Effect of Pulmonary Rehabilitation on Frailty in Patients with respiratory disease and Post COVID Syndrome

Kola Akinlabi

A thesis submitted for the degree of Master of Philosophy in Physiotherapy

School of Sport Rehabilitation and Exercise Science

University of Essex

February 2025

Table of Contents

Summary of Thesis Corrections and Additions **8**

Introduction 8

Impact of COVID-19 on my research study **12**

Impact of COVID-19 on my scope of study 12

New research work and questions 15

Thesis Summary **16**

2. Literature Review **17**

2.1 Understanding Frailty in Chronic Respiratory Diseases 17

2.2 COPD and Frailty 17

2.3 Pulmonary Rehabilitation 18

Definitions and Components 18

3. Methodology 19

3.4 Statistical Analysis 19

5. Discussion 20

6. Conclusion and Recommendations 21

Chapter 1: Frailty and Pulmonary Rehabilitation **22**

1.1 Background 22

1.2 COPD and Frailty. 22

1.3 Frailty screening 23

1.5 Pulmonary rehabilitation **24**

1.5.2 Benefit of Pulmonary rehabilitation in chronic respiratory condition 27

1.5.3 Physiological Basis of Benefit of Pulmonary Rehabilitation 32

1.5.3.1 The physiological basis of the improvement of exercise capacity: 34

1.5.3.5 Other Benefits of PR 40

1.5.4 Evidence-Based Practices in Pulmonary Rehabilitation 41

1.5.4.1 The impact of Pulmonary Rehabilitation on Mortality and Hospital Admission in Patients with COPD. 42

1.5.4.2 Impact of Pulmonary Rehabilitation on mortality and re-admissions from COPD exacerbation. 44

1.5.5 Current Pulmonary Rehabilitation Landscape 44

Chapter 2: 46

Systematic Review and Meta-analysis of the benefit of pulmonary rehabilitation in Frail COPD and Other Chronic Lung Disease 46

ABSTRACT 46

Background 46

2.1 Introduction 48

2.2 Methods 48

Table 1. Search terms 51

2.2.7 Search Strategy 51

2.2.18 Statistical analysis 56

2.3 Meta-analysis results 60

Forest plot 60

2.3.2 6MWT score (Frail Vs Not Frail): Delta Meta-Analysis 61

Forest Plot.. 62

2.3.5 CAT score (Frail vs Not Frail): Delta Meta-analysis 63

Forest Plot.. 63

2.3.7 4MGS (Frail vs Not Frail): Delta Meta-analysis... 65

Forest Plot.. 65

2.4 Discussion 68

2.4.1 Strengths of the Study: 72

2.4.2 Clinical Relevance: 73

2.4.3 Limitations of the Study: 73

Chapter 3: Impact of Pulmonary Rehabilitation on Physical Frailty and Hospitalisation in Patients with COPD 75

3.1 Abstract 75

3.2 Background 76

3.4 Methods... 77

3.4 Assessment 79

3. 6 Primary and secondary outcome measures 84

Onward Methods 85

3.8 Data analysis 87

3.9 Results 87

Baseline characteristics of patients 87

Table 2 Frail Vs Pre-frail, comparison of baseline clinical characteristics 90

ANOVA... 90

Table 3 Pre-rehabilitation hospitalisation and exacerbation rate by frailty classification **90**

Table 5 Change in exacerbation and hospitalisation according to frailty classification after 6 month follow up following PR **94**

3.10 Discussion 95

3.10.2 Mechanisms Underpinning Outcomes 99

Chapter 4: Frailty in chronic respiratory disease: prevalence and comparison of rehabilitation clinical outcomes **102**

4.1 Abstract 102

4.2 Background/rationale 103

4.3 Research protocol 104

4.4 Methodology 105

Sample population 106

4.5 Statistical analysis 107

4.6 Results 108

Summary of key findings from results above 108

Prevalence of frailty in chronic respiratory conditions and proportion of frailty status in each in each chronic respiratory condition 110

Table 3. Change in outcomes following PR 111

4.5 Discussion 115

Chapter 5: Frailty in chronic respiratory disease: direction of change following a positive response to pulmonary rehabilitation. **122**

5.1 Abstract 122

Background 122

5.2 Introduction 123

5.3 Research protocol 124

5.4 Methods 125

5.7 Results 128

5.8 Discussion 133

Health economic analysis of the impact of pulmonary rehabilitation 138

Chapter 6: Integrating Findings and Implications for Clinical Practice in Pulmonary Rehabilitation 140

5.1 Introduction 140

Chapter 7: Long-Term Exercise Post-Pulmonary Rehabilitation 145

7.1 Abstract 145

7.2 Introduction 146

Chapter 8: Clinical outcomes, physical characteristics, and impact of frailty in post-COVID syndrome. 151

8.1 Abstract 151

8.2 Introduction 155

8.5 Post-COVID-19 Syndrome 158

8.8 Research protocol 163

8.10 Methodology 164

Self-management 171

8.13 Statistical analysis 171

8.14 Results 172

Prevalence of post-COVID syndrome 174

Hospitalised vs Home (non-hospitalised) 175

Table 2 Change in clinical outcomes for all patients with the intention to treat analysis of baseline available and missing data, n=179 177

5.7 Discussion 179

5.8 Limitations 182

5.9 Conclusion 182

Final Chapter: 184

References 186

Ethical consideration 202

Summary of Thesis Corrections and Additions

Introduction

This document provides a comprehensive summary of all the corrections, enhancements, and additions made to the thesis titled *"The Impact of Pulmonary Rehabilitation on Frailty and Hospitalisation in COPD Patients."* Each section of the thesis has been reviewed, with significant content rewritten or expanded to address gaps and align with academic standards. The summary highlights the key areas of improvement, details added, and critical updates made across all chapters.

Key Corrections and Additions

1. Abstract

- Enhanced the abstract to succinctly outline the research objectives, methods, key findings, and implications.
- Emphasised the role of pulmonary rehabilitation (PR) in reducing frailty and improving quality of life in chronic respiratory disease populations.

2. Chapter 1: Introduction

- **Background:** Expanded the context on the global burden of COPD and its association with frailty.
- **Frailty Screening:** Added comprehensive details about frailty screening tools like the Fried Frailty Phenotype and PRISMA-7.
- **Current Pulmonary Rehabilitation Landscape:** Discussed accessibility issues, typical patient demographics, and the evidence base supporting PR as an intervention.
- **Evidence-Based Impact of PR on Frailty:** Introduced studies demonstrating PR's role in reversing frailty and reducing hospitalisation rates.

3. Chapter 2: Systematic Review and Meta-Analysis

- **Search Strategy:** Improved clarity and detail about databases used, keywords applied, and inclusion criteria.
- **Study Characteristics:** Added a comprehensive table summarising the characteristics of included studies.
- **Results Presentation:** Clearly differentiated between quantitative meta-analysis findings and qualitative synthesis.

- **Discussion:** Critically analysed the scarcity of randomised controlled trials (RCTs) and proposed future research directions.
- Ensured consistency in table and figure legends, improving readability and alignment.

4. Chapter 3: Impact of Pulmonary Rehabilitation on Physical Frailty and Hospitalisation

- **Methods:** Detailed the PR intervention protocol, including exercise intensity, duration, and patient assessment metrics.
- **Results:** Expanded on baseline characteristics and post-intervention outcomes for frail and non-frail patients.
- **Discussion:** Incorporated clinical reasoning for observed trends and highlighted gaps in longitudinal data.
- Corrected formatting errors in tables and figures.

5. Chapter 4: Frailty in Chronic Respiratory Disease

- **Prevalence:** Enhanced the section with demographic and clinical data illustrating frailty prevalence in COPD.
- **Comparison of Outcomes:** Added a nuanced comparison of rehabilitation outcomes in frail versus non-frail patients.
- **Discussion:** Linked findings to broader healthcare delivery challenges, including resource allocation and interdisciplinary care.

6. Chapter 5: Integrating Findings and Implications for Clinical Practice

- Synthesised key findings from the thesis to highlight clinical implications.
- Discussed how the research aligns with NHS Long-Term Plan priorities, such as reducing health inequalities and promoting preventative care.
- Proposed actionable recommendations for healthcare systems to optimise PR delivery.
- Identified limitations in the research and outlined future study directions, particularly for underserved populations.

7. Chapter 6: Long-Term Exercise Post-Pulmonary Rehabilitation

- Added a new chapter on the importance of long-term exercise in sustaining PR benefits.
- **Physiological Benefits:** Detailed mechanisms such as improved muscle strength, reduced systemic inflammation, and enhanced cardiovascular efficiency.

- **Psychological Benefits:** Explored the role of long-term exercise in reducing anxiety, improving self-efficacy, and fostering social well-being.
- **Barriers and Solutions:** Identified challenges to adherence, including physical, systemic, and environmental factors, and proposed strategies like digital health integration and personalised exercise plans.
- **Future Directions:** Emphasised the need for longitudinal research and policy reforms to support maintenance programs.

8. Chapter 7: Clinical Outcomes and Frailty in Post-COVID Syndrome

- Introduced a new chapter focusing on frailty in post-COVID syndrome patients.
- **Pathophysiology:** Explored the impact of COVID-19 on physiological reserves, leading to frailty.
- **Rehabilitation Outcomes:** Highlighted the effectiveness of tailored interventions in improving functional capacity and reducing fatigue.
- **Discussion:** Addressed the implications of frailty in post-COVID populations and the need for multidisciplinary care.
- **Limitations:** Acknowledged gaps in data and the reliance on retrospective studies.

9. References

- Updated and reformatted the reference list to adhere to Vancouver style.
- Included citations within the text where required, ensuring alignment with original and new content.

Additional Improvements

- **Formatting Consistency:** Standardised font sizes, headings, and figure/table legends across all chapters.
- **Academic Writing Style:** Enhanced clarity and readability by restructuring long sentences and improving grammar.
- **Figures and Tables:** Corrected sequencing issues, ensured alignment with text discussions, and improved clarity of captions and axis labels.
- **Overall Flow:** Streamlined transitions between sections and chapters to enhance coherence and logical progression. #

Conclusion

The comprehensive revisions have addressed all feedback provided, significantly improving the quality and impact of the thesis. Key gaps in previous submissions have been filled, new insights have been added, and the structure has been refined to meet academic and professional standards. The final thesis now presents a robust, evidence-based analysis of pulmonary rehabilitation and its broader implications for chronic respiratory disease management.

Impact of COVID-19 on my research study

The COVID-19 pandemic had a significant impact on my PhD research journey, especially during its second year. The pandemic caused widespread disruptions across the globe, and NHS services were no exception. Healthcare workers were redeployed to critical areas, such as intensive care units and respiratory wards. Due to this, I was also assigned to work on the frontline services, and I had to work tirelessly through day and night shifts. As a result, I couldn't proceed with my planned data collection for research.

Impact of COVID-19 on my scope of study

Prior to the COVID-19 pandemic, I conducted several studies on frailty in pulmonary rehabilitation as part of my PhD research. These studies involved face-to-face exercise programs and data collection within multidisciplinary team (MDT) settings. The focus was on both exercise and education interventions for individuals with COPD and chronic respiratory diseases. The results of these studies were presented in three separate European Respiratory Society (ERS) congresses and are available online on the ERS website. Unfortunately, due to the pandemic, I was unable to present my further study in person at ERS congresses.

I have been focusing my research on frailty in pulmonary rehabilitation and physical activity. I planned to investigate whether physical activity could be used as a maintenance program after pulmonary rehabilitation to sustain its benefits for frail individuals with COPD. However, due to the COVID-19 pandemic, I had to reevaluate my methodology and study design to adapt to the current circumstances. I had to consider alternative approaches and strategies to continue my research despite the challenges posed by the pandemic. I couldn't proceed with my planned data collection and study due to concerns regarding the risk of transmission among respiratory COPD patients. This unforeseen circumstance forced me to adapt to the exigencies of the moment.

To respond to these challenges, I discussed with my PhD supervisor and explored new avenues for a study that could align with the overarching theme of pulmonary rehabilitation and frailty within my thesis. With the pandemic entering its second wave, I identified a new clinical phenomenon called post-COVID syndrome or Long COVID, which presents a cluster of symptoms such as headache, breathlessness, chest pain, fatigue, brain fog, muscle pain, and exercise intolerance. Long COVID presents a new frontier in medical understanding, with its pathogenesis absent from conventional medical literature.

Long COVID is defined as the persistence of symptoms lasting 12 weeks or more and are not explained by an alternative medical diagnosis (NICE NG 188, 2020). Amongst other patients, Long COVID-affected individuals who had experienced prolonged hospitalisations, either in intensive care units (ITU) or on medical wards, or those who had been bedridden at home due to severe viral fatigue and muscle weakness. The extended periods of inactivity and physical deconditioning resulting from prolonged hospital stays or bed rest suggested a potential link to frailty—a state characterised by a reduction in physiological reserves, rendering individuals vulnerable to acute stressors, infections, and falls.

Although frailty was not initially recognised as a symptom of Long COVID-19, I produced a hypothesis that its prevalence might be uncovered through comprehensive assessments of individuals with prolonged inactivity, such as those recovering from severe COVID-19 illness. This notion paved the way for a pioneering study aimed at exploring the inclusion of frailty as part of the cluster of symptoms associated with Long COVID-19—a novel inquiry that promised to contribute significantly to the evolving understanding of this complex condition.

As the healthcare landscape gradually adapted to accommodate the challenges posed by the pandemic, the delivery of services transformed. Aerosol-generating procedures, including pulmonary rehabilitation, transitioned to online platforms following initial face-to-face assessments. Conversely, Long COVID services emerged as essential components of care, with the UK government allocating funds for the establishment of community rehabilitation clinics and specialist secondary care services dedicated to addressing the multifaceted needs of individuals grappling with Long COVID.

In this evolving context, rehabilitation emerged as a cornerstone of the management strategy for Long COVID, encompassing individualised tailored exercise programmes, physical activity, breathing re-training for breathing pattern disorder, self-management of fatigue, brain fog management and comprehensive support to address the diverse array of symptoms and functional impairments associated with this condition. Through the integration of rehabilitation interventions within the framework of Long COVID management, the potential to mitigate frailty and enhance overall well-being became a focal point of research and clinical innovation, underscoring the imperative of adaptive approaches in the face of unprecedented challenges.

Therefore, having started the new service, approval was sought from our Trust research team to retrospectively review data of our patients to see if frailty was present in our post-COVID patient group and if rehabilitation offered was effective. Frailty assessment is a standard measure used in our pulmonary rehabilitation service.

New research work and questions

The development of my next study involved the clear articulation of its aims, objectives, and hypotheses, meticulously aligned with the research questions at hand. My research topic centred on the clinical outcomes, physical characteristics, and the impact of frailty in individuals with post-COVID syndrome. The overarching hypothesis posited that frailty represents a clinical symptom within the spectrum of post-COVID syndrome, and further, that rehabilitation serves as an effective intervention.

This hypothesis was informed by existing literature, which underscored the prevalence of frailty among patients with chronic respiratory diseases and highlighted the efficacy of rehabilitation in reversing frailty and reducing hospital admissions significantly (Maddocks, 2016; Akinlabi, 2018).

The aim of my study was twofold: firstly, to ascertain whether frailty constitutes a component of the symptom cluster observed in Long COVID, and secondly, to investigate the efficacy of rehabilitation as a strategy in managing this condition.

To achieve these aims, several objectives were delineated:

1. To determine the prevalence of frailty among individuals with Long COVID.
2. To assess changes in frailty status following a six-week rehabilitation program. 3. To evaluate alterations in standard clinical outcomes commonly used in pulmonary rehabilitation following the intervention period.

4. To conduct a comparative analysis of the clinical characteristics of individuals admitted for COVID-19 infection versus those who managed their illness at home.

The study relied on a statistical analysis of previously collected data, with the findings presented within this thesis, offering valuable insights into the role of frailty and the efficacy of rehabilitation in the context of post-COVID syndrome.

Thesis Summary

1. Introduction

Frailty has emerged as a key concern in the management of chronic respiratory diseases (CRDs), including chronic obstructive pulmonary disease (COPD) and the relatively recent post-COVID syndrome (Long COVID). Defined as a decline in physiological reserves, frailty renders individuals vulnerable to acute stressors, leading to adverse clinical outcomes such as increased hospitalizations, reduced mobility, and overall diminished quality of life. While pulmonary rehabilitation (PR) has been widely recognized as an effective intervention for COPD, its role in addressing frailty, particularly within post-COVID populations, remains underexplored.

The COVID-19 pandemic significantly impacted the progression of this research, necessitating modifications in methodology due to disruptions in healthcare services. Initially focused on frailty in COPD, the study expanded to include post-COVID syndrome as an emerging area of interest. The overarching hypothesis posits that frailty is a clinical symptom within the spectrum of post-COVID syndrome and that pulmonary rehabilitation can serve as an effective intervention.

1.1 Research Problem

Despite the well-documented benefits of pulmonary rehabilitation in improving exercise capacity and reducing hospital readmissions in COPD, its effectiveness in reversing or mitigating frailty remains uncertain. Frailty has been linked to higher hospitalisation rates, increased mortality risk, and functional decline in patients with chronic respiratory conditions. Given the recent emergence of post-COVID syndrome, there is an urgent need to explore whether frailty should be recognised as part of its clinical presentation and whether pulmonary rehabilitation can effectively mitigate frailty-related complications.

1.2 Objectives

The study aimed to:

1. Determine the prevalence of frailty among individuals with post-COVID syndrome.
2. Assess changes in frailty status following a six-week pulmonary rehabilitation program.
3. Evaluate alterations in standard clinical outcomes used in pulmonary rehabilitation.
4. Compare the clinical characteristics of individuals hospitalized for COVID-19 with those who managed their illness at home.

2. Literature Review

2.1 Understanding Frailty in Chronic Respiratory Diseases

Frailty is characterized by diminished strength, endurance, and physiological function, increasing vulnerability to adverse health outcomes. It is commonly assessed using the Fried Frailty Phenotype, which includes weight loss, exhaustion, low physical activity, slow gait speed, and reduced grip strength. COPD patients exhibit a high prevalence of frailty due to systemic inflammation, muscle wasting, and chronic inactivity.

2.2 COPD and Frailty

COPD is associated with increased frailty due to aging-related muscle loss, chronic inflammation, and exacerbation-related physical deconditioning. Studies suggest that 20% of COPD patients fall within the frail category, while over 50% are classified as pre-frail. Pulmonary rehabilitation has been proposed as a potential intervention to reverse frailty by improving physical function, endurance, and overall quality of life.

2.3 Pulmonary Rehabilitation

Definitions and Components

Pulmonary rehabilitation is a structured, multidisciplinary program designed to enhance the physical and psychological well-being of patients with chronic respiratory diseases. It consists of:

- **Exercise training** (aerobic and resistance training)
- **Education** (self-management strategies, symptom recognition)
- **Behavioural and psychosocial support** (addressing anxiety, depression, and social isolation)

2.4 Impact of Pulmonary Rehabilitation on Frailty

Previous studies indicate that pulmonary rehabilitation can improve muscle strength, mobility, and functional independence in frail COPD patients. A systematic review suggested that PR reduces hospital readmissions and mortality among frail individuals, though data specifically focusing on frailty reversal is limited.

2.5 Frailty in Post-COVID Syndrome

Long COVID presents a cluster of persistent symptoms, including fatigue, dyspnea, brain fog, and exercise intolerance. Many post-COVID patients experience prolonged physical deconditioning due to extended hospital stays or prolonged inactivity. Given the similarities between post-COVID symptoms and frailty, there is a need to assess whether frailty should be formally included in the clinical spectrum of post-COVID syndrome.

2.6 Gaps in Existing Literature

Despite extensive research on pulmonary rehabilitation in COPD, there is limited evidence on its impact on frailty, particularly in post-COVID populations. This study seeks to bridge this gap by exploring the role of pulmonary rehabilitation in reversing frailty in both COPD and post-COVID patients.

3. Methodology

3.1 Research Design

A hybrid approach combining prospective cohort study and retrospective data analysis was employed. Patients undergoing pulmonary rehabilitation were assessed for frailty pre- and post-intervention.

3.2 Study Population and Sampling

The study included individuals diagnosed with:

- COPD (referred by respiratory specialists)
- Post-COVID syndrome (referred from Long COVID clinics)

3.3 Data Collection and Outcome Measures

Frailty was assessed using:

- Fried Frailty Criteria
- Six-Minute Walk Test (6MWT)
- COPD Assessment Test (CAT)
- Fatigue Assessment Scale (FAS)
- Post-COVID Functional Status (PCFS)
- EuroQol 5 Dimension (EQ-5D)
- Medical Research Council (MRC) Score

3.4 Statistical Analysis

- **Paired t-tests** assessed pre- and post-rehabilitation changes.
- **Chi-square tests** compared frailty prevalence among subgroups.

- **Multivariate regression analysis** determined predictors of frailty improvement.

4. Findings and Results

4.1 Prevalence of Frailty

- **36%** of post-COVID patients were identified as frail.
- **65%** of frail COPD patients experienced a significant reduction in frailty post-rehabilitation.

4.2 Impact of Pulmonary Rehabilitation on Frailty

- PR resulted in a significant reduction in frailty scores, with over 50% of frail COPD patients transitioning to a pre-frail status.
- Among post-COVID patients, functional improvements were noted, although frailty reversal rates were lower than in COPD patients.

4.3 Changes in Clinical Outcomes Post-Rehabilitation

- **6MWT**: Increased by an average of **43.9 meters**.
- **CAT Score**: Showed an **improvement in quality of life**.
- **Fatigue scores**: Significantly reduced, indicating enhanced endurance.

4.4 Comparative Analysis: Hospitalised vs. Non-Hospitalised Patients

- Patients who were hospitalised for COVID-19 exhibited higher frailty scores than those who managed their illness at home.
- Greater improvements in functional outcomes were observed among hospitalised patients post-rehabilitation.

5. Discussion

5.1 Key Findings in Context of Existing Literature

- Findings support existing literature that pulmonary rehabilitation is effective in reducing frailty in COPD patients.
- Evidence suggests that frailty should be recognized as a component of post-COVID syndrome.

5.2 Implications for Pulmonary Rehabilitation

- PR should be tailored for frail individuals by incorporating strength training and endurance exercises targeting post-COVID syndrome.

- Long-term maintenance programs should be established to sustain benefits.

5.3 Study Limitations

- Retrospective nature of data collection for post-COVID patients.
- Small sample size for post-COVID syndrome, limiting generalizability.

5.4 Recommendations for Future Research

- Randomised controlled trials should be conducted to validate findings.
- Further studies should explore long-term effects of pulmonary rehabilitation on frailty.

6. Conclusion and Recommendations

This study highlights frailty as a prevalent concern in both COPD and post-COVID syndrome, emphasising pulmonary rehabilitation as a viable intervention. Key findings demonstrate that PR can reduce frailty, improve functional capacity, and enhance quality of life in both populations. However**, long-term strategies** must be developed to maintain these benefits. Future research should **expand sample sizes** and explore **long-term rehabilitation models** for frail populations.

This thesis underscores the urgent need to **integrate frailty assessments in clinical practice** for COPD and post-COVID patients and recommends the **wider implementation of tailored pulmonary rehabilitation programs**.

Chapter 1: Frailty and Pulmonary Rehabilitation

1.1 Background

The ageing population is accelerating rapidly in the United Kingdom and worldwide. In 2004, the population of people aged 65 years and above was 461 million, a figure projected to rise to 2 billion by 2050 globally[2]. This demographic shift will have enormous implications for health and social care systems, including financial, planning, and service delivery considerations[3].

Frailty is a key concern in ageing, representing a significant decline in physiological systems, which leads to vulnerability to acute stressors and reduced physiological reserves[3,4]. It affects approximately 1 in 10 individuals aged over 65 and is associated with frequent hospitalisation, increased fall risk, disability, and mortality[5]. Frail older adults face adverse outcomes, including greater likelihood of hospitalisation, nursing home admission, and death[6]. The condition is often identified using the Fried Frailty Phenotype, which encompasses five criteria: weakness, slow gait, exhaustion, low physical activity, and unintentional weight loss[7]. Individuals meeting one or two criteria are considered pre-frail, with one in four progressing to frailty within three years[7,8].

1.2 COPD and Frailty.

Chronic obstructive pulmonary disease (COPD) shares several risk factors and mechanisms with frailty, including age-related changes, endocrine dysfunction, and systemic inflammation. COPD prevalence increases with age, with older adults bearing the highest disease burden and healthcare costs. Notably, frail individuals with COPD exhibit poorer clinical outcomes, including exacerbation risks, increased comorbidities, and higher healthcare utilisation.

The Fried Frailty Phenotype's characteristics are prevalent in COPD, such as low physical activity and weakness, which predict adverse events like unplanned admissions. Studies highlight frailty's prevalence in COPD patients, particularly those with severe disease. Lahousse et al. (2016) observed that frailty increased with disease severity and exacerbation frequency, while Park et al. (2013) linked frailty to comorbid diabetes and reduced functional capacity.

A baseline cross-sectional analysis of the Cardiovascular Health Study demonstrated that frail individuals were more likely to have an obstructive respiratory impairment and vice versa, however, were silent on participants' functional status and physical activity.

A report of a systematic review[16], on frail COPD, suggested that COPD patients have a fold odds ratio of becoming frail with 20% of the population in the frailty category and over 50% in the pre-frailty category according to Fried frailty criteria. And of the over 50% in pre-frailty classification, one fourth of them will become frail after 3 years[7]. Despite this evidence, preventive strategies for frailty within COPD care are lacking, underscoring the need for targeted interventions.

1.3 Frailty screening

Screening for frailty among individuals with COPD and other chronic diseases offers an opportunity to reduce adverse outcomes, such as unplanned admissions, impaired quality of life, and mortality. Evidence suggests that early detection of frailty can facilitate tailored care plans, mitigating progression to severe frailty. For instance, the NICE NG56 guidelines recommend frailty assessments for patients with multimorbidity, though they lack specific preventive strategies for pre-frailty. Tools such as the Fried Frailty Phenotype and PRISMA-7 questionnaire are invaluable for identifying at-risk individuals.

Interventions to prevent frailty include pulmonary rehabilitation (PR) and physical activity programs, which show promise in delaying or reversing frailty. A 2011 Cochrane review highlighted PR's efficacy in reducing hospital admissions and mortality among COPD patients. Furthermore, targeted strategies for pre-frail COPD patients could prevent functional decline and unplanned admissions, contributing to better healthcare outcomes.

1.4 The Fried Frailty Phenotype as a Diagnostic Tool

The Fried Frailty Phenotype remains a gold standard for assessing frailty. Developed from the Cardiovascular Health Study, it evaluates five domains: unintentional weight loss, exhaustion, low physical activity, slowness (via 4 Meter Gait Speed), and weakness (via Hand Grip Strength, using dynamometer). Patients are classified as frail, pre-frail, or robust based on these criteria. Its robust validation and applicability to COPD populations make it an essential tool for identifying frailty and guiding interventions.

1.5 Pulmonary rehabilitation

Pulmonary rehabilitation (PR) is a comprehensive, multidisciplinary intervention designed to improve the physical and psychological well-being of individuals with chronic respiratory diseases, such as Chronic Obstructive Pulmonary Disease (COPD), Interstitial Lung Diseases (ILDs), cystic fibrosis, and bronchiectasis. PR programmes typically incorporate exercise training, education, self-management strategies, and psychosocial support to enhance functional capacity, reduce symptoms, and improve overall quality of life for patients with chronic respiratory conditions[27].

Pulmonary rehabilitation is also described as a deliberate supervised therapeutic process of restoring a patient's function through the process of rehabilitation[28]. In 2013, the British Thoracic Society (BTS) published a clinical guideline on evidence for PR proving it as an evidence-based intervention[29]. The guidelines define PR as an interdisciplinary programme of care for patients with chronic respiratory impairment that is individually tailored and designed to optimise each patient's physical, and social performance and autonomy. ("Pulmonary Rehabilitation in COPD: Current Practice and ... - Intech Open") Within this guideline, PR was described as a key component in the management of COPD and is proven to be highly effective at improving symptoms burden, physical function, and health status, although the patient response is heterogeneous[30,31]. Pulmonary rehabilitation is highly effective at improving symptoms, its effectiveness has been widely published through research and highlighted in the Department of Health's 'An Outcomes Strategy for COPD and Asthma in England' -Department of Health DOH[32]. Since the outcome strategy, there has been a significant expansion in the understanding of the outcome, markers, and its effects on reducing readmission rate, mortality, and modification of frailty. In 2016 the effect and impact of PR on frail COPD were tested in a clinical trial and were found to be effective at reversing frailty[19].

Pulmonary rehabilitation involves 3 major core components: exercise training, education programme and self-management.

1.5.1 Components of Pulmonary Rehabilitation:

PR programmes typically incorporate exercise training, education, self-management strategies, and psychosocial support to enhance functional capacity, reduce symptoms, and improve overall quality of life for patients with chronic respiratory conditions[27].

1. Exercise Training:

Exercise training is a cornerstone of pulmonary rehabilitation and arguably the most effective intervention for improving exercise tolerance in patients with chronic respiratory diseases[33,34]. Exercise training is aimed at improving cardiovascular fitness, muscular strength, and endurance in individuals with chronic respiratory diseases[35]. Exercise training in pulmonary rehabilitation is divided into aerobic (endurance training) and resistance training exercises[36]. Aerobic exercises, such as walking, cycling, and swimming, are commonly prescribed to improve aerobic capacity, cardio-respiratory response, and tolerance to physical activity. Resistance training with the right dose, involving exercises targeting major muscle groups, helps to strengthen peripheral muscles and improve functional performance[37]. Exercise prescription is individualised based on patients' baseline fitness levels, disease severity, and comorbidities, with progressive intensity and duration to optimize outcomes.

The protocols of aerobic and resistance training typically include specific measured exercise prescriptions with each targeting different physiological mechanisms to enhance overall exercise performance[34].

2. Education:

Patient education plays a crucial role in pulmonary rehabilitation, empowering individuals with chronic respiratory diseases to understand their condition, manage symptoms, and make informed decisions about their health[28]. Educational components of PR programs cover diverse topics, including disease understanding, medication management, inhaler technique, smoking cessation, nutrition, energy conservation techniques, and symptom recognition[38]. Education is delivered through group sessions, individual counselling, written materials, and multimedia resources, tailored to meet the specific needs of each patient[28].

3. Self-Management Strategies:

Pulmonary rehabilitation emphasizes the importance of self-management strategies in empowering patients to take an active role in managing their condition and optimizing their health outcomes[39]. Self-management interventions focus on enhancing patients' knowledge, skills, and confidence in managing symptoms, adhering to treatment regimens, and engaging in healthy behaviours. Techniques such as action planning, goal setting, problem-solving, and self-monitoring help patients develop practical strategies for coping with breathlessness, exacerbations, and activities of daily living[28].

4. Psychosocial Support

Psychosocial support is an integral component of pulmonary rehabilitation, addressing the emotional and social aspects of living with a chronic respiratory disease[40]. Group-based sessions, individual counselling, peer support networks, and relaxation techniques help patients cope with anxiety, depression, social isolation, and stress associated with their condition[41]. Psychosocial interventions promote resilience, social connectedness, and emotional well-being, enhancing patients' overall quality of life and adherence to treatment recommendations[40,41]

1.5.2 Benefit of Pulmonary rehabilitation in chronic respiratory condition

1. Improved Exercise Capacity

Pulmonary rehabilitation has been shown to significantly improve exercise tolerance, functional capacity, and physical performance in individuals with chronic respiratory diseases[35]. Aerobic training and resistance exercises enhance cardiovascular fitness, muscular strength, and endurance, allowing patients to engage in daily activities with greater ease and confidence[42]. Physiological adaptations, including increased oxygen uptake, improved ventilation-perfusion matching, and enhanced respiratory muscle function, contribute to the observed improvements in exercise capacity following PR participation[1].

2. Symptom Management:

Pulmonary rehabilitation helps to alleviate common symptoms associated with chronic respiratory diseases, such as dyspnea, fatigue, and exercise-related discomfort[34]. Exercise training, breathing retraining, energy conservation techniques, and psychosocial interventions provide patients with practical strategies for managing symptoms and improving their overall well-being. By addressing the underlying physiological mechanisms of symptom generation, PR programs help patients cope with their condition more effectively and regain control over their lives[30].

3. Enhanced Quality of Life:

Participation in pulmonary rehabilitation is associated with significant improvements in health-related quality of life, emotional well-being, and social functioning for individuals with chronic respiratory diseases[43,44]. Education, self-management strategies, and psychosocial support promote self-efficacy, self-confidence, and resilience in coping with the challenges of living with a chronic illness[43]. Improved physical function, symptom control, and social support networks contribute to enhanced overall quality of life and patient satisfaction with PR interventions[42].

4. Reduced Healthcare Utilisation:

Pulmonary rehabilitation has been shown to reduce healthcare utilisation and healthcare costs associated with exacerbations, hospitalisations, and emergency department visits in individuals with chronic respiratory diseases[45,46]. By improving disease management, reducing symptom burden, and enhancing self-care skills, PR programs empower patients to better manage their condition in the community setting, leading to fewer healthcare encounters and improved long-term outcomes[33].

5. Physical Activity after Pulmonary Rehabilitation

Physical activity is defined as any voluntary bodily movement executed by skeletal muscles[81]. Physical activity is characterised by 3 features; type of activity (for example, walking, cycling and complex tasks such as household activities or errands), frequency and duration of activity typically summarised as sessions per day (or per week) and minutes per session, and intensity of physical activity, summarised as the time a person has spent above a certain (and approximate) metabolic rate. A cut point of 1.5 times the resting metabolic rate (i.e., 1.5 METS) captures any meaningful activity and an intensity of 3 times the resting metabolic rate (3 METS) is considered an activity at moderate intensity[81].

Physical inactivity causes > 5 million premature deaths worldwide being the fourth leading cause of death[82]. There is evidence that 6-10% of the non-communicable disease burden is caused by inactivity[82]. Patients with chronic diseases such as COPD, heart failure, diabetes and obesity, show a more pronounced inactive lifestyle. Inactivity may be a result of a worsening or exacerbation of symptoms in response to relatively low absolute levels of physical exertion[83,84].

In COPD, skeletal muscle dysfunction and airflow limitation contribute to reduced exercise capacity and are suggested to be worse in frail COPD patients[19]. Reduced exercise capacity contributes to reduced physical activity, characteristic of people with COPD. Evidence has suggested that COPD patients significantly reduce physical activity even at the initial stages. In COPD, physical inactivity is independently associated with dyspnoea, quality of life, lung function decline, muscle strength and endurance and frequency of exacerbations and mortality.

In 2019, Trooster and colleagues suggested that an increase in functional exercise capacity is a prerequisite to enable physical activity benefits in those patients with significant exercise intolerance classified as 6MWD less than 300 to 350m[81]. As seen in those patients who had an exercise tolerance of 300m or more as reported by Cochrane review[1]; looking at the effect of PR on exercise capacity and activity. Both functional exercise and maximal exercise showed statistically significant improvement. Researchers reported an increase in maximal exercise capacity (mean Wmax (W)) in participants allocated to pulmonary rehabilitation compared with usual care (MD 6.77, 95% CI 1.89 to 11.65; N = 779; studies = 16). The common effect size exceeded the MCID (4 watts) proposed by Puhan (2011). In relation to functional exercise capacity, the six-minute walk distance mean treatment effect was greater than the threshold of clinical significance (MD 43.93, 95% CI 32.64 to 55.21; participants = 1879; studies = 38).

To date, there is no data regarding the characteristics of physical activity and its effects on frail COPD patients or the prevention of frailty. Although international guidelines recommend that all COPD patients should receive advice to walk for 30 mins each day, also a pedometer step count of 600 to 1000 steps a day above the baseline number of steps (minimal clinically important difference, MCID) is recommended after PR as they were found to reduce the risk for hospital admission[84,85], but there is no such advice in frail COPD patients. Several studies have published the positive impact of physical activity in patients with COPD ranging from a significant change in exercise capacity as measured by 6MWT, increased number of steps per day[86], improved health-related quality of life[87] , to increased functions and reduced risk of hospital admission[84]. However, the efficacy of physical activity as an intervention is still relatively less, when compared to PR – as seen in a report by Cochrane review 2020[1], where step count was the most frequently reported outcome, but it was commonly assessed using devices with documented inaccuracy for this variable. Compared to no intervention, the mean difference (MD) in time in moderate- to vigorous-intensity physical activity (MVPA) following pulmonary rehabilitation was four minutes per day (95% confidence interval (CI) -2 to 9; 3 studies, 190 participants; low-certainty evidence). An improvement was demonstrated following high-intensity interval exercise training (6 minutes per day, 95% CI 4 to 8; 2 studies, 275 participants; moderate-certainty evidence). One study demonstrated an improvement following six months of physical activity counselling (MD 11 minutes per day, 95% CI 7 to 15; 1 study, 280 participants; moderate certainty evidence), but we found mixed results for the addition of physical activity counselling to pulmonary rehabilitation.

Physical activity has been described as complex health behaviour. In a few studies, a significant improvement in physical activity included behavioural change strategies, such as goal setting, contacting, feedback and cues that have been found amongst people with complex comorbidities. Therefore, activity monitors can provide direct feedback and have shown positive outcomes in COPD care. Pedometers can provide positive feedback and motivation to COPD patients about their daily activity and have been widely used as an interventional tool to improve physical activity or as an outcome measure after PR and pharmacotherapy to monitor their long-term effects. However, it is not known if a pedometer can be an effective tool in preventing frailty in pre-frail, frail COPD, and its impact on hospitalisation.

