical classification of PH, exercise capacity, WHO functional class, haemodynamic severity obtained at RHC, RV strain as assessed by NT-proBNP/BNP and imaging findings.

1.7.1.1 3-Strata Risk Assessment

The 2015 ERS/ESC guidelines advocate the use of a 3-strata risk assessment strategy, whereby patients are stratified one of 3 risk stratum including low- (<5% mortality at one year), intermediate- (5-10% risk) and high- risk (>10%) with the overarching goal of patients achieving a low risk status (Table 4)(40, 65).

Approach to implementation of the 3-strata system has varied. Investigators using the French registry investigated a method whereby the number of low risk parameters present are calculated at baseline and follow up and the risk of mortality was found to inversely correlate with the sum total(82). The COMPERA (“COMPERA 1.0”) and the SPAHR registry groups employ an integer score method, where a value of 1,2 or 3 is assigned to each variable and an average is calculated which designates overall risk (as shown in Appendix 12.5.1 3-Strata (2015))(83, 84). REVEAL investigators use a similar approach, incorporating several non-modifiable risk factors, to develop the REVEAL 2.0 and REVEAL 2.0 Lite risk stratification tools(85-87). These models have primarily been validated in Group I PAH, although some have been validated in a cohort of patients with CTEPH(88).

			Low Risk	Intermediate Risk	High Risk
		1 year mortality	<5%	5-10%	>10%
Test		Variable			
Clinical Assessment		Right heart failure	Absent	Absent	Present
		Symptom Progression	Stable	Slow	Rapid
		Syncope	None	Occasional	Repeated
		WHO FC	I or II	III	IV
Exercise Capacity	- Six Minute Walk Test	Six-minute Walk Distance (6MWD, m)	>440	165 – 440	<165
	- Cardiopulmonary Exercise Test	$VO2_{PEAK}$ (ml/min/kg)	>15	11-15	<11
		VE/VCO2 gradient	<36	36 - 44.9	≥45
Right Ventricular Strain	- Blood	NT-proBNP (pg/ml)	<300	300-1400	>1400
	- Echocardiogram	Right Atrial Area (cm^2)	<18	18 - 26	>26
		Pericardial Effusion	No	No / Minimal	Yes
Invasive haemodynamics - Right heart catheterisation		Right atrial pressure (mmHg)	<8	8-14	>14
		Cardiac Index ($L/min/m^2$)	≥2.5	2.0 – 2.4	<2.0
		SvO_2 (%)	>65	60-65	<60

Table 4. 3-Strata risk assessment tool including commonly assessed variables. Adapted from the 2015 ERS/ESC PH Guidelines.

1.7.1.1 4-Strata Risk Assessment

The 3-strata system has flaws; registry data has demonstrated that few patients achieve the aim of a low risk profile and the majority of patients are intermediate-risk, a therefore heterogeneous group, making it difficult to apply treatment intensification approaches in a uniform and personalized manner(82, 89). A 4-strata model (also referred to as "COMPERA 2.0") was therefore developed by the COMPERA investigators and validated using the French registry(90, 91). COMPERA 2.0 employs refined limits for the non-invasive variables of BNP and NT-proBNP, WHO FC and 6MWD and incorporates an additional stratum by further stratifying intermediate-risk into intermediate-high and

intermediate-low categories (Appendix 12.5.1 4-Strata)(90). When this model is applied, significant differences in overall survival have been demonstrated amongst patients with PAH and furthermore the 4-strata model was more sensitive at detecting clinical improvements, with a greater proportion of patients moving between risk groups(90, 91). The 4-strata model is recommended in the 2022 PH Guidelines as the risk stratification method to apply at follow up(90).

1.7.2 Risk Stratification at Follow Up

Following initiation of targeted pulmonary vasodilator therapy, the first follow up visit is crucial. A retrospective review of the SPAHR registry demonstrated that patients who achieved a low risk profile within 6 months of starting treatment had dramatically improved 5-year survival when compared to patients who remained at, or worsened to, an intermediate or high risk state. Thus, the extent of response to therapy at this stage allows determination of the overall long-term response and the first follow up visit should be used to guide early decisions on whether treatment should be escalated(84).

At SPVU, as advocated by WSPH and ERS/ESC guidelines, patients are seen at 3-6 months following diagnosis(40). The subsequent interval between appointments depends on risk stratification and may be between 3-12 months(40). Follow-up comprises of repeat assessment of the severity of pulmonary hypertension with the aim to repeat risk stratification. Whilst some European centres place an emphasis on regular invasive haemodynamic monitoring alongside non-invasive measurements, at SPVU the limited availability of right heart catheterisation and CPET means that follow-up largely consists of repeating non-invasive variables including WHO functional class, NT-proBNP, emPHasis-10, a 6MWT and physical examination. If a patient is felt to be clinically deteriorating or has an inadequate response to therapy, further investigation may be indicated which may take the form of a repeat CPET and/or CMRI with consideration given to repeat right heart catheterisation to elucidate the cause and severity.

1.7.3 Risk stratification guides therapy in PH

At baseline, the 6th WSPH and 2022 ERS/ESC guidelines advocate the 3-strata model to allocate initial pulmonary vasodilator treatment in patients with Group 1 PH(1). For patients classified without comorbidities, patients in low- and intermediate- risk stratum should be commenced on dual combination therapy; with two pulmonary vasodilator agents from the PDE5i and ERA class. High risk patients are treated with triple therapy, which may include parenteral prostanoid(1). A subset of patients with Group I PAH will show haemodynamic improvement with pulmonary vasoreactivity testing during RHC and should be treated with calcium channel blockers(65).

The 4-strata method is applied at follow up. The 2022 guidelines advocate the following treatment regimens (i) low risk patients should continue on the therapy initiated at diagnosis (baseline therapy), (ii) intermediate-low risk patients should be considered for the addition of an oral prostanoid or a switch from a PDE5i agent to Riociguat, (iii) intermediate-high and high risk patients should be considered for parenteral prostanoid(1, 92). Bilateral lung transplantation referral is considered at baseline and follow up for patients who do not respond to, or deteriorate whilst on, optimal therapy(65, 74). Atrial septostomy may be considered in patients who are felt to be deteriorating on maximal therapy, although is not commonly employed.

1.8 Telehealth in Pulmonary Hypertension

1.8.1 Challenges to Face-to-Face Clinics in PH

The SPVU is based in Glasgow yet covers a large geographical area. Patients undergoing review, particularly around times of diagnosis or treatment change, are required to frequently travel large distances, which incurs travel costs and may be difficult for elderly, unwell or frail patients. Snapshot measurements of certain clinical parameters, such as 6MWD, may lead to error given interval illnesses and inherent variability. In left sided heart failure, NT-proBNP/BNP measurement have been shown to demonstrate daily fluctuations and infrequent measurements may not reflect true cardiac strain(93). Encouraging lifestyle modification and anticipatory care planning are key components of managing pulmonary hypertension yet due to the time constraints of clinic appointments these issues may not always be addressed. Alternatives to the traditional clinic model may help to address these issues.

1.8.2 Impact of COVID on PH Management

The 2019 coronavirus disease (COVID19) pandemic led to the widespread disruption of pulmonary hypertension care in the UK. COVID19 was initially considered to be of high risk to patients with PH given the risk of COVID pneumonitis and venous thromboembolism. There were concerns at the outset of the pandemic that patients with PH who contracted COVID19 would suffer a higher morbidity and mortality than the background population(94), although more recent data has demonstrated that relatively few PH patients suffered severe COVID19 infection(95-97).

During the pandemic, patients with PH were advised to “shield”, effectively isolating patients from society. Data has demonstrated that PH patients avoided healthcare contact when it was offered due to the fear of contracting COVID19(98). The effects from shielding and other public health measures led to reduced daily activity, increased

anxiety and depression and a deterioration in quality of life among patients with PH(98, 99). PH physicians were reassigned to acute hospitals and the availability of investigations, such as echocardiography and right heart catheterisation, were reduced(100). Internationally, these factors led to a sharp reduction in the number of new PH diagnoses and of treatment escalation amongst patients(101, 102).

At the Scottish Pulmonary Vascular Unit, face-to-face contact with patients was severely limited. In February 2020 the SPVU discontinued all routine in-person outpatient appointments whilst a new model of virtual appointments, via telephone calls, was rapidly instigated. However, the outcomes from virtual clinics were reliant on patients giving accurate descriptions of symptoms, such as the extent of oedema, and were not informed by the results of objective investigations or clinical examination(101, 103).

1.8.2 Telehealth in PH

Telehealth broadly describes the use of technology to expand the management of and access to healthcare(104). The impact from the pandemic has led to a greater global interest in telehealth within PH, which prior to the COVID19 pandemic was rarely incorporated into the health delivery strategy of PH centres(105, 106). Despite the widespread use of telehealth in the clinical management of left heart failure, the current use within PH lies largely within the research domain and whilst multiple strategies have been suggested, there are few data to support their use in PH clinical settings(96, 105, 106).

In Chapter 2, the current evidence base of telehealth within pulmonary hypertension is reviewed using the scoping literature review methodology. This is used to explain knowledge gaps within this field in order to design and implement further research.

2. Scoping Literature Review

2.1 Introduction

As described in the Introduction, telehealth is an emerging field for the investigation and management of pulmonary hypertension (PH). Telehealth has the potential to improve the efficiency of current healthcare systems, by allowing a proportion of patients to be managed remotely in certain circumstances, rather than mandating a physical face-to-face visit for each assessment(104). Telemedicine may provide benefits such as reducing the burden of travel for patients, allowing remote ad hoc assessments, providing a broader potential for assessment outside of dictated clinic times and improving communication between patients and healthcare teams. At the conception of this thesis (August 2020) a literature review was performed, similar in scope to a review by GONZALEZ-GARCIA*(106)*, which revealed a limited number of low quality studies involving the use of telehealth within PH. However, this field has changed considerably in the last three to four years and this review is now outdated.

A re-review was planned in January 2023 with the aim of determining the breadth of the body of literature on telemedicine within pulmonary hypertension, to determine the focus of the existing literature and to identify key gaps in the knowledge base. To meet these aims, a scoping review was chosen, as opposed to a systematic review.

2.2 Methods

2.2.1 Eligibility Criteria

To meet the aim of the scoping review, a broad criterion was set. English language conference and journal articles that included any description of telehealth amongst adult patients with pulmonary hypertension were included (Table 5. PICOS Eligibility Criteria). There were no restrictions of gender, education status or ethnic background. Excluded articles formats included opinion articles, technology appraisals and excluded populations included the non-pulmonary hypertension population (such as left sided heart failure without pulmonary hypertension), paediatric populations (aged <18 years) and studies included as original research for this thesis. There was no limit on date of publication. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to structure the review(107).

P - Participants	Pulmonary hypertension, of any 2015 ERS/ESC classification(65), aged ≥18 years

I - Intervention	Any form of remote monitoring or telehealth
C - Control	Studies with and without control arms
O - Outcomes	Any outcome (depending on the format of the trial)
S – Study Designs	Any study format

Table 5. PICOS Eligibility Criteria

2.2.2 Search Strategy

Two databases, Medline 1946 to 20/01/2023 and EMBASE 1974 to 23/01/23, were searched on 23/Jan/23. Databases were searched using a combination of MeSH and unique keywords to identify all studies that included the use of telehealth in patients with pulmonary hypertension (Table 6. Search strategy). The search strategy was modified to suit keywords for both databases. Automatic removal of duplicates was performed followed by manual verification.

	Query	Keywords	Returned Results	
			EMBASE	Medline
1	Pulmonary Hypertension	pulmonary hypertension (MeSH, exploded term) OR pulmonary hypertension OR primary pulmonary hypertension OR pulmonary arterial hypertension OR idiopathic pulmonary hypertension OR idiopathic arterial pulmonary hypertension OR secondary pulmonary hypertension OR PAH OR PH	118550	60089
2	Telemedicine	telemedicine (MeSH, exploded term) OR telecommunication (MeSH, exploded term) OR telehealth (MeSH, exploded term) OR mobile phone (MeSH, exploded term) OR telephone (MeSH, exploded term) OR mobile application (MeSH, exploded term) OR app$ (open ended term) OR smartphone (MeSH, exploded term) OR wireless communication (MeSH, exploded term) OR mobile health application (MeSH, exploded term) OR text messaging (MeSH, exploded term) OR cellphone OR mobile device OR iphone OR android OR iOS OR eHealth OR remote	478653	339044

		OR teleconsul$ (open ended term) OR virtual OR wireless OR mHealth OR e-health OR m-health OR tele-medicine OR tele-health		
3	1 and 2		693	230
4	Automatic removal of duplicates from 3		738	

Table 6. Search strategy

2.2.3 Screening

All identified studies had an abstract and title screened for eligibility based on the inclusion criteria. Full text articles were assessed against the inclusion criteria to complete the screening process. Data were collected on the year of publication, journal, format of the study (article, abstract or letter), authorship, title, study population including the number of participants, the type of the intervention and main outcome(s).

2.2.4 Analysis

Due to the constraints of this scoping review, an appraisal of the study quality, risk of bias and evidence level was not performed. Studies were grouped according to the broad area of telemedicine being studied and were further stratified, where appropriate, according to the modality under investigation. In cases where both an abstract and a full text article had been published regarding the same study, both were included and combined in the synthesis. The synthesis included a brief overview of the studies in each area yet an in depth analysis was outside the remit of the scoping review.

2.3 Results

The search strategy resulted in 738 unique records, of which 683 were excluded based on the exclusion criteria, following review of the title and abstract (Figure 2). The full text of 68 articles were reviewed, of which 10 were excluded as they either studied a non-pulmonary hypertension population, did not study telemedicine or were works included as primary research as part of this thesis. Fifty-eight studies were thus included in this review of which 25 were peer-reviewed full text articles, three were research letters and 30 were conference abstracts (Tables 6-9, abbreviations available on page 15). The studies were categorized into five themes based on the form of

remote assessment: i. Exercise capacity, ii. Haemodynamic monitoring, iii. NT-proBNP, iv. Remote communication & Assessment and v. Physiotherapy & rehabilitation.

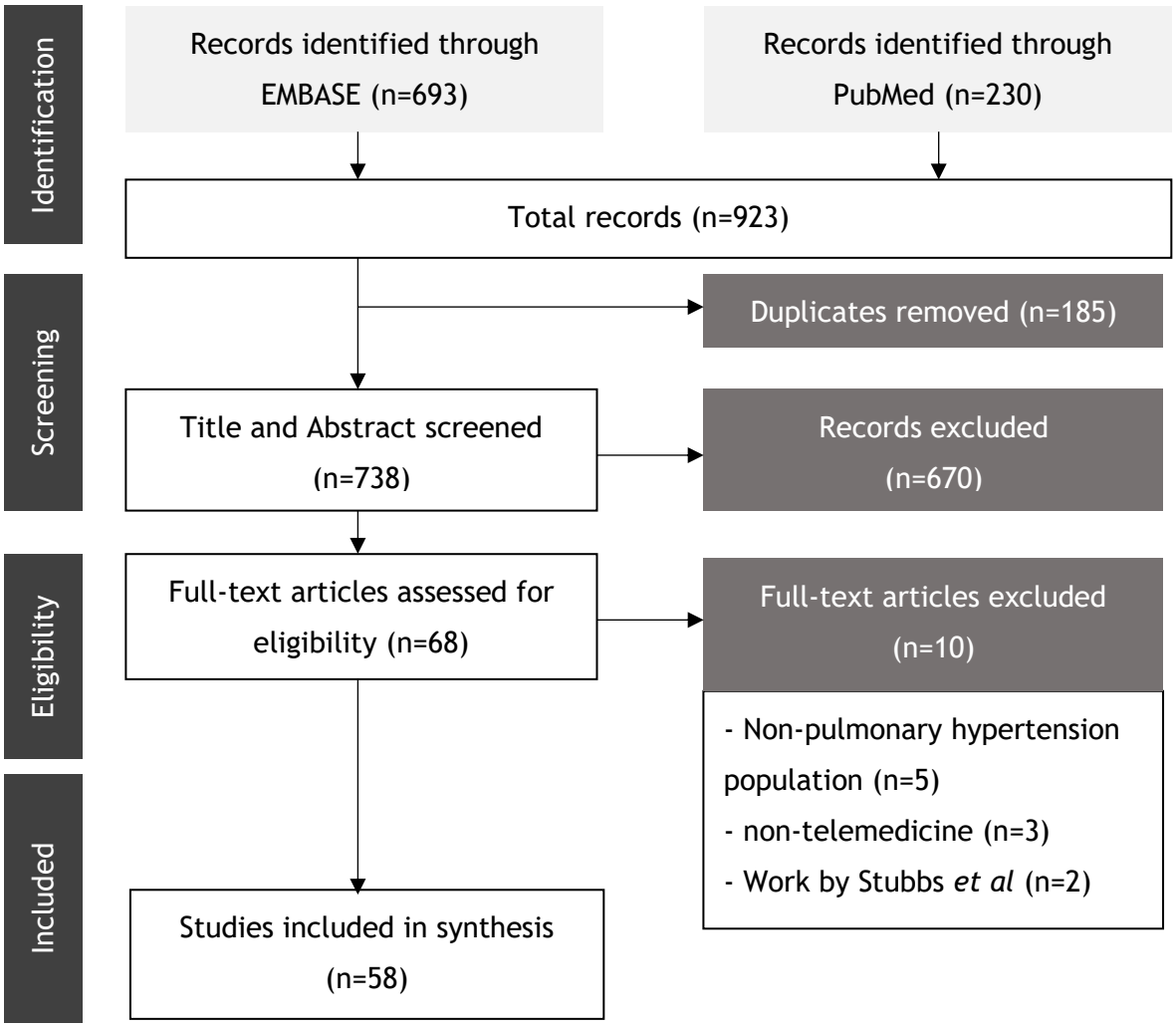


Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flowchart

Figure 3 demonstrates a histogram showing the year of publication of all studies included in the final synthesis. There were few articles studying telehealth in PH prior to 2011 with an increase in the number of publications per year from 2019 onwards.

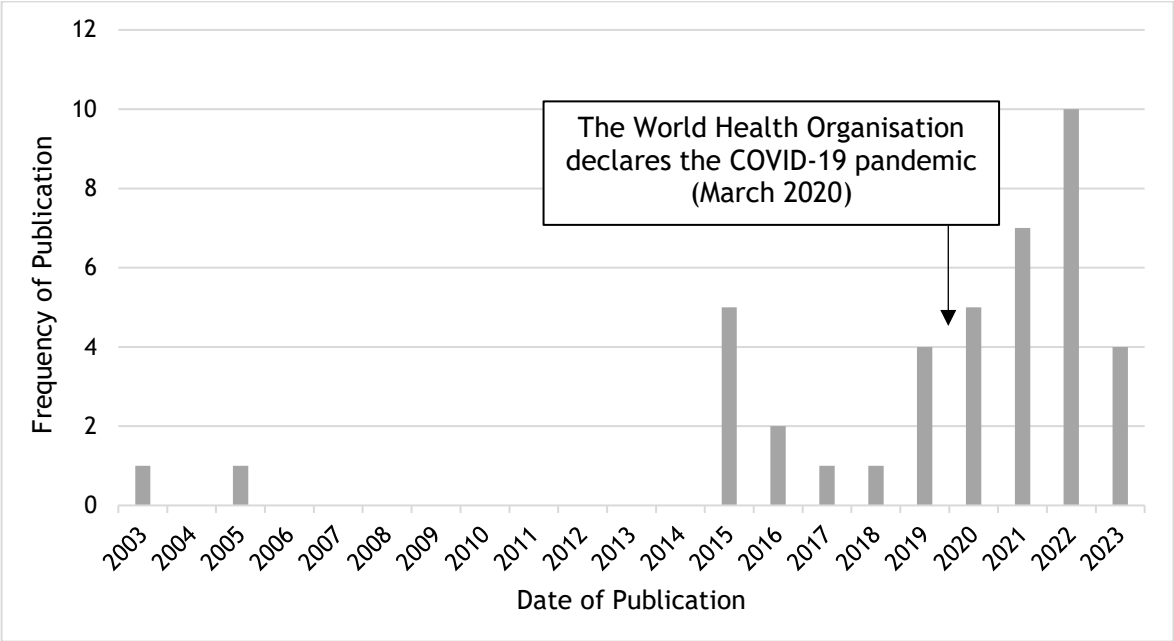


Figure 3. Histogram of the year of publication of telehealth studies in pulmonary hypertension.

2.3.1 Results Synthesis

2.3.1 Exercise Capacity

Several studies investigated the validity of telehealth alternatives to the current standard measures of exercise capacity in PH (Table 7), such as the six-minute walk test (6MWT) or the incremental shuttle walk test (ISWT). KEEN found that the 1-minute sit to stand test (STS) was safe in PH and results were moderately correlated with those of the ISWT (r=0.7)(108, 109). Studies by BROOKS, GLINSKII and SALVI investigated mobile application alternatives to the standard 6MWT which included apps such as *SA-6MWT* (which derives the 6MWD from step count), the *Timed Walk* app (which derives a 6MWD from GPS data when used outdoors) and *Walk.Talk.Track* app (which uses accelerometery data from an Apple Watch)(110-114). Together, these demonstrated good correlation (coefficients reported between 0.75-0.89) and agreement with standard 6MWT results and were felt to be feasible by users, with one self-limiting adverse event in the study by GLINSKII(110-114).

Accelerometery data was used to derive outcomes such as step count and cardiac effort in studies by LACHANT (using a chest strap), CASCINO, MARVIN-PEEK and MACKINNON (using a Fitbit), STOLLFUSS (using an Apple Watch), GREGORIETTI (using a digital pedometer) and SEGHAL(115-120). The outcomes were found to be associated with other prognostic markers in PH, such as hospitalization, step count and 6MWD. PATEL and PUGH investigated daily physical activity (minutes active per day) and step count, finding that lower daily physical activity was associated with a deterioration in prognostic markers

such as a lower 6MWD, and a worse NT-proBNP and WHO FC, with reasonable yet imperfect correlation between 6MWD and step counts (CASCINO r^2=0.51,PUGH r=0.72)(121, 122). HOWARD investigated a subanalysis of patients treated with Selexipag and found whilst the treatment arm had improved risk metrics (such as NT-proBNP and haemodynamic parameters), their step count (measured using an accelerometery device) decreased and the association with daily physical activity was unsatisfactory(123).

LAPATRA found that indoor and outdoor structured 6MWTs, where the outdoor test was remotely supervised, had comparable results(124). The number of steps during a symptom-limited step-test with oximetry testing was demonstrated by FOX to have a strong correlation (R=0.77) with standard 6MWD(125, 126).

Aspect Studied	Author (Article Format / Year / Reference)	Study Population	Intervention	Summary
Exercise Capacity				
1 minute sit to stand test	Keen (Article 2023(109); Abstract 2022(108))	75 patients with pulmonary arterial hypertension or CTEPH	Repetitions during a 1-minute Sit to stand test were compared to the distance walked during the standard Incremental Shuttle Walk Test (ISWT).	No adverse events. Moderate correlation between ISWT and 1MSTS (r=0.70).
Accelerometery Data	Lachant (Article 2022(115))	20 Patients with PAH	A chest accelerometer (BioStamp nPoint MC10) was worn during 6MWT. Remote 6MWTs were performed and compared to standard 6MWT. Cardiac effort (CE=6MWD/HR) was measured.	Accelerometery data correlated strongly with 6MWD (r=0.99). Remote 6MWD were shorter than standard 6MWT distance (mean -17m). No difference in CE during clinic and remote measurements.
Remote 6MWT	Brooks (Article 2015(113); Abstract 2014(112))	32 (phase 1) and 19 (phase 2) patients with heart failure and PH	6MWD calculated by smartphone app (SA-6MWTapp) compared to a standard 6MWT. A survey to patients regarding app usability.	Participants felt the SA-6MWTapp was simple and easy to use independently. Good correlation between distance measured in clinic (r=0.83) and at home (r=0.88) between SA-6MWTapp and standard 6MWT.
Remote 6MWT	Glinskii (Article 2021(114); Abstract 2021(127))	32 patients with PAH	6MWT app performed on an Apple watch at baseline and 3 months, performed indoors and outdoors, compared to standard 6MWT.	Mean difference between 5 - 8.5m indoor and 69m outdoors when using the app, compared with a standard 6MWT (ICC 0.77-0.8). One, self-limited, adverse event.
Remote 6MWT	LaPatra (Letter 2022(128), Abstract 2022(129), Abstract 2022(124))	29 patients with PAH and CTEPH	Standard 6MWT compared to a structured remoted 6MWT in an outdoor, remote location, chosen by participants. The remote 6MWT was supervised by video or audio call.	No clinically significant difference between remote and clinic 6MWD. Masked subjects had a lower 6MWD than unmasked subjects.
Remote 6MWT	Salvi (1. Article 2020(110); 2.	1. Healthy participants and 2 patients with	1. 6MWT calculated by smartphone app (Timed Walk) compared to a standard 6MWT. Discussion	1. Mean difference between Timed Walk 6MWT and standard 6MWD was -2.0m indoors and -

	Article 2021(111))	PH in discussion group. 2. 30 patients with PAH	group regarding the usability of the app. 2. 6MWT calculated by outdoor smartphone app (Timed Walk) compared to a standard 6MWT. Included remote 6MWTs tests performed in community. Survey of app usability.	0.8m, outdoors. The app was felt to be usable in the discussion group. 2. The Timed Walk app was sometimes inaccurate (Bland Altman analysis) with 14.6m mean difference and strong correlation (r=0.89). Community tests were repeatable (ICC 0.91). Timed Walk app was felt to be usable by patients with PAH.
Daily Physical Activity	Patel (Abstract 2023(121))	80 patients with PAH	Daily physical activity (measured by implantable cardiac monitor LinQ) was compared against the WHO FC, NT-proBNP and COMPERA 2.0 risk score.	Lower daily physical activity was related to a poorer WHO FC, NT-proBNP and risk score.
Daily Physical Activity	Pugh (Article 2012(122))	20 patients with PAH, 30 healthy controls	Monitoring of daily physical activity with accelerometery (ActiGraph GT3X).	Daily physical activity moderately correlated to 6MWD (r=0.72).
Daily Physical Activity / Step Count	Howard (Article 2023(123))	108 patients with WHO FC II/III on stable therapy	Change in baseline to week 24 in step count, daily physical activity and time spent performing activities in patients randomised to commence Selexipag or placebo, when monitored with an accelerometer.	No significant changes in daily physical activity. The daily step count reduced in both the treatment and placebo groups.
Step Count	Cascino (Letter 2019(116))	87 patients with pulmonary arterial hypertension	Comparison of 6MWD with step count measured by accelerometery (FitBit Zip).	Average daily step count was moderately associated with 6MWT (r2=0.51).
Step Count	Gregorietti (Abstract 2015(120))	162 patients with PH	A digital pedometer was integrated into a standard 6MWT and the step count was compared to prognostic markers (6MWD, WHO FC and NT-proBNP).	Step count during a standard 6MWT correlated with NT-proBNP and WHO FC.
Step Count	MacKinnon (Abstract 2020(118))	42 patients with PAH	Patients were monitored with a Fitbit Charge 3 and monitored for two weeks. Outcomes were standard 6MWD and TTE indices.	Daily step count was related to 6MWD, TAPSE, FAC and resting heart rate.
Step Count	Marvin-Peek (Letter 2021(130))	41 patients with pulmonary arterial hypertension	Step count, measured by Fitbit Charge 3 compared to time-to-event for hospitalisation.	A greater baseline step count was associated with a decreased risk of hospitalisation (HR 0.26).
Step Count / Daily Physical Activity	Sehgal (Article 2019(131))	20 patients with pulmonary arterial hypertension	Comparison of standard 6MWD with step count and daily physical activity measured by accelerometery.	Changes in step count and physical activity weakly correlate with changes in 6MWD (r=0.43) and health related quality of life.
Step Count / Daily Physical Activity / Remote 6MWT	Stollfuss (Article 2021(119))	18 patients with WHO FC III PAH who were being commenced on nebulised iloprost	Daily physical, step count, distance walked, HR and 6MWD with Apple Watch Series 2 and iPhone 6S) compared to standard 6MWD NT-proBNP and HRQoL.	Step count, physical activity and 6MWD improved following nebulised iloprost. Home monitoring was felt to be feasible.
Step Test	Fox (Article 2013(126); Abstract 2011(132))	86 patients with PAH or CTEPH	Step test, on a 17cm step with pulse oximetry until maximum exertion or 200 steps. Vertical elevation	Vertical elevation was associated with poorer WHO FC. Good correlation between vertical elevation

	during steps compared to markers of prognosis (NT-proBNP, TTE measures and DLCO).	and standard 6MWT (r=0.77). Moderate negative correlation between saturation deviation and DLCO (r=-0.49). Poor correlation with NT-proBNP or haemodynamic parameters.

Table 7. Summary of studies assessing telehealth using exercise capacity in pulmonary hypertension.

2.3.2 Remote Haemodynamic monitoring

Implantable haemodynamic monitors (IHM) are pressure sensors that are implanted into the pulmonary artery, allowing ambulatory monitoring of the mean pulmonary artery pressure (MPAP) and allowing derivation of the total pulmonary resistance (TPR). Results are downloaded through a wireless system and can be relayed back to the healthcare provider. Whilst predominantly studied in patients with left heart disease, several studies have demonstrated the applicability and feasibility of this technology in PH (Table 8). The CardioMEMs device have been the most extensively studied with studies by BENZA and BIEDERMAN demonstrating the safety of the device and its compatibility for use with cardiac MRI(133-137). Biederman demonstrated the potential for CardioMEMs to derive cardiac output (CO), although the formula to derive this is not yet commercially available(136, 137). Studies by AIRHART, BENZA, FRUHWALD and MIDDLETON have demonstrated the potential for IHMs to monitor haemodynamics during changes to PH therapy, in order to investigate the real time effects of treatment and improve the safety of remote treatment changes(134, 138-142). MIDDLETON demonstrated the ability of the device to detect changes in haemodynamic parameters prior to a clinical deterioration in a PAH population(141, 142) using a risk score that was developed to be used in conjunction with CardioMEMs(143). ASSMUS, BENZA and RAINA have demonstrated reduced hospitalization in intervention groups, where data from an implanted CardioMEMs device was used to guide heart failure therapy in a Group II PH population(144-147).

Other forms of haemodynamic monitoring have included investigations with a wireless cardiac impedance device by TONELLI, PANAGIOTU, LEE and ARELLI which were used to derive haemodynamic parameters(148-152).

Aspect Studied	Author (Article Format / Year / Reference)	Study Population	Intervention	Summary
Haemodynamic Monitoring				
Implantable Haemodynamic Monitor	Airhart (Article 2019(138); Abstract 2017(139))	3 patients with PAH, transitioning from IV prostanoid to oral preparation	Outpatient transition of therapy with haemodynamics monitored by a CardioMEMs device.	Outpatient transition from IV to oral prostanoids, as monitored using remote haemodynamics, was feasible.
Implantable Haemodynamic Monitor	Assmus (Article 2022(144))	74 patients with Group II PH and 31 healthy controls	Implantation of CardioMEMs device to guide therapy. Outcomes of quality of life, functional class and heart-failure hospitalisation.	Heart failure therapy as guided by CardioMEMs, reduced hospitalisations (HR 0.37 for CpcPH, 0.45 for IpCPH) and improved quality of life and NYHA class.
Implantable Haemodynamic Monitor	Benza (1. Abstract 2015(134); Abstract 2015(133); Abstract 2016(135): 2. Article 2019(153); Abstract 2015(147))	1. 6-11 patients with PAH with NYHA Class III/IV who have recently been hospitalised with RVF. 2. 314 patients with Group II Pulmonary Hypertension who were WHO FC Class III	1. Implantation of CardioMEMs followed by CMRI. 2. Outpatient medical therapy was guided based on data from an implanted CardioMEMs device implantation data vs unguided therapy with the outcome of hospitalisation.	1. The CardioMEMs device was safe. In one patient the data was used to titrate the dose of IV prostanoid. CardioMEMs was safely used in conjunction with CMRI and was used to calculate haemodynamic parameters. 2. 36% reduction in heart failure hospitalisation rate and a reduction in the composite end point of death and heart failure hospitalisation (HR 0.74) when the CardioMEMs was used to guide therapy. Not significant for effect on survival.
Implantable Haemodynamic Monitor	Biederman (Abstract 2015(136); Abstract 2019(137))	10 patients with PAH	Implantation of CardioMEMs and monitoring of haemodynamics as compared to CMRI indices.	CardioMEMs may be used to non-invasively calculate cardiac output, with similar good correlation to cardiac MRI (r=0.9). It was safe to perform.
Implantable Haemodynamic Monitor	Fruhwald (Article 2013(140))	5 patients with PAH	Insertion of Implantable Haemodynamic Monitor. Data monitored at the time of PAH patients being administered nebulised iloprost.	IHM was used to demonstrate the efficacy on the mean pulmonary artery pressure and therefore quantify the duration of effect of nebulised iloprost.
Implantable Haemodynamic Monitor	Middleton (Abstract 2022(141); Abstract 2023(142); Abstract 2022(143))	Risk score cohort; 3832 patients with PH. Targeted therapy cohort; 22 patients with WHO FC III PAH with a hospitalisation within the last year.	Retrospective analysis to identify prognostic remote risk parameters and develop a remote risk score. CardioMEMs data compared to prognostic markers after change in targeted therapy and to the 30 days preceding hospital admission.	ISWT, HR and TPR were related to mortality and were used to calculate a risk score. Patients who were started on therapy had an improvement in the remote risk score. The risk score deteriorated in keeping with other prognostic markers. In the targeted therapy group, MPAP and TPR was reduced following therapy change, in keeping with changes in NT-proBNP and WHO FC and these increased 10 days prior to a clinical worsening event.
Implantable Haemodynamic Monitor	Raina (Abstract 2014(145))	314 patients with Group II Pulmonary Hypertension who were WHO FC Class III	Outpatient medical therapy was based on data guided by CardioMEMs vs unguided therapy.	There was a lower hospitalisation rate in patients who had the CardioMEMs device implanted (HR 0.64).

			Outcome of hospitalisation rates.	
Wireless Cardiac Impedance Device	Panagiotou (Article 2017(152))	25 patients with PAH	Comparison of cardiac output as assessed by impedance cardiography (PhysioFlow) and measurement at RHC.	There was poor correlation between cardiac output as assessed by the PhysioFlow device and thermodilution cardiac output during RHC.
Wireless Cardiac Impedance Device	Lee (Abstract 2020(148))	37 patients with PH	A portable micro-sensor device (HEMOTAG) was used to analyse surrogate markers of intracardiac pressure, which was compared to measures at RHC	HEMOTAG was able to detect an elevated MPAP (sensitivity 81%, specificity 100%).
Wireless Cardiac Impedance Device	Arelli (Abstract 2012(151))	14 with PAH, 4 patients with Group III or IV PH	A portable Bluetooth wireless cardiac impedance to estimate HR, CO, CI and SV at rest and during a standard 6MWT.	Comparison of non-invasive haemodynamic parameters between rest and exercise when compared to changes in walk distance during 6MWT as measured by a wireless cardiac impedance device was significant.
Wireless Cardiac Impedance Device	Tonelli (Article 2014(150); Abstract 2013(149))	43-50 participants, 20-28 with PAH	Portable Bluetooth wireless impedance cardiograph was used to measure HR, CO, CI, SV during a standard 6MWT. HR slopes were calculated.	Patients with PH had lower distance walked, slower heart rate recovery and CO change than healthy controls during 6MWT when analysed using impedance cardiography. HR slopes were significantly steeper in PH compared to other patient groups.

Table 8. Summary of studies assessing telehealth using haemodynamic monitoring in pulmonary hypertension.

2.3.3 Remote NT-proBNP Measurement

Only one study investigated the use of telehealth with NT-proBNP. DURRINGTON investigated the use of a point-of-care device to measure NT-proBNP in 37 patients with PAH. Capillary samples were taken pre and post rest and exercise and a capillary sample was sent in the post to replicate remote monitoring. These samples were tested on an analyser that was purchased by the hospital and stored in a clinic room. There was good correlation between capillary and venous NT-proBNP samples (r^2=0.99), although the agreement was poorer for higher NT-proBNP results(154).

2.3.4 Remote Communication & Assessment

Studies investigating remote communication and assessment are shown in Table 9. MATURA analysed open discussion forums on the internet, finding that patients with PH were using the internet to seek healthcare advice. They identified recurrent themes within posts from participants which included concern, uncertainty, guidance, support and refocusing their life(155).

Several studies investigated the use of telephone calls and text messaging. TRICARICO demonstrated that patients undergoing regular telephone interviews regarding their PH symptoms had improved quality of life scores compared to patients undergoing standard care(156). HEMNES found that patients randomized to a thrice daily text message that encouraged physical activity over 12 weeks had higher average daily step counts (mean +1367 steps) yet did not improve their 6MWD at the study conclusion(157). TAICHMAN found that telephone neurocognitive testing was feasible with scores comparable to face to face testing(158). VADALA found that in a dedicated PH centre, a nursing model that incorporated telephone calls before and after a diagnostic admission was feasible and shortened the duration of the inpatient stay(159).

Telehealth treatment strategies were investigated. ZAMANANI presented a case where a vasoresponsive patient with PAH was treated with inhaled nitric oxide using a telemedicine approach. Clinical observations were taken by the patient and a care provider at home using standard pulse oximetry, blood pressure manometers and thermometers and relayed to clinicians remotely. A treatment plan including novel inhaled nitric oxide was established and couriers delivered equipment. Consultations were performed twice daily and progress was monitored with 6MWTs performed at home, quality of life questionnaires and an assessment of WHO functional class(160). CORRIS demonstrated the feasibility of a placebo sensor pill to monitor medicines adherence in patients with PAH, used to target patients with low adherence and escalate therapy in deteriorating patients who had good compliance(161). A protocol was presented by PÉREZ PEÑATE with the intention of studying a digital platform (PAHCareTM) which would allow patients to review their results remotely and receive communication from their healthcare provider, with a health related quality of life outcome(162).

Aspect Studied	Author (Article Format / Year / Reference)	Study Population	Intervention	Summary
Remote Communication & Assessment				
Internet Forum	Matura (Abstract 2013(155))	549 patients with PAH posting to an open internet discussion forum	Posts on an internet forum were analysed.	Patients with PH were using the internet to seek healthcare related information. Themes were identified surrounding concern, uncertainty, guidance, support and refocusing life.
Digital Platform	Pérez Peñate (Article – Protocol only - 2022(162))	50 patients with PAH.	Use of a digital platform (PAHCareTM), allowing patients to log health metrics and receive medication reminders and lifestyle/behavioural coaching. Primary outcome will be HRQoL.	Not applicable – protocol.

