Mechanisms of COPD Exacerbation Recurrence

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Declaration

I Jaber S. Alqahtani confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Date:
Abstract

Introduction:
People living with chronic obstructive pulmonary disease (COPD) are susceptible to acute deteriorations in respiratory health termed “exacerbations”. Hospitalisations due to exacerbations of COPD are associated with high global health-care burden and cost. Preventing COPD exacerbations resulting in hospital re-admissions is a major target in COPD care. More work is needed to understand the mechanisms of re-admissions, prevent exacerbation recurrence, and find better approaches to prevent exacerbations.

Aims:
To identify risk factors and potential novel predictors for 30- and 90-day all-cause readmission following admission due to COPD exacerbation, as well as to systematically collect ‘uncertainties’ and prioritise resulting research questions in exacerbations of COPD.

Methods:
Firstly, a systematic review was completed to summarise and assess factors associated with 30- and 90-day all-cause readmission following hospitalisation for an exacerbation of COPD. Secondly, we assessed the feasibility and clinical utility of using Forced Oscillation Technique (FOT) in a COPD population admitted to hospital due to exacerbation. We next conducted a prospective cohort study in COPD patients admitted due to an
exacerbation of COPD to identify risk factors of all-cause readmission within 30 and 90 days and find potential biomarkers that can be targeted to improve readmission burden, specifically examining FOT. In addition, a follow-up study was conducted to assess changes from discharge to a 30-day follow-up in physical activity, peak inspiratory flow rate (PIFR) and expiratory flow limitation (EFL) and how these changes relate to the recovery time for symptoms. Finally, we completed the first research prioritisation exercise for COPD exacerbations, with an equal voice to patient and clinicians’ preferences using the well-established, robust, and transparent James Lind Alliance (JLA) methodology.

**Results:**

Based on current literature, comorbidities, previous exacerbations and hospitalisation, and increased length of stay were significant risk factors for 30- and 90-day all-cause readmission after an index hospitalisation with an exacerbation of COPD. FOT was easily used to detect expiratory EFL during hospitalisation due to a COPD exacerbation and an improvement in EFL was associated with a reduction in breathlessness. Previous exacerbations, higher COPD Assessment Test (CAT) score at discharge, frailty, reduced PIFR and increased length of stay were significantly associated with 30-day readmission. 90-day readmissions were significantly associated with previous exacerbations and hospitalisations, higher CAT score at discharge, frailty, depression, lower PIFR and greater EFL in the supine position. The best predictive variable in multivariate analysis for both 30- and 90-day readmission was PIFR at discharge. A final
A top-ten list of research questions was identified from a list of 51 important research questions worthy of further study. The most highly related question was to identify better ways to prevent COPD exacerbations.

**Conclusion:**

We have identified novel and simple predictors for 30- and 90-day all-cause readmission following a COPD exacerbation that help identify patients at highest risk, and to optimise care prior to discharge. We have found important uncertainties and research priorities in the existing evidence for COPD exacerbations, identifying important areas for future investigations.
Impact statement

Re-admissions following COPD exacerbations have a substantial impact on patients and health services. Preventing readmissions in COPD patients after acute exacerbations has been identified as a high-priority treatment goal globally. Therefore, predicting which patients are at greatest risk of readmission and directing potential treatments to decrease or avoid readmissions are critical in this setting, not only to limit the negative impacts on patient outcomes, but also to reduce the financial and resource burden on healthcare.

This thesis has focused on summarising, evaluating, and identifying risk factors and novel predictors for 30- and 90-day all-cause readmission in COPD, along with determining research priorities in exacerbations of COPD to guide future investigations. The main findings of this thesis are: 1) comorbidities, previous exacerbations and hospitalisation, and increased length of stay were significant risk factors for 30- and 90-day all-cause readmission after an index hospitalisation with an exacerbation of COPD; 2) FOT was easily used to detect EFL in hospitalised COPD exacerbation and help track improvements in symptoms; 3) simple and novel predictors including PIFR, CAT score, frailty, and EFL were found to be associated with 30- and 90-day readmission following COPD exacerbation; and 4) we have completed the first research prioritisation exercise for COPD exacerbations.

This thesis has important clinical and research implications. First, clinicians must take a holistic approach including attention to comorbidities in the pre-
discharge care of patients with COPD exacerbations to lessen the potential risk of readmission. Such outcomes have been generated from our systematic review and meta-analysis that have been published in the European Respiratory Review and were cited in the recent 2021 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report.

Second, detecting EFL at COPD exacerbation could be used to identify those with more severe physiological disturbance and to assess their response to treatment during recovery. This could have clinical value in patient monitoring and personalised treatment, by providing an effort-independent, objective test to measure lung function parameters during a COPD exacerbation requiring hospital admission.

Third, my work emphasises the importance of discharge assessments in predicting COPD readmission risk. Clinicians should check PIFR at discharge to guide COPD treatment options, which may reduce readmission risk. Data from this thesis has already been used to inform an application to the National Institute for Health Research (NIHR) to study pre-discharge PIFR assessment as a way to reduce COPD exacerbation readmissions. In addition to the assessment of symptoms using CAT and FOT could be used as a complimentary option to categorise those patients with EFL at discharge who may benefit from additional therapy and early follow-up, aiming to mitigate symptoms and unresolved EFL, and reduce readmission. Identifying patients with severe frailty would facilitate potential rehabilitation programmes following discharge that could decrease readmission, such as post-exacerbation pulmonary rehabilitation.
Finally, this thesis has produced a list of 51 research priorities in COPD exacerbations that can be used by both researchers and funders to shape future research in diagnosis, prevention, and treatment of COPD exacerbation. The list has already informed an NIHR Research for Patient Benefit (RFPB) call, and a further ‘PICO’ question is currently being considered by the NIHR Health Technology Assessment (HTA). Research is of greatest value where it meets the priorities of those directly affected by the condition, both patients and clinicians. The final outcomes of this research have been published in The Lancet Respiratory Medicine.

Because of the coronavirus pandemic 2019 (COVID-19), non-COVID-19 research was suspended to prioritise COVID-19 studies, and this impacted my research. I therefore conducted a rapid systematic review and meta-analysis to evaluate COVID-19 burden on COPD patients and those with history of smoking. PLOS One Journal published this research in 2020 and it has already received more than 450 citations. It was considered their highest impact paper in 2020, cited in 2020 and 2021 World Health Organisation (WHO) guidelines and also in the recent 2021 GOLD report.

Most of the outcomes of this thesis have been disseminated through scientific journals and conferences and work that is currently unpublished will be disseminated in the same way to maximise the impact of our research.
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Table of Contents

ABSTRACT ........................................................................................................................................... 2

IMPACT STATEMENT .......................................................................................................................... 5

ACKNOWLEDGMENT .......................................................................................................................... 8

LIST OF TABLES ................................................................................................................................... 19

LIST OF FIGURES .............................................................................................................................. 22

1. INTRODUCTION ............................................................................................................................ 30

1.1 Chronic Obstructive Pulmonary Disease (COPD) ................................................................. 31

1.1.1 Airway obstruction and lung volumes in COPD................................................................. 34

1.1.2 Aetiology .................................................................................................................................. 36

1.1.2.1 Tobacco smoke .................................................................................................................... 36

1.1.2.2 Indoor and outdoor air pollution .......................................................................................... 36

1.1.2.3 Occupational exposure ....................................................................................................... 38

1.1.2.4 Genes ................................................................................................................................... 38

1.1.2.5 Age and gender ..................................................................................................................... 39

1.1.2.6 Lung growth .......................................................................................................................... 40

1.1.2.7 Asthma ................................................................................................................................. 41

1.1.2.8 Chronic bronchitis ............................................................................................................... 42

1.1.2.9 Infections, Social factors, and COPD as disease of poverty ............................................. 42

1.1.3 Epidemiology ............................................................................................................................ 43

1.1.4 Diagnosis ................................................................................................................................. 45
1.1.4.1 Spirometry ................................................................. 45
1.1.4.2 Assessment ............................................................. 47
1.1.5 COPD management ...................................................... 48
  1.1.5.1 Management of stable COPD .................................... 49
    1.1.5.1.1 Smoking cessation ........................................ 49
    1.1.5.1.2 Vaccination .................................................. 51
    1.1.5.1.3 Pulmonary Rehabilitation .................................. 52
    1.1.5.1.4 Pharmacological treatment ............................... 55
    1.1.5.1.5 Other treatment modalities ............................... 57
  1.1.5.2 Management of COPD exacerbations .......................... 59
    1.1.5.2.1 Definition ................................................... 59
    1.1.5.2.2 Triggers ..................................................... 61
    1.1.5.2.3 Biomarkers at COPD exacerbations ..................... 63
    1.1.5.2.4 Recognition of COPD Exacerbations .................... 66
    1.1.5.2.5 Consequences of Exacerbations ........................ 67
    1.1.5.2.6 Exacerbation association with other comorbidities .... 71
    1.1.5.2.7 Management options ...................................... 72

1.2 COPD and comorbidities ............................................... 73
  1.2.1 Overview ............................................................ 73
  1.2.2 Prevalence of comorbidities in COPD ........................... 74
  1.2.3 Comorbidity impact on COPD outcomes ........................ 77

1.3 COPD hospitalisation .................................................... 78
  1.3.1 Overview of readmission incidence ............................. 80
  1.3.2 Causes of COPD readmission .................................... 80
1.3.3 Cost of COPD readmissions ..................................................... 81
1.3.4 Readmission reduction efforts ................................................. 82

1.4 Expiratory Flow Limitation (EFL) in COPD ................................. 87

1.4.1 Definition of EFL ................................................................. 87
1.4.2 Mechanisms of EFL ......................................................... 88
1.4.3 Common methods for detecting EFL .......................................... 89
  1.4.3.1 Oesophageal balloon techniques ........................................ 90
  1.4.3.2 NEP technique ............................................................. 91
1.2.3.3 Forced Oscillation Technique (FOT) .................................... 93
  1.2.1.3.1 History of FOT ....................................................... 93
  1.2.3.3.2 The mechanisms behind FOT ...................................... 94
  1.2.3.3.3 FOT in COPD ........................................................ 98

2. HYPOTHESES AND AIMS ............................................................ 102

Aims of the project .......................................................................... 103

3. METHODS ...................................................................................... 105

3.1.1 Mechanisms of COPD Exacerbation Recurrence ....................... 106
  3.1.2 Ethical approval ................................................................. 106
  3.1.3 Research design and Targeted population: ............................. 106
  3.1.4 Study setting: ................................................................. 107
  3.1.5 Method of sampling: .......................................................... 107
  3.1.6 Eligibility Criteria: ............................................................ 107
    Inclusion Criteria ....................................................................... 107
    Exclusion Criteria ....................................................................... 107
3.1.7 Statistical consideration ................................................................. 108
  Primary outcome .................................................................................. 108
  Secondary outcomes ............................................................................. 108
  Power calculation: ................................................................................ 109
3.1.8 Recruitment of participants ............................................................. 110
3.1.9 Study Procedure ............................................................................. 110
3.1.10 Follow-up ...................................................................................... 111
3.1.11 Physiological assessments ............................................................... 113
3.1.12 Questionnaires ............................................................................. 120
3.1.13 Statistical plan: ............................................................................. 121
3.1.14 Data Management: ....................................................................... 123
  Confidentiality: ..................................................................................... 123
  Quality assurance: ................................................................................ 123
  Record Keeping and archiving ............................................................... 123
  Finance: ............................................................................................... 124
  Risk assessment: .................................................................................. 124
  Insurance: ........................................................................................... 124

3.2 Prioritisation in Exacerbations of COPD .......................................... 125
  3.2.1 Ethical approval ............................................................................ 125
  3.2.2 The benefits of Research Prioritisation ........................................ 125
  3.2.3 The James Lind Alliance (JLA) ..................................................... 127
  3.2.4 Principles of the JLA ................................................................. 127
  3.2.5 Aims, objectives and scope of the PSP ....................................... 128
  3.2.6 PSPs process ............................................................................... 130
  3.2.7 The five-stage process of this project ........................................ 132
Stage 1: Establishing the PSP and defining project scope .......... 132
Stage 2: Gathering and identifying questions (first survey) .......... 133
Stage 3: Reducing the questions and processing uncertainties ....... 135
Stage 4: Interim prioritisation (second survey) ...................... 136
Stage 5: Priority setting workshop ..................................... 137
Stage 6: Dissemination ..................................................... 138

4. SYSTEMATIC REVIEW AND META-ANALYSIS ..................... 139

4.1 Aim .............................................................................. 140

4.2 Methods ................................................................. 140
  4.2.1 Protocol and Registration ........................................ 140
  4.2.2 Search Strategy ..................................................... 141
  4.2.3 Inclusion Criteria ................................................... 141
  4.2.4 Exclusion Criteria .................................................. 141
  4.2.5 Data Collection ..................................................... 142
  4.2.6 Quality Assessment ................................................ 142
  4.2.7 Data Synthesis ..................................................... 142

4.3 Results ........................................................................ 143
  4.3.1 Description of included studies ................................. 143
  4.3.2 Meta-analysis results .............................................. 145
  4.3.3 Narrative Synthesis: risk factors for all-cause readmission at 30
days .............................................................................. 158
    4.3.3.1 Comorbidities .................................................. 158
    4.3.3.2 Previous COPD Exacerbations and Hospitalisations ...... 158
4.3.3.3 Patient Demographics................................................................. 159
4.3.3.4 Behavioural Risk Factors......................................................... 159
4.3.3.5 Health System-related risk factors............................................. 160
4.3.4 Narrative Synthesis: Risk factors for 90-day all-cause COPD
readmission .................................................................................... 162
  4.3.4.1 Comorbidities.......................................................................... 162
  4.3.4.1 Previous Exacerbations and Hospitalisations, and COPD
Severity ............................................................................................. 162
  4.3.4.2 System-related risk factors......................................................... 163

4.4 Discussion...................................................................................... 169

4.5 Conclusion .................................................................................... 175

5. RELATIONSHIP BETWEEN FORCED OSCILLATION TECHNIQUE
(FOT) PARAMETERS AND CLINICAL CHARACTERISTICS IN
HOSPITALISED COPD EXACERBATION .............................................. 176

5.1 Introduction .................................................................................... 177

5.2 Research questions ........................................................................ 178

5.3 Study design.................................................................................. 178

5.4 Methodology.................................................................................. 179

5.5 Analysis ......................................................................................... 181

5.6 Results .......................................................................................... 181

5.7 Discussion:...................................................................................... 194
5.8 Conclusion: ................................................................. 198

6. PREDICTORS OF 30- AND 90-DAY COPD EXACERBATION READMISSION: A PROSPECTIVE COHORT STUDY ..................... 199

6.1 Introduction ............................................................... 200

6.2 Research questions ..................................................... 201

6.3 Study design ............................................................. 201

6.4 Methodology ............................................................. 201
   6.4.1 Recruitment of participants .................................... 202
   6.4.2 Measurements ..................................................... 202
   6.4.3 Statistical analysis ............................................... 203

6.5 Results .................................................................. 204

6.6 Discussion ............................................................... 228

6.7 Conclusion: ............................................................. 232

7. CHANGES IN INSPIRATORY AND EXPIRATORY FLOW LIMITATION, AND PHYSICAL ACTIVITY FOLLOWING DISCHARGE FROM HOSPITAL AFTER ACUTE EXACERBATION OF COPD .......... 233

7.1 Introduction: ............................................................. 234

7.2 Methods: ................................................................. 234
   7.2.1 Participants .......................................................... 234
   7.2.2 Measurements ..................................................... 235
9.3.2 Summarising the responses and processing ‘uncertainties’ ..... 271
9.3.3 Summarising the responses and processing ‘uncertainties’ ..... 273
9.3.4 Interim prioritisation (second survey) ................................. 273
9.3.5 Priority setting workshop .................................................. 280

9.4 Discussion .................................................................................. 281

9.5 Conclusion: ............................................................................... 284

10. DISCUSSION, CONCLUSION, AND SUGGESTED FUTURE
STUDIES .......................................................................................... 285

APPENDICES .................................................................................... 337

PUBLICATIONS .................................................................................. 381
List of Tables

Table 1. Classification of airflow severity in COPD (1)................................. 46
Table 2. Common comorbidities associated with COPD............................... 75
Table 3. Characteristics of the included studies, with quality assessment. 146
Table 4. Details of 30- and 90-days risk factors for all-cause COPD

readmission. ........................................................................................................ 151
Table 5. Summary of risk/predictive factors associated with 30- and 90-
day all-cause hospital readmission................................................................. 165
Table 6. Characteristics of the index admission between those with

expiratory flow limitation and those without................................................. 182
Table 7. Forced oscillation technique indices at hospitalised COPD

exacerbation ........................................................................................................ 184
Table 8. Changes from admission to discharge between both groups....... 191
Table 9. Characteristics of the index admission between those with 30
days readmission and those with no 30 days readmission. ...................... 207
Table 10. Spirometry and forced oscillation technique indices at

recruitment assessment during admission...................................................... 209
Table 11. Changes from admission to discharge between patients with 30-
day readmission vs. No readmission. .......................................................... 212
Table 12. Univariate analysis for predictors of readmission within 30 days

of index hospitalisation. .................................................................................. 214
Table 13. Multivariable analysis for predictors of readmission within 30
days of index hospitalisation. ....................................................................... 221
Table 14. Sensitivity and specificity (PPV and NPV) of the best predictors

for 30 days readmission.................................................................................. 222
Table 15. Predictors of readmission within 90 days of index hospitalisation ........................................ 224

Table 16. ROC curve (AUC) of the variables for readmission within 90 days ........................................ 225

Table 17. Multivariable analysis for predictors of readmission within 90 days of index hospitalisation ................. 226

Table 18. Sensitivity and specificity (PPV and NPV) of the best predictor for 90 days readmission .................... 227

Table 19. Characteristics of the index admission between those who attend and did not attend the 30 days follow-up. 238

Table 20. Forced oscillation technique indices during admission for COPD exacerbation between those who attend and did not attend the 30 days follow-up ........................................ 239

Table 21. Change from hospital discharge to 30 days follow-up among those who attended the follow-up. .............. 241

Table 22. Correlations between change in mMRC (breathlessness) and change in other outcomes from discharge to follow-up .............. 242

Table 23. Correlations between change in cat and change in other outcomes from discharge to follow-up .............. 243

Table 24. Characteristics of the included studies ........................................ 255

Table 25. Demographic characteristics of respondents to the JLA COPD exacerbation psp. ........................................ 272

Table 26. Ranked 51 questions, with joint rank giving equal weight to lay and HCP ranks. The top 15 questions that went forward to the final workshop are shaded green ........................................ 274
Table 27. The final top ten research priorities for COPD exacerbations, and rank of all sixteen questions discussed at the final workshop. ..... 280
List of Figures

Figure 1. Airway obstruction in COPD (4). Left side shows normal lung with no pathological changes. Right side demonstrates pathological changes including excess mucus, narrowed bronchioles and alveolar destruction. .......................................................... 32

Figure 2. Air trapping in COPD (4). Left side presents healthy airway with normal airway lumen during inspiration and expiration. The right side of this figure shows the airway narrowing in COPD during inspiration and expiration, which lead to air trapping and hyperinflation, as a result breathlessness increased. ......................................................... 33

Figure 3. Standard lung volumes and capacities in healthy and COPD patients. .............................................................................................................. 35

Figure 4. The refined ABCD assessment tool for COPD (3) .................... 48

Figure 5. A spectrum of support for chronic obstructive pulmonary disease (101). ........................................................................................................ 53

Figure 6. A schematic representation of the mechanisms of EFL and its negative effects on COPD patients......................................................... 89

Figure 7. Flow–volume loops of test breath during the negative expiratory pressure (NEP) technique. In COPD patients without EFL, NEP makes an increased flow (a). In EFL COPD patients, the NEP fails to increase flow compared with the previous tidal volume curve (b). ....... 92

Figure 8. Respiratory impedance and its components. Respiratory impedance includes both resistance and reactance. Resistance represents large airway obstruction, while reactance demonstrates small airways. ........................................................................... 95
Figure 9. Low and high frequencies and lung periphery. Low frequencies reach lung periphery, while high frequencies represent upper and middle airways. ................................................................. 96

Figure 10. Detection of expiratory flow limitation by forced oscillation technique (340). Ca = compliance; Caw = airway compliance; EFL = expiratory flow limitation; Rrs = total respiratory input resistance; Xexp = mean value of Xrs during expiration; Xinsp = mean value of Xrs during inspiration; Xrs = total respiratory system reactance; ΔXrs = mean inspiratory minus mean expiratory reactance. ............................... 97

Figure 11. Flow chart of the collected measurements................................. 112

Figure 12. ndd EasyOne® Air spirometer. .................................................. 114

Figure 13. Resmonpro for measurement of expiratory flow limitation. ...... 116

Figure 14. Yamax digi-walker sw-200 pedometer device and how to wear it. ........................................................................................................ 117

Figure 15. InCheckTM DIAL........................................................................... 119

Figure 16. Logo of research prioritisation in exacerbations of COPD. ...... 126

Figure 17. Usual PSP process........................................................................ 131

Figure 18. The five-stage process described by the JLA. ......................... 133