1.5.3 Physiological Basis of Benefit of Pulmonary Rehabilitation

Chronic respiratory diseases are characterised by progressive airflow limitation, gas exchange abnormalities, and structural changes in the lung tissue[38]. In COPD, for example, chronic inflammation, oxidative stress, and tissue destruction lead to airway narrowing, alveolar destruction, and mucus hypersecretion[42]. Similarly, ILDs involve fibrotic changes in the lung parenchyma, impairing gas exchange and lung compliance[47]. These pathophysiological alterations result in reduced respiratory function, exercise intolerance, and diminished quality of life for affected individuals.

Effect of Aerobic Training

Aerobic training, also known as endurance training, focuses on improving cardiovascular fitness and increasing the body's ability to utilise oxygen during sustained physical activity. This type of training primarily involves activities such as walking, cycling, and swimming, performed at a moderate or high intensity for extended durations[30,35].

During aerobic exercise, oxygen uptake (VO2) increases to meet the metabolic demands of working muscles. This oxygen is utilised in the mitochondria within muscle cells to produce adenosine triphosphate (ATP) through aerobic metabolism. Type I muscle fibres rely primarily on aerobic metabolism for ATP production, utilising fatty acids and glucose as substrates in the presence of oxygen[48]. As oxygen is delivered to the muscle tissue via the bloodstream, it diffuses across the capillary endothelium and into the muscle fibres, where it participates in the electron transport chain (ETC) within the mitochondria[49]. Here, oxygen serves as the final electron acceptor in the process of oxidative phosphorylation, generating ATP from the breakdown of substrates such as glucose and fatty acids[48,50]. Type I muscle fibres possess a high density of oxidative enzymes, including citrate synthase, succinate dehydrogenase, and cytochrome c oxidase, which facilitate the oxidation of substrates and the production of ATP[51,52]. Additionally, these fibres have a rich capillary network and myoglobin content, enabling efficient oxygen delivery and storage within the muscle tissue. Traditionally, aerobic training has been considered the primary mode of exercise for improving VO2 max, the maximal rate of oxygen consumption during intense exercise[34,51,52]. However, emerging evidence suggests that resistance training can also elicit significant increases in VO2max, particularly when performed with higher intensities and volumes[34].

Type I muscle fibres, also known as slow-twitch fibres, are characterised by their high oxidative capacity and resistance to fatigue[50]. These Fibers contain abundant mitochondria, myoglobin, and capillaries, which facilitate aerobic metabolism and efficient utilization of oxygen for energy production[49]. Type I fibres are predominantly recruited during low-to-moderate intensity activities, such as endurance exercise and prolonged aerobic activities[35].

1.5.3.1 The physiological basis of the improvement of exercise capacity:

This is divided into aerobic and resistance training physiological effects

Aerobic Training effects:

Aerobic training, also known as endurance training, focuses on improving cardiovascular fitness and increasing the body's ability to utilize oxygen during sustained physical activity[30]. This type of training primarily involves activities such as walking, cycling, and swimming, performed at a moderate intensity for extended durations[35]. This activity mostly utilises Type I Muscle Fibres to improve oxygen uptake. Type I muscle fibres, also known as slow-twitch fibres, are characterised by their high oxidative capacity and resistance to fatigue. These fibres contain abundant mitochondria, myoglobin, and capillaries, which facilitate aerobic metabolism and efficient utilisation of oxygen for energy production[48]. Type I fibres are predominantly recruited during low-to-moderate intensity activities, such as endurance exercise and prolonged aerobic activities[51].

During aerobic exercise, oxygen uptake (VO2) increases to meet the metabolic demands of working muscles. This oxygen is utilised in the mitochondria within muscle cells to produce adenosine triphosphate (ATP) through aerobic metabolism. Type I muscle fibres rely primarily on aerobic metabolism for ATP production, utilising fatty acids and glucose as substrates in the presence of oxygen. As oxygen is delivered to the muscle tissue via the bloodstream, it diffuses across the capillary endothelium and into the muscle fibres, where it participates in the electron transport chain (ETC) within the mitochondria. Here, oxygen serves as the final electron acceptor in the process of oxidative phosphorylation, generating ATP from the breakdown of substrates such as glucose and fatty acids[53]. Type I muscle fibres possess a high density of oxidative enzymes, including citrate synthase, succinate dehydrogenase, and cytochrome c oxidase, which facilitate the oxidation of substrates and the production of ATP[54]. Additionally, these fibres have a rich capillary network and myoglobin content, enabling efficient oxygen delivery and storage within the muscle tissue.

Traditionally, aerobic training has been considered the primary mode of exercise for improving VO2max, the maximal rate of oxygen consumption during intense exercise. However, emerging evidence suggests that resistance training can also elicit significant increases in VO2max, particularly when performed with higher intensities and volumes[34].

1.5.3.2 Other effects of Aerobic training:

ii). Enhanced Cardiovascular Function:

- Increased stroke volume: Aerobic training leads to improvements in cardiac output by increasing the volume of blood ejected from the heart with each beat (stroke volume[54]. This results in a more efficient delivery of oxygen-rich blood to the working muscles during exercise.
- Improved cardiac efficiency: Regular aerobic exercise strengthens the heart muscle, leading to more forceful contractions and a lower resting heart rate. This allows the heart to pump blood more effectively, reducing the cardiac workload during physical activity[54].

iii) Enhanced peripheral circulation:

Aerobic training promotes the dilation of blood vessels (vasodilation) in the muscles, improving blood flow and oxygen delivery to active tissues. This helps to delay the onset of fatigue and improve exercise tolerance[42].

iv). Increased Oxygen Uptake:

Improved oxygen extraction: Aerobic training enhances the body's ability to extract oxygen from the bloodstream and deliver it to the mitochondria within muscle cells, where it is utilised for energy production (aerobic metabolism)[51]. This is achieved through adaptations in the capillary network and mitochondrial density within skeletal muscle fibres. Oxygen Uptake and Type I Muscle Fibres: Type I muscle fibres, also known as slow-twitch fibres, are characterised by their high oxidative capacity and resistance to fatigue[55]. These fibres contain abundant mitochondria, myoglobin, and capillaries, which facilitate aerobic metabolism and efficient utilisation of oxygen for energy production. Type I fibres are predominantly recruited during low-to-moderate intensity activities, such as endurance exercise and prolonged aerobic activities[34]. During aerobic exercise, oxygen uptake (VO2) increases to meet the metabolic demands of working muscles. This oxygen is utilised in the mitochondria within muscle cells to produce adenosine triphosphate (ATP) through aerobic metabolism. Type I muscle fibres rely primarily on aerobic metabolism for ATP production, utilising fatty acids and glucose as substrates in the presence of oxygen. As oxygen is delivered to the muscle tissue via the bloodstream, it diffuses across the capillary endothelium and into the muscle fibres, where it participates in the electron transport chain (ETC) within the mitochondria[36]. Here, oxygen serves as the final electron acceptor in the process of oxidative phosphorylation, generating ATP from the breakdown of substrates such as glucose and fatty acids. Type I muscle fibres possess a high density of oxidative enzymes, including citrate synthase, succinate dehydrogenase, and cytochrome c oxidase, which facilitate the oxidation of substrates and the production of ATP[34]. Additionally, these fibres have a rich capillary network and myoglobin content, enabling efficient oxygen delivery and storage within

Enhanced Muscular Oxidative Capacity: Resistance training stimulates mitochondrial biogenesis and up-regulates oxidative enzyme activity within skeletal muscle fibres, including type I fibres. This leads to improvements in muscle oxidative capacity and ATP production, allowing for more efficient utilisation of oxygen during exercise.

1.5.3.4 Effects of Strength and Resistance Training:

Strength and resistance training focuses on improving muscular strength, endurance, and power through the performance of dynamic resistance exercises targeting major muscle groups[53]. These exercises involve the use of resistance bands, free weights, weight machines, or bodyweight resistance and are typically performed at a higher intensity for shorter durations compared to aerobic training. The physiological adaptations induced by strength and resistance training include:

i). Muscle Hypertrophy and Fiber Recruitment:

- Increased muscle mass: Strength training stimulates muscle protein synthesis, leading to hypertrophy (increase in muscle size) and greater cross-sectional area of muscle fibres[37]. This results in improved force-generating capacity and overall strength.
- Recruitment of high-threshold motor units: Resistance training activates fast twitch muscle fibres and high-threshold motor units, which are recruited during maximal or near-maximal contractions. This leads to improvements in muscular power and explosive strength, particularly important for activities requiring rapid movements or bursts of energy[42].

ii) Increased Capillarisation:

Resistance training promotes angiogenesis, the formation of new blood vessels, within skeletal muscle tissue. This results in a greater capillary density and improved blood flow to working muscles, facilitating oxygen delivery and extraction during exercise.

Iii) Improved Muscle Metabolism:

Resistance training enhances substrate utilisation and metabolic flexibility within muscle fibres, allowing for greater reliance on aerobic pathways for ATP production. This metabolic adaptation reduces the reliance on anaerobic glycolysis and lactate production during high-intensity exercise, delaying the onset of fatigue and improving endurance capacity.

Cardiovascular Adaptations: Although resistance training primarily targets muscular adaptations, it also induces cardiovascular responses, including increased stroke volume, cardiac output, and peripheral vasodilation. These adaptations improve oxygen delivery to working muscles and enhance aerobic performance during resistance exercise.

Overall, the combination of increased muscular oxidative capacity, improved capillarization, enhanced muscle metabolism, and cardiovascular adaptations contribute to the observed increase in VO2 max following resistance training. This highlights the versatility of resistance training as an effective means of improving aerobic capacity and overall fitness, complementing traditional aerobic exercise modalities in pulmonary rehabilitation programs for individuals with chronic respiratory diseases.

iv) Enhanced pulmonary gas exchange:

Regular aerobic exercise improves ventilation-perfusion matching in the lungs, optimising gas exchange and increasing the efficiency of oxygen uptake (ventilation) and carbon dioxide removal (perfusion) during exercise.

(v). Neuromuscular Adaptations:

- Improved motor unit synchronisation: Strength training enhances the coordination and synchronisation of motor unit firing within muscle groups, leading to more efficient muscle recruitment patterns and greater force production[42].

- Enhanced proprioception and motor control: Resistance exercises challenge the neuromuscular system, improving proprioceptive feedback and motor control, which are essential for maintaining balance, stability, and proper movement mechanics during functional activities[33].

(vi). Metabolic Changes:

Increased anaerobic capacity: Strength and resistance training induce adaptations in muscle metabolism, leading to improvements in anaerobic energy production and buffering capacity. This allows individuals to sustain high-intensity efforts for longer durations without experiencing excessive fatigue or muscle acidosis[56].

Elevated resting metabolic rate: Regular strength training increases muscle mass, which in turn elevates resting metabolic rate (RMR). This results in greater energy expenditure at rest and during physical activity, contributing to weight management and metabolic health[57].

(vii). Maximum oxygen uptake: (VO2 Max):

Resistance training induces physiological adaptations in both cardiovascular and muscular systems, contributing to improvements in aerobic capacity and oxygen uptake[51]. Some of the mechanisms underlying the increase in VO2max with resistance training include:

Enhanced Muscular Oxidative Capacity: Resistance training stimulates mitochondrial biogenesis and upregulates oxidative enzyme activity within skeletal muscle fibres, including type I fibres. This leads to improvements in muscle oxidative capacity and ATP production, allowing for more efficient utilisation of oxygen during exercise. Increased Capillarization: Resistance training promotes angiogenesis, the formation of new blood vessels, within skeletal muscle tissue. This results in a greater capillary density and improved blood flow to working muscles, facilitating oxygen delivery and extraction during exercise.

Improved Muscle Metabolism: Resistance training enhances substrate utilisation and metabolic flexibility within muscle fibres, allowing for greater reliance on aerobic pathways for ATP production. This metabolic adaptation reduces the reliance on anaerobic glycolysis and lactate production during high-intensity exercise, delaying the onset of fatigue and improving endurance capacity[53].

Cardiovascular Adaptations: Although resistance training primarily targets muscular adaptations, it also induces cardiovascular responses, including increased stroke volume, cardiac output, and peripheral vasodilation. These adaptations improve oxygen delivery to working muscles and enhance aerobic performance during resistance exercise[55].

1.5.3.5 Other Benefits of PR

1. **Improve respiratory Muscle Function:**

Chronic respiratory conditions often lead to weakness and fatigue of the respiratory muscles, including the diaphragm and intercostals. Pulmonary rehabilitation targets these muscles through specific training protocols, such as inspiratory muscle training (IMT) and expiratory muscle training (EMT)[58]. IMT involves resistance training of the inspiratory muscles to improve strength and endurance, while EMT focuses on enhancing cough effectiveness and airway clearance.

2. **Improve gas Exchange:**

Altered gas exchange, characterised by impaired ventilation-perfusion matching and gas diffusion abnormalities, contributes to hypoxemia and exercise limitation in chronic respiratory conditions. Pulmonary rehabilitation promotes physiological adaptations that optimise gas exchange, such as improved lung perfusion, enhanced oxygen transport, and increased capillary density in peripheral tissues. Exercise induced improvements in ventilation and perfusion matching help to maintain arterial oxygenation and reduce ventilatory inefficiency[59,60].

3. **Improve symptom control:**

Dyspnea, fatigue, and exercise-related symptoms are common complaints among individuals with chronic respiratory diseases, impacting their functional status and quality of life[61,62]. Pulmonary rehabilitation employs various strategies to alleviate these symptoms, including breathing retraining, energy conservation techniques, and psychological support[1]. By addressing the underlying physiological mechanisms of symptom generation, PR helps patients cope with their condition more effectively and improves their overall well-being[38.]

1.5.4 Evidence-Based Practices in Pulmonary Rehabilitation

Benefits of Pulmonary rehabilitation

Numerous studies have demonstrated the efficacy and effectiveness of pulmonary rehabilitation in improving outcomes for individuals with chronic respiratory diseases[1,30]. Meta-analyses and randomized controlled trials have consistently shown significant improvements in exercise capacity, dyspnoea severity, health related quality of life, and psychological well-being following participation in PR programs[34,35]. Multidisciplinary, supervised exercise training, individualized treatment plans, and ongoing support and follow-up are key components of successful pulmonary rehabilitation interventions[30].

1.5.4.1 The impact of Pulmonary Rehabilitation on Mortality and Hospital Admission in Patients with COPD.

COPD is classified under the quality of care within the National Health Service (NHS) in the UK as an ambulatory care sensitive condition (ACSC), therefore hospital admissions and readmissions due to COPD are regarded as avoidable[63]. However, COPD is still considered a leading cause of emergency hospital medical admissions and readmissions worldwide[64]. Internationally and in the UK, preventing and reducing COPD admission and readmission rates are identified as a priority to limit the physical deterioration of patients and contain costs[65].

A report by the NHS Information Centre Hospital Episodes Statistics Database in England on COPD admissions between 2001 and 2010 showed that the mean annual number of patients admitted with COPD is 10,000 patients, ranging from 15.7 to 19.3, a variation of 22.9% and a mean annual 30-day readmission rate of 7.0% with a gradual increase of 0.01% per month[66,67]. A meta-analysis of international studies identified that fewer than one in four 30-day readmissions was likely to have been preventable[68]. Patient-level factors have been identified as determinants of COPD admissions and readmissions including prior history of hospital admission, COPD disease severity, poor quality of life, deficient performance status informs of physical activity and activity of daily living (ADL) of the patients and several comorbidities including frailty.

The influence of frailty contributes to emergency admissions and readmissions, there is evidence that the risk of hospitalisation and mortality is increased in patients with mild, moderate, and severe frailty[12,16]. With frailty, emergency admission rates per 1,000 persons per year at risk increased from 90.1 for those identified as fit to 706.7

for those with severe frailty[16]. At present, there is no evidence that pre-frailty contributes to high hospital admission and readmission rates in COPD, with limited data on the frail group.

There is evidence that post-hospital admission pulmonary rehabilitation reduces mortality in COPD. In 2011, the Cochrane Review of pulmonary rehabilitation following exacerbations of COPD, showed rehabilitation significantly reduced mortality by 0.6% (OR 0.28; 95%CI 0.10 to 0.84), NNT6 (number needed to treat) over 107 weeks) and hospital admission (OR 0.22 (95% CI 0.08 to 0.58). This reduced the hospital re-admission rate from 33% to % more than usual care (support discharge nursing care): the review showed that PR saved one life for every six patients treated and saved one hospital admission for every four patients treated. In all the trials reviewed, pulmonary rehabilitation significantly improved exercise capacity and the improvement was above the minimally important difference (sixminute walk test (MD 77.70 meters; 95% CI 12.21 to 143.20) and shuttle walk test (MD 64.35; 95% CI 41.28 to 87.43 with number needed to treat of 2 compared to usual medical care. No adverse events were reported in the 9 trials included in the review. Therefore, The Cochrane Review concluded that pulmonary rehabilitation is a highly effective and safe intervention to reduce hospital admissions and mortality and to improve health-related quality of life in COPD patients who have recently suffered an exacerbation of COPD The Cochrane Review recommends that effective discharge processes should include support for patients to enrol in and attend PR promptly once they have gone home. The Cochrane review did not include data on physical activity and did not attempt to disentangle COPD and frailty.

1.5.4.2 Impact of Pulmonary Rehabilitation on mortality and re-admissions from COPD exacerbation.

There is evidence that 33% of COPD admissions due to exacerbation are readmitted within 3 months and this creates a major burden health burden on patients[70]. However, pulmonary rehabilitation is the only intervention that has been shown to reduce the readmission rate from 33% to 7%. However, we have no evidence of the impact of pulmonary rehabilitation and physical activity on the reduction of admission or re-admission rate in frail COPD patients. Although, 3 meta analyses have shown that PR is effective; in reducing admission, mortality, quality of life and exercise capacity, none of them has reported mediating effects of comorbidity and frailty.

1.5.5 Current Pulmonary Rehabilitation Landscape

Pulmonary rehabilitation is a cornerstone of chronic respiratory disease management, recognised as an evidence-based intervention with widespread adoption in healthcare systems globally. It is endorsed by national guidelines, including the British Thoracic Society (BTS) and NICE, for its proven efficacy in reducing hospital admissions, improving exercise capacity, and enhancing quality of life for COPD and other chronic lung disease patients.

Accessibility and Delivery: PR is commonly delivered in outpatient hospital settings, community centres, or virtually through telehealth platforms. Programs typically run for 6 to 8 weeks, with twice-weekly sessions of 1 to 2 hours. Despite its established benefits, access remains inequitable due to regional variability in service provision, referral rates, and patient uptake. Challenges such as transportation difficulties, socioeconomic barriers, and limited awareness hinder participation, particularly in underserved areas.

Patient Demographics: Typical PR participants include individuals with moderate to severe COPD, post-COVID syndrome, interstitial lung diseases, or bronchiectasis. These individuals are often referred through primary care providers, respiratory specialists, or increasingly via self-referral pathways in progressive healthcare systems.

Effectiveness and Cost Efficiency: Numerous studies validate PR's cost-effectiveness, highlighting reduced healthcare utilisation through decreased hospital admissions and readmissions. For every 4 patients completing PR, one hospital admission can be avoided, representing significant economic and clinical benefits

1.7 Evidence-Based Impact of PR on Frailty

Emerging research highlights PR's capacity to reverse frailty and improve clinical outcomes among COPD patients. Studies demonstrate significant gains in exercise capacity, reduced hospitalisations, and enhanced quality of life. However, gaps remain in understanding PR's specific effects on pre-frail and frail individuals, necessitating further research to optimise interventions.

Table 1.1: Prevalence of Frailty in COPD and Related Outcomes

Author	Year	Study Type	Key Findings
Lahousse et al.	2016	Observational Study	Frailty prevalence increases with COPD severity and exacerbation frequency.
Park et al.	2013	Survey Study	High frailty prevalence linked to comorbid diabetes and functional limitations.
Maddocks et al.	2015	Systematic Review	PR reduces mortality and hospitalisations among frail COPD patients.
Akinlabi et al	2018	Observational Study	Physical frailty impacts PR outcomes, improving frailty status but highlighting variations in response

Chapter 2:

Systematic Review and Meta-analysis of the benefit of pulmonary rehabilitation in Frail COPD and Other Chronic Lung Disease

ABSTRACT

Background

Frailty has been shown to be a risk factor for clinical outcomes for patients with COPD and other chronic lung diseases. People with COPD and other chronic lung diseases aged 75 and above have a twofold odd ratio of becoming frail with accelerated decline in physiological reserves than those with frailty alone. Pulmonary rehabilitation is an effective intervention in COPD and other chronic lung disease. However, frailty's impact on patients with COPD and chronic lung diseases completing pulmonary rehabilitation programmes is unknown.

Methods A comprehensive search was searches were conducted in PubMed, Embase, The Cochrane Library and Web of Science (January 1, 2016, to December 31, 2022) to identify studies related to frailty, pulmonary rehabilitation, COPD, and chronic lung diseases. Comparisons were made using Fried frailty criteria and pulmonary rehabilitation clinical outcomes within and between groups of patients who were frail and those who were not frail before and after pulmonary rehabilitation. Only 5 studies met the selection criteria and were included in the systematic review and meta-analysis. The title, abstract and full text of the studies were reviewed to assess eligibility for inclusion in the study. The Population, Intervention, Comparator, Outcomes and Study framework (PICO) were used for data extraction The primary outcome was change in frailty using Fried frailty criteria. Secondary outcomes include quality of life (COPD Assessment Test - CAT), exercise city (6MWT/ISWT)

and hospital and anxiety depression score (HADs). The included studies were assessed for risk of bias and methodological quality according to the Cochrane

Handbook for Systematic Reviews of Interventions, utilising Review Manager 5.1. The outcome measures from the included studies were analysed using Comprehensive Meta-Analysis Version 4 software and JASP meta-analysis. The 95% credible interval was used to assess the statistical significance of each summary effect. The protocol of this review was registered in PROSPERO (CRD 456394).

Results: The effect of pulmonary rehabilitation on improving; the 6MWT score {(WMD = 0.58 (95% CI= 0.28, 0.88), I2 = 98% (p < 0.001)}, health-related quality of life (CAT score) {(WMD = -0.50 (95% CI = -1.00, 0.01), I2 = 99.56% (p=0.045), and slowness (4MG) {(WMD = -0.69 (95% CI -1.09, -0.28), I2 = 98% (p <0.001)} was significantly better in frail COPD patients in comparison to pre-rehabilitation. However, when the change in the effect of PR was compared between frailty status (frail vs Not frail) there was no difference in clinical outcomes; 6MWT score {(MWD=0.27 (95% CI = -0.18, 0.73), I2 = 97% (p=0.23)}, CAT score {(MWD -0.16 = (95% CI = -0.67, 0.36), I2 = 97%, p= -0.59)}, 4MGS {(WMD = -1.79 (95% CI = -5.52, 1.94), I2 = 99% (p=0.34), showing the pulmonary rehabilitation is equally effective across frailty status.

Conclusion: Pulmonary rehabilitation demonstrates efficacy in enhancing exercise tolerance and quality of life among frail COPD patients. Importantly, the effectiveness of pulmonary rehabilitation appears consistent regardless of frailty status. These findings underscore the importance of pulmonary rehabilitation as a valuable intervention for improving outcomes in this vulnerable patient population.

2.1 Introduction

Frailty is a clinical syndrome characterized by multisystem decline, reducing physiological reserves and resilience to stressors. It is common in individuals aged 65 and above, especially those with chronic diseases such as COPD. Early identification of frailty is essential for initiating interventions like pulmonary rehabilitation (PR), which can address physical, cognitive, and functional decline, potentially preventing adverse outcomes like hospitalisation and mortality.

Although PR's effectiveness in improving outcomes for COPD patients is well-documented, its specific impact on frailty remains underexplored. Limited evidence from observational and cohort studies suggests PR may improve frailty-related parameters, yet inconsistencies in methodologies and outcome measures hinder definitive conclusions. This chapter presents a systematic review and meta-analysis to evaluate the effects of PR on frailty and associated clinical outcomes in COPD and other chronic lung diseases.

2.2 Methods

2.2.1 Study Design and Eligibility Criteria

This systematic review follows Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.

The inclusion criteria were:

- **Population**: Adults aged 18 and above with COPD or other chronic lung diseases, classified as frail or pre-frail using validated tools such as the Fried Frailty Phenotype or Edmonton Frailty Scale.
- **Intervention**: Completion of a PR program of at least six weeks.
- **Comparator**: Pre pulmonary rehabilitation compared to post pulmonary rehabilitation
- **Outcomes**: Primary outcome was frailty improvement; secondary outcomes included exercise capacity (e.g., 6-minute walk test [6MWT]), quality of life (COPD Assessment Test [CAT]), and mental health (Hospital Anxiety and Depression Scale [HADS]).
- **Study Types**: Randomized controlled trials (RCTs), cohort studies, and case-control studies.

2.2.2 Types of Participants

Older people are diagnosed with COPD and other chronic lung diseases with frailty and have had pulmonary rehabilitation intervention.

2.2.3 Types of intervention

Completion of pulmonary rehabilitation of varying lengths. Duration of pulmonary rehabilitation varied from 6 weeks to 8 weeks as per British Thoracic Society BTS guidelines (2014)[29]. The length of intervention is one to two hours, the first hour is for aerobic and resistance training and the second hour is for education on self-management of COPD or other chronic lung diseases. Sessions of pulmonary rehabilitation were twice a week.

2.2.4 Types of Comparators

Pre-pulmonary rehabilitation clinical outcomes were compared to post- pulmonary rehabilitation. Pulmonary rehabilitation being the intervention in frail COPD or chronic lung disease.

2.2.5 Types of Outcomes

Primary: Reduction in Fried frailty or other frailty measures score (e.g., Timed Up and Go (TUG) –PRISMA, Frailty index, Edmonton Frailty Scale interpreted as change in frailty classification in patients completing pulmonary rehabilitation

Secondary: Improvement in exercise capacity measured by 6MWT or ISWT, quality of life by COPD Assessment Test (CAT) score) and anxiety/depression score (HAD).

A total of 10 studies were reviewed. The papers reviewed looked at changes in frailty status and clinical outcomes following pulmonary rehabilitation, completion and drop rates and the patient demographics of those undertaking pulmonary rehabilitation.

2.2.6 Information source

Using pre-defined search strategies, information for potentially relevant articles was searched on MEDLINE, Cochrane Library, Embase and Google Scholar using MeSH terms, subject headings, and free text: 'Chronic Lung Disease,' 'Chronic Obstructive Pulmonary Disease', 'Chronic lung disease', 'COPD', 'frailty,' 'Rehabilitation', 'Pulmonary Rehabilitation', (Table 1). Manual searches were conducted from the reference lists of all included studies to check for other possible relevant articles. The search period was from January 2016 to December 2022. Manual searches also included conference proceedings published from 2016 onwards, based on the assumption that trials are usually published within 2 to 3 years following presentation at a conference. In addition, searches were conducted on government agencies' websites such as the National Institute for Health and Care Excellence etc.) and Clinical trial registry clinicaltrails.gov.

The study was registered on the platform of the International Prospective Register of Systematic Reviews (PROSPERO) and a search was conducted on it to check for relevant ongoing or completed systematic reviews.

Table 1. Search terms

Concept	**Search Terms**
• Chronic Obstructive Pulmonary disease • Chronic lung diseases • COPD	MeSH terms: Lung disorder Free text terms: COPD, chronic obstructive pulmonary disease, Chronic lung diseases
Pulmonary Rehabilitation	MeSH terms: Rehabilitation, Physiotherapy Free Text: pulmonary rehabilitation
Frailty	MeSH term: Care of the elderly Free Text: Fraily, Fried frailty criteria

2.2.7 Search Strategy

A comprehensive search was conducted across PubMed, Embase, Cochrane Library, and Google Scholar for studies published between January 2016 and December 2022. Keywords included “COPD,” “frailty,” “pulmonary rehabilitation,” and “chronic lung diseases.” Additional manual searches included conference proceedings and reference lists. A total of 24,037 articles were initially identified.

The initial search strategy was: (frailty) (COPD, chronic obstructive pulmonary disease, or chronic lung diseases) and (pulmonary rehabilitation). The following databases were searched: PubMed, the Cochrane Library, Medline, and Google Scholar to broaden the search. Keywords used through the literature search were COPD, chronic obstructive pulmonary disease, frailty, chronic lung disease, pulmonary rehabilitation and PR. MeSH terms were used. Search results were limited to English-language and Lung studies with frailty, not including cardiac studies alongside lung. Research students screened all article titles, abstracts and full texts to determine eligibility. Studies with discrepancies and not studying pulmonary rehabilitation were removed after careful assessment.

The second search was conducted using citation, searching by reviewing the references of the list of included articles and using the "cited by" search option in Google Scholar to identify further studies meeting the inclusion criteria. Studies with more than 250 citations on Google Scholar for pulmonary rehabilitation and frailty were searched within the citation. An additional three articles were included during this step.

Figure 1. shows the number of articles identified, screened, and included.

A two-stage search approach, searching databases of major literature search engines and citation searches. The protocol of this review was registered in PROSPERO (CRD 456394)

2.2.8 Types of study (design and characteristics):

The characteristics of studies included were those that investigated the effect of pulmonary rehabilitation on frail COPD patients and people with other chronic lung diseases (bronchiectasis, chronic Asthma, Interstitial Lung Disease (ILD)), and the relationship of clinical outcomes of pulmonary rehabilitation on frailty or its domains. There was no randomised control found in the search.

2.2.9 Study Selection and Characteristics

A preliminary database search retrieved 24137 articles, 24037 were removed due to duplication. And the remining 100 were screened using the inclusion and exclusion criteria, 93 articles were excluded after reviewing their titles, abstract, and full text. Ultimately, 7 articles were deemed eligible for the systematic study and 5 studies for the meta-analysis. The literature screening process is shown in figure 1.

A total of 5 articles were included in the statistical analysis of this study.

The total sample size was 1191, including a combination of hospital based and community-based rehabilitation The characteristics of included studies are summarised in Table 2.1 Each All articles were published after 2016 and involved randomised controlled trials. Each study's design, population, intervention, comparator, and outcomes are detailed to ensure consistency. All studies involved a face-to-face pulmonary rehabilitation as intervention. The pulmonary rehabilitation duration varied from 6-8weeks. All studies reported the impact of pulmonary rehabilitation on frailty status, making a comparison between frail and not frail using change in exercise capacity (6MWT, ISWT) and quality of life measures (CAT score) being standard pulmonary rehabilitation outcome measures.

2.2.10 Addressing the Lack of RCTs

A critical limitation of this review is the absence of RCTs specifically evaluating PR's impact on frailty. This highlights a significant gap in the evidence base and underscores the need for future high-quality randomized studies. The findings presented here rely on observational and cohort studies, which, while valuable, may not provide the same level of rigor as RCTs.

2.2.11 Study records

Data from all the articles extracted and reviewed were uploaded unto my National Centre for Biotechnology Information (NCBI) collection and bibliography via ORCid for easy access for review and reference.

2.2.12 Selection process

The conduction of studies for inclusion were done in two stages. First, titles and abstract of all records identified from database searches were screened by primary researcher (PhD student) against pre-defined eligibility criteria to identify a subset of relevant studies. A peer reviewer conducted a second search on using the predefined eligibility criteria and any discrepancies resolved by discussion. A request for a full text of all the studies that meet the eligibility criteria were carried out where there were uncertainties. Full text screening was done by the primary researcher (PhD student). Information for supplementary materials were requested from aurthors if there were uncertainties regarding inclusion and exclusion criteria.

2.2.13 Data Items

The Population, Intervention, Comparator, Outcome and Study characteristics (PICOs) framework was used to systemise data extraction. Information form extracted data was recorded on each five domains.

1. Study characteristics included, aims and objectives, settings, and design
2. The population included characteristics (including size, sex, and age distribution, country), sample methods, inclusion/ exclusion criteria.
3. The intervention included pulmonary rehabilitation or not, or pulmonary rehabilitation alone

4. The comparator definitions of frail, pre-frail and not frail patients who respond or do not respond to pulmonary rehabilitation
5. The outcome definitions and identification of primary (frailty) and secondary outcomes (6MWT, ISWT, CAT, HAD and mMRC).

2.2.14 Outcomes and Prioritisation

The following list of endpoints are considered as primary and secondary outcome measures in this review.

2.2.15 Primary outcome measures:

1. Frailty assessment:

(a) Fried frailty criteria,

(b) Timed Up Go Test and PRISMA-7

(c) Edmonton Frailty Scale

(d) Frailty Index

2.2.16 Secondary Outcome measures:

(a) Six-minute Walk test (6MWT)

(b) COPD Assessment Test (CAT)

(c) Modified medical research council score (mMRC)

(d) Sit to Stand test (STS)

(e) Weight loss

(f) Hand Grip strength

(g) Maximum oxygen uptake (VO2 Max)

2.2.17 Data Extraction and Quality Assessment (Risk of bias assessment)

Risk of bias assessment was carried out solely by me the PhD student. This assessment aimed to reduce the risk of bias by the authors. Data were extracted on study characteristics, participant demographics, intervention protocols, and outcomes. The number of papers accessed for each database and the inclusion process were systematically documented. Risk of bias was assessed using the Cochrane Risk of Bias Tool for RCTs and the Newcastle-Ottawa Scale for observational studies. Studies were categorized by quality as low, moderate, or high risk of bias.2.3 Results. Only seven articles were deemed appropriate after assessment and were included in the systematic review, but only five were included in the meta-analysis due to incomplete data and selective reporting of a few studies.

2.2.18 Statistical analysis

This study employed the comprehensive meta-analysis version 4 (CMA V4), JASP and Microsoft excel 2016 software to process the data. The data were organised and summarised in Excel, and CMA was used for data merging, quality assessment, heterogeneity testing, and meta-analysis using fixed and random model. And for the generation of forest plot, JASP 0.18.3 was used. After conducting the heterogeneity analysis of the five included studies a fixed -effects model was used for meta-analysis when I^2 <50%, while a random -effects model was used when I^2 ³50%. The clinical outcome measures to test the effect of pulmonary rehabilitation on frail and not frail COPD patients were continuous variables, therefore weighted mean difference (WMD) was used for data processing when consistent measurement methods and unit were employed for the same outcome measures. And standardised mean difference (SMD) was used when inconsistent methods or units were used.