Remote Compliance	Corris (Article 2016(161))	21 patients with PAH	Coadministration of a sensor pill with usual medications used to monitor medication adherence and to guide therapy.	Digital feedback determined the cause of lack of response to treatment and allowed targeted escalation of therapy in patients despite good compliance.
Remote Management	Zamanian (Article 2020(160))	1 patient with PAH, infected with COVID19	Outpatient treatment with inhaled nitric oxide via homebased telehealth plan.	Feasibility of outpatient titration and monitoring of therapy with a telemedicine approach during an acute deterioration.
Telephone Calls	Tricarico (Abstract 2020(156))	33 patients with PH	Completion of a survey on activity levels and quality of life. Subsequent randomisation with those in the intervention arm given structured telephone calls at regular interviews regarding PH symptoms over 120 days.	Patients undergoing remote monitoring had improved quality of life scores.
Text Messaging	Hemnes (Article 2021(157))	42 patients with pulmonary arterial hypertensi on	Randomised to usual care or text message three times a day to encourage step counts.	Increase in step count within intervention group that received text reminders yet no difference in 6MWD at 12 weeks.
Telephone Calls	Taichman (Article 2005(158))	23 patients with PAH	Face-to-face neurocognitive testing compared to telephone testing.	Scores from telephone testing correlated with face-to-face testing. Remote neurocognitive testing was felt to be feasible in PAH.
Telephone Calls	Vadala (Abstract 2018(159))	386 patients with PH	Patients referred to a tertiary PH centre are contacted prior to diagnostic admission by a nurse specialist, who coordinates inpatient tests in a single day and follows up with telephone clinics.	A nursing model using regular telephone contact was felt to be feasible and shortened subsequent inpatient length of stay.

Table 9. Summary of studies assessing telehealth using remote communication & assessment in pulmonary hypertension.

2.3.5 Physiotherapy & rehabilitation

Studies investigating physiotherapy and rehabilitation are shown in Table 10. BUTĀNE developed a 12 week individually tailored home exercise physiotherapy programme. 21 patients with PAH were randomised to either a training or control group. Patients in the training group improved their 6MWD and quality of life scores at 12 weeks and 6 months following the programme(163-165). CHIA randomised 16 patients with PAH to a home rehabilitation programme or home walking exercise programme and found an improvement in cardiac MRI indices, quality of life scores and depression and anxiety for both programmes(166). MCCORMACK demonstrated that an intensive home based exercise programme improved 6MWD, body strength and step count in 19 patients with PH(167, 168).

Author (Article Format / Year / Reference)	Study Population	Intervention	Summary
Physiotherapy & Rehabilitation			
Butāne (Article 2022, Article 2022, Article 2022(163-165))	21 patients with PAH on stable PH therapy with half in a training group and half in a control group	The training group consisted of an individually tailored home physiotherapy programme for 12 weeks. Prognostic markers were compared at baseline, 12 weeks and 6 months.	6MWD, quality of life scores and daily physical activity increased in the training group after both 12 weeks and 6 months. Physical activity increased in the training group.
Chia (Abstract 2022(166))	16 patients with PAH	Patients were randomised to either 12 week outpatient rehabilitation or home walking exercise training. Outcomes were measured using CMRI, RHC and 6MWD.	In both cohorts there was an increase in SV, SVI, HRQoL. Depression and anxiety improved with exercise. Patients reported high satisfaction.
McCormack (Article – protocol only – 2021(167); Abstract 2022(168))	19 patients with patient with pulmonary hypertension	All participants participated in a10 week home exercise programme. Outcomes included 6MWD, activity levels, step count and body strength.	There were no adverse events. Activity levels increased after the programme with improvements in 6MWD and body strength.

Table 10. Summary of studies assessing telehealth using physiotherapy & rehabilitation in pulmonary hypertension.

2.4 Discussion

This scoping review gives an overview of the currently published evidence regarding telehealth within the field pulmonary hypertension. In general, telehealth was found to be safe, feasible and received positive feedback from patients. The first study investigating telehealth options in pulmonary hypertension was in 2003, yet as demonstrated in Figure 3, there was a paucity of studies in this area until 2011 with a significant rise in publications since 2019. This may have been further accelerated between 2020 to 2023, as the use of telemedicine grew in many disciplines following the COVID19 pandemic.

There were 22 studies that investigated the role of telehealth in exercise capacity assessment. The measurement of exercise capacity, traditionally performed during follow up using submaximal tests such as the 6MWT, is a key component of risk stratification in PH. Alternatives such as the step test, sit-to-stand test and remote 6MWT may allow remote quantification of exercise capacity. Step count was investigated yet was imperfectly correlated to 6MWD. Daily step counts appear to be modifiable in PH, yet as demonstrated by HOWARD, steps are a behavioural choice and rely on the combination of motivation and exercise capacity(123). Whilst these studies are promising, there are in relatively small patient groups and many of them only assessed tests at a single point in time, without assessment during follow up to assess whether the change in tests was concordant with the change in standard tests of exercise capacity.

IHMs were studied in 18 publications and with promising results especially regarding the early detection of clinical deterioration, raising the possibility of early intervention in order to prevent hospitalisation. The CardioMEMs device has been found to be safe, yet currently its use is limited by cost and due to the expertise required for implantation and the infrastructure required for data download and monitoring by healthcare teams.

Seven publications studied remote communication, including the use of text messaging and telephone calls to modify patient behaviour, although these predominantly were pilot studies with a small cohort of patients.

Six studies investigated the role of home rehabilitation, with promising results and improvement in haemodynamic end points, yet these require further validation in larger cohorts and no studies are yet available that demonstrate the longevity of such exercise programmes or the treatment effects.

Finally, one study investigated the use of point-of-care testing for NT-proBNP. Quantification of NT-proBNP is vital in risk stratification in PH as it provides a surrogate yet objective measure of RV function. Whilst this study had promising results, it used a device that was installed in a hospital and hence has lower use for remote assessment whereby patients could perform this unsupervised at home.

Overall, these studies raise the possibility for multiple future directions for telehealth within PH. However, this review highlights key gaps in the evidence in this field. Further studies may wish to concentrate on the validity of implementing a telehealth solution into routine practice on a longitudinal basis, to assess the feasibility of such a programme over time and to investigate the use of an electronic platform, whereby risk assessment using multiple modalities (e.g., exercise capacity, quality of life, results, communication) are incorporated onto a single platform for patients and clinicians to access.

This review has demonstrated the theoretical benefit of certain targeted telehealth approaches in PH, yet data regarding the feasibility of continuing these scenarios in a true telehealth setting are limited. Whilst the exercise capacity studies are a heterogeneous group, several include low patient numbers and evaluated tests at only one time point, limiting their external validity and ability to provide data on test re-test reliability. Only one study investigated the remote provision of NT-proBNP. Further studies in this field should aim to incorporate these features to allow a robust evidence-based platform on which to build a remote clinic.

2.5 Conclusion

This scoping literature review has provided an overview of the current evidence surrounding the use of telehealth within the field of pulmonary hypertension. Whilst research in this field appears to have accelerated since 2019, there remains a lack of high quality data with which PH-specific remote care could be structured upon. Further research is required to evaluate the feasibility and validity of these approaches over time, including when patients are evaluated at home. The synthesis from this review was used to design the studies included in Chapters 5 (Patient Paradigms in Telehealth for Pulmonary Hypertension), 6 (Remote Exercise Testing in Pulmonary Hypertension) and 7 (Sendaway capillary NT-proBNP testing in Pulmonary Hypertension).

3. Aims and Hypotheses

Risk stratification in pulmonary hypertension guides treatment decisions. Research into new medications and treatment efficacy often contains an assessment of how patients move between risk strata. The 2019 World Symposium and the 2022 European Guidelines placed an emphasis on the role of risk stratification, particularly on the importance of these tools in identifying and treating deteriorating patients.

As has been discussed, the COVID-19 pandemic led to difficulties in performing research internationally, with a pause to multiple trials and difficulties in acquiring ethical approval for non-COVID studies. Concentrating on risk stratification enabled the author to perform retrospective studies with previously collected clinical data and to investigate alternative approaches to traditional research, such as remote monitoring.

For these reasons, this thesis aims to further insight into risk stratification within the pulmonary hypertension population. The thesis is split into two broad themes and the aims and hypotheses of each theme are described below.

3.1 Remote Risk Assessment in Pulmonary Hypertension

As has been discussed in the Introduction, the standard follow-up of patients with PH involves repeated risk assessments, determined initially using a variety of non-invasive parameters. These include an assessment of exercise capacity, measurement of NT-proBNP, quality of life and WHO functional class assessment. As has been explored in the literature review, there is a paucity of evidence surrounding how these metrics could be measured and monitored in a virtual clinic setting, with few studies evaluating telemedicine measures with patients at home, or in a longitudinal setting. Hence, the first theme aims to explore how evidence-based telemedicine approaches could be utilised in assessing these variables in a virtual clinic. Thus, the following hypotheses are examined in separate studies.

1. Quality of life scores can be performed remotely by patients by completing an electronic form.
2. Alternative and simple exercise capacity tests have equal validity to the standard 6MWT and are feasible for patients to perform at home. Deterioration or improvement in exercise capacity, when measured by the 6MWT, will cause proportional changes to the results from these exercise tests.
3. Sendaway capillary NT-proBNP is feasible for patients to perform at home and has good agreement with standard venous NT-proBNP.

If these studies yield promising results, these techniques could then be combined to create a more robust and thus safer "virtual clinic". As demonstrated in Figure 4, the current virtual clinic model is bereft of several of these parameters. In an optimised virtual clinic, patients could provide information prior to a virtual appointment, with the results available in time for clinician contact. Having these results contemporaneously available at the time of a virtual clinic could enhance its utility by providing objective data ahead of clinic appointments. It may allow the chance to intervene sooner, reducing the need for arranging a series of standard tests following the clinic and therefore reduce treatment delays. Furthermore, a robust virtual clinic would incorporate the ability to add other data variables at a later date, such as wearable data (e.g., from watches or smartphones), health metrics (e.g., from Bluetooth enabled weighing scales) and could incorporate messaging functions.

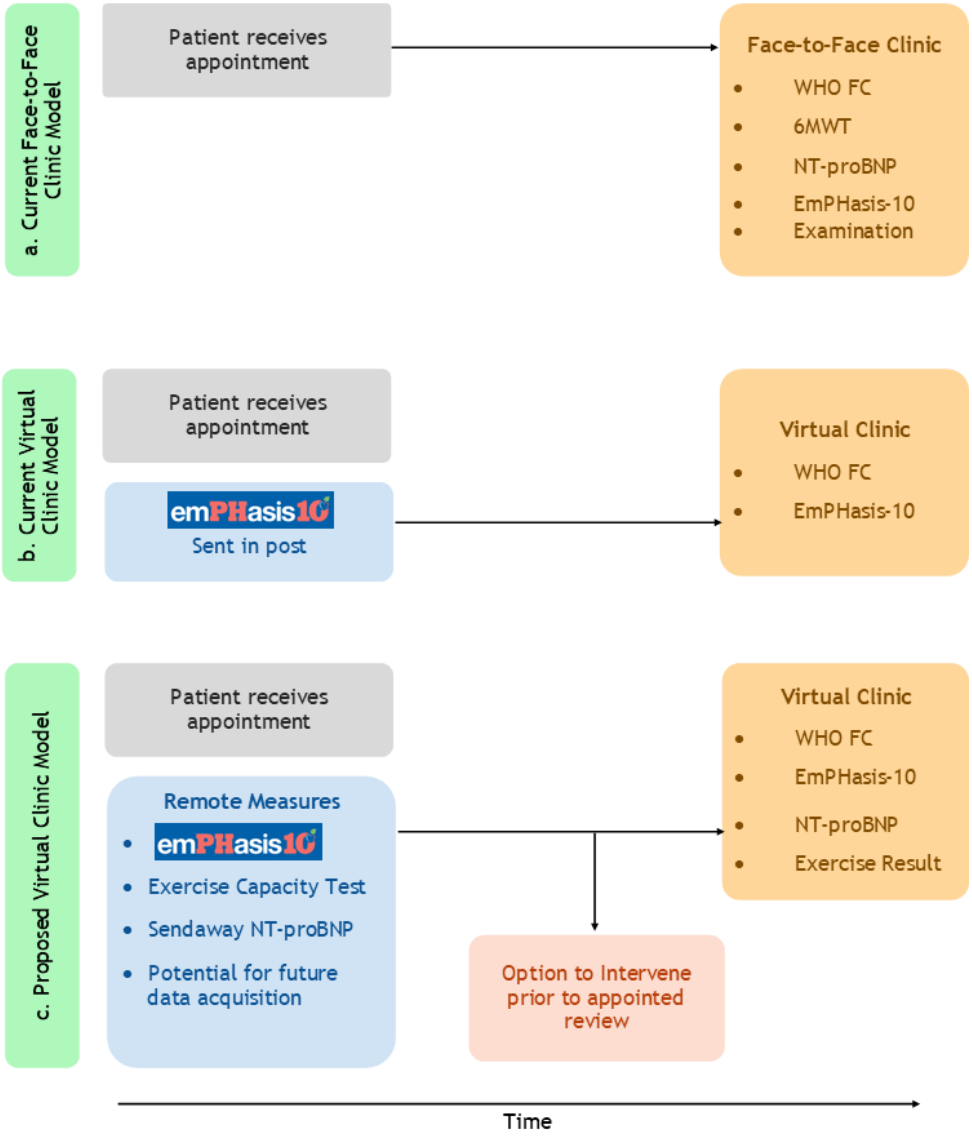


Figure 4. A) 2021 face-to-face clinic follow-up model for patients with pulmonary hypertension at the Scottish Pulmonary Vascular Unit, B) 2021 virtual clinic model and C) proposed virtual clinic model.

3.2 Risk Assessment Modelling in Pulmonary Hypertension

The second theme aims to gain further insight into the risk stratification models in pulmonary hypertension. In Chapter 8, the novel COMPERA 2.0 4-strata risk stratification model is further explored in a cohort of patients with CTEPH, raising the hypothesis;

1. The COMPERA 2.0 risk model is appliable in CTEPH and provides equal or superior performance to the COMPERA 1.0 model.

Current risk models incorporate WHO Functional Class as a measure of functional limitation. In Chapter 9, an alternative measure is incorporated into current risk stratifications models which aims to investigate the following;

2. The hypothesis is assessed that each scale of the MRC Dyspnoea Scale will confer a distinctive prognosis and estimation of survival and will provide equal or superior performance to WHO Functional Class.

The final study, in Chapter 10, deviates from the overall theme of risk stratification, but further concentrates on the evaluation of non-invasive models within PH;

3. The diagnostic accuracy of non-invasive pre-test scoring systems for postcapillary PH are assessed. The hypothesis is examined that the H2FPEF and the OPTICS scores provide sufficient specificity and sensitivity to confidently avoid the requirement of invasive diagnostic assessment.

4. Methods

This chapter will describe the clinical parameters and their testing methods used within this thesis. It will further focus on the statistical methods used in the subsequent chapters and the regulatory approvals for each study.

4.1 Thriva

Thriva Limited is a London-based privately-owned company that offers private blood analysis in the UK to both individuals and to community healthcare providers, such as general practitioners (GPs). Customers choose an array of tests and Thriva delivers capillary blood kits (Figure 5) through the postal service to customers home addresses. Upon receipt of a sample collection kit, participants use a lancet to pierce the skin of a finger-tip in order to draw 600µL of blood which is massaged into a capillary tube. The sample is posted back to Thriva and analysed, with the results released onto a password-protected online dashboard which consumers can access directly, or through their healthcare provider after the results have been vetted.

Figure 5. Thriva capillary blood kit demonstrating the lancets, blood collection tubes and return postal box.

4.2 Patient Assessment

4.2.1 World Health Organisation - Functional Class

The World Health Organisation (WHO) Functional Class (FC) has been derived for use in PH from the New York Heart Association (NYHA) classification for classifying the symptomatic limitation from heart failure (Table 11). It is well established for use in PH and changes in functional class have been found to be associated with the risk of mortality(65, 90, 92).

I	**No limitation of usual physical activity**. Ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain, or presyncope
II	**Mild limitation of physical activity**. No discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain, or presyncope.
III	**Marked limitation of physical activity**. There is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain, or presyncope.
IV	**Unable to perform any physical activity.** May have signs of right ventricular failure. Dyspnoea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

Table 11. World Health Organisation Functional Classification (WHO FC)

4.2.2 N-Terminal Prohormone Brain Natriuretic Peptide (NT-proBNP)

As has been discussed, NT-proBNP is a biomarker that is used in all current pulmonary hypertension risk assessment models. It was collected as part of the studies described in Chapters 6, 8, 9 and 10 and was the substrate under investigation for the work detailed in Chapter 7.

Standard venous measurement of NT-proBNP was performed with venepuncture after a period of 30 minutes rest. This was collected in vacutainers containing ethylenediaminetetraacetic acid (EDTA) and analysed at the biochemical laboratory at either the Golden Jubilee National Hospital (GJNH) or the Queen Elizabeth University Hospital (QEUH) in Glasgow.

4.2.3 emPHasis-10 Quality of Life Questionnaire

The emphasis-10 questionnaire (Appendix: 12.1 Form - emPHasis-10 Quality of Life Questionnaire) is comprised of 10 questions which ask patients to score the impact PH has on aspects of their life on an ordinal 0-5 scale(169). A higher score predicts a worse quality of life and has been shown to be a marker of survival in PH(71, 72). Patients were asked to complete the questionnaire at diagnosis and each follow-up assessment.

4.2.4 Six-Minute Walk Test (6MWT)

Six-minute walk tests were conducted at the Golden Jubilee National Hospital by respiratory physiologists in accordance with the American Thoracic Society (ATS) guidelines(170).

4.2.5 MRC Dyspnoea Scale

The Medical Research Council (MRC) Dyspnoea Scale was developed in 1952 to grade the effect of breathlessness upon daily activities and was revised in 1959(Table 12)(171, 172).

1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on level ground OR walking up a slight hill
3	Walks slower than contemporaries on level ground OR has to stop for breath when walking at own pace on the level
4	Stops for breath after walking about 100 yards (90m) OR after a few minutes on level ground
5	Too breathless to leave the house OR breathless when dressing or undressing.

Table 12. Adapted from the 1959 Medical Research Council (MRC) Dyspnoea Scale

The 1988 modified Medical Research Council (mMRC) dyspnoea scale made small changes to the wording and revised Scale 4 to include 100 metres rather than 100 yards(173).

4.3 Non-invasive prediction scores for Postcapillary Pulmonary Hypertension

Chapter 10 (*Non-invasive prediction of postcapillary pulmonary hypertension*) aims to externally validate two proposed non-invasive scoring systems: the H2FPEF(174) and the OPTICS(175) scores. The scores are expanded upon further in the relevant chapter and their constituent components are presented below.

4.3.0.1 H2FPEF Score

	Variable	Value	Points
H_2	**H**eavy	Body Mass Index >30 kg/m^2	2
	Hypertensive	≥2 anti-hypertensive agents	1
F	Atrial **F**ibrillation	Paroxysmal or Persistent	3
P	**P**ulmonary Hypertension	Echocardiographic Pulmonary Artery Systolic Pressure estimated >35 mmHg	1
E	**E**lder	Age > 60 years	1
F	**F**iling Pressure	Echocardiographic E/e' > 9	1

Table 13. H2FPEF Score components. A score of ≥6 is considered positive, thus predicting the patients has heart failure with preserved ejection fraction.

4.3.0.2 OPTICS Score

Variable	Value	Points
Obesity	Body Mass Index >30 kg/m^2	22
Diabetes Mellitus	T1DM or T2DM	26
Atrial Fibrillation	Paroxysmal or Persistent	21
Dyslipidaemia	Total cholesterol > 5 mmol/L *and/or* HDL-C <1 mmol/L *and/or* LDL-C >3 mmol/L	17
Valvular Surgery	Mitral or aortic valve repair with less-than mild residual left valvular disease on echocardiography	56
Electrocardiogram	Sum of S wave in V1 and R wave in V6	1x [SV1 + RV6]
Left atrial dilation	Left atrial volume > 34 ml/m^2	21

Table 14. OPTICS Score components. A score of ≥104 is considered positive thus predicting the patient has postcapillary pulmonary hypertension.

4.4 Alternative Submaximal Exercise Tests

The following aerobic exercise capacity tests are not commonly employed for use in pulmonary hypertension risk assessment. These were investigated in the questionnaire in Chapter 5. For the study in Chapter 6, written explanations of each were provided to participants, which they could use at a later date as a reminder (Appendix 12.2 Instructions - Explanation of Remote Exercise Tests for Participants). At the first visit, the Sit-to-Stand test, Timed Up and Go test and Step Test were performed in a patient room on Ward 3 East at the GJNH as supervised by Harrison Stubbs. A minimum of five minutes was allocated between each time, in order to allow for recovery. Participants were instructed to terminate the test if they felt unwell or experienced presyncope or chest pain. At subsequent visits, participants were asked to repeat these tests at home; they did not require to be supervised but could use assistance if they felt it was necessary.

4.4.1 1-minute Sit-to-Stand Test (STS)

Results from the Sit-to-Stand test have been shown to correlate with functional class, skeletal muscle strength, daily physical activity and exercise capacity in patients with PH. Previous work has demonstrated excellent test re-test reliability (intraclass correlation coefficient (ICC) 0.95 (95%CI 0.90-0.97)(176).

In order to perform the test, participants begin seated in a straight-backed chair with a hard, flat seat and no arm rests. Participants are instructed to fully stand-up and sit-down as frequently as possible within one minute, whilst their arms are crossed across their chest. One repetition was recorded after they resumed a sitting position.

4.4.2 Timed Up and Go Test (TUG)

The Timed Up and Go (TUG) test has also been demonstrated to have excellent reliability with an ICC of 0.96 (95%CI 0.93-0.98) and outcomes correlate well with other measures of functional limitation and exercise capacity in PH(176, 177).

Participants begin in the seated position in a straight-backed chair. 3 metres was measured outwards from forward portion of the chair. After commencement of a stopwatch, participants walk at a brisk pace to the 3-metre line, turn 180 degrees and return to the sitting position, at which point the timer would stop.

4.4.3 2-minute Step Test (ST)

The Step Test (ST) results correlate well with WHO functional class and 6MWD(126, 132) and it has excellent reliability when measured in other chronic respiratory diseases(178).

Participants begin the test by standing in front of a 15cm exercise step (*Fitness Step, Denny Enterprises Intl Ltd, Irvine, Scotland*) and their baseline heart rate and oxygen saturations were recorded with a pulse oximeter (*PO6L, Kinetik Wellbeing, Tianjun, China*). After commencement of a timer, participants step with both feet in turn onto the step and then back onto the floor, with one step recorded after both feet returned to the ground. The number of steps within two minutes are recorded and HR and SpO_2 are measured immediately upon termination of the test. Participants are given the pulse oximeter and step to use for home testing if they did not already own these.

4.4.4 Tele Six-Minute Walk Test (T6MWT)

The initial Tele Six-Minute Walk Test was performed outside on an area of flat ground beside the River Clyde at GJNH and supervised by the author and an additional member of staff. Patients are given instructions on how to download the free mobile phone application “Timed Walk” (*version 0.2, University of Malmo, Sweeden*) on the iOS Apple App Store or the Android Google Play Store(110, 111). Participants are taken outside using a wheelchair and their baseline oxygen saturations and heart rate are monitored using a pulse oximeter. To commence the test, participants set the application timer to six minutes and pressed start, allowing the location of the mobile phone to be monitored through global positioning satellites (GPS). The application instructs the participant to commence walking and gives a verbal indication of the time remaining at each minute. Participants are instructed to remain nearby the supervisors in the event of an adverse incident. The application terminates the test at six minutes and uses vector displacement from GPS to calculate the total distance walked, which is displayed in the application and saved in its memory with a time and date stamp. SpO_2 and HR are immediately recorded upon test termination and participants are returned to a hospital room using a wheelchair. Participants are given a pulse oximeter to use for home testing if they did not own one. The clinimetric properties of the T6MWT using the *Timed Walk* app are discussed in the Literature Review.

4.5 Scottish Index of Multiple Deprivation

The Scottish Index of Multiple Deprivation (SIMD) was developed by the Scottish Government to allow a geographical assessment of social deprivation in Scotland. It

encompasses the eight domains of income, employment, health, education, skills and training, geographical access to services, crime and housing. The data from these domains combine to form a composite rank from 1 (most deprived) to 6976 (least deprived) based on individual UK postcode areas. Ranks are split into vigintiles with the first vigintile incorporating the most deprived 5% of Scotland. At the timing of the work in Chapter 5, the most recent SIMD update was published on 28/Jan/2020.

4.6 Statistical Analysis

Data and statistical analyses within this thesis were performed using the following software packages; Microsoft Excel (version 2201 for Windows, Microsoft Corp, Redmond, Washington, USA), GraphPad Prism (version 9.3.0 for Windows, GraphPad Software, San Diego, California, USA), IBM SPSS (version 28.0 for Windows, IBM Corp, Armonk, New York, USA) and MedCalc (version 22.014 for Windows, MedCalc Software Ltd, Ostend, Belgium). Significance was set at the $p<0.05$ level for all analyses. Continuous data are presented as mean ± standard deviation, median (interquartile range, IQR) or number (percentage %) unless otherwise stated. Unpaired-t tests and x^2 tests were used to calculate differences between patient groups for continuous and categorical variables respectively. The Shapiro-Wilk test was used to assess the normality of data, where a significant value is obtained when data is non-parametrically distributed.

4.6.1 Survival Analysis

Survival analysis was performed for the work detailed in Chapters 8 and 9.

4.6.1.1 Kaplan-Meier Analysis

Kaplan-Meier analysis was used to assess survival of overall cohorts, to produce survival curves and thus to compare survival between groups. Survival was estimated from the point of diagnosis to the point of an event or right-censoring. The log rank test compared the survival distributions between groups.

4.6.1.2 Cox Proportional Hazard Regression

Cox proportional hazards ratios (HR) were used to assess the risk of a hazard in relation to a reference standard. Harrell's C Statistic was used to assess the goodness-of-fit for survival models, where a value of 0 indicates the model performs poorer than random chance and a value of 1 indicates perfect prediction(179). The Akaike Information Criteria (AIC) was further used to the complexity of the Cox models, where more compel models are penalised and thus a higher figure represents an overfitted model. Models compared with an AIC require the same number of participants, and therefore

this method was not used for comparing the performance of models between baseline and follow up, where participant numbers differed.

4.6.2 Diagnostic Accuracy Analysis

In Chapter 10, diagnosis accuracy analysis was performed. The diagnostic accuracy, i.e., the validity, of a model was evaluated by calculating the true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN) from the model when compared to the gold standard. The characteristics of a model were evaluated by calculating sensitivity (TP/TP+FN) and specificity (TN/TN+FP). The clinical relevance of the model was evaluated with the positive predictive value (PPV; TP/TP+FP) and negative predictive value (NPV; TN/TN+FN). Overall accuracy was calculated as (TP+TN)/(TP+FP+FN+TN). Receiver-operating characteristic (ROC) analysis was used to display an overall assessment of quality of the model. ROC curves were constructed by plotting sensitivity against 1-specificity. The discriminatory power of different models was determined by calculating the area under the curve (AUC). An AUC of 0.5 indicates that a model has no discriminatory power whereas an AUC of 1 indicates perfect discriminatory power.

4.6.3 Method Comparison

In Chapters 6 and 7, the concepts of method agreement and correlation were employed.

4.6.3.1 Bland-Altman Analysis

Agreement using Bland-Altman analysis was performed when two tests measured the same continuous variable. This analysis allows calculation of the mean difference between test results, allowing an assessment of test accuracy, known as the mean bias. 95% limits of agreement between two tests methods are calculated and allow an assessment of test precision, i.e. the maximum systematic error of the test, and these are represented using a Bland-Altman plot(180), where the x axis demonstrates the mean difference between data and the y axis demonstrates the absolute difference.

4.6.3.2 Correlation

Correlation was calculated when two tests measured different continuous variables, in order to assess the degree to which the variables are linearly related. The Pearson's Correlation Coefficient was used for parametric data and the Spearman's Correlation Coefficient for monotonic data(181). The correlation coefficient (r) ranged from -1 to 1 where -1 represents a perfect negative association, 0 represents no association and +1 represents a perfect positive association. For both positive and negative associations an r of 0.01-0.2 was considered very weak, 0.2-0.4 was considered weak, 0.4-0.6 was

considered moderate, 0.6-0.8 was considered strong and 0.8-0.99 was considered very strong.

4.6.3.3 Passing-Bablok Regression

Passing-Bablok methodology is a form of non-parametric linear regression, using ordinary least square regression, that is not sensitive to outliers and does not assume that errors are normally distributed. Hence, this provides an assessment of whether two non-parametric methods assessing the same variable are equivalent and the extent to which they agree (i.e. the bias)(182). Results are presented using a scatter diagram and regression line. The regression equation includes an intercept and a slope. 95% confidence intervals explain whether the intercept crosses the ideal of 0 and the slope crosses the ideal of 1, which if they do allow confirmation of method agreement.

4.6.3.4 Percentage Difference Plot

A percentage difference plot is a form of Bland-Altman analysis, whereby the y axis is replaced with the relative difference (%) between two methods, as opposed to the absolute difference. This provides more utility in measuring non-parametric outcomes.

4.7 Regulatory Approval

All clinical studies conducted in this thesis were reviewed and approved by a UK-based research ethics committee (REC) aside from the questionnaire described in Chapter 5, which did not require formal ethical approval. Table 15 demonstrates the details of each approval.

Chapter	IRAS Study Title	Date	Approving REC	IRAS ID	REC Reference
6	Feasibility and validity of remote exercise testing in patients with pulmonary hypertension.	28/July/2021	South Central - Oxford A	293065	21/SC/0083
7	Assessing the utility of capillary sendaway NT-proBNP in pulmonary hypertension across the UK.	15/Feb/2022	London - Fulham	299472	22/LO/0097
8	Validation of a novel 4-strata risk assessment strategy in medically-managed chronic thromboembolic pulmonary hypertension.	21/Jan/2022	London - Riverside	307471	21/PR/1607
9	MRC Dyspnoea risk stratification in pulmonary hypertension	04/Oct/2022	West of Scotland REC 5	313175	22/WS/0149
10	Validation of the OPTICS and H2FPEF scores for the non-invasive prediction of post-capillary pulmonary hypertension.	15/July/2021	East of Scotland	294965	21/ES/0078

Table 15. Regulatory approvals

Remote Risk Assessment in Pulmonary Hypertension

Chapters

5. Patient Paradigms in Telehealth for Pulmonary Hypertension

5.1 Introduction

As discussed in the Aims, it would be beneficial to develop a robust outpatient telemedicine strategy for pulmonary hypertension (PH). The scoping literature review demonstrated a paucity of evidence within this field and highlighted evidence gaps surrounding the implementation of a telemedicine approach into clinical practice, with patients at home. The aim of the work in this chapter was to identify barriers to the remote assessment of patients and inform the feasibility of such interventions.

Firstly, a questionnaire was developed and distributed among patients with pulmonary hypertension with the aim of assessing the acceptability of home exercise testing and the barriers patients perceived to the individual tests. This data was used to inform whether further study of such tests is reasonable and which types of exercise test to incorporate into future studies. The frailty status of the pulmonary hypertension population will determinate how safe and practical it would be to perform such tests at home and this will be assessed in the questionnaire. Home tests may be administered using a smartphone and so data on smartphone usage and internet access was collected.

Secondly, a review of the social deprivation status of patients with pulmonary hypertension in Scotland was performed. Remote monitoring is often performed using technology, such as wearable devices, smartphones and electronic forms accessed using the internet. The aim was to evaluate social deprivation across the PH population to challenge the assumption that high levels of deprivation may have an impact on the access to such devices.

Thirdly, the feasibility of remote quality of life assessment was assessed by evaluating the performance of an electronic data collection tool. As explained in Chapter 4.2.3, the emphasis-10 score is commonly used in the UK as a patient reported outcome measure and is collected at each patient visit for patients with PH(72). In routine practice, during face-to-face appointments, patients are asked to complete a paper questionnaire (Appendix 12.1) whilst in the clinic waiting room and the score is recorded and available to the team in time for the consultation. Whilst this is efficient, it can lead to emotional distress as patients are required to contemplate emotional and stressful events in a public area. It was anecdotally noted at SPVU that patients were particularly emotionally distressed by the 10th statement on the emPHasis-10 questionnaire which states “I feel like a burden”. In current practice at SPVU, patients

with PH attending virtual follow-up clinics are sent the emPHasis-10 form a few weeks prior to their appointment. The culminative tally is then taken at the time of a telephone consultation. Over the 2021 period, the proportion of obtained emPHasis-10 scores from virtual consultations was only 17% and this low uptake may be due to a combination of factors such as forms not being sent, not being received, clinicians forgetting to ask for results and patients not completing the form. A feasibility study was performed to assess whether the emPHasis-10 form could be completed electronically by patients at home. If this was feasible it would allow forms to be completed *ad hoc*, reduce the administration and environmental costs of posting paper copies and would allow the form to be completed in private. The primary aim of this feasibility study was to trial electronic completion of emphasis-10 for PH patients, which in turn may improve the response rate for quality-of-life measures for patients attending virtual consultations.

5.2 Methods

The study was conducted within the Scottish Pulmonary Vascular Unit (SPVU), a tertiary referral and treatment centre for all patients with PH in Scotland, as has been described in 1.5.4 UK and Ireland Pulmonary Hypertension Centres. As the data collected here was anonymised and due to the service evaluation nature of this work, ethical approval was not required.

5.2.1 Questionnaire

A self-completed questionnaire was distributed in the mail to all patients with pulmonary hypertension who were receiving treatment at the Scottish Pulmonary Vascular Unit over a 4-week period in November 2020. Figure 6 demonstrates the format of the questionnaire and the questions included. There were two sections in this questionnaire. In the first section, patients were given brief textual information on four submaximal exercise tests, including a single diagram for each test (as shown in *Appendix 12.2 Instructions - Explanation of Remote Exercise Tests* for Participants). Patients were questioned on how willing they would be to perform these tests in and around their home and how feasible they believed this would be. The was comprised of questions regarding patient's current technology use, mobility and perceived walk distance. Patient identifiable information was not collected in order to improve the response rate and remove the necessity for patient consent. No reminders were sent and the questionnaires were not discussed separately in clinics.

The questionnaire was designed with best practice elements in order to maximise the response rate and the utility of responses. This included the use of psychometric Likert

scale answers, straightforward wording with the avoidance of double-negatives, the use of at least five options per response, equal spacing between responses and approaching one concept at a time. Furthermore, the questionnaire was paper-based in order to improve the response rate amongst participants who were less computer- or internet-literate, which is vital given the questionnaire has a focus on ascertaining computer literacy and smart device ownership. Pre-paid return envelopes were used in a further attempt to improve the response rate.

Free-text comments were collated and categorized into subcategories. These were analysed using thematic analysis in the results and discussion section.

Your Opinions on Exercise Testing at Home

Thank you for completing this questionnaire. It should take about 10-15 minutes to complete.

On page 4 (*Appendix 12.2 Instructions - Explanation of Remote Exercise Tests* for Participants) you will find the details of four short exercise tests.
In the future you may be asked to do one of these at home just before a telephone clinic. This would be at most once or twice a year.

For each of these tests we will ask you a few questions about how you would feel about doing them.

TEST 1: TIMED UP AND GO TEST
Please read the details for this test on page 4.

1. Do you think you would be able to perform this **at home**? (*Circle one)*

   Yes / No
   If no, why not?
   …….

2. Is there anything that would worry you about doing this test **at home**? *(Tick any)*

   □ I don't have any worries about performing this test at home
   □ I'm worried I may fall
   □ I'm worried it might make me feel unwell
   □ I'm worried I wouldn't be able to finish the test
   Other (please specify)……

3. How happy would you be to take this exercise test **at home**? *(Circle one)*

   Very Happy Happy I wouldn't mind Unhappy Very Unhappy

NB: Questions 1 to 3 were then repeated for the remaining three tests: the Step Test, the Sit to Stand test and the Tele-Six Minute Walk Test.

WHAT ARE YOU CURRENTLY LIKE AT HOME?

1. How often do you go out of your home and garden (*Circle one)*
   - Every day
   - Not every day but more than once per week
   - Not every week but more than once per month
   - Less than once per month

2. How far do you think you can walk on the flat without having to stop?
   (You can answer in metres, yards, or whatever suits you, just let us know which)

   How far:
   ……
   □ I can't walk

3. When you walk **indoors**, how often do you use a walking aid? (*Circle one)*
   □ Every time I walk
   □ A lot
   □ A moderate amount
   □ A little
   □ I don't use a walking aid

4. When you walk **outdoors**, how often do you use a walking aid? (*Circle one)*
   □ Every time I walk
   □ A lot
   □ A moderate amount
   □ A little
   □ I don't use a walking aid

5. How often do you use oxygen when you are **inside** your home? (*Circle one)*
   □ All the time
   □ A lot
   □ A moderate amount
   □ A little
   □ I don't use oxygen inside

6. How often do you use oxygen when you are **outside** your home? (*Circle one)*
   □ All the time
   □ A lot
   □ A moderate amount
   □ A little
   □ I don't use oxygen outside

7. What type of mobile phone do you use? (*Circle one)*
   □ I don't use a mobile phone
   □ A basic mobile phone (not a smartphone)
   □ iPhone
   □ Android
   □ A different type of smartphone
   □ I don't know

8. Do you use a pulse oximeter at home?
   (This is a finger probe which measures the levels of oxygen in your blood)
   Yes / No

Thank you for filling in this questionnaire. It will make a difference to how we plan our service in the future. If you have any questions, please get in touch on 01421 951 5497 or spvunit@gjnh.scot.nhs.uk.

Figure 6. Questionnaire assessing patients' opinions of remote exercise testing, current technology use and baseline mobility.

5.2.2 Social Deprivation Index

All patients who underwent right heart catheterisation with pulmonary hypertension between 2010 and 2020 were included. Postcode data was taken from the date of diagnosis and were truncated to the first three digits, allowing anonymization of patient records. These three-digit postcodes were analysed by the 2020 Scottish Index of Multiple Deprivation (SIMD) database.

5.2.3 Remote Quality of Life Assessment

An electronic emPHasis-10 form was created using Google Forms (*Google, Alphabet Incorporated, California, United States*), a free online tool that enables results to be uploaded to a live spreadsheet. To our knowledge, this is the first time a virtual version of this form has been employed. The form content was identical to the paper emPHasis-10 and included the same questions and response options.

5.2.3.1 Pilot

In order to assess the accessibility and usability of the form, it was initially trialled in a face-to-face clinic. A brief set of instructions (Appendix 12.5), including a quick response (QR) code and an internet-address to the Google Form, was given to all the patients attending a face-to-face clinic in January 2022 and the number of responses appropriately recorded on the spreadsheet was counted.