Figure 19. PSP evidence checking strategy. ............................................... 136

Figure 20. PRISMA flow diagram............................................................... 144

Figure 21. Summary of risk factors associated with 30- and 90-day all-cause hospital readmission following a hospitalised exacerbation of COPD. ...................................................................................... 164

Figure 22. Pooled adjusted ORs for heart failure........................................ 167

Figure 23. Pooled adjusted ORs for renal failure. ..................................... 167
Figure 24. Pooled adjusted ORs for depression. ................................. 168
Figure 25. Pooled adjusted ORs for alcohol use.............................. 168
Figure 26. Pooled adjusted ORs for female gender......................... 169
Figure 27. Consort diagram....................................................... 185
Figure 28. Correlation between FEV\textsubscript{1} and EFL................... 186
Figure 29. Correlation between FEV\textsubscript{1} and Rrs\textsubscript{5Hz}........... 187
Figure 30. Correlation between FVC and EFL.............................. 188
Figure 31. Correlation between BMI and EFL............................. 188
Figure 32. Consort diagram....................................................... 206
Figure 33. ROC curve of the significant predictors in the univariate logistic regression. ............................................................. 215
Figure 34. ROC curve of the combined variables for readmission within 30 days. .............................................................................. 221
Figure 35. ROC curve of the combined variables for readmission within 90 days. .............................................................................. 227
Figure 36. A summary of the used methods in this chapter. ............... 235
Figure 37. Consort diagram of the study....................................... 237
Figure 38. PRISMA flow diagram............................................... 254
Figure 39. Pooled prevalence of COPD with confirmed COVID-19, (es: effect size). ................................................................. 258
Figure 40. Pooled prevalence of current smokers with confirmed COVID-19, (es: effect size). ................................................................. 260
Figure 41. Five-stage James Lind Alliance priority setting partnership for exacerbations of COPD: a summary. ................................. 270
Abbreviations

$\Delta$Xrs$_{5Hz}$: Within Breath Difference in Reactance At 5Hz

6MWT: Six-Minute Walking Test

AATD: Alpha1-Antitrypsin Deficiency

ABG: Arterial Blood Gas

ARNS: Association of Respiratory Nurse Specialists

ACE2: Angiotensin Converting Enzyme 2

ACO: Asthma-Chronic Obstructive Pulmonary Disease

ACPRC: Association of Chartered Physiotherapists in Respiratory Care

AECOPD: Acute Exacerbation Of COPD

ATS: American Thoracic Society

BAME: Black Asian and Minority Ethnic

BLF: British Lung Foundation

BMI: Body Mass Index

BNP: Brain Natriuretic Peptide

BOLD: Burden of Obstructive Lung Diseases

BTS: British Thoracic Society

CAT: COPD Assessment Test

CHF: Congestive Heart Failure

CI: Confidence Interval

COLD: Canadian Obstructive Lung Disease
COPD: Chronic Obstructive Pulmonary Disease

COVID-19: Coronavirus Pandemic 2019

CPAP: Continuous Positive Airway Pressure

CRP: C-Reactive Protein

DH: Dynamic Hyperinflation

DPI: Dry Powder Inhaler

EBV: Endobronchial Valves

EELV: End Expiratory Lung Volume

EFL: Expiratory Flow Limitation

eGFR: Estimated Glomerular Filtration Rate

ERV: Expiratory Residual Volume

ES: Effect Size

EXACT: Exacerbations of Chronic Obstructive Pulmonary Disease Tool

FDA: Food and Drug Administration

FEV₁: Forced Expiratory Volume in One Second

FL%: Flow Limitation Percentage

FOT: Forced Oscillation Technique

FRC: Functional Residual Capacity

FVC: Forced Vital Capacity

GOLD: The Global Initiative for Chronic Obstructive Lung Disease

HADS: Hospital Anxiety and Depression Scale
HCPs: Health Care Providers

HF: Heart Failure

HRA: Health Research Authority

Hrql: Health-Related Quality of Life

HRRP: Hospital Readmissions Reduction Program

HTA: Health Technology Assessment

IC: Inspiratory Capacity

ICS: Inhaled Corticosteroid

ICU: Intensive Care Unit

IL-6: Interleukin 6

ISWT: Incremental Shuttle Walk Test

JLA: James Lind Alliance

JRO: Joint Research Office

KPa: Kilopascal

LABAs: Long-Acting Beta₂ Agonists

LAMAs: Long-Acting Antimuscarinics

LBW: Low Birth Weight

LLN: Lower Limit of Normal

LVRS: Lung Volume Reduction Surgery

MCID: Minimal Clinically Important Difference

MERS: Middle East Respiratory Syndrome
mMRC: Modified Medical Research Council

MTS: Mental Test Score

NEP: Negative Expiratory Pressure

NHS: National Health Service

NIHR: National Institute for Health Research

NIV: Non-Invasive Ventilation

NPV: Negative Predictive Value

OR: Odd Ratio

OSA: Obstructive Sleep Apnoea

Pao\textsubscript{2}: Partial Pressure of Oxygen

PCR: Polymerase Chain Reaction

PCRS: Primary Care Respiratory Society

PCT: Procalcitonin

PCV13: Pneumococcal Vaccine 13

PEEP: Positive End Expiratory Pressure

PIFR: Peak Inspiratory Flow Rate

PPSV 23: Pneumococcal Polysaccharide Vaccine 23

PPV: Positive Predictive Value

PR: Pulmonary Rehabilitation

PRISMA: Preferred Reporting In Systematic Reviews And Meta-Analyses

PSP: Priority Setting Partnership
REFS: Reported Edmonton Frailty Scale

RFPB: Research for Patient Benefit

ROC: Receiver Operating Characteristic

Rrs: Resistance

$\text{Rrs}_{5\text{Hz}}$: Resistance At 5 HZ

RSV: Respiratory Syncytial Virus

RV: Residual Volume

SABAs: Short-Acting Beta$_2$ Agonists

SAMAs: Short-Acting Antimuscarinics

SARS: Severe Acute Respiratory Syndrome

SARS-Cov-2: Severe Acute Respiratory Syndrome Coronavirus 2

SPSS: Statistical Package for The Social Sciences

UK: United Kingdom

ULN: Upper Limit of Normal

US: United States

WCC: White Cell Count

WHO: World Health Organisation

Xexp: Within-Breath Expiratory Reactance

Xinsp: Within-Breath Inspiratory Reactance

Xrs: Reactance

Zrs: Impedance
1. Introduction
The introduction sets out the context to the main subject areas explored in this PhD thesis: Chronic Obstructive Pulmonary Disease (COPD) and, particularly, COPD exacerbations and COPD Readmission with brief literature regarding the possibility of using the Forced Oscillation Technique (FOT) for COPD exacerbations.

1.1 Chronic Obstructive Pulmonary Disease (COPD)

COPD is defined by The Global initiative for Chronic Obstructive Lung Disease (GOLD) strategy document as “a common preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases” (1). COPD is best characterised as a clinical condition of persistent respiratory problems, anatomical abnormalities of the pulmonary system, including airway diseases or emphysema or both, loss of lung function, which is not reversible, or combination of these (2). The main physiological site of airflow obstruction in COPD is in the small airways. Progressive disease changes are also seen in the large airways (chronic bronchitis) or in lung parenchyma (emphysema) (Figure. 1). Such pathological changes are generally caused by significant exposure to harmful particles or gases, such as tobacco smoke. The most common symptoms of COPD patients include dyspnoea, cough with or without phlegm production, chest tightness and wheezing (3).
Due to structural changes in the lungs, airflow limitation through COPD is not reversible in many cases. Such structural changes include chronic bronchiolitis, due to fibrosis of the small airways (<2mm internal diameter) and emphysema, which is characterised by alveoli extension and alveolar wall destruction. Indeed, chronic bronchitis is associated with mucus hypersecretion and has been clinically described as a “chronic productive cough for 3 months in each of 2 successive years in a patient in whom other causes of productive chronic cough have been excluded” (5). On the other hand, emphysema results in lower alveolar surface area due to the...
destruction of pulmonary alveoli, which impairs gas exchange and ultimately contributes to hypoxia. The loss of alveolar attachments due to emphysema, in addition to the fixed narrowing of small airways, leads to a premature closure of the small airways upon expiration, which subsequently causes air trapping (1, 5). Air trapping causes lung hyperinflation, known as increased total lung capacity (TLC), and a rise in resting lung volume, which is represented by functional residual capacity (Figure 2) (6).

**Figure 2. Air trapping in COPD (4).** Left side presents healthy airway with normal airway lumen during inspiration and expiration. The right side of this figure shows the airway narrowing in COPD during inspiration and expiration, which lead to air trapping and hyperinflation, as a result breathlessness increased.
1.1.1 Airway obstruction and lung volumes in COPD

The imbalance between the elastic recoil of the lungs that promotes flow and the resistance of the airways that restricts flow is the major cause of airflow obstruction in COPD (7). Elastic recoil is defined as the lung’s ability to deflate after expansion, which preserves small airway patency through radial alveolar attachments and contributes to the driving pressure during expiration (8). Damage to elastic fibres and loss of alveolar surface area in emphysema results in a loss of elastic recoil, which consequently leads to narrowing and premature closure of the airways. There are other factors that can contribute to airway obstruction such as secretions, the increased tone of bronchial smooth muscle and the hypertrophy of submucosal glands (9).

Figure 3 shows a summary for the standard lung volumes and capacities in healthy people and COPD patients. A decrease in elastic recoil forces leads to an increase in functional residual capacity (FRC) and TLC, a condition known as static hyperinflation (10). An increased FRC decreases inspiratory capacity (IC) and restricts the rise in tidal volume (VT) that occurs in response to increasing ventilatory demands caused by exercise or other stresses (7). During exercise, end expiratory lung volume (EELV) increases in COPD and can lead to dynamic hyperinflation (DH) that can also impede venous return to the thorax, worsening gas exchange and cardiopulmonary hemodynamic even more (10). Hyperinflation has previously been demonstrated to be the primary cause of decreased inspiratory muscle strength in COPD patients, which can negatively affect PIFR (11). All in all, reduced elastic recoil forces in COPD can cause static
hyperinflation, DH, and expiratory airflow limitation. All of which are likely important causes to resting dyspnoea and decreased exercise capacity in emphysema patients (7, 10).

**Figure 3.** Standard lung volumes and capacities in healthy and COPD patients.
1.1.2 Aetiology

The most widely known global trigger factor for COPD is cigarette smoke. However, COPD can also be formed in non-smokers (1). Nevertheless, COPD is a clinical syndrome outcome of a dynamic interaction of long-term chronic exposure to toxic gases, coupled with a number of body host variables, including airway hyperresponsiveness and impaired lung development (12, 13). The risk factors associated with the development of COPD are now described.

1.1.2.1 Tobacco smoke

Globally, the main cause of COPD is cigarette smoking; a high percentage of people diagnosed with COPD have had history of smoking, indicating that those who smoke are more likely to develop COPD (6). Indeed, compared to non-smokers with chronic airflow limitation, people who smoke have a higher prevalence of respiratory symptoms and lung function abnormalities, a greater annual decreased rate of FEV₁ and greater mortality rate (14). Further studies have also showed that other tobacco types (such as pipe, cigar, and water pipe) and marijuana were found to be risk factors for developing COPD (15-18).

1.1.2.2 Indoor and outdoor air pollution

Results from the increased number of published studies over the past decade have shown that other risk factors aside from smoking strongly
relate to COPD, such as indoor and outdoor air pollution. Around 50% of
global city households and 90% of rural households use biomass fuel
(wood, carbon, and animal dung) and coal as their main source of domestic
energy. Worldwide, around 3 billion people are exposed to the use of
biomass fuel compared to 1.01 billion smoking tobacco, proposing that the
most important global risk factor for COPD may be exposure to biomass
smoke (19). Several studies consider biomass smoke to be a significant risk
factor for COPD (20-22). A meta-analysis conducted by June et al. showed
that exposure to biomass smoke was significantly associated to COPD (odd
ratio 2.3, 95% CI 1.5–3.5), acute respiratory-tract infections (3.64, 2.1–6.4)
and wheezing (2.1, 1.5–2.9) (23). On the other hand, in the UK in 1958, the
contribution of outdoor air pollution to COPD was studied in postal staff
where the prevalence of COPD was higher for workers in more polluted
areas; the association of which was independent of smoking (24). These
findings were reinforced by studies carried out with the UK and the United
States’ (US) general public for people living near a road with heavy traffic
(25-27). Especially in developing countries, increased gas and particulate
matter levels in urban ambient air were found to be related to an increase
in respiratory morbidity and cardiovascular death, and possibly COPD (28).
The link between high outdoor air pollutant concentrations and COPD
exacerbation and the deterioration of existing COPD is supported by robust
evidence (29, 30).
1.1.2.3 Occupational exposure

The correlation between specific occupational exposure (crop farming, animal farming, dust, chemicals, pollutants) and the development of COPD has been demonstrated by several studies, accumulated over the past two decades (22). In 2003, the American Thoracic Society (ATS) conducted a comprehensive analysis of contemporary literature and its relevant role in occupational causes of obstructive airway disease pathogenesis (asthma and COPD). They found that nearly 15% of COPD cases could be attributable to workplace exposure (31). A systematic review was conducted in 2014 to reassess the relationship between occupational exposure and the risk of COPD and found strong and consistent evidence to support a causal association between multiple categories of occupational exposure and COPD, both within and across industry groups (32).

1.1.2.4 Genes

Though COPD incidence is closely linked to smoking, the variable nature of the obstruction of persistent airflow among smokers often indicates certain factors can also affect its occurrence and progression. The likelihood of having COPD at a primary stage is around three times greater in the family of COPD patients who smoke tobacco than smokers in the general public, while the incidence of persistent airflow obstruction by the non-smoking first-grade families of COPD patients is comparable, albeit small, relative to the risk of non-smokers in the general community (33-36). Alpha1-antitrypsin deficiency (AATD) has been the most prominent genetic risk
factor for COPD so far, although others exist (37). α1-Antitrypsin (AAT) is a serine protease inhibitor, which is a potent enzyme with large substrate specificity, which defends lungs against proteolytic damage by inhibiting neutrophil elastases. Asymptomatic AATD diagnosis is particularly helpful because strong associations occur between smoking cessation and improved physical and psychosocial outcomes; people with AATD are aware that they are predisposed to COPD (38). Hobbs et al. found in a larger cohort of patients, 22 COPD related genetic loci, of which 13 represented new associations with COPD. The odd ratios for these 22 loci ranged from 1.05 to 1.25, suggesting that only a small proportion of COPD risk is explained by human genetic variability (39). Indeed, it is important to fully grasp the impact of these genetic and epigenetic modulators until they can be incorporated into clinical settings.

1.1.2.5 Age and gender

Among subjects over 40 years of age, COPD prevalence is more prevalent when compared to those under 40 years of age, independent of the diagnosis criterion used (1). Although most longitudinal studies reported that the incidence of COPD increases with age, it is not known if age can be considered as a contributing factor for the development of COPD owing to long-term causative agent exposure (40). COPD has been identified in the past as a condition predominantly impacting elderly men, indicating the high incidence of smoking among men (41). Nevertheless, the condition has shifted, and today COPD is regularly found in women, as the incidence of
female smokers has steadily risen. COPD remains much more common in women than men in many developing countries (42). Indeed, according to a gender difference study, COPD in females with an early age condition (<60 years) tend to have more severe disease, despite lower levels of smoking exposure (43). A systematic review and meta-analysis of 11 studies found that female smokers had an annual FEV\textsubscript{1} decline higher than males, while they consume fewer cigarettes (44). Generally, female smokers are also about 50% more likely than men to experience COPD. In fact, female patients with severe COPD are at a higher risk of hospitalisation and mortality from respiratory failure and comorbidity (45). Lastly, recognising gender disparities in COPD vulnerability and development aims to give fresh perspectives into fundamental causes and strengthen treatment options.

1.1.2.6 Lung growth

Conditions that affect pulmonary development during pregnancy and infancy, such as low birth weight (LBW) or respiratory diseases, can increase an individual's likelihood of developing COPD (1). A study conducted to assess the influence of birth weight and respiratory infection during childhood on lung function reported that LBW and respiratory diseases in infants are correlated with decreased lung function in adults and increased COPD mortality (46). Another study found that premature children of smoking mothers had some respiratory function impairment compared to their born-at-term siblings (47). Indeed, having a plan for
tracking the progress of chronic respiratory diseases with prematurely born babies is important in protecting them from COPD as adults.

1.1.2.7 Asthma

Longitudinal studies have shown a relationship between childhood asthma and low lung function, which resulted in reduced either FEV₁, escalated decline in FEV₁ or premature onset of decline in FEV₁ (48). Low lung function parameters predispose eventual COPD. These findings were supported by a long-term population cohort (it was followed from birth to age 38, including 1,037 subjects) conducted in New Zealand, which showed that 40% of persistent childhood asthmatics developed COPD (49). Furthermore, a major retrospective study of 3,099 patients tracked over a span of 20 years showed that asthma patients are 12.5 times more likely to develop COPD (50). A recent systematic review and meta-analysis reported that people with a asthma background (childhood or adult asthma) have a 7.2-fold rise in risk of developing COPD (51). While the two disorders share several similar clinical characteristics (cough, wheezing and breathlessness) and anatomical anomalies (obstruction of airflow), they are typically treated as different entities with distinct pathologies (52). However, asthma-chronic obstructive pulmonary disease (ACO) is an overlap syndrome, proposed and introduced as a separate entity. ACO is a specific clinical presentation with chronic airway disorder where individuals with some symptoms, generally asthma-related, and others commonly COPD linked (53). Thus far, there is no standard definition of ACO, therefore future
research and debates should be continued to explore whether ACO is a distinct clinical entity in order to improve patient care and clinical outcomes.

1.1.2.8 Chronic bronchitis

Chronic bronchitis is present in about 14 to 74% of COPD patients, while air pollution, the inhalation of toxic gases and gastrointestinal reflux disease, have also been associated with this condition (54). The cumulating rate of chronic bronchitis in continuous smokers was 42%, 26% in former smokers, and 22% in those who have never smoked in a 30-year longitudinal study that included 1,711 subjects (55). Chronic mucus hypersecretion was found to be an early developmental phase of COPD in middle-aged smokers. This was significantly associated with greater FEV₁ decline in COPD patients (56). Altogether, chronic bronchitis is subject to numerous clinical effects including increased exacerbation, accelerated decline in lung function, poorer health quality of life, and potentially increased death (57-59).

1.1.2.9 Infections, Social factors, and COPD as disease of poverty

Early-life respiratory infections are one of the main factors for increased the risk of developing COPD (40). Viruses primarily trigger infant respiratory diseases, and such viruses can lead to long-lasting changes in the airways, which would increase susceptibility to COPD (60-62). Therefore, other significant determinants of COPD are respiratory infections in infancy and
such a history of these infections can be considered in future COPD treatment plans.

Several studies have also reported a strong link between low socioeconomic status (poverty) and a higher prevalence of COPD, as well as poorer COPD outcomes (63, 64). Nowadays, a growing share of the burden of COPD increasingly falls in low- and middle-income countries, which also indicates COPD as a disease of poverty (65). Determinants of socioeconomic disparity, such as poor indoor and outdoor air quality, differences in health behaviours, socio-political factors, low birth weight, incomplete immunisation and undernutrition and crowding can also have a major role in the increased prevalence of COPD in these countries (66, 67). Developing strategies to targeting disparities in respiratory diseases are needed to reduce the magnitude of COPD in these vulnerable people.

1.1.3 Epidemiology

According to a Global Burden of Disease study (68), there were 251 million COPD cases worldwide in 2016. An estimated 3.17 million deaths were caused by COPD in 2015, accounting for 5% of all global deaths, and projections suggest COPD will soon be the third leading cause of death worldwide (68). Research in high-income countries have recorded broad differences in the prevalence and occurrence of COPD, both within and across nations. This is attributable to inherent demographic variations between regional areas, which may also be attributed to a variety of
variables, including the sampling processes, different communities surveyed, and the number of parameters used to identify COPD (69). In the US, prevalence rates vary from 10.2% to 20.9%, where spirometry standards used were associated with this variation in reported studies (70-72). Similar to these studies, the Burden of Obstructive Lung Diseases (BOLD) study reported a prevalence of 19.6% at its US site and this study was using the GOLD definition of COPD (73). In Canada and Australia, the prevalence was self-reported, but still, physician-diagnosed COPD ranged from 8.5% to 18% (71, 74), which demonstrates similar terms to US estimates, but the rates reported in BOLD and Canadian Obstructive Lung Disease (COLD) studies were 19.3% and 17.4% for Canada correspondingly, and 19.2% in Australia (73, 75).

Throughout Europe, COPD rates ranged from 3% to 26.1% and this prevalence is in line with GOLD criteria (76, 77). However, when using physician diagnoses, similar differences were recorded in a survey of some European countries with 2.8% in Italy, 12% in Sweden and 6.2% in a combined survey of eight European cities (78-80). In the UK, the number of individuals reported with COPD is estimated at 1.2 million in 2012, far higher than the Department of Health’s initial 835,000 in 2011. This illustrates that COPD is the second most prevalent lung condition following asthma in the UK across reported cases (81); around 2% of all people and 4.5% over 40 years of age live with a COPD diagnosis. The rate of cases with COPD over the past decade has risen by 27%, from fewer than 1,600 to nearly 2,000 per 100,000. This could be justified by an increase in non-diagnosed COPD
cases. In fact, the prevalence of COPD in men is estimated to be 10% higher than in women in 2012.