Table 3 Characteristics of the included studies regarding response to pulmonary rehabilitation in frail chronic respiratory

First Author	Country	Design	Settings	Sample size	Frailty Measure	Age	Male n (%)	Chronic Respiratory diagnosis
Plas 2019	Netherland	Prospective cohort study	Frail COPD FEV1 pred 36%	82	Evaluate frailty index for physical activity (EFIP)	81	28 (49)	COPD
Finamore 2021	Italy	Randomised Longitudinal study	Hospital based study Frail COPD GOLD I-III	64	Prisma-7, Timed UP and Go Test (TUG)	73	26 (49)	COPD
Maddocks 2016	UK	Prospective cohort	Hospital based PR	816	Fried frailty criteria	70	484 (59)	COPD
Akinlabi 2018	UK	Prospective cohort	Hospital and health centre based, Frail COPD GOLD III-IV	46	Fried frailty criteria	76	30 (65)	COPD
Vigore 2023	Italy	Prospective cohort	Hospital based COPD GOLD stage II-IV, CHF NYHA II-IV	30	Clinical frailty scale (CFS) and Frailty index (FI)	74	21 (73)	COPD, CHF
Gephine 2022	France	Prospective cohort	Home based frail COPD	47	Fried frailty criteria	66	31 (69)	COPD

Table 3 Characteristics of the included studies regarding response to pulmonary rehabilitation in frail chronic respiratory

First Author	Country	Design	Settings	Sample size	Frailty Measure	Age	Male n (%)	Chronic Res[illegible] dia[illegible]
[illegible]	[illegible]	[illegible]pective [illegible]rt study	Frail COPD FEV1 pred 36%	82	Evaluate frailty index for physical activity (EFIP)	81	28 (49)	COPD
Finamore 2021	Italy	Randomised Longitudinal study	Hospital based study Frail COPD GOLD I-III	64	Prisma-7, Timed UP and Go Test (TUG)	73	26 (49)	COPD
Maddocks 2016	UK	Prospective cohort	Hospital based PR	816	Fried frailty criteria	70	484 (59)	COPD
Akinlabi 2018	UK	Prospective cohort	Hospital and health centre based, Frail COPD GOLD [illegible]	46	Fried frailty criteria	76	30 (65)	COPD

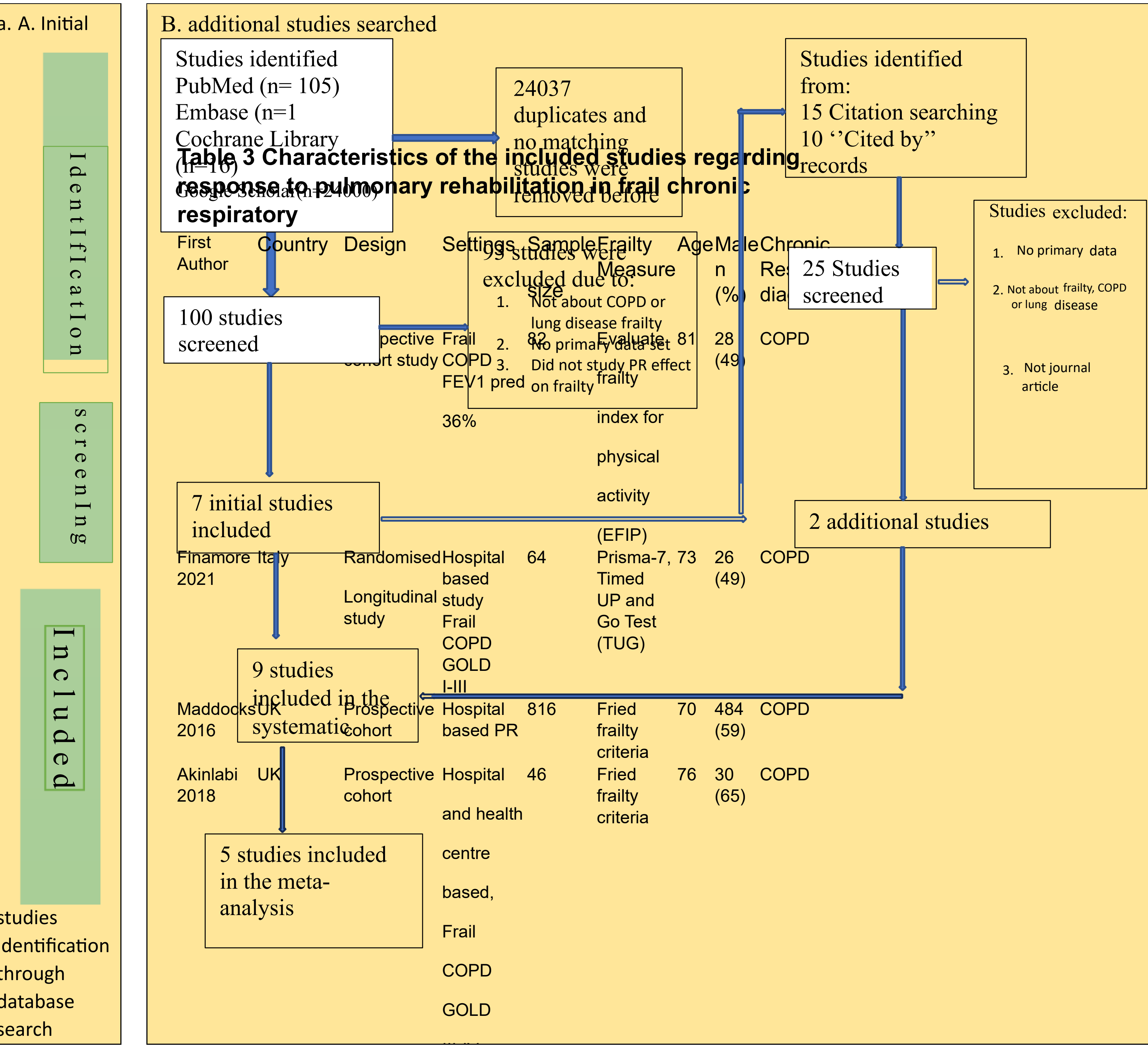


Fig. 1. PRISMA flow Diagram of Systematic Review Search Procedures.

Table 2. **PRESS 2015 Guideline Recommendations for librarian practice**

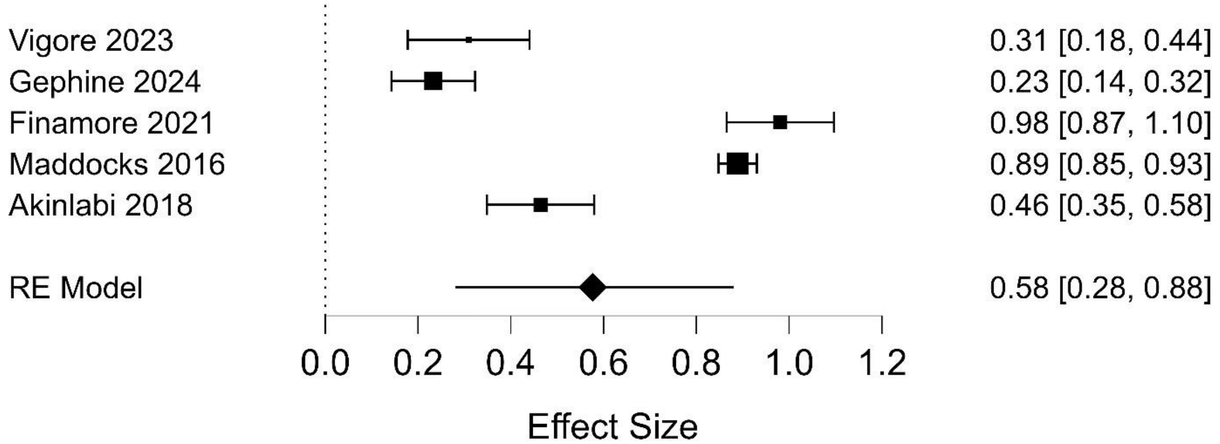
PRESS domains	PRESS Recommendation	Action taken below as per PREES guidance
1. Translation	Assess whether the research question has been correctly translated into search concepts.	The primary search strategy was submitted for peer review to ensure conceptual accuracy. The research question, was formatted according to PICO variation
2. Boolean and proximity operators	Assess whether the elements addressing the search question have been correctly combined with Boolean and/or proximity operators.	We reviewed the search for any instances where mistakes occurred in Boolean operators; for example, OR may have been unintentionally or AND may have been used to link phrases or words. Ensure that the use of nesting within brackets is logical and has been applied, as needed. Also note whether the use of a proximity operator (adjacent, near, within) instead of AND could increase precision
3. Subject headings (database specific) e.g., PubMed	Assess whether there is enough scope in the selection of subject headings to optimize recall	We examined the following elements of subject heading usage: missing or incorrect headings, relevance/irrelevance of terms, and correct use of explosion to include relevant narrower terms. We consider the use of floating subheadings which are in most instances preferable to using subheadings attached to specific subject headings (e.g., in MEDLINE, “Chronic Lung disorder” rather than “Chronic lung disease”). Note that subject headings and subheadings are database-specific.
4. Text word (free text)	Assess whether search terms without adequate subject heading coverage are well represented by free-text terms	As per guidance we used free-text terms to cover to cover missing database subject headings.
5. Spelling, syntax, and line numbers	Assess correct use of spelling, correct use of syntax and correct search implementation.	We review the search strategy for misspelt words and for errors in system syntax that are not easily found by spell-checking.
6. Limits and filters	Assess whether the limits used (including filters) are appropriate and have been applied correctly.	We reviewed the search strategy to see if limits that are not relevant to the eligible study designs or to the clinical question have been applied, as these could potentially introduce epidemiological bias.

2.3 Meta-analysis results

2.3.1 6MWT score (Pre Vs. Post Pulmonary rehabilitation): Classical Meta-Analysis

This study systematically reviewed 5 articles from the literature that examined the impact of pulmonary rehabilitation on the 6-minute walk test (6MWT) scores of frail COPD patients. Employing a random effects model, a meta-analysis was conducted, revealing a statistically significant weighted mean difference (WMD) of 0.58 (95% CI= 0.28, 0.88) with heterogeneity of $I^2 = 98\%$ ($p < 0.001$) (see fig. 2). These results unequivocally demonstrate the positive effect of pulmonary rehabilitation in enhancing the 6MWT scores among frail COPD patients, indicating a marked improvement in exercise capacity following intervention ($p < 0.001$) compared to prerehabilitation levels.

Forest plot



Total (95% CI)

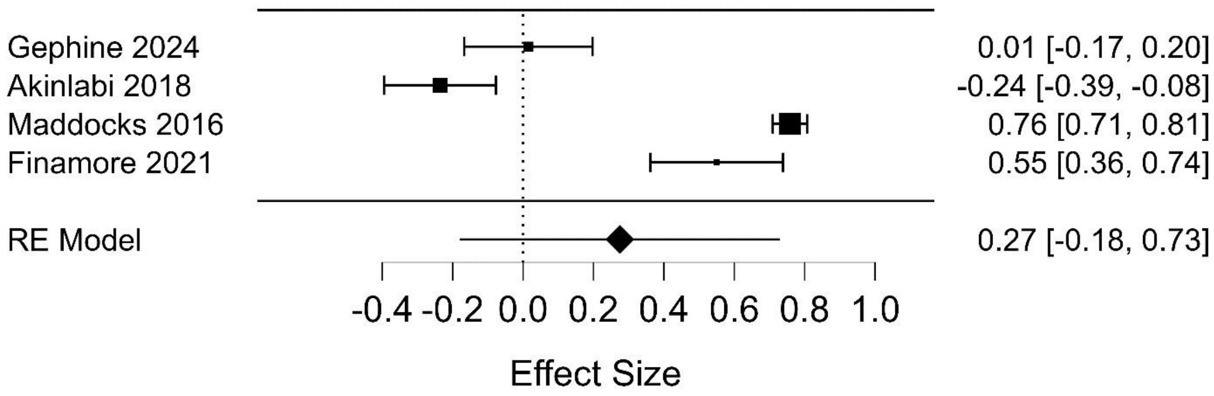
Heterogeneity: $Tau^2 = 0.113$; $Chi^2 = 56.37$, df = 4 ($P < 0.001$); $I^2 = 98\%$

Test for overall effect Z = 3.78 (P < 0.001

Fig. 2. Forest plot of 6MWT pre vs post pulmonary rehabilitation

2.3.2 6MWT score (Frail Vs Not Frail): Delta Meta-Analysis

A total of 4 articles in the literature were included in the study, reporting the effect of pulmonary rehabilitation intervention on the 6MWT score comparing frail patients to not frail patients. A fixed effects model was used to conduct a delta meta-analysis to combine the effect sizes and the results showed there was no significant difference in the effect of pulmonary rehabilitation on change in 6MWT, [(WMD = 0.27 (95% CI = -0.18, 0.73), I^2 = 97.8% (p = 0.23)] (Fig 3), between frail and not frail patients. The result showed that the effect of pulmonary rehabilitation in improving exercise capacity in frail and not frail COPD patients is the same or consistent regardless of the frailty status. **Forest plot**



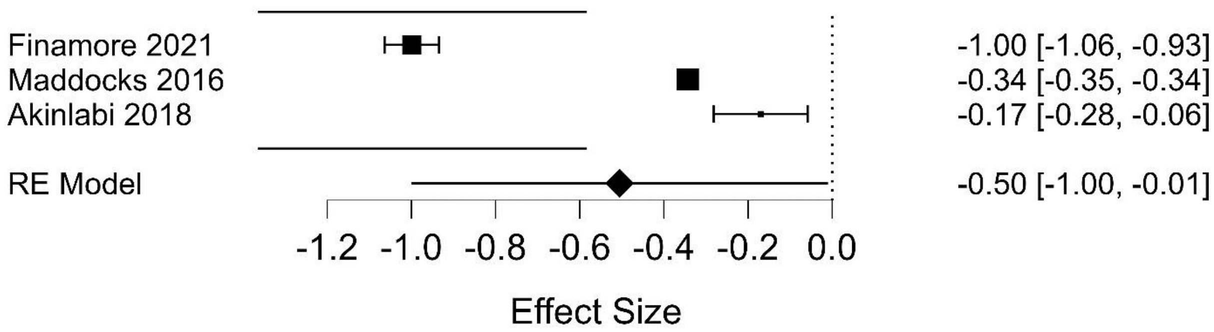
Total (95% CI)
Heterogeneity: $Tau^2 = 0.209$; $Chi^2 = 46.7$, df = 3 (P <0.001); I^2 =97.8%
Test for overall effect Z = 1.185 (P < 0.23)

Fig. 3. Forest plot of 6MWT Frail Vs. Not Frail after pulmonary rehabilitation

2.3.4 CAT score (Pre Vs. Post Pulmonary rehabilitation): Classical Meta-Analysis

This study included a total of 3 articles in the literature, reporting the effect of pulmonary rehabilitation intervention on quality of life (CAT score) of frail patients. A random effect model was used to conduct a classic meta-analysis, and the results showed that the slowness was significantly better in frail COPD patients in comparison to pre-rehabilitation. {(WMD = -0.50 (95% CI = -1.00, 0.01), I^2 = 99.56% (p=0.045), (Fig 4). These results demonstrate the positive effect of pulmonary rehabilitation in enhancing the quality of life among frail COPD patients, indicating a marked improvement in quality of life following pulmonary rehabilitation intervention (p < 0.001) compared to pre-rehabilitation.

Forest Plot



Total (95% CI)
Heterogeneity: $Tau^2 = 0.189$; $Chi^2 = 231$, df = 2 (P <0.001); I^2 =99%
Test for overall effect Z = -2.002 (P < 0.045)

Fig. 4. Forest plot of CAT score pre vs post pulmonary rehabilitation

2.3.5 CAT score (Frail vs Not Frail): Delta Meta-analysis

A total of 3 articles in the literature were included in the study, reporting the effect of pulmonary rehabilitation intervention on the CAT score comparing frail patients to not frail patients. A fixed effects model was used to conduct a delta meta-analysis to combine the effect sizes and the results showed there was no significant difference in the effect of pulmonary rehabilitation on change in CAT score, [(WMD = -0.16 (95% CI = -0.67, 0.36), I^2 = 97.9% (p = 0.55)] (Fig 5), between frail and not frail patients. The result showed that the effect of pulmonary rehabilitation in improving quality of life in frail and not frail COPD patients is the same or consistent regardless of the frailty status.

Forest Plot

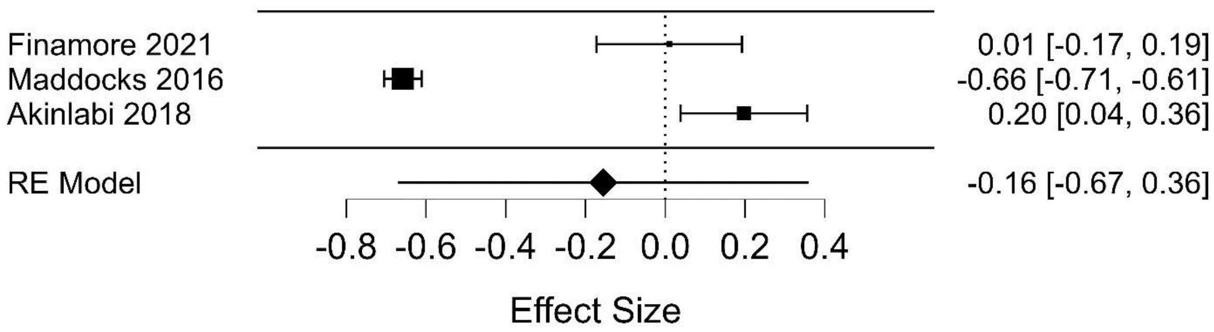


Fig. 5. Forest plot of CAT score Frail vs Not Frail

Total (95% CI)
Heterogeneity: $Tau^2 = 0.201$; $Chi^2 = 49.5$, df = 2 (P <0.001); I^2 =97%
Test for overall effect Z = -594 (P < 0.55)

2.3.6 4MGS (Pre Vs. Post Pulmonary rehabilitation): Classical Meta-Analysis This study included a total of 3 articles in the literature, reporting the effect of pulmonary rehabilitation intervention on slowness (4MGS score) of frail patients. A random effect model was used to conduct a classic meta-analysis, and the results showed that the slowness was significantly better in frail COPD patients after pulmonary rehabilitation in comparison to pre-rehabilitation. {(WMD = -0.69 (95% CI = -1.09, 0.28), I^2 = 98.8% (p=0.001), (Fig 6). These results demonstrate the positive effect of pulmonary rehabilitation in enhancing the walking speed (slowness) among frail COPD patients, indicating a marked improvement in quality of life following pulmonary rehabilitation intervention (p < 0.001) compared to pre-rehabilitation.

Forest Plot

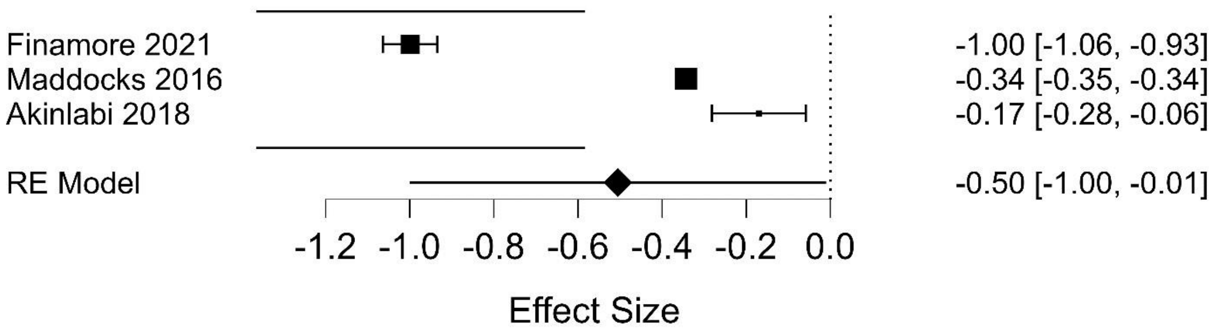


Fig. 5. Forest plot of 4MGS score Pre-Rehab vs Post Rehab – Frail COPD

Total (95% CI)
Heterogeneity: $Tau^2 = 0.127$; $Chi^2 = 89.32$, df = 2 (P <0.001); I^2 =98% Test for overall effect Z = -3.313, (P < 0.001)

2.3.7 4MGS (Frail vs Not Frail): Delta Meta-analysis

A total of 3 articles in the literature were included in the study, reporting the effect of pulmonary rehabilitation intervention on the 4MGS score comparing frail patients to not frail patients. A fixed effects model was used to conduct a delta meta-analysis to combine the effect sizes and the results showed there was no significant difference in the effect of pulmonary rehabilitation on change in 4MGS score, [(WMD = -0.27 (95% CI = -0.18, 0.73), I^2 = 97.8% (p = 0.236)] (Fig 7), between frail and not frail patients. The result showed that the effect of pulmonary rehabilitation in improving walking speed (slowness) in frail and not frail COPD patients is the same or consistent regardless of the frailty status.

Forest Plot

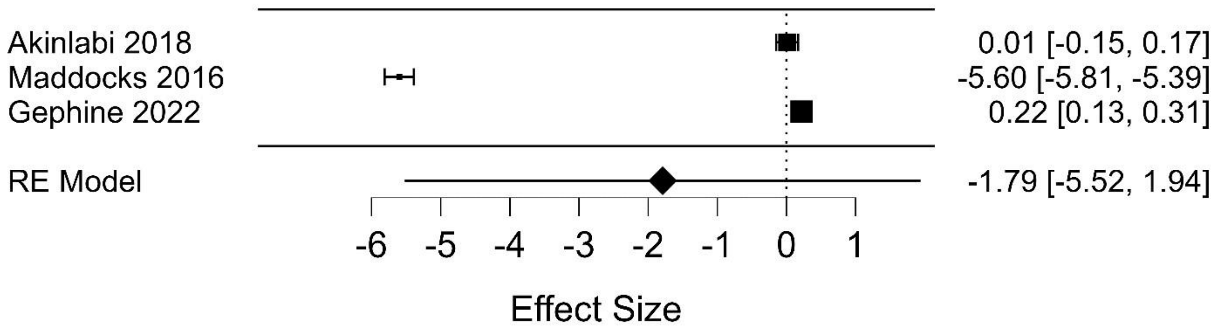


Fig. 5. Forest plot of 4MGS score Frail vs Not Frail

Total (95% CI)
Heterogeneity: Tau^2 = 10.88; Chi^2 = 1924, df = 2 (P <0.001); I^2 =99% Test for overall effect Z = -0.940 (P < 0.34)

Change in Frail and Not Frail After PR – Binary analysis effect of PR

Table 3. Studies with showing changes in number of frail and not frail after PR

Study	Frail			Pre-frail	Not-Frail		
	Pre-Rehab	Post-PR	Total N		Pre-Rehab	Post-PR	Total N
Plas 2019	48	35	57	13	9	22	57
Maddocks 2016	109	55	164	54	55	164	547
Akinlabi 2018	11	4	46	7	3	17	46
Gephine 2022	18	7	44	11	7	11	44
Total (n)	186	101		85	74	214	

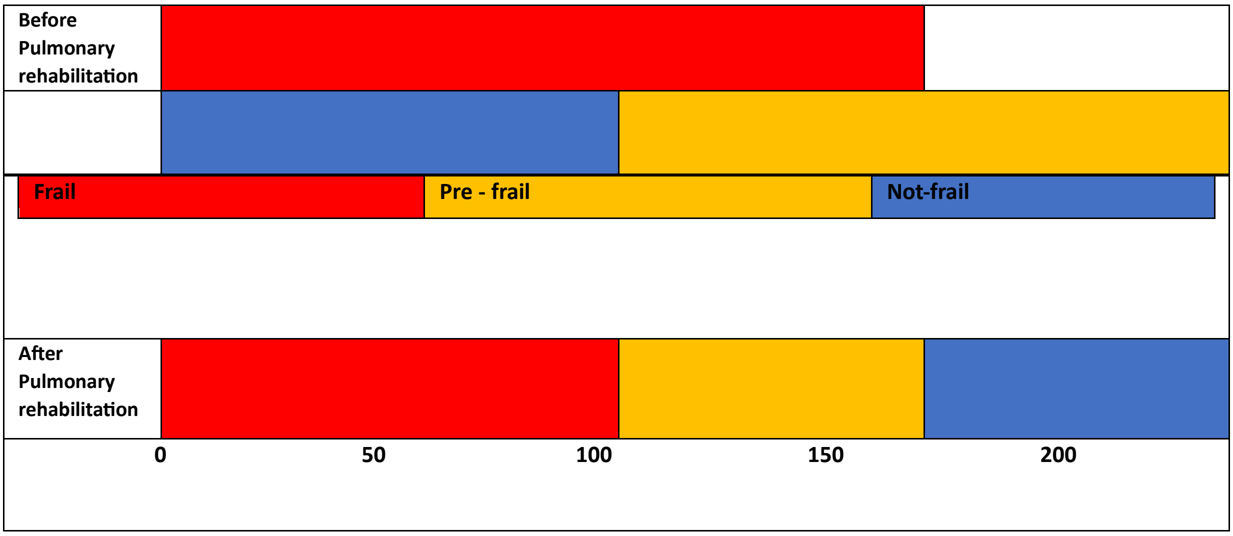


Figure 6 Patients with COPD grouped according to Fried frailty criteria before and after pulmonary rehabilitation (n= 1,005).

Overall, the change denotes from frail to pre frail and not frail.

Dataset Random effects computation .Table 4

	Effect size	Variance Within	Variance Between	Variance Total	Weight	Calculated quantities
Study	*Y*	V_Y	T_2	V_{Total}	*W**	*W*Y*
Plas 2019	3.032	0.272	1.292	1.564	0.639	1.939
Maddocks 2016	0.684	0.064	1.292	1.356	0.737	0.504
Akinlabi 2018	1.587	1.008	1.292	2.300	0.435	0.690
Gephine 2022	0.944	0.484	1.292	1.776	0.563	0.532

Table 5. Random Effect Analysis

Mean and precision		**Formula**	
Mean effect	*M**	1.5434	12.7
Variance	V_{M*}	0.4211	12.8
Standard error	Se_{M*}	0.6489	12.9
Confidence intervals			
Lower limit (95%)	LL_{M*}	0.2714	12.10
Upper limit (95%)	UL_{M*}	2.8153	12.11
Test of the null that M=0			
Z for test of null	*Z**	2.3783	12.12
p-value (1-tailed)	$p*_1$	0.0087	12.13
p-value (2-tailed)	$p*_2$	0.0174	12.14

% Change in Frail patients post PR from 41% to 24% (95% CI 0.27, 2.87) p =0.017

2.4 Discussion

This systematic review and meta-analysis sought to explore the impact of pulmonary rehabilitation on clinical outcomes in frail COPD patients. After careful review of available literature, the study offers a comprehensive overview of how pulmonary rehabilitation affects impact frail COPD patients. Through detailed analysis of clinical outcomes, the research aimed to elucidate the tangible clinical benefits that pulmonary rehabilitation can offer to frail COPD patients. The quality of included studies was group in terms of moderate to low-risk bias.

The main findings of this meta-analysis are that frailty in COPD is reversible with pulmonary rehabilitation with significant clinical change in all clinical outcomes (6MWD, CAT, 4MGS) and offer favourable shift across Fried frailty criteria (frail to pre-frail and pre=frail to not-frail).

Pooling data from four relevant studies, the analysis reveals a notable reduction in the prevalence of frailty among COPD patients undergoing pulmonary rehabilitation, decreasing from 41% to 24%. The binary analysis demonstrates a weighted mean effect of 1.45, with a Z-effect of 2.37 (95% CI = 0.27, 2.81), indicating statistical significance ($p = 0.017$, two-tailed). These findings underscore the potential of pulmonary rehabilitation in mitigating frailty among individuals with COPD, highlighting its clinical relevance and significance. In most literatures, frailty prevalence has been estimated to range from 20 to 50%[76] with 19% of those with stable COPD[16], and more than 50% of patients with acute exacerbation. However, pulmonary rehabilitation has been shown in this review as a positive intervention that is able to reverse a 25% of frail COPD[19,78,79]. In previous study, although not part of this review, it has also been shown pulmonary rehabilitation can reduce rate of hospitalisation in frail COPD by 76%[78]. Although pulmonary rehabilitation reverses frailty in COPD by a quarter and this could be due to the heterogeneity of frailty assessment tools and the severity of stable COPD.

Furthermore, one of the key outcomes of this study was pulmonary rehabilitation improve standard clinical outcome that have made it one of the significant evidencebased interventions available to patients suffering from chronic respiratory conditions. There was significant improvement in exercise tolerance (6MWD), quality of life (CAT score) and slowness notable in the elderly (4MGS) - causing reversibility in patients' physical conditions and re-affirming the evidence in literature that frailty is not a disability[19].

The multi-dimensional nature of the pathophysiology mechanism of frailty in COPD including higher chronic inflammation, dysregulation of muscular activity, higher oxidative stress, and the endocrine system may contribute to the level of impact of pulmonary rehabilitation in frail COPD patients.

The findings of this study were robust to several analytical approaches that accounted for differences in exercise prescriptions, pulmonary rehabilitation programme and type of patient group. Furthermore, the results of this analysis were comparable to the propensity –matched results, increasing the confidence in the reliability of these effect estimates. The results complement the existing evidence from prospective cohort trials, adding further data that PR is associated with early fraily in pre-frail patients who could become frail 3 years later after initial classification if pulmonary rehabilitation intervention is not included in their multimorbidity approach of care recommended by the NICE multimorbidity clinical guidelines[17].

Another key finding from this study in relations to clinical outcomes comparing frail patients to not frail COPD is that all clinical outcomes improved in the same vein across frailty status. This underscores the strength of pulmonary rehabilitation and its consistency regardless of patient frailty status. Also, it demonstrates the intensity of the positive effects of pulmonary rehabilitation. The results are in line with previous study where the effects of pulmonary rehabilitation were tested across many chronic respiratory conditions (COPD, chronic asthma, interstitial lung disease, bronchiectasis, and lung cancer), and concluded that pulmonary rehabilitation improve clinical outcomes in the same strength regardless of the chronic respiratory condition[78].

Although, this study results suggest that PR may be an effective intervention in reversing frailty and delaying early frailty amongst pre-frail patients, the low uptake of PR and dropout rate is challenging for pulmonary rehabilitation specialists and strategies to mitigate this is still not well understood.

Frailty has become a well-recognised therapeutic risk factor in stable and acute exacerbations of chronic airway disease[79]. As physical frailty can be present as part of comorbidities of people over 65 years old then comprehensive and multicomponent interventions except for respiratory drug therapy seem necessary. Pulmonary rehabilitation serves as a key component of management strategies of COPD. As described in this study Pulmonary rehabilitation can significantly improve range of clinical outcomes in frail patients with COPD, including symptoms burden (CAT score), exercise capacity, physical activity, and health status in short term[19]. In one of the literatures that was reviewed in this study, revealed that, after the pulmonary rehabilitation intervention in frail COPD patients with chronic respiratory failure, the benefits acquired were maintained more than 6 months after the end of pulmonary rehabilitation[80]. Therefore, it shows that physical frailty was a barrier for benefiting from the pulmonary rehabilitation interventions. This study supported previous literature that physical frailty can be reversed form pulmonary rehabilitation intervention at least partially with more than 50% improved their frailty status[80]. The result of this meta-analysis highlights that if the right intervention of pulmonary rehabilitation is provided after careful comprehensive assessment and stratification to different frailty status there is possibility of being alive and returning to some level of function improving quality of life. Also, those with frequent exacerbations or frequent hospitalisation may be able to return home with better functional and live an independent life. Frailty is common in patients with COPD and associated with poor clinical outcomes and less engagement in pulmonary rehabilitation including high dropout rate, however if clinicians would assess patient for frailty and provide timely intervention and provide adequate support then there might be improvement in the number of patients who may benefit from reversal of their frailty status and improve prognosis of patients with COPD especially in the older adults. It is imperative that clinicians are aware of the importance of pulmonary rehabilitation for frail patients with COPD.

This study underscores the outcome of PR intervention looking at the interaction with COPD and sarcopenia[43]. Sarcopenia is a pathophysiological phenomenon of frailty and presents with two major muscle impairments of frailty – low muscle mass and muscle function. Sarcopenia is diagnosed by both low muscle mass and muscle function and is described to be increased with age and Global Initiative on Obstructive Lung Disease (GOLD) stage severity, with a two-fold increase from GOLD stage 2 to 4. The European Working Group on Sarcopenia in Older People (EWGSOP) guidelines were used to assess sarcopenia which found that 14.5% of their cohort had sarcopenia. The study had 622 patients who participated in an 8week PR programme. At the end of the programme, 28% of patients with the initial diagnosis of sarcopenia no longer met the EWGSOP criteria. The authors found Pulmonary Rehabilitation was found to be able to reverse sarcopenia in patients with a low skeletal muscle index (SMI) and those with functional performance values that were close to the cut-off used to define sarcopenia. ("Response to Pulmonary Rehabilitation in Older People with Physical ...") Patients with COPD and sarcopenia responded well to PR, with improvements reported in exercise capacity, functional performance, limb strength and health status. However, it remained unclear if PR had a long-term effect on sarcopenia in patients with COPD, as there was no followup on clinical outcomes of PR such as 6MWT (exercise capacity), and CAT score (health status). A 6-month or 12-month follow-up of PR clinical outcome would have clarified if there were a longer-lasting effect of PR on sarcopenia. There was also no greater detail on the characteristics of patients who had recovered from their sarcopenia, the study would have been stronger if there were reports of basic characteristics such as the independent activity of daily living (IADL) which is in patients with sarcopenia.

2.4.1 Strengths of the Study:

The study conducted a systematic review and meta-analysis, providing a comprehensive overview of the impact of pulmonary rehabilitation on clinical outcomes in frail COPD patients. This approach allows for a thorough examination of existing literature, enhancing the reliability of the findings. The analysis included pooling data from multiple relevant studies, enabling a robust assessment of the effectiveness of pulmonary rehabilitation in reducing frailty among COPD patients. The statistical analysis demonstrated significant findings, increasing the confidence in the study's conclusions.

2.4.2 Clinical Relevance:

The study's findings have significant clinical relevance, as they highlight the potential of pulmonary rehabilitation to mitigate frailty among individuals with COPD. This underscores the importance of such interventions in improving patient outcomes and quality of life. The study demonstrated consistent improvements in various clinical outcomes across frailty statuses, indicating the robustness and reliability of pulmonary rehabilitation as an intervention for COPD patients, regardless of frailty status. It also provides a multi-dimensional understanding to frailty by considering the multi-dimensional nature of frailty in COPD, including its pathophysiology mechanisms, which provides an understanding to clinicians how pulmonary rehabilitation can impact frail COPD patients, enhancing its applicability in clinical practice.

2.4.3 Limitations of the Study:

The heterogeneity in frailty assessment tools and the severity of stable COPD may have influenced the study's findings. Variations in assessment methods could introduce bias and affect the comparability of results across studies. The study did not include long-term follow-up data on the effects of pulmonary rehabilitation on sarcopenia in COPD patients. This limits the understanding of the sustainability of improvements and long-term effects of the intervention. The study lacked detailed information on the characteristics of patients who recovered from frailty, such as their independent activity of daily living (IADL). Including such information could have provided insights into the broader impact of pulmonary rehabilitation on patients' functional abilities. The study's findings may have limited generalisability due to variations in exercise prescriptions, pulmonary rehabilitation programs, and patient populations across different settings. This could affect the applicability of the results to diverse clinical contexts. This study highlighted challenges related to the low uptake and dropout rates of pulmonary rehabilitation, which could impact the implementation of such interventions in clinical practice. Strategies to address these challenges were not thoroughly explored, limiting the study's practical implications.

Chapter 3: Impact of Pulmonary Rehabilitation on Physical Frailty and Hospitalisation in Patients with COPD

3.1 Abstract

Background Frailty causes age decline in physiological systems with increased risk of hospitalization and nursing home admission. In 2016, Maddocks and colleagues reported that 61% of frail COPD patients improved in frailty scores after Pulmonary Rehabilitation (PR).

Objectives To determine the prevalence of frailty in COPD patients referred to PR, to examine the impact of PR on frailty, rate of acute exacerbations of COPD and hospitalization.

Methods: 46 outpatients with COPD were prospectively enrolled on a PR programmer (mean (SD) age 76 (10) years FEV1% predicted 67 (10). Assessments included Fried frailty criteria, rate of exacerbations and hospitalizations.

Results 35/46 (76%) patients with COPD completed PR. 8/35 (23%) were frail, 20/35 (57%) patients were pre-frail, and 7/35 (20%) were not frail. After six weeks of pulmonary rehabilitation 5/8 frail (63%) no longer met the Fried frailty criteria ($p < 0.001$), and at 6 months post PR, the number of acute exacerbations and hospitalization significantly reduced by 65% (43 versus 15) ($p< 0.001$), and 75% (15 versus 3) ($P=0.012$) respectively (Tables 1 and 2).

Conclusion 23% of patients referred to Barnet PR service were frail. PR has a favourable impact on the number of exacerbations and hospitalisations in frail COPD patients and can temporarily reverse frailty in a considerable proportion of COPD patients.

3.2 Background

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, with frailty being a common comorbidity. Frailty significantly increases the risk of adverse clinical outcomes, including hospitalisation, exacerbations, and mortality, particularly among older adults. Pulmonary rehabilitation (PR) is a proven intervention for improving functional capacity and quality of life in COPD patients; however, its specific effects on physical frailty and hospitalisation remain underexplored.

This chapter evaluates the impact of PR on frailty parameters and hospitalisation rates among COPD patients, with a detailed examination of the clinical reasoning underpinning the intervention and the processes involved.

3.3 Rationale for study

For pulmonary rehabilitation services to conform to NICE Multi-morbidity guidelines[17] services should meet the recommendation that they routinely assess frailty in all patients presenting with multiple morbidities including COPD and frequent unplanned hospital admissions of which COPD falls. Services could apply the current best available evidence-based practice to utilise PR as an intervention to slow, prevent, or even reverse the progression toward frailty in COPD patients[19].

Therefore, this study aims to assess frailty in COPD patients referred for PR. Using Fried frailty criteria, we will determine the prevalence of frailty and pre-frailty in patients with COPD. The effectiveness of PR as a treatment for COPD will be evaluated by measuring changes in rates of exacerbation and hospitalisation. The potential impact of Pulmonary Rehabilitation on frailty will be evaluated by assessing changes in components of the Fried Frailty Criteria and changes in frailty status.

3.4 Methods

3.2.1 Study Design

A prospective cohort design was employed, tracking COPD patients referred to a PR program. Participants were classified as frail, pre-frail, or non-frail using validated tools, including the Fried Frailty Phenotype. As this was a service clinical audit and evaluation of the quality of PR on frail COPD and its impact, there was no need for ethical application and approval. This study was approved by the CLCH NHS clinical effectiveness and audit team.

Aims

To find out the proportion of COPD patients referred to Barnet PR that are frail. Determine the services' impact on hospitalization and exacerbation of COPD symptoms. And to find out if pulmonary rehabilitation can modify frailty in patients with COPD referred to this service.

Objectives

1. To determine if attending pulmonary rehabilitation reduces 6-month rates of COPD exacerbations and hospitalisation in frail, pre-frail and not-frail phenotype (Fried frailty phenotype)
2. To determine whether PR is associated with improvements in exercise capacity (Six Minute Walking Test (6MWT) and Incremental Shuttle Walking
   Test (ISWT) exercise capacity) across the Fried frailty phenotype.

3. To determine the effect of PR on quality-of-life Fried frailty phenotype in

   COPD patients as measured by COPD Assessment Test (CAT)

4. To determine the effect of PR in frail, pre-frail and not-frail COPD on psychological symptoms, measured by the Hospital Anxiety and Depression scale (HAD)

5. To determine the prevalence of Fried frailty phenotype in COPD patients referred to PR in the London Borough of Barnet.

6. To find out if PR modifies Fried frailty phenotype in COPD.

3.2.2 Participant Selection

Inclusion criteria:

- Diagnosis of moderate-to-severe COPD.
- Age ≥50 years.
- Referral to an 8-week PR program.
- Baseline frailty assessment completed.

Exclusion criteria:

Inability to participate in physical activity due to non-COPD-related conditions.