5.2.3.2 Feasibility

The process for roll out of a remote electronic emphasis-10 form is described below. In March 2022, an annual mailshot was sent to all patients on the SPVU register who were receiving pulmonary vasodilator therapy. In addition to general information about SPVU and PH advice, this asked patients to complete an electronic emPHasis-10 and included a single A4 instruction sheet (Appendix 12.5). A paper copy of the E-10 was included for patients who were unable to complete this electronically. If patients were unable to complete the form electronically, they were asked to report their cumulative result back using telephone, post or email. The response rate for the electronic and paper method was collected. Results from the electronic form were automatically stored on a secure spreadsheet and the total score was automatically calculated.

As this was a pilot study and incorporated into a mailshot, patient details were not recorded. When using the electronic form, patients were asked to input a unique 3-digit code they were provided with and no other patient identifiable data was collected.

5.3 Results

5.3.1 Questionnaire Results

Questionnaires were distributed to 460 patients who were identified as receiving treatment at the SPVU. Responses were received from 189 patients (response rate 41%).

5.3.1.1 Technology Use

Figure 7 demonstrates smartphone usage. 121 (68%) patients owned a smartphone, of which 69 (57%) used an Apple iPhone and 52 (43%) used an Android device. 41 (23%) patients used a mobile phone that did not have internet access. 12 patients (7%) did not use any form of mobile phone. 76 (43%) patients were in possession of a pulse oximeter. 30% of patients did use an internet-enabled phone.

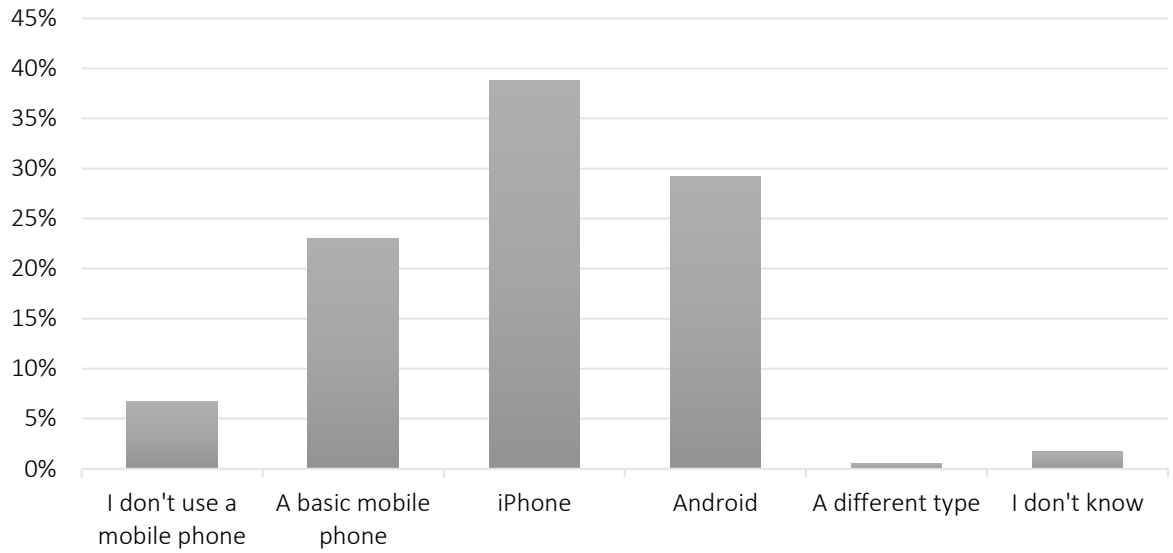


Figure 7. Participants response: What type of mobile phone do you use?

5.3.1.2 Mobility

31 (18%) patients left their home and garden less than once a week, while 84 (49%) patients were more active and left their home more than once a week, and 58 (34%) patients went out every day. The median distance patients perceived they were able to walk without stopping on the flat was 357 metres, with an interquartile range of 45-1247m. 7 patients (5%) reported they were unable to walk any distance.

Table 16 shows the proportion of patients who use a walking aid or oxygen. 42% of patients were using oxygen indoors. 17% of patients used a walking aid indoors, rising to 30% when outdoors.

Frequency	Walking Aid		Oxygen	
	Indoors	Outdoors	Indoors	Outdoors
All the Time	13 (7%)	37 (21%)	30 (17%)	32 (18%)
A Lot	9 (5%)	4 (2%)	18 (10%)	6 (3%)
A Moderate amount	6 (3%)	4 (2%)	20 (11%)	14 (8%)
A Little	4 (2%)	9 (5%)	8 (5%)	11 (6%)
Don't Use	142 (82%)	120 (69%)	99 (57%)	112 (64%)

Table 16. Frequency of using a walking aid or oxygen when indoors and outdoors.

5.3.1.3 Opinions on Home Exercise Testing

The proportion of patients who responded to suggest that it was possible to perform the exercise tests at home is shown in Figure 8. There was no significant difference between patients who felt they would be able to perform the TUG (n=169, 90%) ST (n=160, 85%) and STS (n=158, 86%) at home yet there was significant difference for the T6MWT (n= 125, 68%, x^2 $p<0.0001$). The mean number of tests patients felt they were able to perform at home was 2.9. 20 (10%) patients felt that they will be unable to perform any of the four tests.

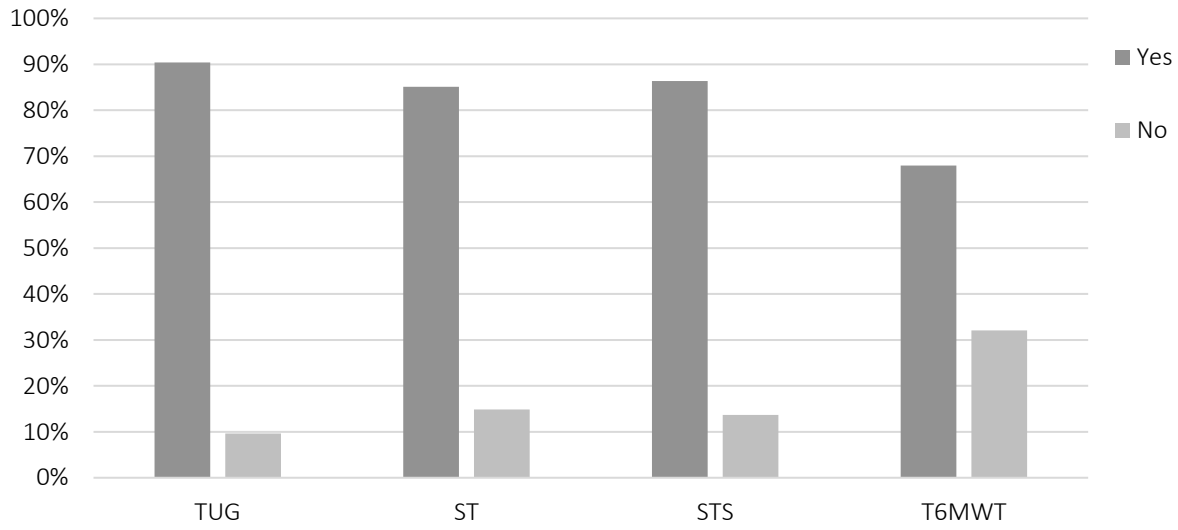


Figure 8. Participants responses; Do you think it would be possible to perform this exercise test at home?

Figure 9 shows how patients felt about completing the test at home. 70% (n=132) of patients in the survey responded that they would be overall very happy or happy to perform the TUG at home, 69% (n=128) the ST, 67% (n=121) the STS and 63% (n=105) the T6MWT. There was a weak correlation between the distance patients felt they could walk and the number of tests they felt they would be able to perform ($r=0.36$, $p<0.001$).

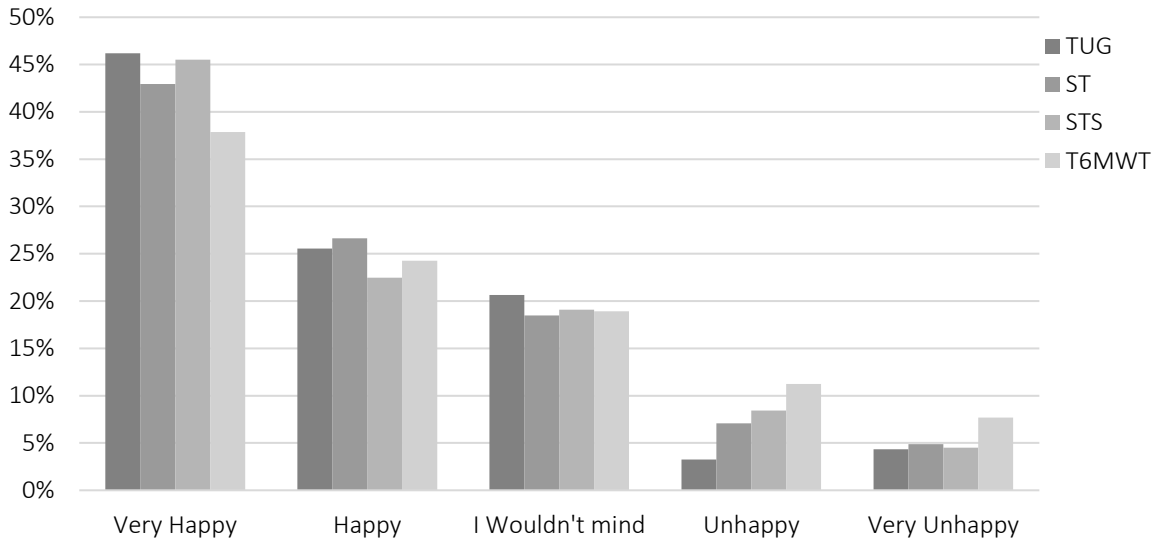


Figure 9. Participants response: How happy would you be to perform this exercise test at home?

Table 17 shows the concerns patients had about each test. There was no difference between the exercise tests with regard to the proportion of patients who were concerned they may fall or the test may make them feel unwell. There was a smaller proportion of patients who were worried they wouldn't be able to finish the TUG (3%) compared to the other three tests.

	I don't have any worries	I'm worried I may fall	I'm worried it might make me feel unwell	I'm worried I wouldn't be able to finish the test	Other
TUG	151 (86%)	12 (7%)	3 (2%)	5 (3%)	4 (2%)
ST	134 (77%)	18 (10%)	3 (2%)	15 (9%)	3 (2%)
STS	136 (79%)	10 (6%)	5 (3%)	14 (8%)	7 (4%)
T6MWT	111 (71%)	14 (9%)	6 (4%)	14 (9%)	12 (8%)

Table 17. Participants response: Is there anything that would worry you about doing this test at home?

Using the opportunity to provide free-text, patients reported a range of concerns out with the concern of falling or feeling unwell for each of the four study tests. Generally, these included concerns surrounding joint pain limiting mobility (10 participants, 5.3%), feeling too breathless to complete the test (12 participants, 6.3%) and feeling too unwell to commence the test (20 participants, 10.6%).

Patients had concerns that were specific to the type of test. Concerning the TUG, 1 patient was unsure how far 3 metres was and did not have tools to measure this. Concerning the ST, 6 (3%) patients were unable to walk upstairs, 4 (2%) patients

required a banister or stick to stabilise them for this test and 3 (1%) patients felt they did not have a suitable step at home. With regard to the STS, 12 patients (6%) felt they would be unable to sit up without using their arms. For the T6MWT, patients were concerned they did not have a smartphone or pulse oximeter at home and would be unable to download and use the mobile application. 5 (3%) patients were concerned the area surrounding their home was too unsafe or was too hilly to complete the test. 5 (3%) patients were concerned of being unable to complete the test in winter due to inclement weather. 5 (3%) patients were concerned a pulse oximeter may not work as they had Raynaud's disease.

5.3.2 Social Deprivation

1514 patients were included. The SIMD median vigintile was 9 with an interquartile range of 4 to 15 and a range of 1 to 20. The results are displayed in Figure 10. 6.9% of patients with PH lived in the most deprived vigintile in Scotland, 31.2% in the least deprived 25% of Scotland and 55.3% in the most deprived half of Scotland.

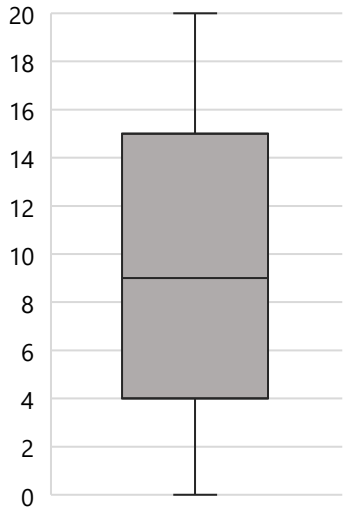


Figure 10. Box-and-whisker plot demonstrating distribution of Scottish Index of Multiple Deprivation vigintiles for patients under the care of SPVU between 2010-2020. These are very similar characteristics to the whole Scottish population, which will be evenly split between the vigintiles.

5.3.3 Remote Quality of Life Assessment

5.3.3.1 Pilot

16 patients were provided with the instruction sheet. 12 results were successfully recorded, giving a participation rate of 75%.

5.3.3.2 Feasibility Study

At the time of the 2022 mailshot, 420 patients were on the SPVU register as being treated with pulmonary vasodilators. In response to the request to complete an E-10, there were 141 results recorded (response rate 33.5%) over the following 21 days. Of the 141, 111 (79%) were completed using the electronic form and 30 (21%) were completed manually. Therefore, of the total population who received the mailshot, 26% were able to successfully fill in the electronic emPHasis-10.

5.4 Discussion

The primary finding of these evaluations is that remote exercise testing could be acceptable for patients with pulmonary hypertension. The survey demonstrates that the majority of patients with pulmonary hypertension were happy to perform home exercise tests and felt that these tests were feasible to be performed at home. 90% of patients felt it would be possible to perform at least one of the four tests at home.

A remote six-minute walk test would be a useful test as the standard 6MWT has been extensively validated for use in PH and T6MWT results could be interpreted to known standards. However, the proportion of patients who were overall happy to complete the T6MWT was the lowest of the four at 63%, with 68% of patients feeling it was feasible to perform at home. This reflects the increased complexity of testing time and requirements such as an internet-enabled smartphone, a strong GPS signal, good weather conditions and a suitable environment around patients' homes. Smartphone use in this cohort was 68%, compared to the UK 2019 national average of 88%(183) which would add further limitation to the use of app-based exercise assessments. It is clear that any mobile-phone application designed for this purpose would need to be optimised to work on both Apple iOS and Android operating systems given the high uptake of both of these platforms in this study.

The TUG is the simplest of the four tests to perform as it requires little equipment and few instructions, which is reflected in the high proportion of patients (70%) who would be overall happy to perform it at home and the low number of concerns regarding its implementation. Although the vast majority of patients were happy to do the ST at home, repeated stepping was an identified barrier for patients with pulmonary hypertension or other co-morbidities. Equally, the STS will be limited by the arm strength of patients. The need for simple and short tests is reflected in the high proportion of patients who have limited mobility, reduced walking distance and require a walking aid and/or ambulatory oxygen.

Having an array of exercise tests on offer will allow patients and clinicians to choose which test is best suited for individuals. Ensuring each patient is content and capable of performing home exercise tests will improve compliance and safety whilst unsupervised at home.

Despite the strengths of the questionnaire, it was limited by the response rate of 41%. Whilst this rate could be considered high for an unsolicited questionnaire, it means a substantial proportion of the pulmonary hypertension population in Scotland were not represented. Furthermore, the results may be skewed by response bias as, for example, participants with a more positive experience of their PH care or their disease limitation may have been more inclined to respond.

The results from this questionnaire differ from the results from a similar study by the UK Pulmonary Hypertension Association (PHA) in 2022, which ascertained the views of 112 patients with PH from across the UK with a section devoted to views on telehealth(184). Surrounding smartphone use, the findings included that 95% of patients owned a smartphone, 87% felt confident in using smartphone applications, and 96% would be happy to share smartphone health metrics with their clinician. Regarding telehealth, 55% found an element of difficulty and/or stress in attending face-to-face visits, 93% were happy for some aspects of their care to be remote and 56% were concerned about contracting COVID19 whilst in hospital. Of particular note, 81% felt confident in performing an outdoor 6MWT using a smartphone application, as opposed to 63% in this questionnaire. The reasons behind the differences seen between this and the PHA questionnaire are unclear, but may be partially attributable to selection bias; the PHA used the online tool SurveyMonkey to distribute the questionnaire, and technologically-confident users may have been more prone to access this(184).

The results from SIMD analysis demonstrate that the social deprivation across the PH cohort was concordant with that of the general Scottish population. Hence, the level of deprivation should not provide significant barriers to remote exercise testing, out with that of the overall population.

This pilot study into remote quality of life assessment demonstrated that remote reporting of quality-of-life scores, performed using an electronic form was feasible for a quarter of patients. This was a simple method of administering the emphasis-10 questionnaire that has the potential to mitigate the administrative issues of misplaced mail, reduced administration and environmental costs and allowed for patients to rapidly respond. A limitation of this study is that it did not collect data on patient demographics. Factors such as age, comorbidities, smartphone use and social deprivation would have been pertinent given as they may influence the ability to access

the internet or use a device such as a smartphone. As shown in *Chapter 5.3.1.1* , the proportion of patients within SPVU who own a smartphone is lower than the general population at 68%, reducing the utility of such a method amongst this cohort of patients.

5.5 Conclusion

The results from this questionnaire shows that a large proportion of patients with pulmonary hypertension would be willing to perform home exercise tests and believe that this would be feasible. Patients have concerns relating to performing tests at home and a knowledge of these concerns will be used to structure the methodology of future work in this thesis in order to suit the largest variety of patients, therefore improving the compliance and safety. An electronic emPHasis-10 questionnaire is a simple and practical method of obtaining quality of life scores for patients with pulmonary hypertension. However, its implementation in routine clinical practice is likely to be limited to patients with the motivation to fill in the form and those who own and can use a smartphone or alternative electronic device.

6. Remote Exercise Testing in Pulmonary Hypertension

6.1 Introduction

Exercise intolerance is a hallmark feature of pulmonary hypertension (PH) which predominantly results from the inability of a reduced cardiac output to meet increased tissue oxygen requirements during exertion(40). As has been discussed in the Introduction, the six-minute walk test (6MWT) is a validated tool for the assessment of exercise capacity in PH and the six-minute walk distance (6MWD) is incorporated into risk assessment tools at baseline and follow up(1, 43). The 6MWT is low cost, standardised, simple and easily interpretable, yet it requires a technician to administer the test, a corridor of sufficient length and patients to travel to a healthcare facility for assessment and supervision(170). Furthermore, a proportion of patients with PH will be unable to undertake a 6MWT due to disease severity, frailty or other mobility issues, such as joint pain. During the 2019 coronavirus pandemic, face-to-face contact between healthcare providers and PH patients was limited and whilst PH centres responded rapidly and many outpatient services continued in a teleclinic setting, these were not informed by the results of functional capacity testing(96, 101, 105, 185).

As has been discussed in the literature review, studies over the last decade have investigated the feasibility and benefits of remote assessment of exercise capacity and alternative capacity tests among patients with PH(109, 110, 112-114, 126, 186). However, few studies have assessed the ongoing feasibility of performing such tests at home, or whether change in study test results are concordant with other measures of risk stratification. Alternative and remote tests may allow a greater proportion of patients to participate in an assessment of exercise capacity, including those who cannot use or own a smartphone, or who cannot complete a conventional face-to-face 6MWT. The majority of PH patients in the UK have a travel time of greater than one hour to attend clinic appointments, are concerned about contracting nosocomial infections whilst in hospital and 93% would be happy for some of aspects of their PH care to be remote(184). Patients are willing to participate in remote exercise capacity assessments and feel this is feasible(187). The Remote Exercise Testing in Pulmonary Hypertension (PHRET) study aimed to assess the feasibility, safety and validity of four exercise capacity tests that could be performed by patients with PH when tested at home whilst further examining patients' opinions on such tests.

6.2 Methods

6.2.1 Participant Selection

Participants were recruited between June 2021 and November 2022, at the time of their diagnosis with PH during a diagnostic admission at SPVU. Participants aged ≥16 years old, who were able to give informed consent and with pulmonary hypertension based on the European Respiratory Society / European Society of Cardiology 2015 guidelines from any clinical classification were included in this study(188). Participants who were deemed to be clinically unstable (e.g., due to syncope, PH-associated chest pain, decompensated right ventricular failure) or who could not perform any of the four tests (due to the severity of PH symptoms or underlying mobility issues) were excluded.

6.2.2 Study Structure

The study exercise tests were chosen based on the results of the Literature Review and the results from the questionnaire in Chapter 5. The tests were chosen as they were felt to represent a spectrum of user-friendliness for PH patients. These included four exercise tests which are described in more detail in the Methods chapter; a 3-metre Timed Up and Go test (TUG), a 2-minute step test (ST), a 1-minute sit-to-stand test (STS) and a tele-6MWT (T6MWT). The research team and participant chose which of the four exercise tests the participant would prefer to perform, based on pre-existing symptoms, mobility, joint pain, whether a participant required long term oxygen and whether they owned and felt confident operating a smartphone.

A standard 6MWT was performed at visit 1 and visit 4 in a 30m corridor according to standardised protocols(170). Complaints and complications were collected during administration of the tests at all Visits.

Data was collected on safety, by noting the number of adverse events. Participants were permitted to use an assistant for time keeping at home. Routine clinical data were extracted from electronic records at the time of diagnosis and first follow up (visits 1 and 4). The visit structure was as follows;

1. *Visit 1*: During standard diagnostic admission. Following completion of the standard 6MWT, participants would rest for at least 30 minutes and then were observed in completing the study tests once fully recovered. The tests were performed in the same order on each occasion. Participants were commenced on pulmonary vasodilator treatment prior to discharge if clinically appropriate.
2. *Visit 2*: Within seven days of discharge home, participants perform the study tests at home and relay the results to the research team by email or telephone.

3. *Visit 3*: At home, participants perform the study tests within the seven days prior to the first follow up.
4. *Visit 4*: Standard first follow up face-to-face review, including a standard 6MWT. A brief questionnaire concerning the study tests was completed by participants at the end of the study (Appendix 12.4).

6.2.3 Aims

The primary outcome was whether the study test could be used to predict improvement or deterioration in a participant's exercise capacity following treatment for PH. This was assessed by evaluating the longitudinal comparison between study tests and the standard 6MWT, i.e., did the change in study test outcome (Δoutcome) between visit 1 and visit 3 agreed with the Δoutcome of the standard 6MWT (between visit 1 and visit 4).

Secondary measures included;

i. Assessment of the performance of the study tests at baseline: agreement between the study tests and the standard 6MWT at visit 1.
ii. Safety – measured by the number and type of any adverse events recorded in the hospital or at home
iii. Feasibility was assessed using two methods. The first was the proportion of participants who elected, and were able to, perform each of the study tests remotely. Secondly, a questionnaire was used to assess participants views on home testing and the study tests.

6.2.4 Statistical analysis

Agreement between tests with the same outcome measure was performed using Bland-Altman analysis(180). Pearson's and Spearman's Correlation Coefficient (r) with 95% confidence intervals were used for parametric and non-parametric data respectively. The agreement of concordance of change (where the study test agreed with improvement, no change or deterioration to the standard 6MWT) was assessed at follow up. A sensitivity analysis was performed on the results, with outliers systematically removed and the results reviewed following each removal to detect the effect on models. The statistical methods and ethical approvals for this study are described in detail in the Methods chapter, sections 4.6 and 4.7.

6.2.4.1 Sample Size Calculation

The sample size was calculated based on the analysis between study tests and the standard 6MWT at visit 1 (i.e. correlation) and the concordance of change between visit

1 and visit 4 (i.e. concordance of change). Presuming a correlation coefficient of 0.5, a sample of 29 was required for each test, falling to 13 for an r of 0.7. For a significant of 0.05 and a power of 0.8, an estimated sample of 25 participants performing each test was required to provide sufficient power for concordance of change.

6.3 Results

6.3.1 Participant demographics

61 participants were approached and 2 participants declined participation as they felt the week of the diagnostic admission was too many clinical tests without including additional study tests. Therefore, 59 participants were included in the baseline cohort with demographics provided in Table 18. Most patients were female (56%), the mean age of 63 years and the majority of patients were diagnosed with Group I (33.9%) or Group IV (35.6%) pulmonary hypertension. The majority of patients were classified as WHO functional class II (54%) or III (42%), although one patient with WHO FC IV was included. The median NT-proBNP was 810 pg/ml and the mean 6MWD at baseline was 340 metres. Patients from all four of the ERS/ESC risk strata were represented, although the majority were intermediate-low risk.

	Total = 59
Diagnosis	
Group I - Pulmonary arterial hypertension (PAH)	20 (33.9)
- Idiopathic Pulmonary Arterial Hypertension	- 9 (15.3)
- Pulmonary Veno-occlusive Disease	- 1 (1.7)
- Connective Tissue Disease-PAH	- 6 (10.2)
- Drug-Induced-PAH	- 1 (1.7)
- Congenital Heart Disease-PAH	- 2 (3.4)
- Portopulmonary Hypertension	- 1 (1.7)
Group II - PH due to left heart disease	6 (10.2)
Group III - PH due to chronic lung disease and/or hypoxia	7 (11.9)
Chronic thromboembolic pulmonary hypertension	21 (35.6)
Group V – PH due to miscellaneous causes	3 (5.1)
Age (yrs.)	63 ± 13
Male, n (%)	26 (44)
BMI (kg/m^2)	29.2 ± 6.5
WHO Functional Class	
- I	1 (2)
- II	32 (54)

- III	25 (42)
- IV	1 (2)
NT-proBNP (pg/ml); median (IQR)	810 (236 – 2569)
Diffusion capacity of carbon monoxide (DL_{CO})	
- mmol/(min*kPa)	4.2 ± 2.0
- % predicted	53 ± 21
6MWT Distance (m)	340 ± 13
COMPERA 2.0 Risk Score	
- Low Risk	16 (27)
- Intermediate-Low Risk	23 (39)
- Intermediate-High Risk	13 (22)
- High Risk	7 (12)
Emphasis-10 score	28 ± 13
Internet-enabled smartphone owners, n (%)	50 (86)
Long term oxygen therapy, n (%)	8 (14)
Right heart catheterisation	
Right atrial pressure (mmHg)	7 ± 5
Mean pulmonary artery pressure (mmHg)	39 ± 11
Pulmonary artery wedge pressure (mmHg)	9 ± 4
Cardiac index (L/min/m^2)	2.5 ± 1.1
Pulmonary vascular resistance (woods units, WU)	7.5 ± 4.3
Mixed venous saturation (%)	62.7 ± 8.2

Table 18. Participant demographics and haemodynamics at baseline visit (Visit 1). Data are presented as mean±SD or number (%) unless otherwise stated.

The flow of participants into the follow up cohort is shown in Figure 11. In total 9 patients discontinued from the study (discontinuation rate 15.3%) due to a lack of engagement, death or joint pain. 5 patients were too unwell following diagnosis to continue the study and 3 patients were discharged, hence 42 patients completed full follow up (71.8% continuation when compared to Visit 1).

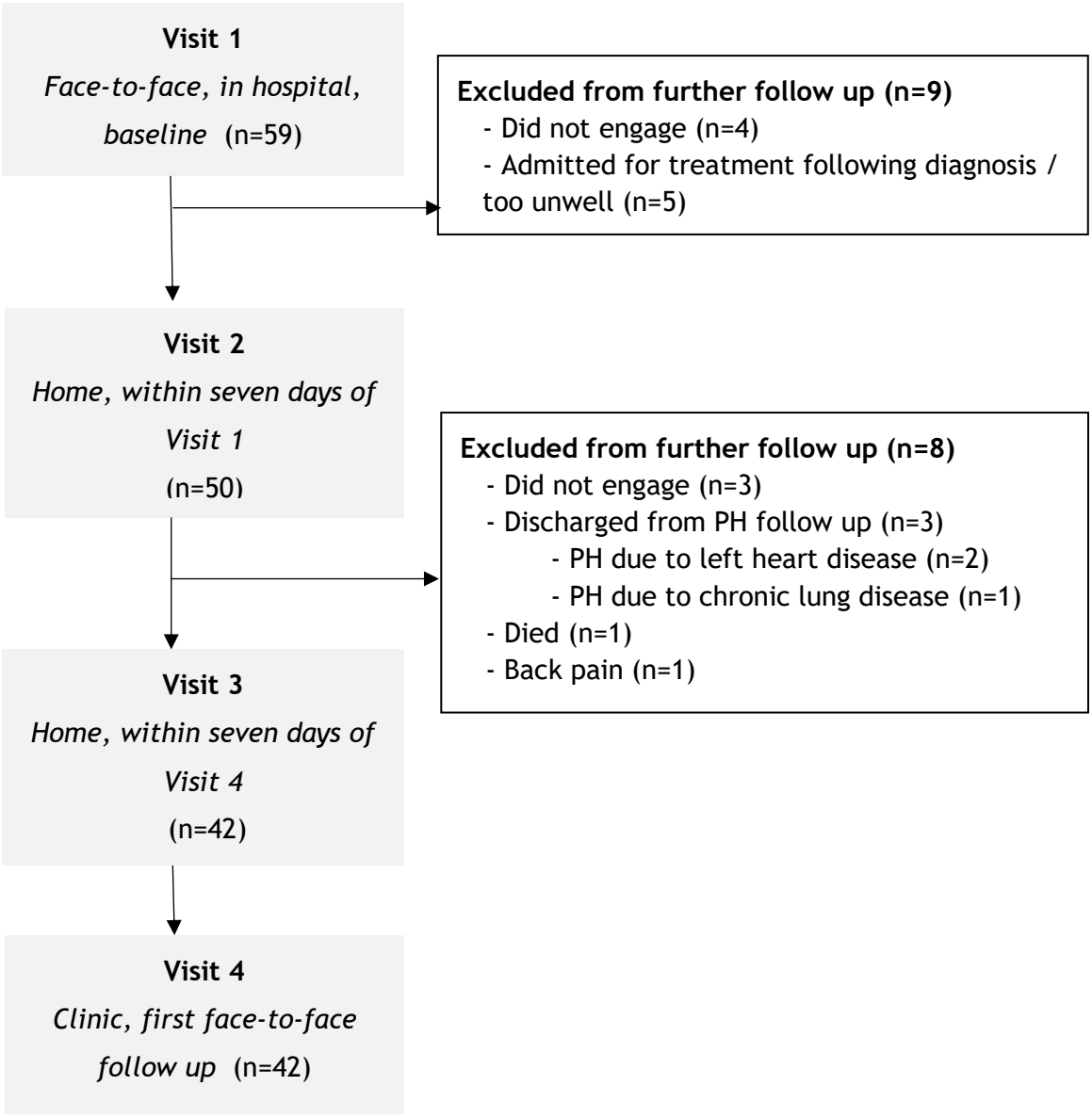


Figure 11. CONSORT Participant inclusion flow diagram.

6.3.1 Choice of Study Test

After consultation between the participant and research team, 59 (97%) of participants elected to participate in the TUG, 43 (73%) a ST, 54 (92%) a STS and 29 (49%) a T6MWT. 8 participants (13.5%) cited joint pain as the predominant reason for being unable to participate in the ST and T6MWT, 4 participants (6.7%) wished to take part in the T6MWT at baseline, but this could not be performed outdoors due to inclement weather on that day. 45.7% of participants were able to perform all four study tests.

6.3.2 Performance of Study Tests at baseline

Comparison between the standard 6MWT and study tests at Visit 1 are shown in Figure 12.There was very strong correlation between the T6MWT walk distance and the standard 6MWD (r=0.93, 95%CI 0.85-0.96, p<0.001, Figure 12a). Bland-Altman analysis shows T6MWT results were systematically higher than standard 6MWD (bias +25m, SD±38) with limits of agreement from -50 to +101m (Figure 12b). The correlation between the standard 6MWT and the ST was 0.78 (95%CI 0.62-0.87, p<0.001) and STS 0.71 (95%CI 0.54-0.82, p<0.001) (Figure 12c-d). Sensitivity analysis of the TUG demonstrated the effect from three outliers (TUG >30 seconds, Figure 13) and following removal the correlation was r=-0.76 (95%CI -0.86,-0.64, p<0.001)(Figure 12e).

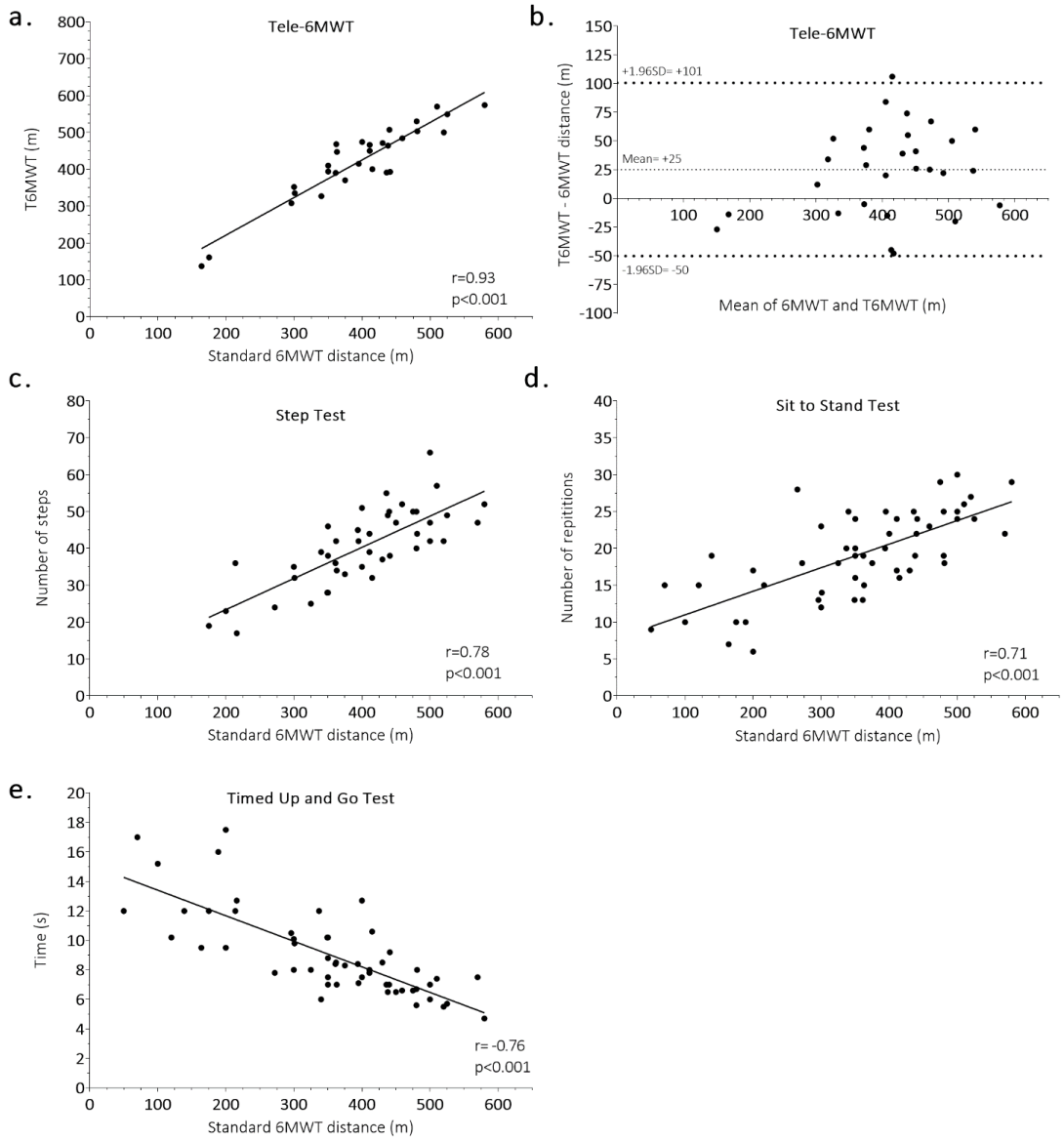


Figure 12. Performance of the study tests at baseline (visit 1) as compared to the standard six-minute walk test. Correlation (a) and Bland-Altman analysis (b) are shown for the Tele-6MWT (T6MWT). Correlation is shown for the (c) Step Test, (d) Sit to Stand Test and (e).

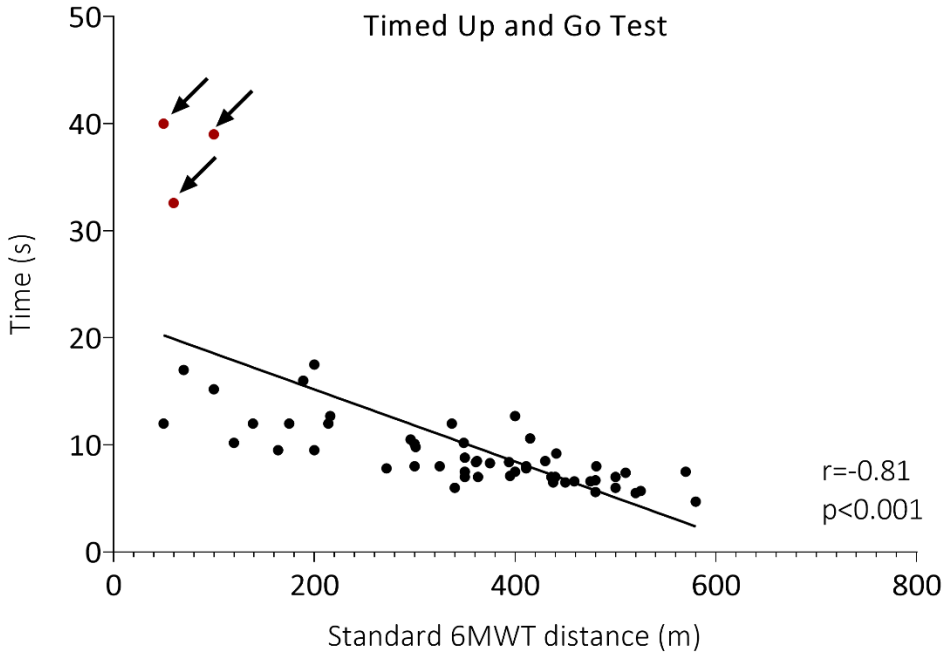


Figure 13. Correlation between the Timed Up and Go test and the standard six-minute walk test at Visit 1; r=-0.81 (95%CI -0.88 to -0.69, p<0.0001). For the main analysis the three outliers highlighted in red (arrow) were removed.

6.3.3 Remote study tests at Visit 2

The mean time between visit 1 and 2 was 5 days (SD±2). Nine participants did not proceed to visit 2 for reasons detailed in Figure 11, with 50 participants proceeding to visit 2. All patients who proceeded to Visit 2 were able to perform the tests at home without adverse incident. Agreement analysis between the study tests at Visit 1 and Visit 2 is demonstrated below, but review of this analysis should be viewed with the knowledge that results are affected by the confounding effect from targeted pulmonary arterial vasodilator therapy between these time points.