Throughout 2012, there were 29,776 COPD fatalities (5.3% of overall UK mortality and 26.1% of lung-related fatalities). Indeed, COPD is one of the three leading contributors to respiratory mortality, along with lung cancer and pneumonia, in developed countries such as the UK (81).

1.1.4 Diagnosis

Based on GOLD, COPD should be suspected in any individual suffering from dyspnoea, sputum production, exacerbation, or chronic cough, and/or a history of exposure to disease risk factors.

1.1.4.1 Spirometry

A pulmonary function examination, specifically spirometry, is needed in order to validate the diagnosis if one or more of the above symptoms arise (1). Pulmonary function testing is required to confirm a COPD diagnosis and the spirometric ratio for airflow limitation demonstrating FEV$_1$/FVC < 0.70 post-bronchodilator. However, compared to the use of a cut-off based on the lower limit of normal (LLN), the use of fixed FEV$_1$/FVC ratio to confirm COPD diagnosis may lead to under-diagnosis in young adults and over-diagnosis of COPD in elderly (82, 83). LLN values depend on valid reference equations, and thus far there is no studies validating the use of LLN. According to GOLD 2021, the use of the fixed ratio is favoured over LLN because of the diagnostic simplicity and consistency (1).
Spirometry is not only helpful in diagnosis, but also in the assessment (such as therapeutic decisions) and follow-up of COPD to assess those with rapid decline.

The classification of airflow limitation severity is based on post-bronchodilator FEV₁, which ranges from GOLD 1 (mild) to GOLD 4 (very severe) (3). Such classifications are demonstrated in Table 1 (1).

### Table 1. Classification of airflow severity in COPD (1).

<table>
<thead>
<tr>
<th>GOLD grade</th>
<th>Severity</th>
<th>FEV₁ % predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD 1</td>
<td>Mild</td>
<td>FEV₁ ≥80% predicted</td>
</tr>
<tr>
<td>GOLD 2</td>
<td>Moderate</td>
<td>50%≤ FEV₁ &lt;80% predicted</td>
</tr>
<tr>
<td>GOLD 3</td>
<td>Severe</td>
<td>30%≤ FEV₁ &lt;50% predicted</td>
</tr>
<tr>
<td>GOLD 4</td>
<td>Very severe</td>
<td>FEV₁ &lt;30% predicted respiratory failure</td>
</tr>
</tbody>
</table>
1.1.4.2 Assessment

In order to eventually direct treatment, COPD assessments should be conducted to evaluate the degree of airflow limitation, its effect on a patient's health condition, and the possibility of potential events (such as exacerbations, hospitalisations or death) (1).

The COPD assessment must independently consider the following elements of the disease to accomplish these objectives:

- Evidence and extent of spirometric abnormality
- Acute nature and severity of symptoms of the individual
- Exacerbation history
- History of comorbidity

Due to a weak correlation between FEV₁, symptoms and impairments to quality of life, and exacerbation, the ‘ABCD’ tool, introduced in the 2011 GOLD update, included a patient symptoms assessment. It involved a combined assessment consisting of spirometric classification, symptomatic assessment (such as dyspnoea) and exacerbation history (Figure 4) (84).

Patients should undergo a spirometry test, then an assessment of symptoms, and finally their history of exacerbations ought to be recorded.

To summarise, the spirometric grading from one to four can provide clinical information on the severity of airflow limitation, while the letter groups (A to D) can provide information regarding the symptoms and exacerbations burden, which can be used to guide clinicians to initiate appropriate therapy, independent of the spirometric value. The ‘ABCD’ assessment recognises
the limitations of FEV₁ in making treatment decisions and the importance of patient-reported outcomes in guiding COPD interventions (84).

**Figure 4. The refined ABCD assessment tool for COPD (3).**

![Refined ABCD assessment tool for COPD](image)

1.1.5 COPD management

Effective interaction between patients and clinicians and appropriate follow-up is important to optimise COPD management (85). Emphasis on non-pharmacological and pharmacological care is also required as well as on the behaviour of patients, not simply medication adherence (86). Self-management strategies are common, but caution is needed as self-management trials have produced inconsistent findings (4). To guide management in COPD patients, an assessment of airflow obstruction severity, symptoms, history of exacerbations, previous exposure to risk factors and a history of co-morbidities should be conducted (1). The
management of COPD is divided into two sections: stable COPD management and non-stable (exacerbation) management.

### 1.1.5.1 Management of stable COPD

The management of stable COPD (non-exacerbating illness) can be categorised into: decreased exposure to harmful substances and, relieve symptoms and reduce risk, including risks of exacerbation (1). According to the NICE guidelines, the overarching five fundamentals of care in COPD are: 1) offering support and treatment to stop smoking, 2) offer pneumococcal and influenza vaccinations, 3) offer pulmonary rehabilitation, 3) co-develop a personalised self-management plan, and 5) optimise treatment for co-morbidities (87). Such interventions should be checked at each patient visit. The stable COPD management includes non-pharmacological and pharmacological interventions, as discussed below.

#### 1.1.5.1.1 Smoking cessation

The primary cause of COPD is cigarette smoke. Therefore, the cessation of smoking is the most effective way to influence the natural background of all prevention approaches. Smoking cessation has a considerable effect on future COPD development and death rate on top of other symptoms (88). Nonetheless, because COPD is the result of accumulated exposure, internationally biomass fuel exposure plays an important role, thus the reduction in exposure must be viewed in a wider sense (4). Indeed,
cessation of the smoking cycle is not a simple or easy process, and on average, a smoker may attempt to quit many times before success. In general, the rate of success in long term tobacco cessation about 25% (89). However, in comparison to single smoking prevention measures, the success rate was seen to increase following public building smoking bans (90).

According to a systematic review concerning the impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness and inflammation, smoking cessation was found to greatly reduce respiratory symptoms and bronchial hyperreaction and reduce the accelerated decline in FEV₁ (91). Symptoms such as cough, phlegm and wheeze were decreased within 1–2 months after smoking cessation. Indeed, cessation is the most successful non-pharmacological intervention to combat COPD progression and to improve mortality and decrease morbidity. An adequate counselling system, either individual or in groups, should be conducted to support cessation trials for COPD patients (92). According to a Cochrane systematic review, a mixture of behavioural management and pharmacotherapy is in effect in assisting COPD smokers to quit (93).

It’s also important to reduce exposure to smoke from biomass fuel in order to decrease the prevalence of COPD. Such reduction can be done using efficient ventilation and non-polluting cooking stoves (1). Therefore, smoking cessation and reducing exposure to biomass smoke should be the highest priority in stable COPD management.
1.1.5.1.2 Vaccination

Vaccination against influenza prevents hospitalisations owing to reduced lower airway infections resulting in hospitalisation and mortality in COPD patients (94, 95). A population-based research study also shows that COPD patients, particularly older patients with influenza vaccines had a decreased risk of ischemic heart disease over several years (96). Any patients aged 65 and over are indicated for pneumococcal vaccination with Pneumococcal vaccine 13 (PCV13) and Pneumococcal Polysaccharide Vaccine 23 (PPSV23) (1). For certain younger patients with serious chronic lung and/or cardiovascular disorder, PPSV23 is recommended over PCV13 (1). For severe COPD patients younger than 65 with FEV$_1$ <40% who obtained the PPSV23 vaccine, the prevalence of community-acquired pneumonia declined (97). Regarding PCV13 vaccine, in adults aged 65 years or older, the impact of PCV13 was substantially successful in preventing vaccine-acquired pneumonia and its efficacy lasted for a period of four years (98). Concerning COVID-19 vaccination, patients with COPD were prioritised with other lung diseases such as bronchiectasis and cystic fibrosis to receive the vaccination within the first phase of vaccination.

To sum up, vaccination against influenza is recommended annually for all stable patients with COPD, the PPSV23 pneumococcal is recommended in younger COPD patients with FEV$_1$ <40% of predicted, and lastly, the PCV13 vaccination is recommended for all patients 65 and older (1). As COPD patients are considered clinically extremely vulnerable group,
receiving the vaccination as soon as possible would lessen the COVID-19 burden on COPD patients.

1.1.5.1.3 Pulmonary Rehabilitation

Pulmonary rehabilitation (PR) is defined as “a comprehensive intervention based on thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, self-management intervention aiming at behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors” (99). It was originally established by the American College of Physicians Committee in 1974, which depended on a holistic strategy to reduce the effects of COPD, enhance the health-related quality of life (HRQoL) and increase physical and emotional participation in daily life (100). Indeed, PR has been recognised as a core component in COPD integrated care to optimize the management of the complex nature of COPD (Figure 5).
PR can begin at any stage of the disease, including clinical stabilisation periods or during or immediately after a COPD exacerbation (102). Assessing the efficacy of a PR programme is typically achieved by evaluating exercise capacity at the start and the end. The six-minute walking test (6MWT) and the incremental shuttle walk test (ISWT) are the most common measures when assessing exercise capacity and general patient performance in PR programmes (99). The 6MWT is a self-paced exercise that tests a person's distance on a 30-meter pathway, continuously walking back and forth for six minutes. The minimal clinically important difference (MCID) of 6MWT for COPD was estimated to be 54 (95% CI, 37–
71) m (103), whereas other studies indicate lower estimates between 25 and 35 m (104-106), whereby the average improvements after PR are approximately 50 m (99). On the other hand, the ISWT is a pre-pace exercise that tests the distance travelled in a 10-meter course where patients move up and down synchronising with bleeps that become more frequent and allow patients to quicken their step in line with the bleeps (107). Unlike 6MWT, the walking speed in the ISWT is set and less influenced by motivation or self-selected pacing. Therefore, the ISWT is more standardised and a symptom-limited maximal exercise capacity test in reality when compared to 6MWT (108). The MCID of ISWT is 47.5 m, with overall improvements ranging between 50 and 75 m (99, 109). Recently, the MICD of ISWT changed to 35.0 and 36.1 m (110).

Indeed, several prior studies have noted the importance of PR in improving COPD outcomes. Compared to usual care following PR completion, continued supervised maintenance exercise reduces exacerbations, hospital admissions and COPD mortality (111). Two Cochrane reviews published in 2015 and 2016 found that PR improves dyspnoea and fatigue, increases emotional function, HRQoL and exercise capacity, and boosts the sense of control that COPD patients have over their condition (112, 113).

In conclusion, PR has already been identified as a preferred non-pharmacological intervention with numerous benefits for a large number of elderly people with COPD. Therefore, apart from other therapies and coping techniques such as smoking cessation, it is recommended that PR should be available and provided to all COPD patients to achieve better outcomes.
1.1.5.1.4 Pharmacological treatment

COPD pharmacology is used to alleviate symptoms, minimise the occurrence and frequency of exacerbations and enhance exercise capacity and wellbeing. There are many pharmacological agents that used in the management and stability of COPD; for instance, bronchodilators, anti-inflammatory agents and mucolytics. Bronchodilator therapy is the cornerstone of the pharmacological control of symptoms, mainly treating breathlessness (1). Such bronchodilators include β2-agonists and muscarinic receptor antagonists (anticholinergics) such as short-acting beta2 agonists (SABAa) and long-acting beta2 agonists (LABAa), and short-acting antimuscarinics (SAMAa) and long-acting antimuscarinics (LAMAs). According to GOLD, in improving FEV1 and symptoms, a combination of SABA and SAMA is superior compared to each drug alone (1).

Indeed, when managing a stable COPD patient, inhaled long-acting 12–24-hour bronchodilators are favoured, in which LABAs and LAMAs are equally efficient in improving lung function, symptoms, quality of life and reducing COPD exacerbations (85). The symptomatic influence of long-acting bronchodilators is attributed, not to reduced airflow limitations in COPD, but to the effect on active lung volumes. For this cause, there is a limited association between FEV1 effects and patient symptoms (114). Side effects of β2-agonists are primarily restricted to tremor and hypokalaemia, while anticholinergics are often restricted to mouth dryness (115). Cardiovascular side effects of long-acting bronchodilators have been discussed, but recent findings suggest that they are effective in patients with stable cardiovascular
disease (116, 117). Although these interventions induce successful bronchodilation, they do not address underlying inflammatory conditions in COPD patients (118).

COPD is a persistent inflammatory disorder, which means that successful anti-inflammatory therapies may minimise the risk of mortality and reduce worsening and exacerbation, as well as reduce COPD-related comorbidities. Anti-inflammatory agents such as inhaled corticosteroid (ICS) can be administered to improve lung function and reducing exacerbations (1). However, the ratio of benefits to negative consequences is inadequate in recommending ICS for symptomatic treatment. It has been reported that use of ICS alone to treat COPD was correlated with an elevated risk of pneumonia, oropharyngeal candidiasis, and hoarseness. However, ICS can be used in combination with bronchodilators for moderate to very severe cases (119). According to GOLD, in certain cases, initial LABA /ICS therapy might be the first choice; this approach is more effective to alleviate exacerbations in those with one exacerbation per year and with blood eosinophil counts ≥300 cells/μL. Further, a cut off level of ≥100 cells/μL can be used to initiate LABA /ICS therapy in those with more than 2 moderate exacerbations per year or at least one severe exacerbation requiring hospitalisation in the prior year (1).

In COPD patients with a history of asthma, LABA/ICS can also be the first option. In a recent RCT that compared the benefits of triple therapy (LAMA/LABA plus ICS) with dual bronchodilation (either ICS/LABA or LAMA/LABA), the rate of moderate or severe COPD exacerbations and hospitalisations was significantly reduced in the triple therapy arm than the
dual bronchodilation group (120). Additionally, antibiotics may be used as a prophylactic strategy in stable COPD patients as they have been related to fewer exacerbations in mild to severe COPD patients (121). Indeed, for those with frequent exacerbations at maximum inhaled treatment or with side effects from ICS, oral macrolides are helpful. However, care should be considered as they can cause bacterial resistance and hearing impairment, and are not recommended for patients with cardiac problems, such as arrhythmia (121). Furthermore, standard treatment with mucolytics (usually used to facilitate sputum expectoration) such as erdosteine, carbocysteine and N-acetylcysteine in COPD patients, not receiving inhaled steroids, can minimise exacerbations and improve health status, but not on lung function or HRQoL (122).

1.1.5.1.5 Other treatment modalities

All COPD patients should be tested for resting hypoxemia. Adding oxygen decreases the risk of mortality when patients have a saturation of less than 88% or a partial pressure of arterial oxygen (PaO₂) of less than 7.3 kPa when patients breathe ambient air at sea level (3). However, supplementary oxygen is not effective to impact survival in COPD patients with intermittent desaturation during exercise (123).

Non-invasive ventilation (NIV) can be used in stable very severe COPD patients who have chronic ventilatory failure (partial pressure of arterial carbon dioxide > 7 kPa or 53 mm Hg). This ventilation modality can improve outcomes and reduce the rate of hospitalisation (124). There are also
significant advantages in patients with both COPD and obstructive sleep apnoea (OSA) associated with using continuous positive airway pressure (CPAP) to increase survival and decrease hospital admissions (125, 126).

In certain patients with advanced emphysema, bronchoscopic lung volume reduction such as endobronchial valves (EBV) can be used to reduce end-expiratory lung volume and improve exercise capacity and the overall health status (1). Surgical interventions such as Lung Volume Reduction Surgery (LVRS) can also be considered in severe COPD patients. LVRS is a surgical technique that resects portions of the lungs to minimise hyperinflation (127), allowing respiratory muscles to have more efficient pressure drivers by enhancing their mechanical effectiveness (128, 129).

If surgical interventions are not of any benefit, lung transplantation is one of the available options for COPD patients. Lung transplantation was shown to enhance health status and functional capacity in properly chosen patients with extremely severe COPD, but not prolong survival (130, 131). About 70% of lung transplants in COPD patients are double-lung; the remaining are single-lung transplants (132). Double lung transplants in COPD patients, in particular those <60 years old, have recorded longer survival rates than single lung transplant patients (132).

In conclusion, the management of stable COPD approaches should be primarily focused on individualised symptom identification and the likelihood of exacerbations. Such management should be accompanied by effective non-pharmacological approaches such as smoking cessation and PR and not limited to pharmacological therapies, with the overall aim to reduce both symptoms and exacerbation risk.


### 1.1.5.2 Management of COPD exacerbations

COPD is punctuated by periodic deteriorations in respiratory symptoms called exacerbations; the leading cause of most hospitalisations, with significant effects on morbidity and mortality (3). Exacerbations of COPD are events characterised by a further deterioration in symptoms—often, dyspnoea, which can be a result of air trapping, coughing and increased purulent sputum production (3). Airway bacteria, viruses and pollutants are significant causes of exacerbation, but their interplay should also be considered. It is known that immunity and host defects contribute to repeated acute exacerbations of COPD (AECOPD) (1).

In addition, with growing prevalence of COPD, exacerbations are increasing pressure on healthcare services and reflect more than 10 million unplanned attendances in the US each year (133). Indeed, the total costs of COPD services in the US are more than $32 billion a year, with exacerbations expected to account for 50% to 75% of health care expenses (134, 135).

#### 1.1.5.2.1 Definition

The Oxford English Dictionary defines an exacerbation as ‘the process of making a problem, bad situation, or negative feeling worse’ and it comes from a Latin word stemming from the verb *exacerbare* meaning ‘exasperate, irritate, provoke’ (136). Definitions for COPD exacerbations differ, but symptom-based or event-driven definitions are the most used. According to the recent global initiative for COPD (GOLD) statement 2021 (1), an exacerbation of COPD is defined as ‘an acute worsening of respiratory symptoms that results in additional therapy’. Such events can be
categorised as mild (treated with short acting bronchodilators only), moderate (treated with bronchodilators, antibiotics, or oral steroids) or severe (patients require hospitalisation or emergency admission). A variety of characteristics, including elevated airway inflammation, mucus hypersecretion and air trapping, have been associated with COPD exacerbations (1). There’s some debate about the exact definition of exacerbation incidents. One of the limitations of the GOLD definition of exacerbation: ‘an acute worsening of respiratory symptoms that results in additional therapy’, is that it does not count for some events where exacerbation severity does not need prompt therapy, or where COPD exacerbation is mistakenly identified with an unrelated cause, or when there is failure to receive medication or care (137). Therefore, measuring the rise in symptoms and classifying an exacerbation when deterioration is crossing a threshold (no matter whether the patient requires treatment) would add a holistic approach to tackle exacerbations. This process was generally adopted in studies using multiple reliable and validated patient-reported outcome (PRO) techniques, such as symptom/treatment diary cards and questionnaire instruments such as the Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT) (138, 139). Once introduced, a substantial number of exacerbations were found to be unreported and not treated (138). Studies using symptom-based definitions generally show a frequency of exacerbations almost double that of health care use definition, and this is due to symptoms-related definitions that can capture more mild exacerbations that do not need intervention, which increases risk of overdiagnosis of exacerbations (140). Yet such unreported events cannot
be inconsequential, but the diagnosis challenges are many, such as determining the exacerbation threshold, the ceiling impact and, in case of inadequate exacerbation recovery, how and when to restore the baseline symptoms (141).

To date, the heterogeneity of the clinical diagnosis of COPD exacerbation is of great concern as it must account of potential reasons for acute deterioration such as cardiac disease, pneumothorax, pulmonary embolism or anxiety. Infective exacerbations are historically thought to be triggered by airway lumen infection, while pneumonia reflects alveolar infection, but these different pathological changes are potentially interacting (142). During COPD exacerbation, chest imaging is not regularly conducted and consolidation may be not detected whether it is early in the infection phase or by the test's insensitivity (143). Indeed, exacerbation of COPD is a clinical diagnosis of exclusion; despite the limitations of this approach, it remains the gold standard diagnosis.

1.1.5.2.2 Triggers

Exacerbations are airway inflammatory events, mostly caused by an infection. The primary cause for exacerbations is often respiratory virus infection, but also these events are caused or exacerbated by bacterial infections and environmental factors such as air quality and the atmospheric temperature (144, 145). Early research focused on bacteria as the main cause of exacerbations, but particularly molecular testing methods have demonstrated that viruses have a significant role in exacerbations (146,
As there is a variation in the aetiology of exacerbation, the rate of an exacerbation in patients can vary by year and from season to season (148). In winter, the rate of exacerbations is approximately two times higher than in summer, possibly as a result of intensified respiratory viral infection (149, 150). Moreover, the sluggish recovery of symptoms is related to the exacerbations that occur in winter where respiratory infections are more common.

In earlier research using culture dependent approaches, the rate of respiratory viruses in COPD exacerbations was underestimated. With the advent of polymerase chain reaction (PCR) techniques, virus identification in COPD exacerbations improved to 22% and 64% (137). Rhinoviruses account for up to 60% of all viral exacerbations, the most commonly reported (151), while influenza viruses and respiratory syncytial virus (RSV) are regularly found in up to 36% and 28% of viral exacerbations, respectively (152, 153).