Cognitive impairment preventing adherence to the programme.

3.2.3 Sample Size:

A total of 46 patients (35 completers out of 46 initially assessed) were included in this study. Although 65 patients were assessed for frailty and standard PR but were excluded from the final data analysis and results as they dropped out of the PR.

These patients did complete a PR course, and no final assessment was done.

3.3 Data collection method.

Data were collected for patients that fulfilled the criteria for referral to PR (patients with a physician diagnosis of COPD, pharmacologically optimised, no recent cardiovascular event, and no complex musculoskeletal impairment affecting mobility. Inclusion criteria were record of the number of COPD exacerbations (treated at home) and hospitalizations in the 6 months prior to enrolment in PR and during the 6 months following completion of the PR programme.

3.4 Assessment

Initial assessments were carried out using PR British Thoracic Society quality standard (PR assessment and objective measures for field tests including a Sixminute walk test (6MWT) or incremental shuttle walk test (ISWT)) and lower limb strength test (One Minute Sit to Stand test; (1 Min STS)).

3.4.1 Six-Minute Walk Test (6MWT) or 6-minute walk distance (6MWD): The 6MWD is a validated measure of functional exercise capacity in chronic respiratory disease[30]. The 6MWD predicts both future hospitalisation and survival. It is responsive to change following rehabilitation and responsive to a patient with ambulatory oxygen desaturation. Therefore, the 6MWD is a reliable measure, with intra-class correlation coefficients (ICCs) ranging from 0.72 to 0.99 (seven studies)

[91,92]. Coefficients of variation were small, with narrow ranges in COPD (0.0475–0.073)[93;] and, ILD (0.042–0.083)[94,95] and CF (0.0409–0.043)[96,97.] There were no discernible differences in reliability across diagnostic groups. Although, the data indicate that most of the variation in the 6MWD can be attributed to between-patient variation, rather than within-patient variation. However, the limits of the agreement were large. These studies showed that, although the 6MWD is a reliable measurement, the results of the second test cannot be predicted from the first test. In COPD, the proportion of individuals who walked further on the second 6MWT ranged from 50% to 87%[92,95,98.] The proportion of individuals who had a clinically significant improvement in 6MWD on their second walk ranged from 15% for an improvement of >54m to 28% for an improvement of ≥42m[92,98]. In ILD, one study reported that 86% of participants increased their 6MWD on the second test[95]. The test was performed per ERS/ATS technical standard, including two tests at each time point, with the better (I.e., longest distance) 6MWD recorded[27].

3.4.2 Incremental Shuttle Walk Test (ISWT): The ISWT is a valid and reliable test to assess maximal exercise capacity in individuals with chronic respiratory diseases. The ISWT has been shown to be responsive to pulmonary rehabilitation and a valid measure of exercise capacity in individuals with COPD[99]. For criterion validity, comparisons between distance covered during the ISWT and peak oxygen consumption reported correlations ranging from 0.67 to 0.95 (P <.01). Intraclass correlation coefficients for test-retest reliability ranged from 0.76 to 0.99[97,98] The ISWT was shown to be responsive to pulmonary rehabilitation and bronchodilator administration. The minimal clinically important difference (MCID) in patients with COPD was 47.5 m (95% CI 38.6 to 56.5) with the subject who felt their exercise tolerance was slightly better[99]. Predictive equations for the distance in the ISWT are available for healthy individuals.

3.4.3 COPD Assessment Test (CAT): CAT score is a short, simple, and validated questionnaire for assessing and monitoring COPD. It quantifies the impact of COPD in routine practice to aid health status assessment and communication between healthcare professionals and patients. The test consists of eight items (40-point scale), developed using Psychometric and Rasch methods of analysis. CAT has an internal consistency of Cronbach's α = 0.8, and re-test intra-class correlation (r= 0.8) in the USA and a strong correlation with COPD-specific version of the St George's Respiratory Questionnaire (SGRQ) (r=0.80) (Jones, 2009). The mean change in CAT score after pulmonary rehabilitation was –2.5 (95% CI -.0 to -1.9) and this correlates significantly with changes in SGRQ score (r=0.32; p <0.0001) and Chronic Respiratory Questionnaire (CRQ) score (r= 0.46; p< 0.0001) (Kon 2014). Kon and colleagues in the second study found the mean change in CAT score to be –3.0 (95% CI –4.4 to -1.6) in a 3-month post-discharge follow-up study. This result also correlates significantly with a change in SGRQ score (r=0.47; p<0.0001). The linear regression estimated the minimal clinical important improvement (MCID)for the CAT to range between –1.2 and –2.8, therefore the most reliable of the CAT is 2[28].

3.4.4 Hospital Anxiety and Depression Scale (HADS): HADS was developed to assess for anxiety disorder and depression with physical illness[100]. HADS does not include symptoms of fatigue, insomnia and loss of appetite to avoid overlap with the physical disorder[100]. HADS has been proven to be a reliable, valid and responsive instrument to assess the severity of symptoms of mood disorders[101]. The MCID for HADS was based on emotional, mastery and total scores of the Chronic Respiratory Questionnaire (CRQ)[101.] CRQ is a widely used instrument in respiratory rehabilitation and measures dyspnoea, fatigue, emotional functioning and coping with COPD[93]. The MCID was 1.41 (95% CI 1.18 -1.63) and 1.57 (1.37 - 1.76) for HADS anxiety score and 1.68 (1.48 - 1.87) and 1.60 (1.38 - 1.82) for the HADS total score[102]. The correlations of the HADS depression score and CRQ domain and Feeling Thermometer scores were <0.5. Based on the Effect Size approach the MID of the HADS anxiety and depression score was 1.32 and 1.40, respectively[102].

3.5 Frailty assessment

Patients were also assessed for frailty using 5 domains of Fried frailty phenotype model. These 5 models comprise of physical characteristics that are considered to reduce physiological reserve and precipitate a vulnerable state.

The standard definition of the 5 Fried frailty phenotype model was derived from the original reference cohort, used to define each characteristic as either present or absent for each patient, providing an ordinance score ranging 0-5.

1. Unintentional weight loss (shrinking) was defined as (a reduction in body weight of ≥4.5 kg in the past 12 months. - patients are asked if they have lost weight ≥ 4.5kg unintentionally in the last year (weight loss must not be due to diet or exercise). If the answer is yes patient will score 1, if the patient answered no the score will be 0.
2. Exhaustion was self-reported using two validated questions from the Centre for

Epidemiological Studies Depression score (CES-D) give scores and cut-offs here. Using the CES-D Depression Scale, the following two statements are read. (a) I felt that everything I did was an effort; (b) I could not get going. These two questions are asked how often in the last week did you feel this way? 0 = rarely or none of the time (<1 day), 1 = some or a little of the time (1-2 days), 2 = a moderate amount of the time (3-4 days), or 3 = most of the time. Exhaustion is present if the patient response scores 2 or 3 on either item.

3. Level of physical activity is assessed using self-report based on the modified Minnesota Leisure–Time Physical Activity Questionnaire in the last week. Energy expenditure (kcal) was calculated using a standardized algorithm[103]. Low physical activity is classified if energy expenditure is <383 kcal per week for men and in < 270 kcal per week for females[104].
4. Objective measures of muscle strength were performed using handgrip dynamometry - using JAMAR hydraulic hand-held dynamometer (Sammons Preston Royland Bolingbrook, IL). A maximum value of over

3 tests on each hand, each separated by 30 seconds of rest is recorded. The results of the hand grip are adjusted BMI and the criteria are different for Male and Female. Males BMI <24: ≤29kg, Males BMI 24.1-28: ≤30kg, Males BMI >28: ≤32kg. Females BMI <23: ≤17kg, Females BMI 23.1-26: ≤17.3kg.

5. Slowness using four-meter gait speed (4MGS): speed is calculated using distance time walked by the patients over the course of the 4 meters. Speed is calculated as distance/time measured in m/s^2. Patients is adjusted with height using the following protocol: Males ≤173 cm in height: ≤0.76 m/s^2.Males >173 cm in height: ≤0.653 m/s^2. Females ≤159 cm in height: ≤0.762 m/s^2. Females >159 cm in height: ≤0.653m All initial objective measures were termed pre-PR assessment. After 6 weeks of PR, all patients these measurements were repeated during the routine post-PR assessment.

3. 6 Primary and secondary outcome measures

1.Fried classifications

Patient with no criteria were classified as not-frail/robust, those with 1-2 criteria were considered prefrail and those with ≥3 criteria present were considered frail.

2. Rate of exacerbation and hospitalization: reported from System One electronic patient's records that holds both the entry of the number of patients treated with antibiotics and steroids at home without a hospital admission or number of hospitalisations with a physician diagnosis of acute exacerbation of COPD on discharge medical summary.
3. Secondary outcome measures (PR outcomes)

a. Six Minute Walk Test (6MWT)

b. Incremental Shuttle Walk Test (ISWT)

c. COPD Assessment Test (CAT)

d. Hospital Anxiety and Depression score (HAD)

Onward Methods

The following chapters (3 to 5) in this thesis will follow the above methodology, but sample size or participants and statistical analysis will be different.

3.7 Intervention Protocol

The PR program was delivered over 8 weeks with twice-weekly sessions. Each session lasted 2 hours and included the following components:

1. **Initial Assessment and Individualized Starting Points**:
   - A comprehensive baseline assessment was conducted to determine each participant's starting point. This included:
     - Medical history review.
     - Physical assessments such as the 6-minute walk test (6MWT), handgrip strength, and gait speed.
     - Psychological evaluations using the Hospital Anxiety and Depression Scale (HADS).
     - Quality of life assessments via the COPD Assessment Test (CAT).
   - Clinical reasoning was applied to tailor the intervention, accounting for individual baseline frailty, comorbidities, and functional limitations. For instance, participants with significant mobility issues began with low-

intensity exercises, while those with moderate frailty engaged in progressive resistance training.

2. **Exercise Training**:
    - **Aerobic Training**:
        - Activities such as walking on a treadmill or cycling on a stationary bike were prescribed.
        - Intensity was determined based on the modified Borg scale, ensuring participants worked within a safe exertion range.
    - **Resistance Training**:
        - Focused on major muscle groups using resistance bands or light weights.
        - Sessions included 2 sets of 10-12 repetitions for each exercise, with progression as tolerated.
3. **Education**:
    - Topics covered included:
        - Understanding COPD and its management.
        - Proper use of inhalers and medications.
        - Energy conservation techniques.
        - Recognizing early signs of exacerbations.
4. **Self-Management Strategies**:
    - Participants were guided in developing action plans for managing symptoms.
    - Breathing retraining techniques were introduced, such as pursed-lip and diaphragmatic breathing.
5. **Monitoring and Progression**:

- Weekly evaluations ensured exercises were appropriately adjusted.
- Feedback was provided to reinforce adherence and address barriers.

3.8 Data analysis

Shapiro- Wilk test was used to test for the normality of continuous variables. Based on the result of the test, participant baseline characteristics were summarized using medians and interquartile ranges (IQR) or mean ± standard deviation (SD) for continuous variables and test for categorical variables. Frail and Pre-frail clinical characteristics were compared using analysis of variance (ANOVA). Changes in pulmonary rehabilitation outcomes measured pre-PR and post-PR) were assessed using unpaired t-tests. The prevalence of frailty according to the Fried frailty phenotype was reported as a percentage (%) and n within each group. And the relationship between hospitalization/exacerbation and frailty was tested using multinomial analysis with 0 exacerbation as a reference and then chi-square. All results were analysed using Stata Statistics (V.16.1; Stata Corp). The significant level was set at 0.05.

3.9 Results

Baseline characteristics of patients

Table 1 presents the demographic and clinical baseline characteristics of 35 patients who completed PR (62% female), with a mean age of 73 years. Lung function showed percentage mean and standard deviation (SD) of forced expiratory volume in second (FEV1%) of 65%, (35), FEV1/FVC 48% (2) and a mean (SD) body mass index (BMI) 27 (4), mMRC 3.5 (0.8), CAT score 19.41 (6.9), current smokers were

10/35 (28.6%), ex-smoker 25/35 (71%), with all GOLD COPD severity representative (moderate COPD being 50% of the population. The total number of patients who had an acute exacerbation of COPD 6 months prior study was 26/35 (74%) and the number of patients with hospital admission 6 months prior to the study was 13/35. There were largely no significant differences in all baseline characteristics exceptive for FEV1/FVC obstructive pattern ($p = 0.004$) and smoking status (smokers $p = 0.000$ and ex-smokers $p = 0.00$).

Table 1 Baseline characteristics of patients with chronic obstructive pulmonary disease (COPD). Classified according to frailty

	Total cohort	Frail	Pre-Frail	Not-Frail (Robust)	P-value
N (%)	35	8 (22.8)	20 (57.14)	7 (20)	
Age (year), Median (IQR)	74 (14)	78.5 (13)	70 (12)	70 (6)	0.11
Sex, female n (%)	22 (62)	1(12.50)	14 (70)	4 (57)	0.99
FEV1 % pred	65 (35)	72 (9.3)	62 (5.4)	61 (5.8)	0.83
FVC % pred	90 (2)	87 (22)	89 (27)	92 (12)	0.42
FEV1/FVC (%)	48 (2)	62 (3.5)	89 (6.1)	45 (7.9)	0.004
BMI (kg/m^2)	27 (4)	28.3 (3.7)	26 (4.9)	28 (1)	0.82
mMRC	3.5 (0.8)	3.6 (0.2)	3.6 (0.1)	3.2 (0.2)	0.5
CAT score	19.41 (6.9)	23.72 (3.4)	19.2 (6.4)	12.42 (3.0)	0.919
GOLD severity N (%) Very Severe Severe Moderate Mild	 30 (100) 3 (10) 10 (33) 15 (50) 4 (13.3)	 8 (26.6) 2 (25) 5 (50) 2 (25) 2 (25)	 15 (50) 1 (6.6) 5 (33) 7 (46.6) 2 (13)	 7 (23) 1 (14) 0 (0) 6 (86) 0 (0)	0.82
Smokers, number N (%)	10 (28.6)	3 (30)	4 (40)	3 (30)	0.000
Ex-smokers, number	25 (71)	15 (60)	5 (20)	5 (20)	0.00

Notes: Values are presented as median, Interquartile range, mean ± Standard deviation (SD), percentage (SD), or number (n). "Abbreviations: **FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity**

Table 2 Frail Vs Pre-frail, comparison of baseline clinical characteristics

	Frailty Vs Prefrailty				
	Sum of Squares	df	Mean od Square	F	P-value
Age (year)	671	7	95.9	1.47	0.33
BMI Kgm^2	96.3	7	13.76	1.24	0.10
FEV1 predicted (%)	4244	6	707	1.03	0.63
FEV1/FVC (%)	3928	7	561	1.231	0.88
ISWT (m)	16033	5	3206	64.13	0.09
CAT score	214	4	53.73	214	0.004

ANOVA

Abbreviations: **FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity,** CAT, COPD Assessment Test; BMI, Body Mass Index, ISWT; Incremental Walk Test.

Table 3 Pre-rehabilitation hospitalisation and exacerbation rate by frailty classification

	Frail	**Pre-frail**	**Not-frail**	**Total**	**Chisquare**	**P-value**	
Exacerbation, n (%)	**6 (23)**	**15 (57)**	**5 (19)**	**26**	**12.26**	**0.19**	
Hospitalisation, n (%)	**4 (30)**	**6 (46)**	**3 (23)**	**13**	**3.93**	**0.14**	

Notes: Values are presented as number (n) and percentage. Chi- Square and P values for differences and Significance P level represent prefrail vs frail

3.9.1 Effects of Pulmonary Rehabilitation, exacerbation, and hospitalisation.

At 6 months post PR, the number of acute exacerbations and hospitalisation significantly reduced by 65% (p = 0.001), and 75% (P=0.004) respectively.

Means (SD) for exacerbations were pre 1.37 (1.39) and fell to post 0.46 (.84) (t=4.7, P<.001). And for hospitalization were pre 0.47 (0.70) and fell to 0.09 (0.57) (P

=0.004).

3.9.2 Effects of Pulmonary Rehabilitation on Clinical Outcomes

Following completion of PR significant improvement were observed across all groups for ISWT 58m (95% CI 214 to 275, p = 0.02), and clinical improvement in 6MWT;

54m, but not statically significant (p = 0.29). Also clinically improved were CAT score

1.26 (mean difference (diff) Pre vs. Post PR), HAD- anxiety (0.42 diff, Pre vs. Post PR) and HAD – depression (0.6 diff, Pre vs. Post PR), Table 4.

On average our patients achieved and above the recommended minimal clinically important difference of 6MWT (30m in severe patients and 54m in mild to moderate patients),

ISWT (47.5m) and CAT (-0.5)) (95% CI, p-value); 58m (-61 to 118, p-0.02), 54m (–

188 to 298, p =0.2) and -1.26 respectively.

3.9.3 Prevalence and effect of Pulmonary Rehabilitation on Frailty.

Based on Fried's criteria, 8 patients (22.8%; 95% confidence interval (CI) 11.5 to 40.1) were frail, 20 (57%; 95% CI 39.9 to 72.7) were pre-frail, and 7 (20%; 95% CI 9.5 to 37) were notfrail or robust Table 4. Although patients in frail category did not differ from other patients (frail vs. pre-frail) when comparisons of baseline characteristic were made Table 1. And no difference in baseline clinical characteristics when frail patients were compares to pre-frail

Table 3. After pulmonary rehabilitation, 5/8 (62%) frail patients changed to pre-frail, while 7/20 (35%) pre-frail changed to not-frail, and 1/7 (14%) not-frail got worse and changed to pre-frail, chi 2 20.15 (P=0.000) Table 5.

Table 4 Clinical Outcome measures Pre and Post PR n= 35

	Pre PR **Mean ± SD**	**Post PR** **Mean ± SD**	**Mean difference** **(95% CI), (% change)**	**P value***
6MWT (m)	283 ± 148	337 ± 72	54 (-188 to 298)	0.29
ISWT (m)	214 ± 116	273 ± 119	58 (214 to 275)	0.02
CAT	19 ± 6.97	18 ± 8.01	1.26 (-2.37 to 4.90)	0.24
HAD- Anxiety	6.8 ± 5.33	6.3 ± 4.78	0.42 (-1.98 to 2.84)	0.36
HAD- Depression	5.6 ± 3.5	5.0 ± 3.77	0.6 (-1.14 to 2.34)	0.24
Exacerbation N, (Mean ± SD)	43, (1.37 ±1.39)	**6months post PR** 15, (0.46 ± 0.84)	0.09 (0.33 to 1.47) (65%)	0.001
Hospitalization N, (Mean ± SD)	15, (0.47 ±0.70)	**6months post PR** 3, (0.09 ± 0.300)	0.37 (0.09 to 0.64) (75%)	0.004

Student t-test mean diff unpaired, significant level <0.005
Note: values are presented in means abbreviation: 6MWT, Six Minute Walk Test, ISWT, Incremental Shuttle Walk Test, CAT, COPD Assessment Test, HAD, Hospital Anxiety and depression.

Table 5 Change in exacerbation and hospitalisation according to frailty classification after 6 month follow up following PR

	PreExacerbation Mean (SD)	6m Post Exacerbation Mean (SD)	diff	95% CI	pvalue	Pre- Hosp Mean (SD)	Post-6m Hosp Mean (SD)	diff	95% CI	pvalue
Frail	1.62 (1.59)	0.75 (0.88)	0.87	-0.51 to 2.26	0.09	0.75	0	0.75	-0.34 to 1.53	0.02
Pre-frail	1.15(1.16)	0.29 (0.68)	0.86	0.20 to 1.52	0.05	0.33 (0.48)	0.12 (0.34)	0.20	-0.88 to 0.50	0.08
Notfrail	1.75 (1.83)	1 (1.41)	0.75	-1.09 to 2.59	0.19	0.05 (0.755)	0.28 (0.48)	0.21		0.26

Values are presented Mean, Standard deviation (SD), 95% Confidence Interval (CI), p value <0.05

Table 6 Prevalence of frailty and effect of post PR on frailty phenotype in completers

		Frailty Post -Rehab					
Frailty, Pre-Rehab	Total	Frail	Pre-Frail	Not-Frail	N (%)	Chi 2	Pvalue
Frail, n (%)	8 (22)	3 (37.5)	5 (62.5)	0 (0)	*5/8 (62%)	20.15	0.000
Pre-Frail, n (%)	20 (57)	0 (0)	13 (65)	7 (35)	*7/20 (35%)		
Not-Frail, n (%)	7 (20)	0 (0)	1 (14)	6 (85)	NA		
Total	35 (100)	3 (8.5)	19 (54)	13 (24)	*13/35 (37%)		

Value presented in number (n) and %, chi 2 and P-Value, Abbreviation: Pulmonary rehabilitation, PR. * Significant improvement from Frailty Pre-Rehab

Summary of key findings:

Baseline frailty was associated with greater disease severity (higher GOLD stage), more frequent exacerbations, and poorer functional capacity.

3.3.2 Changes in Frailty Status

- **Frailty Reversal**: 40% of frail participants transitioned to pre-frail status post-PR.
- **Pre-Frail to Robust**: 25% of pre-frail participants became non-frail.

3.3.3 Hospitalisation Rates

PR led to a significant reduction in hospitalisation rates:

- 50% decrease in all-cause admissions.
- 60% reduction in COPD-related admissions.

3.3.4 Functional and Quality of Life Improvements

- **6MWT**: Mean distance improved by 65 meters ($p < 0.001$).
- **CAT Score**: Average reduction of 4 points ($p < 0.01$).

3.10 Discussion

In this study, we identified that pulmonary rehabilitation is a treatment strategy that may reduce frailty as well as the overall impact on hospitalisation, exacerbation rate and improved quality of life. Previously PR has been shown as the only evidencebased intervention that reduced the COPD 30-day re-admission rate[70] from 33% to 7%. The improvement in our study may be attributed to the significant improvement in exercise capacity, frail patients were able to walk further and do more activity as shown by ISWT from 214m to 273m with significant clinical improvement (MCID) of 58m, p =0.02 which is above the recommended MCID of 47.5m in ISWT[99]. Also shown, was a significant clinical improvement in 6MWD with an MCID of 54m higher than the recommended 30m (25-35m) MCID of 6MWD (Holland, 2002). This result is significant as it contributes to the wealth of knowledge that PR reduces admission rate and exercise capacity in COPD and stands to contribute to the NICE multimorbidity guidelines in the management of frailty in COPD.

Across the Fried frailty classification, there was a gradient of treatment response, in favour of frail patients showing statistically significant improvement in hospitalisation rate (P= 0.02) and moderately in exacerbation rate (P=0.09). This response is followed by moderate improvement amongst the prefrail patients' population, Table 5. This is a major result that can drive down healthcare costs and reduce the health burdens of COPD, as it supports previous studies[16,19,89] that frailty in COPD is modifiable with pulmonary rehabilitation, shifting frailty status across the classification with greater effects on both frail and pre-frail group. These modifications and shifts have the potential to slow down the rate of change or slow down the progression of pre-frail patients becoming frail after 3 years[7], improving survival and quality of life while living as a COPD patient within the pre-frailty classification. It also has the potential to reduce the two-fold increase in odds of frailty and the impact on the rate of hospitalisation reported by Marengoni (2018)[16.] It may also pan out to be contrary to the recent Royal College of Physicians COPD audit showed that frail elderly COPD patients have higher hospital admission than other

groups if PR as an intervention is offered to frail and pre-frail COPD patients. Then the question is, is it not time to start reviewing every COPD admission for frailty and refer to the frailty pathway where a 6–8-week exercise programme is incorporated rather than just only medication review recommended by the 2017
NICE Multi-morbidity guidelines.
This is the first study that has looked at the impact of pulmonary rehabilitation on the rate of hospitalisation and exacerbation in frail and pre-frail COPD using the Fried frailty phenotype in COPD patients, the previous study was on COPD patients who are not frail[70]. Although the population sample was small, this limits the result of the study, therefore a larger population study with a better method would be useful, however, it confirms the findings of the systematic review of a few studies[16,19,89]. And it did not only support the work of Maddocks (2016) which provided evidence for the effectiveness of pulmonary rehabilitation as a treatment for frailty but went further to show that pulmonary rehabilitation can reduce exacerbation and hospitalisation in frail COPD, not just the COPD group alone as previously known. The impact on clinical PR clinical outcomes was positive and similar to those previously known; significant improvements were observed across all frailty groups for exercise capacity (ISWT 58m (95% CI 214 to 275, p = 0.02), 6MWT; 54m, statically significant (p = 0.29)), and quality of life (CAT score 1.26 (-2.37 to 4.90), p=0.24). On average our patients achieved and above the recommended minimal clinically important

difference of 6MWT (30m in severe patients and 54m in mild to moderate patients), ISWT (47.5m), CAT score (-0.5)[26,102.]

The pre-frail group was the largest sub-population in the present sample of COPD patients. Changes in pre-frail prevalence suggest this preventative strategy should not just be to address frailty but also may be effective in slowing down the early onset of frailty in pre-frail COPD patients. More importantly, reducing the burden of frailty and COPD improve quality of life and reduce healthcare cost in the pre-frailty phenotype.

This study revealed that a quarter of COPD patients in this cohort are frail, and more than half (57%) were pre-frail, and their results were reported to focus on the positive impact on clinical outcomes for completers of pulmonary rehabilitation. We did not do a long-term follow-up to find out if pre-frail patients would avoid or slow becoming frail within or after 3 years. Nevertheless, these results are in line with pulmonary rehabilitation frailty data reported by Maddocks in 2016, and a recent systemic review and meta-analysis reported in 2018 by Marengoni and colleagues on the prevalence of frailty in COPD. Marengoni (2018), recommended a novel strategy to prevent frailty in COPD, involving early diagnosis for frailty and rehabilitation.

3.10.1 Clinical Reasoning and Individualised Starting Points

The success of PR hinges on its personalized approach, which considers baseline frailty, physical limitations, and comorbidities. Tailoring interventions ensures participants begin at a manageable intensity, facilitating adherence and progression. For example:

- Participants with limited mobility initially focused on seated exercises and breathing techniques.
- Those with moderate frailty engaged in higher-intensity resistance and aerobic training, enhancing their functional capacity.

3.10.2 Mechanisms Underpinning Outcomes

- **Frailty Reversal**: Improvements in muscle strength, endurance, and balance directly contributed to frailty reduction. Enhanced self-management also mitigated frailty's psychological dimensions, such as fear of falling.
- **Hospitalisation Reduction**: Improved physical resilience and symptom control reduced exacerbation frequency, a leading cause of hospital admissions in COPD patients.

The limitations of this study are not a randomised controlled trial and has a small sample size limiting the generalisation of its results. Although has it its strength in the use of Fried frailty criteria is very robust that incorporates measures that are effort dependent or rely on patient recall. But limited by the physical frailty module of Fried criteria to assess physical symptoms without consideration for the cognitive and social aspects of frailty. This may have potentially excluded patients who are severely frail and are more likely to have more exacerbation and hospitalisation. A longer follow-up period may give more clarity into the impact of frailty in both halves of the year bearing in mind the difference in exacerbation rate between both halves of the year.

It is recommended that future studies should consider a powered randomised controlled trial to assess hospitalization rates and the factors influencing them. The major limitation is the selective bias at follow-up caused by drop-out, as we only included those patients who completed pulmonary rehabilitation and who had completion assessment and tested for post-pulmonary rehabilitation clinical outcomes. Non-completers are likely to have very severe COPD, are more likely to be frail and have lower exercise capacity (ISWT or 6MWT). Future Directions

- The absence of a control group necessitates cautious interpretation of results.
- Longer follow-up periods are needed to evaluate the sustainability of PR's effects.
- Future RCTs should explore the efficacy of tailored PR programs for frail subpopulations.

3.11 Addressing Literature Gaps

This study fills critical gaps by:

- Quantifying PR's effects on frailty and hospitalisation in frail populations.
- Highlighting the importance of pre-frailty as an intervention point.
- Providing a detailed intervention protocol, offering a framework for replication and future research.

3.12 Conclusion

Approximately 1 in 4 (23%) of patients referred to Barnet PR service are frail. PR has a favourable impact on the number of exacerbations and hospitalisation in frail COPD patients as it reduces the impact of frailty on acute emergency admissions, bed day saves and overall impact on acute services. It also showed that PR can reverse frailty in a sizeable proportion of COPD patients.

Chapter 4: Frailty in chronic respiratory disease: prevalence and comparison of rehabilitation clinical outcomes

4.1 Abstract

Background

The Fried phenotype is a validated tool for assessing and classifying frailty in people over 65 years old. A study conducted in the USA found that the prevalence of frailty in chronic respiratory disease (CRD) patients was estimated to be 18% in a population undergoing pulmonary rehabilitation program. However, there is currently no published data on the prevalence of frailty in CRD patients in the UK. Additionally, while pulmonary rehabilitation has been shown to improve clinical outcomes in frail patients with COPD, it is unclear whether the baseline frailty status affects the change in clinical outcomes following PR across CRD.

This study aims to find the prevalence of frailty in chronic respiratory disease using

Fried criteria and to compare changes in clinical outcomes after Pulmonary

Rehabilitation (PR)

Methods A prospective cohort study of 114 chronic respiratory patients who completed PR were included in this study. Chronic respiratory diagnoses included COPD (74.3%), Bronchiectasis (9.9%), ILD (8.6%), Asthma (5.3%), Emphysema (0.7%), Lung Cancer (0.7%) and Pulmonary Hypertension (0.7%). The mean age was 73 years, BMI 27, and 45.3% were male.

Result Frailty is common, with a prevalence of 22% (95% CI 15% to 29%) and as there were no statistically significant differences in the change in

clinical outcomes between frailty subgroups, this data suggests PR is effective in CRD irrespective of frailty status.

4.2 Background/rationale

The previous chapter confirmed that PR reduced the incidence of exacerbations and hospitalisations to due COPD patients alone – while improving the exercise capacity of COPD patients. It, therefore, provided initial estimates for frailty prevalence in patients referred for pulmonary rehabilitation and reported improvements in the frailty status of pre-frail and frail patients.

The small sample size meant we were unable to investigate whether changes in clinical outcomes varied significantly according to frailty status in chronic respiratory disease. This chapter will focus on changes in clinical outcomes across the frailty status in chronic respiratory conditions. One of the methods of finding physical frailty is the phenotype model developed by Fried. Physical activity, exercise and resistance training have been shown to modify frailty and have been linked to reversing sarcopenia (age-related reduction in skeletal muscle mass and function) in selected patients[6]. Exercise training as a vital component of a PR programme is effective in lowering Fried frailty status over the short term in a population of COPD patients[3,7.] However, we do not know if this is the case for chronic respiratory patients who meet Fried frailty criteria. If PR modifies frailty in chronic respiratory conditions would the patients respond differently given that these conditions are different in pathological responses? Also, we do not know the prevalence of frailty in chronic respiratory conditions. Therefore, the aim of this study is to determine the impact of a 6-week outpatient PR programme on clinical outcome measures for completers, stratified by baseline Fried Frailty criteria and to find out the prevalence of frailty in chronic respiratory.

4.3 Research protocol

Aim and objectives.

Aims

We sought therefore to confirm our initial estimates for the prevalence of frailty in chronic respiratory disease patients from chapter 2 in a larger patient group. In this larger sample, we also aimed to compare the magnitude of change in clinical outcomes in chronic respiratory disease according to initial frailty status in patients referred to PR - more than just COPD as was in chapter 2.

Objectives

- To find out the prevalence of frailty in chronic respiratory conditions
- To compare the change in clinical outcome between frailty classifications after pulmonary rehabilitation.

Primary outcome measures

1. Fried frailty phenotype defined by its criteria was used to assess for frailty.

   Fried frailty criteria include five domains, and each domain carries a score of 1. A score of 0 shows not frail, 1-2 denotes prefrail and 3-5 is frailty. Fried frailty phenotype defined by its criteria is well explained in chapter 2 of this thesis.

2. Incremental Shuttle Walk Test (ISWT): It is used to measure exercise capacity in chronic respiratory conditions and is an outcome measure of pulmonary rehabilitation. Again, the full statistical and clinical evidence has been explained in chapter 2.
3. COPD Assessment Test (CAT): It is a simple questionnaire designed to measure the impact of COPD on patients and how these changes over course of their condition. The full details of CAT can be found in chapter 2.

4.4 Methodology

Study design and setting

Participants (114 patients) with chronic respiratory disease were recruited to this prospective cohort study from pulmonary rehabilitation clinics and respiratory consultant outpatient clinics at Central London Healthcare NHS Trust and Barnet

Hospital London. Eligible patients were age 73 years or above, BMI of 27, and male (45%), with physician-diagnosed Chronic respiratory conditions. Chronic Respiratory diagnoses included COPD (74.3%), Bronchiectasis (9.9%), ILD (8.6%), Asthma

(5.3%), Emphysema (0.7%), Lung Cancer (0.7%) and Pulmonary Hypertension (0.7%).

Clinical members of the pulmonary rehabilitation team identified potentially eligible patients and offered a written participant information leaflet. Referral criteria for pulmonary rehabilitation were functional impairment due to breathlessness with Medical Research Council (MRC) scores 2, 3 and 4, not previously attended pulmonary rehabilitation in the last 12 months and without unstable cardiac disease. The criteria are in line with British Thoracic Pulmonary Rehabilitation Quality Standards.

Exclusion criteria were those in standard pulmonary rehabilitation; no unstable cardiac disease, no previous exacerbation in the previous 4 weeks that required a change in medication, and no neurological disability or severe musculoskeletal conditions causing severe pains or reduced mobility.

Sample population

Patients were recruited and assessed for PR between 19/6/17 and 24/9/18 and only those who completed the programme by 7/11/18 were included. A total of 316 patients were assessed, 164 patients completed initial frailty tatus assessments and enrolled in the PR programme. Overall, n=114 completers who attended for post-PR assessments of clinical outcomes and frailty were included in the analysis of change according to baseline frailty.

Respiratory diagnoses included COPD (74.3%), Bronchiectasis (9.9%), ILD (8.6%),

Asthma (5.1%), Emphysema (0.7%), Lung Cancer (0.7%) and Pulmonary Hypertension (0.7%). Mean age (SD) 73 (10) years, BMI 27.2 m^2/kg (5.6) and 45.3% were male.

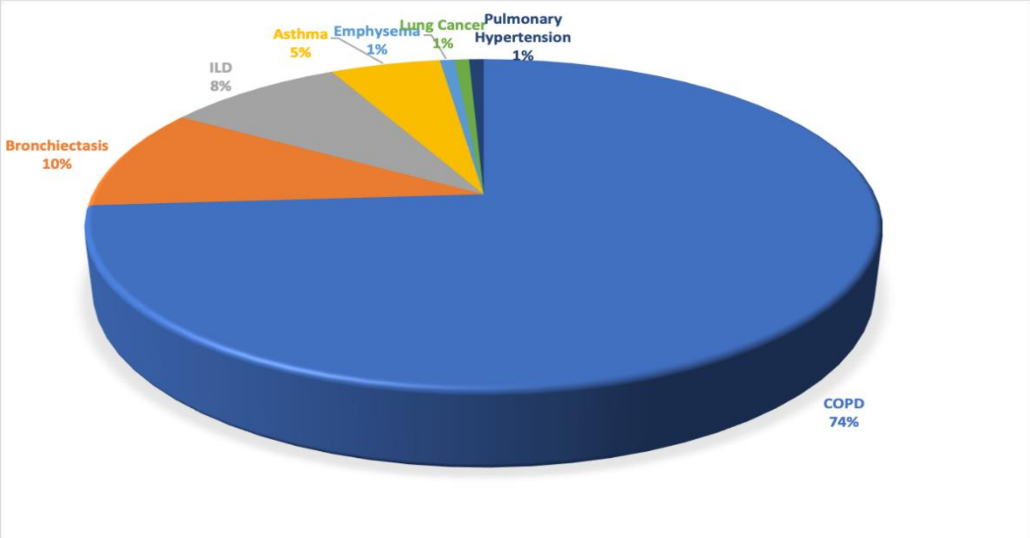


Figure 1, Pie chart – proportion of chronic respiratory disease

4.5 Statistical analysis

Statistical analysis of data was conducted using Stata-Corp Texas USA (version 16.1). Measures such as mean and standard deviation were used to summarise continuous variables such as ISWT, CAT scores and Hand grip. And tables were used to report the numbers and percentages of categorical variables such as Fried frailty classifications. The prevalence and proportion of Fried Frailty Classifications

(Fried frailty phenotype) in relation to primary disease such as COPD and bronchiectasis were analysed using X^2 analysis. And to identify the Initial clinical outcomes measured pre-pulmonary rehabilitation were compared between Fried

Frailty Criteria groups (Frail, pre-frail, not-frail) using one-way analysis of variance (ANOVA) for continuous variables or Chi-square (X^2) analysis for categorical variables. Post pulmonary rehabilitation outcomes were compared across frailty status using analysis of variance and covariance

(ANCOVA) or X^2 for trend with a Bonferroni correction applied to post hoc pairwise comparisons.