The mean difference (limits of agreement) and correlation coefficient (95%CI, p value) between the study tests when performed in hospital (visit 1) and at home (visit 2) were respectively: T6MWT -16m (-97, 66), r=0.86 (95%CI 0.71-0.94, p<0.001), ST -4.9 steps (-16.5, 6.5), r=0.87 (95%CI 0.76-0.93, p<0.001), STS -1.9 repetitions (-9.1, 5.4), r=0.79 (95%CI 0.65-0.88, p<0.001) and TUG 0.5 seconds (-1.6, 2.6), r=0.93 (95%CI 0.88-0.96, p<0.001) (Figure 14). Overall, participants had improved test results at visit 2 (i.e., when performed at home compared to visit 1) for all four tests.

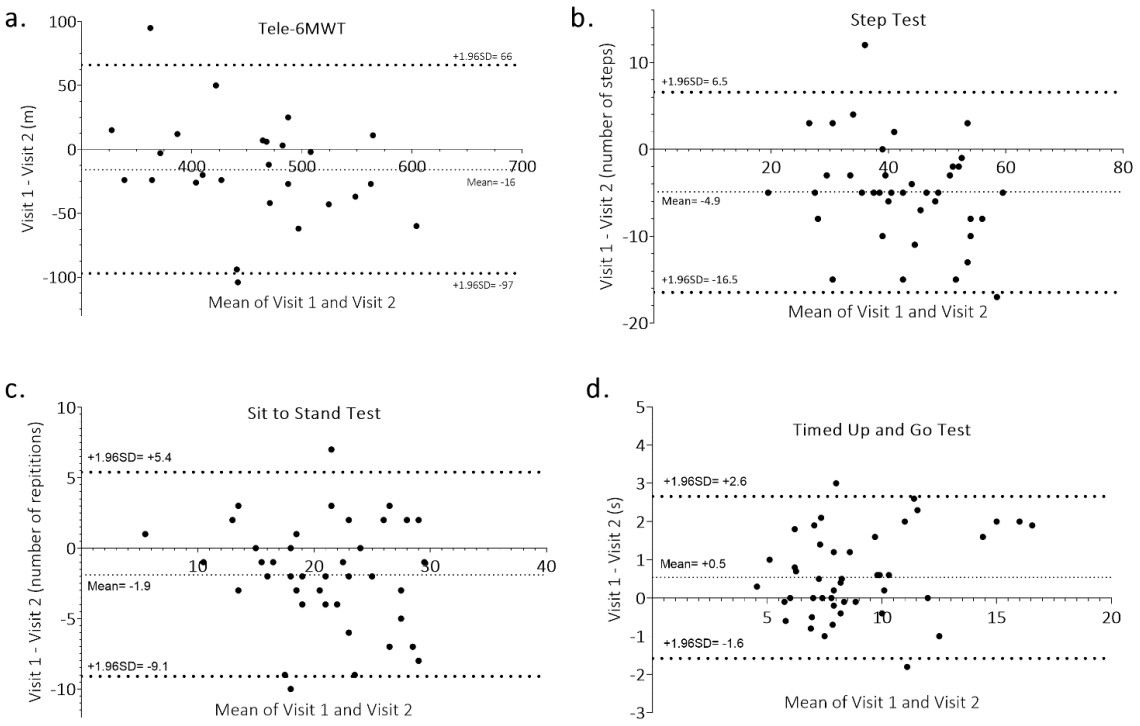


Figure 14. Bland-Altman analysis demonstrating the agreement between the (a) T6MWT, (b) Step Test, (c) Sit to Stand Test and (d) Timed Up and Go Test between when performed in the hospital (Visit 1) and within seven days of discharge at home (Visit 2).

6.3.4 Concordance of change following treatment

Eight participants did not proceed from visit 2 as detailed in Figure 11, with 42 participants proceeding to visit 3 and 4. The mean time between visit 1 and 4 was 116 days (SD± 33). Between visit 1 and visit 4, 8 participants (14%) moved into a higher risk COMPERA 2.0 stratum and 19 (32%) moved into a lower risk stratum. The mean change in standard 6MWT distance was +29 (SD ± 70m) and NT-proBNP was -1165 pg/ml (SD± 2113).

Sensitivity analysis was performed with outliers removed from results at follow up. Two participants were removed from the STS analysis (>100% increase in STS result) and one participant was removed from TUG and STS analysis (197% increase in standard 6MWT), as shown in Figure 15. Figure 16 demonstrates the proportion of change in each study test (at visit 1 and visit 3) when compared to the standard 6MWT (at visit 1 and 4). Direction of change in the study test agreed with that in the standard 6MWT in 79% of the follow up T6MWT, 68% of the ST, 66% of the STS and 71% of the TUG. When the 4-strata thresholds for 6MWD are applied(90) and when compared to the standard 6MWT, 8 (33%) of participants were classed into a different risk stratum based on the T6MWT result (Figure 17).

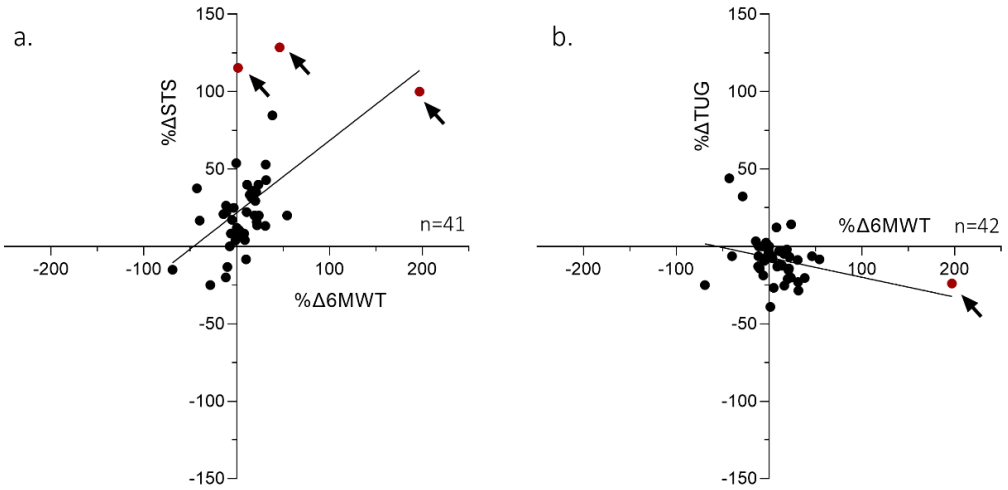


Figure 15. The percentage change of the (a) Sit to Stand Test and (b) Timed Up and Go Test between visit 1 and visit 3 when compared to the percentage change in the standard 6MWT between Visit 1 and Visit 4. For the main analysis, the outliers highlighted in red (arrow) were removed.

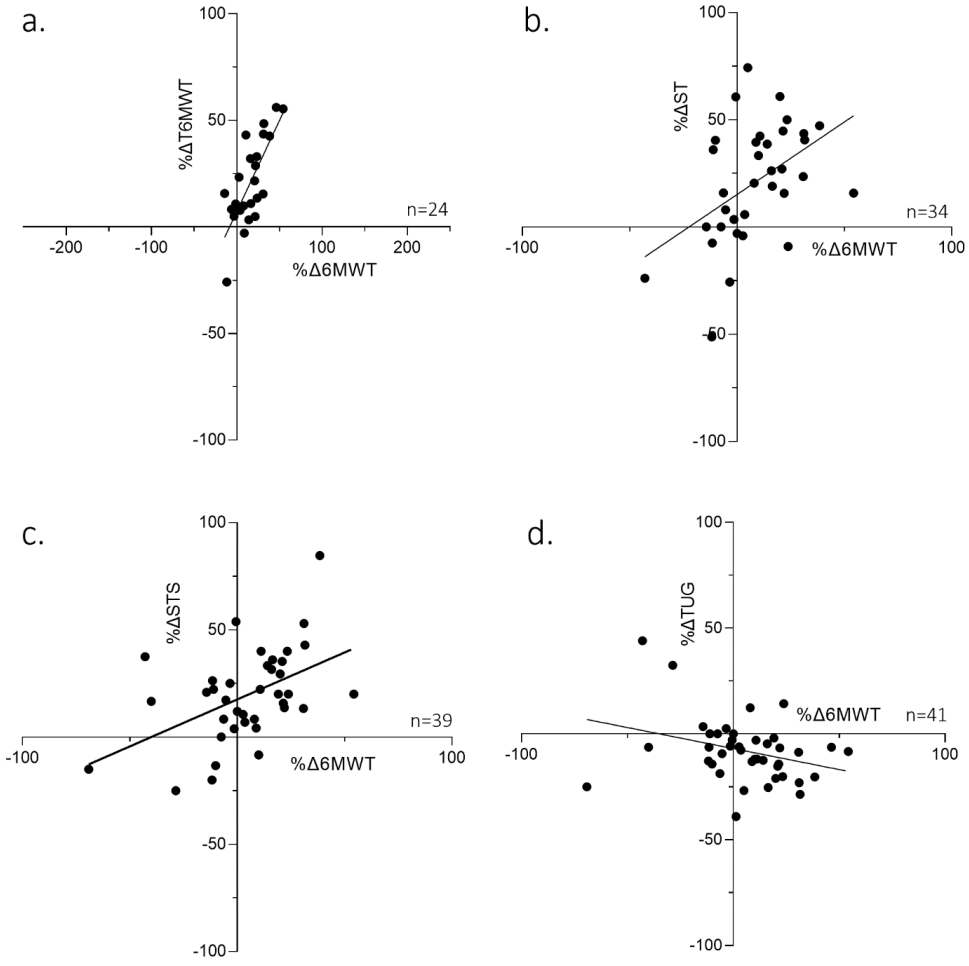


Figure 16. The percentage change of the (a) T6MWT, (b) Step Test, (c) Sit to Stand Test and (d) Timed Up and Go Test between Visit 1 and Visit 3 when compared to the percentage change in the standard 6MWT between Visit 1 and Visit 4.

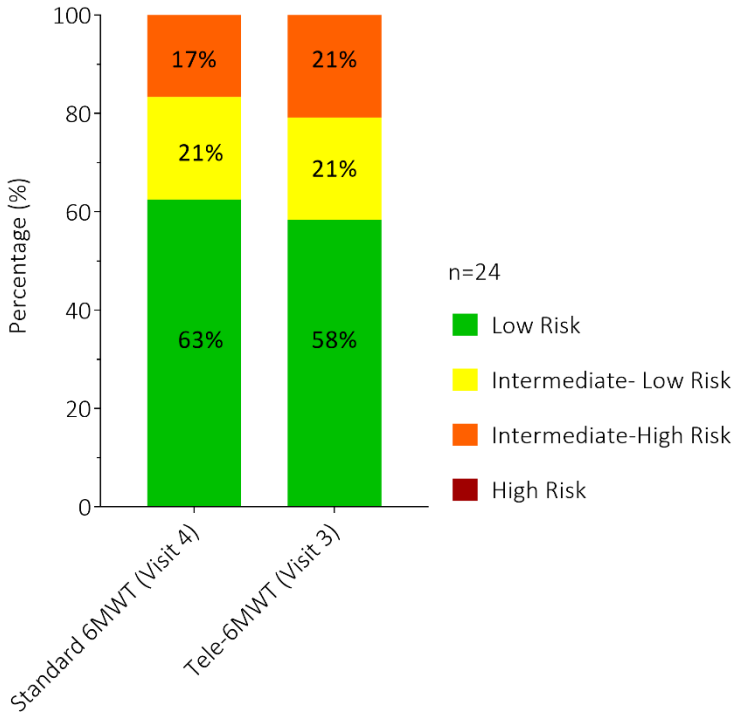


Figure 17. Categorization of risk strata between during follow up as assessed by the standard 6MWT and the Tele-6MWT.

In 92% of cases, there was agreement of concordance with at least one of the study tests, when compared to the standard 6MWT.

Between baseline and follow up (visit 1 and visit 4), 66% (n=27) of the participants had study tests all of which had agreement of concordance (i.e., in these participants, the study tests all agreed there had been an improvement, deterioration or no change). In these 27 cases, the comparison of agreement to the change in the standard 6MWT was 81%.

6.3.5 Subanalyses

Three separate subanalyses were performed, although the conclusions from ii and iii are significantly limited by the small numbers involved.

i. Further analysis was performed, replacing the Δoutcome from the standard 6MWT with the Δoutcome of NT-proBNP (pg/ml). This demonstrated the concordance of change was poorer; respectively 68% for the T6MWT, 58% of the STS, 68% of the STS and 66% of the TUG.

ii. A subanalysis was performed, only including participants with Group 1 PH (PAH) who were aged ≤70 years (n=15), in order to assess a group who may have fewer co-morbidities and therefore potentially fewer confounders to the outcomes of

the study test. The concordance of change improved to 82% for the T6MWT, 80% for the ST, 82% for the STS and 91% for the TUG.

iii. A subanalysis was performed which included only participants who performed a T6MWT and went on to complete this test at Visit 3 (n=24). In this cohort, the concordance of change improved to 75% for the ST, 83% for STS and 79% for the TUG.

6.3.6 Safety

There were no adverse events reported during any of the study visits. Four participants provided results demonstrating their end exercise oxygen saturation was <80% but did not report syncope, chest pain or presyncope during the test. Three participants reported difficulties using the pulse oximeter at home.

6.3.7 Feasibility and Acceptability

Thirty-nine participants (response rate 93%) completed the end of study questionnaire. 100% of participants reported they were able to complete their allocated study tests at home. 97% of respondents were “Very happy” or “Happy” to continue performing the TUG at home, 97% the STS, 93.3% the ST and 92% the T6MWT. No participants reported they would be “Unhappy” or “Very Unhappy” to continue any of the tests. Positive feedback was similar for all four tests; 12 participants felt the tests allowed them to see improvement within themselves. 2 participants reported the tests built their confidence in performing exercise at home independently, 2 participants reported the T6MWT was a better reflection of their capacity than an inside corridor walk test, 1 person reported the *Timed Walk* app was easy to use and 2 participants reported finding the instructions easy to use.

Negative feedback included 4 participants reporting the test was limited due to joint pain (particularly for the step test), 3 participants reported finding the tests made them feel very breathless, 3 participants reported the TUG was too short and 1 participant reported the T6MWT was difficult to perform outside in poor weather.

6.4 Discussion

Remote risk assessment in PH could introduce benefits such as reducing lengthy transport to specialist centres, reducing participant exposure to nosocomial infections and allowing ad hoc assessments at home(106). However, remote assessment must be informed by objective results that can allow an accurate quantification of whether a participant is stable, improving or deteriorating. This study demonstrates that the

remote assessment of exercise capacity is feasible, acceptable and safe in an incident pulmonary hypertension population, but that results may not be as reliable as those obtained during on site testing. There was a relatively high discontinuation rate which may impact the utility of remote tests in a real virtual clinic.

Participants were willing and able to perform a range of unsupervised home tests and high satisfaction rates were recorded without adverse events.

The T6MWT had good cross-sectional correlation and agreement to the standard 6MWT. It had a mean bias of +25m which is less than most estimates of the minimally important clinical difference in pulmonary arterial hypertension, which range from 33 to 41.8m(189-192). Longitudinally, the T6MWT had acceptable concordance of change when compared to the standard 6MWT (79%). However, the lowest proportion of participants (49%) felt they would be able to perform this test at home.

The other study tests were able to be performed by a greater number of participants with acceptable performance at baseline (correlation coefficients all above 0.7). Concordance at follow up was less satisfactory, with wide limits of agreement. This improved in the subgroup of participants who were able to perform a T6MWT, suggesting the reduced performance in these tests may be attributable to the cohort of participants rather than the tests *per se*.

The study tests were performed at baseline, whilst supervised at the hospital (Visit 1) and within seven days of returning home (Visit 2). Overall, the study test results between visit 1 and visit 2 were better at home than when observed in the hospital and demonstrated poor agreement. However, this does not indicate that the study tests are not reproducible at home. These results may be explained by a training effect and furthermore patients commenced targeted therapy between these visits. Whilst only on these treatments for a few days this is likely to have influenced the results. Visit 2 should instead be viewed as an early measure of feasibility that the tests could be performed at home.

The subanalysis of younger Group 1 PAH patients suggests that the study tests may be more applicable in such a cohort, although given the low numbers for these subanalyses, strong conclusions cannot be drawn. The main objective of using remote tests in patients with PH would be the additional information it could provide on whether patients had deteriorated, remained stable or improved from the last assessment and in 92% of cases at least one study test was able to identify this. However, to achieve this for a real cohort of patients, all four tests would have to be initially trialled for each patient, with a subsequent decision at follow up to determine

which test was best for an individual, which would be impractical and laborious for patients.

As discussed in the literature review, other work has studied alternative and remote exercise tests in PH with similar results to this study. Outdoor, remotely supervised 6MWTs have been shown to be safe with comparable results to the standard test(128). Other mobile application alternatives to the standard 6MWT have demonstrated good correlation (r=0.83 to 0.88) and agreement with standard 6MWT results and were felt to be feasible by users(112-114). The *Timed Walk* app was used in this study, and previous work by SALVI found the results were repeatable and had good correlation (r=0.89) to a standard walk test but agreement analysis demonstrated similar inaccuracies to those found in this study(110, 186). As with this study during visit 1, the number of steps during a symptom-limited step test with oximetry testing has been shown to have a strong correlation (r=0.77) with the standard 6MWD(126, 193).

This study had several limitations in addition to those listed above. The study was not powered for between-group comparisons for participants performing each of the four submaximal tests. Only one study test was performed at each visit and hence the intra-test reliability and intra-observer variability were not recorded. The study tests were performed in the same order for each participant at Visit 1 in order to maintain consistency across the study population, however this may have led participants tiring when performing the later study tests. There was a high discontinuation rate at follow-up (9 of 59 participants, 15.3%). Ten participants were unable to proceed due to the severity of their illness, reflecting that remote assessment can be difficult in a newly diagnosed PH population who can be unstable. Seven participants failed to engage with study follow up. The reasons for this are unknown and whilst it could be related to the study tests themselves, this seems less likely given the positivity for the tests that was demonstrated in the questionnaire. The lack of adherence seen in this study may pose a significant barrier to real virtual clinic testing, where adherence may be poorer than in a study setting.

Further work could study the validity and feasibility of remote exercise tests when implemented in a clinical setting of a PH clinic, potentially using a more defined cohort of participants, with fever co-morbidities who are less likely to suffer mobility issues from other health conditions and hence may provide a clearer signal as to the validity of these tests.

6.5 Conclusion

In conclusion, this study demonstrates that remote testing is feasible in PH. However, there are significant challenges to be addressed before implementation could be considered. Whilst the results reported here are promising regarding a mobile application-based 6MWT, there was insufficient validity demonstrated in this study to currently recommend its use. The other study tests may be used in patients who feel they are unable to complete an unsupervised, outdoor, home walk test although results would need to be interpreted with the above caveats. The high discontinuation rate seen in the study may impact the utility of remote tests in a real virtual clinic.

7. Capillary NT-proBNP in Pulmonary Hypertension

7.1 Introduction

Dysfunction of the right ventricle (RV) is the primary driver behind the symptom burden in PH, leading to exercise intolerance, exertional dyspnoea, fatigue and RV failure as the disease progresses with fluid retention, chest pain and syncope (35, 194). The assessment of right ventricular function is used to risk stratify patients at the point of diagnosis and to monitor the response to treatment(1). As has been discussed, B-type natriuretic peptide (BNP) and N-terminal prohormone of BNP (NT-proBNP) are biomarkers that are released in proportion to the extent of cardiac ventricular wall stress(56, 195). NT-proBNP has become established as a surrogate marker of RV function and is incorporated into all contemporary PAH risk stratification models(82, 85, 86, 90, 91, 196). In current practice at UK PH centres, samples are collected as venous serum or plasma blood through venepuncture at the time of a patient' face-to-face assessment and results are commonly available ≥24 hours. NT-proBNP has superior stability than BNP, but is still prone to degradation, especially at higher temperatures(195). Many PH centres now use NT-proBNP for the above reasons, yet this adds complexity when comparing to historical BNP results due to the lack of a simple conversion factor between the two(197).

The effects of the COVID-19 pandemic on PH care and the resultant limitations in the availability of objective measurements have already been discussed. It remains that NT-proBNP data are often unavailable at the time of virtual clinic appointments due to the restrictions on the use or funding for these tests within primary care networks and the lack of a global remote blood monitoring facility within the National Health Service (NHS)(59, 198).

Point-of-care testing (POCT) for NT-proBNP has been studied in the left heart failure population(199) and in the REPEAT-PAH study in PH(154, 200) both with acceptable agreement to standard NT-proBNP. However, it remains that POCT requires patients to travel to a healthcare facility. Sendaway tests, through capillary sampling, can be performed by patients at home and are sent for processing at a central laboratory with results sent either directly to the patient or the referring medical team. Sendaway samples may allow PH centres to obtain NT-proBNP results in a telemedicine setting. Capillary samples are obtained through fingerpick blood draw, similar to how capillary blood glucose measurements are obtained, and collected in serum microtainer bottle. Venous sendaway sampling could enable patients to have blood drawn locally, such as by a general practitioner, with the result funded and followed by a specialist team.

This UK-wide study aimed to assess the validity of results from sendaway NT-proBNP with standard venous NT-proBNP and to assess the effect of delayed processing on the results.

7.2 Methods

7.2.1 Participant Selection

Participants ≥16 years old with pulmonary hypertension (mean pulmonary artery pressure ≥ 25 mmHg, regardless of pulmonary vascular resistance) and from any 2015 ERS/ESC clinical classification, were included(65). Therapy with anticoagulation or antiplatelet medication was not considered an exclusion.

7.2.2 Study Structure

Samples were collected between April 2022 and April 2023 over seven of the adult national centres for pulmonary hypertension in Great Britain (Figure 18). During a single visit (Day 0), during patients' standard care, blood was drawn in sequence, following thirty minutes of rest and without participant exertion between tests, as outlined below;

i. **1x Reference Venous NT-proBNP** – transported by Royal Mail post to a reference laboratory and analysed upon arrival.
ii. **1x Local Venous NT-proBNP** – analysed as per standard protocol at the laboratory based at each participating site.
iii. **2x Sendaway Venous NT-proBNP**
iv. **2x Sendaway Capillary NT-proBNP** - each with 600µL of blood from different fingers.

Sendaway samples were obtained using kits from Thriva LTD (London, UK), sent to the Thriva lab by Royal Mail post and analysed using Thriva infrastructure at Day 3 and Day 7 from the day of the blood draw. Sendaway samples were analysed using a Roche Cobas e 411 device (Roche, Switzerland) with a 4.2 – 6.3% coefficient of variation (Table 19). In cases where one sample was insufficient, the Day 3 sample was prioritised. Reference samples were performed at the Royal Brompton Hospital (London) using Roche Cobas e 411 device and Elecsys proBNP II assay. This method was chosen for the reference sample to maintain reproducibility. Postal samples were sent immediately and were not refrigerated prior to postage. Study data were collected and managed using REDCap electronic data capture tools hosted at the Royal Brompton Hospital.

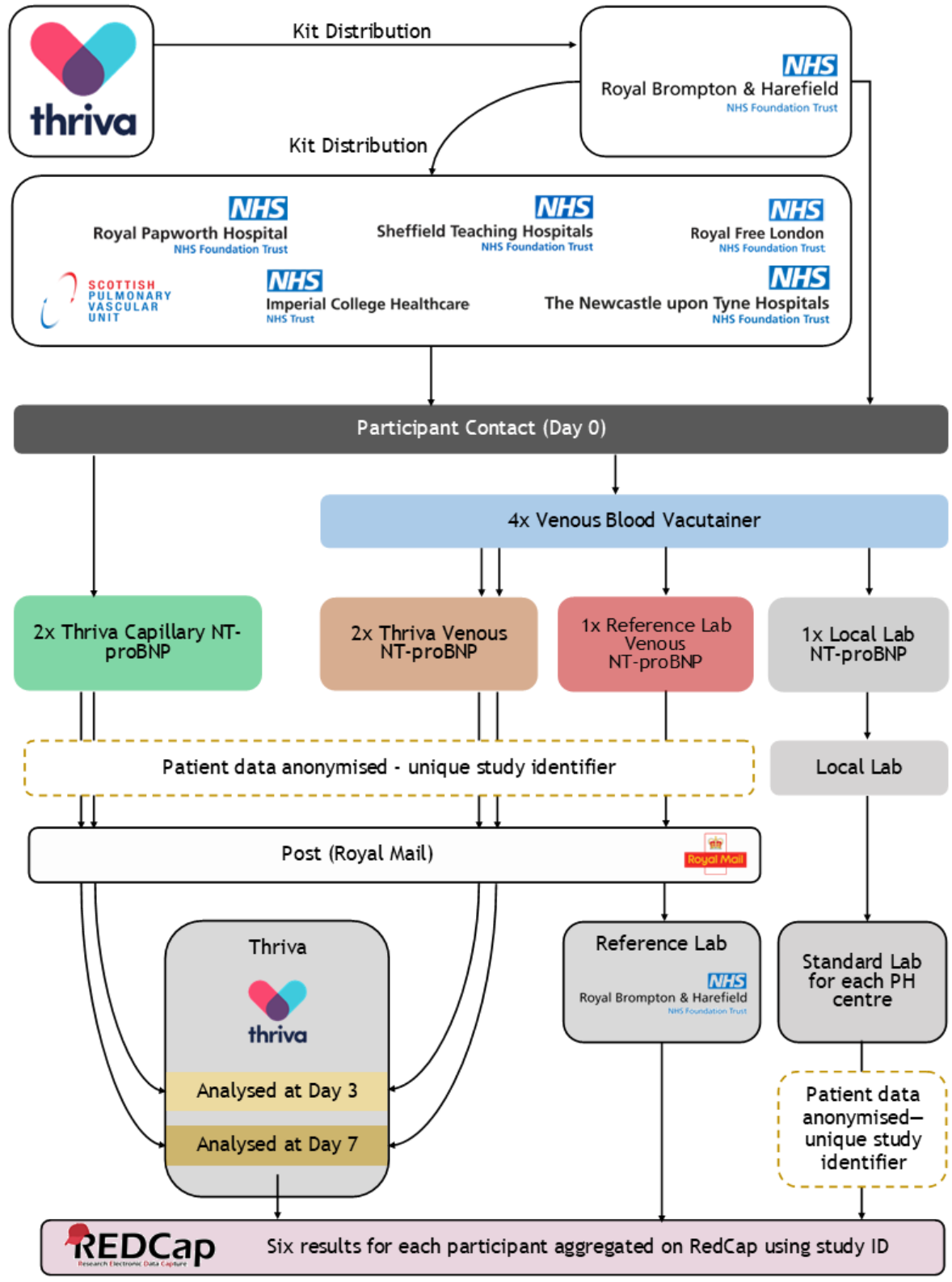


Figure 18. Schematic for study design

Quality Control Target NT-proBNP (pg/mL)	Mean (pg/mL)	Standard Deviation (pg/mL)	Coefficient of Variation (CV%)	Uncertainty of Measurement (95%)
Lower value: Target NT-proBNP = **135**	128	5.27	4.21	8.25
Higher value: Target NT-proBNP = **5022**	4673	280	6.28	12.3

Table 19. Intra-test reliability of Thriva laboratory NT-proBNP assay. Data collected from Thriva, internal quality control audit, 2021. When tested against a known lower and higher value of NT-proBNP, the intra-test reliability of the Thriva assay is shown.

7.2.3 Aims

The primary outcome was the agreement between reference and Day 3 Capillary NT-proBNP results. The secondary outcomes included the assessment of (i) the agreement between reference and Day 3 Venous sendaway NT-proBNP results and (ii) the effect of delayed processing (stability) on capillary and venous sendaway NT-proBNP results by comparing the agreement between reference and Day 7 results.

7.2.4 Statistical Analysis

The Shapiro-Wilk test was used to assess the normality of the data. Multiple methods were used to assess the relationship between the reference and studied NT-proBNP including; (i) median difference (interquartile range), (ii) traditional Bland-Altman plots(180), (iii) percentage difference plot, (iv) Passing-Bablok regression(182) with (v) Spearman's Rho (r) correlation(201) and (vi) Risk Stratification assessment. Reference NT-proBNP results were assigned a risk status based on the COMPERA 2.0 thresholds(90) and the proportion of participants who would have been assigned a different risk stratum based on study NT-proBNP results was calculated. The relationship between the local lab and studied NT-proBNP were additionally assessed with the above analyses. These analyses are expanded upon in the Methods chapter. The viability of sendaway sampling was measured by assessing the number and causes of invalid samples. Where results were reported below the analytical range, they were analysed using the value closest to the reporting limit (e.g., <10 was analysed as 9).

7.2.1.1 Sample Size Calculation

The ICC for the repeatability of standard venous lab NT-proBNP in patients with PAH has been shown to be strong at 0.77(202). We aimed to replicate this . Assuming a null intra class correlation of 0.50 and a power of 90%, a sample size of 82 was required.

Calculation of for the Bland-Altman analysis was complicated by the scarcity of data on the test re-test reliability of NT-proBNP. Presuming a mean change of 5 pg/ml with a SD of 10 pg/ml and a maximum difference of 30pg/ml, using a criterion of a power of 0.8 and a significance level of 0.95, this estimated a required sample size of 83 participants for Bland-Altman analysis(180, 203). Therefore, to allow for sufficient power, and accounting for errors (such as mislabelled samples, missing samples and blood bottle issues) a recruitment target was set at 98 participants. This would involve 14 participants from each of the seven sites.

7.3 Results

7.3.1 Participant demographics

120 participants were approached, with six participants declining participation to the study for reasons of time (4), and fear of pain (2). Therefore, 114 participants were recruited into the study with one participant with CTEPH excluded as they were unable to produce sufficient blood for either capillary or venous samples. Participant demographics are shown in Table 20.

	Total = 113
Diagnosis, n (%)	
Group I – Pulmonary Arterial Hypertension (PAH)	67 (59)
- Idiopathic Pulmonary Arterial Hypertension	30 (27)
- Hereditary Pulmonary Arterial Hypertension	4 (4)
- Pulmonary Veno-occlusive Disease	1 (1)
- Connective Tissue Disease-PAH	22 (19)
- Drug Induced-PAH	1 (1)
- Congenital Heart Disease-PAH	7 (6)
- Portopulmonary Hypertension	2 (2)
Group II – PH due to left heart disease	6 (5)
Group III – PH due to chronic lung disease and/or hypoxia	16 (14)
Chronic thromboembolic pulmonary hypertension	21 (19)
Group V – PH due to miscellaneous causes	2 (2)
Undefined	1 (1)

Age (yrs.)	60 ± 14.8
Male, n (%)	39 (35)
Reference NT-proBNP, pg/ml	514 (167 – 1890)
Estimated Glomerular Filtration Rate (eGFR) (ml/min/1.73m^2) <60	20 (18)
Haemoglobin (g/dL)	139 ± 20

Table 20. Participant demographics

The range of NT-proBNP results from all study data sets are shown in Table 21; all were non-parametrically distributed ($p<0.001$; Figure 19).

Data set	Reference	Local Lab	Sendaway Capillary		Sendaway Venous	
			Day 3	Day 7	Day 3	Day 7
Median (interquartile range)	514 (167 - 1890)	546 (171 - 2039)	494 (166 – 1770)	404 (139 – 1586)	516 (184 -2252)	441 (152 – 1938)

Table 21. NT-proBNP dataset overview. All units are pg/ml.

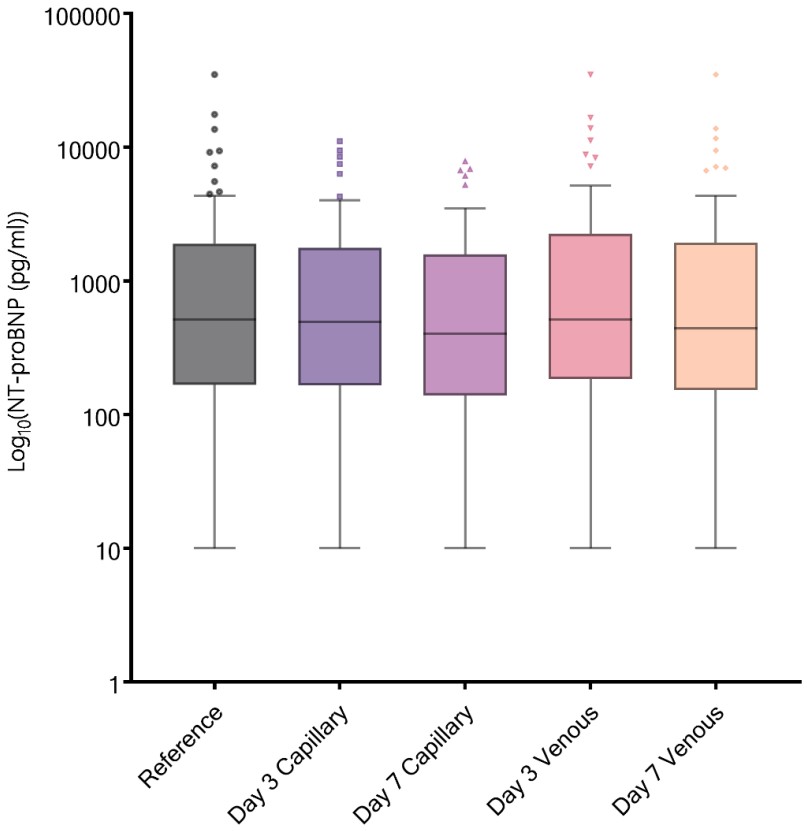


Figure 19. Box-and-whisker plot demonstrating reference and sendaway NT-proBNP results (pg/ml).

7.3.2 Invalid Samples

Valid results were obtained for all reference samples, 81% of Day 3 Capillary samples, 74% of Day 7 Capillary samples and 88% of Day 3 and Day 7 Venous samples. Of the invalid results, 13% of Day 3 Capillary, 19% of Day 7 Capillary and 1% of Day 3 Venous samples were not processed due to an insufficient quantity of blood in the container. One participant with severe Raynaud's was unable to provide any quantity of capillary blood yet was able to provide venous blood. Overall, 24 samples were delayed in the postal service and therefore not suitable for processing. Four samples were received by Thriva laboratories but were not processed, 1 sample was incorrectly labelled and 2 samples did not arrive to Thriva for reasons unknown. There was no significant difference in the proportion of invalid samples obtained during the summer months (April to September) when compared to the winter months (October to March).

7.3.3 Sendaway Capillary NT-proBNP

As shown in Figure 20, (a) the median relative difference between reference and Day 3 Capillary NT-proBNP was -7% (IQR -15% to 0%), (b) Passing-Bablok regression showed an estimated slope of 0.9 (95%CI 0.88 to 0.93), intercept of 6.0 (95% CI 0.2 to 15.9) and an r of 0.99 ($p<0.0001$) indicating there was excellent correlation yet the measures were not equivalent and (c) Bland-Altman analysis further demonstrating that Day 3 Capillary results were systematically lower than reference results (bias -88.9, SD 479.6 pg/ml) with limits of agreement from -1029 to 851 pg/ml. The median absolute difference was -30 pg/ml (IQR -137 to 0 pg/ml; Figure 21). Although the absolute differences were greater at higher values, the performance of the percentage difference was uniform across the range of values. Differences between reference and Day 3 Capillary results led to a different assignment of risk strata in 6 of 92 (6.5%) cases (Figure 22).

7.3.4 Sendaway Venous NT-proBNP

As shown in Figure 23, (a) the median relative difference between reference and Day 3 Venous NT-proBNP was 0% (IQR -4.5% to 7.4%), (b) Passing-Bablok regression showed an estimated slope of 1.0 (95% CI 0.9 to 1.02), intercept of 0.0 (95% CI -5.4 to 6.1) and an r of 0.99 ($p<0.0001$) indicating measurements were equivalent and (c) Bland-Altman analysis showing Day 3 Venous results were systematically higher than laboratory results (mean 76.6, SD 497 pg/ml) with limits of agreement from -897.5 to 1051 pg/ml. The median absolute difference was -4 pg/ml (IQR -85 to 13; Figure 21). Differences between reference and Day 3 Venous results led to a different assignment of risk strata in 8 of 88 (9.1%) cases (Figure 22).

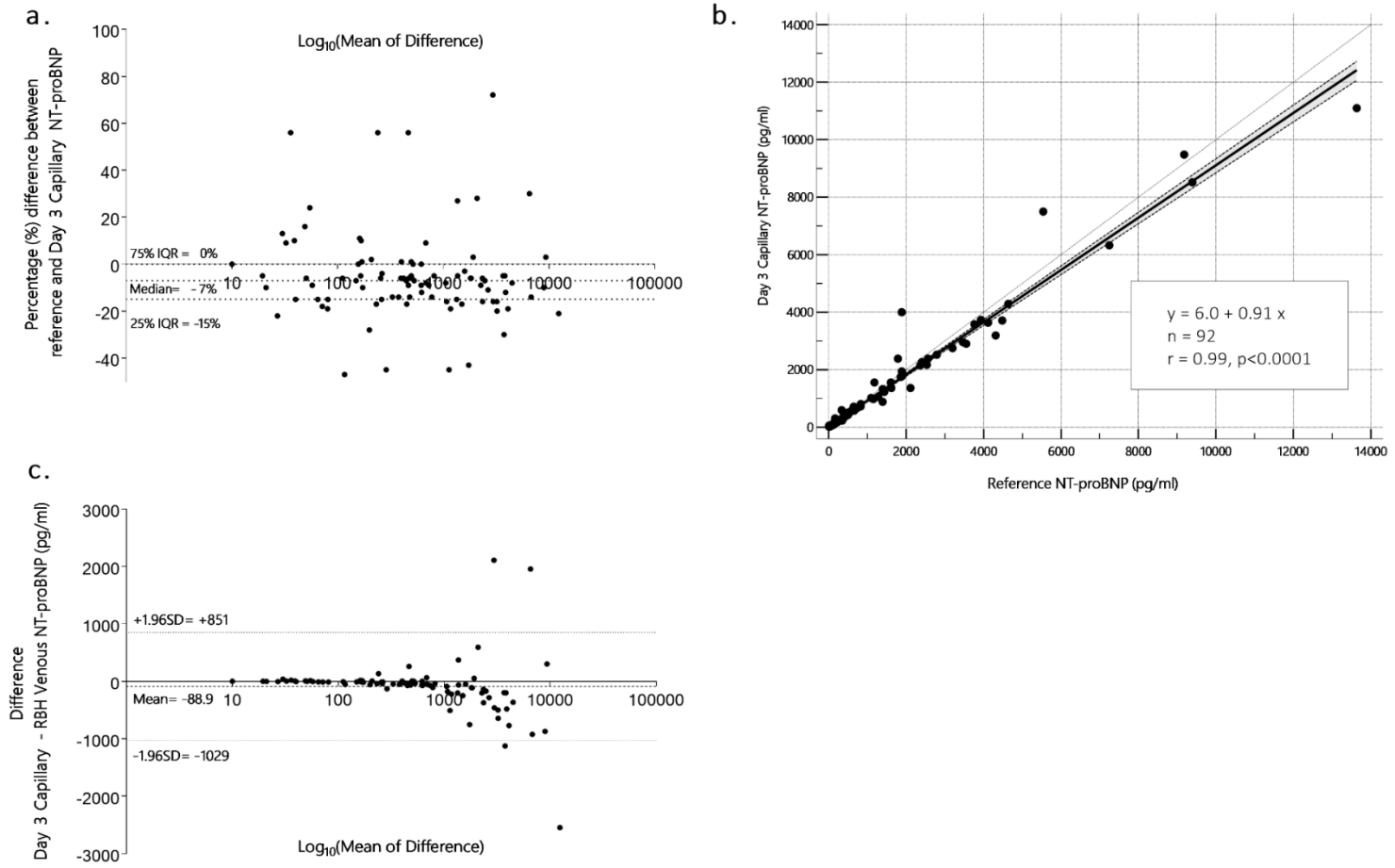


Figure 20. Analysis comparing Reference and Sendaway Day 3 Capillary NT-proBNP (pg/ml) using (a) percentage difference plot demonstrating a median difference of -7%, (b) Passing-Bablok regression showing strong correlation (r=0.99), with a slope of 0.91 (95%CI = 0.88 to 0.93) and intercept of 6.0 (95% CI = 0.2 to 15.9) and (c) Bland Altman plot showing a bias of -89.9 with limits of agreement -1029 to 851.