In the pathogenesis of exacerbations of COPD, bacteria are also particularly important. Indeed, trials using conventional sputum culturing procedures have detected bacteria in 40-60% of COPD exacerbations (146, 154). In the literature, Nontypeable Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae and Pseudomonas aeruginosa are the most described pathogens (155-157). However, atypical bacteria are rarely isolated, with just 4% to 5% of episodes triggered by Mycoplasma pneumonia and Chlamyphila pneumonia (154). Nevertheless, thus far it is not known from these studies whether the development of new bacterial strains or the outgrowth of existing bacteria contributes to exacerbations.
Viral-bacterial coinfection is frequent with exacerbations occurring in 6% to 27% (155, 156). A study has investigated the mechanisms of this coinfection in COPD (158). They observed that 29% of patients had viral infection at the start of exacerbation, in which bacteria were isolated in 5 days following the exacerbation onset. Another study confirmed that 60% of patients acquired a bacterial infection in 14 days when Rhinoviruses were observed at the start of the exacerbation (159). Exacerbations of viral and bacterial coinfection are correlated with greater airflow obstruction, elevated airway inflammation and prolonged recovery (156, 160). However, the mechanisms underlying this phenomenon in which virus infections progress to a secondary bacterial infection were not completely known. This could be due to viral damage of macrophage reaction to bacteria, which causes a drop in neutrophil counts and bacterial clearance.

1.1.5.2.3 Biomarkers at COPD exacerbations

To help accurate assessments and direct adequate care, a clear and impartial biomarker of the AECOPD may be indispensable. Serum or plasma are the most studied biomarkers, but sputum, urine or exhaled air may often produce important biomarkers (1).

C-reactive protein (CRP) is the most used biomarker in respiratory infection investigation and monitoring. The CRP level has been gradually increased in AECOPD relative to recovery across many trials (161). However, in AECOPD the CRP failed to make a distinction between viral and bacterial causes. A significantly higher CRP level was found in 118
patients examined for 1 year in bacterial compared to viral AECOPD or non-pathogen cases (58.3 mg/L, IQR 21–28.2 vs. 37.3 mg/L, IQR 18.6–79.1) (162). The highest degree of CRP was detected in AECOPD associated with *H influenza* or *S pneumonia*, which a fourfold rise in the risk of hospital admissions was linked to CRP values >100 mg/L (163). The relationships between exacerbation recovery, recurrent exacerbation and CRP have been investigated by Perera et al. 2007 (164). They found that a high CRP concentration two weeks after an index exacerbation could be used to predict recurrent exacerbations within 50 days.

**Procalcitonin (PCT)** values above 0.25 ng/mL have been shown to suggest an AECOPD requiring hospital admission for more than 7 days (165). A meta-analysis of procalcitonin-based protocols to direct antibiotic use during an AECOPD has seen clinical effectiveness and safety (166). However, including insufficient studies into this meta-analysis raises a point of doubt in these findings.

**Brain natriuretic peptide (BNP)** is a non-invasive biomarker for cardiac diseases—it substantially increased in 60 patients with COPD exacerbations (79.9 ±16.2 pg/mL at exacerbation vs. 41.2 ± 8.7 pg/mL at stable state (167).

**Plasma fibrinogen** is the first biomarker drug development tool eligible for use in COPD as a prognostic biomarker for subject enrichment in COPD exacerbation and mortality trials under the Food and Drug Administration (FDA) and European Medicines Agency drug development tool qualification programme (168). Fibrinogen is a soluble glycoprotein predominantly synthesised by hepatocytes in the liver and usually elevated
in patients with chronic diseases that have chronic inflammation. During the COPD exacerbation, fibrinogen levels rise (0.36 g/L SD=0.74), and then return over 2 to 6 weeks to the patient's baseline (169, 170). This mechanism is concurrently linked to a rise in Interleukin 6 (IL-6). According to an individual participant meta-analysis of prospective studies of over 154,000 patients, per a 1-g/L increase in fibrinogen level there is a 3.7-fold increase in COPD-specific mortality and this risk increased to 4.52-fold after the first 5 years of follow-up (171).

IL-6 has proven to be a better mortality indicator than CRP and fibrinogenic plasma respectively in a large cohort of subjects with COPD studied over 3 years (172). However, they concludes that the addition of a selected panel of biomarkers such as IL-6, CRP, IL-8, and fibrinogen significantly increases the ability of clinical variables to predict mortality in patients with COPD (172).

Blood eosinophil has demonstrated a great ability to direct systematic corticosteroid therapy at time of exacerbation, in which eosinophilic exacerbations of COPD were associated with quick recovery and lower intervention failures compared to non-eosinophilic exacerbations of COPD (173). Circulating eosinophil counts more than the 2% cut-off at exacerbation time were linked with increased risk of all-cause (OR 2.32, 95% CI 1.10–4.92) and COPD related readmission (OR 3.59, 95% CI 1.67–7.82) (174). Those patients with a severe eosinophilic exacerbation of COPD (defined as ≥ 200 cells/μL and/or ≥ 2% of the total leukocyte count) were associated with a shorter length of stay compared to non-eosinophilic exacerbations of COPD (175). In contrast, another study found that those
with less than 50 cells per μL at the time of an exacerbation were associated with increased length of stay (176) and 2.76 fold an increase in risk of mortality compared with those with normal eosinophils (177).

Few urinary independent biomarkers in AECOPD are clinically beneficial. One study that showed hope for the future revealed that some metabolomics can be used to distinct COPD from asthma with >90% accuracy (178).

Sputum eosinophil levels were found to interact negatively with exacerbation bacterial load (179). The easiest indicator of sputum eosinophilia is potentially the serum peripheral blood eosinophils count at a cut of 2%, which has a sensitivity of 90% and specificity of 60% (180).

Exhaled nitric oxide has been investigated as a potential biomarker for AECOPD. Generally, it increased at exacerbation mainly in the presence of cold weather, but its use is less common in COPD than in asthma due to uncertain clinical benefits (181, 182).

1.1.5.2.4 Recognition of COPD Exacerbations

Exacerbation in COPD patients is usually unrecognised and unrecorded. About three-quarters of patients have difficulty with recognising the word ‘exacerbation’. Indeed, nearly 40% of patients did not respond promptly to the onset of an exacerbation (such as calling their healthcare provider) and took a ‘wait and see approach’ (183, 184). Many factors can influence exacerbation reporting, including healthcare access, location from a
hospital, access to personal or public transportation, the patient's condition, and resource constraints which may restrict the ability to provide home care. Those with unreported exacerbations have a delayed recovery (185), while rapidly identifying, disclosing and managing exacerbations of COPD decreases the period of time to which exacerbations occur (186). Therefore, such unreported exacerbations will stay without treatment or prevention, which means that it might not be simple to define or classify exacerbations depending upon the treatment given (142).

1.1.5.2.5 Consequences of Exacerbations

Recent research has revealed that a single COPD exacerbation has a detrimental effect on lung function, which may dramatically decline (187), and the risk is increased of more frequent exacerbations (188). Compared to those with no previous exacerbation experience, patients who had experienced \(\geq 1\) exacerbation of any severity since their last study visit had a negative impact on quality of life (189). Furthermore, patients were at highest risk of more exacerbations within 2 to 3 months following a severe exacerbation (188). Also, each exacerbation raised the odds of another event. Comparing with the first severe exacerbation, the risk was raised three-fold after a second severe exacerbation and 24-fold after a tenth severe exacerbation (188). The length of an exacerbation is often correlated with a growing risk of more exacerbations and decline in health status in COPD patients. Exacerbations in which lung function was not restored were correlated with symptoms of viral infection and increased lung decline (190).
Many studies have reported the effect of COPD exacerbations on **lung function**. COPD exacerbations are strongly correlated with rapid pulmonary function loss, especially in people with limited airflow obstruction and a history of severe exacerbations (191). Indeed, those patients with recurrent COPD exacerbations are often typically the most symptomatic with the greatest reduction in a pulmonary function test (192, 193). The improvement of pulmonary function outcomes after an exacerbation can be delayed, with data indicating that the 25% of pulmonary lung function results do not return to patients’ pre-exacerbation values five weeks following an event and that lung function does not return to pre-exacerbation values after 3 months for 7% of incidents. In contrast to the risk of a slower recovery during a COPD exacerbation on future exacerbations, a faster improvement of lung function during care was found to be substantially correlated with a lower risk of COPD exacerbation (194).

COPD exacerbations have numerous negative effects on patients’ **quality of life** and physical activity. There was a substantial decline in the quality of life of patients with recurrent exacerbations (a total of 3 or more a year), relative to those with fewer than three exacerbations a year (138). Severity of exacerbations can play a major role in patient quality of life, whereby those who had a recent severe exacerbation had more loss of activity and poorer quality of life than people who had a recent moderate COPD exacerbation (195). Nevertheless, not only severe exacerbations, even mild incidents, can have a detrimental effect on quality of life; reduced incidence
of COPD exacerbations correlated with a greater quality of life in COPD patients (196). An international patient study showed that most COPD patients find that exacerbations stopped them from making plans and impaired everyday tasks such as sleeping, outdoor walking, eating, and chatting (184).

**Physical inactivity and functional loss** were associated with COPD exacerbations related hospitalisation and such a limitation continues to decline more within 30 days following hospital discharge (197). Exercise capacity and muscle function and strength declined, even due to a mild COPD exacerbation and decreased levels of physical activity were correlated with increased risk of more exacerbations and even death (198, 199). Furthermore, balance impairments are common in COPD patients, which is associated with elevated dyspnoea and decreased muscle power. This could be present in patients with COPD and may lead to a high rate of falls suffered after hospitalisation (200). Therefore, a reduction in levels of physical activity following an exacerbation of COPD can contribute to lower muscle mass, which further contributes to more physical disability.

As per the latest Global Burden of Disease study published in 2017, 3.2 million **deaths** have been reported worldwide caused by COPD (200); exacerbations are a prevailing cause of death in COPD (188, 201). One longitudinal study that followed patients for 5 years found that exacerbations requiring hospitalisation were independently associated to mortality and
that the risk of mortality increased with higher exacerbation frequencies (202). These results held after adjusting for factors such as ageing, FEV$_1$, body mass index and Charlson index. Indeed, mortality was found to peak in the first week after a severe exacerbation (188). Evidence has shown that a COPD exacerbation is associated with 3% mortality during hospitalisation and 4% during the 30-day post-discharge period. The mortality rate varies between 2.5 to 30% based on patients’ and hospital characteristics (202-205). The UK national audit in 2014 reported an inpatient mortality rate of 4.3% in patients hospitalised for a COPD exacerbation (206). In addition, a meta-analysis of studies that followed patients for at least 1.5 years after admission to hospital showed a predicted 16% rate of fatalities, which is defined as additional mortality caused by a COPD exacerbation (207). Following the first hospitalised COPD exacerbation, a Canadian mortality study showed rates of mortality of 50% and 75% were in 3.6 years and 7.7 years, respectively (188). Furthermore, more than one in five COPD patients died within one year of discharge following the first-ever severe COPD exacerbation (201), and around half had survived within 3.6 years (188). Rothnie et al. (208) demonstrated a clear association between both an increasing frequency and severity of exacerbations and mortality in a large analysis of a UK primary care population.
1.1.5.2.6 Exacerbation association with other comorbidities

COPD exacerbations are associated with many different comorbidities and the length and cost of hospitalisation are significantly increased and associated with the presence and number of comorbidities (209). Patients with two mild or severe comorbidities also have an increased risk of exacerbation recurrence (210). Comorbidities, such as high blood pressure, diabetes mellitus, chronic heart failure, ischemic heart disease, anaemia and dyslipidemia, are common in patients with COPD exacerbation in addition to mental health comorbidities (210). Indeed, the risk of cardiovascular disease, including myocardial infarction and stroke, has been increased by COPD exacerbations (211-213). In addition to this, frequent (≥2 per year) exacerbations are associated with cardiovascular failure, visual deficiency, lung cancer, coexisting anxiety and/or depression, prostate disturbances, asthma, osteoporosis, diabetes, gastroesophageal reflux, and peripheral vascular conditions (214, 215). There has also been a strong increase in the frequency of severe exacerbations when there is coexisting asthma (216).
1.1.5.2.7 Management options

The aim of COPD exacerbation therapy is to mitigate the detrimental consequences of the presenting exacerbation and avoid more incidents (217). In the outpatient or hospital setup, an exacerbation can be managed in accordance with the severity and/or the severity of any underlying disease (1). More than 80% of exacerbations were treated outside hospital settings with pharmacologic medications involving bronchodilators, corticosteroids, and antibiotics (73). In acute events, therapy requires SABAs, typically provided by nebulizers. Short-acting anticholinergic agents should be applied if the response is minimal.

Systematic corticosteroid treatment improves airflow limitation, gas exchange and symptoms (218); thus, a prednisone dose of 40 mg or its daily equivalent for just 5 days is as effective as a 10-day course (219). The occurrence of psychosis (in elderly people) on electrolytes, hyperglycaemia and high blood pressure are reduced by this strategy. Antibiotics are particularly useful and should be selected based on the local bacterial resistance patterns. Five to seven days is the recommended length of using antibiotic therapy (1). When indicated, it can reduce recovery time, risk of treatment and early relapse and lastly, hospitalisation. Hospitalisation can be required in patients with severe breathlessness, or hypoxemia, or hypercapnia or those with comorbid conditions (1).
Moreover, arterial blood gas (ABG) can be assessed in patients with an oxygen saturation of 88-92% as patients breathe room air. Accordingly, if no hypercapnia is present but hypoxemia is, then low-flow oxygen is indicated in order to achieve a Pao$_2$ value of 7.9 to 8.6 kPa (oxygen saturation 91 to 94%) (219). Patients with severe decompensated hypercapnia (pH less than 7.35) can be treated with NIV to improve outcomes, including decreased risk of death. Indeed, invasive mechanical ventilation should be considered in some situations, for instance, unstable patients, and an inability to protect airway and NIV failure (1, 219). Clinicians should take a holistic approach including attention to comorbidities in the pre-discharge care of patients with COPD exacerbations to reduce the potential risk of readmission (220).

1.2 COPD and comorbidities

1.2.1 Overview

COPD is a leading cause of global morbidity and mortality. In 2010, COPD was placed second in the USA as the cause of disability-adjusted life years (221). While it is characterised by abnormal spirometry, COPD is well known to be more than respiratory. Comorbidities, described as the coexistence of other medical conditions with COPD, which can contribute to the severity of the disease (222). While the presence of COPD is not necessarily causal, it potentially raises the risk of other diseases (223). In patients with any degree of airflow limitation, comorbidities may take place and are not limited to advanced COPD patients (224). In addition,
comorbidities are related to greater morbidity and mortality. It is therefore likely that such connections exist between COPD and comorbidities, which increases our understanding of COPD as a systemic disease (225). Therefore, besides to conventional pharmacological treatment aimed at addressing persistent COPD symptoms and exacerbations, COPD care also needs a more systematic strategy that involves evaluating and managing co-morbid symptoms accordingly (1).

1.2.2 Prevalence of comorbidities in COPD

The co-morbidity of COPD patients is widespread and exists across the continuum of disease severity (226). In COPD, there are often several comorbidities that occur together, and various clusters of comorbidities can be identified (227). Indeed, 32% had one additional illness in a study of the prevalence of co-morbidities related to COPD, while 39% reported two or more concomitant medical conditions (228). These reported numbers increased to a median of nine comorbidities in one study to report a coexistence with COPD (229). Common COPD related comorbidities are listed below in table 2 (225).
Table 2. Common comorbidities associated with COPD.

**Comorbidity Type**

<table>
<thead>
<tr>
<th>Comorbidity Type</th>
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<tbody>
<tr>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>➢ Hypertension</td>
</tr>
<tr>
<td>➢ Coronary artery disease</td>
</tr>
<tr>
<td>➢ Systolic and/or diastolic left ventricular dysfunction</td>
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<tr>
<td>➢ Pulmonary hypertension</td>
</tr>
<tr>
<td>➢ Peripheral vascular disease</td>
</tr>
<tr>
<td>➢ Cerebrovascular disease</td>
</tr>
<tr>
<td>➢ Stroke</td>
</tr>
<tr>
<td>Skeletal muscle dysfunction and loss of muscle mass</td>
</tr>
<tr>
<td>Osteoporosis, osteopenia or osteoarthritis</td>
</tr>
<tr>
<td>Psychological disturbances</td>
</tr>
<tr>
<td>➢ Depression</td>
</tr>
<tr>
<td>➢ Anxiety</td>
</tr>
<tr>
<td>Cognitive impairment</td>
</tr>
<tr>
<td>Anaemia</td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
</tr>
<tr>
<td>Diabetes/metabolic syndrome</td>
</tr>
<tr>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Gastro-oesophageal reflux disease</td>
</tr>
<tr>
<td>Lung cancer</td>
</tr>
<tr>
<td>Infections</td>
</tr>
</tbody>
</table>
The prevalence of any type of comorbidity or combination of conditions differs significantly between trials, based on the examined patient group, patient assessment procedures used and condition definitions (227). The most common reported comorbidities are cardiovascular; COPD patients are 2 to 3 times more likely to develop cardiovascular diseases when compared to age-matched controls adjusted for tobacco smoking (230, 231). The prevalence of hypertension in a large COPD cohort was found to be 40% (232) and in another study was 50% - but with those suffering advanced COPD disease (233). Over 20% of COPD patients suffer from heart failure (HF) (234, 235). Furthermore, after controlling for age and other cardiovascular risk factors, the risk for HF development in COPD patients was 4.5-fold higher than the risk level of disease-free control individuals (236).

Other essential comorbidities of COPD are skeletal muscle weakness and lack of fat-free mass (237). Such a dysfunction can result in a decline in strength, endurance and exercise capacity as well as poor quality of life associates with hospitalisation and death (238). Furthermore, approximately 50% of COPD patients suffer from osteoporosis with this percentage increasing with more cases of severe airflow obstruction (239, 240).

According to a study population of 35,722 patients with COPD and 35,722 patients without COPD, following an initial COPD diagnosis, new-incidence diagnoses of depression was 16.2/1,000 person-years in the COPD group, whereas only 9.4/1,000 found in the COPD-free group (241). Similarly, when compared with healthy matched controls, COPD patients were 85%
more likely to develop anxiety disorders (242). The prevalence of anaemia was 10–30% (243-245), while around 10% of COPD patients demonstrated OSA and up to 20% of OSA patients had concurrent COPD (246).

Renal insufficiency prevalence has been estimated at between 20–22% (247), whereas up to 60% prevalence for gastro-oesophageal reflux disease in COPD patients was found (248, 249). A recent systematic review that included 1,682,908 individuals with COPD found that the pooled prevalence for lung cancer was 2.79% (95% CI: 1.88–3.88) and reported that patients were 6.35 times more likely to develop lung cancer than controls (250). Lastly, respiratory infections, both chronic and acute, have a likely more prominent effect on COPD patient outcomes (251).

1.2.3 Comorbidity impact on COPD outcomes

The social and economic burden of COPD is increased by comorbidities; the total average burden of COPD is linked to the number of comorbidities (252). Comorbidities are key indicators for potential healthcare expense as well as age and the prevalence of recurrent conditions (253). An increased risk of hospitalisation is associated with the presence of comorbidities, whereby the incidence of non-respiratory hospital admissions in patients with COPD significantly increases compared to COPD-only related (232, 253). In fact, there is a detrimental effect on the majority of people with COPD owing to the prevalence and incidence of comorbidities. In general, compared to patients without comorbidities, COPD patients with comorbidities, especially cardiovascular disorders, and diabetes, are more
dyspnoeic and have less exercise capacity, even after taking age, sex, and smoking backgrounds into account (254). Indeed, the existence of anxiety or depression is correlated with breathlessness, health quality, exercise output and treatment adherence in patients with mild to severe pulmonary emphysema (255, 256). Similarly, patients with anaemia have worse shortness of breath, decreased exercise capacity and poorer quality of life (257). A coexistence of three or more comorbidities in COPD is more predictive than other socioeconomic or clinical predictors for reduced health status (258). In summary, comorbidity is linked to an increased risk of death in COPD (253). Since comorbidities have detrimental effects on patient presentation, socioeconomic record, vulnerability of hospitalisation, health treatment and mortality, it is vital to holistically minimise the comorbidity burden on COPD outcomes.