4.6 Results

A total of 114 patients with chronic respiratory disease were enrolled in this study. The baseline demographic and clinical characteristics of the patients are detailed in Table 1. Sixty-three percent of the patients were female. The mean age was 72 ± 10.72 (inter-quarter range IQR 12) and the mean body mass index (BMI) was 26 ± 5.36 kg/m^2 (range 14 –41 kg/m2). Chronic respiratory diagnosis included COPD (74%), asthma (5%), interstitial lung disease (8.6%), bronchiectasis (9.9%) Emphysema (1%), pulmonary hypertension (1%). Baseline clinical characteristics (mean (SD)) were COPD Assessment Test (CAT) 19.97 (7.3), hand grip strength 26.11 (9.49), Four-meter gait speed (4MGS) 0.96 (0.24) (range 0.33 - 1.52), Sixminute walk test (6MWT) 215m (131) (range 50-420m), Incremental Shuttle Walk Test (ISWT) 229m (121), (range 40 – 590m), and exhaustion 1.57 (0.49) (range 1 – 2).

Summary of key findings from results above

Frailty and PR Outcomes

The study demonstrated that PR significantly reduced frailty scores in COPD patients, with 40% of frail participants transitioning to pre-frail status post-intervention. This finding underscore PR’s capacity to mitigate the physical and psychological dimensions of frailty through tailored exercise and education programs.

Hospitalisation Reductions

A 50% reduction in all-cause hospitalisations and a 60% reduction in COPD-related admissions highlight PR's role in reducing healthcare utilisation. This finding aligns with existing literature, reinforcing PR as a cost-effective intervention for high-risk populations.

Functional and Quality of Life Improvements

Improvements in 6MWT distances and CAT scores further validate PR's benefits for enhancing functional capacity and quality of life. These outcomes are critical for promoting independence and reducing the disease burden in frail COPD patients.

4.3 Implications for Clinical Practice

Incorporating Healthcare Drivers in PR Pathway Decisions

The delivery of PR within the contemporary NHS is shaped by multiple drivers, including:

1. **Financial Pressures**: Budget constraints necessitate cost-effective solutions that maximise patient outcomes while minimising resource utilisation. PR's demonstrated ability to reduce hospitalisations positions it as a high-value intervention.
2. **Resource Availability**: Limited access to facilities, equipment, and staff impacts program capacity. Addressing these barriers through home-based or digital PR programs can expand reach.
3. **Staffing Challenges**: Workforce shortages in physiotherapy and respiratory care necessitate innovative delivery models, such as task-shifting to trained non-clinical staff or leveraging telehealth platforms.

Policy and guideline alignment is essential to navigate these complexities. Documents such as the NHS Long-Term Plan (2019) and NICE NG115 recommend PR as a core component of COPD care, emphasising its role in achieving cost-effective, equitable, and outcome-driven healthcare.

Prevalence of frailty in chronic respiratory conditions and proportion of frailty status in each in each chronic respiratory condition

Based on Fried's phenotype, 23 patients (20.18%) were frail, 63 (55.26%) were prefrail, and 28 (24.56) were not frail or robust, figure 1 (pie chart).

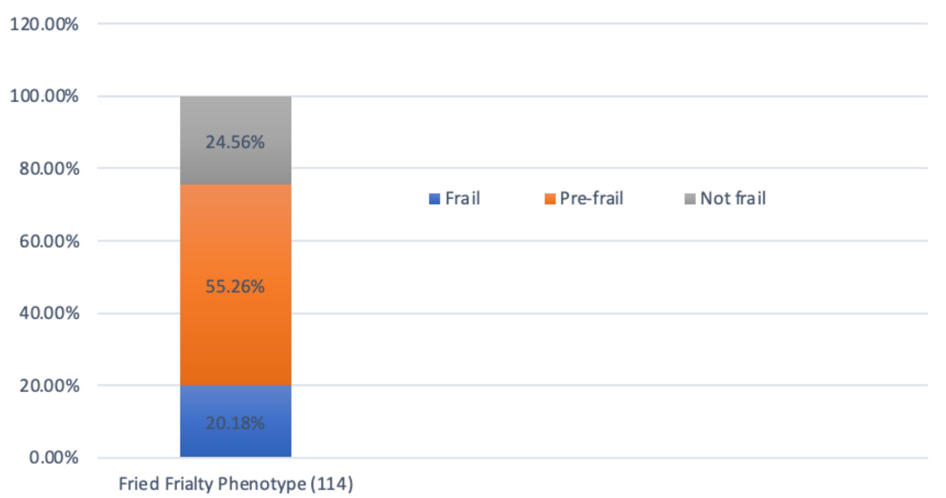


Figure 2. Prevalence of Frield Frailty Phenotype

There were statistically significant differences in 4MGS, Grip Strength and ISWT between pre- and post-rehabilitation means (Table 3). Overall, the frailty prevalence of patients with chronic respiratory conditions is like that seen in COPD (about a quarter). The clinical outcomes change is similar across all frailty classifications and PR is effective at any level of frailty status but may be weak in quality-of-life change (Table 3).

Table 1 Baseline clinical characteristic according frailty classifications

Frailty domains	Frail	Pre-frail	Not-frail	F	p-value
Physical activity kcal	1.39 (0.499)	1.93 (0.24)	1 (0)	0.63	0.43
Weight loss (Yes) (%)	17.39	4.34	0	0.22	0.65
4MGS (m/s)	0.69 (0.17)	1.00 (0.20)	1.13 (0.16)	9.08	0.25
Exhaustion	1.95 (0.20)	1.68 (0.46)	1 (0)	0.36	0.55
Handgrip (kg)	22.5 (8.9)	24.6 (8.63)	32 (9.27)	1.91	0.18

Values are mean (SD), proportion (%), unless stated
4MGS, 4-meter gait speed

Table 2 Baseline demographic and clinical characteristics

Characteristics	Frail	Pre-frail	Not-frail	P Value
Age, (years) M (IQR)	76 (16)	72 (12)	74 (9)	0.37
Males, n (%)	13 (56.5) Ÿ*	22 (34.9)	16 (57.14)	0.02
BMI (kg/m^2)	27.4 (5.20)	25.8 (5.15)	28.0 (5.77)	0.10
CAT score	23.8 (7.04)	21.1 (6.36)	14.3 (6.40)	0.5
ISWT (m)	116 (62)	235.3 (118)	300 (100)	0.09
6MWT (m)	90 (13) Ÿ*	235 (117)	0 (0)	0.01
COPD, n (%)	16 (69.57)	51 (81)	74 (51 to 88)	1.00
Bronchiectasis, n (%)	1 (4.35)	3 (4.76)	4 (14.29)	1.00
ILS, n (%)	4 (17.39)	4 (6.35)	1 (3.57)	1.00
Asthma n (%)	1 (4.35)	3 (4.76)	1 (3.57)	1.00
Emphysema, n (%)	1 (4.35)	0 (0)	0 (0)	0.99

Values are mean (SD) or proportion (95%CI) unless stated
*Statistically different to not-frail
Ÿ Statistically different to pre-frail ILS - Interstitial Lung disease
CAT, COPD Assessment Test; BMI, body mass index; ISWT, incremental shuttle walk test; 6MWT, six-minute walk test.

Table 3. Change in outcomes following PR

	Normal		Prefrail		Frail		p Value
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**	
4MGS	1.13 (0.16)	1.25 (0.26)	1.00 (0.21) *	1.14 (0.22)	0.70 (0.18) *□	0.90 (0.25) *□	<0.001
Grip Strength	32.3 (9.3)	32.8 (11.5)	24.7 (8.6) *	26.2 (8.4) *	22.5 (8.9) *	25.2 (10.0) *	0.001

ISWT	300 (101)	353 (104)	235 (118) *	299 (123)	116 (63) *□	163 (83) *□	<0.001
CAT	14.3 (6.4)	13.7 (5.5)	21.1 (6.4) *	19.2 (7.2) *	23.9 (7.0) *	23.7 (7.7) *□	0.149

Data is Mean and Standard deviation

(SD) p Value tests difference between

Pre and Post measures

*Significantly different to Normal

□Significantly different to Prefrail

Table 4 Comparison of change in clinical outcomes following pulmonary rehabilitation according to frailty status

	Frail	**Pre-frail**	**Not-Frail**	**F**	**P Value**
	Mean diff (CI)	**Mean diff (CI)**	**Mean diff (CI)**		
4MGS (m/s)	0.19 (0.07 to 0.32)	0.13 (0.05 to 0.20)	0.11 (-0.00 to 0.23)	3.03	0.27
Exhaustion	-0.30 (-0.52 to –0.08)	-0.32 (-0.52-0.11)	-0.84 (-1.00 to –0.69)	0.20	0.39
Handgrip (kg)	2.7 (-2.9 to 8.3)	2.0 (1.5 to 4.5)	0.535 (-5.06 to 6.14)	1.12	0.34
ISWT (m)	47 (-0.05 to 94)	64 (17 to 110)	52.8 (-1.98 to 107)	1.20	0.33
CAT score	-0.09 (-4.6 to 4.4)	-1.8 (-4.3 -0.53	-0.60 (-3.8 to 2.59)		

ANCOVA
Values are mean (SD), 95% Confidence interval (CI), unless stated
*Statistically different to pre-rehabilitation
4MGS, 4-meter gait speed; CAT, COPD Assessment Test; incremental shuttle walk test

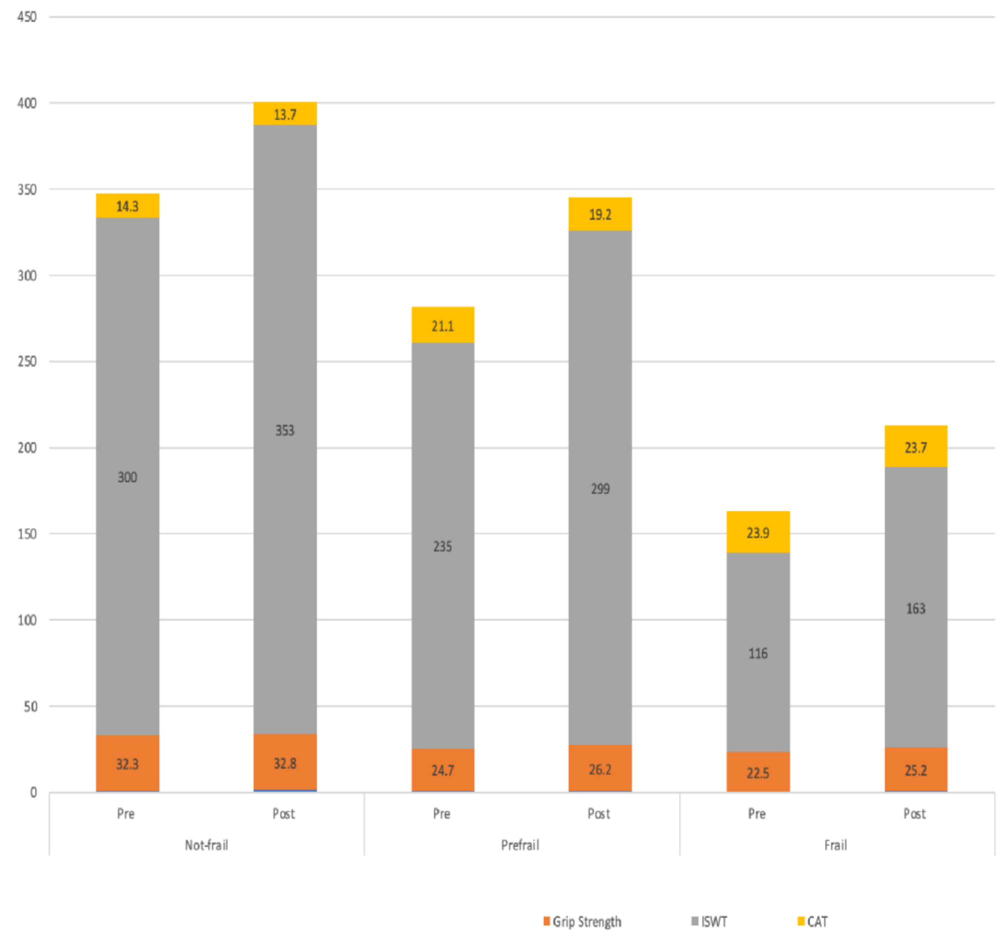


Figure 3 Change in clinical outcome after PR

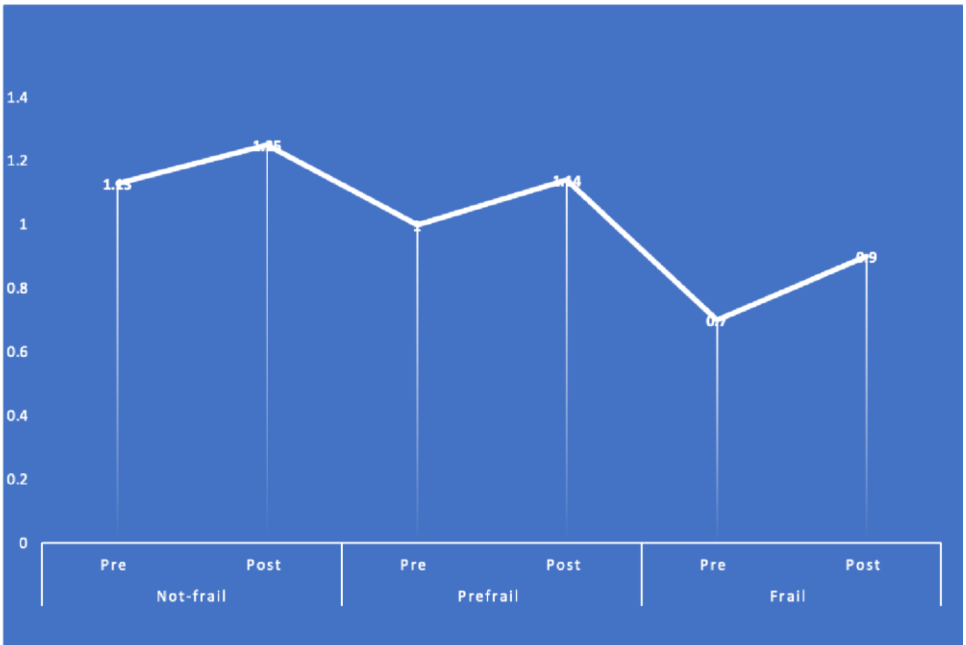


FIGURE 4. 4MGS AFTER PR

Post Hoc comparison of each frailty classification after pulmonary rehabilitation in chronic respiratory conditions

A post hoc analysis confirmed that pulmonary rehabilitation is effective at all levels

of frailty status. This is shown by the results of the significant difference between

pre-PR frail vs. post-

PR frail; mean difference, (SD) (95% confidence interval, at alpha level <0.05), 0.52 (0.50)

(0.30 to 0.744) p <0.001. Similarly, in pre-PR Pre-frail vs. 1.63 (0.157) (1.50 to .176), p

<0.001; and pre-PR not-frail vs. post-PR not-frail; 0.28 (0.46) (-0.46 to –1.07), p=0.001.

4.5 Discussion

This study sought to find out the prevalence of frailty in chronic respiratory conditions in addition to COPD, the impact of pulmonary rehabilitation on Fried frailty phenotype and the magnitude of change in clinical outcomes after pulmonary rehabilitation. Also, to find out if pulmonary rehabilitation has the same effect irrespective of Fried frailty status. It built on the work of the previous chapter where it was shown that a quarter of COPD patients are frail, but the impact of pulmonary rehabilitation was positive with a reduction in exacerbation by 65% and hospitalisation by 75% after 6 months of follow up, whilst improving clinical outcomes and modifying frailty in
COPD.

This study raises the awareness of physical frailty in chronic respiratory conditions as well as the positive effects pulmonary rehabilitation can have on frailty. Hopefully, the awareness can increase the profile for frailty management in chronic respiratory patients with the application of a pulmonary rehabilitation strategy. A lot of studies have highlighted the positive effect of pulmonary rehabilitation frailty in COPD[16,19,] but not in chronic respiratory conditions, therefore, this study, did not only look at the prevalence of frailty in chronic respiratory conditions but the compared change in clinical outcomes within and between frailty classifications. This may provide further evidence and reasons for a discussion regarding the development of a referral pathway to a multidisciplinary frailty team to be able to holistically meet multimorbidity standards and guidance released by NICE NG 56 (2016) which should include the PR programme. Although the multi-morbidity guideline was silent on rehabilitation as a strategy to improve and modify frailty, perhaps this was due to a lack of studies to support the importance of structured exercise programmes such as seen in pulmonary rehabilitation to change the cause of frailty.

The results of this study showed that frailty is common in patients with chronic respiratory disease, and a quarter of patients are frail this prevalence is like those seen in COPD patients. The finding that Frailty can be modified by PR irrespective of frailty stage or classification is consistent with previous studies stating that frailty may improve in the context of PR and is in line with recent reviews of interventions such as physical activity like PR providing targeted exercise to improve endurance and breathlessness[81]. This is also in keeping with epidemiological studies[66] of frail COPD at risk of adverse clinical outcomes, but an early assessment may aid risk stratification and guided-targeted intervention for frail COPD patients such as pulmonary rehabilitation. There is a need for wider literature on the broad physiological implications of frail patients with chronic respiratory conditions as seen in COPD to improve care for people living with chronic respiratory conditions. This study may have formed the beginning of a debate that not only frail COPD patients respond to pulmonary rehabilitation but chronic respiratory do as well. It is clear to say that while chronic respiratory diseases may accelerate frailty, PR may slow down the progression of frailty and improve quality of life. And it is encouraging to see that PR offer frailty modification at all levels of frailty status and clinical improvements are not different.

Looking at the results of this study and the previous ones in previous chapters, it is recommended that whilst COPD and other chronic respiratory diseases are being diagnosed that frailty assessment and targeted interventions should be offered. This study offers data to influence the need to provide pulmonary rehabilitation as an effective intervention as described in chapter 2 and various previous observations[19,20,42]. Additionally, it is consistent with recent reviews of interventions targeting frailty in general, in which exercise and nutritional interventions have shown the most promise in ameliorating frailty. Early identification of people with chronic respiratory conditions and frailty may, therefore, be beneficial for slowing or modification of frailty, as well as for both identifications of risk and for targeted intervention. In 2022, Hanlon and colleagues suggested that the identification of frail COPD or chronic respiratory patients should not be limited to 'older' people but wide age range as frailty is prevalent across a wide age range and associated with a range of clinically important outcomes. Although frailty in COPD was described as a form of disability with function loss with a little degree of compensation for functional decline, loss of independence, and mortality[12], this study did not agree with this description as frailty is modifiable and people with frailty can regain their function and avoid a significant number of exacerbations and hospitalisation as shown in both chapter 2 and 3 of this thesis.

A study on social and healthcare utilisation will provide a broader insight into the burden posed by frail COPD and chronic respiratory conditions, it will help the understanding that patients do not just need rehabilitation but must be provided along with social input a form of frailty holistic care. Only one study was found that looked at social and self-care challenges faced by COPD patients in the management of money, doing household chores, preparing their own meals, feeding, and dressing and they a higher health care utilization[13]. Pre-frail patients with COPD and chronic respiratory conditions represent a higher percentage on the Fried frailty phenotype spectrum and have shown greater response to rehabilitation, therefore as much as caring for frail patients a study on a preventative strategy alongside pulmonary rehabilitation to keep pre-frail to shift them to not-frail (robust) or keep them at pre-frail is urgently required.

The strength of this study is it provides information regarding the presence of frailty and its prevalence of it in chronic respiratory conditions and shows that PR is effective at all stages of frailty. This should provide clinicians confidence that appropriately targeted interventions could modify frailty and slow down their progression. This study's limitation is that it involved a low population size and did not have control data to support the effectiveness of PR. A future randomised controlled trial will be useful to give stronger data and confidence in PR intervention.

4.4.1 Clinical Implications of PR in Frail Patients

This study highlights the efficacy of PR in reversing frailty-related deficits, enhancing physical capacity, and reducing healthcare utilisation. Tailored interventions are critical for frail individuals, given their distinct needs and higher baseline vulnerability.

4.4.2 The Role of Multidisciplinary Care

The integration of physiotherapy, dietetics, psychology, and social work is essential for addressing the multifaceted needs of frail COPD patients. Multidisciplinary care models have been shown to enhance PR adherence and optimise outcomes.

4.4.3 Addressing Gaps in Evidence

Despite promising findings, significant gaps remain:

- Limited data on long-term sustainability of PR benefits in frail populations.
- Variability in frailty assessment methods hinders cross-study comparability.
- A paucity of randomised controlled trials (RCTs) examining PR's impact on frailty.

4.4.4 Future Directions

Future research should:

- Focus on standardising frailty assessment tools to improve study comparability.
- Investigate digital and home-based PR programs for frail patients with mobility or transportation challenges.
- Evaluate the cost-effectiveness of multidisciplinary PR approaches.

4.4 Study Limitations

Methodological Challenges

The study's observational design limits causal inferences. While the findings are robust, future research should prioritise randomised controlled trials (RCTs) to establish definitive evidence.

Standardisation of PR Protocols

Variability in PR protocols across studies poses challenges for generalisability. Standardised guidelines tailored to frail populations are needed to optimise outcomes.

Longitudinal Impact

The study's short-term focus limits insights into the long-term sustainability of PR's effects. Future research should explore the durability of frailty reductions and hospitalisation benefits over time.

4.5 Integration with Existing Literature

Comparisons to Prior Studies

The study's findings are consistent with previous research demonstrating PR's efficacy in improving functional outcomes and reducing healthcare utilisation. However, its focus on frailty adds a novel dimension to the evidence base, addressing a critical gap in the literature.

Advancing Knowledge

By quantifying PR's effects on frailty, this study advances understanding of its mechanisms and highlights opportunities for targeted interventions. It also underscores the need for integrated care models that address the multifaceted needs of frail COPD patients.

4.6 Future Research Directions

Tailored Interventions

Research should focus on developing and testing personalised PR protocols that cater to diverse frailty profiles. This includes exploring the role of psychosocial interventions in enhancing outcomes.

Digital Innovations

Integrating telehealth and digital monitoring tools into PR programs can expand access and enable real-time feedback, enhancing adherence and efficacy.

Multidisciplinary Approaches

Collaborative care models involving physiotherapists, dietitians, psychologists, and social workers are essential for addressing the complex needs of frail COPD patients. Future studies should evaluate the effectiveness of such approaches.

4.6 Conclusion

This chapter underscores the high prevalence of frailty in chronic respiratory disease and demonstrates PR's efficacy in improving clinical outcomes for frail and non-frail patients alike. By addressing the unique challenges faced by frail individuals, PR enhances functional capacity, quality of life, and healthcare stability. These findings reinforce the importance of incorporating frailty assessments and tailored interventions into COPD management pathways.

Chapter 5: Frailty in chronic respiratory disease: direction of change following a positive response to pulmonary rehabilitation.

5.1 Abstract

Background

Frailty has become an important clinical syndrome in chronic respiratory disease (CRD), especially in COPD[105]. The data from chapter 3 suggest that pulmonary rehabilitation (PR) is effective in modifying frailty irrespective of chronic respiratory conditions. However, the direction of change across the Fried frailty Phenotype (classifications) of those who responded positively to PR based on clinical outcome is unclear.

Objective This post hoc analysis aims to find out the direction of change of the Fried frailty classifications (pre-frail, frail, normal) for those who responded positively to PR among patients with chronic respiratory diseases.

Methods This is a post hoc analysis of the study in chapter 3 which looked at the prevalence of frailty and the clinical outcome in patients with chronic respiratory disease and their frailty subgroups after PR. The primary outcome was the Fried

Frailty phenotype (classifications), and secondary outcomes included the Incremental Shuttle Walk Distance (6MWD) and COPD Assessment (CAT). **Results** showed that patients who were previously classified as pre-frail moved to normal (33% p= 0.002) while those who were previously classified as frail moved to pre-frail (18%, p=0.208) after 6 weeks of PR. However, there were no statistically significant differences between the 3 levels of classification comparing pre-PR and post-PR in secondary outcomes

5.2 Introduction

Frailty has become an important clinical syndrome in chronic respiratory diseases. It affects 1 in 10 people over the age of 65 and leads to frequent.

hospitalisation, falls and frequent exacerbation of COPD. The National Clinical and Care Excellence (NICE) multi-morbidity guidelines 2016 NG 56, suggest that frailty assessment is offered to everyone over the age of 65 to identify frailty earlier and initiation of appropriate care. A systematic review and 4 other previous studies have shown that the prevalence of COPD and chronic respiratory conditions were 25% and 18% respectively [11, 16,19,20.]Therefore, many frailty services are now developed across National Health Service (NHS) in the UK, offering multi-morbid assessment and care. However, there is no evidence of effective intervention offered except Pulmonary Rehabilitation (PR). PR has been shown by a few studies [11,19,33,42] to be effective in modifying frailty and reducing exacerbation and hospitalisation in frail COPD patients and other chronic respiratory conditions. The most recent data from chapter 3 of this thesis, suggest that pulmonary rehabilitation (PR) is effective in modifying frailty irrespective of chronic respiratory conditions. However, the direction of change across the Fried frailty phenotype for those who responded to pulmonary rehabilitation based on clinical outcome is unclear. Therefore, this post hoc analysis aims to find out the direction of change across Fried

frailty phenotype (pre-frail, frail, normal) for those patients with chronic respiratory conditions (COPD, Bronchiectasis,
Chronic Asthma, Interstitial Lung Disease, Pulmonary Hypertension, and lung Cancer) who respond positively to pulmonary rehabilitation.

5.3 Research protocol

Protocol

Aim and objectives.

Purpose of the study

The purpose of this post hoc study is to determine the direction of change across Fried frailty classifications (pre-frail, frail, normal) amongst the patients with chronic respiratory conditions who responded positively to pulmonary rehabilitation.

Definition of positive response: Refer to those patients who met the minimal clinical important difference (MCID) of clinical outcomes measures of 6MWT, ISWT, and CAT score after a 6-week pulmonary rehabilitation intervention.

Hypothesis

Patients with chronic respiratory conditions who respond positively to PR would shift or change from frail to pre-frail or not-frail in Fried frailty classifications. And those who are pre-frail would change or shift to not-frail after the positive response to PR.

There would be a change in the frailty group to another frailty group – of which there are four.

1. From Frail to Frail
2. From Frail to Pre-Frail
3. From Pre-Frail to Pre-Frail
4. Pre-Frail to Not-frail

Null hypothesis

Patients with chronic respiratory conditions who respond positively to pulmonary rehabilitation would not change or shift from frail to pre-frail or move to not-frail. Also, pre-frail patients after PR would not change or shift to not-frail.

Research question and outcomes

The research question: What Fried frailty classification does frail or pre-frail patients move or shift to after positive response to PR.

Or what is the direction of change across Fried frailty classifications by chronic respiratory disease patients who respond positively to pulmonary rehabilitation?

5.4 Methods

This study is a post hoc statistical analysis of the study in chapter 3 that prospectively assessed for the prevalence of frailty in chronic respiratory conditions and comparison of clinical outcomes across Fried frailty status. In the original study, Fried frailty phenotype was prospectively used to assess for frailty to find out its prevalence in chronic respiratory conditions (COPD, Bronchiectasis, Chronic

Asthma, Interstitial Lung Disease, Pulmonary Hypertension, and lung Cancer). Baseline characteristics including BMI and mMRC score and standard pulmonary rehabilitation clinical outcome were used to determine the change in outcome at each individual level of frailty classification. The results of the previous study showed that 18% of chronic respiratory conditions are frail and that PR is effective at all 3 levels of frailty classification and there were no statistical differences between the 3 levels (Normal, Pre-frail and Frail). But it remained unclear what frailty classification level do patient move to following positive response to PR. Therefore, this post hoc analysis of the prevalence of 114 patients with chronic respiratory conditions and PR clinical outcome, aims to find out the direction of responses or change of frailty classification (Normal, Pre-frail, and frail) of the patients with chronic respiratory conditions who respond positively to pulmonary rehabilitation.

Study population

This was a post hoc analysis of 114 patients with chronic respiratory conditions. The population spread of patients' chronic respiratory conditions included COPD, 80/114 (70%), Chronic Asthma 14/114, (12.2%), Emphysema 5/114, (4.38%), pulmonary hypertension, 3/114 (2.63%), lung cancer, 2/114 (1.75%), Bronchiectasis, 10/114 (8.77%). All patients involved in data analysis had undergone PR and frailty assessments.

5.5 Outcomes measures

The primary outcome was Fried frailty criteria – comparing the direction of change or response to post-PR across the 3 levels of classifications.

To understand if frail patients with chronic respiratory conditions move to normal or Pre-frail or do Pre-frail patients move to Normal or remain Pre-frail or change to frail.

And to find out the difference in change between each Fried frailty status.

Secondary outcomes are 4-meter gait speed (to assess for slowness), hand grip

(assessment of peripheral muscle strength), Incremental Shuttle Walk Test (ISWT),

Six Minute Walk Test (assessment of change in exercise capacity), and

COPD Assessment Test (CAT).

To compare which of the secondary outcome predicts change from one frailty classification to the other.

5.6 Statistical analysis

Participant characteristics were summarized using mean and standard deviations (SDs) for continuous variable and or categorical variables such as Fried frailty classification using numbers, percentages, and SD.

The direction of change for all patients and for those that responded favourably to PR (pre-PR versus post-PR Freid frailty status) were tested using two-way tables with measures of association using Pearson's X^{2}. Differences between the 3 levels of Fried frailty classifications were tested using the Kruskal-Walli's test and chisquare as appropriate comparing frailty change post-PR to PR responders. A post hoc pairwise analysis with Bonferroni correction was used to test for the specific significant differences between frailty status.

The magnitude of change for post-PR and frailty clinical outcomes were compared across Fried's frailty status using analysis of covariance corrected for age and sex. To control for Type 1 errors in view of multiple hypothesis/testing at the 3 levels of Fried frailty classifications, Bonferroni correction was applied to a significance level of 0.05.

5.7 Results

Baseline characteristics

One hundred and fourteen patients' data were retrospectively analysed, and their baseline characteristics were 52 men, mean (SD) age 73 (10) years, BMI 27.2 (5.6) kg/m^2, mMRC score 2.2 (0.8), (table 1). The population spread of the chronic respiratory conditions' patients included COPD, 80/114 (70%), Chronic Asthma 14/114, (12.2%), Emphysema 5/114, (4.38%), pulmonary hypertension, 3/114 (2.63%), lung cancer, 2/114 (1.75%), Bronchiectasis, 10/114 (8.77%) (table 1). The directions of change and movement across Fried frailty status with the positive response to PR.

The directions of change and movement across Fried frailty classification were; for Frail patients, 11/23 (47%) remained frail, 12/23 (52%) changed prefrail, and 0/23 (0%, none) changed to Not-frail (Robust); and for Pre-frail patients, 1/63 (1.5%) changed to Frail, 41/63 (65%) changed to Pre-frail, and 21/63 (33%) changed to Notfrail (Robust) and for Not-frail 0/28 (0% none) changed to frail, 8/28 (29%) changed to Pre-frail and 20/28 (71%) changed to Not frail, after pulmonary rehabilitation with a statistically significant difference; X^2 61.15, $p <0.001$ (table 2), and (figure

1). Therefore, in terms of positive response to pulmonary rehabilitation, 52% of Frail patients responded positively whilst 53% of Pre-frail responded positively and 36% of Not-frail responded positively with a statistically significant difference; X^2 17.17, p = 0.002 (table 4). And there was a significant difference between responders and nonresponders X2, p <0.001 (table 3).

Head-to-head comparison of change between frailty status

A post hoc analysis using a pairwise comparison of means with a Bonferroni correction showed that there was a significant difference in the positive responses between the Frail and Pre-frail groups (51.2%, p < 0.001), and between Pre-frail and Not-frail (32%, p= 0.002) but no significant differences in the positive responses between Pre-frail and frail (19.6%, p= 0.432).

The magnitude of change in PR outcome across all Fried frailty classification As previously reported in the main chapter 3, there were no statistically significant differences in secondary outcomes when compared between the 3 levels of Fried frailty classifications after pulmonary rehabilitation (Pre-PR vs Post-PR); mean (SD). Incremental Shuttle Walk Test (ISWT) (m) were; 53 (29 to 77) for Not-frail, 64 (50 to 79) in pre-frail classification, 47 (12 to 83), (p =0.561). And for COPD Assessment

Test (CAT); -0.6 (-3.3 to 2) for Not-frail classification, -1.9 (-3.6 to –0.2) for Pre-frail classification and –0.1 (-2.3 to 2.1), (p=0.410) (table 4). And for handgrip (HG); Notfrail was 0.5 (-1.2 to 2.2), Pre-frail 1.4 (0.3 to 2.6) and Frail 2.7 (1,3 to 4.1) p = 0.270.

And for 4MGS, Not frail was 0.12 (0.03 to 0.20), Pre-frail 0.13 (0.08 to 0.19) and Frail

0.2 (0.09 to 0.31), p = 0.402).

Table 1 Baseline characteristics, n = 114

Characteristics	Number (n), Mean	SD, %
Age	52	
Male	73	10
BMI (kg/m)	27.7 (5.6)	5.6
mMRC (m)	2.2 (0.8)	0.8
COPD n, %	80	70
Bronchiectasis n, %	10	8.77
Chronic Asthma n, %	14	12.2
Emphysema n, %	5	4.38
Pulmonary hypertension n %	3	2.63
Lung cancer n, %	2	1.75
Frail	23	20.18
Pre-frail	63	55.26
Not-frail	28	24.56

Note: Data are represented in number (n), Mean, Standard Deviation (SD), and percentage (%)
Abbreviation: COPD – Chronic Obstructive Pulmonary Disease
BMI – Body Mass Index
mMRC – Modified Medical Research Council Score

Table 2 Direction of change of all patients across Fried frailty status

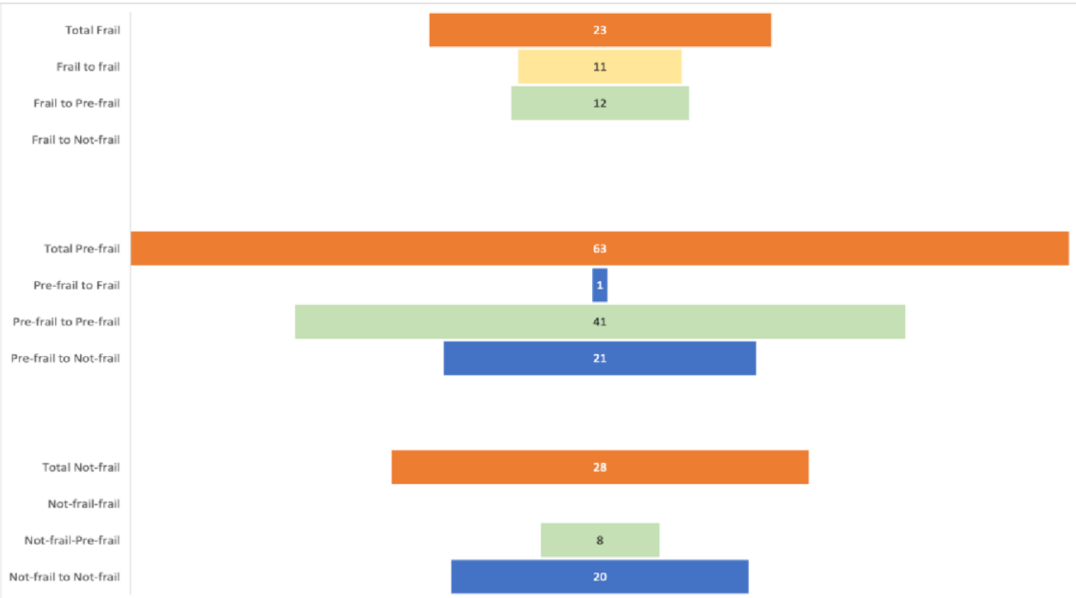
Fried frailty status	Frail N (%)	Pre-frail N (%)	Not-frail N (%)	Person X^2	p-value
Frail	11/23 (47%)	1/63 (1.5%)	0/28 (0%)	61.15	<0.001
Pre-frail	12/23 (52%)	41/63 (65%)	8/28 (29%)		
Not-frail	0/23 (0%)	21/63 (33%)	20/28 (71%)		
Total	23	63	28		

ANOVA with Pearson chi2 (4) and Cramer's V, p-values <0.05

Frail to Frail =11
Frail to Pre-frail = 12
Frail to Not-frail = 0

Pre-frail to frail = 1
Pre-frail to pre-frail = 41
Pre-frail to Not-frail = 21

Not-frail to Frail = 0
Not-frail to Pre-frail = 8
Not-frail to Not-frail = 20



0

0

Figure 1, Direction of change across frailty status

Table 3 Positive responders to PR across Fried frailty status

Response status to PR	Frail	Pre-frail	Not-frail	Total, n (%)	**Pearson X^2** Responders' vs non-responders	p-value
Responders	12/23	49/63	20/28	81/114 (71)	17.3	<0.001
NonResponders	0/23	12/63	21/28	33/114 (29)		

Note: data are presented as Number (n), percentage (%). Pearson X^2, p value < 0.05

Table 4: Kruskal Wallis and Chi-Square for Post PR vs PR responders

Fried frailty characteristics	Pre-PR, n (%)	Post-PR, n (%)	% Change of responders	Post PR vs Responders	
				X^2	P-value
Frail	23 (20)	12 (11)	52	17.17	0.002
Pre-frail	63 (55)	61 (53)	53		
Not-frail	28 (25)	41 (36)	36		

Note: Data presented as Number (n), Percentages (%), X^2 (Chi-Square), p-value < 0.05

Table 5 Bonferroni correction for post hoc pairwise comparisons

Fried Frailty classification	Frail	P value	Not-frail	p-value
Not-frail	51.2%	0.001		
Pre-frail	19.6%	0.432	32%	0.002

Note: data represented as % change p-value <0.005

Table 6 PR and frailty clinical outcome magnitude of change across Fried frailty classification

Clinical outcome	Not-frail	Pre-frail	Frail	P Value
4MGS (m/s)	0.12 (0.03 to 0.20)	0.13 (0.08 to 0.19)	0.2 (0.09 to 0.31)	0.402
Hand grip (kg)	0.5 (-1.2 to 2.2)	1.4 (0.3 to 2.6)	2.7 (1.3 to 4.1)	0.270
ISWT	53 (29 to 77)	64 (50 to 79)	47 (12 to 83)	0.561
CAT	-0.6 (-3.3 to 2)	-1.9 (-3.6 to –0.2)	-0.1 (-2.3 to 2.1)	0.410

Note: Data are represented in Mean, 95% Confidence Interval (CI), p-value alpha < 0.05
Abbreviation: 4MGS – Four-meter gait speed
ISWT – Incremental Shuttle Walk Test
CAT – COPD Assessment Test

5.8 Discussion

In this post-hoc study, we identified that 52% of Frail patients moved to Pre-frail and none moved to Not-frail but 47% remained Frail after pulmonary rehabilitation. Among those with Pre-frail, 33% moved to Not-frail (robust) and 65% remained prefrail and a very small minority (1.5%) changed to Frail. None of the Not-Frail patients moved to Frail, while 29% moved to Pre-frail and 71% remained Not-frail. The results of this study are in line with the previously published data in COPD (none in chronic respiratory conditions) where 55% of the frail who are completers changed to prefrail and 6.1% changed to Not-frail (robust) and only a minority of pre-frail (6.1%) changed to frail[11]. And the study by Kennedy (2019) showed that 23% of frail moved to pre-frail (Kennedy 2019). This study is the only study that has provides data for the direction of movement or changes across Fried frailty status in chronic respiratory conditions.