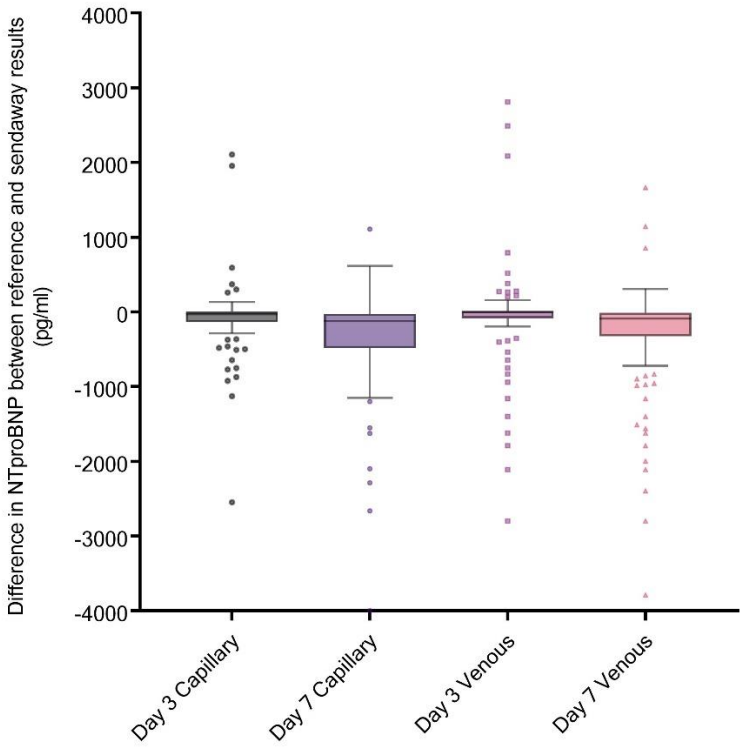


Figure 21. Box-and-whisker plot demonstrating the median difference (interquartile range) between each sendaway tests and reference NT-proBNP (pg/ml). Day 7 results are systematically lower than Day 3 results, reflecting the reduced stability of NT-proBNP over time.

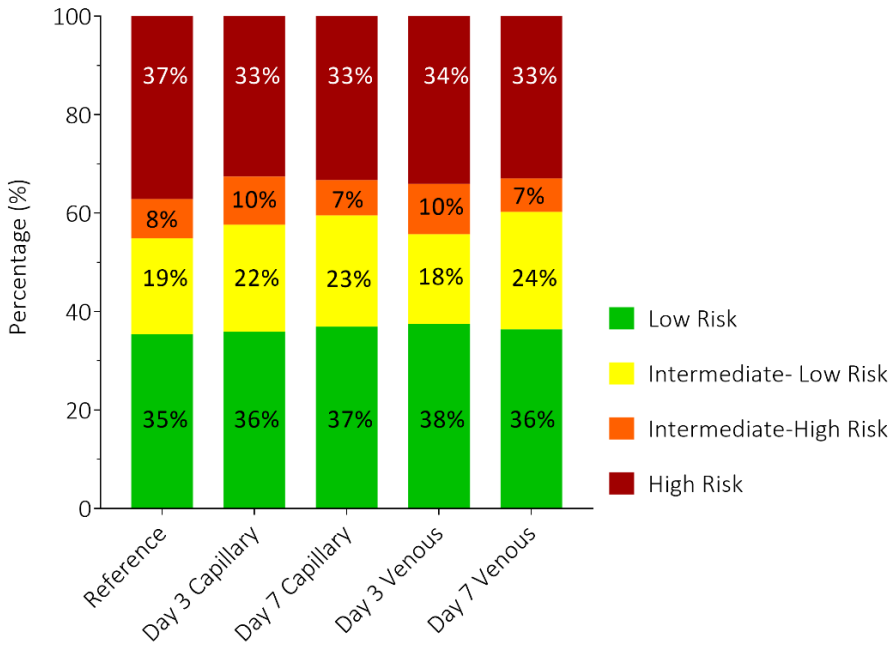


Figure 22. Percentage of participants as classified by COMPERA 2.0 risk status as based on reference and study NT-proBNP results.

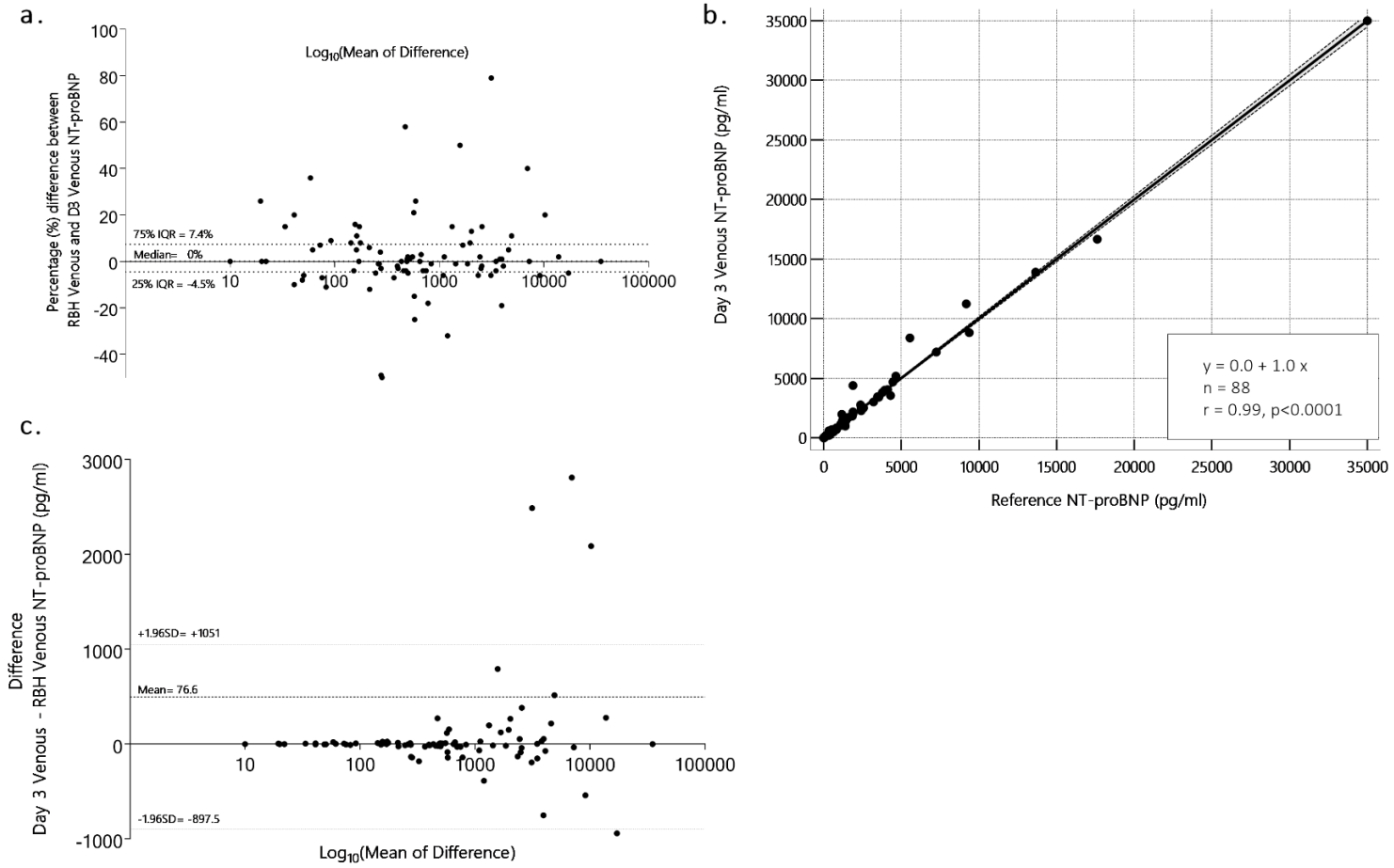


Figure 23. Analysis comparing Reference and Sendaway Day 3 Venous NT-proBNP (pg/ml) using (a) percentage difference plot demonstrating a median difference of 0%, (b) Passing-Bablok regression showing strong correlation (r=0.99), with a slope of 1.0 (95%CI = 0.9 to 1.0) and intercept of 0.0 (95% CI = -5.4 to 6.1) and (c) Bland Altman plot showing a bias +76.6 with limits of agreement -897.5 to 1051.

7.3.5 Stability of Sendaway NT-proBNP

Overall, capillary and venous samples at Day 7 had poorer agreement to the reference NT-proBNP, when compared to the Day 3 results. Day 7 results systematically underestimated the reference NT-proBNP.

7.3.5.1 Sendaway Day 7 Capillary NT-proBNP Results

As shown in Figure 24, (a) the median relative difference between reference and Day 7 Capillary NT-proBNP was -28% (IQR -37.6% to -16.9%), (b) Passing-Bablok regression showed that results were significantly different to the reference with greater deviation when compared to Day 3 Capillary results and (c) Bland-Altman analysis demonstrated a mean difference of -392.4 pg/ml (SD 819) and limits of agreement -1999 to 1214 pg/ml. The median absolute difference was -122 pg/ml (IQR -483 to -28, Figure 21). Differences between reference and Day 7 Capillary results led to a different assignment of risk strata in 10 of 84 (11.9%) cases (Figure 22).

7.3.5.2 Sendaway Day 7 Venous NT-proBNP Results

As shown in Figure 25, (a) the median relative difference between reference and Day 7 Venous NT-proBNP was -18.4% (IQR -28.1% to 6.7%), (b) Passing-Bablok regression showed that results were significantly different to the reference with greater deviation when compared to Day 3 Venous results and (c) Bland-Altman analysis demonstrated a mean difference of -227 pg/ml (SD 643) and limits of agreement -1488 to 1034 pg/ml. The median absolute difference was -87.5 pg/ml (IQR -325.5 to -10.8, Figure 21). Differences between reference and Day 7 Venous results led to a different assignment of risk strata in 12 of 88 (13.6%) cases (Figure 22).

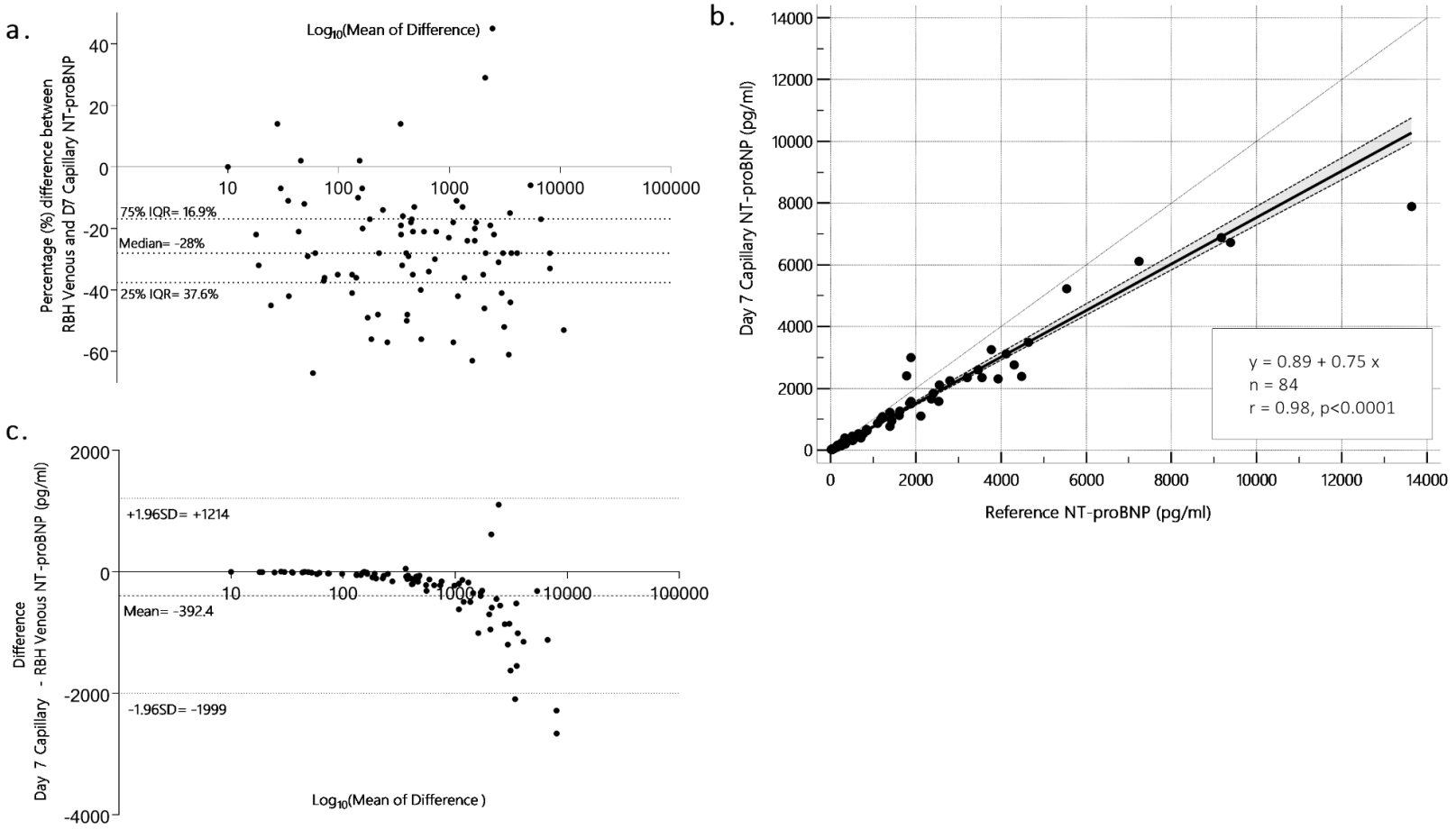


Figure 24. Analysis comparing Reference and Sendaway Day 7 Capillary NT-proBNP (pg/ml) using (a) percentage difference plot demonstrating a median difference of -28%, (b) Passing-Bablok regression showing strong correlation (r=0.98), with a slope of 0.75 (95%CI = 0.73 to 0.79) and intercept of 0.89 (95% CI = -5.2 to 7.09) and (c) Bland Altman plot showing a bias of -392.4 with limits of agreement -1999 to 1214.

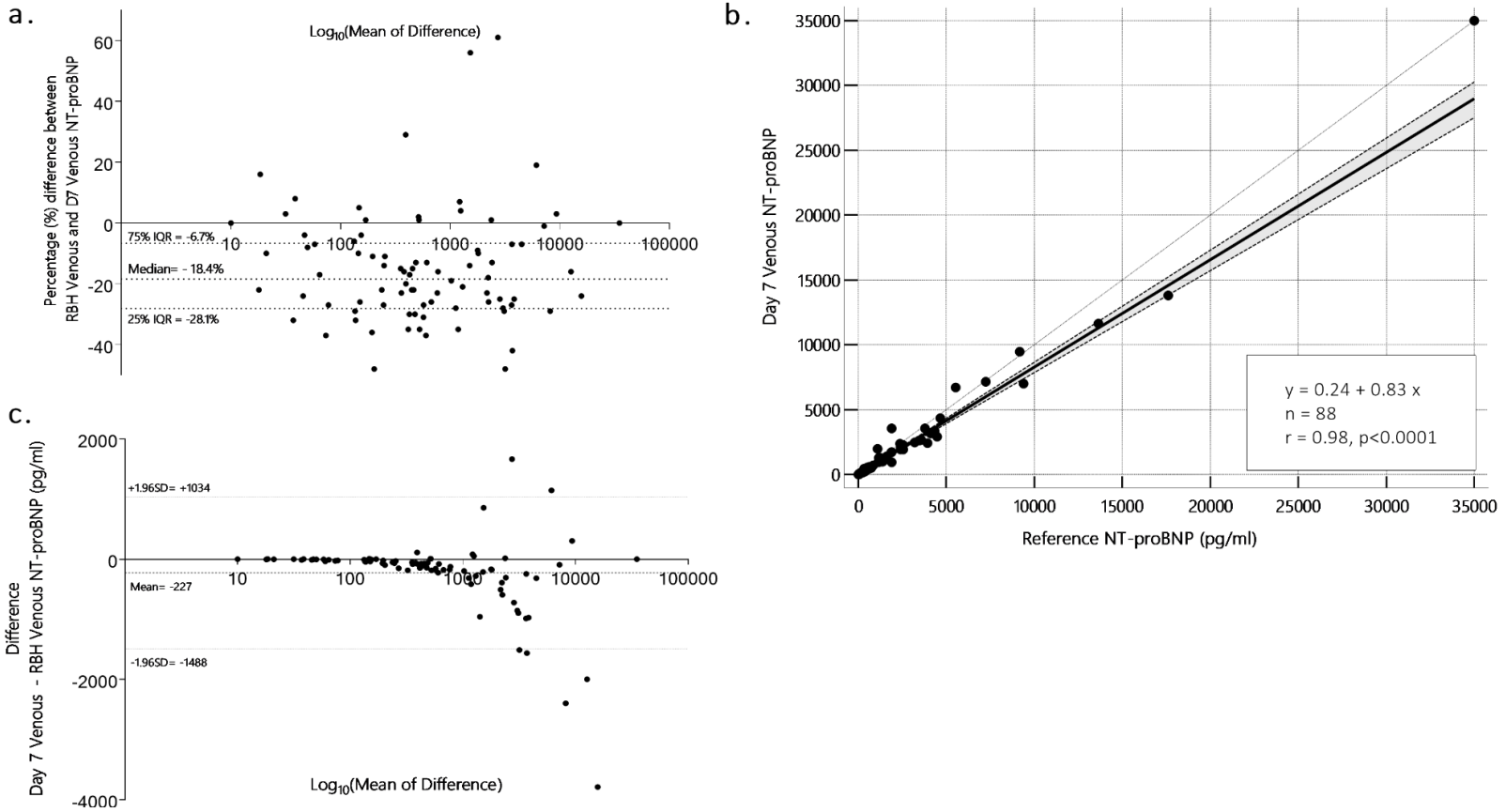


Figure 25. Analysis comparing Reference and Sendaway Day 7 Venous NT-proBNP (pg/ml) using (a) percentage difference plot demonstrating a median difference of -18.4%, (b) Passing-Bablok regression showing strong correlation (r=0.98), with a slope of 0.83 (95%CI = 0.78 to 0.86) and intercept of 0.24 (95% CI = -9.6 to 8.0) and (c) Bland Altman plot showing a bias of -227 with limits of agreement -1488 to 1034.

7.3.6 Comparison with Local NT-proBNP Results

Further analysis was performed, replacing the Royal Brompton Hospital laboratory results as the reference standard with the Local laboratory results. Overall, the agreement between the Local and studied NT-proBNP was similar yet slightly poorer to when compared to RBH reference NT-proBNP.

7.3.6.1 Local Lab and Day 3 Capillary NT-proBNP

As shown in Figure 26, (a) The median relative difference was -11% (IQR -20% to -6%). (b) Passing-Bablok regression showed an estimated slope of 0.91 (95%CI 0.88 to 0.93), intercept of -2.4 (95%CI -6.8 to 2.0) and an r of 0.99 (p<0.0001) indicating there was excellent correlation yet the measures were not equivalent. (c) Bland-Altman analysis demonstrates that Day 3 Capillary results were systematically lower than reference results (bias -165, SD 340 pg/ml) with limits of agreement from -832 to 502 pg/ml. Differences between Local lab and Day 3 Capillary results led to a different assignment of risk strata in 14 of 92 (15.2%) cases.

7.3.6.2 Local Lab and Day 3 Venous NT-proBNP.

As shown in Figure 27, (a) The median relative difference was -1% (IQR -8% to 5%). (b) Passing-Bablok regression showed an estimated slope of 1.02 (95%CI 0.99 to 1.04), intercept of -8.1 (95%CI -16.2 to -2.7) and an r of 0.99 (p<0.0001) indicating there was excellent correlation yet the measures were not equivalent. (c) Bland-Altman analysis demonstrates that Day 3 Venous results were systematically higher than reference results (bias 27, SD 389 pg/ml) with limits of agreement from –736 to 789 pg/ml. Differences between Local lab and Day 3 Venous results led to a different assignment of risk strata in 14 of 88 (15.9%) cases.

7.3.6.3 Local Lab and Day 7 Capillary NT-proBNP.

As shown in Figure 28, (a) The median relative difference was -32% (IQR -47% to -23%). (b) Passing-Bablok regression showed an estimated slope of 0.74 (95%CI 0.71 to 0.76), intercept of -4.65 (95%CI -9.3 to 2.8) and an r of 0.99 (p<0.0001) indicating there was excellent correlation yet the measures were not equivalent. (c) Bland-Altman analysis demonstrates that Day 7 Capillary results were systematically lower than reference results (bias -469, SD 761 pg/ml) with limits of agreement from -1962 to 1022 pg/ml. Differences between Local lab and Day 7 Capillary results led to a different assignment of risk strata in 14 of 84 (16.7%) cases.

7.3.6.4 Local Lab and Day 7 Venous NT-proBNP.

As shown in Figure 29, (a) The median relative difference was -23% (IQR -36% to -11%). (b) Passing-Bablok regression showed an estimated slope of 0.83 (95%CI 0.80 to 0.86),

intercept of -8.58 (95%CI -18.1 to -0.39) and an r of 0.99 ($p<0.0001$) indicating there was excellent correlation yet the measures were not equivalent. (c) Bland-Altman analysis demonstrates that Day 7 Venous results were systematically lower than reference results (bias -292, SD 592 pg/ml) with limits of agreement from -1452 to 867 pg/ml. Differences between Local lab and Day 7 Venous results led to a different assignment of risk strata in 18 of 88 (20.5%) cases.

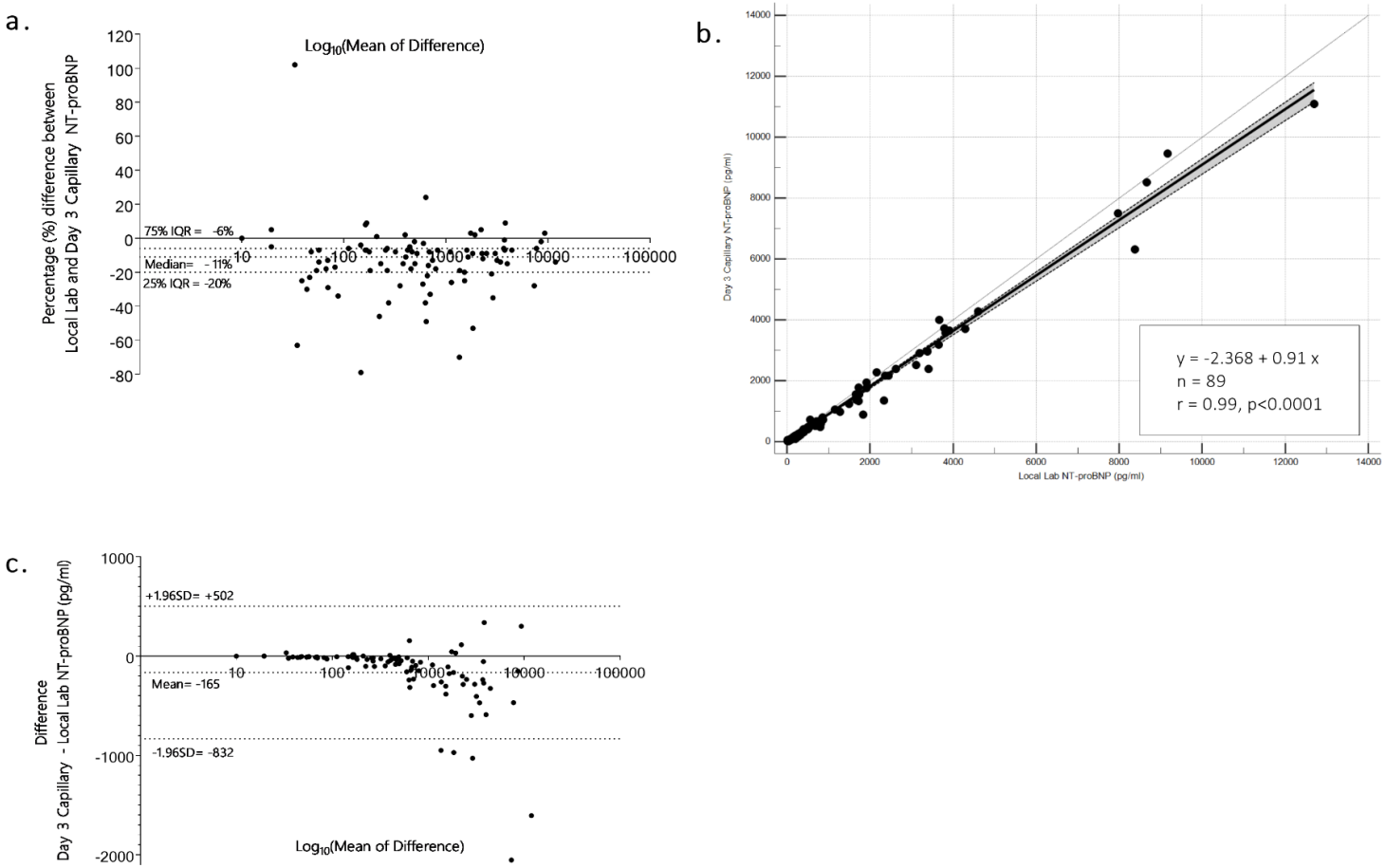


Figure 26. Comparison between Local Lab and Day 3 Capillary NT-proBNP. (a) The median relative difference was -11% (IQR -20% to -6%). (b) Passing-Bablok regression showed an estimated slope of 0.91 (95%CI 0.88 to 0.93), intercept of -2.4 (95%CI -6.8 to 2.0) and an r of 0.99 ($p<0.0001$). (c) Bland-Altman analysis demonstrates a bias of -165 with limits of agreement from -832 to 502 pg/ml.

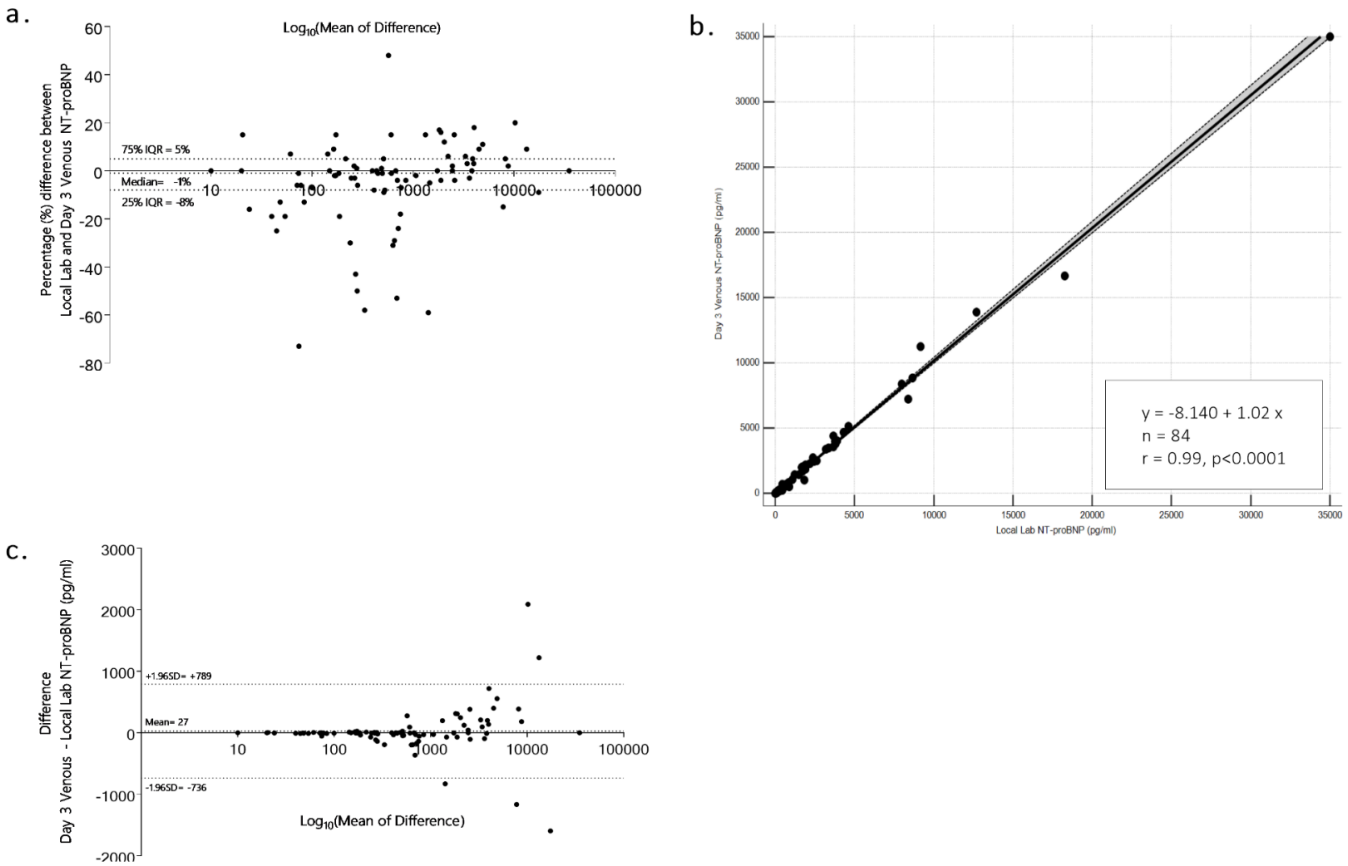


Figure 27. Comparison between Local Lab and Day 3 Venous NT-proBNP. (a) The median relative difference was -1% (IQR -8% to 5%). (b) Passing-Bablok regression showed an estimated slope of 1.02 (95%CI 0.99 to 1.04), intercept of -8.1 (95%CI -16.2 to -2.7) and an r of 0.99 (p<0.0001). (c) Bland-Altman analysis demonstrates a bias of 27 with limits of agreement from –736 to 789 pg/ml.

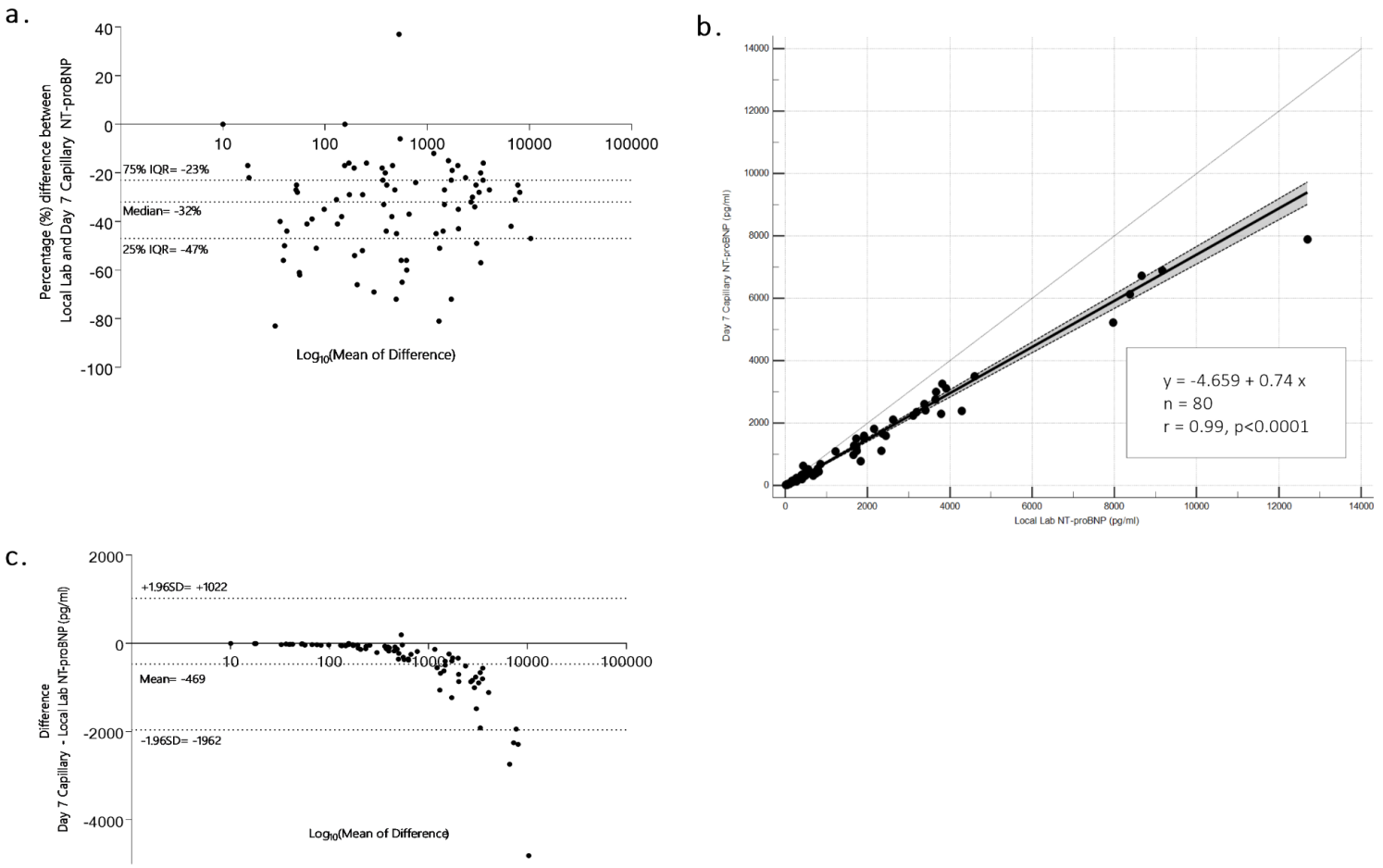


Figure 28. Comparison between Local Lab and Day 7 Capillary NT-proBNP. (a) The median relative difference was -32% (IQR -47% to -23%). (b) Passing-Bablok regression showed an estimated slope of 0.74 (95%CI 0.71 to 0.76), intercept of -4.65 (95%CI -9.3 to 2.8) and an r of 0.99 ($p<0.0001$). (c) Bland-Altman analysis demonstrates a bias of -469 with limits of agreement from -1962 to 1022.

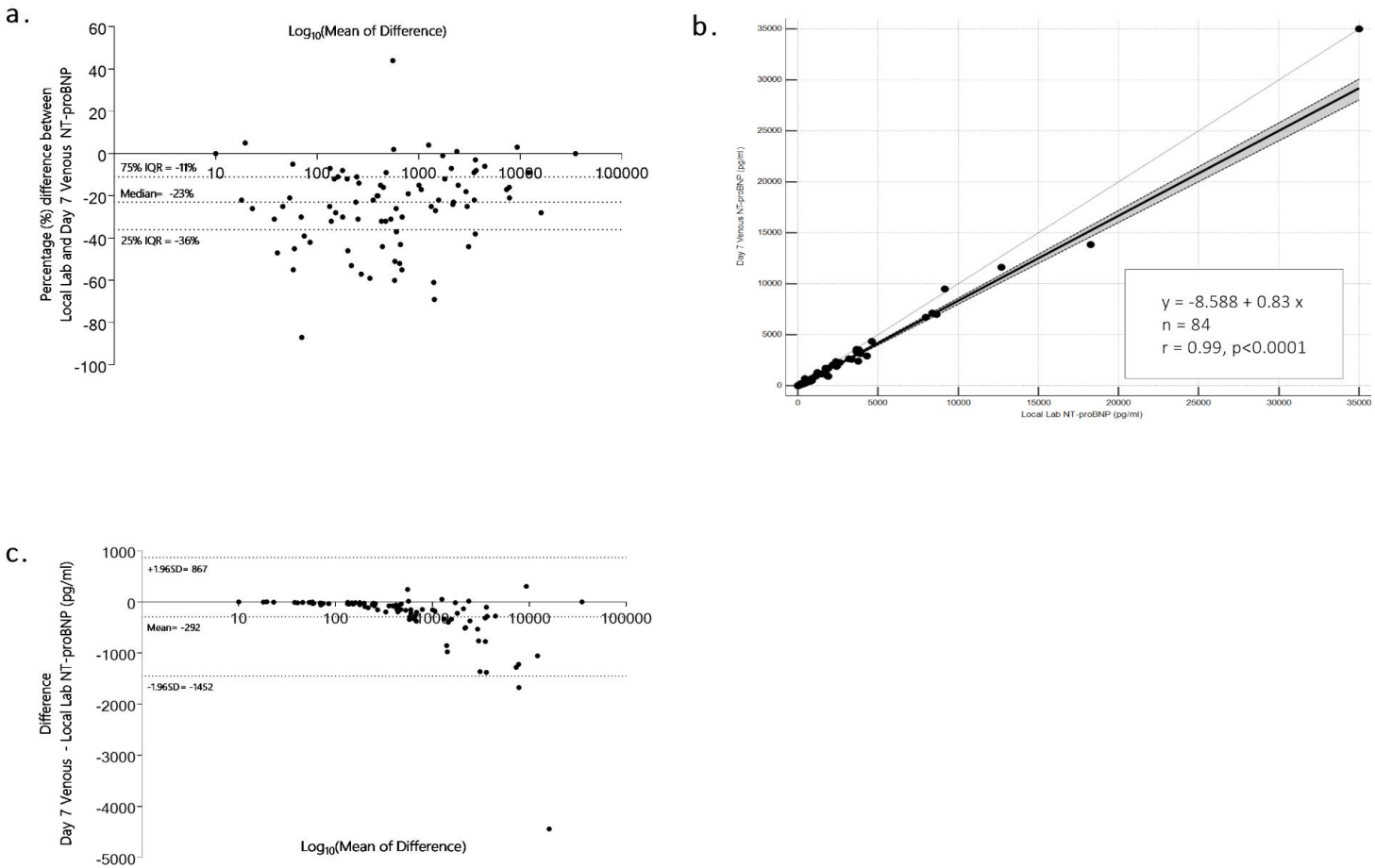


Figure 29. Comparison between Local Lab and Day 7 Venous NT-proBNP. (a) The median relative difference was -23% (IQR -36% to -11%). (b) Passing-Bablok regression showed an estimated slope of 0.83 (95%CI 0.80 to 0.86), intercept of -8.58 (95%CI -18.1 to -0.39) and an r of 0.99 ($p<0.0001$). (c) Bland-Altman analysis demonstrates a bias of -292 with limits of agreement from -1452 to 867.