### 1.3 COPD hospitalisation

COPD hospital admissions due to COPD exacerbation are common, often frequent, and can lead to considerably poor outcomes (259). It has been reported that a previous hospitalised exacerbation in the past year was a strong predictor of future hospitalisation (214). COPD exacerbation that resulted in hospitalisations were accounted for 90% of the total costs of exacerbations (260). Further, hospitalisations due to COPD exacerbation represented more than 70% of all COPD-related medical care costs (261). This highlights the substantial economic burden caused by COPD hospitalisation on societies.
During **COVID-19 pandemic**, there was a 50% reduction in COPD hospitalisations during the COVID-19 lockdown in the UK compared with the same period in 2019 (262). This in turn increased community managed exacerbation events in 2020 by 38% compared to the same period 2019. Another interesting study in Singapore had compared COPD exacerbations during the ‘pandemic’ period February–July 2020 to the ‘pre-pandemic’ period January 2018 through January 2020 (263). They found that more than 50% drop in COPD exacerbation admissions per month and a decrease in the proportion of COPD exacerbations testing positive for respiratory viruses from 49% to 11%. Such a reduction in hospital admissions due to COPD exacerbations were also observed in other studies conducted in Hong Kong (264) and Germany (265). This could be explained by the effect of coronavirus prevention measures. A recent systematic review and meta-analysis reported a 50% reduction in admissions for COPD exacerbations during the COVID-19 pandemic period compared to pre-pandemic times, likely associated with a reduction in respiratory viral infections that trigger exacerbations (266). They recommended future guidelines to include recommendations on respiratory virus infection control measures to reduce the burden of COPD exacerbations beyond the pandemic period.

All things considered, identifying and reporting potential risk factors for COPD hospitalisation would facilitate targeted interventions to lessen this health and economic burden.
1.3.1 Overview of readmission incidence

For patients surviving hospitalisation due to COPD exacerbations, readmission to hospital is a major problem. Identifying and mitigating risk factors or predictors for readmission is therefore important (206, 267). COPD hospital readmissions contribute to a clinical and economic burden on society (268). In the US, around 19% of COPD patients were readmitted within 30 days, while in the UK the all-cause readmission rates were 24% within 30 days and 43% within 90 days of discharge (206, 269).

Data from the European COPD Audit show that the risk of in-hospital mortality was substantially higher in readmitted patients compared to non-readmitted patients (13.4% vs. 2.3%) (270). Differences in rates have been associated with unexplained variations in care quality (271). In the USA, the Centres for Medicare and Medicaid Services have applied financial penalties to hospitals that have high rates and have considered readmissions a marker of quality of care (272, 273). Similar penalties have been applied in the UK’s National Health Service to reduce readmission rates and improve quality of care (274).

1.3.2 Causes of COPD readmission

The causes of COPD readmission could be COPD or all-cause related readmission. Around 50% of COPD readmission were associated with respiratory-related causes, in which COPD alone was accounting for 28% of all readmissions (275). According to the UK COPD Audit published July 2020, which included 15,629 patients, the top five reasons for readmissions
within 30 days of index discharge were respiratory diseases (39.5%), Pneumonia (13.5%), chronic kidney disease (2.6%), other sepsis (2.0%) and heart failure (1.8%) (276). Such data highlight the role of multiple comorbidities in COPD readmissions, therefore, effort to address multimorbidity can help in reducing the burden of readmission following a hospitalised exacerbation of COPD.

To review the efforts to address COPD readmissions, I have conducted a systematic review and meta-analysis to summarise and evaluate the factors associated with 30- and 90-day all-cause readmission following hospitalisation for an exacerbation of COPD.

1.3.3 Cost of COPD readmissions

The burden of COPD readmission is increasing over time. The direct cost of COPD in the USA is approximately $50 billion annually, while the total cost of COPD care can reach up to double the direct costs because of related comorbidities (277). Indeed, exacerbations account for close to 70% of the cost to hospitals due to COPD; while patient readmissions alone account for more than $15 billion indirect expenses each year in the US (278, 279). The problem in recent years has been that one in five patients require rehospitalisation within 30 days after having AECOPD (275, 278).

In the UK, COPD constitutes 10% of emergency medical admission, and the number of admissions have risen 50% in the last decade (280). Within 28 days following hospital discharge, many of these patients would be readmitted. The National Health Service (NHS) is expected to spend £491
million a year for COPD admissions (281). Compared to other respiratory conditions in the UK, COPD accounted for 29% of the overall expense of pulmonary diseases; the NHS spends around 10 times more for the care of severe COPD patients than for those with mild disease (280, 282).

Given the current economic cost of AECOPD and related readmission, improving the management of hospitalised COPD patients poses a major challenge for health care professionals. Therefore, until now it was not clear whether we should consider COPD readmission a marker of quality of care or a marker of a more severe disease with a worse prognosis. It remains debatable as some (283) related readmissions to the severity of the disease, while others have considered readmissions as a marker of quality of care (272, 273).

1.3.4 Readmission reduction efforts

In several developing nations, early readmissions have been a quality measure; a tool to determine the process and performance outcomes in healthcare delivery (260, 274). Potential regional variations can occur across developed countries in 30-day readmission rates; whilst 22% of the admissions to AECOPD are readmitted within 30-day period in the USA, the average in Taiwan is 16.7% and in the UK between 14% and 20% (284, 285). Around 10% to 55% of readmissions could be preventable after following indexed admission for AECOPD (286).
As part of the Medicare Hospital Readmissions Reduction Program (HRRP) initiative (2014), COPD was listed as a requirement that forced hospitals to cut excess all-cause 30 days readmission after AECOPD, to prevent the 3% penalty on Medicare incomes (272). The financial penalty of the HRRP leads to huge advantages and also major concerns about its aim of transforming the COPD paradigm into a value-based treatment. On a plus side, hospitals now dedicate resources to COPD-specific hospital care, which was once under-supported and/or incompletely implemented in a patient-focused and evidence-based COPD care system (273). Hospitals have started working with post-care suppliers (post-care services), such as qualified healthcare and home-health bodies, to smooth care transitions - actions which have not previously been promoted under traditional payment structures. In contrast, the HRRP can generate unintended incentives, such as encouraging hospitals to code AECOPD patient discharges for other reasons, transfer patients to other healthcare systems in order to escape penalties or to postpone necessary readmissions (287). Whether a 30 day decrease in readmissions is linked to better patient outcomes remains unknown (273). Recently in 2020, a retrospective cohort study of readmission and mortality rates in a national cohort (N=4,587,542) was conducted and found a reduction in 30 day all-cause readmission rates during the implementation period of HRRP compared to the pre-announcement phase (288). However, this was associated with a significant increase in 30-day mortality following discharge from COPD hospitalisation. Increasingly, lower, not higher, mortality was linked to higher 30 day readmission rates for congestive heart failure (CHF), and that the higher
readmission rates for COPD were likely to be similarly safe (289). About 25% of patients do not recover from AECOPD by day 35, and thus readmission within a normal high-risk 30 day period could be needed (290). Indeed, several approaches have been proposed to lessen the COPD readmission burden on healthcare systems, as discussed below.

**Intervention components that may reduce COPD readmission**

In addition to emerging recommendations for AECOPD care and management guidelines, many strategies demonstrate the potential to reduce early readmissions after AECOPD (1, 291). The examples of such intervention components that may reduce COPD readmission (286) are listed below:

- Patient self-management
- Smoking cessation (Ottawa Model)
- Inhaler device training
- Early outpatient follow-up within 30 days after discharge
- Pulmonary rehabilitation
- Telehealth care
- Receipt and filling of all respiratory medications prior to hospital discharge
- Pharmacist-supervised medication reconciliation
- Hospital-at-home
A recent Cochrane review showed that successful COPD self-management was linked to reductions in both respiratory and all-causing readmissions (292). Self-management research ranged from a clinical to a professional emphasis on some, but not all, of the following topics: COPD as a disease, action strategies, diet, smoking cessation, coping and drug strategies. Training of inhaling devices is necessary and can be effectively taught; approximately 86% of patients misuse respiratory inhalers (293).

Another technique that can discourage faster readmissions in COPD patients is early follow-up within 30 days of discharge, as about a third of patients being readmitted in the 30 day timeframe return in the first week following discharge (275). Such follow-up arrangement has been recommended by GOLD 2020 to review, evaluate and ensure patients are coping and following the right treatment plan (1). According to Auerbach et al., the most important reason for possibly preventable readmission is the failure to hold follow-ups following discharge (294).

Nevertheless, PR is one of the rapidly growing interventions for reducing early readmission, morbidity, and mortality. Initial data indicates that PR can minimise readmissions, although it is uncertain if PR affects all-cause COPD readmissions within 30 days as well as whether PR programmes would be safe, directly post AECOPD. A 2016 Cochrane study gathered data from eight trials involving 810 patients who had PR after hospitalisation due to AECOPD and reported a substantial drop in hospital readmissions (pooled odds ratio (OR) 0.44, 95% CI, 0.21 to 0.91) (113). However, this result was affected by heterogeneity among studies that resulted from the
variation in scope and methodological standards of the included studies of
the PR programmes. Nowadays, face-to-face PR programmes have been
suspended globally due to COVID-19 pandemic to ensure effective
shielding from the virus. Nevertheless, because of the need to have such
programmes, tele-rehabilitation has been suggested as an alternative
option at a time of social distancing (295).

Telehealth care in COPD was seen as a means of minimising early receipt
in the era of using technologies and broaden the scope of health services
to patients’ homes. The latest systematic literature review concluded that
telehealth care interventions over one year can significantly lessen the risk
of emergency visits (OR = 0.27; 95% CI = 0.11 to 0.66) and hospitalisation
(OR = 0.46; 95% CI = 0.33 to 0.65) (296). Furthermore, another systematic
review found that home telemonitoring tended to minimise AECOPD,
hospitalisations and boost quality of life (297). Ensuring all patients have in-
house medicines needed before they are discharged is an intervention
strategy that may reduce COPD readmission. According to Blee et al., when
a pharmacist-educator model used to improve respiratory inhalers
technique for patients before discharge, a 30-day decline of all-cause
readmissions was reported from 21.4% to 8.7% (298). Similarly, hospital-
at-home can play a role in this process; a Cochrane review of eight trials
showed a risk ratio of 0.77, preferring treatment of AECOPD at home
instead of hospital, with an increasing tendency in the home group towards
lower mortality (299).
All in all, COPD readmissions represent a daunting medical challenge for patients, healthcare providers and policymakers as well as a significant healthcare concern. To lessen the readmission burden of COPD, more research is required to identify key risk factors and interventions with a focus on both quality and expense. Therefore, I have measured EFL using FOT during COPD hospitalisation to assess its ability to predict COPD readmission and this will be detailed in the following chapters.

1.4 Expiratory Flow Limitation (EFL) in COPD

1.4.1 Definition of EFL

The term EFL applies when the maximal expiratory flow is reached during tidal breathing despite increasing expiratory muscle effort, which is a common pathophysiological condition. It can occur at rest or during exercise, also in supine and later on in the sitting position (300). EFL is generally presented in the peripheral airways (301-304). EFL during tidal breathing indicates in ventilation, with a concomitant gas exchange deficiency; an unevenly distributed stress and strain within the lung which is exacerbated by tissue interdependence and may lead to a small airway injury (305). Although EFL is common in COPD patients, it can also be identified in other respiratory and non-respiratory diseases such as asthma, acute respiratory distress syndrome, heart failure and obesity.
1.4.2 Mechanisms of EFL

Our understanding of the pathophysiology of COPD exacerbations continues to grow as new mechanisms become identified. Around 31%-41% of COPD patients have EFL (306, 307), which is considered a critical pathophysiological hallmark of the disease (308). EFL is defined as a lack of ability to increase expiratory flow, even with increasing expiratory muscle effort. Several mechanisms can contribute to EFL development including age-related increase in FRC and RV (lead to airway closure at small volume), body position, exercise, airway collapsibility and reduced lung elastance in those with COPD, and lastly, breathing at a lower lung volume (near residual volume), as commonly seen in obese and restrictive lung subjects (309). In those with COPD, the narrowing points or ‘choke points’ within the airway are usually present during expiration and can cause EFL (310).

This limitation increases EELV because of reducing the time available for lung emptying. The level of EELV fluctuates and depends on the extent of EFL and a patient’s ventilatory demand. When EELV increases above relaxing volume, critical airway closure occurs with gas trapping and this leads to hyperinflation (308). During exercise in flow limited patients, EELV starts to increase whilst IC declines, which is indicative of DH. This process is often associated with limiting a patient’s ability to increase their tidal volume at the available lung volumes and this may progress to acute respiratory failure (311) (see Figure 6).

IC is a simple and reliable measurement to reflect EELV changes during COPD exacerbations (312). Therefore, any reduction in IC indicates a rise
in EELV, strongly associated with increased breathing difficulty. An increase in EFL results in acute DH, which is associated with increased threshold load and can result in the functional weakness of inspiratory muscles. Such mechanisms lead to respiratory muscle fatigue, negatively affecting a patient’s ability to exercise, which may lead to acute respiratory failure (313). Hence, the presence of EFL and thus DH could be independent risk factors or predictors for COPD readmission. Understanding why some COPD patients are readmitted remains a key area of unmet need.

**Figure 6. A schematic representation of the mechanisms of EFL and its negative effects on COPD patients.**

1.4.3 Common methods for detecting EFL

There are many existing physiological techniques assessing EFL through studies that include invasive and non-invasive strategies.
1.4.3.1 Oesophageal balloon techniques

The concept of EFL indicates that a further rise in transpulmonary pressure would not result in increased expiratory flow (314). The precise measurement of the expiratory flow is limited, therefore includes the determination of isovolume associations between flow and transpulmonary pressure, which were first identified and developed by Fry et al. in the 1950s (315). In this method, repeating the effort of the expiratory vital capacities of a subject sitting in a volume body plethysmograph, flow, volume, and oesophageal pressure ($P_{oes}$) are concurrently measured. Each patient is instructed to exhale with different breathing efforts that can be identified by changes in $P_{oes}$. When around 30 of such breathing efforts are reached, the plot of the flow against $P_{oes}$ can be applied at any lung volume (314).

In 1954, the Mead and Whittenberger method was introduced to identify EFL using an oesophageal balloon, which estimated the trans-pulmonary pressure while measuring flow in a body box. It directly related alveolar pressure to flow whereby EFL could be calculated by plotting the flow measured at the airway opening versus the resistive pressure drop during a single breath. However, this method is considered invasive and time consuming.

In 1961, the Conventional (Hyatt’s) Method was introduced to detect EFL during tidal breathing (316). This method depended on superimposing a flow–volume loop of a tidal breath within a maximum flow–volume curve. However, this strategy has many limitations, such as thoracic gas compression artefacts, incorrect alignment of tidal and maximal expiratory flow–volume curves, effects of previous volume and time history and
requires patient cooperation (317, 318). Indeed, this technique has been compared to the negative expiratory pressure (NEP) technique and was found inaccurate, and accordingly, no longer recommended because the detection of EFL based on the comparison of tidal and maximal flow–volume curves is not valid, even when a body-box is used (319-321).

1.4.3.2 NEP technique

The NEP methodology was developed to address the previous technological and conceptual limitations of measuring EFL (317, 320, 322, 323). The NEP methodology was first introduced and tested in patients with manually ventilated intensive care units (ICUs), through the simultaneous assessment of the isovolume flow-pressure relationship (324, 325). Indeed, this approach does not involve FVC tests, patient coordination or the use of a body-box, which can be used in any body posture during regular breathing (326), during exercise (320, 327) and in the ICU setting (328, 329).

When regular breathing is resumed, a negative pressure (NEP, usually set at -5 cmH₂O) is added to the breathing system at the beginning of expiration, either by a vacuum cleaner or a venturi unit, then the elevated pressure difference between the opening of the airway and the alveoli contributes to a rise in flow. This rise will not happen if the patient is already breathing at maximal flow at tidal volume breathing. Therefore, EFL is present if NEP fails to increase the flow by increasing the pressure gradient and this can be assessed by visual inspection and through the interpretation of flow-volume curves (Figure 7) (305). However, this technique can cause
an extra expiratory flow from the upper airways that making it challenging
to determine whether breathes were flow limited or not. Such artefact can
be reduced by using a lower NEP but complete avoidance is not universal
(330).

Figure 7. Flow–volume loops of test breath during the negative
expiratory pressure (NEP) technique. In COPD patients without EFL, NEP
makes an increased flow (A). In EFL COPD patients, the NEP fails to increase
flow compared with the previous tidal volume curve (B).
1.2.1.3 Forced Oscillation Technique (FOT)

1.2.1.3.1 History of FOT

Dubois et al. 1956 first developed FOT in the 1950s to calculate the mechanical impedance of the respiratory system (331). This occurs by generating sine oscillations across the surface of the body and the resultant flow is calculated during voluntary apnoea at the opening of the airways. In this ground-breaking work, the experiment was repeated with various oscillatory frequencies and a fundamental observation was made whereby respiratory mechanics characteristically differ with frequency.

In 1965, one well-known early experiment on mechanically ventilated humans assessed the effect of applying different frequencies on the chest wall and lung compliance, resistance and impedance and found that compliance and resistance were frequency-dependent, even in normal subjects (332). The research activity continued in mechanically ventilated patients and other healthy human subjects to assess respiratory systems and optimise ventilator outcomes on a range of normal breathing frequencies (333-335). Indeed, all through spontaneous breathing, a great percentage of FOT studies were conducted on humans with the medium frequency scale rating from 2 to 4 Hz up to 30 to 40 Hz. As result of this expanded use of FOT through this frequency spectrum, it prompted the preparation of methodological guidelines for lung function laboratory investigations that included adults and children (336, 337). Although numerous options of the FOT have been developed, it only recently received clinical acceptance.
1.2.1.3.2 The mechanisms behind FOT

The magnitude of COPD dyspnoea is more reliably measured by EFL in tidal breathing relative FEV₁ (322, 338). A simple method of EFL detection would thus be a potentially helpful clinical tool during tidal breathing. The concept of FOT depends on a quantitative assessment, which does not involve respiratory manoeuvres and provides a simple, comprehensive and routine approach to the mechanical properties of the respiratory system (330, 339). This procedure consists of administering sinusoidal pressure variation (oscillation waves) to induce and quantify the flow response of the respiratory properties at frequencies greater than the standard breathing rate.

Both respiratory system resistance and reactance (a measure of the elastic properties of the system) can be calculated. Therefore, how the lung reacts to external pressure at different frequencies allows us to measure the impedance ($Z_{rs}$), which represents how air flows in and out of the lungs, and where and how much the lungs may be obstructed. $Z_{rs}$ consists of Resistance ($R_{rs}$) and Reactance ($X_{rs}$), Figure 8 shows this.
Respiratory impedance and its components. Respiratory impedance includes both resistance and reactance. Resistance represents large airway obstruction, while reactance demonstrates small airways.

The frequencies applied to the lung during FOT at normal breathing are in the range of 5 to 40 cycles per second (Hz). Indeed, lower frequencies are more sensitive to changes in lung periphery, particularly at 5 Hz (Figure 9). As EFL happens, the principle of wave speed projects a choke point in the airway where oscillatory pressure would not travel down to the alveoli any further; the response represents the physiological features of the peripheral airway wall rather than the whole respiratory system. As a result, $X_{rs}$ turns into much more negative resulting in a clear within-breath difference between inspiration and expiration. Such a large difference in within-breath inspiratory ($X_{insp}$) and expiratory reactance ($X_{exp}$) that occurs due to the development of choke points throughout the bronchial tree can be detected by FOT. Therefore, EFL is measured by within breath difference in
reactance at 5Hz, (∆Xrs\text{5Hz}) which can detect flow limited breaths in COPD with a sensitivity and specificity of 100% (Figure 10) (340). The optimal range was 2.53-3.12 cmH\textsubscript{2}O/ (L/s) and optimal threshold value was 2.8 cmH\textsubscript{2}O/ (L/s). Figure 10 demonstrates how EFL is detected by FOT using ∆Xrs\text{5Hz}.

In 2004, FOT was validated against the gold standard approach method of Mead and Whittenberger and was found to be simple, accurate, reliable and non-invasive (340). In 2007, FOT was compared to the NEP approach to assess EFL in COPD and the outcomes showed robust agreement between both methods, but FOT was automatic and could measure multiple breaths over long periods; therefore, it is recommended for continuous EFL monitoring (330).

**Figure 9. Low and high frequencies and lung periphery.** Low frequencies reach lung periphery, while high frequencies represent upper and middle airways.
Indeed, a significant difference between \(X_{\text{insp}}\) and \(X_{\text{exp}}\) leads to a significant EFL that is associated with the development of DH, exercise limitation and ultimately increases dyspnoea (341). Therefore, when \(\Delta X_{\text{rs}}^{5\text{Hz}} > 2.8 \text{ cmH}_2\text{O/(L/s)}\), EFL is presented and this index can be used to quantify the effect of pre-post treatment outcomes (330, 339). All things considered, FOT has been found to be as sensitive as spirometry in detecting lung function impairments and more appealing because it requires minimal cooperation and no effort from patients (336).

**Figure 10. Detection of expiratory flow limitation by forced oscillation technique** (340). \(C_{\text{a}}\) = compliance; \(C_{\text{aw}}\) = airway compliance; EFL = expiratory flow limitation; \(R_{\text{rs}}\) = total respiratory input resistance; \(X_{\text{exp}}\) = mean value of \(X_{\text{rs}}\) during expiration; \(X_{\text{insp}}\) = mean value of \(X_{\text{rs}}\) during inspiration; \(X_{\text{rs}}\) = total respiratory system reactance; \(\Delta X_{\text{rs}}\) = mean inspiratory minus mean expiratory reactance.
1.2.1.3.3 FOT in COPD

FOT can identify EFL in COPD when the development of choke points throughout the bronchial tree occurs, which causes a major difference in within-breath inspiratory and expiratory reactance. The 5 Hz FOT was used by Dellacà et al. (2004) to detect EFL in 15 COPD patients (339). This study studied and compared the parameters of Zrs throughout the breathing cycle with the gold standard oesophageal balloon management method. By drawing on the concept of FOT, authors were able to show that $\Delta X_{rs}$ (difference between mean $X_{insp}$ and mean $X_{exp}$) was the best parameter to detect EFL with high sensitivity and specificity. The value of $\Delta X_{rs}$ (2.8 cmH$_2$O) was established as the threshold of EFL, where higher values were associated with more severe COPD patients (339).