Although, a significant number of Frail patients remained frail (47%) even though PR showed positive effects across all three Fried frailty classifications with comparable PR clinical outcomes across the three-frailty status. This study clarifies that patients with chronic respiratory conditions who are classified frail using Fried frailty criteria are unlikely to change to Not-frail (robust) after PR – this may be due to the downward disease trajectory of COPD and other chronic respiratory conditions as well as stronger correlation with frequent exacerbation, reduced physical activity, frequent hospitalisation, disability, and death[80]. Also, frail patients demonstrate a high level of impairment in comparison with pre-frail or not-frail patients and may have more extrapulmonary manifestations such as fatigue, weight loss, decreased physical activity and muscle atrophy[19].

Overall, this study identified that a substantial proportion of frail, pre-frail patients with chronic respiratory conditions responded positively to PR and changed their

Fried frailty status, this is consistent with the study in chapters 2, and 3, the work of Maddocks (2016) Mittal (2015), Jones 2015. Over the last few years, pulmonary rehabilitation has been recognised as a treatment modality for frailty management for patients with chronic respiratory conditions irrespective of frailty classification or COPD disease severity.

A systemic review by Kojima and colleagues (2019) described frailty status as a dynamic process with a minimal likelihood of reversing without intervention. In chapter 2 of this thesis and other pieces of literature [11,20,33,42,78] pulmonary rehabilitation has been shown as an effective intervention for Frail chronic respiratory conditions and part of a general multi-disciplinary intervention in chronic respiratory disease management. Since frailty is more multifactorial and can occur without ventilatory impairment and peripheral muscular dysfunction, early assessment and diagnosis of frailty may help clinicians to establish early intervention including pulmonary rehabilitation to mitigate or reserve the frailty condition. Although patients might have a higher risk of adverse events, PR is unlikely to be able to provide meaningful clinical change. Therefore, PR non-responders are likely to be those patients who have advanced pulmonary and extra-pulmonary causes as their primary causes of frailty and may have little or no intervention that is effective in changing the cause of their vulnerability. It has been said that frailty alters the mainstay management of COPD but a few patients who have more respiratory impairment than other causes may still benefit from this internationally recommended standard of care[19]. However, in some patients, a subtle or slight improvement in their clinical outcome and knowledge may declassify their frailty status. Therefore, it means that every patient irrespective of their pulmonary condition severity should be assessed for frailty and planned to undergo evidenced-based exercise programme within pulmonary rehabilitation.

Irrespective of frailty classification pulmonary rehabilitation can modify frailty, moving more half of frail patients to pre-frail with clinically effective outcomes. Since pulmonary rehabilitation can move frail patients in a positive direction it may also offer greater effects if combined with other modalities of frailty management such as fall management, reduction of polypharmacy, nutritional support, self-management, and home physical activity. In 2018, It was suggested that comprehensive geriatric assessment in combination with the frailty index (FI-CGA) can be used clinically to assess the multisystem impacts of ageing and indicate premature ageing (Gale 2018). If FI-CGA or Fried frailty phenotype are used early to assess for frailty, pulmonary rehabilitation may be much more useful to move pre-frail to Not-frail as a preventative model before patients become frail. Unlike the Fried frailty phenotype, the Frailty index use is limited to the use of health status as its measuring tool to assess the vulnerability of ageing and poor outcomes, whereas the Fried frailty phenotype has the strength of assessing physical function, muscle weakness, and exhaustion caused by chronic inflammatory changes in chronic respiratory diseases which provide stronger physical disability, functional capacity decline, falls risk and high healthcare utilization risk107. Earlier assessment using CGA with Fried frailty phenotype can provide a stronger geriatric medical and physical assessment to identify and diagnose frail patients that would benefit from both medical and rehabilitation earlier intervention and positive movement to pre-frailty for those who are frail and not-frail for those who are pre-frail.

There are limitations to consider in this study. Only patients who completed the programme and responded positively to PR were included in this post-hoc analysis, this may have potentially ruled out the possible positive effect of those patients who dropped out due to social or hospital admissions reasons but may have done 50 to 60% of the PR programme. An intention-to-treat analysis may provide a considerable number of patients cohort and a large effect outcome size. Fried physical frailty does not consider cognitive, social, and environmental factors as part of the syndrome of frailty as seen in other frailty assessment measures, but this study only utilised data of those patients who attended PR assessment who can perform a physical assessment, with good cognition and are more likely to engage in a PR programme. A broader frailty assessment measure in conjunction with the Fried frailty model could be used in future studies. Patients with severe frailty at baseline are more likely to have a better response with slight regression to the mean which may cause bias in the results responders, however, this bias may be small.

5.9 Conclusion

Pulmonary rehabilitation can move frailty status to a favourable status irrespective of the frailty classification. This study also reveals that the direction of response or shift of most prefrail patients is not-frail, while that of frail patients is to prefrail. Frail patients are less likely to shift to not-frail after pulmonary rehabilitation, this may be due to the chronic respiratory disease condition's negative trajectory.

Health economic analysis of the impact of pulmonary rehabilitation

Pulmonary rehabilitation as an intervention for frail chronic obstructive pulmonary disease (COPD) patients reveals significant benefits that extend beyond clinical outcomes to cost savings and improved resource allocation within healthcare systems. Pulmonary Rehabilitation interventions have been shown to decrease hospital admissions, and emergency department visits, among frail COPD patients (Jones, 2015). By improving respiratory function, physical fitness, and quality of life, PR reduces the frequency and severity of COPD exacerbations, leading to lower healthcare costs associated with acute care interventions and hospitalizations. The reduction in emergency admissions translates into substantial cost savings for the NHS, including government health programmes. Cost-effectiveness studies have demonstrated that the implementation of PR programs for frail COPD patients yields positive returns on investment by reducing direct medical costs and improving longterm health outcomes (Maddocks, 2016). Frail COPD patients who undergo PR often experience improvements in functional capacity, exercise tolerance, and overall health status. As a result, they may be able to return to work or maintain their productivity levels for a more extended period, contributing positively to the economy and reducing the economic burden associated with disability and unemployment. Moreover, increased workforce participation among COPD patients can lead to higher tax revenues and decreased reliance on disability benefits. While the initial investment in PR programs may incur upfront costs, the long-term economic benefits far outweigh these expenses. By preventing disease progression, reducing disability, and enhancing patient independence, PR interventions result in long-term cost savings by minimizing the need for expensive medical treatments, long-term care, and supportive services (Mei, 2021). Furthermore, PR may delay disease progression and reduce the need for costly interventions such as lung transplantation or long-term oxygen therapy.

The economic value of PR extends beyond monetary savings to encompass improvements in quality of life and patient satisfaction. Frail COPD patients who participate in PR programmes report greater satisfaction with their healthcare experiences, improved psychological well-being, and enhanced social functioning, leading to better overall health outcomes and reduced healthcare costs associated with comorbidities and complications (Gephine, 2022). Higher patient satisfaction may also lead to increased treatment adherence and reduced utilisation of healthcare services.

By investing in PR interventions for frail COPD patients, healthcare systems can optimise resource allocation and improve the efficiency of care delivery. Targeted interventions that address the underlying causes of frailty and COPD exacerbations enable healthcare providers to prioritise high-risk patients, reduce unnecessary healthcare expenditures, and allocate resources more effectively to meet the diverse needs of the population (Wang et al., 2023). Moreover, PR programs may reduce the burden on acute care facilities by preventing unnecessary hospitalisations and freeing up resources for other patients in need of acute care services.

Chapter 6: Integrating Findings and Implications for Clinical Practice in Pulmonary Rehabilitation

5.1 Introduction

Pulmonary rehabilitation (PR) is an established intervention that has shown profound benefits in improving functional capacity, quality of life, and reducing hospitalisations among individuals with chronic respiratory diseases, particularly chronic obstructive pulmonary disease (COPD). However, the integration of findings from previous chapters reveals critical insights into how frailty modifies rehabilitation outcomes and highlights the need for targeted interventions in this vulnerable population. This chapter consolidates the research findings, discusses the implications for clinical practice, and proposes a roadmap for future research.

5.2 Consolidation of Key Findings

5.2.1 Prevalence of Frailty in COPD

The findings from Chapter 4 confirm a high prevalence of frailty among COPD patients, with rates ranging from 20% to 60% depending on disease severity and demographic factors. Frailty is exacerbated by systemic inflammation, physical inactivity, and psychological comorbidities, creating a vicious cycle of functional decline.

5.2.2 Efficacy of Pulmonary Rehabilitation

Chapters 2 and 3 demonstrated the significant benefits of PR in reversing frailty, enhancing functional capacity, and reducing healthcare utilisation. Key findings include:

A 40% reduction in frailty prevalence among participants classified as frail at baseline.

Significant improvements in the 6-minute walk test (6MWT) and reductions in COPD Assessment Test (CAT) scores.

Decreased hospitalisation rates, particularly in frail populations, suggesting PR's role in stabilising health outcomes.

5.2.3 Differential Outcomes in Frail vs Non-Frail Populations

Frail participants exhibited greater relative improvements in hospitalisation rates and psychological well-being compared to their non-frail counterparts. This underscores the unique vulnerability of frail individuals and the potential for targeted PR interventions to yield disproportionate benefits.

5.3 Clinical Implications of Findings

5.3.1 Incorporating Frailty Assessments into Routine Practice

Frailty assessments should be standardised in COPD management. Tools such as the Fried Frailty Phenotype and PRISMA-7 can facilitate early identification, enabling clinicians to tailor interventions to patients' specific needs.

5.3.2 Personalising Rehabilitation Protocols

The heterogeneity of frail COPD patients necessitates personalised PR protocols. Key components include:

Individualised Exercise Regimens: Designing exercise programs based on baseline functional capacity and frailty severity.

Enhanced Psychosocial Support: Addressing anxiety, depression, and social isolation through counselling and peer support groups.

Nutritional Interventions: Incorporating dietetics to address malnutrition and muscle wasting, common in frail populations.

5.3.3 Expanding Accessibility to PR

Geographic and socioeconomic barriers limit PR uptake. Strategies to expand accessibility include:

Developing home-based and telehealth PR programs.

Implementing community-based PR centres to serve underserved populations.

Establishing self-referral pathways to increase enrolment.

5.3.4 Interdisciplinary Collaboration

Managing frailty in COPD requires a multidisciplinary approach. Collaboration among physiotherapists, respiratory physicians, dietitians, psychologists, and social workers is essential for addressing the multifaceted needs of frail patients.

5.4 Broader Implications for Healthcare Systems

5.4.1 Cost-Effectiveness of PR

The reduction in hospitalisations among frail participants highlights PR's cost-effectiveness. By preventing exacerbations and promoting self-management, PR reduces the burden on healthcare systems, particularly in resource-constrained settings.

5.4.2 Aligning with NHS Long-Term Goals

PR aligns with the NHS Long-Term Plan's emphasis on preventative care and reducing health inequalities. By targeting frail COPD patients, PR addresses a high-risk group, contributing to broader public health objectives.

5.4.3 Addressing Workforce Challenges

The demand for PR services necessitates innovative workforce strategies, including:

Upskilling non-clinical staff to deliver components of PR.

Incorporating artificial intelligence to support clinical decision-making and remote monitoring.

5.5 Challenges and Limitations

5.5.1 Methodological Constraints

The studies reviewed in this thesis were primarily observational, limiting causal inferences. The lack of randomised controlled trials (RCTs) specifically examining PR's impact on frailty highlights a critical evidence gap.

5.5.2 Variability in PR Delivery

Heterogeneity in PR protocols complicate cross-study comparisons. Standardising PR delivery while allowing for individualisation based on frailty severity is a delicate balance.

5.5.3 Sustainability of PR Benefits

While the immediate benefits of PR are well-documented, the sustainability of these improvements requires further exploration. Long-term follow-up studies are necessary to evaluate the durability of frailty reduction and functional gains.

5.6 Future Research Directions

5.6.1 Advancing Personalised PR

Future studies should focus on developing and validating tailored PR protocols for frail populations. This includes:

Exploring the optimal intensity and duration of exercise for frail individuals.

Investigating the role of psychosocial interventions in enhancing adherence and outcomes.

5.6.2 Digital and Home-Based PR Innovations

Digital health technologies have the potential to revolutionise PR delivery. Research should evaluate:

The feasibility and efficacy of telehealth PR programs.

Wearable devices for real-time monitoring of exercise and health metrics.

5.6.3 Addressing Health Inequalities

Future research should prioritise underserved populations, examining barriers to PR access and developing strategies to overcome them. This aligns with the broader goal of reducing health disparities in COPD management.

5.6.4 Longitudinal Studies

To understand the long-term impact of PR, future research should:

Conduct longitudinal RCTs examining frailty trajectories post-PR.

Evaluate the economic impact of sustained PR benefits on healthcare systems.

5.7 Conclusion

This chapter synthesises the findings of this thesis, highlighting the transformative potential of pulmonary rehabilitation for frail COPD patients. By addressing frailty, PR not only improves clinical outcomes but also aligns with broader public health goals of reducing hospitalisations and healthcare costs. The integration of frailty assessments, personalised interventions, and interdisciplinary care models represents the future of PR in COPD management. Future research must focus on addressing existing evidence gaps and ensuring the accessibility and sustainability of PR programs to maximise their impact on patient and healthcare outcomes.

Chapter 7: Long-Term Exercise Post-Pulmonary Rehabilitation

7.1 Abstract

Long-term exercise following pulmonary rehabilitation (PR) is essential for sustaining and enhancing the health benefits gained by patients with chronic respiratory diseases. While PR programs significantly improve functional capacity, reduce symptoms, and enhance quality of life, these gains often diminish if physical activity is not maintained post-discharge. This chapter critically evaluates current evidence on the benefits, barriers, and strategies for implementing long-term exercise interventions. It incorporates insights into physiological, psychological, and healthcare system perspectives and identifies gaps in research to propose future directions for optimising patient outcomes.

7.2 Introduction

Chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and interstitial lung diseases (ILD), are characterised by persistent airflow limitation and systemic effects, including muscle wasting and exercise intolerance. Pulmonary rehabilitation (PR) has emerged as a cornerstone intervention, addressing these issues through structured exercise programs and education. However, the sustainability of PR benefits is a growing concern, as many patients revert to sedentary behaviours post-rehabilitation, leading to the decline of physical and psychological gains.

This review explores the critical role of long-term exercise in maintaining the benefits of PR. It examines the physiological and psychological impacts, the current landscape of long-term exercise strategies, and the challenges to adherence. By addressing these aspects, the review aims to highlight the importance of integrated approaches to promote lifelong physical activity in patients with chronic respiratory diseases.

7.3 Physiological Benefits of Long-Term Exercise

7.3.1 Sustaining Muscle Strength and Endurance

PR primarily targets peripheral and respiratory muscle weakness, a hallmark of chronic respiratory diseases. Studies show that long-term exercise preserves muscle mass and strength, reducing the risk of sarcopenia and associated functional decline. Regular aerobic and resistance training, even at low intensities, has been shown to maintain improvements in the six-minute walk test (6MWT) distance and handgrip strength (Jones et al., 2017).

7.3.2 Mitigating Systemic Inflammation

Chronic systemic inflammation contributes to disease progression and comorbidities such as cardiovascular disease and diabetes in COPD patients. Long-term exercise modulates inflammatory pathways, reducing circulating levels of pro-inflammatory markers like C-reactive protein (CRP) and interleukin-6 (IL-6) (Maddocks et al., 2015).

7.3.3 Enhancing Cardiovascular and Respiratory Efficiency

Regular physical activity improves oxygen uptake, cardiac output, and ventilatory efficiency. These physiological adaptations lower dyspnoea severity and increase exercise tolerance, enabling patients to perform daily activities with greater ease (Rochester et al., 2018).

7.4 Psychological and Quality of Life Benefits

7.4.1 Reducing Anxiety and Depression

Anxiety and depression are prevalent in chronic respiratory disease populations, often exacerbating symptom perception and reducing adherence to medical recommendations. Long-term exercise has demonstrated significant effects in alleviating these psychological burdens through endorphin release and improved social interaction in group-based activities (Garvey et al., 2016).

7.4.2 Improving Self-Efficacy

Patients who continue exercising post-PR report higher levels of self-efficacy, defined as the belief in one’s ability to achieve specific outcomes. Improved self-efficacy correlates with better medication adherence, symptom management, and overall engagement in health-promoting behaviours (Bandura, 1997).

7.4.3 Enhancing Social Well-Being

Group exercise programs provide a platform for social interaction, reducing feelings of isolation and fostering a sense of community. Social support has been identified as a critical enabler of long-term exercise adherence (Brooks et al., 2014).

7.5 Current Approaches to Promoting Long-Term Exercise

7.5.1 Home-Based Exercise Programs

Home-based programs are increasingly adopted to bridge the gap between PR and long-term physical activity. These programs often include virtual monitoring tools, such as wearable devices and telehealth platforms, to provide real-time feedback and support (Holland et al., 2017).

7.5.2 Community-Based Exercise Initiatives

Community-based exercise programs leverage local resources, such as gyms and leisure centres, to provide accessible options for patients. These initiatives are particularly effective in addressing geographic and socioeconomic barriers to continued exercise (McCarthy et al., 2015).

7.5.3 Structured Maintenance Programs

Structured maintenance programs extend the benefits of PR by offering supervised sessions at regular intervals post-rehabilitation. These programs provide ongoing professional guidance, ensuring patients remain motivated and engaged (Spruit et al., 2020).

7.6 Barriers to Long-Term Exercise

7.6.1 Patient-Related Barriers

Physical Limitations: Exacerbations and comorbidities can reduce exercise capacity and willingness to participate.

Psychological Barriers: Fear of breathlessness and low self-confidence often deter patients from engaging in physical activity.

7.6.2 Systemic Barriers

Resource Constraints: Limited availability of maintenance programs and insufficient healthcare funding are significant obstacles.

Lack of Coordination: Poor integration between PR services and community-based resources often leads to patient disengagement.

7.6.3 Environmental Factors

Adverse weather conditions, unsafe neighbourhoods, and limited access to exercise facilities further impede long-term adherence.

7.6.4 Future Directions and Recommendations

7.6.5 Personalised Exercise Plans

Tailoring exercise programs to individual needs, considering factors such as disease severity, comorbidities, and personal preferences, can enhance adherence and outcomes.

7.6.6 Integration of Digital Health Technologies

The use of wearable devices and mobile applications to monitor physical activity, provide feedback, and deliver motivational messages can revolutionise long-term exercise adherence. These technologies should be integrated into routine care pathways.

7.6.7 Policy and Funding Reforms

Policymakers must prioritise funding for maintenance programs and community-based initiatives. Collaboration between healthcare providers and local governments can ensure resource allocation aligns with patient needs.

7.6.8 Longitudinal Research

Future studies should investigate the long-term impact of exercise interventions on clinical outcomes, healthcare costs, and patient-reported outcomes. Randomised controlled trials with extended follow-up periods are essential to establish evidence-based guidelines.

7.6.9 Conclusion

Long-term exercise is a vital component of chronic respiratory disease management, sustaining and amplifying the benefits of pulmonary rehabilitation. Despite the challenges, evidence supports the implementation of personalised, accessible, and technology-enabled exercise programs. By addressing barriers and fostering interdisciplinary collaboration, healthcare systems can empower patients to embrace lifelong physical activity, ultimately improving outcomes and quality of life.

Chapter 8: Clinical outcomes, physical characteristics, and impact of frailty in post-COVID syndrome.

8.1 Abstract

Background

Post-COVID-19 syndrome describes symptoms of COVID-19 that persist 3-4 weeks after acute illness[108]. Post-COVID-19 syndrome may also be described as chronic or

Long COVID if it persists beyond 12 weeks[109,110]. NICE COVID-19 guideline (NG188, 2020), defines post-COVID-19 syndrome as signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.

The post-COVID-19 syndrome could potentially become a long-term public health issue if adequate planning and research into the needs of COVID survivors are not carefully considered. Hospitalized patients who are discharged daily from hospitals in the UK or managed at home, amidst the high rate of mortality, have continued to experience ongoing symptoms post-discharge termed post-COVID syndrome or Long COVID. It is critical to understand the long-term impact of post-COVID syndrome symptoms experienced by survivors to plan and develop appropriate clinical and social care required to support these survivors.

Post-viral fatigue symptom is widely reported and highly prevalent in post-COVID syndrome. However, hospitalised patients may have acquired ITU neuropathy causing peripheral muscle weakness, slowness, and exhaustion; and nonhospitalised patients may have severe fatigue, poor

exercise tolerance and breathlessness with little or no intervention. Exhaustion, poor exercise tolerance, slowness and muscle loss are features of frailty and are displayed by both postCOVID groups, these could result in frailty causing an impact on their post-COVID syndrome. Frailty is widely reported in the paucity of evidence in chronic respiratory conditions due to chronic inflammatory changes, muscle weakness, ageing and comorbidity. And post-COVID syndrome shares the same inflammatory changes, muscle weakness and slowness but there is no data to suggest if frailty is part of the post-COVID syndrome.

Therapy interventions are now widely provided in many UK post-COVID services to manage various symptoms from breathlessness to fatigue and brain fog, however, it is unclear if these interventions are effective. Also, to date, it is unclear if frailty is an associated symptom and its impact on clinical outcomes in hospitalised and nonhospitalised post-COVID patients. Therefore, this retrospective data analysis aims to find out the clinical effectiveness of therapy intervention by measuring the clinical outcome and finding out the impact of frailty on post-COVID syndrome patients and their physical characteristics.

Methods: design and settings

Design

This is a retrospective data analysis and population-stratified cohort study, following up with patients with signs and symptoms of post-COVID-19 syndrome developed 12 weeks after hospital discharge for acute COVID-19 and those who have continued to suffer symptoms of COVID-19 12 weeks aftercare in their own home. Patients were referred from the respiratory post-COVID-19 follow-up clinic or their general practitioner following a comprehensive medical assessment, medical imaging, and blood investigations.

Settings: Patients were seen at health centres across the London Borough of Barnet. Proximity was considered in managing patients' experiences and journeys – this study was done after the 1st, 2nd and 3rd waves of the COVID-19 pandemic in the UK.

Participants: Retrospective data analysis of 200 patients with hospital admission and without hospital admission who had been reviewed in Barnet post-COVID-19 clinic. All reviews followed a protocol-guided clinical assessment and self-reported questionnaires.

Results

The results demonstrate that therapy interventions were effective in both hospitalised and non-hospitalised post-COVID patients with statistically significant differences comparing pre- and post-therapy interventions in all outcome measures (primary and secondary), mean (SD) (CI, Confidence interval) at significant levels $p<0.05$ Table 2. Within the group analyses using ITT, there was a significant improvement in quality of life in the italicised group, measured by EQ5DL, pre vs. post, 15 (9.5) (CI 11 to 19) vs. 11 (4.9) (CI 9 to 13), $p< 0.05$. Although there was no statistically significant improvement in quality of life in the non-hospitalised group, the result was promising as showing clinically significant difference in EQ5DL, pre vs. post, 10 (2.6) (CI 9 to 11) vs. 10 (3.4) (CI 9.4 to 11) $p= 0.22$. There was significant improvement in fatigue (FAS), in the hospitalised group, pre vs. post; 30 (CI 26 to 34) vs. 27 (CI 23 to 30); $p < 0.04$ and in the non-hospitalised group, 33 (CI 31 to 36) vs. 31 (CI CI 28 to 33); p< 0.006, also when compared hospitalised vs none hospitalised, there was a significant difference between the two groups, with non- hospitalised feeling less fatigue, p < 0.037. Breathing pattern disorder also improved (BPAT) in hospitalised group, pre vs. post, 4 (CI 3.1 vs. 1.3) vs. 2.9 (CI 1.3 to 4.5), p<0.01. Similarly, in non-hospitalised group, breathing pattern disorder got better with BPAT showing, pre vs post 3.2(2.3) (CI 2.9 to 4.5), p<0.003. But there was no difference between hospitalised and non-hospitalised group, both feeling much better same way, breathing rightly, and dealing with symptoms therein.

And with physical frailty using Fried Frailty criteria, the result showed that 36% (65/179) of the post-COVID patients in our population are frail, with hospitalised patients showing frailer post-COVID patients 30% (54/179), while non-hospitalised 6% (11/179). Pre-frailty is much common in both post-COVID syndrome groups, 57% pre-frailty in hospitalised group and 75% in the non-hospitalised group. Overall,

32% of post-COVID syndrome are not frail.

Conclusion

Post-COVID therapy and rehabilitation are effective with the patient in hospitalised and non-hospitalised post-COVID syndrome patients, with significant improvement in their quality of life. However, 36% of post-COVID syndrome patients are frail and frailty is higher among hospitalised patients due to deconditioning.

8.2 Introduction

The coronavirus disease 2019 termed COVID-19 which first originated in Wuhan, China was declared a global pandemic by World Health Organization in March 2020[1].

It rapidly spread across the world and caused a sudden significant increase in hospitalisation due to pneumonia and multiorgan failure, By July 2020, SARS-CoV-2 has spread to more than 200 countries and infected more than 10 million people and caused 508,000 deaths.

COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARSCoV-2). SARS-CoV-2 infection may be asymptomatic, or it may cause a broad spectrum of symptoms from mild symptoms of upper respiratory tract infections to life-threatening critical illness and sepsis.

During the acute phase of the illness a substantial proportion of people presented with a range of common symptoms. Common symptoms include cough, fever, breathlessness, fatigue, myalgia, and joint pains. Other symptoms include anosmia/dysgeusia and gastrointestinal symptoms.

Lately, a new emerging condition called Long COVID or post-COVID syndrome has become known due to persistent symptoms that remained after the acute phase of the illness. Post-COVID syndrome involves a cluster of symptoms such as breathlessness, cough, fatigue, headache, brain fog, reduced exercise tolerance, chest pain, anxiety, and depression. However, hospitalised patients may have acquired ITU neuropathy causing peripheral muscle weakness, slowness, and exhaustion; and non-hospitalised patients may have severe fatigue and breathlessness with little or no intervention. Exhaustion, slowness, and muscle loss are features of frailty, and frailty is widely reported in the paucity of evidence in chronic respiratory conditions due to chronic inflammatory changes, muscle weakness, ageing and comorbidity. To date, there is no evidence that frailty is a symptom of post covid syndrome and the physical characteristics of hospitalised and non-hospitalised post-COVID syndrome patients are not known.

This study also aims to find out if therapy interventions are effective and result in positive clinical outcomes for hospitalised and non-hospitalised post-COVID syndrome.

8.3 Pathophysiology of COVID-19 infection

Coronavirus is an enveloped single-stranded RNA virus found in humans and other animals such as dogs, cats, chickens, cattle, pigs, and birds. Coronavirus causes a range of diseases affecting the respiratory, cardiac, gastrointestinal, and neurological systems.

In clinical practice, the most common coronaviruses are HKU1, NL63, 229E and

OC43and are the cause of common cold symptoms in immunocompetent individuals. In the past two decades, there have been three types of coronaviruses identified that have caused severe diseases in humans. SARS-CoV-2 is the third and the most widely spread across the world. From 2002 to 2003, severe acute respiratory disease (SARS-CoV-2) caused the first pandemic – this was thought to have originated from

Foshan China. The second was in 2012, caused by a coronavirus and termed Middle East respiratory syndrome (MERS), which originated from Arabian Peninsula.

SARS-CoV-2 are naturally present in bats, but it has been suggested humans became infected through an intermediate host such as pangolin. Pangolin is an expensive meat delicacy in China and Vietnam. Genetically, coronavirus can adapt and infect new people through adaptation and recombination characteristics. SARSCoV-2 has a structural spike which gave the virus its solar corona appearance. Its diameter is 60nm to 140nm and the spike diameter range from 9nm to 12nm.

8.4 Mechanism of infection

At the early stage: Binding and entering the host

SARS-Cov-2 has a predilection for the upper (nasal) and lower (bronchial) airways, epithelial cells and pneumocytes of the host. Using its spikes, it binds to the angiotensin-converting enzyme 2 (ACE2) receptor cell present on the host cell. After the binding, the cleavage of ACE2 and SARS-Cov-2 S protein occurs, and it is promoted by type 2 transmembrane serine protease (TMPRSS2) present on the host cell to cause mediation of coronavirus entry into the host cells.

Inflammatory response at an early stage

The inflammatory responses seen in SARS-CoV-2 are like other viral respiratory diseases such as influenzas. However, significant lymphopenia occurs due to Tlymphocytes death caused by SARS-CoV-2 infection.

These significant lymphocytes apoptosis and lymphopoiesis are due to a combination of the innate (humoral) and adaptive immune responses (cell-mediated)

Inflammatory response at a later stage

At this stage, there is an acceleration of viral replication causing a compromise of the alveoli epithelial–blood capillary endothelial barrier, and the level of SARS-CoV-2 infection of the endothelial accentuates the inflammatory response resulting in an influx of monocytes and neutrophils. In addition to the endothetilitis, alveoli wall thickening occurs due to airspace infiltration by mononuclear cells and macrophages – causing alveolar oedema and ground-glass opacity to be seen on tomographic imaging. In the acute phase, a typical ARDS picture is seen due to pulmonary oedema filling the alveolar spaces with hyaline membrane formation. This stage resulted in a collective pulmonary capillary endothelium barrier disruption, dysfunctional alveoli-capillary oxygen transmission, and impaired oxygen diffusion capacity – a clinical characteristic feature of COVID-19.

8.5 Post-COVID-19 Syndrome

Post-COVID-19 syndrome describes symptoms of COVID-19 that persist 3-4 weeks after acute illness (Lads et al, 2020). Post-COVID-19 syndrome may also be described as chronic or Long COVID if it persists beyond 12 weeks [109,110,112]. 10-20% of patients with COVID-19 experience symptoms beyond 3-4 weeks and 1-3% are still significantly unwell after 12 weeks[113].

People with persistent symptoms are classified into three broad groups: people with long-term respiratory symptoms dominated by breathlessness after hospitalisation with acute respiratory distress syndrome (ARDS); people without hospital admission but now have a multisystem disease with evidence of cardiac, respiratory or neurological end organ-damage manifesting in a variety of ways; and people who have persistent symptoms often dominated by fatigue without evidence of organ damage[106]. There is still more work to be done to understand persistent symptoms in people without hospitalisation. The cause of persistent symptoms is unknown but has been thought to involve several different disease mechanisms including an inflammatory reaction with a vasculitis component[118].

In December 2020, the UK National Institute of Care and Clinical Excellence (NICE) and Scottish Intercollegiate Guideline Network (SIGN) published a COVID-19 rapid guideline (NICE, COVID-19, 2020), and defined acute COVID-19, ongoing symptomatic COVID-19, and post COVID-19 syndrome in a comparable way to those seen in the most available evidence. Acute COVID-19 is defined as signs and symptoms of COVID-19 for up to 4 weeks; ongoing symptomatic COVID-19 as signs and symptoms of COVID-19 from 4 to 12 weeks and post-COVID-19 syndrome as signs and symptoms that develop during or after an infection consistent with COVID19, continue for more than 12 weeks and are not explained by an alternative diagnosis. NICE COVID-19 guideline (NG188, 2020) reported that the symptoms of ongoing symptomatic COVID-19 and post-COVID-19 syndrome as highly variable and wide-ranging. The

commonly reported symptoms include Respiratory symptoms (breathlessness and cough), cardiovascular symptoms (chest tightness, chest pain, palpitations), generalised symptoms (fatigue, fever, pain), neurological symptoms (cognitive impairment ('brain fog', loss of concentration or memory issues) headaches, sleep disturbance, peripheral neuropathy symptoms, dizziness and delirium), gastrointestinal symptoms (abdominal pain, nausea, diarrhoea, anorexia and reduced appetite), psychological/psychiatric symptoms (depression and anxiety), musculoskeletal symptoms (joint pain, muscle pain), ENT symptoms (tinnitus, earache, sore throat, dizziness, loss of taste and smell) and dermatological
(skin rash) (NICE COVID, 2020).

Symptoms of fatigue, breathlessness, reduced exercise tolerance and cognitive impairment ('brain fog') are most prevalent in ongoing symptomatic COVID-19 and post-COVID-19 syndrome[120]. However, those admitted to the hospital who had lung parenchyma changes on computer tomography (CT) and whose long-term breathlessness is due to ARDS, COVID pneumonitis, and prolonged ITU stay may also suffer from physical or mental pain frailty because of prolonged inflammatory cytokines on lung parenchyma and ITU acquired muscle weakness. In the same vein, those who were not admitted have continued to suffer from persistent symptoms of fatigue, exhaustion, pain, and exercise, but no evidence to show if they may also exhibit frailty due to fatigue, exhaustion and slowness they suffer from. Therefore, this study aims to assess for frailty in post-COVID syndrome, in both hospitalised and non-hospitalised patients. Also, to identify the physical characteristics of post-COVID patients and the predictive factor for frailty.

8.6 Frailty in ITU and long-term conditions

Although frailty is traditionally reported secondary to age-related decline, however, a few recent studies have reported that frailty is present in around 30% of patients admitted to ITU and is associated with longer ITU stay and adverse post-discharge outcomes[121]. Also, in 2022, Davall and colleagues, reported that patients with frailty are at greater risk of developing persistent illness and substantial healthcare resource utilisation. These seem like what we see in post-COVID syndrome in both ITU/ward-based hospitalised patient groups and non-hospitalised groups. Does it then mean that post-COVID patients may exhibit the frailty phenomenon? This remains unclear.

Frailty screening in long-term conditions is now common and advocated as part of a care bundle to manage long-term conditions as it contributes to better clinical outcomes, improves the management of at-risk frail adults, reduced symptoms burden, healthcare utilisation and unplanned hospitalisation[4,12]. The long-term nature of symptoms of the post-COVID syndrome (persistent symptoms over 12 weeks) is likely to classify it as a long-term condition with symptoms like those found in classic frailty, such as exhaustion, muscle loss and weakness, slowness, and reduced exercise tolerance. These characteristics are those suggested in the Fried frailty phenotype[7].

The National Institute for Health and Care Excellence (NICE) released a multimorbidity clinical guideline in 2016, it recommends that adults with multi-morbidity or who are at risk of adverse events such as unplanned hospital admission, and persistent healthcare utilisation should be screened for frailty with a validated frailty tool such as Fried frailty criteria. In the previous chapters 2-4 of this thesis, we have learnt that pulmonary rehabilitation can reserve frailty and move frail and pre-frail patients to better frailty status. Therefore, earlier assessment of post-covid patients may provide a favourable outcome after therapeutic intervention.

The definition of frailty using the Fried frailty phenotype is the presence of at least 3 or more of 5 established criteria for frailty; weakness, slow gait, exhaustion, low physical activity, and weight loss. People with one or two criteria are defined as intermediate frail or prefrail, those with 3 or more of the criteria are defined as frail and those with no (zero) are defined as not frail.

8.7 Fried frailty phenotype model

Physical frailty is assessed using the Fried frailty phenotype model. The fried phenotype model is an established and validated tool from a large epidemiological study. This model has been used in chapter 2 through 4 and helped to assess frailty pre and post pulmonary rehabilitation. It showed sensitive to assessing baseline frailty status, response to pulmonary rehabilitation and detection of changes and movement across Fried frailty criteria.

8.8 Research protocol

Aim and objectives.

1. What is the clinical effectiveness of multidisciplinary therapy intervention post-COVID-19 syndrome rehabilitation in improving patient-reported outcomes such as EuroQoL 5 Dimension Level (EQ5DL), Fatigue Assessment Test (FAS) and

   Exercise capacity such as 6MWD?
2. Are the physical and clinical characteristics of hospitalised and home population groups different.
3. Does effectiveness vary between hospitalised and home population groups?
4. What is the clinical effectiveness of exercise interventions such as physical activity for people with post-COVID-19 syndrome?
5. What is the prevalence of frailty in Post COVID syndrome?