7.4 Discussion

The study investigated the agreement of sendaway capillary NT-proBNP when compared to a standard venous NT-proBNP, in order to consider whether such an approach could be used in a virtual pulmonary hypertension clinic.

When assessed for percentage difference, sendaway Day 3 Capillary NT-proBNP demonstrated good agreement and accurately risk stratified participants as per COMPERA 2.0 thresholds in 93.5% of cases. However, Day 3 Capillary sampling was not equivalent to standard venous NT-proBNP when using Passing-Bablok analysis. This level of agreement for risk stratification for Day 3 Capillary samples would likely be acceptable for a virtual clinic, although clinicians would need to take into account the unreliability of delayed samples. This is especially pertinent as patients are more likely to be misclassified into a lower risk category, and hence the situation may arise where the opportunity for a treatment escalation is missed as a patient is erroneously misclassified as low risk. Remote capillary sampling could be best used for PAH patients in lower risk strata, where remote tests are used to confirm stability, and a significant rise in NT-proBNP would prompt urgent face-to-face assessment.

Sendaway Day 3 Venous results accurately risk stratified participants in 90.1% of cases and were equivalent by Passing-Bablok regression. Sendaway venous NT-proBNP could have practical applications, allowing the tertiary PH centre to cover the cost, infrastructure and follow-up of the test, yet this method would rely on a third party – such as a local phlebotomist, district nurse or General Practitioner – performing venepuncture.

Delayed sampling of sendaway tests led to an unacceptable level of agreement with a systematic underestimation of NT-proBNP. The systematically lower capillary NT-proBNP results in both venous and capillary results, are likely due to the reduced stability of NT-proBNP over time(56, 195), as further shown by the poorer agreement when compared between Day 3 and Day 7 results.

There was a high proportion of insufficient capillary samples (13%), with feedback from the healthcare practitioners performing the test commenting that obtaining the required 600µL of blood could be occasionally difficult. Furthermore, 24 samples were delayed in the postal service, although it was noted that the study took place during a period of UK Royal Mail industrial action between August to December 2022(204). The high number of invalid results in a real-world setting may reduce the overall utility of sendaway capillary testing and further disruption to the postal service may jeopardise this model.

One patient was unable to provide any capillary samples due to severe Raynaud's. However, this study included a high proportion of patients with CTD-PAH, potentially demonstrating that some patients with poor peripheral perfusion due to scleroderma are able to perform capillary testing. However, this study did not collect data on whether patients with scleroderma subsequently experienced adverse effects, such as digital ulceration, and future work should include this.

Previous studies have investigated the use of NT-proBNP point-of-care testing (POCT). In left heart failure, POCT has been extensively studied for use in screening, overall demonstrating acceptable agreement when samples were tested contemporaneously(59, 199, 205-207). The REPEAT-PAH study investigated the agreement between reference and POCT NT-proBNP in patients with PH using a Quidel Triage MetrePro device, where a capillary sample is obtained by a healthcare professional with a result available within 20 minutes. Between reference and POCT NT-proBNP, the intraclass correlation coefficient was 0.98 and Bland-Altman analysis demonstrated the bias increased proportional to the magnitude of reference NT-proBNP, as seen in this study(154, 200). The effect of delayed processing was investigated (mean delay 2.6 days) with an ICC of 0.99 between results, yet a more comprehensive analysis including Passing-Bablok regression was not performed.

This study was limited by the lack of a patient feedback questionnaire on the process of capillary sampling. As this was primarily an agreement study, capillary samples were obtained by healthcare professionals, not by patients, and hence the feasibility of fingerpick samples at home in this population is unknown. This is clearly relevant given the high proportion of insufficient capillary samples in the study. Furthermore, an assessment of intra-test reliability was not performed as only one capillary sample was taken for Day 3 and Day 7 results respectively. This study relied on the UK national postage service and therefore may not be applicable in all countries. Future work will focus on implementing capillary NT-proBNP sampling in a group of patients in an existing virtual clinic to assess the following (i) feasibility, (ii) patient perceptions and (iii) adverse effects of capillary sampling. Future work should aim to reduce the number of invalid samples by increasing patient education of how to perform the test and allowing "practice runs" in order to refine the fingerpick technique. NT-proBNP has been demonstrated to show diurnal variation, with higher values later in the day. Future work could focus on assessing the difference in haemodynamics and NT-proBNP levels throughout the day using an implantable haemodynamic monitor, to assess whether samples should be always taken at a similar time to allow accurate intra-patient comparison(60).

7.5 Conclusion

In conclusion, capillary sendaway NT-proBNP sampling may allow specialist PH teams to incorporate an assessment of right ventricular function into virtual clinics, without requiring patients to travel. Capillary results were within acceptable limits of agreement and accurately risk stratified patients in the majority of cases, however they must be interpreted with caution in cases of delayed sampling. Venous sendaway NT-proBNP demonstrated superior statistical agreement with reference values yet with a similar accuracy at risk stratification and therefore could also be relied upon. These could be obtained by patients attending their local health provider.

Risk Assessment Modelling in Pulmonary Hypertension

Chapters

8. COMPERA 2.0 risk stratification in medically-managed Chronic Thromboembolic Pulmonary Hypertension

8.1 Introduction

Risk stratification tools are employed in pulmonary hypertension at diagnosis and during follow up. As has been discussed in the Introduction, risk assessment allocates patients to a risk stratum which guides clinical management decisions, identifies patients who are likely to deteriorate, and informs prognosis. In 2015 the European Respiratory Society (ERS) / European Society of Cardiology (ESC) guidelines advocated the 3-strata risk assessment model for patients with Pulmonary Arterial Hypertension (PAH), using a multi-metric model to categorise patients into low-, intermediate- or high- risk of mortality at 1 year. However, using this approach, registry data shows a large proportion of patients are classified as *intermediate* risk, a therefore heterogenous group which led to difficulty in applying uniform treatment decisions.

In 2021 the 4-strata model, known as COMPERA 2.0, was proposed which incorporated an additional stratum which aimed to divide the previous *intermediate* risk group into an *intermediate-low* and *intermediate-high* group, aiming to improve the granularity of risk assessment(90, 91). This method uses three non-invasive variables from the 3-strata model (NT-proBNP, 6MWT and WHO FC), and yet incorporates different thresholds and allowed a robust non-invasive follow up risk assessment strategy. The 4-strata method was subsequently incorporated into the 2022 ERS/ESC guideline as the method that should be used during follow up(1).

Chronic thromboembolic pulmonary hypertension (CTEPH) occurs as the result of persistent pulmonary vascular occlusion by organized thrombi following an acute pulmonary embolism, with subsequent vascular remodelling(29). The mechanisms and epidemiology underpinning CTEPH are discussed in the introductory chapter. Whilst a distinct entity to PAH, the pulmonary vascular obstruction seen in CTEPH leads to a similar clinical phenotype of increased pulmonary vascular resistance which may progress to right heart failure and ultimately death if untreated(76). When the burden of disease is predominantly proximal (known as Central CTEPH), patients may be eligible for interventional treatment, either with major cardiothoracic surgery (Pulmonary Endarterectomy, PEA) or via catheter-mediated Balloon Pulmonary Angioplasty (BPA)(79). Patients with a distal disease burden (surgically-inoperable or Distal CTEPH), or who are unable to undergo interventional treatment, due to medical co-morbidities or inclination, may be treated with pulmonary vasodilator therapy.

Patients in this cohort, alongside patients who have had interventional treatment yet still have pulmonary hypertension at repeat haemodynamic assessment (Residual CTEPH), may be described as medically-managed CTEPH.

The 3-strata model was retrospectively validated in medically-managed CTEPH in 2018 using the COMPERA registry(88). Whilst the novel COMPERA 2.0 model has been validated in pulmonary arterial hypertension(90, 91) and pulmonary veno-occlusive disease (PVOD)(208) it awaits validation in other PH groups, including CTEPH. Therefore, this study aimed to validate the COMPERA 2.0 model in patients with medically-managed CTEPH.

8.2 Methods

A retrospective analysis was undertaken of all records of patients who were diagnosed with CTEPH at the Scottish Pulmonary Vascular Unit (SPVU) over ten years between 1st January 2010 and 31st December 2020. Patients were included if they met the following criteria; (i) ≥18 years, (ii) diagnosed with CTEPH as according to the 2015 ERS/ESC standard diagnostic criteria(5, 76) and based on multi-disciplinary team (MDT) consensus, (iii) incident diagnosis of treatment-naïve CTEPH and did not have pulmonary endarterectomy (PEA) or balloon angioplasty (BPA) during follow-up or (iv) patients who had residual PH following PEA or BPA. Patients with Residual CTEPH were included at the point of repeat right heart catheterisation confirming residual PH. Patients were excluded if they were missing any of baseline WHO FC, 6MWD or NT-proBNP. Diagnostic admission, including right heart catheterisation, served as the baseline visit. Risk according to the 3-strata method and 4-strata method was performed as had been previously described by HOEPER (Appendix 12.5 Risk stratification methodology(90)). Repeat non-invasive risk stratification was performed at first follow-up, with mortality calculated from the date of first follow up.

8.2.1 Statistical Analysis

The primary outcome was all-cause mortality with survival time calculated from the date of diagnosis until death, truncated at 5 years. Survival analysis was performed with Kaplan-Meier analysis with the log rank test. Cox proportional hazard ratios (HR) were calculated in reference to the high risk category. Harrell's C Statistic and the Akaike Information Criteria (AIC) were used to compare Cox models for mortality. Sankey diagrams provided a visual representation of patient flow between risk groups at baseline and first follow up. The statistical methods are covered in further detail in the Methods chapter.

8.3 Results

8.3.1 Patient Characteristics

A total of 218 patients met the inclusion criteria of newly diagnosed CTEPH or residual PH following PEA/BPA (Figure 30). 20 patients were excluded as they were missing baseline data and 70 patients had no residual PH following PEA. 128 patients were therefore included in the baseline cohort of whom 52 (40.6%) were surgically inoperable, 26 (20.3%) were medically inoperable, 23 (17.9%) declined PEA, 19 (14.8%) had residual PH following PEA or BPA and 7 (5.4%) died whilst PEA was being considered. Patient characteristics at baseline are demonstrated in Table 22 and are similar to those presented in the 2018 COMPERA validation cohort(88). The median follow up observation time was 2.96 years (IQR 1.6 – 4.6) and during follow up 61 (47.6%) patients died. Overall survival for the cohort at 1-, 3- and 5-years was 86.6%, 67.6% and 50.9%.

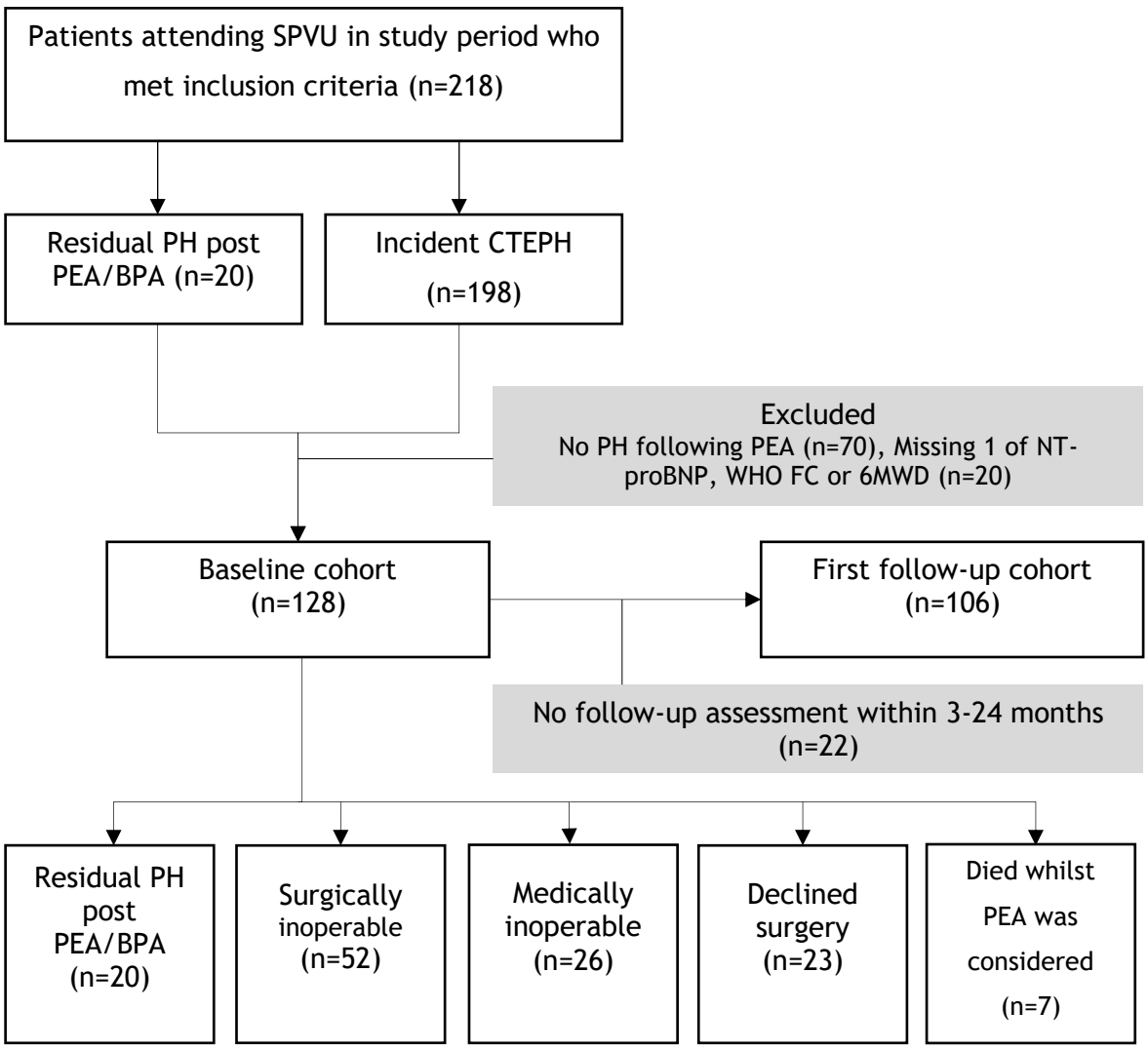


Figure 30. Study flow diagram for inclusion into the COMPERA 2.0 study

	All	Low Risk	Intermediate-Low Risk	Intermediate-High Risk	High Risk
Number	128	8	32	63	25
Age (yrs.)	69 ± 12	66 ± 10	65 ± 11	69 ± 12	77 ± 11
Male, n (%)	69 (54)	7 (88)	21 (66)	34 (54)	7 (28)
BMI	27.9 ± 6.0	27.6 ± 3.3	27.5 ± 5.8	28.9 ± 6.1	26.1 ± 6.0
CTEPH sub-group, n (%)					
Surgically inoperable	52 (41)	6 (75)	14 (44)	24 (38)	8 (32)
Medically inoperable	26 (20)	1 (13)	3 (9)	11 (17)	11 (44)
Declined PEA	23 (18)	1 (13)	5 (16)	13 (21)	4 (16)
Residual PH	20 (16)	0	8 (25)	10 (16)	2 (8)
Died during consideration of PEA	7 (5)	0	2 (6)	5 (8)	0
Co-morbidities, n (%)					
Obesity	35 (27)	1 (13)	7 (22)	21 (33)	6 (24)
Coronary Heart Disease	12 (9)	0	2 (6)	6 (10)	4 (16)
Diabetes Mellitus	14 (11)	0	2 (6)	7 (11)	5 (20)
Systemic Hypertension	39 (30)	3 (38)	11 (34)	16 (25)	9 (36)
Atrial Fibrillation	12 (9)	0	3 (9)	4 (6)	5 (20)
WHO Functional Class, n (%)					
I / II	24 (19)	8 (100)	14 (44)	2 (3)	0
III	99 (77)	0	18 (56)	60 (95)	21 (84)
IV	5 (4)	0	0	1 (2)	4 (16)
Baseline data and right Heart catheterisation haemodynamics					
6MWD, m	263 ± 133	488 ± 65	365 ± 99	244 ± 93	110 ± 38
NT-proBNP, pg/ml	2244 ± 2582	130 ± 88	835 ± 1124	2398 ± 2021	4356 ± 3719
RAP, mmHg	7.7 ± 5.5	5.9 ± 3.1	4.8 ± 4.0	8.7 ± 5.4	9.3 ± 6.4
mPAP, mmHg	40.2 ± 9.9	36.8 ± 7.4	35.5 ± 10.0	42.0 ± 10.0	43.1 ± 7.6
PAWP, mmHg	9.2 ± 4.4	9.9 ± 2.7	8.8 ± 4.9	8.9 ± 4.3	9.9 ± 4.3
CI, L/min/m^2	2.1 ± 0.6	2.2 ± 0.4	2.46 ± 0.6	2.0 ± 0.5	1.9 ± 0.5
PVR, WU	8.8 ± 4.4	6.8 ± 2.5	6.2 ± 3.2	9.6 ± 4.6	10.7 ± 4.2
SvO2, %	60.9 ± 9.0	68.5 ± 4.8	67.4 ± 6.7	59.6 ± 8.0	53.6 ± 7.6
Initial Treatment Strategy, n (%)					
No therapy	33 (26)	2 (25)	8 (25)	18 (29)	5 (20)

Monotherapy	89 (70)	6 (75)	24 (75)	43 (68)	16 (64)
Dual therapy	6 (5)	0	0	2 (3)	4 (16)

Table 22. Characteristics of the baseline cohort with risk-strata calculated using the COMPERA 2.0 4-strata model

8.3.2 Mortality Risk Assessment at Baseline

At baseline, the proportion of patients within each risk group as calculated by either strata model is demonstrated in Table 23.

3-strata				
	Low Risk	Intermediate Risk		High Risk
N, %	10 (7.8)	93 (72.7)		25 (19.5)
4-strata				
	Low Risk	Intermediate-Low Risk	Intermediate-High Risk	High Risk
N, %	8 (6.3)	32 (25)	63 (49.2)	25 (19.5)

Table 23. Risk stratification according to 3-strata and 4-strata models at baseline

The 4 strata model calculated survival at 1, 3 and 5 years respectively as 100%, 100%, 100% for low risk, 93%, 79.4%, 57% for intermediate-low risk, 91.5%, 68.4%, 42.8% for intermediate-high risk and 83.3%, 46.2% and 22.9% for high risk ($p<0.0001$ for between group comparison, Figure 31A).

Survival calculated by the 3-strata model was 100%, 100%, 100% for low risk, 86.9%, 68.8%, 48.3% for intermediate risk and 80%, 48.5%, 36.3% for high risk ($p<0.0001$, Figure 31B). As no patients died in the low risk groups using either model at baseline, these patients were censored from analysis of both models and hazard ratios were calculated in reference to the high risk group. Using Cox proportional hazard regression models, there was a decreasing risk of death for patients in the intermediate risk groups compared to high risk at baseline for both strata models (Table 24) although the confidence intervals overlapped.

There was no difference in the discrimination of overall mortality at baseline for either strata method; Harrell's C Statistic (95% confidence interval) was 0.62 (0.54-0.69) and AIC was 482.4 using the 4-strata method compared to 0.62 (0.55-0.68) and 481.3 for the 3-strata method.

	Baseline		Follow Up	
Risk Strata	Hazard Ratio	95% CI	Hazard Ratio	95% CI
3-strata				
Low	-	-	0.07	0.01-0.27
Intermediate	0.44	0.25-0.79	0.38	0.19-0.86
High	1	-	1	-
4-strata				
Low	-	-	-	-
Intermediate-Low	0.32	0.15-0.69	0.21	0.08-0.54
Intermediate-High	0.47	0.27-0.86	0.48	0.23-1.1
High	1	-	1	-

Table 24. Hazard ratios with reference to the high risk group.

8.3.3 Mortality Risk Assessment at First Follow Up

The median time to first follow-up was 3.6 months (IQR 2.9-4.2) and information for NT-proBNP, WHO FC and 6MWD were available in 106 (83%) of cases. 80% of patients were on monotherapy, 5% dual and 15% were untreated. At follow up, the proportion of patients within each risk group as calculated by either strata model is demonstrated in Table 25.

3-strata				
	Low Risk	Intermediate Risk		High Risk
Number (%)	18 (17.0)	74 (69.8)		14 (13.2)
4-strata				
	Low Risk	Intermediate-Low Risk	Intermediate-High Risk	High Risk
Number (%)	11 (10.4)	31 (29.2)	50 (47.2)	14 (13.2)

Table 25. Risk stratification according to 3-strata and 4-strata models at follow-up

At follow-up, using the 4-strata model 1-, 3- and 5- year survival was calculated at 100%, 100%, 100% for low risk, 95.6%, 90.8%, 67.4% for intermediate-low risk, 88.9%, 68.2%, 49% for intermediate-high risk and 83.7%, 52.2%, 22.3% for high risk ($p<0.0001$, Figure 31C). Using the 3-strata model this was 100%, 100%, 87.5% for low risk, 90.5%, 72.2%, 48.9% for intermediate risk and 78.7%, 44%, 22.3% for high risk ($p<0.0001$, Figure 31D).

At follow up, using Cox proportional hazard regression models, there was a decreasing risk of death for patients in the intermediate risk groups compared to high risk at baseline for both strata models (Table 24) although these data were non-significant.

The 4-strata model discrimination for 1-year mortality after diagnosis was modestly higher compared to the 3-strata model (Harrell's C 0.70 (95% CI 0.62-.77), AIC 336 vs. Harrell's C 0.65 (0.58-0.71), AIC 341) although non-significant.

8.3.4 Change in Survival

Sankey diagrams for both strata methods were used to represent changes in risk strata from baseline to follow up (Figure 32). Overall, 35 (33%) patients changed risk group between diagnosis and first follow-up when the 4-strata model was used, as opposed to 25 (23.6%) for the 3-strata model. Within the intermediate risk groups, 31.6% of patients moved out of an intermediate risk group with the 4-strata model as opposed to 10.4% with the 3-strata model.

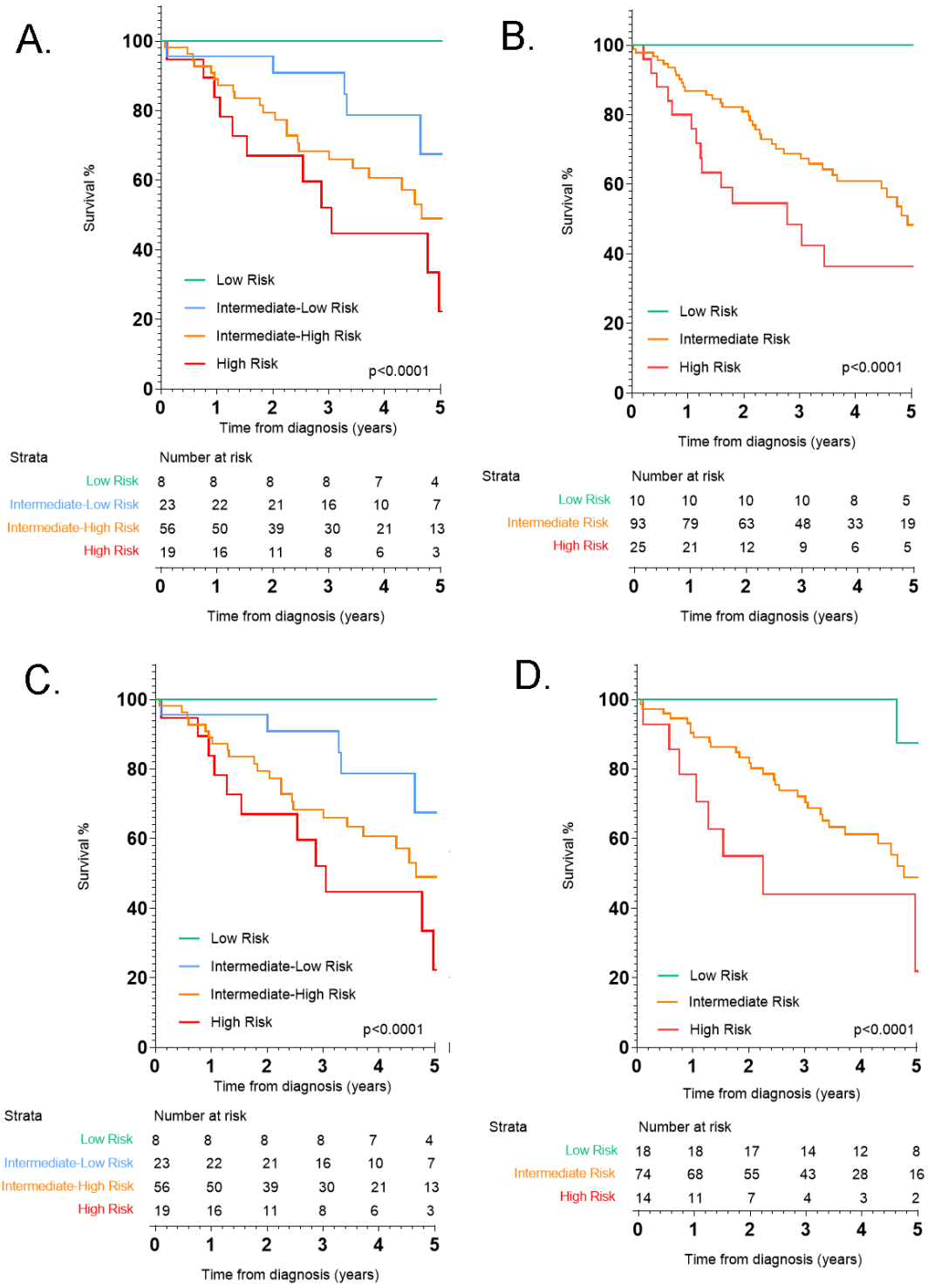


Figure 31. Kaplan-Meier curves demonstrating five-year survival for medically-managed CTEPH as calculated by the a) 4-strata model from baseline, b) 3-strata model from baseline, c) 4-strata model from follow-up d) 3-strata model from follow-up.

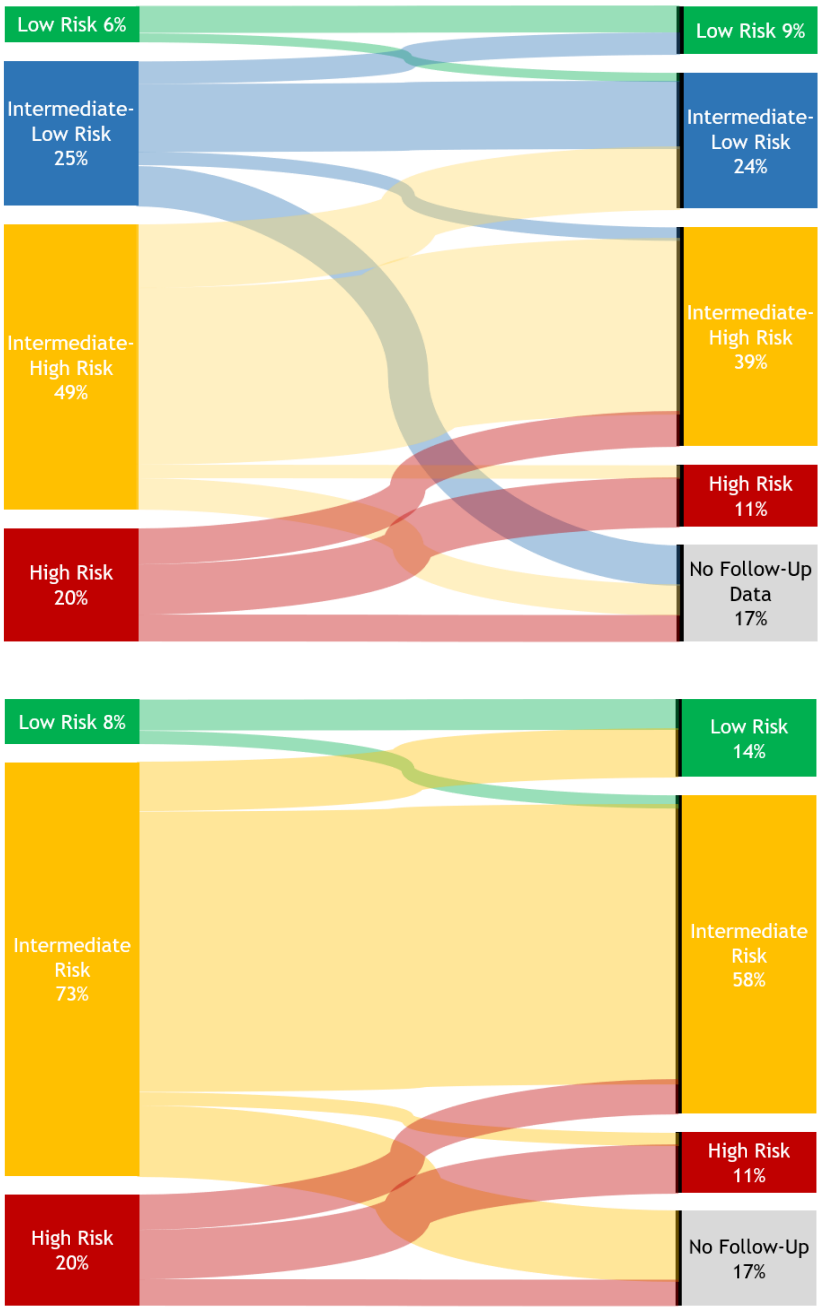


Figure 32. Sankey diagram demonstrating the proportion of patients moving between risk strata between baseline and follow up for a) 4-strata method b) 3-strata method.

8.4 Discussion

This study investigated whether the novel 4-strata COMPERA 2.0 model is applicable in patients with medically-managed CTEPH. The main conclusion is that the 4-strata model was able to identify four distinct prognostic groups with different survival profiles. Therefore, this allows a more nuanced risk stratification, when compared to the 3-strata model, in medically-managed CTEPH patients and provides a platform for more

personalised treatment approaches. The 4-strata method had improved discrimination of overall mortality at follow up when compared to baseline and to the 3-strata model.

More patients moved risk group using the 4-strata method, compared to the 3-strata method, both overall and within the intermediate risk groups, demonstrating that this is a sensitive model for detecting temporal improvement or deterioration.

The 4-strata model conforms to the established model of estimating 1-year mortality at <5% for low risk and >10% for high risk, enhancing its applicability within the existing guidelines. The model is strengthened by simplicity, relying on three non-invasive variables and therefore can be calculated at both baseline and follow-up without repeat invasive haemodynamic measurements. The utility of this model depends on which treatments are used for patients within each risk group. The current PH guidelines do not allocate treatment strategies based on risk strata in CTEPH and this is a consideration for future work.

The patients reported in this study had relatively more severe disease at baseline when compared to European registry data; for example, 19.5% of participants were in the high risk strata, compared to ~14% in the COMPERA registry during the same time period. There are two possible explanations for this; firstly, Scotland has a particularly co-morbid population with a high prevalence of cardiovascular disease which may have affected the baseline health of patients, leading to a higher risk status at diagnosis. Secondly, it may be that that patients were being diagnosed later into their clinical course. This could be due to the long waiting times for transthoracic echocardiography in Scotland, the lack of general awareness on CTEPH/CTEPD and/or the lack of a robust post-PE service in several Scottish health boards.

This study has limitations. The study includes relatively low study numbers (n=124), compared to 1655 participants in the HOEPER COMPERA 2.0 trial and 2879 in the BOUCLY validation trial. This figure reflects the smaller Scottish population; in 2010, when data collection was started, there were 9 incident diagnoses of CTEPH at SPVU, whilst in 2017 this figure had increased to 34. This figure gives an estimated incidence of 6.18 cases per million per year, which is in line with global estimated incidence of CTEPH. Furthermore, the relatively small proportion of patients who moved between risk groups may be as a result of the high proportion of untreated patients, a consequence of including patients between 2010-2015, when PAH-specific therapy use in CTEPH was often delayed whilst an opinion on surgical intervention was sought. In addition, dual therapy for CTEPH was not advocated until the later part of the 2010-2020 decade therefore most patients were treated with monotherapy with a PDE5i such as Sildenafil

and hence that population will have different treatment characteristics to a modern cohort leading to a lack of homogeneity in the survival analysis.

8.5 Conclusion

The COMPERA 2.0 model is applicable for risk stratification in medically-managed CTEPH and offers greater clinical discrimination of mortality than the COMPERA 1.0 3-strata model. The COMPERA 2.0 model should prove a more sensitive tool for prognostication and escalation of therapy.

9. Risk Stratification using the MRC Dyspnoea Scale in Pulmonary Arterial Hypertension

9.1 Introduction

Risk assessment in Pulmonary hypertension is an important component in managing the disease, enabling clinicians to monitor progress and allowing informed treatment changes. As has been discussed in the Introduction, the 2022 ERS/ESC guidelines advocate the use of the 4-strata (COMPERA 2.0) model at the first follow up, following the initiation of disease targeted therapy, in order to assess the therapeutic response and consider treatment escalation(2). COMPERA 2.0 incorporates the non-invasive variables of NT-proBNP, World Health Organisation Functional Class (WHO FC) and 6MWD which are used to allocate patients into low, intermediate-low, intermediate-high or high risk strata(3, 4).

As discussed in the Methods, WHO FC was derived from the New York Heart Association (NYHA) class, a measure of functional disability originally designed for use in patients presenting with left sided heart failure. WHO FC has been shown to predict mortality at diagnosis and follow up in pulmonary arterial hypertension and a deterioration in FC is an indicator of disease progression(5-7). However, international registry data and local SPVU data demonstrates that the majority of PH patients are classified within WHO FC III (defined as a “marked limitation of physical activity”), at both baseline (~70% of patients) and follow up (~60 of patients) and therefore this represents a heterogeneous group(2, 8). The broad definition of disability for WHO FC III limits the stratification abilities of the risk models into which it is incorporated.

The 1959 Medical Research Council (MRC) Dyspnoea Scale measures the perceived disability arising from breathlessness, categorising this into one of five scales(9, 10). Respiratory physicians, who in many centres are responsible for the care of PH patients, are better acquainted with the MRC Dyspnoea Scale, as opposed to the WHO FC model. Whilst validated for assessing disability and predicting survival in interstitial lung disease and chronic obstructive pulmonary disease(11-15), the MRC Dyspnoea Scale has not been studied in a PH population and the association with survival is unknown. The fact that the MRC Dyspnoea Scale has a greater number of categories (five) compared with WHO FC (four) may enable it to stratify patients in WHO FC III into separate classes and thereby improve prognostication.

Consequently, this study aimed to assess the performance of the MRC Dyspnoea Scale model at predicting survival and how it performed when compared to the WHO FC and

COMPERA 2.0 models for the assessment of mortality risk. Furthermore, we aimed to assess whether replacing WHO FC with the MRC Dyspnoea Scale in the COMPERA 2.0 model improved the ability of this model at predicting survival.

9.2 Methods

A retrospective analysis of records was taken for all patients who were diagnosed with pulmonary arterial hypertension at SPVU between 01/01/2010 and 30/12/2021. Patients were included into the baseline cohort at the point of diagnosis if they met the following criterial; (i) ≥18 years (ii) treatment-naïve, (iii) diagnosed via multidisciplinary team with Idiopathic, Hereditary or Drug Induced Pulmonary Arterial Hypertension (IPAH/HPAH/DPAH), (iv) baseline haemodynamics demonstrated an mPAP ≥25mmHg, PAWP ≤15 and PVR ≥3.0 and (v) all three of NT-proBNP, six-minute walk distance and WHO functional class were available at baseline as part of routine care. Patients were excluded from the first follow up cohort if they had not undergone follow up within two years of diagnosis or were missing more than 1 of the above non-invasive measures at follow up.

The 1959 MRC Dyspnoea Scale was retrospectively applied at baseline and first follow up using a combination of patient clinical notes, records from 6MWD tests and WHO functional status. An algorithm was devised for the purpose of this study, which was used to retrospectively allocate patients into an MRC Dyspnoea Scale when this was not explicitly stated in previous documentation (Figure 33). In cases of doubt, the investigators used their discretion in assigning the MRC Dyspnoea Scale according to this algorithm. The ENRIGHT equations were used to calculate the proposed lower limits of normal for 6MWD within the algorithm(16).

The performance of three models was assessed which included (i) the COMPERA 2.0 4 strata, (ii) WHO FC and (iii) the MRC Dyspnoea Scale. Risk stratification was performed at baseline (i.e., at diagnosis, prior to pulmonary arterial vasodilator therapy) and at first follow up following treatment commencement. The primary outcome for each model was all cause mortality with survival time calculated from both the date of diagnosis and first follow up until death, truncated at 5 years, as calculated for each model.