Another study by the same group was conducted to evaluate whether the previous approach ($\Delta X_{rs5Hz}$) using FOT could be useful to COPD patients during NIV (342). Using oesophageal pressure and the Mead and Whittenberge method as a reference, $\Delta X_{rs}$ was calculated in seven COPD patients connected to NIV at 0, 4, 8 and 12 cmH$_2$O. EFL scoring using FOT matched with Mead and Whittenberge in 95% of the breaths and the values of $\Delta X_{rs}$ decreased as NIV pressure was increased in those who had EFL. Indeed, FOT identification of EFL can modify the CPAP titration level to correct the EFL by eliminating haemodynamic side effects due to increased lung volume.
In 2007, a comparative study involving FOT and NEP with 21 COPD patients were studied by applying both techniques to the same breath (330). The authors found that FOT sensitivity and specificity were 93% and 91% respectively. Both techniques have been reported to be efficient in the detection of EFL, although various methodologies were used, FOT showed more a quantitative measurement.

Longitudinal changes of forced oscillometry variables using impulse oscillometry during and through the 6 weeks following an exacerbation of COPD were first evaluated by Stevenson et al. 2005 (307). The study reported no significant change of airway resistance or tidal FL during hospitalisation and during recovery from the exacerbation, whereby only the forced vital capacity (FVC) and IC increased significantly, and reactance also improved. Longitudinal changes during an exacerbation of COPD was carried out by Johnson et al. (2007) using FOT in comparison with spirometry, gas exchange, symptoms and a quality of life questionnaire (343). They found that changes in Xinsp and Xexp were easily detected during an exacerbation and were widely correlated with changes in symptoms and quality of life scores.

Mikamo et al. in 2014 found some predictors of EFL measured by FOT which were emphysema extent, peripheral airway obstruction, hyperinflation, and airway calibre (344). Indeed, within-breath reactance in COPD is associated with dyspnoea (ΔXrs >0.1 kPa·L⁻¹·s⁻¹), and generally COPD patients have higher ΔXrs values and greater variations when compared to healthy subjects (345). Another study looked at the presence of EFL during COPD exacerbations and found that EFL, during acute COPD
exacerbations, occurred in some admitted patients and reduced in nearly half of those during recovery time. Also, the greater the decrease in ΔXrs, the greater the reduction in breathlessness (306). Concerning other COPD outcomes such as 6MWD, exacerbations and mortality, Aarli et al. in 2017 reported that patients with ΔXrs ≥ upper limit of normal (ULN) defined using the 97.5th percentile of ΔXrs (0.09 kPa·s·L\(^{-1}\)), had a deterioration in exercise performance, more exacerbations, greater hospitalisations, and higher mortality (346). Hence, it can be considered as a novel marker for COPD patients. COPD exacerbations formed the central focus of a study by Kamada et al. in 2017, and it was found that exacerbations of COPD not only cause a decrease in the function of lungs, but also increased impedance of the respiratory system (347). Also, there was an association between reactance components and risk of COPD exacerbations, in which reactance was decreased more in exacerbators than in nonexacerbators (348).

While the early detection of COPD exacerbations to reduce hospitalisation is appealing, the efficacy of at-home monitoring of lung mechanics using FOT on COPD outcomes was not fully investigated. Recently, a multicentre, randomized clinical trial recruited 312 patients with a history of exacerbation in the previous year and at least one non-pulmonary comorbidity was published in 2018 (349). However, the results were negative - remote monitoring of lung function by FOT did not change time to first hospitalisation and quality of life. Notably, it significantly decreased healthcare costs, commonly due to a reduction in duration and frequency of subsequent hospitalisations.
A prospective observational study compared impedance in COPD and asthma and found ΔX at 5 Hz more negative and associated with more negative annual changes in COPD than in asthma patients (350). In another study, respiratory impedance components were associated with lung hyperinflation and gas trapping and could be used to detect changes such as outcomes following long-acting bronchodilator use (351). It has been demonstrated that ΔX at 5 Hz was variable among morphological phenotypes based on quantitative CT in patients with COPD. Such measurements for respiratory impedance may reflect the degree of airway disease (352). For the clinical management of ventilator-dependent patients with COPD, monitoring EFL during NIV is critical, as it provides valuable data for tailoring positive end expiratory pressure (PEEP) for each patient to customise it in line with changing conditions. Recently, this has been validated by using FOT, which can support the abolishment of EFL by monitoring ΔXrs at 5Hz (353).

In summary, along with the findings reported in the historical analysis, these findings have shown that FOT is a potential clinical tool that can contribute to COPD exacerbation prevention and diagnosis. However, the routine use of FOT during hospitalisation is yet to be widely recognised. Therefore, this PhD research is intended to evaluate FOT values as a potential novel biomarker in addition to the other measures reported in the methods chapter to predict COPD readmission.
2. Hypotheses and Aims
This thesis examines the hypothesis that exacerbation recurrence is more closely associated with underlying COPD biology (such as disease severity and co-morbidity), rather than the changes seen at exacerbation (such as exacerbation severity and aetiology).

**Aims of the project**

1. To complete a systematic review and meta-analysis to explore the risk factors for all-cause 30- and 90-day hospital readmission following an exacerbation of COPD.

2. To explore the characteristics of COPD patients who are and are not readmitted following an acute exacerbation, within 30 and 90 days. This will include the following outcomes:
   - Factors that determine readmission to hospital within 30- and 90-days post discharge.
   - Incidence of readmission rate at 30 and 90 days.
   - Prevalence of comorbidities.
   - EFL measurements ($\Delta X_{r5Hz}$), measured by FOT.
   - PIFR measurements, measured by using the InCheck$^\text{TM}$ DIAL.
   - Quality-of-life measures
   - Level of anxiety and depression by Hospital Anxiety and Depression Scale.
   - Prevalence of frailty.
   - Physical activity using a pedometer (Yamax Digi- Walker SW-200)
   - Changes in blood and sputum biomarkers.
• Length of stay.
• Previous admissions, exacerbations numbers in the previous year.
• Use of long-term oxygen therapy (LTOT), non-invasive ventilation (NIV), previous admissions to the ICU and history of intubation.

3. To conduct a Research Prioritisation ‘Priority Setting Partnership’ (PSP) exercise for COPD exacerbations to identify unanswered questions about diagnosis, prevention, and treatment of exacerbations of COPD from patient, carer and clinical perspectives and then prioritise those that patients, carers and clinicians agree are the most important for research to address.
3. Methods
In this thesis, we were interested to explore the clinical characteristics and risk factors associated with COPD patients' readmission within 30- and 90-days following exacerbation of COPD, and to identify unanswered questions about COPD exacerbation diagnosis, prevention and treatment from patient, carer and clinical perspectives and then prioritise those that patients, carers and clinicians agree are the most important for research to address. This chapter describes two different methods and below is a description for each method.

3.1.1 Mechanisms of COPD Exacerbation Recurrence

3.1.2 Ethical approval

Ethical approval was obtained from the Health Research Authority (HRA) (Appendix 1). Patients’ identification data such as name, address, and phone number were saved in a password protected file on a UCL computer and kept separately from research data, with patients identified using a study number. Only the researcher, chief investigator, and the research assistant in the respiratory medicine department had access to such data. The trial was registered at ClinicalTrials.gov (NCT number): NCT04024735 (354).

3.1.3 Research design and Targeted population:

The study design was a prospective observational cohort study. The target population of this study was COPD patients admitted to hospital because of COPD exacerbation.
3.1.4 Study setting:

The patients were recruited from Royal Free London NHS Foundation Trust at the Royal Free Hampstead site.

3.1.5 Method of sampling:

We used convenience sampling in this research.

3.1.6 Eligibility Criteria

**Inclusion Criteria**

- Patients who have a primary diagnosis of COPD.
- Patients admitted to hospital with an exacerbation of COPD.

**Exclusion Criteria**

- Patients in whom an initial diagnosis of an AECOPD was revised to an alternative at a later phase.
- Patients who have a predominant history of asthma
- Patients with a confirmed active malignancy
- Patients who have a predominant history of bronchiectasis.
- Cognitive impairment patients with a Mental Test Score (MTS) of 6 or less.
- Inability to give informed consent to take part in the study
3.1.7 Statistical consideration

**Primary outcome**

The primary outcome was factors that determine readmission to hospital within 30 days post discharge.

**Secondary outcomes**

- Factors that determine readmission to hospital within 90 days post discharge.
- Readmission rate at 30 days and at 90 days.
- Prevalence of comorbidities between those who were and were not readmitted within 30 and 90 days.
- Changes in admission-to-discharge in within breath reactance ($\Delta X_{rs5Hz}$) between patients who were and were not readmitted to the hospital within 30 and 90 days.
- Changes in quality-of-life measures by measuring CAT, modified Medical Research Council scale (mMRC) and the Hospital Anxiety and Depression Scale (HADS) at admission, discharge and after 30 days follow-up or at readmission.
- Prevalence of frailty using Reported Edmonton Frailty Scale (REFS) between those who were and were not readmitted to the hospital within 30 and 90 days.
- Change in physical activity level following the discharge between patients who were and were not readmitted within 30 and 90 days.
• Changes in admission-to-discharge PIFR between patients who were and were not readmitted within 30 and 90 days.

• Change in blood biomarkers: [CRP, white cell count (WCC), eosinophils, neutrophils, haemoglobin, and Estimated Glomerular Filtration Rate (eGFR)] and sputum microbiology samples at admission, discharge and at readmission.

• Length of stay in hospital following index admission between groups.

• Difference in previous admissions and exacerbations in the previous year.

• Previous admissions to the ICU and history of intubation.

Power calculation:

We sought statistical advice about our sample size calculation and data analysis from the Biostatistics Group at the Joint Research Office (JRO). It has been recommended to have 10 events as a minimum number of events per variable in a multivariable method of analysis as has been reported in the literature (355, 356). In our study, readmission is our event of interest, therefore having 30 to 40 readmitted patients will allow us to reliably examine 3 to 4 variables in the logistic regression model. As per the National COPD Audit in the UK, the national readmission rate for COPD patients is 24% within 30 days (206). Accordingly, we need to recruit 125 to 166 patients to have 30 to 40 readmissions. This number of patients was used as a minimum-targeted number. Due the explanatory nature of our study that looks to identify the nature of cause-and-effect relationships of several variables on readmission to
the hospital; we aimed to recruit as many patients as we could within duration of 18 months.

3.1.8 Recruitment of participants

Patients were consecutively recruited from the Royal Free Hospital in London over a period of one year started from May 2019 to March 2020 (I stopped recruitment due to the COVID-19 pandemic). They were approached during their admission on the wards by attending clinicians who were caring for them to introduce the study as soon as possible. Patients who showed an interest in taking part was provided with a written information leaflet describing the study further. Following that, any patients expressing a willingness to be included in the study were introduced to the research team for further explanations. At recruitment, participants were provided with a clear verbal and written description that included the objectives of the study and the benefits of making the study happen for patients and healthcare systems. Furthermore, an open discussion with interested participants was followed to answer any questions that needed to be clarified. Each participant was provided with the student researcher contact information. At this point, patients who agreed to participate were provided with a written consent form to sign (Appendix 2 and 3).

3.1.9 Study Procedure

Demographic and relevant clinical information were gathered from the patients and their medical record using a participant’s assessment sheet (appendix 4). Social support was assessed by asking questions about whether or not the
subject has a partner at home, their marital status, if there is daily support from the partner or others, and if the subject receives community care for COPD. At admission, four questionnaires were distributed to participants to scale their breathlessness, quality of life, hospital anxiety and depression and prevalence of frailty. Their breathlessness was evaluated by using the mMRC scale. The participants’ quality of life was assessed using CAT to measure the impact of COPD. The HADS was used to assess symptoms of anxiety and depression. Frailty was assessed using REFS. We collected baseline values of spirometry (FEV₁, FVC, FEV₁/FVC). In addition, we used the FOT device to determine the presence of EFL by measuring changes in within breath reactance (ΔXrs₅Hz). Following that, we collated from the records or obtained a peripheral venous blood sample for measurement of inflammatory markers including CRP, WCC, eosinophils, neutrophils, and haemoglobin. All patients were consented for the collection of a blood sample for research purposes. This sample was drawn from the patient at the same time as routine samples to prevent the patient having additional blood withdrawal procedures.

At discharge, the assessment of the breathlessness, quality of life, spirometry, IC and FOT were repeated. Blood and sputum samples results were collected where performed. Patients’ clinical progression was recorded which included the LOS in hospital, the use of oxygen, NIV and any admission to the ICU (Figure 11).

3.1.10 Follow-up

At discharge, participants were asked to be followed up for 30 days and 3 months for re-evaluation. If the participant agreed to be followed up, the step counter (pedometer) was given to wear throughout the 30-day period. The re-
evaluation assessment was repeated for participants readmitted before 3 months (any readmission occurring between 1-3 months), or after 30 days if there was no readmission. A telephone follow-up of 3 months was used.

Figure 11. Flow chart of the collected measurements.

Patients' Enrolments at Royal Free Hospital

Baseline Measurements at Admission

- FOT
- FIFR
- Spirometry
- Blood sample
- Frailty (REFS)
- mMRC
- CAT
- HADS
- Social factors
- Past History (Charlson Index)

At discharge

- FOT
- FIFR
- Blood sample
- Spirometry
- mMRC
- CAT
- HADS
- Community support

Patients' Physical Activity will be monitored for 30 days by using:
- Step Counter (Pedometer)

Patients' clinical progress will be recorded which include:
- (LOS) in hospital, use of (NIV and IMV), and (ICU) admission

The same assessment will be repeated for participants when any one of the following occurs first if participant doesn't not readmit to the hospital:

Readmission before 30 days post discharge

After 30 days as a follow up

A follow up after 3 months to record patients' clinical progress which include:
- readmission within 3 months, cumulative number of deaths for all-causes and time to death
3.1.11 Physiological assessments

- Measurements of Spirometry (FEV₁, FVC, FEV₁/VC, IC)

Spirometry is a non-invasive test to assess lung function of the participants, which is the gold standard to assess COPD severity. The test was conducted using ndd EasyOne® Air spirometer according to published guidelines (357). The ndd EasyOne® Air spirometer is a portable, rechargeable, accurate and proven spirometer (Figure 12). Patients were instructed to sit in the upright position during the test. To prevent leak from the participant’s nose, a soft nose clip was used. The patient was asked to inhale fully to TLC and then with a good seal around the mouthpiece, exhale forcefully and quickly into the spirometer. To measure IC, the patients were instructed to take a deep, fast breath back in at the end of a normal breath out (maximum volume of air that can be inspired from FRC). During the test, patients were given encouragement to breathe out for a minimum of 6 seconds. The test was performed a total of three times and the best result was recorded for each patient if acceptable repeatability was achieved. This was achieved when the difference between the largest and the next largest FVC is ≤0.150 L and the difference between the largest and next largest FEV₁ is ≤0.150 L (357).
Figure 12. ndd EasyOne® Air spirometer.
- **FOT measurements:**

FOT is a non-invasive tool to measure patients’ respiratory mechanics [resistance (Rrs) and reactance (Xrs)] by employing small amplitude pressure oscillations, which superimpose on the patient’s regular breathing (358). EFL is measured by within breath difference in reactance at 5Hz, (∆Xrs5Hz) and can detect flow limited breaths with a sensitivity and specificity of 100% (340). The optimal range was 2.53-3.12 cmH2O/(L/s) and optimal threshold value was 2.8 cmH2O/ (L/s). This method does not need any patient effort. When EFL is present, oscillations cannot pass through the constricted part of the peripheral airways (or “choke points”) and reach the alveoli, resulting in a marked reduction in compliance and a consequent increase in the value of (∆Xrs5Hz).

This test was conducted according to standard recommendations (358). The patient was instructed to be in a sitting position with the head in a neutral or slightly extended position to perform the test (Figure 13). The patient cheeks and the base of the mouth were firmly supported using both hands by the patient to prevent mouth leaks. A nose clip was used to eliminate any leak. The patient was instructed to breathe in and out normally for 10-20 breaths into the ResmonPro (ResTech, Milan, Italy). FOT measurements were taken in a supine position to compare them with an upright position.
Figure 13. ResmonPro for measurement of expiratory flow limitation.
• Physical activity monitoring by step counter (pedometer)

A step counter (pedometer) is a non-invasive portable device used to measure physical activity (Yamax Digi-walker SW-200). Data show that this pedometer provided a reliable measure of step count in fit people, relatively obese patients, and COPD patients (359, 360). At discharge, patients were provided with a step counter (pedometer) and asked to wear it on their waist all day except for sleeping and showering to record their daily physical activity (Figure 14). Furthermore, patients were asked to wear it after their discharge and return it at the follow-up visit or at their readmission within the first 30 days. To have complete and objective measurements, patients were requested to record their daily steps on a diary card (Appendix 5). Patients were followed up after a week post discharge to check if they have any difficulties using the pedometer.

Figure 14. Yamax Digi-Walker SW-200 pedometer device and how to wear it.
• **PIFR measurements:**

We measured PIFR at admission, discharge, and readmission or 30-day follow-up from patients. The main determinants of PIFR are the intrinsic resistance of the devices and inspiratory effort of the patients, in which older COPD patients had reduced PIFR due to poor inspiratory effort (361). PIFR measurement was performed by using the InCheckTM DIAL (Clement Clarke International Ltd, Harlow, UK and Alliance Tech Medical) (Figure 15). This tool is validated and can measure inspiratory flow rates between 15 and 120 L/min (362, 363). It has an excellent test–retest reliability and is accurate to within 10% or 10 L/min. The repeatability is good, within 5 L/min (362, 363). Suboptimal PIFR was defined as below 60 L/min and it was set to simulate resistance of the DISKUS® dry powder inhaler (DPI), a commonly used DPI device (364). We instructed patients to be in the seated position while doing this test, who were advised to inhale from FRC as fast and as hard as they could through this device, and the best of three efforts was taken. We chose FRC over RV because FRC varies from baseline values less following an episode of AECOPD than RV (114).
• Blood sampling:

We collected the results of blood samples at admission, discharge and readmission or 30 days follow-up from participants in line with the patient consent form and information sheet. It was collected to evaluate inflammatory biomarkers comparing admission, discharge, and readmission.

• Sputum sampling:

Sputum samples results if done were obtained from medical care system to identify the main pathogens for COPD exacerbations.
3.1.12 Questionnaires

- **mMRC Dyspnoea Scale**

The mMRC scale is a five-point scale ranges from 0 to 4 which used to classify the level of disability associated with breathlessness (Appendix 6). The mMRC is the most frequently used validated scale to assess dyspnea in clinical practice in COPD patients (365, 366).

This scale includes five points scale as follow:

Grade 0: I only get breathless with strenuous exercise

Grade 1: I get short of breath when hurrying on the level or walking up slight hill.

Grade 2: Walks slower than people of the same age because of dyspnoea or has to stop for breath when walking at own pace.

Grade 3: Stops for breath after walking 100 yards (91 m) or after a few minutes.

Grade 4: Too dyspnoeic to leave house or breathless when dressing.

- **CAT**

The CAT is an eight-item questionnaire to measure quality of life in COPD patients (Appendix 7). It can assess several COPD symptoms include cough, sputum, dyspnoea, chest tightness, and impact COPD on sleep. It has been widely reported that CAT is a valid and reliable tool to assess the impact of COPD on the patients’ health status (367, 368). The MCID for CAT is two points (369).
• **HADS**

This tool was developed to evaluate both anxiety and depression in hospitalized patients. It has 14 questions, 7 questions for anxiety and 7 questions for depression. Each question can be scored from 0 to 3 with a maximum total of 21 for each domain (anxiety or depression) (Appendix 8). The test is considered positive with a score of over 8 for each domain is recorded (370).

• **REFS**

This is a self-reported questionnaire that composed of nine domains; cognition, general health status, functional independence, social support, medication use, nutrition, mood, continence and self-reported performance (371). It ranges from 0 to 18 with higher scores indicating more severe frailty (Appendix 9). The collected score is categorised to four levels: ‘Not Frail or Vulnerable’ (0–7), ‘Mild Frailty’ (8–9), ‘Moderate Frailty’ (10–11), and ‘Severe Frailty’ (12–18) (372).

**3.1.13 Statistical plan:**

In the first instance, data were inspected using histograms to look for outliers and tested for normality using a Kolmogorov–Smirnov test. If normally distributed (parametric), data were expressed as mean (SD) and if not normally distributed data was expressed as median (IQR) (non-parametric) as appropriate. Categorical variables were compared using the χ² test or the
Fisher exact test. The power calculation of the primary outcome has been described in the sample size section.