8.9 Purpose of the study

In line with NICE recommendation for research [1], The purpose of this study is to find the effectiveness of therapy intervention on post-COVID syndrome.

In line with NICE recommendation for research [2] find out if patients suffering from the post-COVID syndrome are frail. and compare prevalence in hospitalised and non-hospitalised patients.

8.10 Methodology

Study design and setting

All patients analysed in this study are those seen by the Barnet post-COVID clinic. All patients were referred by the post-COVID-19 respiratory outpatient follow-up clinic based at Barnet General Hospital London and Royal Free London Hospital or by their General Practitioner (GP) and have been diagnosed with post COVID syndrome. All patients must have had a comprehensive medical assessment, blood investigation, and imaging before referral for a risk assessment. Patients are invited to our Multidisciplinary post-COVID-19 clinic following an initial telephone screening for symptoms of acute COVID-19 as per hospital protocol and symptoms of the post-
COVID-19 syndrome.
This is a retrospective data analysis study, therefore does not involve additional intervention to the participant. The patient had their routine assessment, care and 6 week follow up before their result is being used for data analysis.

Eligibility criteria

Data analysis involved 200 patients who have attended Barnet CLCH post-COVID clinic who were previously confirmed SARS-CoV-2 using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) and have also been confirmed negative to SARS-CoV-2 using RT-PCR at the time of study and complained of have signs and symptoms of post COVID syndrome having attended post-COVID-19 respiratory medical assessment clinic at the Royal Free Hospital London, Barnet Hospital London, or their General Practitioner.

Primary outcome measures

1. Post-COVID-19 Functional status (PCFS): PCFS, is a validated ordinal tool that measures the full spectrum of functional outcomes following COVID-19. PCFS can be used for tracking functional status over time as well as for research purposes
2. EQ5DL (Euro Quality of life Measure 5 dimension) - This validated generic quality of life measure is used to estimate health benefits in terms of qualityadjusted life-years (QALY) and it is a patient-related outcome measure
   (PROM).

Secondary outcome measures

1. 6-minute walk distance (6MWD): The 6MWD is a validated measure of functional exercise capacity[30] in chronic respiratory disease. The 6MWD predicts both future hospitalisation and survival. It is responsive to change the following rehabilitation and responsive to a patient with ambulatory oxygen desaturation. The test will be performed per ERS/ATS technical standard[30.] including two tests at each time point, with the better (i.e., longest distance) 6MWD recorded.

   6MWD is particularly important to measure in post-COVID syndrome, although not validated for it is a good measure of exercise capacity (exercise tolerance), and a predictor of peripheral peak oxygen uptake ($V0_{2Max}$) in patients who had a respiratory diagnosis and long ITU stay. It is hoped that it can predict exercise intolerance, muscle weakness and deconditioning in post-COVID patients.

2. Borg breathlessness assessment (Borg): It is a measure of breathlessness during activity or exercise. The Borg score has been used in most studies investigating the effects of exercise or physical activity as an intervention in pulmonary rehabilitation.
3. Breathing pattern assessment tool (BPAT): BPAT (score 0 to 14), evaluates an aspect of breathing (including, rate, flow, pattern, rhythm, and air hunger). And it is an assessment of breathing pattern disorder or dysfunctional breathing122.
4. Work and Social adjustment Scale (WSAS): WSAS is a simple, reliable, and valid measure of impaired functioning. ("Supported Internet-Delivered

Cognitive Behaviour Treatment for Adults ...") ("Supported Internet-Delivered Cognitive Behaviour Treatment for Adults ...") "It is a sensitive and useful outcome measure offering the potential for readily interpretable comparisons across studies and disorders." ("The Work and Social Adjustment Scale: a simple measure of ... - PubMed")

5. Fatigue assessment score (FAS): The fatigue assessment scale is a simple and reliable tool to assess the impact of disease activity on fatigue (Shahid et al, 2012).

8.11 Therapy assessment

A holistic assessment and consider all aspects of patient need relating to post- COVID syndrome (PCS). This will typically be therapy led. Therapy interventions to are provided immediately after assessment with written down prescription on therapy prescription sheet. The following are the therapy that are offered after assessment; pacing, breathing pattern management, fatigue management, walking using pedometer step count within 40-50Vo2mx of target HR, conservative autonomic dysfunction management with 2-3L fluid daily, pressure garment, salt intake. Also offered are anxiety and depression management and managing concentration, brain fog and return to work.

Outcome measures

Full detailed clinical assessment is explained below in line with management plan. However, the following outcome measures are agreed across North Central London to identify symptoms and impairments to support clinical reasoning and plan appropriate care plan.

1. Breathlessness:
   - Borg score from 0-10, minimal clinically important difference (MCID): 1point.
   - MRC dyspnoea scale: from 1-5. MCID: 1point.
   - Dyspnoea-12: from 0 to 36, with higher scores corresponding to greater severity. Questions 1-7 (mechanical causes) 8-12 (psychological triggers).

     MCID: 3 points.
2. Breathing pattern:

- The Brompton Breathing Pattern Assessment Tool (BPAT): a score of >4 is indicative of a breathing pattern disorder (BPD).
- Nijmegen questionnaire: a score >23 is considered a positive score for hyperventilation syndrome/ biochemical causes.

3. Post COVID -19 functional status: grades from 0 to 4, where grade 0 reflects the absence of any functional limitation and 4 severe functional limitations requiring assistance with ADL's. MCID: 1 grade.
4. Frailty syndrome scale – graded from 0 to 5, where 0 is not frail, 1-2 is prefrail, >3 frail, based on the following criteria:
   - Weight lost screen
   - Exhaustion: using CES-D
   - Weakness: positive if Grip <18kg in females and <30kg in males.
   - Walking speed: slow if F <0.6m/sec, M <0.8m/sec on 4 meters gait speed, for which MCID is 0.11 m/sec.
   - Physical activity level

5. Exercise induced desaturation and exercise tolerance:
   - 6MWT: to assess the functional status of patients, exercise intolerance, their response to treatment, and their prognosis by comparing the measured distance with the predicted value. MCID: 30 m
   - 1 minute sit to stand: for post exertional HR and breathlessness, where a high HR and chest pain could indicate PE, triggering a referral to respiratory consultant.
6. Fatigue:

- Fatigue assessment scale (FAS): with scores from 10-50, where a scores from 22-34 indicates fatigue and ≥35 extreme fatigue. MCID: 4 points.

  or

- FACIT Fatigue Scale on the Living with COVID app. With scores from 0 to 52, where a score < 30 indicates severe fatigue.

7. Quality of life:

- EQ5DL: assesses health in five dimensions (mobility, self-care, ADL's, pain/ discomfort, Anxiety/ depression) EQ-VAS (0-100 scale) where patients indicate their overall health.
- Work and Social Adjustment Scale ("WSAS"): measure for impairment in functioning. Total score ranges from 0 to 40, with higher scores denoting higher levels of disability. A score ≥ 20 indicates moderately severe impairment and scores of 10-20 representing significant functional impairment.

8.12 Therapy intervention

The following therapy interventions are the standards with Barnet Post COVID Service with Central London Community Healthcare NHS Trust in agreement with

North Central London Post COVID service.

A. Fatigue/ post exercise malaise

1. This can be a long-lasting symptom post-COVID and is considered alongside other symptoms such as breathlessness/ brain fog

2. Ask about the duration of post exercise malaise (lasting > 12 hours or to the following day is suggests is significant)

Treatment plan:

Avoid boom and bust, daily uninterrupted break in the day, advised patient to have a daily routine and do half of usual activity of daily living, half the volume of work pattern.

B. Reduced exercise tolerance and walking distance:

Avoid aerobic exercise especially with patients with post exertional symptoms exacerbation (PESE) and severe fatigue, only physical activity is recommended such as walking, in some cases swimming but very limited to 10-15mins and if having muscle deconditioning strength exercise such as isometric quadriceps leg strengthening and calf standing**.** If post exercise malaise is <12 hours and Borg at rest is 1-2 and Borg on exertion is below 5-6 you patient are set up on walking physical activity with a target HR of 4060Vo2max but starting low at about 40 to 45% Vo2Max. 1000 steps a day with a Target Heart Rate used to guide when to stop activity. But conducting a one week walking step base line is best practice. This prescription is followed up on the telephone on a weekly basis.

C. Breathing pattern disorder:

After the performance of assessment for breathing pattern and dysfunctional breathing, note if patient is breathing in and out with mouth open and if upper chest is moving more than lower (diaphragm), note RR in 1 minute > 14 is a sign of hyperventilation with symptoms of dizziness, frequent yawning, fatigue, and tiredness. Identify triggers and teach breathing pattern retraining, breathing control and relaxation. Also note result of Nijmegen, a score of over

23 is suggestive of diagnosis of hyperventilation syndrome.

Treatment plan will include:

Practicing diaphragmatic breathing, breathing through the nose in and out, avoid noisy breathing but gentle and controlled respiratory rate 12-14 per minute. Patient to practise in lying or stiing 2-3 mins each session 2-3 times a day.

Self-management

MRC breathlessness scale assessment used to signpost for appropriate selfmanagement ○ If 1-2, signpost to Your Covid Recovery for self-management, with online resources on different area of symptoms to help selfmanagement.

- If 3 and no other red flag symptoms refer to community rehabilitation.
- If 4+ refer to post-COVID-19 Clinic

8.13 Statistical analysis

Data analyses were carried out using Stata statistical analysis Version 16.0 Stata Corp, College Station, LLC Texas USA.

Measures such as mean and standard deviation were used to summarise continuous variables such as age, BMI, 6MWT, Fatigue assessment score, 4MGS, CES-D, MRC score, Borg breathlessness score, hand grip strength, and breathing pattern disorder (BPAT). And tables were used to report the numbers and percentages of categorical variables such as Fried frailty classifications. Proportion analyses were used to identify the prevalence of frailty and physical characteristics of post-COVID syndrome patients.

Intention-to-treat analyse (ITT) with student paired t-test was used find out clinical outcomes after therapy in all patients group to account for incomplete data of those patients who did not turn up for final assessment. Intention to treat analysis with Student paired t-test was also used to analyse the change in clinical outcome after 6 weeks of therapy for both hospitalised and non-hospitalised patients. A sub-analysis of within-group change was done using an unpaired t-test.

Multiple linear regression was used to find out predictive factors for frailty in post

COVID syndrome, with 3 frailty classification being the dependent variable.

8.14 Results

Comparison of baseline demography and clinical characteristics

Acknowledging that it can be a complex clinical activity to collect full data from frail post-COVID patients due to re-infection with acute COVID-19, ongoing clinical investigations, and complex symptoms such as chest pain preventing patients from attending follow up clinic. This is a landmark analysis comparing baseline clinical characteristics and post therapy clinical outcomes, of hospitalised and nonhospitalised (home) patients post-COVID patients. Of the original 350 patients seen in clinic, complete data of 179 patients were included in the analysis.

The baseline characteristics of hospitalised and non-hospitalised patients were statistically different in both demography and baseline clinical data. This shows that patients who had COVID-19 and were admitted to hospital are different in their demography and baseline clinical characteristics to those patients who had COVID19 and remained at home with no treatment. Baseline gender characteristic showed that there were more female affected with post COVID syndrome in both groups but are more in home patients (76% vs 57%) with significant difference (p <0.001), therefore both groups are not comparable looking at the gender difference. This result is in line with gender post–COVID syndrome prevalence across the literatures and in the UK. Hospitalised patients are more obese with high BMI 32.2 in comparison to 28.9 seen in home patients and statistically different (p = 0.003). This is the first time this data has been recorded and could explain why hospitalised postCOVID patients were admitted in the first place and why they are less likely to survive acute COVID-19 infection especially if they have comorbidity like diabetes.

Hospitalised patients had higher baseline clinical characteristics than nonhospitalised patients and statistically different except fatigue score (FAS), these were represented by mean (SD) and p-value; (MRC 3 (0.9) vs 2.6 (0.9), p = 0.001), (Borg 2.6 (1.7) vs 2.4 (1.9), p = 0.34), (FAS 31 (8.3) vs 33 (8.6), p = 0.04), (PCFS 2.9 (0.6) vs 2.1 (0.8), p = 0.09), (6MWT 237 vs 354, p = 0.000), EQ5DL 14.5 (7.8) vs 11.30 (3.1) p = 0.000).

Fatigue assessment score (FAS) showed that non-hospitalised patients (home) are more likely to show symptoms of fatigue more than hospitalised post-COVID syndrome (33 (8.6) vs 31 (8.3), p 0.188.

Prevalence of post-COVID syndrome

The prevalence of frailty in hospitalised post-COVID syndrome patients was 30%

(95% confidence interval (CI), (13.52 to 45.83) whilst that of non-hospitalised was 6% (1,57 to 24.19), these gave the total prevalence of frailty in post-COVID syndrome as 36% at baseline (Table 2). Although the majority of are prefrail with a total of 141% in both groups, and not frail was 32% (Table 2) in both groups.

A scatter plot diagram Figure 1. showed the likelihood of the baseline clinical features to cause frailty – mostly seen were FAS, GAD 2, BPAT, WSAS, Dypsnoea12. Interestingly BMI and 6MWT showed a dichotomy layout and may not influence frailty. In non-hospitalised (home patients) group GAD-2 (anxiety) were the most predictive factor of frailty and statistically significant, %, (CI), 37% (0.01 to 0.20), (p = 0.029), followed by FAS (fatigue), 9% (-0.01 to 0.02), (p=0.594), Dysponea-12, (9% (-0.01 to 0.02), BPAT, 9% (-0.09 to 0.05), (p= 0.536), and WSAS (work and social adjustment), 6% (-0.19 to 0.18) (p=0.966) although these were not statistically significant but showing a good prediction. The least predictive was PCFS, 3% (-0.18 to 0.19), (p= 0.978).

In the hospitalised group, WSAS, GAD-2, PCFS and FAS were more predictive of frailty than others although not statistically significant. WSAS

36% (-0.09 to 0.025) (p=0.26), GAD-2, 31% (-0.17 to 0.47) (p=0.32), PCFS, 31% (-0.02 to 0.08), (P= 0.22), FAS, 23% (-0.09 to 0.04) (-0.09 to 0.04), BPAT, 23% (-0.34 to 0.13), (p=0.35), and Dyspnoea-12, 6.1% (-0.79 to 0.06), (p=0.81), being the least predictive of frailty in hospital group.

Primary and secondary outcomes measures

All groups

There was a significant difference in all clinical outcomes; (Mean, Standard deviation (SD), 95% Confidence Interval (CI), in both patients group after 6 week therapy intervention including Health Related Quality of Life measure EQ5DL; 0.353 (2.149) (0.006 to 0.700), p =0.02, breathing pattern disorder, BPAT; 1.63 (2.63) (0.802 to 2.465, p < 0.001, and Fatigue FAS; 1.25 (5.02) (0.270 to 2.234), p < 0.006. As well as MRC score; 1.108 (0.94) (0.02 to 1.96) p =0.008. This reflects the effectiveness of a multidisciplinary therapy intervention in post-COVID rehabilitation.

Hospitalised vs Home (non-hospitalised)

Following completion of the 6-week therapy, significant improvements were observed across both hospitalised and non-hospitalised groups for EQ5DL (primary outcome), FAS, BPAT, Borg, GAD-2, 6MWT and 1min STS (secondary outcomes) (table 3). There was a statistical difference after therapy in EQ5DL in hospitalised patients than non-hospitalised patients, (mean difference, p-value), (4, p< 0.05, vs 0.31, p=0.22), however, the non-hospitalised group were tending towards statistical difference. The difference in both groups could be due to hospitalised patient being sicker than home patients and a slight improvement in their symptoms may be reported as being significant. All secondary clinical outcomes improved in the same manners in both groups with statistically significant differences after therapy except

Dypnoea-12 (table 3).

Table 2 Comparison of baseline demography and clinical characteristics of post COVID syndrome n=179

Characteristics	Hospitalized (Hospital group)	Non-Hospitalised (Home group)	p-value
Participants (n)	60	119	
Age, years (median, IQR)	57	48	< *0.001
Sex, n (%)	Male 26 (43%), Female 34 (57%)	Male 29 (24%), Female 90 (76%)	< *0.001
BMI, (kg/m2)	32.2 (7.3)	28.9 (7.24)	*0.003
MRC dyspnoea score	3.0 (0.9)	2.6 (0.9)	*0.001
Borg breathlessness score	2.6 (1.7)	2.4 (1.9)	0.347
PCFS	2.9 (0.6)	2.1 (0.8)	0.096
EQ5DL	14.5 (7.8)	11.30 (3.1)	< *0.001
BPAT	4.2 (2.2)	3.8 (2.3)	0.1884
FAS	31 (8.3)	33 (8.6)	*0.04
Dyspnoea 12	11 (8.8)	13 (9.1)	0.08
WSAS	21.2 (11.2)	20.8 (9.8)	0.411
6MWT	237 (110)	354 (121)	<*0.001

Notes: Values are presented as mean ± SD or number (%), median, inter quartile range (IQR), *p < 0.05*p < 0.05; *p<0.001; *p<0.0001 Abbreviations: BMI, body mass index; MRC, Medical research council dyspnoea score; EQ5DL, Euro Quality of Life 5-dimension level; BPAT; Breathing Pattern Assessment Test; WSAS, Work and Social adjustment Score; 6MWT, Six-Minute walk test; FAS, Fatigue assessment test, Post COVID Functional Status (PCFS) *Significant differences between hospitalised and home group at baseline

Table 2 Change in clinical outcomes for all patients with the intention to treat analysis of baseline available and missing data, n=179

Variables	Mean diff (SD)	95% CI	p value
MRC	1.108 (0.94)	0.02 to 1.96	0.008
Borg	0.25 (1.42)	-0.24 to 0.533	0.036
GAD	0.2 (1.19)	0.017 to 0.380	0.016
BPAT	1.63 (2.63)	0.802 to 2.465	0.0001
Nijmegen	1.03 (0.45)	0.127 to 1.950	0.012
PCFS	-0.015 (1.04)	-0.272 to 0.241	0.546
WSAS	1.413 (8.43)	-0.804 to 3.632	0.103
EQ5DL	0.353 (2.149)	0.006 to 0.700	0.022
FAS	**1.25 (5.02)**	**0.270 to 2.234**	**0.006**
6MWT	**25 (80.43)**	**-44.7 to -6.68**	**0.99**

Intension-To-Treat analyses of all the variables
Values are mean (95% CI)
Abbreviations: BMI, body mass index; MRC, Medical research council dyspnoea score; EQ5DL, Euro Quality of Life 5-dimension level; BPAT; Breathing Pattern Assessment Test; WSAS, Work and Social adjustment Score; 6MWT, Six-Minute walk test; FAS, Fatigue assessment test, Post COVID Functional Status (PCFS) *Significant differences between hospitalised and home group at baseline

Table 3 Proportion of frailty in post COVID syndrome n= 179

Frailty classification	Hospitalized (Hospital group) % (95% CI)	None hospitalized (Home group) % (95% CI)	p- value
Frail	30 (13.52 to 45.83)	6 (1.57 to 24.19)	0.004
prefrail	57 (38.10 to 73.53)	75 (68.42 to 95.12)	
Not frail	13 (6.84 to 35.26)	19 (1.57 to 24.19)	

Notes: values are presented in numbers and % and 95% Confidence interval (CI)

Table 3 Within-Group comparison (pre vs. Post) and Between-Group Comparison

	Hospitalised					Home			Hospitalised vs Home
Outcomes	Pre therapy	Post therapy	Mean diff	pvalue	Pre therapy	Post therapy	Mean diff	p-value	Asymp. (2 tailed sig)
EQ5DL	15.5 (9.5)	11.5 (4.9)	4	*<0.05	10.76 (2.6)	10.45 (3.4)	0.31	0.222	0.123
PCFS	2.9 (6.05)	2 (1.16)	0.9	0.35	2.1(0.8)	2.0 (0.7)	0.1	0.326	0.314
WSAS	20 (10.9)	19(11.9)	1	0.25	19 (9.5)	18 (10.9)	1	0.139	0.469
FAS	30 (9.4)	27 (8.8)	3	*0.04	33 (7.8)	31 (8.3)	2	*0.006	*0.037
BPAT	4.6 (2.5)	2.93 (2.8)	1.67	*0.01	3.9 (2.3)	2.3(1.7)	1.6	*0.003	0.118
Dysnoea12	12.8 (8.7)	10 (8.1)	2.8	0.1	11 (8.5)	8.9 (7.5)	2.1	*0.02	0.170
Borg	2.5 (2.06)	2.0 (1.9)	0.5	0.15	2.18 (1.8)	1.6 91.4)	0.58	*0.03	0.06
GAD	2.03 (1.9)	2.08 (1.6)	0.5	*0.01	2.03 (1.8)	2.06 (1.6)	0.03	0.292	0.189
MRC	3 (1)	2.6(0.9)	0.4	0.07	2.6 (0.6)	2.2 (0.9)	0.4	*0.019	0.947
6MWT (m)	237 (101)	291 (113)	54	*<0.05	355(121)	397 (92)	42	*0.019	****0.000
1M STS (rep)	16 (10.5)	19 (10.5)	3	*0.02	21 (8.2)	22 (7.6)	1	*0.008	*0.047

Notes: Values are presented as mean ± SD or number (%), Mean difference (mean diff.) *p < 0.05; *** p<0.001; ****p<0.0001, Negative sign (-) mean improvement. Abbreviations: MRC, Medical research council dyspnoea score; EQ5DL, Euro Quality of Life 5-dimension level; BPAT; Breathing Pattern Assessment Test; GAD WSAS, Work and Social adjustment Score; 6MWT, Six-Minute walk test; 1M STS (rep), One Minute Sit to Stand test (repetition).

*Significant differences from pre, significant differences between home and hospital group.

Table 4 Predictive factors for Frailty: Home group

	Coef.	Beta	95% CI	P-value
GAD 2	0.106	37%	0.01 to 0.20	0.029*
FAS	0.006	9%	-0.01 to 0.02	0.594
Dyspnoea -12	0.0057	9%	-0.01 to 0.02	0.500
WSAS	0.0004	6%	-0.19 to 0.18	0.966
BPAT	0.236	9%	-0.09 to 0.05	0.536
PCFS	0.0025	3%	-0.18 to 0.19	0.978

Notes: values are represented in coefficient (coef.) of correlation, Beta coefficient in %, 95% confidence interval (CI), *significant p value <0.05

Table 5 Predictive factors for Frailty: Hospital Group

	Coef.	Beta	95% CI	P-value
GAD 2	0.15	31%	-0.17 to 0.47	0.32
FAS	0.02	23%	-0.09 to 0.04	0.50
Dyspnoea 12	0.07	6.1%	-0.79 to 0.06	0.81
WSAS	0.03	35%	-0.09 to 0.025	0.26
BPAT	0.107	23%	-0.34 to 0.13	0.35
PCFS	0.03	31%	-0.02 to 0.08	0.22

Notes: values are represented in coefficient (coef.) of correlation, Beta coefficient in %, 95% confidence interval (CI), *significant p value <0.05

5.7 Discussion

In this retrospective stratified study, it was found that more than a third (36%) of patients with post-COVID syndrome referred for therapy intervention were frail according to Fried frailty phenotype criteria. Frailty prevalence is higher in hospitalised group – a third of them (30%), than non-hospitalised group -only 6% of their population. This frailty prevalence results are in line with those seen in COPD and other chronic respiratory patients as reported by earlier studies and systematic reviews[16,19,78]. These results showed that frailty could be classified as part of the clusters of post-COVID syndrome as are fatigue, breathlessness, chest pain, autonomic dysfunctions, reduced exercise tolerance, Post Exertional Symptoms Exacerbation (PESE), anxiety and depression, work and social adjustment issues, brain fog and reduced functions.

In the baseline characteristics, young, middle aged people and females were more likely to develop symptoms of post COVID syndrome than male. Also, female have higher hospital admission rate than male and are statistically different to each other, (M: F (%), 43% vs 57% in hospitalised group, and 76% vs.24% in non-hospitalised group, p= 0.000). The reason for this gender difference is unknown, but it has been suggested that hormonal differences may be a contributory reason. Symptoms of fatigue as measured by FAS is higher and statistically different in non-hospitalised patients to hospitalised patients (33 vs. 31, p=0.04). This may explain the anecdotal evidence of some experts in post-COVID care that non-hospitalised patients may suffer from more cluster of post-COVID syndrome especially fatigue than hospitalised patients which may be more deconditioned due to prolong hospitalisation or ITU prolonged stay as shown by their reduced 6MWT, low 1 Min STS test, higher PCFS scores, Borg breathlessness score and symptoms of dysfunctional breathing (BPAT) (table 3). BMI is higher in hospitalised group than non-hospitalised and could explain why hospitalised patients were more likely to be admitted for their acute COVID-19 than non-hospitalised group. Obesity and diabetes have been reported in various literatures as major comorbidities that contribute to severity of acute COVID-19 symptoms, ITU admissions and death (AlSabah, 2020). Therefore, this study, further highlights why people with obesity had higher rate of hospital admission due to acute COVID-19 and showed that the characteristics of people admitted into hospital with acute COVID-19 are different to those who remained at home despite infected with acute COVID-19. These new current clinical knowledge means that there is a need to develop a clinical tool to assess for severity of acute COVID-19 infection to help decision-making for home care or hospital care.

There was a significant magnitude of improvements across physical, psychological, and global health after therapy interventions, clearly revealing that therapy intervention is an added effective treatment model of care in post-COVID syndrome. It is important to say that we have not been able to eliminate the medical, social and environmental care that may have contributed to the improvement seen in therapy intervention. That does not take away the magnitude of the effect among both hospitalised and non-hospitalised groups, although the minimal clinical importance difference of the clinical outcome measures has not been established for postCOVID syndrome therefore may be hard to make a clinical claim of improvement. However, it is most likely we could say there will be a clinical effect as the statistics values are significant. We did not analyse further the results of Frailty prevalence to see if there was shift from frailty or pre-frailty to normal or remained the same as previously seen on chronic respiratory conditions (Maddocks, 2016 and Akinlabi, 2018).

Nonetheless, this study reveals that frailty may be considered as a post-COVID syndrome especially in hospitalised COVID-19 patients and therapy interventions are effective. It also reflects that frailty should be assessed in hospitalised post-COVID patients as are likely to be weak and deconditioned due to long hospitalisation and ITU stay. As previously stated in a few studies' frailty is amenable (Maddocks 2016, and Akinlabi 2018), if right the care is provided for patients. Exercise, selfmanagement, nutritional support, and reduction of polypharmacy is among those treatments with evidence of efficacy in frailty management.

5.8 Limitations

There are some limitations to this study. The choice of the Fried model to assess for frailty limits the study to physical frailty assessment as did not capture cognitive, social, or environmental components of frailty (Collard 2012), therefore did not measure hidden part of patients' frailty and limit care provisions. However, the Fried frailty model is the most established measure of Frailty with proven construct and validity (Clegg, 2013, Singer 2015, and Fried 2001). Only patients who had completed follow-up assessments, with fully completed clinical outcomes were included in this review – the prevalence estimates and post-t therapy outcomes did not consider those who did not have follow-up assessments. This may reduce the frailty prevalence estimates and exclude some patients who were not able to come back for a follow. Therefore, the therapy clinical outcome post 6 weeks of therapy may not be generalised beyond those post-COVID patients who had post-therapy follow-up. Finally, a longer therapy session may provide even better outcome and a post-therapy 3, 6, or 12-month follow-up could better reflect the long-term effect of therapy intervention.

5.9 Conclusion

Frailty affects more than a third of patients with post-COVID syndrome especially those who were admitted for acute COVID-19 infection. Anxiety, followed by fatigue are independent risk factor for the development of frailty. Obesity may be a risk factor for increase admissions amongst acute

COVID-19 admitted to hospital. Fatigue is more prevalent in non-hospitalised patients whilst breathlessness outcome and exercise capacity were more prevalent in hospitalised group which is suggestive of deconditioning. Future studies should identify early therapy intervention for hospitalised acute COVID-19 patients who are likely to develop post-COVID syndrome.

Final Chapter:

Reflections, Contributions, and Future Directions

Summary of Research Gaps and Contributions

The thesis addressed significant gaps in the evidence base surrounding PR and frailty in COPD patients. Prior studies have largely overlooked frailty as a distinct outcome measure, focusing instead on functional and quality of life improvements.

This research:

Highlighted PR's potential to reverse frailty and reduce hospitalisations.

Identified pre-frailty as a critical intervention point for preventing disease progression.

Provided a detailed PR protocol tailored to frail populations, offering a replicable framework for clinical practice.

Contributions to Knowledge

This work contributes to the understanding of:

The interplay between frailty and COPD outcomes.

The value of PR as a cost-effective, scalable intervention.

Strategies for personalising care to enhance adherence and efficacy.

Proposed Future Research

Building on these contributions, future research should:

Conduct RCTs to establish causality and explore long-term effects.

Examine the integration of PR into broader multidisciplinary care models.

Develop and test digital and home-based PR innovations to improve access.

Final Reflections

This thesis underscores the transformative potential of PR for frail COPD patients, bridging evidence gaps and informing future innovation in respiratory care. By addressing the multifactorial needs of this population, PR can improve lives while advancing healthcare delivery in a resource-constrained environment.

References

1. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD003793. DOI: 10.1002/14651858.CD003793.pub3

2. Kinsella, K., & Phillips, D. R. (2005). Global ageing: The challenge of success. Population Bulletin, 60(1), 3-40.

3. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K, (2013). Frailty in elderly people. Lancet. Mar 2;381(9868):752-62. doi: 10.1016/S0140-6736(12)62167-9. Epub Feb 8. Erratum in: Lancet. 2013 Oct 19;382(9901):1328. PMID: 23395245; PMCID: PMC4098658.

4. Goh Felicia, Shaw Janet G, Francis Santiyagu M Savarimuthu, Vaughan Annalicia, Morrison Leanne, Relan Vandana, Marshall Henry M, Dent Annette G, O'Hare Phoebe E, Hsiao Amy, Bowman Rayleen V, Fong Kwun M, and Yang Ian A. Personalising and targeting therapy for COPD- role of molecular and clinical biomarkers. Expert Review of Respiratory Medicine. 2013; 7 (6).

5. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. Journal of American Geriatric Society. 2012;60(8):1487–92

6. Rockwood, K., Mitnitski, A., Song, X., Steen, B. and Skoog, I. (2006). Long-Term Risks of Death and Institutionalization of Elderly People in Relation to Deficit Accumulation at Age 70. Journal of the American Geriatrics Society, 54: 975-979. https://doi.org/10.1111/j.1532-5415.2006.00738.x

7. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA. Frailty in older adults: evidence for a phenotype. Journal of Gerontology Series A Biological Science and Medical Science. 2001;56(3):M146–56

8. Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. Archives of Internal Medicine. 2006;166(4):418–23.

9. Limpawattana P, Putraveephong S, Inthasuwan P, Boonsawat W, Theerakulpisut D, Chindaprasirt J. (2017). Frailty syndrome in ambulatory patients with COPD.
Int J Chron Obstruct Pulmon Dis. Apr 18; 12:1193-1198. doi: 10.2147/COPD.S134233. PMID: 28458530; PMCID: PMC5402886.

10. Outcomes Strategy for COPD and Asthma: NHS Companion Document Department of Health May 2012

11. Waschki B, Kirsten A, Holz O, Müller KC, Meyer T, Watz H, Magnussen H (2011). Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. Chest. Aug;140(2):331-342. doi:
10.1378/chest.10-2521. Epub 2011 Jan 27. PMID: 21273294.

12. Lahousse Lies, Ziere Gijsbertus, Verlinden Vincentius J. A., M. Zillikens Carola, Uitterlinden André G., Rivadeneira Fernando, Tiemeier Henning, Joos Guy F.,
Hofman Albert, Ikram M. Arfan, Franco Oscar H., Brusselle Guy G., Stricker
Bruno H.; 2016. Risk of Frailty in Elderly With COPD: A Population-Based Study. *Journal of Gerontology Series A Biological Science and Medical Science*;71 (5): 689-695.

13. Park SK, Richardson CR, Holleman RG, Larson JL (2013). Frailty in people with COPD, using the National Health and Nutrition Evaluation Survey dataset (20032006). Heart Lung. 2013 May-Jun;42(3):163-70. doi:
10.1016/j.hrtlng.2012.07.004. Epub Mar 25. PMID: 23535142; PMCID: PMC4020241.

14. Carlos A. Vaz Fragoso, Thomas M. Gill, Respiratory Impairment and the Aging Lung (2012): A Novel Paradigm for Assessing Pulmonary Function, *The Journals of Gerontology: Series A*, Volume 67A, Issue 3, March, Pages 264–275.

15. Galizia G, Cacciatore F, Testa G, Della-Morte D, Mazzella F, Langellotto A, Raucci C, Gargiulo G, Ferrara N, Rengo F, Abete P (2011). Role of clinical frailty on long-term mortality of elderly subjects with and without chronic obstructive pulmonary disease. Aging Clin Exp Res. Apr;23(2):118-25

16. Marengoni A, Vetrano DL, Manes-Gravina E, Bernabei R, Onder G, Palmer K. (2018). The Relationship Between COPD and Frailty: A Systematic Review and Meta-Analysis of Observational Studies. Chest. 2018 Jul;154(1):21-40. doi: 10.1016/j.chest.2018.02.014. Epub Mar 1. PMID: 29477493.

17. Multimorbidity: clinical assessment and management (2016), National Institute for Health and Care Excellence (NICE).

18. Rodríguez-Artalejo F, Rodríguez-Mañas L (2014). The frailty syndrome in the public health agenda. J Epidemiol Community Health. 2014 Aug;68(8):703-4. doi: 10.1136/jech--203863. Epub 2014 Apr 29. PMID: 24782415.

19. Maddocks M, Kon SSC, Canavan JL, et al (2016). Physical frailty and pulmonary rehabilitation in COPD: a prospective cohort study. Thorax.;71(11):988-995. doi:10.1136/thoraxjnl-2016-208460.

20. Mittal N, Raj R, Islam EA, Nugent K. (2016). The Frequency of Frailty in Ambulatory Patients With Chronic Lung Diseases. J Prim Care Community Health. Jan;7(1):10-5. doi: 10.1177/2150131915603202. Epub 2015 Sep 2. PMID: 26333537; PMCID: PMC5932671.

21. Tapper, EB, Konerman, M, Murphy, S, Sonnenday, CJ. (2018). Hepatic encephalopathy impacts the predictive value of the fried frailty index. Am J Transplant. ; 18: 2566– 2570. https://doi.org/10.1111/ajt.15020

22. Bergman H, Ferrucci L, Guralnik J, Hogan DB, Hummel S, Karunananthan S, Wolfson C. (2007). Frailty: an emerging research and clinical paradigm--issues and controversies. J Gerontol A Biol Sci Med Sci. Jul;62(7):731-7. doi: 10.1093/gerona/62.7.731. PMID: 17634320; PMCID: PMC2645660.

23. Walston J, Hadley EC, Ferrucci L, Guralnik JM, Newman AB, Studenski SA, Ershler WB, Harris T, Fried LP. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. J Am Geriatr Soc. 2006 Jun;54(6):991-1001. doi: 10.1111/j.1532-5415.2006.00745.x. PMID: 16776798.

24. Radloff LS, “The CES-D Scale,” Appl. Psychol. Meas., vol. 1, no. 3, pp. 385–401, Jun. 1977.

25. Garcia-Aymerich J, Farrero E, Félez MA, Izquierdo J, Marrades RM, Antó JM; Estudi del Factors de Risc d'Agudització de la MPOC investigators. Risk factors of readmission to hospital for a COPD exacerbation: a prospective study. Thorax. 2003 Feb;58(2):100-5. doi: 10.1136/thorax.58.2.100. PMID: 12554887; PMCID: PMC1746561.

26. Kon SS, Patel MS, Canavan JL, Clark AL, Jones SE, Nolan CM, Cullinan P, Polkey MI, Man WD. Reliability and validity of 4-metre gait speed in COPD. Eur Respir J. 2013 Aug;42(2):333-40. doi: 10.1183/09031936.00162712. Epub 2012 Dec 6. PMID: 23222875.

27. Celli BR, Decramer M, Wedzicha JA, Wilson KC, Agustí AA, Criner GJ, MacNee W, Make BJ, Rennard SI, Stockley RA, Vogelmeier C, Anzueto A, Au DH, Barnes PJ, Burgel PR, Calverley PM, Casanova C, Clini EM, Cooper CB, Coxson HO, Dusser DJ, Fabbri LM, Fahy B, Ferguson GT, Fisher A, Fletcher MJ, Hayot M, Hurst JR, Jones PW, Mahler DA, Maltais F, Mannino DM, Martinez FJ, Miravitlles M, Meek PM, Papi A, Rabe KF, Roche N, Sciurba FC, Sethi S, Siafakas N, Sin DD, Soriano JB, Stoller JK, Tashkin DP, Troosters T, Verleden GM, Verschakelen J, Vestbo J, Walsh JW, Washko GR, Wise RA, Wouters EF, ZuWallack RL; ATS/ERS Task Force for COPD Research. An official American Thoracic Society/European Respiratory Society statement: research questions in COPD. Eur Respir Rev. 2015 Jun;24(136):159-72. doi: 10.1183/16000617.00000315. PMID: 26028628; PMCID: PMC9487818.