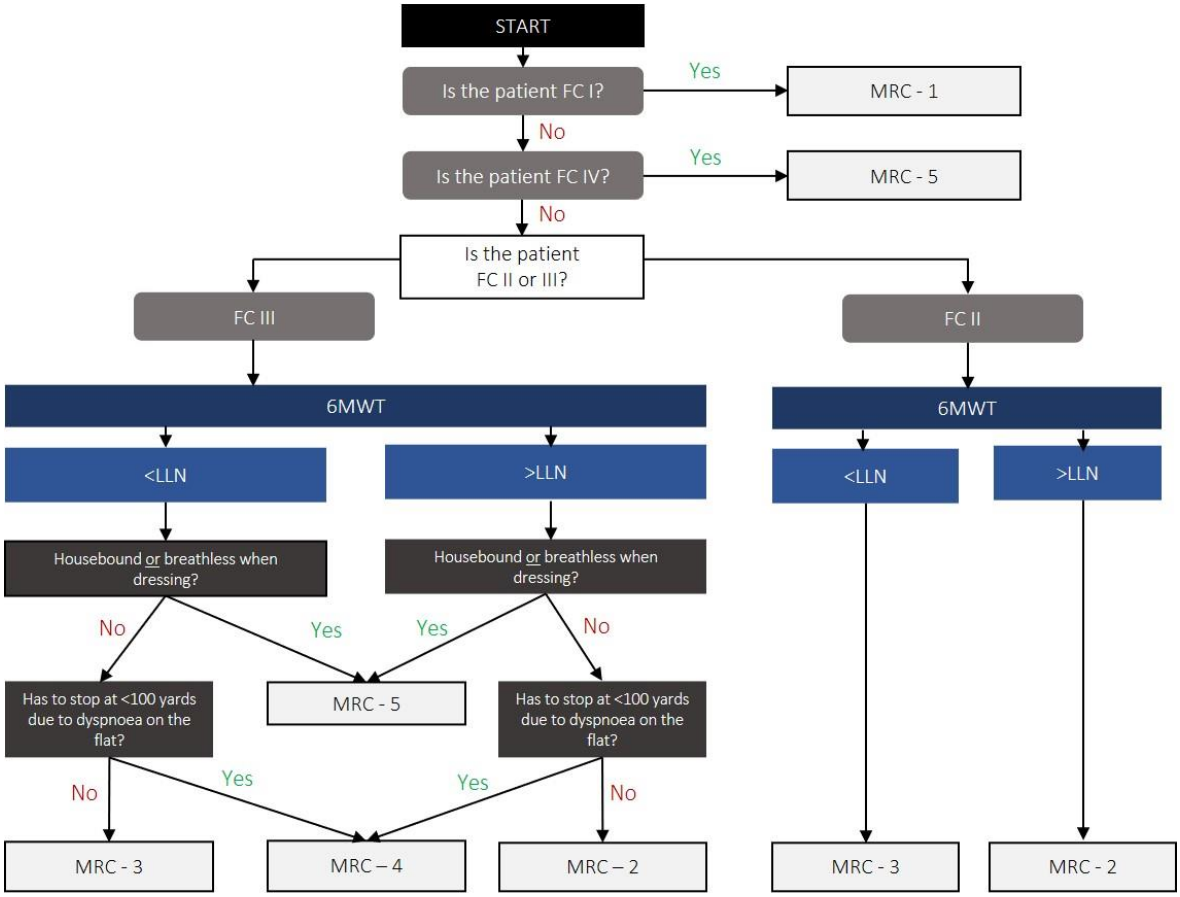


Figure 33. Algorithm for retrospectively applying the MRC Dyspnoea Scale.

9.2.1 Model Refinement: "MRC Dyspnoea Risk Score"

An alternative 4 strata model was developed, described henceforth as the "MRC Dyspnoea Risk Score". Using the basis of the 4-strata COMPERA 2.0 model, WHO functional class was replaced with the MRC Dyspnoea Scale. The MRC Dyspnoea Scale was weighted using a similar methodology to the weighting of WHO FC, in that MRC Dyspnoea Scales one and two were attributed 1 point, scale three and four attributed 3 points and scale five 4 points. This was added to the established variable cuts offs of the COMPERA 2.0 for 6MWD and NT-proBNP with an overall designation of risk calculated from the integer of the mean for the MRC Dyspnoea Risk Score (i.e., 1 = low risk, 2 = intermediate-low risk, 3= intermediate-high risk, 4= high risk).

9.2.2 Statistical Analysis

Survival analysis was performed with Kaplan-Meier analysis and the log rank test. Patients who underwent lung transplantation and patients who were lost to follow up were censored at the date of the last contact. Cox proportional hazard ratios (HR) were calculated in reference to the high risk category (due to no deaths in the lowest risk strata for each model) and are presented as hazard ratios (with 95% confidence

intervals). Model scores were analysed as ordinal categorical data. Harrell's C Statistic was used to compare Cox models for mortality. The Akaike information criterion (AIC) was used to further evaluate the goodness-of-fit for each model. Sankey diagrams provided a visual representation of patient flow between risk groups at baseline and first follow up and between WHO FC and MRC Dyspnoea scale at baseline.

9.3 Results

9.3.1 Patient Characteristics

216 patients were diagnosed with IPAH/HPAH/DPAH in the study period. Figure 34 demonstrates the flow of participants into the cohort at baseline and follow up. 35 participants were excluded as they were missing data at baseline, giving a baseline cohort of 181 participants. A further 27 participants were excluded from the follow up cohort due to a delay in their follow up of >2 years, death or loss to follow up.

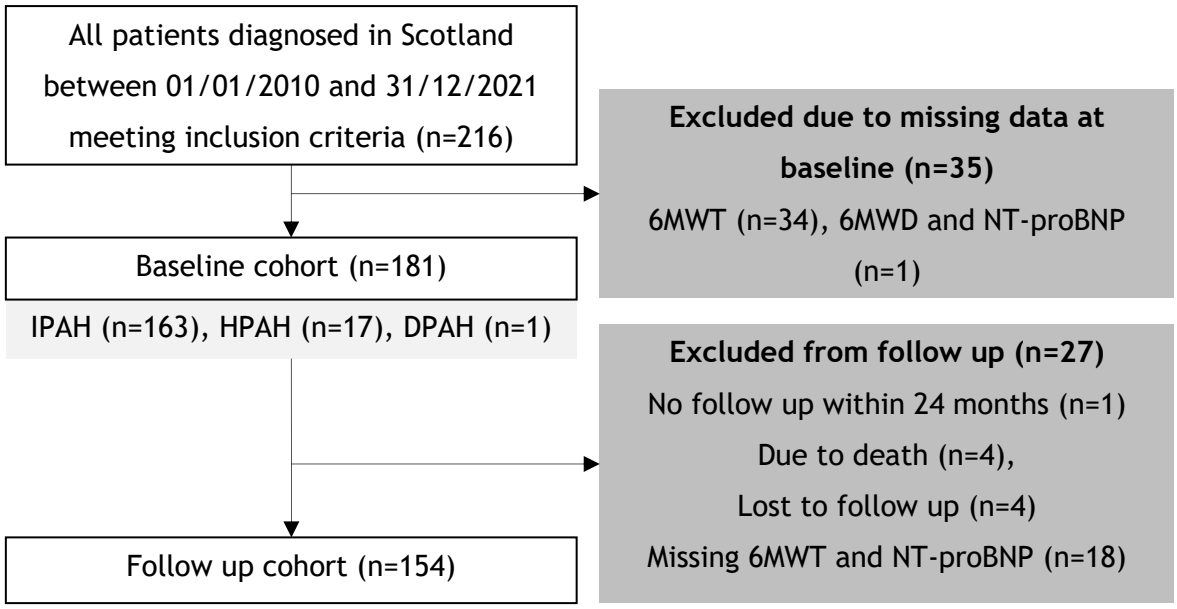


Figure 34. CONSORT diagram showing inclusion into the baseline (diagnosis) and first follow up cohort.

Characteristics at baseline are demonstrated in Table 26. The overall 1-, 3- and 5- year survival for the cohort was 94%, 76% and 66% respectively, with an overall 28.7% mortality at the end of the follow-up. The median follow-up duration was 2.7 (1.4 – 5.6) years.

	All	MRC Dyspnoea Scale				
		1	2	3	4	5
Number	181	1	34	27	86	33
Age (yrs.)	60 ± 17	16	48 ± 18	58 ± 18	64 ± 15	61 ± 14
Male, n (%)	75 (41)	1 (100)	8 (24)	16 (59)	35 (41)	15 (45)
PAH aetiology, n (%)						
IPAH	163 (90)	0	31 (91)	27 (100)	76 (88)	29 (88)
HPAH	17 (9)	1	2 (6)	0	10 (12)	4 (12)
DPAH	1 (1)	0	1 (3)	0	0	0
Comorbidities, n (%)						
Obesity	79 (44)	0	11 (32)	10 (37)	47 (55)	11 (33)
Coronary Heart Disease	51 (28)	0	2 (6)	3 (11)	28 (33)	18 (55)
Diabetes Mellitus	53 (290	0	4 (12)	7 (26)	34 (40)	8 (24)
Systemic Hypertension	59 (33)	0	7 (21)	10 (37)	32 (37)	10 (30)
Atrial Fibrillation	20 (11)	0	0	4 (15)	12 (14)	4 (12)
WHO Functional Class, n (%)						
I / II	40 (22)	1	25 (74)	13 (48)	1	0
III	120 (66)	0	9 (26)	14 (52)	85 (99)	12 (36)
IV	21 (12)	0	0	0	0	21 (64)
COMPERA 2.0 Risk Strata, n (%)						
Low Risk	14 (8)	1	11 (32)	2 (7)	0	0
Intermediate-Low Risk	42 (23)	0	19 (56)	7 (26)	13 (15)	3 (9)
Intermediate-High Risk	84 (46)	0	4 (12)	18 (67)	53 (62)	9 (27)
High Risk	41 (23)	0	0	0	20 (23)	21 (64)
Baseline data and right heart catheterisation haemodynamics						
6MWD, m	250 (150 - 374)	525	422 (361 - 498)	285 (203 - 395)	201 (129 - 291)	145 (75 - 337)
NT-proBNP, pg/ml	1835 (552 - 3914)	13	465 (115 - 1527)	1901 (753 - 3846)	1632 (548 - 3598)	2735 (964 - 5257)
RAP, mmHg	8.5 ± 5.4	5	5.7 ± 5.4	8.6 ± 4.2	9.3 ± 5.2	8.8 ± 5.2
mPAP, mmHg	48.6 ± 12	47	49.5 ± 13	52.2 ± 16	49.5 ± 12	50 ±11
PAWP, mmHg	7.7 ± 3.6	10	6.6 ± 3.6	7.9 ± 3.2	7.6 ± 3.6	7.4 ± 3
CI, L/min/m^2	2.0 ± 0.5	2.9	2.1 ± 0.5	1.9 ± 0.4	1.9 ± 0.5	1.8 ± 0.4
PVR, WU	12.1 ± 5.8	8.6	12.1 ± 6.1	13.7 ± 7.1	12.6 ± 5.8	13.4 ± 5.5

SvO2, %	59.5 ± 10	77	66 ± 7	58 ± 9	59 ± 10	58 ± 9
Initial Treatment Strategy, n (%)						
Monotherapy	98 (54)	1	23 (68)	19 (70)	43 (50)	12 (26)
Dual oral therapy	70 (39)	0	10 (29)	7 (26)	39 (45)	14 (42)
Oral + IV therapy	5 (3)	0	0	0	2 (2)	3 (9)
Oral + Neb Iloprost	2 (1)	0	0	0	1 (1)	1 (3)
Triple oral therapy	1 (1)	0	0	0	0	1 (3)
Dual oral + IV therapy	5 (3)	0	1 (3)	1 (4)	1 (1)	2 (6)

Table 26. Patient demographics at baseline as stratified by MRC Dyspnoea Scale.

9.3.2 Mortality Risk Assessment at Baseline

The proportion of patients within each stratum per model at baseline are demonstrated in Table 26. The majority of patients were MRC Dyspnoea Scale 4 (47.5%). Of 120 patients classified as WHO FC III, 7.5% were MRC Dyspnoea Scale 2, 11.6% scale 3, 70.8% scale 4 and 10% scale 5. Survival at baseline for 1-, 3- and 5 years is demonstrated within Table 27. Kaplan Meier curves are compared in Figure 35(a-c). A comparison of overall model performance is demonstrated in Table 28(a-c).

All three models were unable to delineate risk with sufficient accuracy at baseline; for the MRC Dyspnoea Scale and WHO FC model, survival curves and confidence intervals overlapped. The COMPERA 2.0 model failed to delineate risk between the low risk and intermediate-low risk groups (HR 0.08 vs 0.07).

Model	Survival at 1-, 3- and 5- years (%)				
COMPERA 2.0					
	Low Risk	Intermediate-Low	Intermediate-High	High	
Baseline	100, 100, 100	100, 96, 93	95, 71, 63	83, 57, 30	
First Follow Up	100, 95, 89	97, 95, 83	87, 69, 61	63, 22, 0	
MRC Dyspnoea Scale					
	1	2	3	4	5
Baseline	100, 100, 100	100, 97, 97	96, 76, 69	93, 71, 60	88, 69, 50
First Follow Up	100, 100, 100	100, 93, 90	89.8, 79.8, 60.5	85, 68, 60	66, 24, 24
WHO Functional Class					
	I	II	III	IV	
Baseline	100, 100, 100	97, 94, 89	95, 71, 62	81, 75, 55	
First Follow Up	100, 100, 100	100, 93, 78	86, 69, 64	70, 26, 26	

Table 27. Survival at 1-, 3- and 5- years as calculated for each model per stratum at baseline and first follow up. Percentages have been rounded to the nearest integer.

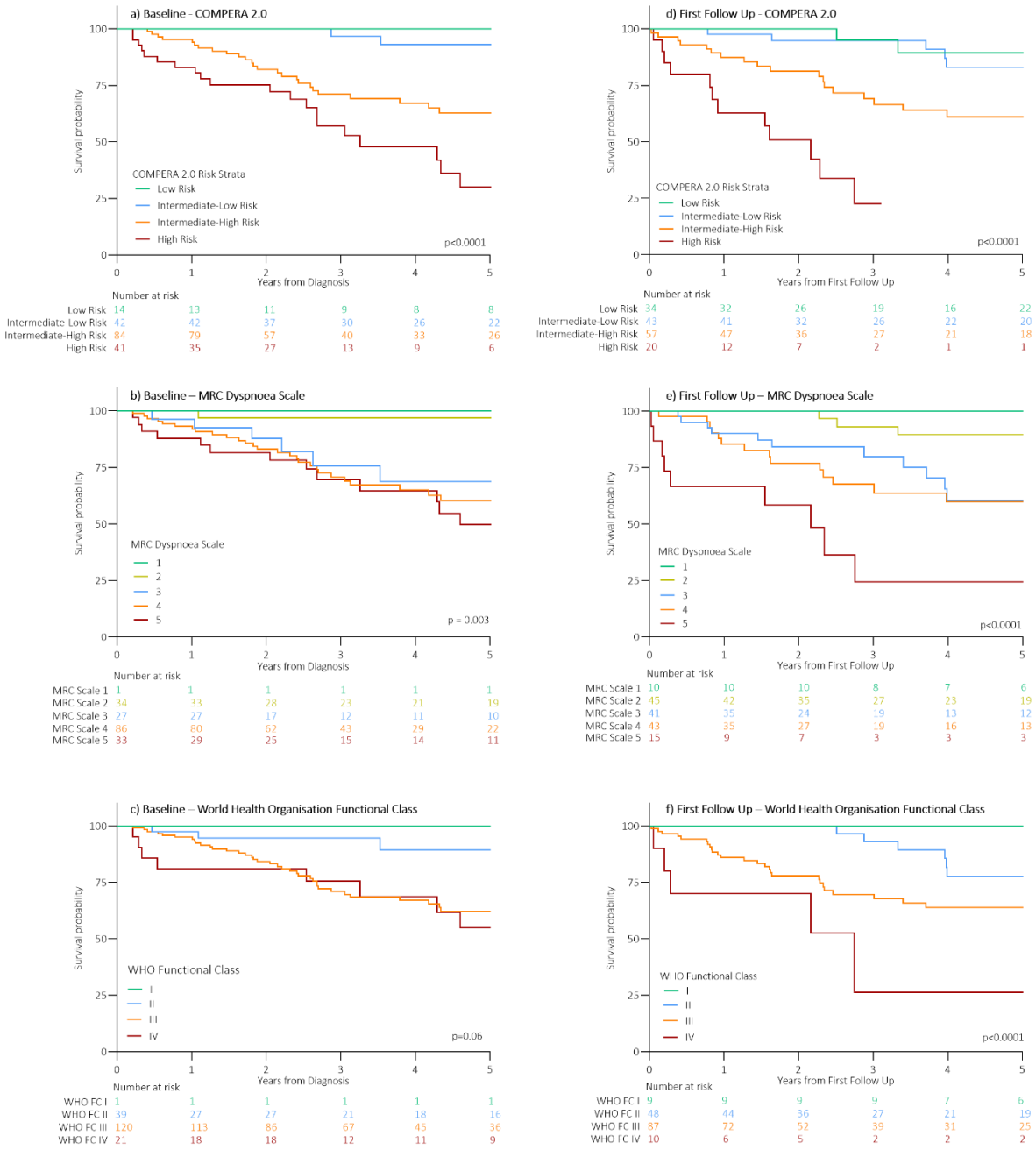


Figure 35. Kaplan-Meier curve demonstrating the respective survival estimates of the COMPERA 2.0 model, the MRC Dyspnoea Scale model and the WHO functional class model at baseline (a,b,c) and first follow up (d,e,f).

Model	Cox Hazard Ratios								C Statistic	AIC
a) COMPERA 2.0										
	Low Risk	95% CI	Intermediate -Low	95% CI	Intermediate -High	95% CI	High			
Baseline	0.08	0-0.4	0.07	0.02-0.21	0.45	0.25-0.81	-		0.71	457.7
First Follow Up	0.04	0-0.13	0.11	0.04-0.27	0.20	0.10-0.49	-		0.75	359.6
b) MRC Dyspnoea Scale										
	1	95% CI	2	95% CI	3	95% CI	4	95% CI	5	
Baseline	0	-	0.05	0-0.26	0.59	0.23-1.44	0.84	0.45-1.63	-	0.63	470.8
First Follow Up	0	-	0.06	0.02-0.17	0.25	0.11-0.60	0.27	0.12-0.64	-	0.74	351.6
c) WHO Functional Class										
	I	95% CI	II	95% CI	III	95% CI	IV			
Baseline	0	-	0.26	0.07-0.84	0.92	0.45-2.13	-		0.59	482.0
First Follow Up	0	-	0.10	0.04-0.28	0.28	0.13-0.65	-		0.69	363.7
d) MRC Dyspnoea Risk Score										
	Low Risk	95% CI	Intermediate -Low	95% CI	Intermediate -High	95% CI	High			
First Follow Up	0.04	0-0.14	0.09	0.03-0.24	0.23	0.11-0.47	-		0.76	349.0

Table 28. Cox proportional hazard ratios and 95% confidence intervals (CI), as calculated in reference to the highest risk strata and the Harrell's C and AIC for each model.

9.3.3 Mortality Risk Assessment at First Follow Up

The median time between diagnosis and first follow up was 109 days (IQR 95-137). Follow up information was available in 154 (85%) cases (Figure 34). 54% of patients were on monotherapy (75% phosphodiesterase 5 inhibitor, 18% endothelin receptor antagonist) and 39% were on dual oral therapy with 5.5% on parenteral Epoprostenol. In the COMPERA 2.0 model, 75 (41%) of patients changed risk strata compared to 90 (50%) for the MRC Dyspnoea Scale model and 59 (33%) for the WHO functional class model (Figure 36). Kaplan Meier curves are compared in Figure 35d-f. Survival at 1-,3- and 5 years is shown in Table 27. Hazard ratios and model performance are shown in Table 28.

At follow up, 87 (56%) patients were classified as WHO functional class III, of which 12 (14%) were MRC Dyspnoea Scale 2, 29 (33%) scale 3, 40 (46%) scale 4 and 6 (7%) scale 5. A survival curve demonstrating the survival estimates for WHO FC III as broken down by MRC Dyspnoea Scale at follow up is shown in Figure 37, which demonstrates that WHO FC III patients may be further stratified by MRC Dyspnoea Scale to obtain a more detailed assessment of exercise capacity.

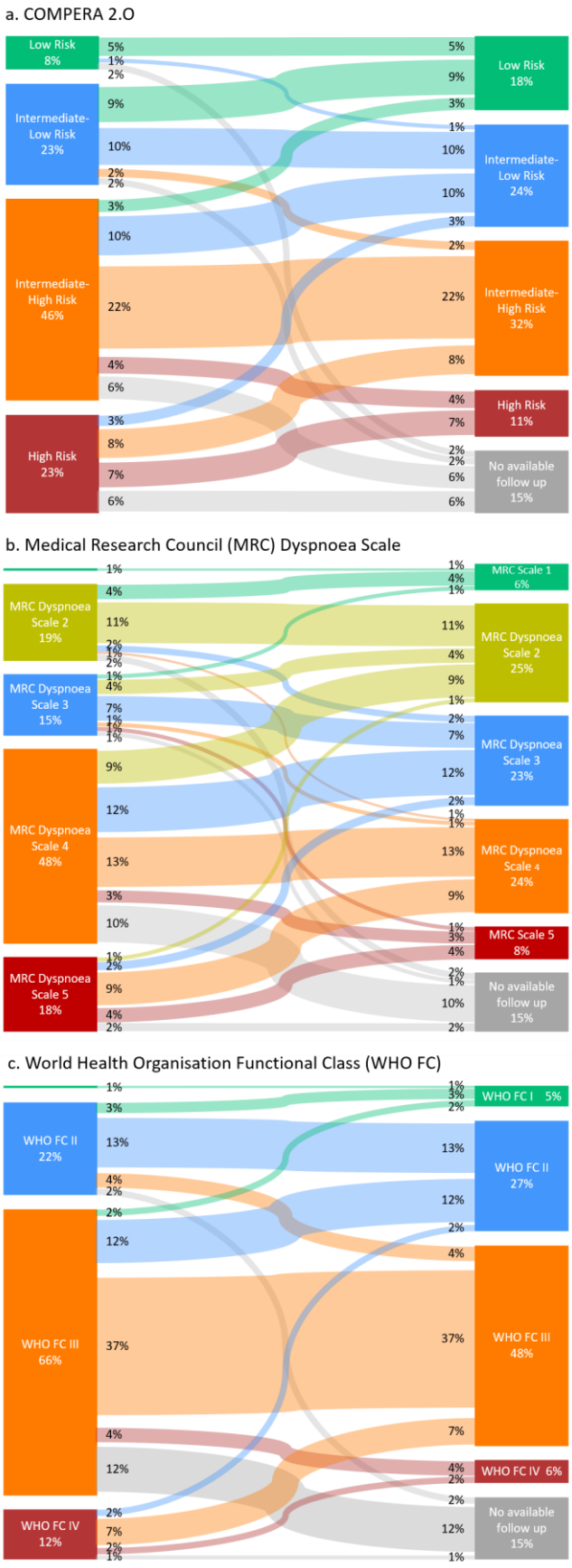


Figure 36. Sankey diagrams representing change in risk strata between baseline (left) and first follow up (right) for each model.

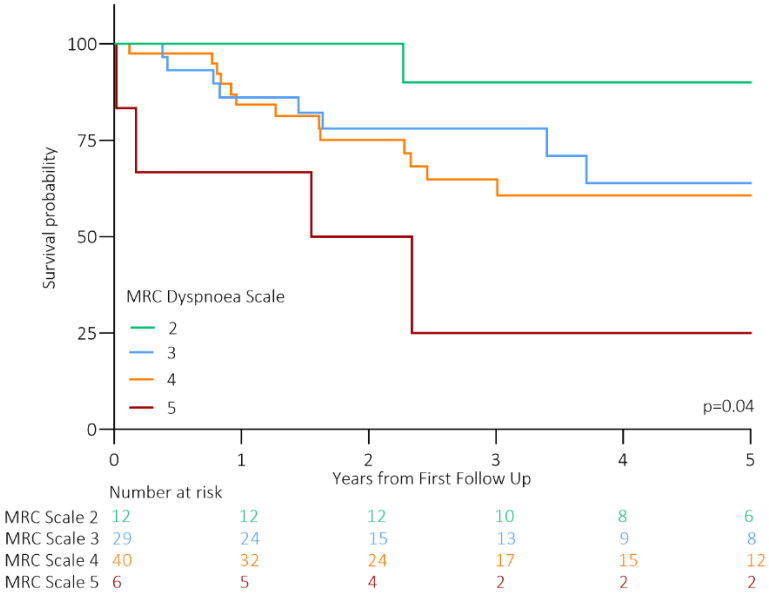


Figure 37. Kaplan-Meier curve demonstrating the survival estimates of patients classified as World Health Organisation Functional Class III at follow up, as stratified by MRC Dyspnoea Scale.

9.3.4 MRC Dyspnoea Risk Score

As the WHO FC, MRC Dyspnoea Scale and COMPERA 2.0 models performed poorly at baseline compared to at first follow up, the novel 4 strata MRC Dyspnoea Risk Score was only analysed at first follow up. The survival curve is demonstrated in Figure 38. 33 (21.4%) patients were low risk, 37 (24%) patients intermediate-low risk, 61 (39.6%) patients intermediate-high risk and 23 (14.9%) patients high risk. Survival at 1-, 3- and 5- years in the low risk category was 100%, 94.8%, 89.4%, intermediate-low risk 97%, 97%, 87%, intermediate-high risk 89.7%, 72.7%, 61.9% and high risk 63.3%, 25.4%, 25.4%. Hazard ratios and the overall model performance are demonstrated in table 2d.

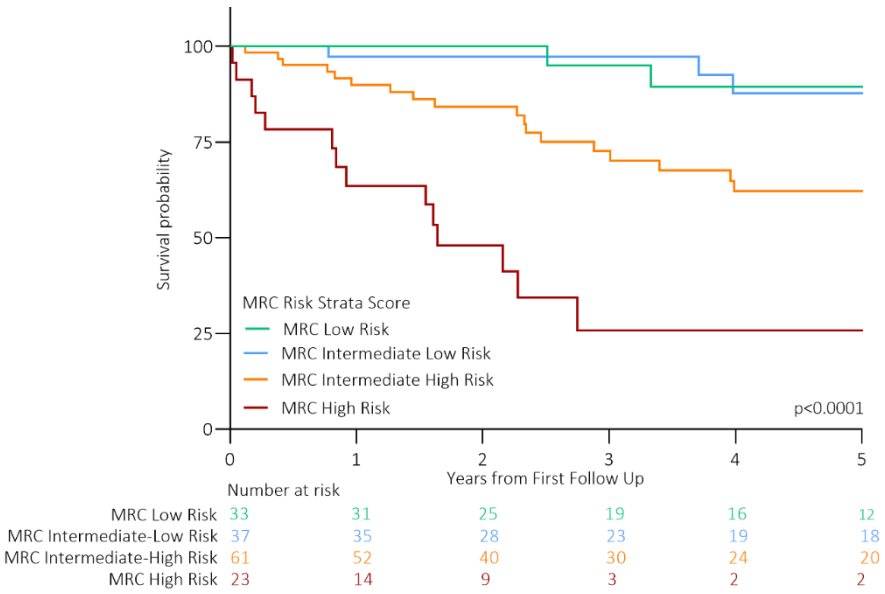


Figure 38. Kaplan-Meier curve demonstrating the survival estimates of patients at follow up when stratified by the MRC Dyspnoea Risk Score (where the MRC Dyspnoea Scale replaces WHO FC in the 4 strata COMPERA 2.0 model).

9.4 Discussion

This study investigated the MRC Dyspnoea Scale as a risk assessment tool within pulmonary arterial hypertension and has demonstrated it is able to predict survival in PAH. WHO FC III patients may be subdivided using the MRC Dyspnoea Scale, which has the potential to further stratify this risk group based on exercise capacity. Replacing WHO FC with the MRC Dyspnoea Scale (the MRC Dyspnoea Risk Score) within the COMPERA 2.0 model led to a similar performance at estimating mortality risk at first follow up. Overall, this study demonstrates the potential for the MRC Dyspnoea Scale to be used as an alternative risk assessment tool in PAH at the point of first follow up.

All models performed poorer at baseline compared to first follow up, with inferior C-statistics alongside reduced delineation of mortality on survival curves. However, compared with WHO FC both baseline and follow up, the MRC Dyspnoea Scale allowed greater resolution in assessing perceived disability due to dyspnoea since patients within WHO FC III were able to be further subdivided into MRC Dyspnoea Scales. Furthermore, a greater number of patients moved risk category between baseline and follow up using the MRC Dyspnoea Scale model compared to the other models. At first follow up, the MRC Dyspnoea Scale model outperformed the WHO functional class model (C statistic 0.74 vs 0.69) with comparable performance to the current COMPERA model (C statistic 0.75). This may indicate a role for the MRC Dyspnoea Scale as an alternative and more granular measure to WHO FC. Compared to the validation cohort in the COMPERA 2.0

study, this study demonstrates similar discrimination for the COMPERA 2.0 model at baseline (C-statistic 0.71 versus 0.64) and follow up (0.75 versus 0.73)(4).

Exchanging the WHO FC for the MRC Dyspnoea Scale at follow up within the 4 strata system gave a novel model (MRC Dyspnoea Risk Score) that had an equivalent performance and fit to the COMPERA model (C statistic 0.76). Patients were reasonably distributed between risk strata, although the survival curves crossed between the low and intermediate-low risk population.

The first follow up has been shown to be a vital point for assessing ongoing treatment response and mortality; patients who fail to achieve a lower risk status within 3-6 months of starting disease targeted treatment are less likely to improve in the future and have poorer outcomes(17). The MRC Dyspnoea Scale model performed well in assessing these changes, with a large number of patients moving between risk groups with a superior C-statistic, therefore suggesting it is a more sensitive tool in detecting clinical change.

WHO FC is not only an assessment of dyspnoea, but also includes the symptoms of chest and presyncope/syncope and these features are not included in the MRC Dyspnoea Scale. Further work could consider studying participants categorised as WHO FC III and further dividing them based on the presence or absence of these additional symptoms, to assess whether this could further delineate prognosis in this cohort.

This study has limitations. It is a retrospective study from a single centre, in a small cohort of participants. Retrospective analysis gives rise to issues with missing values and lack of standardised timings for patient visits. A reasonable proportion of patients (~15%) were unable to be included in the first follow up cohort. The algorithm used to assign MRC Dyspnoea Scale was designed to closely mirror the criteria of the MRC scale and therefore create a robust functional assignment as possible, yet regardless this remains a retrospective process and will be prone to biases and error. Ideally, assignation of the MRC Dyspnoea Scale would be performed contemporaneously, at the same time as assigning WHO FC, by an independent assessor, however due to the retrospective nature of this study this was not possible.

Furthermore, the process of assigning the MRC Dyspnoea Scale relies on clinicians accurately describing WHO FC and therefore the improved performance of the MRC Dyspnoea Scale when compared to WHO FC may be partially due to a refined allocation of functional status. Further work would be required to validate the MRC Dyspnoea Risk score a prospective analysis.

9.5 Conclusion

This study demonstrates the potential for the MRC Dyspnoea Scale to replace WHO functional class as an alternative risk assessment strategy at first follow up for pulmonary arterial hypertension. In this small, retrospective study, the MRC Dyspnoea Scale outperformed the WHO functional class model. Furthermore, when incorporated within a 4 strata risk assessment model, the MRC Dyspnoea Scale had equivalent performance to the COMPERA 2.0 model. Further analysis and validation would be required in a separate cohort to confirm these findings.

10. Non-invasive prediction of postcapillary pulmonary hypertension

10.1 Introduction

As has been outlined, pulmonary hypertension (PH) can be broadly categorised as precapillary and postcapillary. It is crucial to distinguish postcapillary from precapillary PH and this is particularly important when considering pulmonary arterial hypertension (PAH, Group I PH), due to the significant differences in management and prognosis of these two aetiologies(7).

Group II PH, attributable to left heart disease, is defined by an elevated PAWP (≥15 mmHg) during RHC, in conjunction with pulmonary hypertension (mPAP ≥25 mmHg)(5, 7). It is vital to distinguish between Group 1 PAH, Group 2.1 PH due to heart failure with preserved LV ejection fraction (HFpEF) and Group 2.2 PH due to heart failure with reduced LV ejection fraction (HFrEF), yet this can be challenging. Previous evidence from COMPERA registry data has demonstrated patients with "atypical" IPAH (i.e. patients with ≥3 cardiovascular risk factors) are older, more obese, have lower exercise capacity and are less responsive to treatment than patients with typical IPAH, despite similar haemodynamics(209). Furthermore, multiple studies have demonstrated lack of efficacy and potential harm when pulmonary vasodilator therapy is employed in Group II PH(7), underlining the necessity for a clear delineation of PH aeitology. Treating multi-morbid and elderly patients with pulmonary vasodilators can lead to the adverse effects of fluid retention, systemic hypotension thus increasing the risk of falls, hypoxemia through congestion and shunting, liver toxicity and reduced quality of life due to a high side effect burden.

Prior to invasive testing, Group II PH can be diagnosed when there is clear evidence of left heart disease on echocardiogram and other testing modalities(7). However, in the absence of clear features, or in cases where the extent of left heart disease appears insufficient to explain the elevated pulmonary artery pressure, RHC may be required in order to clarify the aetiology(65, 210).

Patients with HFpEF are a heterogeneous group, who are more elderly and comorbid, and in whom clear echocardiographic features of left heart disease can be lacking(211, 212). RV dysfunction is highly prevalent in the HFpEF population and when pulmonary hypertension is present these patients have a poorer prognosis(213). Scoring systems have been developed to aid clinicians in determining the pre-test probability of Group II PH at the time of referral in order to manage the allocation of RHC(174, 175, 212, 214-

217). The H2FPEF score (*Chapter 4.3.1*) is a non-invasive score developed to elicit the probability of HFpEF in patients who are not clinically fluid overloaded (i.e., euvolaemic) who present with the primary symptom of dyspnoea(174). It has been reported to provide a specificity between 69% and 91% of HFpEF if a total score of equal to or greater than 6 is calculated(174, 218) and provides prognostic information among patients with HFpEF(219, 220). Although not specifically designed for this purpose, it has been suggested as a diagnostic tool to predict Group II PH. In a prospective cohort in the Netherlands, the H2FPEF score was found to predict Group II PH with a low to moderate sensitivity of 48%. However, in this cohort the H2FPEF score had a number of false positives, predicting HFpEF in a significant number of patients who subsequently went on to be diagnosed with Group I PH at RHC, with an overall positive predictive value of 88%(175). The H2FPEF score weights atrial fibrillation (AF) highly in the probability assessment for Group II PH and whilst AF is a predictor of HFpEF, it co-exists in patients with Group I pulmonary hypertension due to right atrial dilation(221, 222) or as a non-contributing comorbidity, potentially leading to overestimation of Group II PH in this cohort. The OPTICS score (*Chapter 4.3.2*) was created for evaluating the pretest probability of Group II PH in new referrals to tertiary PH centres(175). The sensitivity of diagnosing Group II PH has been reported as 100% if an OPTICS score of ≥104 is calculated(175). This score weights previous valvular surgery highly, whilst AF is less highly weighted.

The Scottish population has high rates of AF, obesity and diabetes with a substantially higher premature cardiovascular disease death rate than other European countries (including England and the Netherlands), which are likely to alter the diagnostic accuracy of both scores in this population(223). Consequently, the objective of this study was to investigate and compare the diagnostic accuracy of the H2FPEF and OPTICS scores for predicting Group II PH among patients referred to SPVU.

10.2 Methods

The Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines were used to structure the study (224). A retrospective analysis was undertaken of all patients who were referred to SPVU between 1st January 2016 and 31st December 2020. Patients investigated at SPVU follow a standard diagnostic protocol of thoracic and cardiac imaging, exercise capacity testing and right heart catheterisation. A final diagnosis is based on multidisciplinary consensus between pulmonary vascular physicians and cardiopulmonary imaging specialists.

Patients were included if they had been accepted for invasive investigation as determined by either multidisciplinary team (MDT) or consultant decision during an

outpatient clinic. Patients were included if they had undergone right heart catheterisation and were subsequently diagnosed with Group II pulmonary hypertension, or with Group I pulmonary hypertension that included the subtypes IPAH, HPAH and PVOD, as defined by established criteria(5). Patients were excluded if they had other suspected aetiologies for precapillary PH (such as evidence of chronic thromboembolic disease or underlying connective tissue disease) in order to reflect true-to-life circumstances where the suspicion of a Group I cause is great enough in these cases to proceed with investigation, even when left heart disease risk factors are present.

Individual patient records were screened for the constituent components of the H2FPEF and OPTICS score. The established cut offs of ≥6 for the H2FPEF and ≥104 for the OPTICS scores were used to denote whether the score indicated the presence of Group II pulmonary hypertension(174, 175). This was compared to the MDT consensus diagnosis of Group II pulmonary hypertension, which was taken as the gold standard. Group II PH was used to define cases of both isolated postcapillary and combined pre- and postcapillary PH as either subgroup are not candidates for pulmonary vasodilator therapy outside clinical trials. False-positive cases, where patients who were diagnosed with Group I PH by MDT consensus but were predicted to have Group II PH by either score (false positive cases) were analysed in further detail. This was performed by comparing their baseline demographic data, including comorbidities, and assessing how individual patients responded to pulmonary vasodilator treatment following the diagnosis and subsequent treatment of precapillary PH, in each case. Calibration was performed by systematically making incremental adjustments to the cut offs and weighting of components for both scores with an attempt to measure the sensitivity and specificity at different cut-offs, whilst not adversely impacting specificity.

10.2.1 Statistical Analysis

Sensitivity, specificity, positive predictive value, negative predictive value, receiver operating curves and area under the curve (AUC) were calculated for both the H2FPEF and OPTICS scores. These analyses are described in detail in section *4.6 Statistical Analysis*.

10.3 Results

10.3.1 Participant Demographics

Seven hundred and eighty one diagnostic right heart catheterisation were performed in the study period with 107 patients with IPAH, HPAH or PVOD and 86 patients with Group II pulmonary hypertension included in the analysis. Patient demographics are presented

in Table 29. When compared to patients with Group I PH, patients with Group II PH were more elderly, had a higher BMI, were more likely to have multiple cardiovascular risk comorbidities, were more likely to present with a raised E/e' ratio and LA dilation and had a lower mean pulmonary artery pressure and pulmonary vascular resistance at right heart catheterisation.

	Group I Pulmonary Hypertension	Group II Pulmonary Hypertension	p value
Number	107	86	
Diagnosis, n (%) IPAH HPAH PVOD	 76 (71) 7 (6) 25 (23)		
Age (yrs.)	62 ± 15	69 ± 10	<0.001
Male, n (%)	40 (37)	33 (38)	0.99
BMI (kg/m^2)	30 ± 7	33 ± 6	0.01
BMI >30, n (%)	43 (40)	52 (49)	0.008
Medical History			
Diabetes Mellitus, n (%) T1DM T2DM	 2 (2) 36 (34)	 0 (0) 30 (35)	 0.5 0.87
Atrial Fibrillation, n (%)	13 (12)	64 (74)	<0.001
Systemic Hypertension Number of antihypertensive medications Antihypertensive medications ≥2, n (%)	 0.8 ± 1.0 24 (22)	 1.1 ± 0.9 29 (34)	 0.01 0.1
Dyslipidaemia, n (%)	44 (41)	52 (60)	0.009
Left-heart valvular surgery, n (%)	3 (3)	6 (7)	0.19
ECG index of SV1 + RV6 (mm)	11 ± 5	15 ± 7	<0.001
Transthoracic Echocardiogram			
E/e' ratio	9 ± 4.8	16 ± 7.5	<0.001
LA Dilation, n (%)	17 (16)	68 (79)	<0.001
Right Heart Catheterisation			
Mean Pulmonary Artery Pressure (mmHg)	46 ± 10	42 ± 10	0.007
Pulmonary Artery Wedge Pressure (mmHg)	7 ± 3	20 ± 4	<0.001
Cardiac Output (L/min)	3.8 ± 1.0	4.6 ± 1.8	<0.001

Pulmonary Vascular Resistance (woods units, WU)	11 ± 4	5 ± 3	<0.001
Mixed venous saturations (%)	61 ± 9	61 ± 9	0.95

Table 29. Patient demographics and haemodynamic characteristics.