A univariate analysis was performed to identify variables associated with 30- and 90-days readmission (the dependent variable). A multivariable logistic analysis was applied in which re-admission at 30 and 90 days was the dependent variable, whilst the independent variables were identified from the univariate analysis to be more associated with 30- and 90-days readmission.

We sought statistical advice about our sample size calculation and data analysis from the Biostatistics Group at the JRO. It has been recommended to have 10 events as a minimum number of events per variable in a multivariable method of analysis as has been reported in the literature (355, 356). In our study, readmission is our event of interest, therefore having 30-40 readmitted patients will allow us to reliably examine 3 to 4 variables in the logistic regression model. For other comparisons, Wilcoxon signed-rank was used for non-parametric paired data and T-test (paired test) was used for parametric data. As our research is an exploratory analysis, we did not correct for multiple comparisons, because a Bonferroni test in the context of our data would be too conservative. Relationships between variables were analysed using Spearman rank correlation coefficient test for non-parametric variables and for normally distributed variables we used the Pearson correlation coefficient. We analysed our data using the software Statistical Package for the Social Sciences (SPSS), Version 25.
3.1.14 Data Management:

Confidentiality:

The participants’ data was confidential and managed by coding and numbering participants’ information. A study code and number were used for storing confidential information. Original paper questionnaires, forms and participants’ contacts were collected from patients in accordance with the patient consent form and patient information sheet. This information was kept securely on UCL computers with password access and was not disclosed to anyone outside of the research team. UCL is the data controller and Professor John Hurst will act as the data custodian for the study. Only the investigators involved with this study have the original code for patient identifiable data. We processed, stored and disposed of original paper questionnaires assessment forms and participants’ contact details in accordance with all applicable legal and regulatory requirements under supervision of the Chief Investigator/Academic Supervisor. This project was covered by the UCL Data Protection Registration, reference No Z6364106/2019/01/113 health research.

Quality assurance:

This study was performed in accordance with Good Clinical Practice (GCP).

Record Keeping and archiving

At the end of this study, all required files and data that were collected from participants’ will be securely archived by the research team for a minimum of 10 years. Only the research team and authorised inspectors will be allowed to have access to these files. Source documentation will be stored on hard paper
files in a locked office at UCL. All archived files will continue to be accessible for inspection by appropriate authorities upon request.

**Finance:**

This PhD research study was funded by the Saudi Arabia Cultural Bureau (SACB) through Prince Sultan Military College of Health Sciences (PSMCHS).

**Risk assessment:**

The study design is an observational non-interventional study, which doesn’t fall under the scope of interventional clinical studies. Hence, the research team was not expecting any significant harm or risks to participants. There might be slight discomfort when taking lung function measurements, and so, the researchers made sure that there was a sufficient rest time between measurements as required. Researchers ensured bronchodilators were available with them to manage breathlessness in case any participant developed bronchospasm. Participants may experience bruising after the blood test; however, the blood collection was taken by qualified and trained researchers. There was no anticipation of any risk or discomfort of using the diary, the reporting questionnaires, or the step counter.

**Insurance:**

In clinical trials, participants may, accidently, be exposed to any harm during their participation. University College London holds insurance which covers those claims related to injuries and the request can be made by the participant at any stage of the trial proceedings. Participants were eligible to obtain compensation if there was clear evidence of participant neglect by UCL. As this trial was conducted at health-care site, thus, the hosting site was expected
to ensure the participant’s safety in all clinical settings. UCL was not liable for any misconduct /negligence of the health-care workers or any breach in the NHS Trust duty of care, or any negligence on the part of NHS employees. Participants may be able to claim compensation for injury caused by participation in this trial without the need to prove negligence on the part of UCL or another party.

3.2 Prioritisation in Exacerbations of COPD

3.2.1 Ethical approval

This project did not need ethical approval because it does not come under the remit of HRA approvals, where research priority setting is seen as service evaluation and development. There was no need for participants to tell us any contact details unless they wanted to take part in the next phase of the process, or they wanted to know about the survey results. All data collected in this survey were held anonymously and securely.

3.2.2 The benefits of Research Prioritisation

This project was to conduct a Research Prioritisation exercise for COPD exacerbations. Prioritising research questions using rigorous methodology will position the UK COPD community to submit commissioned and investigator-led research calls, in the knowledge that these have been co-developed via a multi-professional team, in partnership with patients and carers, and that they are considered both relevant to people living with COPD and practice
changing. Research proposals developed in this way are much more likely to be funded. In 2007, for example, a Research Prioritisation was conducted in asthma (6), resulting in successful NIHR Health Technology Assessment (HTA) funding and an answer to the question of whether breathing exercises improve quality of life (373). This project was therefore to create a legacy of COPD exacerbation research excellence (Figure 16).

Figure 16. Logo of Research Prioritisation in Exacerbations of COPD.
3.2.3 The James Lind Alliance (JLA)

Robust methodology exists for research prioritisation, championed by the JLA ([http://www.jla.nihr.ac.uk/](http://www.jla.nihr.ac.uk/)). The JLA was established in 2004. It sits within the NHS NIHR, and is a non-profit organisation established to bring patients, carers and clinicians together in ‘Priority Setting Partnerships’ (PSPs) to address treatment uncertainties. PSPs are designed to identify, agree, and prioritise the most important research questions in a particular field with the intention of ensuring grant giving bodies (such as NIHR NETSCC – the NIHR Evaluation, Trials and Studies Co-ordinating Centre) are aware of what matters to patients, carers and clinicians. The successful 2007 asthma PSP was conducted with the JLA (6). This process has been applied to more than 50 PSPs, including 2007 asthma PSP and cystic fibrosis (6, 374). In brief, the JLA approach establishes a partnership of patients, carers, clinicians, and scientists. The PSP identifies key research uncertainties and then works together to prioritise these. The output is a list of top-ten questions that patients and clinicians want the research community to address. Over twenty JLA PSPs have now been completed. Full detail of the proposed methodology is available on the JLA website ([http://www.jla.nihr.ac.uk/jla-guidebook/](http://www.jla.nihr.ac.uk/jla-guidebook/)).

3.2.4 Principles of the JLA

JLA’s priority setting process is tailored to meet the needs of different groups while keeping its fundamental principles that include equality, inclusion, openness, and commitment to use and contribute evidence within each PSP.
Such concepts are seen in a variety of characteristics that allow PSPs to maintain continuity and optimum knowledge:

- Transparency of procedure, strategies, and desires.
- Balanced representation and experiences of patients, carers, and specialised clinicians.
- Not including non-clinician researchers for voting purposes, though could be included in certain areas of the procedure which can be beneficial.
- Exclusion of individuals or entities, for example pharmaceutical firms, who are of major competitive or business values.
- Audit trail to the final target set of initial uncertainties that had been submitted.
- Formal evidence checks for the submitted uncertainties should be started first before Priority setting has been delivered.

3.2.5 Aims, objectives and scope of the PSP

The aim of the COPD Exacerbations PSP was to identify unanswered questions about exacerbations of COPD from patient, carer and clinical perspectives and then prioritise those that patients, carers, and clinicians agree are the most important for research to address (appendix 10, PSP protocol).
The objectives of the PSP were to:

- work with patients, carers, and clinicians to identify uncertainties about the management and prevention of exacerbations in people with COPD
- to agree by consensus a prioritised list of those uncertainties, for research
- to publicise the results of the PSP and process
- to take the results to research commissioning bodies to be considered for funding.

The scope of the COPD Exacerbations PSP was defined as:

The main themes were diagnosis, prevention, and management of exacerbations incorporating treatment. These can be conceptualised as:

- Why did this event happen? What causes exacerbations?
- How can we treat exacerbations while they are happening? This includes self-care, additional support e.g., physiotherapy, occupational therapy, psychological support, and clinician led support.
- What can we do to prevent them from happening in the future, both self-care and multi-disciplinary clinical support?

The PSP agreed that the PSP cannot cover all elements of COPD. Therefore, it was agreed that the PSP would concentrate on exacerbations in people with COPD. The group recognised the need to include those who may refer to their disease using alternative terms such as emphysema or chronic bronchitis. This was reflected in the survey when we ask who is completing the survey.
Included in the COPD Exacerbation PSP scope:

- Any participant above 18 years of age (adult).
- We only considered responses from the UK.

Excluded from the COPD Exacerbation PSP scope:

- Asthma.
- Responses from industry or pharmaceutical companies.

The Steering Group was responsible for discussing what implications the scope of the PSP would have for the evidence-checking stage of the process. Resources and expertise were put in place to do this evidence checking.

3.2.6 PSPs process

Here is a flow diagram that illustrates the normal PSP process adapted from the JLA Guidebook (http://www.jla.nihr.ac.uk/jla-guidebook/) (Figure 17).
Figure 17. Usual PSP process.

- Initial enquiry
  - read JLA Guidebook
  - enquire via NETSCC
  - discuss readiness with NETSCC
  - NETSCC allocates JLA Adviser

- Steering Group convened
  - with JLA adviser as Chair
  - agree and sign off protocol

- Initial awareness meeting
  - optional, depending on needs

- Gathering of uncertainties
  - collected via survey
  - harvested from literature

- Interim priority setting
  - Remote interim vote on long list of uncertainties by all interested parties

- Presentation of uncertainties
  - Uncertainties combined or split as appropriate
  - peer review and input from Steering Group essential

- Checking
  - Information Specialist checks literature to make sure uncertainties are true unknowns
  - peer review and input from Steering Group essential

- Processing responses
  - Information Specialist reviews responses and removes duplicates, starting to create PICO research questions
  - peer review and input from Steering Group essential

- Analysis of interim results
  - by Steering Group
  - check balance of responses
  - creation of shortlist for final workshop

- Identify and publish Top 10
  - final PSP workshop participants rank the 20-30 shortlisted uncertainties
  - publish agreed Top 10 uncertainties from workshop

- Next steps
  - more development of uncertainties into research questions by Steering Group

- Follow up
  - dissemination to research programmes/researchers
  - publish paper/final report
  - long term tracking of resulting research
3.2.7 The five-stage process of this project

Stage 1: Establishing the PSP and defining project scope

Funding to deliver this COPD Exacerbation PSP was obtained from the British Lung Foundation (BLF; now the Asthma UK – British Lung Foundation Partnership) in October 2018 following a competitive grant application. We first established a steering group chaired by a JLA advisor, comprising three people living with COPD, nine multi-professional clinicians including doctors, nurses and physiotherapists working across primary, community and secondary care COPD services and a clinically trained ‘information specialist’ responsible for the evidence searching (see below). The aim of the steering group was to provide consensus on the scope and methodology, and to monitor progress of the project and agreed priorities. All participants completed declaration of interests’ forms. The steering group met a total of 14 times during the PSP process, in person or by teleconference. It was agreed that at least six members in total and at least two patient representatives were required for the steering group to be quorate.

The steering group first agreed and published the PSP protocol on the JLA website: https://www.jla.nihr.ac.uk/documents/copd-exacerbations-psp-protocol/24398.

In summary, the aims of the COPD Exacerbations PSP were to identify unanswered questions about exacerbations of COPD from patient, carer and clinical perspectives and then prioritise those that patients, carers, and clinicians agree are the most important for research to address.
The project then followed the five-stage process described by the JLA (http://www.jla.nihr.ac.uk/jla-guidebook/), summarised as Figure 18.

**Figure 18. The five-stage process described by the JLA.**

Stage 1: Establishing the Priority Setting Partnership and defining project scope

Stage 2: Gathering and identifying questions (first survey)

Stage 3: Reducing the questions and processing uncertainties

Stage 4: Interim prioritisation (second survey)

Stage 5: Priority setting workshop

**Stage 2: Gathering and identifying questions (first survey)**

The first survey was used to gather potential research questions as widely as possible. Whilst conducted in the UK, the questions raised are not specific to that setting. The survey was developed by the steering committee, piloted in SurveyMonkey and then live from 17th April 2019 to 12th July 2019. The survey collected basic demographic information and explained what people
were being asked to do. Respondents were invited to leave any number of questions they had about the prevention, diagnosis, and treatment of COPD exacerbations. Respondents to the survey are not themselves research participants and the UK Heath Research Authority decision aid indicates no need for research ethics approval. There were no exclusion criteria, provided that the question was within scope. We developed a webpage describing the survey, hosted by the British Lung Foundation. Invitations were disseminated to BLF supporters including ‘Breathe Easy’ patient support groups, and via social media. The PSP had its own Twitter account (@COPDPSP) and utilised the hashtag #COPDhaveyoursay. Dissemination was aided by links between the steering committee and organisations including the British Thoracic Society (BTS), Primary Care Respiratory Society (PCRS), Association of Respiratory Nurse Specialists (ARNS) and the Association of Chartered Physiotherapists in Respiratory Care (ACPRC).

Clinicians were also able to distribute paper copies to patients unable to take part online but were themselves responsible for uploading the patients’ views. At the mid-point of the survey the demographic profile of the respondents was reviewed by the Steering Committee. We recognised that we had few Black Asian and Minority Ethnic (BAME) respondents and made additional efforts in discussion with a BAME advisor (who provided information on BAME organisations and how to approach them) to reach these communities including attending a Festival of Health in the East Midlands and direct approach in clinical environments including PR classes.
Stage 3: Reducing the questions and processing uncertainties

At this stage, each individual response was identified to create a total list of responses. Responses that were out-of-scope (defined in the protocol) were excluded, leaving a list of questions. At each stage, the steering group reviewed, discussed, and approved the process. Similar questions were then combined into broader over-arching questions. We then sought to answer whether there was evidence to answer these questions by searching the GOLD 2020 strategy (1), the Cochrane Library and UK NICE 2019 COPD guidance (87). We specifically sought one or more high quality randomised controlled trials, or a systematic review/meta-analysis of such studies published within the preceding five years (Figure 19).

For each question, three clinicians from the steering committee independently decided if a question had been adequately answered or not. Where there was disagreement, the question was discussed by the all the clinicians on the steering committee. At the end of this stage, questions identified to have been answered were excluded from indicative questions list. The rest of the questions were confirmed as uncertainties and moved forward to the interim prioritisation stage. As with all stages of the JLA method, the process is completely transparent, and it is possible to track individual responses to indicative questions and evidence on the files available on the JLA website.
Stage 4: Interim prioritisation (second survey)

The interim prioritisation reduces the number of questions taken to the final prioritisation workshop by asking people to vote for their own top ten questions.

This second survey, also run in SurveyMonkey and disseminated through similar routes to the first, was open between 29 July 2020 and 15 September 2020. We added a question about whether the change of delivery of care for people with COPD during COVID-19 pandemic would change the listed top-ten priorities if participants been asked this time last year.
We were also able to directly contact respondents to the first survey who had agreed in advance to being contacted for the second stage. The number of votes for each question was counted, separately for lay versus clinical respondents to create two ranked lists. The final ranking gave equal weight to lay versus clinician responses. From this overall list, the steering committee had a priori agreed to take the top 15 ranked questions to the final priority setting workshop.

**Stage 5: Priority setting workshop**

The final top ten list was agreed at a full-day online workshop on Thursday 1st April 2021, conducted via ZOOM and including patients, carers, and Health Care providers (HCPs) wider than the steering committee. In total 14 people took part (seven multi-professional clinicians and seven patients, of whom in total seven were steering committee members), with four JLA advisors to enable break-out group discussion. Prior to the workshop, the top 16 questions (15 position had two equal ranks) were distributed to the participants to ensure familiarity with the questions and process, supported by video resources explaining the process.

A nominal group technique was used, with both small and large groups. The small groups were established to achieve a balance between individuals with COPD and clinicians, as well as those who were and were not part of the steering committee. Priority setting was distributed across the day and included four stages. Participants were first divided into three groups and each person was encouraged to express their top bottom three priorities, with discussion after all had their say. In the second phase, the same small groups
were required to rank the 16 questions based on their phase 1 discussion, with all questions shown on the screen.

The facilitation team then combined the results of all three groups’ rankings of the questions, resulting into a combined ranking. In the third phase, participants were re-grouped into three new groups working in separate virtual rooms, again matched by the background of the participants. Participants were encouraged to reflect on the ranking and were offered the chance to adjust the order of questions through discussion. After the final phase, ranks were pooled and analysed with the whole group. This combined ranking was agreed by the entire group together at the fourth stage.

**Stage 6: Dissemination**

Our published paper provides the formal summary of the process, but results will also be disseminated via the Asthma UK and British Lung Foundation partnership to people living with COPD and written as a policy brief for research funders. Ultimately, we hope that these results will be of use to the community in lobbying for research questions which have been developed using robust and transparent methodology, as a partnership between patients and clinicians. The impact of the PSP will be monitored by the Principal Investigator and reported on to the Asthma UK and British Lung Foundation.
4. Systematic Review and Meta-analysis
Risk factors for all-cause hospital readmission following exacerbation of COPD: a systematic review and meta-analysis

An overview was provided above about the current literature. When I finished my literature review, it became clear that whilst there is a 2007 systematic review examining risk factors for COPD-related readmissions (375), there is no existing review investigating risk factors for all-cause COPD readmission. Therefore, besides being a necessary background to my PhD, we moved on to write and publish this systematic review and meta-analysis.

4.1 Aim

Readmission rates following hospitalisation for COPD exacerbations are unacceptably high, and the contributing factors are poorly understood. Our objective was to summarise and evaluate the factors associated with 30- and 90-day all-cause readmission following hospitalisation for an exacerbation of COPD.

4.2 Methods

4.2.1 Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting in Systematic Reviews and Meta-Analyses (PRISMA) guidelines (376) and the review was prospectively registered on PROSPERO (Reg. No.: CRD42019119364).
4.2.2 Search Strategy

We searched Medical Literature Analysis and Retrieval System Online, or MEDLARS Online (MEDLINE), Excerpta Medica database (Embase), Cumulative Index of Nursing and Allied Health Literature (CINAHL) and Scopus from inception to November 05, 2019. We used an extensive search strategy developed for retrieving this type of evidence, which included the reference list of eligible papers and previous reviews (see Appendix 11).

4.2.3 Inclusion Criteria

The PICO framework [P – population (COPD patients admitted due to COPD exacerbation); I – intervention (n/a); C – comparison (patients get readmitted vs not readmitted); O – outcome (readmission within 30 and 90 days)] was used in our search strategy. We included studies that investigated: (1) readmission/rehospitalisation after an initial admission with COPD exacerbation; (2) ‘all-cause’ readmission defined as any emergency (non-elective) readmission to hospital; and (3) studies that investigated all-cause readmissions and analysed the contribution of risk factors and/or predictors associated with readmission or rehospitalisation.

4.2.4 Exclusion Criteria

We excluded the following: (1) studies that examined readmission risk more than 1 year after discharge from index admission; (2) intervention studies that did not include examination of risk factors for all-cause hospital readmission for patients with COPD in the control group; (3) studies that included factors/predictors/causes for readmission but did not specifically analyse all-cause COPD readmission-related factors; (4) conference abstracts, editorial
reports, correspondence, reviews, qualitative studies and theses; (5) non-English manuscripts; and (6) non-full text articles.

4.2.5 Data Collection

Two authors (JSA and JRH) independently screened titles and abstracts of potential studies and conflicts were resolved through a discussion with a third author (SM). Full-text articles of potential studies were then independently read by two authors (JSA and CMN) to identify studies meeting the inclusion criteria. The reference lists from all identified studies and reviews were scrutinised for eligible articles. Disagreement on selected papers was resolved through discussion with a third author (JRH).

4.2.6 Quality Assessment

Two authors independently evaluated the methodological quality of included studies using a modified version of the Newcastle-Ottawa Scale (377). This scale utilises a ‘star’ system with a maximum score of nine stars for each study. Study ratings are categorised as good (7-9 stars), fair (4-6 stars) or poor (1-3 stars). Any disagreement in the quality assessment was resolved by discussion with a third author.

4.2.7 Data Synthesis

We were not able to perform a meta-analysis on all results because of the heterogeneity of included studies and the risk factors were reported inconsistently across studies. However, we did conduct a meta-analysis using summary data from 14 studies to synthesise adjusted odds ratios for risk factors where results were reported consistently (for example, similar age ranges) and where a variable was reported in at least four studies in total. To
account for study heterogeneity, we used the random-effects model in Stata 11.0. Data are displayed using forest plots. We examined between-study heterogeneity using the I² statistic. A narrative synthesis of the results was conducted, guided by study quality.

4.3 Results

An initial search generated 3533 potentially relevant papers, of which 1657 were immediately excluded due to duplication. After the first screening of title and abstract, 208 papers were potentially relevant according to the inclusion criteria. An additional 176 papers were excluded after full-text review, which resulted in 32 studies that satisfied all criteria. The reference list of the relevant papers was also examined and did not result in any new papers (see Figure 18, PRISMA flow diagram).

4.3.1 Description of included studies

A summary of the included studies is presented in Table 3. Of 32 studies, 27 were conducted retrospectively and five were conducted prospectively; 21 studies were conducted in the USA, three in the UK, two in Canada and one each in Spain, Korea, Hong Kong, Israel, Australia and Europe. All papers were published between 2013 and 2019 and included a total of 3,982,881 patients. Among the 32 studies, three were rated as ‘fair’ in the quality assessment. The remaining papers were ranked as ‘good’ quality. A detailed description of the studies is presented in Table 3. The all-cause readmission rates ranged from 8.8% to 26.0% at 30 days, 17.5% to 39.0% at 90 days, and from 8.8% to 65.2% at one year. Studies described several risk factors for all-cause COPD readmission at different time points, the results of which are
summarised in Figure 20 and Table 4. The details of the quality assessment of each study are presented in Appendix 11.