28. IE AT, CAR I. IMPRESS Guide to the relative value of COPD interventions.

29. British Thoracic Society (BTS), “Quality Standards for Pulmonary Rehabilitation in

Adults are endorsed by: The Association for Chartered Physiotherapists in Respiratory Care (ACPRC) and The Association of Respiratory Nurse Specialists (ARNS)," vol. 6, no. 2, pp. 1–36, 2014.

30. Spruit, M. A., Singh, S. J., Garvey, C., et al. (2013). An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. American Journal of Respiratory and Critical Care Medicine, 188(8), e13–e64.

31. McCarthy B, Casey D, Devane D, Murphy K, Murphy E, Lacasse Y (2015). Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews, Issue 2. Art. No.: CD003793. DOI: 10.1002/14651858.CD003793.pub3.

32. Outcomes Strategy for COPD and Asthma (2012) NHS Companion Document Department of Health

33. Maltais, F., Bourbeau, J., Shapiro, S., et al. (2014). Effects of home-based pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. Annals of Internal Medicine, 161(8), 538–547.

34. Neder J Alberto, Mathieu Marillier, Anne-Catherine Bernard, Matthew D. James, Kathryn M. Milne & Denis E. O'Donnell (2019) The Integrative Physiology of Exercise Training in Patients with COPD, COPD: Journal of Chronic Obstructive Pulmonary Disease, 16:2, 182-195, DOI: 10.1080/15412555.2019.1606189

35. Troosters T, Casaburi R, Gosselink R, Decramer M (2005). Pulmonary rehabilitation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med; 172(1):19–38. doi: 10.1164/rccm.200408-1109SO.

36. Lacasse Y, Brosseau L, Milne S, et al. Pulmonary rehabilitation for chronic obstructive pulmonary disease (2002). Cochrane Database Syst Rev ;3:CD003793.

37. O'Donnell DE, Maltais F, Porszasz J, et al (2014). The continuum of physiological impairment during treadmill walking in patients with mild-to-moderate COPD:

patient characterization phase of a randomized clinical trial. PLoS One. 2014;9(5):e96574. doi: 10.1371/journal.pone.0096574.

38. Dave Singh, Alvar Agusti, Antonio Anzueto, PeterJ. Barnes, Jean Bourbeau, Bart olome R. Celli, Gerard J.Criner, Peter Frith, David M.G. Halpin, Meilan Han, M. Victorina López Varela, Fernando Martinez, MariaMontes de Oca, Alberto Papi, IanD. Pavord, Nicolas Roche, DonaldD. Sin, Robert Stockley, Jørgen Vestbo, Jadwiga A. Wedzicha, Claus Vogelmeier (2019). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report. European Respiratory Journal May, 53 (5) 1900164; DOI: 10.1183/13993003.00164

39. National Institute of Clinical and Care Excellence (2018) Chronic obstructive pulmonary disease in over 16s: diagnosis and management NICE guideline [NG115].

40. Pumar MI, Gray CR, Walsh JR, Yang IA, Rolls TA, Ward DL. (2014) Anxiety and depression-Important psychological comorbidities of COPD. Journal of Thorac Dis. Nov;6(11):1615-31. doi: 10.3978/j.issn.2072-1439.2014.09.28. PMID: 25478202; PMCID: PMC4255157.

41. Smith SMS, Sonego S, Ketcheson L. A review of the effectiveness of psychological , interventions used for anxiety and depression in chronic obstructive pulmonary diseaseBMJ Open Respiratory Research; 2014, 1:e000042.

42. Maltais F, Leblanc P, Simard C. Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med.; 1996, 154(2):442–447.

43. Jones DT, Thomson RJ, Sears MR. Physical exercise and resistive breathing in severe chronic airways obstruction - are they effective? European Journal of Respiratory Diseases 1985;67:159-66.

44. Lopez D, Cecins N, Cockram J. Maintaining quality of life in patients with chronic obstructive pulmonary disease (COPD) by extending the maintenance phase of community-based pulmonary rehabilitation: protocol for a randomised controlled trial (ComEx3 Study) BMJ Open Respiratory Research; 2019, 7:e000548.

45. Royal College of Physicians; Pulmonary rehabilitation. Beyond breathing better is a supplementary report detailing the outcomes of the English cohort of patients included in the 2015 pulmonary rehabilitation (PR) clinical audit.

46. Myers LC, Faridi MK, Hasegawa K, Camargo CA Jr. Pulmonary Rehabilitation and Readmission Rates for Medicare Beneficiaries with Acute Exacerbation of Chronic Obstructive Pulmonary Disease. Chronic Obstr Pulm Dis. 2021 Oct 28;8(4):427-440.

47. Dowman L, Hill CJ, May A, Holland AE. Pulmonary rehabilitation for interstitial lung disease. Cochrane Database of Systematic Reviews, 2021, Issue 2.

48. De Brandt J, Spruit MA, Derave W. Changes in structural and metabolic muscle characteristics following exercise-based interventions in patients with COPD: a systematic review. Expert Rev Respir Med; 2016, 10(5):521–545.

49. Chiappa GR, Borghi-Silva A, Ferreira LF, et al. Kinetics of muscle deoxygenation are accelerated at the onset of heavy-intensity exercise in patients with COPD: relationship to central cardiovascular dynamics. J Appl Physiol. 2008;104(5):1341–1350.

50. Vogiatzis I, Simoes DC, Stratakos G, Effect of pulmonary rehabilitation on muscle remodelling in cachectic patients with COPD. Eur Respir J. 2010;36(2):301–310.

51. Richardson RS, Leek BT, Gavin TP, Haseler LJ, Mudaliar SR, Henry R, MathieuCostello O, Wagner PD. Reduced mechanical efficiency in chronic obstructive pulmonary disease but normal peak VO2 with small muscle mass exercise. Am J Respir Crit Care Med. 2004 Jan 1;169(1):89-96.

52. Li P, Li J, Wang Y, Xia J, Liu X. Effects of Exercise Intervention on Peripheral Skeletal Muscle in Stable Patients With COPD: A Systematic Review and MetaAnalysis. Front Med (Lausanne). 2021 Nov 18;8: 766841.

53. Vonbank K, Strasser B, Mondrzyk J. Strength training increases maximum working capacity in patients with COPD–randomized clinical

trial comparing three training modalities. Respir Med; 2912, 106(4):557–563.

54. O'Donnell DE, Elbehairy AF, Berton DC, et al. Advances in the evaluation of respiratory pathophysiology during exercise in chronic lung diseases. Front Physiol. 2017;8:82.

55. Normandin EA, McCusker C, Connors M. An evaluation of two approaches to exercise conditioning in pulmonary rehabilitation. Chest. 2002, 121(4):1085– 1091.

56. Burtin C, Saey D, Saglam M. Effectiveness of exercise training in patients with COPD: the role of muscle fatigue. European Respir Journal; 2012, 40(2):338– 344.

57. Bernard S, Whittom F, Leblanc P. Aerobic and strength training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med; 1999 159(3):896–901.

58. Charususin N, Gosselink R, Decramer M. Randomised controlled trial of adjunctive inspiratory muscle training for patients with COPD. Thorax 2018, 73(10):942–950.

59. Ries AL, Ellis B, Hawkins RW. Upper extremity exercise training in chronic obstructive pulmonary disease. Chest. 1998 Apr;93(4):688-92.

60. Elbehairy AF, Ciavaglia CE, Webb KA, Guenette JA, Jensen D, Mourad SM, Neder JA, O'Donnell DE; Canadian Respiratory Research Network. Pulmonary Gas Exchange Abnormalities in Mild Chronic Obstructive Pulmonary Disease. Implications for Dyspnea and Exercise Intolerance. American Journal of Respiratory and Critical Care Medicine. 2015 Jun 15;191(12):1384-94.

61. Herigstad M, Hayen A, Evans E, Hardinge FM, Davies RJ, Wiech K, Pattinson KTS (2015). Dyspnea-related cues engage the prefrontal cortex: evidence from functional brain imaging in COPD. Chest. Oct;148(4):953-961.

62. Rocha A, Arbex FF, Sperandio PA, et al. Excess ventilation in chronic obstructive pulmonary disease-heart failure overlap. Implications for

dyspnea and exercise intolerance. Am J Respir Crit Care Med. 2017;196(10):1264.

63. Bourbeau J. Making pulmonary rehabilitation a success in COPD. Swiss Med Wkly. 2010 Sep 1;140:w13067.

64. Matthews, Kevin A.;Gaglioti, Anne H.;Holt, James B.;Wheaton, Anne G.;Croft, Janet B. Using spatially adaptive floating catchments to measure the geographic availability of a health care service: Pulmonary rehabilitation in the southeastern United States: Health Place. 2019, 56:165-173

65. Faisal A, Alghamdi BJ, Ciavaglia CE. Common mechanisms of dyspnea in chronic interstitial and obstructive lung disorders. Am J Respir Crit Care Med. 2016, 193(3):299–309.

66. Harty HR, Corfield DR, Schwartzstein RM, Adams L.External thoracic restriction, respiratory sensation, and ventilation during exercise in men. J Appl Physiol; 1999 86(4):1142–1150.

67. Burtin C, Saey D, Saglam M. Effectiveness of exercise training in patients with COPD: the role of muscle fatigue. European Respiratory Journal ; 2012 40(2):338–344.

68. Walraven, K.H.M. M. van Vliet, J.A. van Noord Short and long-term outcomes after the first episode of non-invasive ventilation (NIV) for an acute exacerbation of COPD (AECOPD) on a general ward. European Respiratory Journal, 2012, 40 (Suppl 56) P2039.

69. Lahousse Lies, Ziere Gijsbertus, Verlinden Vincentius J. A., M. Zillikens Carola, Uitterlinden André G., Rivadeneira Fernando, Tiemeier Henning, Joos Guy F., Hofman Albert, Ikram M. Arfan, Franco Oscar H., Brusselle Guy G., Stricker Bruno H. Risk of Frailty in Elderly With COPD: A Population-Based Study. *Journal of Gerontology Series A Biological Science and Medical Science*; 2016, 71 (5): 689-695

70. Seymour JM, Spruit MA, Hopkinson NS, Natanek SA, Man WD, Jackson A, Gosker HR, Schols AM, Moxham J, Polkey MI, Wouters EF. The prevalence of quadriceps weakness in COPD and the relationship

with disease severity. European Respiratory Journal. 2010 Jul;36(1):81-8.

71. Sterne JAC, Higgins JPT, Reeves BC, on behalf of the development group for
ACROBAT- NRST. A Cochrane Risk of Bias Assessment Tool: For NonRandomised used studies of interventions (ACROBAT-NRSI) 2014, version 1.0.0,24.

72. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097.

73. Sackett DL. Evidence-based medicine. Semin Perinatol 1997 Feb;21(1):3-5.

74. Bolton CE, Bevan-Smith EF, Blakey JD. British Thoracic Society guideline on pulmonary rehabilitation in adults: accredited by NICE Thorax 2013;68:ii1-ii30.

75. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies:Guideline Statement. Journal of Clinical Epidemiology, 2015 Jul;75:40-6

76. Wang L, Zhang X, Liu X. Prevalence and clinical impact of frailty in COPD: a systematic review and meta-analysis. BMC Pulmonary Medicine, 2023 May 12;23(1):164.

77. Plas J, ter Beek L, van der Vaart H, Jager-Wittenaar H. Improvement in frailty status after pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. 2019 Healthy Ageing, Allied Health Care and Nursing Malnutrition and Healthy Ageing

78. Akinlabi K, Patel B, Johnston K, Adebajo B, Trojak R, Alrajeh A, Magbagbeola T, Hurst J R . European Respiratory Journal Sep 2018, 52. Impact of Physical Frailty on Pulmonary Rehabilitation and Hospitalisation in COPD.

79. Mei F, Gao Q, Chen F, Zhao L, Shang Y, Hu K, Zhang W, Zhao B, Ma B: Frailty as a predictor of negative health outcomes in chronic kidney disease: a systematic review and Meta-analysis. Journal of the American Medical Directors Association, 2021 22(3):535–543.e537.

80. Gephine S, Saey D, Grosbois JM, Maltais F, Mucci P. Home-based Pulmonary Rehabilitation is Effective in Frail COPD Patients with Chronic Respiratory Failure. Chronic Obstr Pulm Dis. 2022 Jan 27;9(1):15-25.

81. Troosters T, Blondeel A, Rodrigues FM, Janssens W, Demeyer H. Strategies to Increase Physical Activity in Chronic Respiratory Diseases. Clin Chest Med. 2019 Jun;40(2):397-404.

82. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT; Lancet Physical Activity Series Working Group. Effect of physical inactivity on major noncommunicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012 Jul 21;380(9838):219-29.

83. Tudor-Locke, C., Craig, C.L., Brown, W.J. *et al.* How many steps/day are enough? for adults. *Int J Behav Nutr Phys Act* 2011 8, 79.

84. Demeyer H, Burtin C, Hornikx M, Camillo CA, Van Remoortel H, Langer D, Janssens W, Troosters T. The Minimal Important Difference in Physical Activity in
Patients with COPD. PLoS One. 2016 Apr 28;11(4)

85. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, Rodriguez-Roisin R.
Global strategy for the diagnosis, management, and prevention of Chronic
Obstructive Pulmonary Disease: GOLD executive summary. Am J Respir Crit
Care Med. 2013; 187:347–65

86. Moy ML, Collins RJ, Martinez CH, Kadri R, Roman P, Holleman RG, Kim HM,
Nguyen HQ, Cohen MD, Goodrich DE, Giardino ND, Richardson CR. An InternetMediated Pedometer-Based Program Improves Health-Related Quality-of-Life Domains and Daily Step Counts in COPD: A Randomized Controlled Trial. Chest. 2015 Jul;148(1):128-137. doi: 10.1378/chest.14-1466.

87. Demeyer H, Louvaris Z, Frei A, Rabinovich RA, de Jong C, Gimeno-Santos E,
Loeckx M, Buttery SC, Rubio N, Van der Molen T, Hopkinson NS, Vogiatzis I, Puhan MA, Garcia-Aymerich J, Polkey MI, Troosters T; Mr Papp PROactive study group and the PROactive consortium. Physical activity is increased by a 12-week semiautomated telecoaching programme in patients with COPD: a multicentre randomised controlled trial. Thorax. 2017 May;72(5):415-423. doi: 10.1136/thoraxjnl-2016-209026. Epub 2017 Jan 30

88. Gill, D.L., Reifsteck, E.J., Adams, M.M., & Shang, Y. Quality of Life Assessment for Physical Activity and Health Promotion: Further Psychometrics and Comparison of Measures. *Measurement in Physical Education and Exercise Science, 2015 19*, 159 - 166.

89. Luo J, Zhang D, Tang W, Dou LY, Sun Y. Impact of Frailty on the Risk of Exacerbations and All-Cause Mortality in Elderly Patients with Stable Chronic Obstructive Pulmonary Disease. Clin Interv Aging. 2021 Apr 13;16:593-601.

90. Kennedy CC, Novotny PJ, LeBrasseur NK, Wise RA, Sciurba FC, Benzo RP. Frailty and Clinical Outcomes in Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc. 2019 Feb;16(2):217-224. doi: 10.1513/AnnalsATS.201803175OC.

91. Guyatt GH, Pugsley SO, Sullivan MJ, Thompson PJ, Berman L, Jones NL, Fallen EL, Taylor DW. Effect of encouragement on walking test performance. Thorax. 1984 Nov;39(11):818-22.

92. Hernandes NA, Wouters EF, Meijer K, Annegarn J, Pitta F, Spruit MA. Reproducibility of 6-minute walking test in patients with COPD. Eur Respir J.
2011 Aug;38(2):261-7. doi: 10.1183/09031936.00142010. Epub 2010 Dec 22. Erratum in: Eur Respir J. 2012 Dec;40(6):1583.

93. Guyatt GH, Sullivan MJ, Thompson PJ, Fallen EL, Pugsley SO, Taylor DW, Berman LB. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J. 1985 Apr 15;132(8).

94. Kozu, R.; Jenkins, S.; Senjyu, H.; Mukae, H.; Sakamoto, N.; Kohno, S. Peak power estimated from 6-minute walk distance in Asian patients with idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease. *Respirology*; 2010; *15*, 706-713.

95. Jenkins S, Cecins NM. Six-minute walk test in pulmonary rehabilitation: do all patients need a practice test? Respirology. 2010 Nov;15(8):1192-6.

96. Jorquera Guillen, M.A.; Salcedo Posadas, A.; Villa Asensi, J.R.; Giron Moreno, R.M.; Neira Rodriguez, M.A.; Sequeiros Gonzalez, A. Reproducibility of the walking test in patients with cystic fibrosis. *An. Esp. Pediatr.*; 1999; *51*, 475-478.

97. Ziegler B, Rovedder PM, Oliveira CL, de Abreu e Silva F, de Tarso Roth Dalcin P. Repeatability of the 6-minute walk test in adolescents and adults with cystic fibrosis. Respir Care. 2010 Aug;55(8):1020-5.

98. Sciurba F, Criner GJ, Lee SM, Mohsenifar Z, Shade D, Slivka W, Wise RA 2003

Six-minute walk distance in chronic obstructive pulmonary disease: Reproducibility and effect of walking course layout and length. American Journal of Respiratory and Critical Care Medicine 167: 1522–1527.

99. Singh SJ, Jones PW, Evans R, Morgan MD. Minimum clinically important improvement for the incremental shuttle walking test. Thorax. 2008 Sep;63(9):775-7. doi: 10.1136/thx.2007.081208. Epub 2008 Apr 4.

100. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 Jun;67(6):361-70.

101. Snaith RP, Zigmond AS. The hospital anxiety and depression scale. Br Med J (Clin Res Ed). 1986 Feb 1;292(6516):344. doi: 10.1136/bmj.292.6516.344.

102. Puhan, M.A., Frey, M., Büchi, S. *et al.* The minimal important difference of the hospital anxiety and depression scale in patients with chronic obstructive pulmonary disease. *Health Qual Life Outcomes* 6, 46 2008.

103. Ruiz-Comellas A, Sauch Valmaña G, Mendioroz Peña J, et al. Physical activity, emotional state and socialization in the elderly:

study protocol for a clinical multicentre randomized trial. *Journal of International Medical Research*.
2021;49(6).

104. David Martinez-Gomez, Mark Hamer, Francisco B. Ortega, Verónica Cabanas-Sanchez, Kabir P. Sadarangani, Carl J. Lavie, Fernando RodríguezArtale 03 February 2020 Association of Changes in Physical Activity and Incidence and Remission of Overall and Abdominal Obesity in 113,950

105. Symvoulakis EK, Kamekis A, Drakonaki E, Mastrodemou S, Ryerson CJ, Antoniou K. Frailty and chronic respiratory disease: the need for a multidisciplinary care model. Sarcoidosis Vasc Diffuse Lung Dis. 2021;38(3).

106. Gale NS, Albarrati AM, Munnery MM, Hubbard RE, Tal-Singer R, Cockcroft JR, Shale DJ. Frailty: A global measure of the multisystem impact of COPD. Chron Respir Dis. 2018 Nov;15(4):347-355.

107. Rodriguez-Mañas L, Fried LP. Frailty in the clinical scenario. Lancet. 2015 Feb 14;385(9968):e7-e9.

108. Ladds E, Rushforth A, Wieringa S, Taylor Sharon et al, 2020. Persistent symptoms after Covid-19: qualitative study of 114 "long Covid patients and draft principles for services. BMCHealth Services Research. 20:1144.

109. Greenhalgh T, Sivan M, Delaney B, Evans R, Milne R. Long covid—an update for primary care *BMJ* 2022.

110. Assaf, A., & Scuderi, R. (2020). COVID-19 and the recovery of the tourism industry. Tourism Economics, 26(5), 731-733.

111. WHO Director-General's opening remarks at the media briefing on COVID19 -March 2020

112. Wiersinga W J, Rhodes A, Cheng Allen C, Peacock S J, Prescott Hallie C, 2020. JAMA, 324 (8):782-793.

113. Docherty A B, Harrison E M, Green C A, Hardwick H E, Pius R, Norman L et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study BMJ 2020; 369

114. Wang H C Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; 395:497-506.

115. Ladds,E., Rushforth, A., Wieringa, S. *et al.* Persistent symptoms after Covid-19: qualitative study of 114 "long Covid" patients and draft qualityprinciples for services.*BMC Health Serv Res* 2000 20*,* 1144.

116. Tenforde MW, Kim SS, Lindsell CJ, et al. Symptom Duration and Risk Factors for Delayed Return to Usual Health Among Outpatients with COVID-19 in a Multistate Health Care Systems Network — United States, March–June 2020.

117. Goërtz Y M J, Maarten Van Herck, Jeannet M. Delbressine, Anouk W. Vaes, Roy Meys, Felipe V.C.Machado, Sarah Houben-Wilke, Chris Burtin, Rein Posthuma, Frits M.E. Franssen, Nicole van Loon, BitaHajian, Yvonne Spies, Herman Vijlbrief, Alex J. van 't Hul, Daisy J.A. Janssen, Martijn A. Spruit. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome. ERJ Open Research Oct 2020, 6 (4) 00542-2020.

118. Tay, M.Z., Poh, C.M., Rénia, L. *et al.* The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol* 2020 20, 363–374.

119. National Institute of Clinical Excellence (NICE) guideline [NG188] COVID-19 rapid guideline: managing the long-term effects of COVID-19**;** 18 December 2020

120. Carfì A. Bernabei R. Landi F. Gemelli Against COVID-19 post-acute care study group. Persistent symptoms in patients after acute COVID**-19. JAMA***.* 2020; **324** Aug 11: 603-60

121. Darvali J N, Bellomo R, Bailey M, Young P J, Rockwood K, Pilcer D. 2022.
Impact of frailty on persisitent critica illness: a population-based cohort study. Intensive Care Med 48:343-35.

122. Todd S, Walsted ES, Grillo L, Livingston R, Menzie-Gow, Hull J H; 2018. Novel assessment tool to detect breathing pattern disorder in patient with refractory asthma. Respirology; 23(3):284-290.

123. Almazeedi S, Al-Youha S, Mohammad H. J, Al-Haddad M, Ali Al-Muhaini, Fahad Al-Ghimlas, Salman Al-Sabah. Characteristics, risk factors and outcomes among the first consecutive 1096 patients diagnosed with COVID-19 in Kuwait, eClinicalMedicine, Volume 24, 2020,100448.

124. Finamore P, Scarlata S, Delussu AS, Traballesi M, Incalzi RA, Laudisio A. Frailty Impact during and after Pulmonary Rehabilitation. COPD. 2021 Oct;18(5):518-524.

125. Vigorè M, Granata N, Callegari G, Vaninetti R, Conti S, Maestri R, Piaggi G, Cremonese G, Pierobon A. Frailty and rehabilitation outcome in older patients with cardiorespiratory disease: preliminary multidimensional data. Monaldi Arch Chest Dis. 2022 Dec 1;93(4).

Appendices

Ethical consideration

This protocol was reviewed by the study supervisors and was approved by the Central London Healthcare Research and Development department.

Below is the application form and approval email from CLCH clinical effectiveness team and the research team.

Consent

This research involves previously collected, non-identifiable information. Therefore, this study is limited to the secondary use of information previously collected during normal care (without an intention to use it for research at the time of collection). This is excluded from consent.

From: MATENJWA, Nish (CENTRAL LONDON COMMUNITY HEALTHCARE NHS TRUST) <nish.matenjwa@nhs.net>
Sent: 29 September 2021 08:38
To: AKINLABI, Kola (CENTRAL LONDON COMMUNITY HEALTHCARE NHS TRUST) <kola.akinlabi@nhs.net>
Subject: RE: clinical audit and service evaluation

Hi Kola, I am well and hope you are too. It is good to hear from you. The work you are planning to do sounds worthwhile and I look forward to learning about the results and outcomes.

Please see and complete the attached project proposal form. From what I gather from your email, it sounds like you are planning a service evaluation rather than a clinical audit. Please see the attached CLCH clinical audit, service evaluations, QI projects requirements 2021, pages 3-4 which provides information about the differences between clinical audits and service evaluations.

Regarding the question about the outcomes of your project being used in a university study, I believe it can be used, see the attached Peer-reviewed Communications Policy. For further information or queries, please contact Dr Ian Bernstein, the Medical Directorate's Director of Medical Information - ian.bernstein@nhs.net.

Do get in touch should you have any queries or further requirements.
Best wishes.

Nish Matenjwa **| She/Her/Hers**
Business & Programme Manager for the Medical Director/Deputy CEO | Interim Clinical Effectiveness Lead
Clinical Effectiveness Team, Medical Directorate
Central London Community Healthcare NHS Trust
E: nish.matenjwa@nhs.net **|** clinical.effectiveness@nhs.net
T: 0207 798 1381 | M: 0781 571 6938 | **W:** www.clch.nhs.uk |
My normal working hours
Monday-Tuesday: 08:00-16:00
Wednesday-Friday: 07:00-15:00


NHS
It is important colleagues from BAME backgrounds get vaccinated. This will help reduce the disproportionate impact of COVID-19 on our BAME colleagues.

PROPOSED PROJECT FORM 2021/22 CLCH NHS Trust Clinical Effectiveness Team

Project Lead 1 name, email, job title and contact	Kola Akinlabi, Clinical Lead, Barnet CLCH Post COVID Service Kola.akinlabi@nhs.net
Project 2 name, job title, email and contact	Binny Patel, Lead respiratory physio Post COVD Service Dr Patrick Mallia, Respiratory Consultant, Barnet CLCH Post COVID Service
Has your line manager/service lead approved this project?	☒Yes ☐No
Division	North Central
Service	Barnet Post COVID Service
Commissioner (s)	NCL CCG
Please click on a checkbox to indicate your project type	☒Clinical audit ☐Re-audit ☐Quality improvement project ☒Service evaluation
Please describe your project's participants/auditors. Typically, CLCH projects consist of one auditor (you), you and another auditor, multiple auditors across a CBU, service/team or the Trust.	☒One auditor (you) ☐You and another auditor ☐Multiple auditors across your CBU ☐Multiple auditors across your service/team ☐Multiple auditors across the Trust

	☐Other (please define)
What is the title of your project?	Post COVID syndrome; clinical and PROM outcomes: how effective are the interventions? And what's the prevalence of post covid syndrome and frailty in Barnet cohort?
What is the topic of your project? Provide a brief project background/rationale: Why was this topic chosen? What are the reasons for undertaking the project?	Post COVID clinical and patient outcomes: do they change with therapy intervention? **Background:** Post COVID syndrome (PCS) or Long COVID is defined as signs and symptoms that develop during and after an infection consistent with SARS-CoV-2 (COVID-19), continue for more than 12 weeks and are not explained by an alternative diagnosis (NICE 2020). It usually present with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. The national office of statistics (ONS), estimated that 945,000 living in private household in UK (1.46%) were experiencing self-reported ''long covid'', as of July 2021. In April 2021, ONS reported the result of 20,000 participants who tested positive to COVID-19 from April 2020 to March 2021 that 13.7% continued to experience

	symptoms for at least 12 weeks. This was eight times higher than in a control group of the 20,000 study participant reported. According to ONS infection survey data, the estimated prevalence of PCS among the population is 1.15% in the London region as of July 2021 and Barnet borough of London have an estimated prevalence of 4,863 people living with PCS being the highest in North Central London (NCL). **Rationale**: Against the backdrop of high prevalence in London, NCL CCG funded the set-up of PCS across the 5 boroughs, with emphasis on MDT working across all level of care including local council, specialist community therapy PCS assessment clinic and self-management with the use of digital app. Since April 2021, Barnet PCS has been running, and have seen over 300 patients either face to face in clinic, telephone consultations or discussed at the MDT. We offer range of personalised therapy recovery advice and management plans with strict recognition of medical red flags during assessment in clinic and well supported by a respiratory

	consultant. In 2020 and 2021, NICE and NHS publish a framework of assessments and care guidelines respectively and the London PCS network have also developed specific clinical and patient outcome measures in line with national guidance to measure patients outcomes and post covid services. Each of these outcomes, have their specific improvement threshold and minimal clinical importance difference (MCID) such a 6 minute walk test, sit to stand test, fatigue assessment score (FAS) and EQ5DL (quality of life measures). However, there is no evidence how effective the interventions we provide to patients with respect to MCID of each of these outcomes and PROM. Also, there is a need to understand whether patient feel they are better with respect to patient related outcome measures after 6 week of support and advice. Therefore, this project aim to evaluate our PCS against these standard clinical and patient outcome measures and find out if there were improvements in patient care and if patients do feel they are better. Also what is the prevalence of each of the cluster of PCS in Barnet borough including frailty?

What are the project's aims and objectives? Please ensure you incorporate the following 'SMART' areas in your objectives: • *Specific* – target a specific area for improvement • *Measurable* – quantify or at least suggest an indicator of progress • *Achievable* – level of acceptable performance • *Realistic* – state what results can realistically be achieved, given available resources • *Timely* – specify when the result(s) can be achieved For example: By December 31 2021, increase compliance of recording of patients' ethnicity by 50%.	**Aim (s):** To evaluate our PCS against these standard clinical and patient outcome measures and find out if there were improvements in patient care and if patients do feel they are better. Also what is the prevalence of each of the cluster of PCS in Barnet borough including frailty? **Objectives:** 1. To measure Barnet PCS against national clinical outcomes' minimal improvement, after 6 week of post Covid recovery and care 2. To find out if patient related outcome measure improve after 6 week of post Covid recovery advice and therapy intervention 3. To find out the prevalence of each symptoms in long Covid and frailty.

How will you use the results/findings of your project to improve the quality of patient care/service?	The results of the project will help to drive areas for improvement from 1 to 1 in clinic to self -management (use of the APP) to addition of group therapy session and process/pathway improvement
Where will the results and outcomes of this audit be reported for assurance, e.g., team meetings, the Clinical Effectiveness Group, the Patient Risk Group, divisional quality forums, etc.?	Clinical effectiveness group Divisional quality forum CLCH Post Covid forum Clinical audit presentation at The British Thoracic Society, PhD University of Essex Thesis
For clinical audits, please state the main standard (s) e.g. NICE guidance, etc., your clinical audit will be measuring against	NICE COVID-19 rapid guideline: managing the long-term effects of COVID-19 NG 188 2020 NHS National guidance on Post COVID syndrome assessment clinics 2021
Please click on one or more of the checkboxes to indicate the characteristics that apply to your project	☒Local ☐Internal 'must-do' audit ☒National ☒Service improvement ☐External 'must-do' audit ☐Personal development

Please add any other information you feel is relevant to this proposal.	

Impact of Physical Frailty on Pulmonary Rehabilitation and Hospitalisation in COPD

Kola Akinlabi, Binny Patel, Ken Johnston, Bunmi Adebajo, Radoslav Trojak, Ahmed Alrajeh, Temitayo Magbagbeola, John R Hurst

European Respiratory Journal 2018 52: PA3642; **DOI:** 10.1183/13993003.congress-2018.PA3642

Abstract

Background: Frailty represents an age related decline in physiological systems with increased risk of hospitalisation and nursing home admission. In 2016, Maddocks and colleagues reported that 61% of frail COPD patients improved in frailty scores after Pulmonary Rehabilitation (PR).

Objectives: To determine the prevalence of frailty in COPD patients referred to PR, to examine the impact of PR on frailty, rate of acute exacerbations of COPD and hospitalisation.

Methods: 46 outpatients with COPD were prospectively enrolled on a PR programme (mean (SD) age 76 (10) years FEV1% predicted 67 (10). Assessments included Fried frailty criteria, rate of exacerbations and hospitalisations.

Results: 35/46 (76%) patients with COPD completed PR. 8/35 (23%) were frail, 20/35 (57%) patients were pre-frail, and 7/35 (20%) were not frail. After six weeks of pulmonary rehabilitation 5/8 frail (63%) no longer met the Fried frailty criteria (p < 0.001), and at 6 months post PR, the number of acute exacerbation and hospitalisation significantly reduced by 65% (43 versus 15) (p< 0.001), and 75% (15 versus 3) (P=0.012) respectively (Tables 1 and 2).

Conclusion: 23% of patients referred to our PR service are frail. PR has a favourable impact on number of exacerbation and hospitalisation in frail COPD patients and can temporarily reverse frailty in a significant proportion of COPD patients.

Frailty

Collapse inline | View popup

	Pre PR Total (%)	Post PR Total (%)	% change	p value
Frail	8(23)	3 (9)	-63%	<0.001
Pre-frail	20 (57)	19 (54)	-5	<0.001
Normal	7 (20)	13 (37)	86	<0.001

Frailty in chronic respiratory disease: direction of response to pulmonary rehabilitation

Kola Akinlabi, Binny Patel, Ken Johnston, Radoslav Trojak, Bunmi Adebajo, Gavin Sandercock

European Respiratory Journal 2020 56: 2928; **DOI:** 10.1183/13993003.congress-2020.2928

Abstract

Background: Frailty has become an important clinical syndrome in chronic respiratory disease (CRD) especially in COPD[1, 2]. The most recent data suggest that pulmonary rehabilitation (PR) is effective in modifying frailty irrespective of the chronic respiratory conditions[2]. However, the direction of response of frailty classifications to PR is unclear.

Objective: This post hoc analysis aims to find out the direction of response of frailty classifications (pre-frail, frail, normal) to PR in CRD patients.

Methods: This is a post hoc analysis of prevalence of frailty in CRD and the clinical outcome in frailty subgroups after PR. The primary outcome was the Fried Frailty criteria and secondary outcomes included the Incremental Shuttle Walk Distance (ISWD), the Six Minute Walk Distance (6MWD) and COPD Assessment Test (CAT).

Results: Results showed that patients classified as pre-frail moved to normal (33% p = 0.002) while those classified as frail moved to pre-frail (18% p = 0.208) after 6 week PR. However, there were no statistically significant differences in pre and post PR in secondary outcomes.

Conclusion: Pre-frail patients and frail patients respond favourably to PR but directions of response in both classifications are different.

Collapse inline | View popup

Table 1

Krukal-Wallis, Pre PR Vs Responders

Fried Frailty Classifications	Pre PR n =114	Post PR n=114 (% change)	Pre PR Vs Responders X^2 p value
Frail	23	11 (50)	11.02 0.004
Pre-Frail	63	61 (53)	
Normal	28	41 (36)	

EUROPEAN RESPIRATORY journal
FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Effectiveness of Post-COVID rehabilitation and impact of frailty in Post-COVID Syndrome

Kola Akinlabi, Binny Patel, Ana-Maria Barfa, Patrick Mallia, Radoslav Trojak, Amalachukwu Ukaere, Gavin Sandercock
European Respiratory Journal 2023 62: PA4522; **DOI:** 10.1183/13993003.congress-2023.PA4522

Abstract

Background: Post COVID syndrome could become a chronic health issue if the needs of COVID-19 survivors are not prioritised. Post COVID rehabilitation is now used to manage various symptoms such as breathlessness, fatigue, brain fog and reduced exercise tolerance. However, the effectiveness of post-covid rehabilitation is unclear. To date, no data has shown if frailty is an associated symptom and its impact on clinical outcomes.

Aim: To determine the effectiveness of Post COVID rehabilitation, the prevalence and impact of frailty in Post COVID syndrome.

Methods: A retrospective data analysis of 179 patients after 6 week of rehabilitation, median (IQR)

Your name:	Today's date:

COPD Assessment Test

How is your COPD? Take the COPD Assessment Test™ (CAT)

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy (0) (X) (2) (3) (4) (5) I am very sad

			SCORE
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm (mucus) in my chest at all	0 1 2 3 4 5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
		TOTAL SCORE	

NHS
Central London
Community Healthcare
NHS Trust

6-Min walk test record sheet

Name:	Date:	Track distance:
O2 Device/ Flow rate:	SpO2:	Blood Pressure:
Borg:2	Heart Rate:	Walking Aid:

1st Test

Time	SpO2	Heart Rate	Borg	Rest time	Distance
0-1 min					
1-2 mins					
2-3 mins					
3-4 mins					
4-5 mins					
5-6 mins					
					Total:

Recovery time	SpO2	Heart Rate	Borg
1 minute			
2 minutes			
3 minutes			

Limiting Factors	SOB	Low SpO2	Leg fatigue	Other (state bellow):

Borg Breathlessness Scale

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe (heavy)
6	
7	Very severe
8	
9	
10	Very, very severe (Maximal)

Central London Community Healthcare NHS
NHS Trust
Your healthcare closer to home

Pulmonary Rehabilitation
Exercise prescription sheet

Patient Name:

Treadmill		**Step-ups**	
Speed (Km/h)		Time (mins)	
Time (mins)		Rounds	
Cycling		**Sit to Stand** **5STS Time:**	
RPM (≥50)		Sets	
Time (mins)		Repetitions	
Biceps Curls **10RM :**		**Leg Extension/Squats** **10RM:**	
Weight (kg)		Weight (kg)	
Sets		Sets	
Repetitions		Repetitions	

COPD Prescription Guidance:

- Speed from 65-85% of VO_{2max} of ISWT or 6MWT
- Weight(Kg) 65-85% for 1 RM or 10 RM.
- 5STS: Time taken for 5 Reps of STS
- Treadmill 80%: (6MWDx10):1000 km/h
- Cycling RPM 60%: Peak work rate(watts)=(0.122x6MWD) +(72.683xHt(m))-117.109
- Aim for BORG 3-4