10.3.2 Score Performance

Table 30 demonstrates the sensitivity and specificity for both scores from this cohort. Retrospective application of the OPTICS score demonstrates that pretest scoring would allow detection of between 1 in 4 and 1 in 3 cases of Group II pulmonary hypertension (sensitivity 0.28) yet at the cost of misdiagnosing 4% of referred Group I cases (specificity 0.96). The H2FPEF score had a far greater sensitivity (0.70) yet at the cost of reduced specificity (0.91) implying 9% of Group I cases would be misdiagnosed. ROC analysis demonstrated a similar area under the curve for both scores (Figure 39).

	Sensitivity	Specificity	PPV	NPV	Accuracy
OPTICS	0.28	0.96	0.86	0.62	0.66
H2FPEF	0.70	0.91	0.86	0.79	0.81

Table 30. Validation metrics for the H2FPEF and OPTICS scores at predicting Group II pulmonary hypertension.

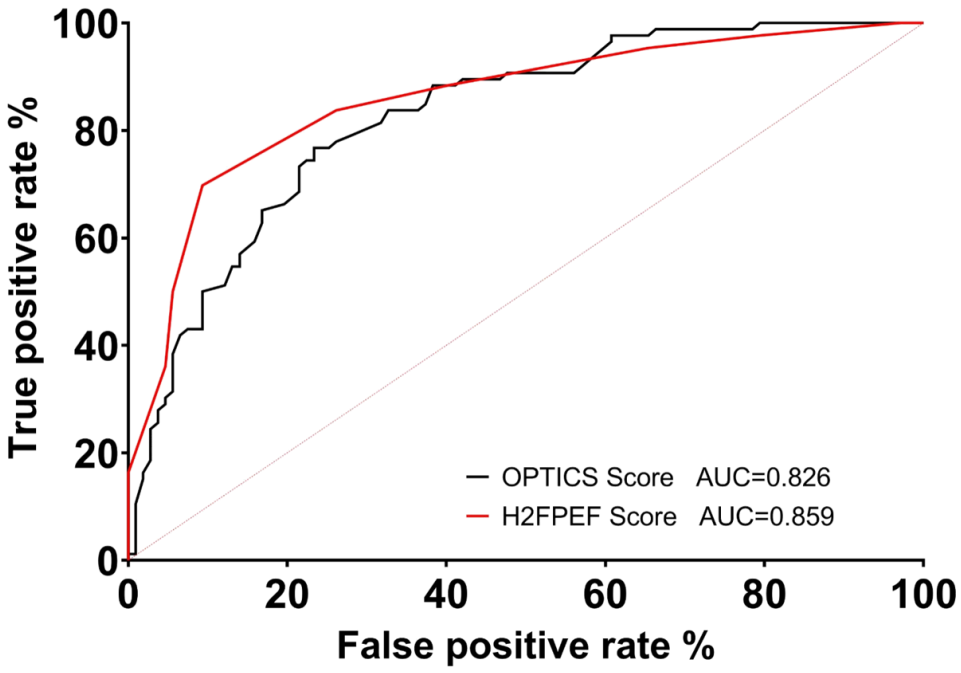


Figure 39. Receiver Operator Curve for the H2FPEF and OPTICS score. AUC represents area under the curve.

10.3.3 Analysis of False Positive Cases

Table 31 demonstrates the characteristics of false-positive cases for both scoring systems. Of 107 cases of Group I PH, 4 (3.7%) cases were mislabelled as Group II PH by the OPTICS score, all of whom were diagnosed with IPAH. Individual analysis of these patients reveals a high prevalence of cardiovascular risk factors, a mean OPTICS scores of 122 and a mean age of 78 years. Of these four patients, one patient did not symptomatically improve with treatment and three patients died within eight months of diagnosis. 10 cases (9.3%) were false-positive by the H2FPEF score. In this subgroup the mean age was 74 years and the mean H2FPEF score was 7.1. Of these, four patients had symptomatic and objective improvement with treatment, five patients had no benefit from treatment and one patient was lost to follow up. Two of these patients died within a year of diagnosis. There was an overlap of two patients who were mislabelled by both scores.

	OPTICS Score	H2FPEF Score
Number	4	10
H2FPEF Score	6.7 ± 1.5	7.1 ± 0.9
OPTICS Score	121 ± 14	92 ± 27
Diagnosis, n (%) - IPAH - PVOD	- 4	- 9 - 1
Age (yrs.)	77 ± 9.9	74 ± 7.2
Male, n (%)	2 (50)	4 (40)
BMI (kg/m^2)	30 ± 5.2	33 ± 6
Medical History		
Diabetes Mellitus, n (%)	2 (50)	4 (40)
Atrial Fibrillation, n (%)	3 (75)	9 (90)
Systemic Hypertension, n (%)	0	3 (30)
Dyslipidaemia, n (%)	4 (100)	6 (60)
Left-heart valvular surgery, n (%)	2 (50)	2 (20)
ECG index of SV1 + RV6 (mm)	10 ± 8	9.7 ± 4
Transthoracic Echocardiogram		
E/e' ratio	24 ± 8	13.7 ± 5
LA Dilation, n (%)	4 (100)	8 (80)
Right Heart Catheterisation Haemodynamics		
Mean Pulmonary Artery Pressure (mmHg)	44 ± 11	41.6 ± 7.2

Pulmonary Artery Wedge Pressure (mmHg)	11 ± 1.7	9.8 ± 3.5
Pulmonary Vascular Resistance (woods units, WU)	9.8 ± 0.8	8.9 ± 2.3

Table 31. Characteristics of patients diagnosed with Group I pulmonary hypertension who were predicted to have Group II pulmonary hypertension (false positive) as based on the OPTICS and H2FPEF score.

10.3.4 Score Calibration

Figure 40 demonstrates the proportion of individual patients stratified by diagnosis and OPTICS and H2FPEF scores. The OPTICS score was unable to be calibrated without significantly increasing the chance of false positives. Applying the scores consecutively, in either order, did not improve sensitivity or specificity. However, by changing two variables of the H2FPEF score (BMI cut off >35 as opposed to 30 and reducing the weighting of atrial fibrillation from 3 to 2) the specificity improved to 0.98 and the sensitivity fell to 0.41. This method identified two false-positive cases, neither of whom derived benefit from treatment.

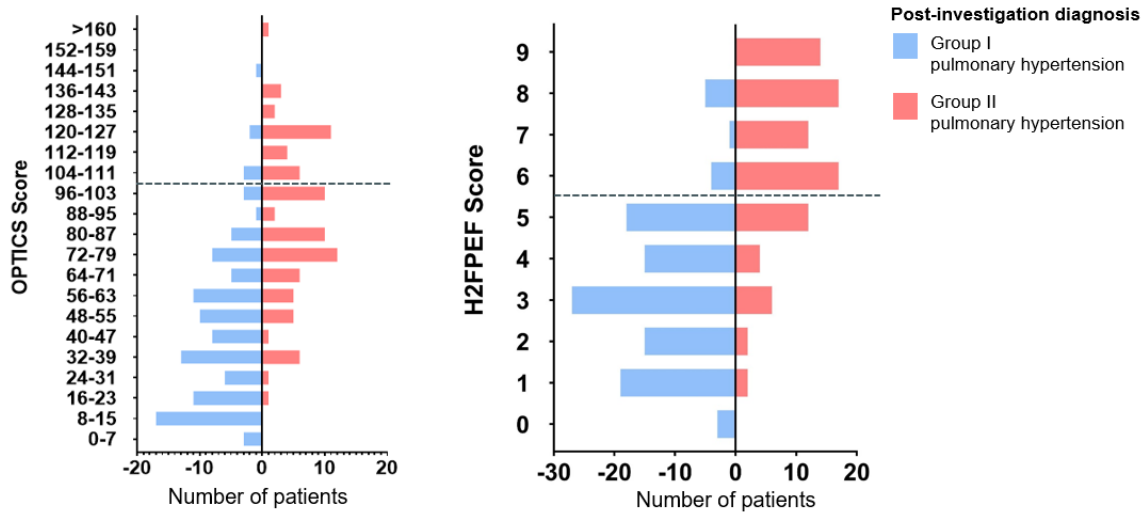


Figure 40. Comparison of pyramid charts for the H2FPEF and OPTICS scores. Blue lines represent the number of patients with precapillary PH and red lines the number of patients with postcapillary PH, as stratified according to score. The dotted line represents the cut off of ≥104 for the OPTICS score and ≥6 for the H2FPEF score.

10.4 Discussion

Retrospective application of the OPTICS score demonstrated that pretest scoring would detect 28% of cases with Group II pulmonary hypertension correctly, yet this was at the cost of misdiagnosing 4% of patients with Group I PH as Group II PH (specificity 0.96).

The H2FPEF score had a far greater sensitivity (0.70) but reduced specificity (0.91), leading to misdiagnosis of 9% of Group I PH cases. This study is a further demonstration that the OPTICS score is able to correctly predict Group II PH in only a minority of patients whilst maintaining a low false positive rate. The H2FPEF score performed similarly, with a greater sensitivity yet crucially a lower specificity and hence a higher risk of false positives. Whilst the specificity of these scores was high, the lack of 100% specificity might result in pulmonary hypertension centres failing to proceed with invasive investigations in a subgroup of patients with Group I pulmonary hypertension if the score is applied to screen new referrals. This has the subsequent potential to lead to a delayed, or missed, diagnosis and poorer health outcomes in these patients.

The results from this study are similar to the findings from JANSEN(175), in which the OPTICS score was found to have a sensitivity of 0.22 and specificity 1.00 whilst the H2FPEF score's sensitivity was 0.48 and specificity 0.92. The methodology in this study differed to that of JANSEN, in that patients with clear other attributable causes of pulmonary hypertension, such as evidence of CTEPH and connective-tissue disease, were not included in this study, as it is likely that regardless of left heart disease risk factors these patients are likely to be accepted for further investigation. This may explain that while the validation results from this cohort are overall similar to the JANSEN *et al*. results, the OPTICS score had a lower specificity in this study.

Whilst this study did not systematically collate cardiovascular comorbidities, the study population is noticeable for the high prevalence of risk factors for left heart disease in both Group I and Group II cohorts, underlining the difficulties in defining these conditions based on scoring systems alone, without proceeding to invasive investigation. This is further evidenced by the 4 out of 107 patients who had IPAH and were mislabelled by the H2FPEF score yet went on to improve with pulmonary vasodilator treatment. The accuracy of any test is dependent upon the studied population and the high prevalence of cardiovascular comorbidities in Scotland, as compared to the Netherlands, is likely to have had an impact in decreasing the sensitivity and specificity of the OPTICS score, as both patients with Group I and Group II PH had a high prevalence of left-heart disease risk factors(225).

Furthermore, recent research suggests that IPAH (pre-capillary PH), pre- and post-capillary PH and post-capillary PH cannot be clearly defined based on haemodynamic criteria alone. These entities may instead exist on a spectrum, with a rising number of cardiovascular co-morbidities, rising PAWP and reducing efficacy of disease targeted treatment in patients with a greater contribution from left heart disease. Therefore, the differentiation between these entities should not solely be based on the PAWP, but the overall phenotype, such as the number of co-morbidities present and how well they

are controlled(209, 226). In the last decade, different phenotypes for comorbid PAH have been suggested; patients with lung disease and IPAH were identified(227) and the AMBITION trial used a sub-analysis of patients with risk factors for left heart disease(228). Phenotyping from registry data using machine learning has identified three clusters within the spectrum of IPAH; (i) Classical Phenotype; younger, predominantly female patients without comorbidities, (ii) Left Heart Phenotype; older females with frequent comorbidities but preserved gas exchange and (iii) Cardiopulmonary Phenotype; older men with a history of smoking and a DLCO <45%(229, 230). Compared to Classical patients, patients with Left Heart and Cardiopulmonary phenotypes tolerate pulmonary vasodilator therapy poorly, are unable to achieve a low risk status and have worse survival(231-235). This development has led to the inclusion of new treatment group "Group I PH with co-morbidities" into the 2022 ERS/ESC guidelines, with a recommendation for initial monotherapy in this cohort, rather than combination therapy(1).

Given these difficulties, highlighting the need for clinical gestalt in differentiating Group 1 and Group 2 PH, it is perhaps unsurprising that a non-invasive scoring algorithm fails to differentiate the disease. The ultimate use for such scoring systems may be limited to prompting clinicians to consider provocative testing (such as exercise testing or fluid challenge provocation, as explained in *Chapter 1.5.5.8 Right Heart Catheterisation*) during right heart catheterisation in order to unmask left heart disease, rather than a diagnostic tool in their own right(236, 237). Another use could be in aiding prognostication; a recent study by KIANZAD has demonstrated that patients with a high H2FPEF score were older, had a higher BMI, were more often male and had poorer survival when compared to patients with a score <1(238). However, it is interesting to note that this did not predict the response to pulmonary vasodilator therapy(238).

This study has several limitations. Whilst ethnicity was not collected as part of this study, it can be presumed due to the relatively low representation of ethnic minorities in Scotland, that this was generally a homogeneous white European population. The haemodynamic definition of PH may be changing, with a revised mPAP cut of >20 mmHg being considered. This will affect the performance of these scores and a reassessment would be required. This study was additionally limited by lack of a prospective cohort to validate our proposed revision of the H2FPEF score, which may be a future consideration for research. Ongoing research in this area includes the use of echocardiographic and cardiac magnetic resonance imaging indices to non-invasively predict postcapillary PH, and it may be that a multi-metric score could be defined in the future to predict, if not Group II PH, then the response to PH targeted therapy.

10.5 Conclusion

This study quantifies the probability of misdiagnosing patients with Group II PH, prior to invasive investigations, based on the OPTICS and H2FPEF scores. Overall, the utility of both these scores in their current versions is diminished by the small but measurable risk of missing true Group I PH, which would deprive patients of effective treatment and potentially put them at risk of poorer health outcomes. The scores may, however, play a role in helping to support clinical decisions or to suggest the need for provocative testing at RHC. Further research should aim to validate these scores further with a focus on calibration to perfect the specificity without affecting sensitivity.

11. Discussion and Conclusions

The overarching aim of this thesis was to expand upon the understanding of risk assessment within pulmonary hypertension (PH) and to explore the role of remote medicine in providing novel risk stratification tools. Categorising PH patients into risk strata enables the allocation of patients into prognostic groups. Such groups are employed in treatment algorithms to determine targeted pulmonary vasodilator therapy and consideration for further intervention, such as referral for lung transplantation.

This chapter shall provide an overview of the results from the individual studies within this thesis and shall contextualise their potential influence on the clinical management for patients with pulmonary hypertension.

11.1 Remote Assessment of Risk in Pulmonary Hypertension

11.1.1 Major Findings

At the conception of this body of work, there was a paucity of evidence surrounding the remote assessment of risk in PH. As shown within the literature review, this field has experienced increasing research interest since the advent of the 2019 coronavirus pandemic, which effectively halted face-to-face interactions and led to a far less robust virtual PH clinic, bereft of objective clinical data such as exercise capacity testing or NT-proBNP assessment. Despite this, few studies had effectively studied remote risk assessment tools in a clinical context or had longitudinal data to ascertain the validity of such techniques over time. Therefore, the first work package aimed to bridge this evidence gap by ascertaining the challenges to telehealth in PH, to study the validity and feasibility of remote exercise tests in PH and to assess the validity of sendaway NT-proBNP.

Chapter 5 explored the potential challenges to the implementation of telehealth and remote monitoring within routine PH patient care. The smaller studies within this chapter employed a patient questionnaire, an analysis of the Scottish Index of Multiple Deprivation among PH patients in Scotland, and a pilot study of electronic EmPHasis-10 quality of life outcome data. Patients with pulmonary hypertension were happy to perform home exercise tests and 90% would feel it would be feasible and safe to perform at least one form of exercise tests. However, only 68% of the response cohort owned an internet-enabled smartphone which raised concerns over the information technology-literacy of this population, which was further reflected in the small number (~1/4) of patients who were able to complete an electronic EmPHasis-10 score. Whilst

the level of IT-literacy appeared low, an analysis of the SIMD database revealed that the Scottish PH population existed in similar socio-economic brackets to the general population.

The results from the literature review and the work included in Chapter 5 influenced the design and implementation of the subsequent studies. In chapter 6, four alternative exercise tests to the standard 6MWT were piloted among patients with PH, supervised once within a hospital setting and twice unsupervised remotely. The results demonstrated that remote exercise capacity testing was safe, acceptable, and feasible. However, the results did not support the hypothesis that these tests were all valid measures and hence they could not be relied upon for accurate risk stratification. The Tele-6MWT had the most promising results in terms of accuracy, with a 79% agreement in the concordance of change when compared to the standard 6MWT, but only 49% of participants were able to complete the Tele-6MWT test at home.

In chapter 7, sendaway capillary NT-proBNP was compared to a reference venous NT-proBNP. This yielded promising results and confirmed that such sampling, analysed within 3 days of blood draw, was able to provide an acceptably accurate measure of NT-proBNP and therefore provide a remote surrogate marker of right ventricular strain. The Day 3 Capillary results were able to accurately risk stratify patients in 93.5% of cases and the results were similarly positive for sendaway venous NT-proBNP. However, the study confirmed that delayed sampling using these methods did not display sufficient validity (due to the degradation of the protein over time) and this combined with a relatively high invalidity rate (19% for Day 3 Capillary samples) raised concerns surrounding the utility of such a test in a real-world setting, and further research is needed in this area.

11.1.2 Strengths and Limitations

The studies included within the first work package had several limitations which are discussed in depth within the individual chapters. The limitations of the work in Chapter 6 included a low number of participants, a lack of intra-test and intra-observer validity and a high discontinuation rate. Overall, these drawbacks may have contributed to some of the observed disappointing results. Given the opportunity to redesign the study, consideration could be given to including a stricter cohort of younger patients with fewer co-morbidities that may be more likely to adhere to follow up, with results that would be less impacted upon by other diseases and mobility issues. Additionally, selecting fewer high risk patients, who would go on to need parenteral treatment or who were at high risk of mortality, may have reduced the discontinuation rate. Furthermore, the timing of the testing visits between home and the hospital settings

could have been stricter to ensure stronger conclusions about the validity of home testing could be made. Multiple tests at each visit should have been included to enhance intra-test validity. This approach could have then provided pilot study data with which to progress to a larger study, with a broader inclusion criterion. The study in Chapter 7 was limited by the high number of insufficient samples (~11%), and lack of patient feedback.

Despite these drawbacks, it is a notable that these studies were both successfully conducted during the 2019 coronavirus pandemic, where internationally research was stunted. The study in Chapter 7 required co-ordination across multiple hospital research departments, the tracking of over six hundred blood samples across multiple sites and closely working with third-party industry. This has provided an invaluable experience in conducting larger and more complicated trials. Given the promising results within Chapter 7, the research group are planning a further pilot study within ~50 participants to assess the feasibility of capillary NT-proBNP testing, performed by participants at home.

11.2 Modelling in Pulmonary Hypertension

11.2.1 Major Findings

The 2019 World Symposium and the 2022 European Respiratory Society and European Cardiology Society pulmonary hypertension guidelines both emphasised the importance of the concept of risk stratification in PH. Revisions to the previous 3-strata model have been adopted, with the 4-strata model now recommended for the derivation of risk during the follow up of PH patients. Alongside this recommendation, studies over the last decade have focused on the refinement of risk stratification tools. The second work package focused on validating and optimising the COMPERA 2.0 4-strata model.

In Chapter 8, the COMPERA 2.0 model was validated in a cohort of patients with medically managed CTEPH, and its accuracy was compared against the 3-strata model. This demonstrated that the model was able to identify four distinct prognostic groups at follow up and led to improved discrimination of the risk of mortality. A greater number of patients moved between risk groups, demonstrating the sensitivity of this tool at detecting improvement or deterioration in this cohort, following the commencement of treatment.

Chapter 9 focused on patients with PAH, and whether the COMPERA 2.0 model could be refined by exchanging the WHO Functional Class measure of functional disability with the MRC Dyspnoea Scale. The retrospective study, using a purpose-designed algorithm to

assign the MRC Scale, demonstrated that the MRC Dyspnoea Scale alone was superior to WHO FC in derivation mortality and improved the 4-strata model when it was incorporated in PAH risk assessment.

The previously proposed OPTICS and H2FPEF scores were externally validated in Chapter 10. This demonstrated that whilst these scores were largely able to non-invasively predict postcapillary pulmonary hypertension, they were insufficiently specific to be recommended for use in routine clinical practice as they provided a small yet significant risk of misclassifying patient with true IPAH.

11.2.2 Strengths and Limitations

The two risk stratification studies in Chapters 8 and 9 demonstrated novel insights into the applicability and utility of the 4-strata system. The study in Chapter 8 confirmed that the novel models of risk are suitable in the medically-managed CTEPH population. World Health Organisation Functional Class has long been recognised for its drawbacks, including a heterogenous FC III group, in whom discerning the correct treatment approach can be less clear. The MRC Dyspnoea Scale provides a pragmatic alternative functional disability tool and the results from the study are promising. Chapter 10 provides the important data that the H2FPEF and OPTICS scores are unreliable and recommends against their use. This will reduce the risk of misdiagnosis and delayed treatment in a cohort of patients with PH who may significantly benefit from pulmonary vasodilator therapy.

However, all three studies have similar significant limitations. They are all retrospective studies and are prone to the issues endemic to this type of study, such as missing or erroneous data. The MRC Dyspnoea Scale study used a purpose-designed and non-validated algorithm to designate the Scale which hence is prone to misinterpretation and error. These studies all have relatively small sample sizes, a result of the low incidence of PH in Scotland, and hence are at higher risk of Type II error. Furthermore, the treatment algorithms in PH have significantly changed over the last two decades; patients in 2010, when all three studies began collating data, would have been treated differently to those towards 2020, such as with monotherapy in the place of dual oral therapy. All three studies lack prospective or external validation cohorts.

11.3 Clinical Implications

When viewed together, the conclusions from the first work package provide an insight into the possibilities for a remote pulmonary hypertension clinic. As hypothesised in the aims (Chapter 3; Figure 4), a virtual clinic could incorporate multiple remote metrics to

form a reliable method of risk assessment and therefore inform treatment decisions. The COMPERA 2.0 model requires an assessment of exercise capacity, NT-proBNP and functional disability to designate a risk stratum at follow up. The studies herein show that this could be possible, providing a remote exercise test, a sendaway capillary NT-proBNP, an emPHasis-10 score and, at the time of the consultation, a functional assessment. However, this form of clinic model would only be successful in a narrow cohort of patients; those who were motivated, technology-literate and, perhaps, those with a lower-risk status.

These tests could be employed in alternate ways such as in *ad hoc* testing, whereby if a patient were to contact a PH centre with a concern of a deterioration in their health then a remote non-invasive testing approach could be rapidly instigated in order to triage and time the face-to-face review or treatment escalation.

The models used to risk stratify are undergoing regular refinement to enhance their utility. The results from the main work package demonstrate the applicability of the COMPERA 2.0 model in medically managed CTEPH and recommend the avoidance of the use of non-invasive scoring systems for postcapillary PH. The MRC Dyspnoea Scale could provide a better alternative to WHO Functional Class in these models.

11.4 Future Research

Despite relaxed restrictions following the coronavirus pandemic, many patients still elect for virtual consultations due to reasons such as wishing to avoid travel, concerns of nosocomial infections and feeling their health is stable and therefore does not necessitate face-to-face assessment. Future research into the area of remote assessment in PH could focus on the implementation of a virtual clinic in remote clinical practice, using an approach similar to that hypothesised in Chapter 3, Figure 4. The format could take the form of a pilot study, with a cohort of patients who are in a period of relative clinical stability, are comfortable with information technology and are motivated by the concept of objective remote assessment. This could form the basis of a pragmatic study design, including outcome measures of patient feedback, feasibility, safety, avoidance of travel and cost-effectiveness.

The work within this thesis raises the possibility for a virtual 4-strata risk stratification score. The virtual metrics examined in Chapters 5, 6, 7 and 9 (i.e. a measure of functional disability (WHO FC or MRC Dyspnoea Scale), EmPHasis-10 score, NT-proBNP and 6MWD) could be combined at follow up to create and validate a novel risk model which would solely rely on remote metrics.

The author plans to further develop the utility of remote NT-proBNP and is in the process of developing a feasibility study to assess whether patients with PH (including those diagnosed with scleroderma) would be able to perform capillary NT-proBNP testing unsupervised at home. This will be a joint study between the RBH and GJNH. We will also explore whether other key blood tests, such as a full blood count, urea and electrolytes and liver function testing could be performed via capillary sampling contemporaneously.

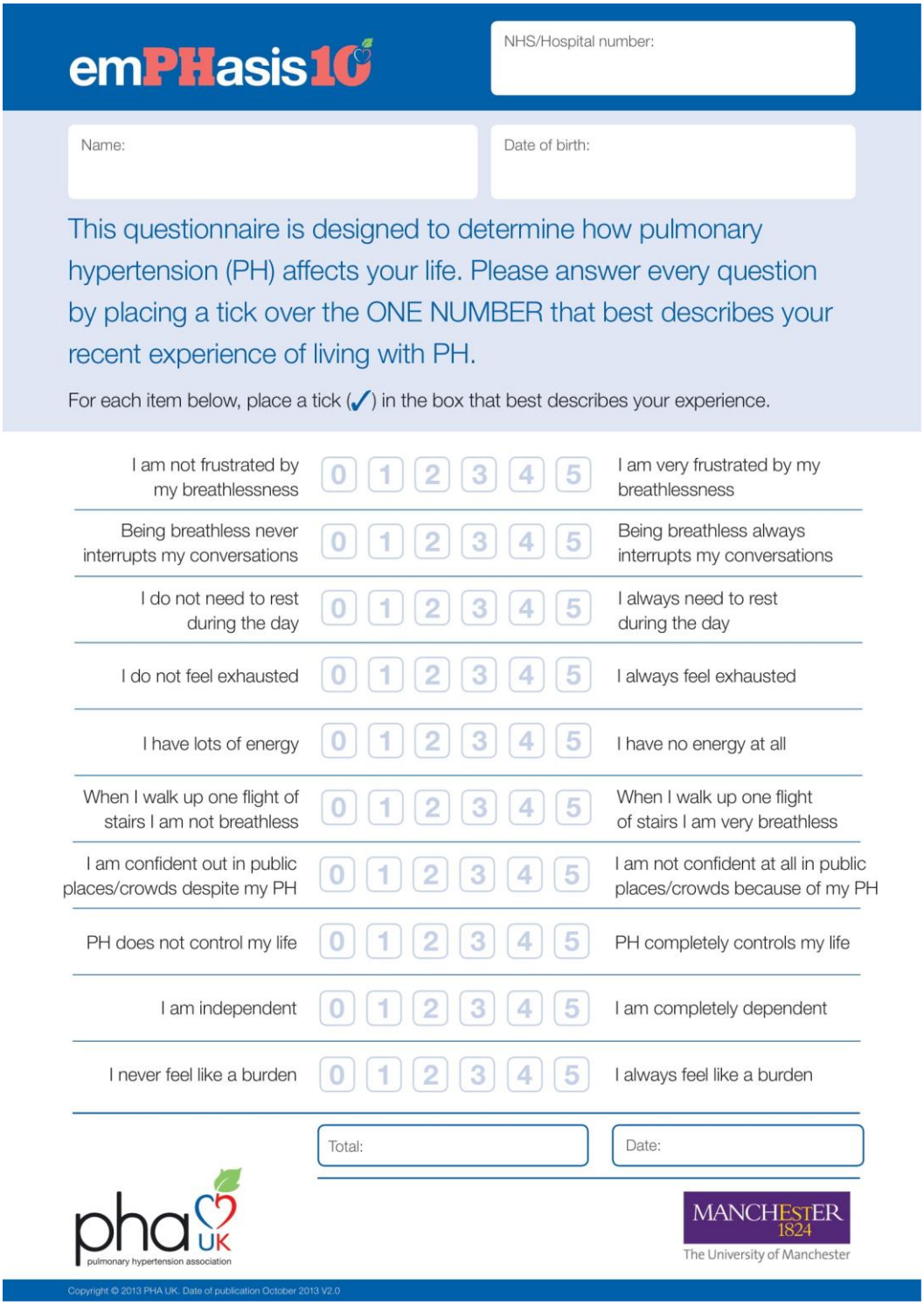
The MRC Dyspnoea Scale has the potential to give a more nuanced calculation of risk in patients with pulmonary arterial hypertension. However, for reasons discussed, the study presented here has limitations and prospective and/or external validation will be required before its use could be recommended.

11.5 Final Comment

The remote assessment of risk pulmonary hypertension is safe and feasible. It remains an important subject, especially for patients who must travel a significant distance to pulmonary hypertension centres. A virtual clinic could be implemented for motivated patients, to provide objective and timely risk stratification, to improve patient convenience and potentially reduced healthcare costs.

12. Appendices

12.1 Form - emPHasis-10 Quality of Life Questionnaire



emPHasis10

NHS/Hospital number:

Name:

Date of birth:

This questionnaire is designed to determine how pulmonary hypertension (PH) affects your life. Please answer every question by placing a tick over the ONE NUMBER that best describes your recent experience of living with PH.

For each item below, place a tick (✓) in the box that best describes your experience.

I am not frustrated by my breathlessness	0 1 2 3 4 5	I am very frustrated by my breathlessness
Being breathless never interrupts my conversations	0 1 2 3 4 5	Being breathless always interrupts my conversations
I do not need to rest during the day	0 1 2 3 4 5	I always need to rest during the day
I do not feel exhausted	0 1 2 3 4 5	I always feel exhausted
I have lots of energy	0 1 2 3 4 5	I have no energy at all
When I walk up one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up one flight of stairs I am very breathless
I am confident out in public places/crowds despite my PH	0 1 2 3 4 5	I am not confident at all in public places/crowds because of my PH
PH does not control my life	0 1 2 3 4 5	PH completely controls my life
I am independent	0 1 2 3 4 5	I am completely dependent
I never feel like a burden	0 1 2 3 4 5	I always feel like a burden

Total:

Date:

pha UK pulmonary hypertension association

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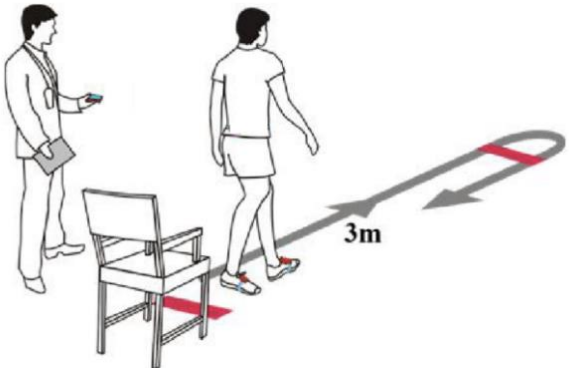
12.2 Instructions - Explanation of Remote Exercise Tests for Participants

TIMED UP AND GO TEST

This test measures how quickly you can stand up, walk three metres, turn around, and then sit down again.



1. Before starting the test, you will need to mark out a distance of 3 metres from the base of a chair. You can use a measuring tape to do this. You will need to be able to walk in a straight line for 3 metres. We may be able to provide a timer and a measuring tape for you.
2. You start the test sat down in a chair.
3. You start a timer.
4. You stand up from the chair and walk three metres.
5. You turn around (180 degrees).
6. You walk back to the chair.
7. You sit down again.
8. You stop the timer
9. Please record how long it took to complete the test.

STEP TEST

This test measures how many times you can walk up and down onto a step. You stop the test after 2 minutes.

1. Before starting the test, you need to find a good step to use. This could be any step in your home, ideally near something for you to hold onto in case you feel unsteady. We may be able to provide a step for you.
2. You start the test stood below the step.
3. You start the timer.
4. You walk up onto the step and then walk back off it. One repetition is counted every time your feet go back to the bottom of the step.
5. You repeat this as many times as you can in 2 minutes and count the number of repetitions that you can manage.
6. You stop when 2 minutes are finished.
7. Please record how many repetitions you managed in 2 minutes.

SIT TO STAND TEST

This test measures how many times you can stand up and sit down on a chair within 1 minute (repetitions).

1. Before starting the test, you will need to find a good chair to use. This chair shouldn't be too low. It should be high enough that when you sit down your back can be straight, like in the picture below.
2. You start the test sat in a chair with your arms crossed across your chest.
3. You start the timer.
4. You stand up until you are fully standing, and then you sit down. You cannot use your arms. One repetition is counted every time you sit back down onto the chair.
5. You repeat this as many times as possible within 1 minute and count how many repetitions you can do.
6. You stop when one minute is up.
7. Please record how many repetitions you managed.

TELE 6-MINUTE WALK TEST

This test measures how far you can walk in 6 minutes. You would need to do this test outside for it to be accurate. You would be allowed to use any walking aids or oxygen you normally use. You will need a finger probe to monitor your oxygen levels and a smartphone to do this test. If you do not have a finger-probe we may be able to provide this.

1. On your smartphone, download the 'Timed Walk' app onto your smartphone (this should have been done at your first visit, but if you have any questions, please see below).
2. Before starting the test, think of a good place you can walk. This should be somewhere near your home, ideally from your doorstep. It should be flat and somewhere you can safely walk for 6 minutes. You're allowed to walk in a loop or the same route several times.
3. You start the test outside.
4. You check your oxygen levels with the finger probe and write the result down.
5. Open the 'Timed Walk' app. Click on the 'Walk' button. Read the instructions. Set the time to 6 minutes.
6. You start the timer on the app – press 'Start'
7. Put your phone in your pocket or hold it in your hand.
8. You walk for 6 minutes.
9. The app will let you know when 6 minutes are up and tell you how far you've walked.
10. Check your oxygen levels again as soon as the test ends.
11. Please write down what your oxygen levels were at the beginning and end and how far you walked.

12.3 Questionnaire – Patients' opinions on home exercise testing in pulmonary hypertension – Following participation in study

Thank you for taking part in this study. We would like to ask you a series of questions about how you felt about the exercise tests that you performed as part of the study.

In the future, we may perform *some* of our clinic appointments using a telephone clinic. We would still see our patients face-to-face *at least* once a year, but if a patient is stable and well, we may perform one or two of their clinics by telephone. We are thinking of using these exercise tests before a telephone clinic to give us more information on how our patients are doing.

Therefore, we particularly want to hear your opinions on how you find performing these tests at home and whether you think they would be good tests to use in the future for patients with pulmonary hypertension.

This questionnaire should take about 10-15 minutes to complete. You should only answer for the tests that you performed as part of the study.

1. Name	
2. Date of Birth	
3. Participant Study ID (if known, otherwise leave blank)	

4. Which of the exercise tests did you perform as part of the study? *(Circle any)*
- Timed Up and Go Test
- Sit to Stand Test
- Step Test
- Tele- Six Minute Walk Test

Please turn to the next page.

TIMED UP AND GO TEST

This was the test where you stood up from a chair, walked for 3 metres, turned around and sat back down while you timed yourself.

5. Did you choose and perform this test as part of the study?

   - ☐ Yes
   - ☐ No (skip this section and go to the next test)

6. Were you **able** to perform this test when you were at home?

   - ☐ Yes (go to question 8)
   - ☐ No

7. If you were unable to perform this test at home, **what stopped you from performing it**? *(Select any)*

   - ☐ I couldn't remember how to do the test
   - ☐ I couldn't understand the test instructions
   - ☐ I was worried I would fall
   - ☐ I felt too breathless to perform the test
   - ☐ I felt too tired to perform the test
   - ☐ I didn't have the right equipment to complete the test
   - ☐ Other: ……

8. In the future, how **happy** would you be to perform this test up to three times a year while you were at home? (*Select one)*

Very Happy Happy I wouldn't mind Unhappy Very Unhappy

9. Do you think there was anything particularly **good** about this test?

   .....

10. Do you think there was anything particularly **bad** about this test?

    .....

NB: Questions 5 to 10 were then repeated for the remaining three tests: the Step Test, the Sit to Stand test and the Tele-Six Minute Walk Test.

12.4 Instructions - emPHasis-10 electronic survey

emPHasis10

We are trying a new way of doing the emPHasis-10 questionnaire using your smart phone.

If you don't have a smart phone, we can provide you with a paper copy instead.

1. **Scan the image below** using the camera, or QR code scanner, on your phone

If the scan doesn't work, you can go to this website on your phone:

www.tinyurl.com/emphasis10

2. Enter your three-digit code
(we will provide you with this)

3. Fill in the 10 questions about the impact pulmonary hypertension has on your life.

4. Press "Submit"
That's it, you're finished – thank you!

12.5 Risk stratification methodology

12.5.1 3-Strata (2015)

The 3-strata model categorises patients into low-, intermediate- or high- risk groups. Using the COMPERA 1.0 methodology, at each patient visit, the variables described in Table 32 are assigned a grade depending on their severity. The sum of all grades is divided by the number of variables used and are rounded to the nearest integer. This defines the overall risk group where 1 is low risk, 2 is intermediate risk and 3 is high risk.

	Grade		
Variable weight	1	2	3
WHO FC	I or II	III	IV
6MWD (m)	>440	165-440	<165
NT-proBNP (pg/ml)	<300	300-1400	>1400
RAP (mmHg)	<8	8-14	>14
CI (L/min/m^2)	≥2.5	2.0-2.4	<2.0
SvO2 (%)	>65	60-65	<60

Table 32. Variable grading according to 3-strata risk model

12.5.1 4-Strata (2021)

The 4-strata model categorises patients into low-, intermediate-low, intermediate-high or high- risk groups. Using the COMPERA 2.0 methodology, at each patient visit, the three variables described in Table 33 are assigned a grade depending on their severity. The sum of all grades is divided by three, thus defining the overall risk stratum where <1.5 is low risk, 1.5-2.49 is intermediate-low risk, 2.5-3.49 is intermediate-high risk and >3.5 is high risk.

	Grade			
Variable weight	1	2	3	4
WHO FC	I or II		III	IV
6MWD (m)	>440	320-440	165-319	<165
NT-proBNP (pg/ml)	<300	300-649	650-1100	>1100

Table 33. Variable grading according to 4-strata risk model

12.6 Enright Calculations

The Enright calculations(47) provide an prediction of the lower limit of distance from predicted six-minute walk distances (p6MWD) based on age, gender, height and BMI. Where h = Height (cm), a = age (years) and m = mass (kg).

	Predicted Six-Minute Walk Distance (p6MWD, m)	Lower Limit of Normal 6MWD (m)
Male	(7.57*h) – (5.02*a) – (1.76*m) – 309	p6MWD - 153
Female	(2.11*h) – (2.29*m) – (5.78*a) + 667	p6MWD - 139

Table 34. Enright Calculations for predicting six-minute walk distance

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