Figure 20. PRISMA flow diagram
4.3.2 Meta-analysis results

We conducted a meta-analysis on 14 studies examining five risk/protective factors associated with all-cause 30-day readmission, including a total of 3,792,506 patients, which represents around 95% of the total sample size of the included papers. These studies were included because the reported risk factors in such studies were consistent among them. This included 2,442,314 participants in eight studies, which reported heart failure as a risk factor, 2,349,651 in six studies which reported depression as a risk factor, 2,331,529 in six studies which reported alcohol use as a risk factor, 2,261,874 in four studies which reported renal failure as a risk factor and 3,506,458 in nine studies which found that female sex was a protective factor. There was heterogeneity between studies with significant I² values that ranged from 59.8%–96.7%; therefore, we calculated the pooled adjusted OR values using a random-effect model. There was no adjustment for FEV₁ in the selected ORs because there were no confirmatory spirometry values available to clinicians at the time of management. The pooled adjusted ORs for heart failure, renal failure, depression, alcohol use, and female sex are presented using forest plots (Figures 22–26). Heart failure was associated with the highest odds of readmission followed by renal failure then depression.

In general, the significant risk factors for 30- and 90-day all-cause readmission were comorbidities, previous exacerbations and hospitalisations, and increased length of initial hospital stay. A narrative synthesis of the 30-day and 90-day studies appears below.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Sample size</th>
<th>Age mean ±SD or range</th>
<th>GOLD Severity</th>
<th>Readmission time</th>
<th>Causes and rates of readmission, in order of prevalence</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Almagro et al. 2014 (378)</td>
<td>P</td>
<td>983</td>
<td>72.25±9.7</td>
<td>Gold 3</td>
<td>90 day and 1 year</td>
<td>➢ All readmission at 90 day 34.2%  ➢ All readmission at 1 year 53.8%</td>
<td>Good</td>
</tr>
<tr>
<td>Baker et al. 2013 (379)</td>
<td>R</td>
<td>6095</td>
<td>46–65</td>
<td>Not reported</td>
<td>1, 3 and 12 months</td>
<td>➢ All readmission at 30 day 8.3%  • 67.6% readmitted for COPD  • 32.2% non-COPD  ➢ All readmission at 90 day 17.5%  • 67% were readmitted for COPD  • 33% non-COPD  ➢ All readmission at 1 year 41.5%  • 66.5% readmitted for COPD  • 33.5% non-COPD</td>
<td>Good</td>
</tr>
<tr>
<td>Bashir et al. 2016 (380)</td>
<td>R</td>
<td>461</td>
<td>71.7 ±13.3</td>
<td>Not reported</td>
<td>30 days</td>
<td>➢ Overall rate of 16.5%</td>
<td>Good</td>
</tr>
<tr>
<td>Bollu et al. 2013 (381)</td>
<td>R</td>
<td>2463</td>
<td>72.5 ±12</td>
<td>Not reported</td>
<td>30 days</td>
<td>➢ Overall rate 20.6%  • Rate in arformoterol patients (8.7%)  • Rate in nebulized SABA patients (11.9%)</td>
<td>Good</td>
</tr>
<tr>
<td>Bottle et al. 2018 (382)</td>
<td>R</td>
<td>96053</td>
<td>36±285</td>
<td>Not reported</td>
<td>30 days</td>
<td>➢ Overall rate 16.5%  • Non-COPD (60.9%)  • COPD related (39.1%)</td>
<td>Good</td>
</tr>
<tr>
<td>Candrilli et al. 2015 (383)</td>
<td>R</td>
<td>264,526</td>
<td>30 days = 67.69 ±11.26  90 days = 67.42 ±11.23</td>
<td>Not reported</td>
<td>30 days and 90 days</td>
<td>➢ Overall rate at 30 days 19.82%  ➢ Overall rate at 90 days 28.31%</td>
<td>Good</td>
</tr>
<tr>
<td>Chan et al. 2011 (384)</td>
<td>R</td>
<td>85497</td>
<td>76.81 ±9.6</td>
<td>Not reported</td>
<td>30 days</td>
<td>➢ Overall rate 24.2%</td>
<td>Good</td>
</tr>
<tr>
<td>Study</td>
<td>Outcome</td>
<td>Males</td>
<td>Females</td>
<td>Median Age</td>
<td>Study Duration</td>
<td>Overall Rate</td>
<td>Cause of Admission</td>
</tr>
<tr>
<td>-----------------------------</td>
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</tr>
<tr>
<td>Chawla et al. 2014 (385)</td>
<td></td>
<td>64</td>
<td></td>
<td>70±12</td>
<td>30 days</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Choi et al. 2018 (386)</td>
<td></td>
<td>704</td>
<td></td>
<td>72.4±9.5</td>
<td>Gold 2-3</td>
<td>9.3%</td>
<td></td>
</tr>
<tr>
<td>Couillard et al. 2017 (174)</td>
<td></td>
<td>167</td>
<td></td>
<td>71.4±10.3</td>
<td>Gold 2</td>
<td>58%</td>
<td></td>
</tr>
<tr>
<td>Echevarria et al. 2017 (387)</td>
<td></td>
<td>2417</td>
<td></td>
<td>72.5±10.1</td>
<td>Gold 3</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>Epstein et al. 2018 (388)</td>
<td></td>
<td>539</td>
<td></td>
<td>68.19±11.75</td>
<td>Gold 3</td>
<td>9.5%</td>
<td></td>
</tr>
<tr>
<td>Ehsani et al. 2019 (389)</td>
<td></td>
<td>42</td>
<td></td>
<td>70±8.6</td>
<td>Not reported</td>
<td>9.5%</td>
<td></td>
</tr>
<tr>
<td>Genao et al. 2015 (390)</td>
<td></td>
<td>32,741</td>
<td></td>
<td>71.4±10.3</td>
<td>Not reported</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Goto et al. 2018 (391)</td>
<td></td>
<td>845,465</td>
<td></td>
<td>69±6.01</td>
<td>Not reported</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Gershon et al. 2019 (392)</td>
<td></td>
<td>126,013</td>
<td></td>
<td>35-85+</td>
<td>Not reported</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Total</td>
<td>M</td>
<td>F</td>
<td>Sex</td>
<td>Age</td>
<td>Hospitalization Duration</td>
</tr>
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</tr>
<tr>
<td>Hakim et al. 2018 (393)</td>
<td>R</td>
<td>2,662</td>
<td>M=1418</td>
<td>F=1243</td>
<td>(53%)</td>
<td>(47%)</td>
<td>72.5 ±12</td>
</tr>
<tr>
<td>Hijawi et al. 2015 (394)</td>
<td>P</td>
<td>160</td>
<td>M=76 (47.5%)</td>
<td>F=84 (52.5%)</td>
<td>65.77 ±12.47</td>
<td>Gold 1-4</td>
<td>30 days</td>
</tr>
<tr>
<td>Jacobs et al. 2018 (395)</td>
<td>R</td>
<td>1,055,830</td>
<td>M=437,812</td>
<td>F=618,018</td>
<td>(41%)</td>
<td>(59%)</td>
<td>68 (58-77)</td>
</tr>
<tr>
<td>Kon et al. 2015 (396)</td>
<td>P</td>
<td>213</td>
<td>M=111 (52%)</td>
<td>F=102 (48%)</td>
<td>72.1 ±10.8</td>
<td>Gold 3</td>
<td>90 days</td>
</tr>
<tr>
<td>Loh et al. 2017 (397)</td>
<td>R</td>
<td>123</td>
<td>M=65 (52.8%)</td>
<td>F=58 (47.2%)</td>
<td>64.9 ± 11.3</td>
<td>Gold 3</td>
<td>30 and 90 days</td>
</tr>
<tr>
<td>Nguyen et al. 2014 (398)</td>
<td>R</td>
<td>4,596</td>
<td>M=2040</td>
<td>F=2556</td>
<td>(44%)</td>
<td>(56%)</td>
<td>72.3 ±11</td>
</tr>
<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Gender Distribution</td>
<td>Mean Age ± SD</td>
<td>Follow-up Period</td>
<td>Cause of Death</td>
<td>Timing of Death</td>
<td>Overall Rate</td>
</tr>
<tr>
<td>--------------------------------------------</td>
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</tr>
<tr>
<td>Nguyen et al. 2015</td>
<td>2910</td>
<td>M=1248 (43%)</td>
<td>72 ±11</td>
<td>30 days</td>
<td></td>
<td>Gold 2</td>
<td>Overall rate 23 %</td>
</tr>
<tr>
<td>Rinne et al. 2017</td>
<td>20,472</td>
<td>M= not presented</td>
<td>73</td>
<td>30 days</td>
<td></td>
<td>Not reported</td>
<td>Overall rate 20.2%</td>
</tr>
<tr>
<td>Rinne et al. 2017</td>
<td>33,558</td>
<td>M= 32417 (96.6%)</td>
<td>68.7</td>
<td>30 days</td>
<td></td>
<td>Not reported</td>
<td>Overall rate 18%</td>
</tr>
<tr>
<td>Roberts et al. 2015</td>
<td>306</td>
<td>M=135 (44%)</td>
<td>71</td>
<td>30 and 90 days</td>
<td></td>
<td>Not reported</td>
<td>Overall rate at 30 days 9.2% Non COPD 50% Respiratory related 50%</td>
</tr>
<tr>
<td>Shah et al. 2015</td>
<td>947,084</td>
<td>M=392,187 (41.41%)</td>
<td>73.55 ±10.87</td>
<td>30 days</td>
<td></td>
<td>Not reported</td>
<td>Overall rate 20.2%</td>
</tr>
<tr>
<td>Sharif et al. 2014</td>
<td>8,263</td>
<td>M=3,401 (41%)</td>
<td>56.55 ±5.73</td>
<td>30 days</td>
<td></td>
<td>Not reported</td>
<td>Overall rate 8.9%</td>
</tr>
<tr>
<td>Simmening et al. 2016</td>
<td>286,313</td>
<td>M= 130497 (45.5%)</td>
<td>46-90+</td>
<td>30 days</td>
<td></td>
<td>Not reported</td>
<td>Overall rate 12.2%</td>
</tr>
<tr>
<td>Study</td>
<td>N</td>
<td>M</td>
<td>F</td>
<td>Age</td>
<td>Race</td>
<td>30-day readmission rate</td>
<td>Top reasons</td>
</tr>
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</tr>
<tr>
<td>Singh et al. 2016 (405)</td>
<td>R</td>
<td>135,498</td>
<td>M=53940 (36%)</td>
<td>F=81558 (62%)</td>
<td>66-74, 75-84, ≥85</td>
<td>Not reported</td>
<td>30 days</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>30-day readmission rate for patients with COPD with coexisting psychological disorders (23.80%)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td>30-day readmission rate for patients with COPD without coexisting psychological disorders (16.25%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Top reasons: COPD (30.89%), Pneumonia (10.62%), Heart failure (6.55%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>M</th>
<th>F</th>
<th>Age</th>
<th>Race</th>
<th>30-day readmission rate</th>
<th>Top reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Space et al. 2018 (406)</td>
<td>R</td>
<td>2,391</td>
<td>M= 2,319 (97%)</td>
<td>F= 72 (3%)</td>
<td>68.0 ±10.4</td>
<td>Not reported</td>
<td>30 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>M</th>
<th>F</th>
<th>Age</th>
<th>Race</th>
<th>30-day readmission rate</th>
<th>Top reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tzy-Chyi Yu et al. 2015 (407)</td>
<td>R</td>
<td>18,282</td>
<td>M=6,869 (37.6 %)</td>
<td>F=11,413 (62.4%)</td>
<td>56.6 ±5.8</td>
<td>Not reported</td>
<td>30 days</td>
</tr>
</tbody>
</table>

**Abbreviations:** AECOPD: acute exacerbations of chronic obstructive pulmonary disease; COPD: chronic obstructive pulmonary disease; F: female; GOLD: The Global Initiative for Chronic Obstructive Lung Disease; M: male; MI: myocardial infarction; P: prospective; R: retrospective; SABA: short acting beta agonist.
Table 4. Details of 30- and 90-days risk factors for all-cause COPD readmission.

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk/protective factors for all-cause readmission (OR/RR, 95% CI) from high OR/RR/HR to low (significant factors only)</th>
</tr>
</thead>
</table>
| Almagrao et al. 2014 (378) | **Multivariable analysis:**  
  - The CODEX index was significantly related to hospital readmission at both 90 days (mean ±SD in readmitted group 5.7 [2.2] vs mean ±SD in non-readmitted group 3.5 [3.3], P=0.0001)  
  - The CODEX index was significantly related to hospital readmission at 1 year (mean ±SD in readmitted group 5.5 [2] vs 4.7 [2.2] in non-readmitted group, P =0.001)  
  - The CODEX index was also associated with mortality at 3 months HR 1.5 (1.2–1.8) and 1 year HR 1.3 (1.2–1.5) |
| Baker et al. 2013 (379) | **Multivariable analysis of readmission within 30 days:**  
  - Moderate or severe liver disease, OR 3.09 (1.36–7.02)  
  - Metastatic solid tumor, OR 2.44 (1.35–4.44)  
  - Number of inpatient hospitalisations in pre-index period (22 versus 0), OR 2.25 (1.61–3.14)  
  - Heart failure, OR 1.41 (1.11–1.78)  
  - Diabetes, OR 1.35 (1.10–1.66)  
  - Year of index hospitalisation (2009 versus 2008), OR 0.77 (0.61–0.97)  
  - Age group (70 vs 69), OR 1.50 (1.25–1.79)  
  - Plan type (HMO versus comprehensive), OR 1.46 (1.11–1.92)  
  - Renal disease, OR 1.43 (1.09–1.89)  
  - Number of inpatient hospitalisations in pre-index period (1 versus 0), OR 1.39 (1.14–1.69)  
  - Myocardial infarction, OR 1.31 (1.00–1.72)  
  - Malignancy, OR 1.29 (1.01–1.65)  
  - Number of ED visits in pre-index (2 versus 0), OR 1.27 (1.05–1.53)  
  - Systemic corticosteroids, OR 1.22 (1.06–1.41)  
  - Diabetes, OR 1.20 (1.03–1.41)  
  - Number of ICU days in index hospitalisation, OR 1.04 (1.00–1.07)  
  - Number of ED visits in past 6 months (≥4 vs 0), OR 6.40 (1.25–32.87)  
  - Number of comorbidities (≥7 vs 1–3), OR 3.03 (1.36–6.75)  
  - Discharge destination (SNF vs W/o home care), OR 3.03 (1.36–6.75)  
  - No. of comorbidities (4–6 vs 1–3), OR 1.52 (0.71–3.23)  
  - Female, OR 0.51 (0.29–0.91) |
| Bashir et al. 2016 (380) | **Univariate analysis:**  
  - No. of comorbidities (≥7 vs 1–3), OR 23.70 (3.17–177.32)  
  - No. of comorbidities (4–6 vs 1–3), OR 11.61 (1.57–86.06)  
  - No. of ED visits in past 6 Months (≥4 vs 0), OR 4.37 (1.83–10.46),  
  - No. of discharge medications (≥15 vs 0–8), OR 4.21 (2.02–8.64)  
  - No. of ED visits in past 6 Months (3 vs 0), OR 3.82 (1.42–10.26)  
  - LACE Index (11–12 vs 5–6), 3.43 (1.08–10.88)  
  - Discharge destination (SNF vs W/o home care), OR 3.20 (1.81–5.67)  
  - No. of ED visits in past 6 Months (2 vs 0), OR 2.60 (1.25–5.44)  
  - No. of ED visits in past 6 Months (1 vs 0), OR 1.90 (1.01–3.58)  
  - Insurance (Private vs Medicare), OR 0.49 (0.29–0.85)  
  - Female, OR 0.47 (0.28–0.77)  
  - Race (black vs white), OR 0.25 (0.09–0.71)  
  - Moderate or severe liver disease, OR 3.09 (1.36–7.02)  
  - Metastatic solid tumor, OR 2.44 (1.35–4.44)  
  - Number of inpatient hospitalisations in pre-index period (22 versus 0), OR 2.25 (1.61–3.14)  
  - Heart failure, OR 1.41 (1.11–1.78)  
  - Diabetes, OR 1.35 (1.10–1.66)  
  - Year of index hospitalisation (2009 versus 2008), OR 0.77 (0.61–0.97)  
  - Age group (70 vs 69), OR 1.50 (1.25–1.79)  
  - Plan type (HMO versus comprehensive), OR 1.46 (1.11–1.92)  
  - Renal disease, OR 1.43 (1.09–1.89)  
  - Number of inpatient hospitalisations in pre-index period (1 versus 0), OR 1.39 (1.14–1.69)  
  - Myocardial infarction, OR 1.31 (1.00–1.72)  
  - Malignancy, OR 1.29 (1.01–1.65)  
  - Number of ED visits in pre-index (2 versus 0), OR 1.27 (1.05–1.53)  
  - Systemic corticosteroids, OR 1.22 (1.06–1.41)  
  - Diabetes, OR 1.20 (1.03–1.41)  
  - Number of ICU days in index hospitalisation, OR 1.04 (1.00–1.07) |
| Bolu et al. 2013 (381) | **Multivariable analysis:**  
  - All Patient Refined™ Diagnosis-Related Groups (APR-DRG) severity of illness classes (Extreme vs Mild), OR 2.48 (1.27–4.84)  
  - All Patient Refined™ Diagnosis-Related Groups (APR-DRG) severity of illness classes (Major vs Mild), OR 1.89 (1.02–3.49)  
  - Arformoterol treatment vs nebulized SABA, OR 0.68 (0.51–0.92) |
| Bottle et al. 2018 (382) | **Multivariable analysis:**  
  - Hospital size (per 100 beds), OR 2.27 (1.40–3.66)  
  - Staff rating of effective team working (possible scores range from 1 to 5), OR 1.65 (1.21–2.24)  
  - Mental health (excluding dementia), OR 1.43 (1.36–1.51)  
  - Age group (≥90 vs 65–69), OR 1.50 (1.35–1.66)  
  - Cancer–with metastases, OR 1.45 (1.24–1.71)  
  - Age group (85–89 vs 65–69), OR 1.42 (1.32–1.53)  
  - Cancer–without metastases, OR 1.38 (1.27–1.49)  
  - Age group (80–84 vs 65–69), OR 1.36 (1.27–1.46)  
  - Pneumonia, OR 1.36 (1.29–1.44)  
  - Stroke, OR 1.31 (1.12–1.52)  
  - Cognitive impairment (senility and dementia combined), OR 1.28 (1.20–1.37)  
  - Age group (75–79 vs 65–69), OR 1.23 (1.15–1.31)  
  - Renal disease, OR 1.21 (1.13–1.28)  
  - Heart failure, OR 1.19 (1.12–1.26)  
  - Arrhythmia, OR 1.19 (1.14–1.25)  
  - Inpatient interventions (Echoangiography vs None), OR 1.19 (1.10–1.29)  
  - Deprivation quintile (5 vs 1-least deprived), OR 1.19 (1.12–1.28)  
  - Living alone, OR 1.17 (1.10–1.23)  
  - Deprivation quintile (3 vs 1-least deprived), OR 1.14 (1.06–1.22)  
  - Ischaemic heart disease, OR 1.14 (1.10–1.19)  
  - Age group (≥70–74 vs 65–69), OR 1.14 (1.06–1.22)  
  - Electrolyte disorders, OR 1.14 (1.04–1.24)  
  - Deprivation quintile (4 vs 1-least deprived), OR 1.13 (1.06–1.21) |
- Peripheral vascular disease, OR 1.12 (1.04–1.20)
- Diabetes mellitus, OR 1.11 (1.06–1.17)
- Missed (per appointment), OR 1.09 (1.07–1.11)
- Females, OR 0.90 (0.87–0.93)
- Age group (60–64yrs 65–69), OR 0.89 (0.83–0.97)
- Length of stay (2 days vs 0), OR 0.88 (0.81–0.95)
- Age group (55–59 vs 65–69), OR 0.85 (0.77–0.93)
- Age group (45–49 vs 65–69), OR 0.83 (0.75–0.96)
- Age group (18–44 vs 65–69), OR 0.81 (0.69–0.94)
- Ethnic group (not known vs white), OR 0.74 (0.67–0.81)

Multivariable analysis of readmission within 30 days:
- Charlson Index (3 vs 0), OR 2.17 (2.04–2.32)
- Length of stay (>10 vs 1–3 days), OR 1.64 (1.56–1.72)
- Charlson Index (2 vs 0), OR 1.42 (1.32–1.52)
- Renal failure, OR 1.37 (1.32–1.43)
- Charlson Index (1 vs 0), OR 1.23 (1.15–1.32)
- Length of stay (6–10 vs 1–3 days), OR 1.25 (1.18–1.32)
- Pneumonia, OR 1.15 (1.12–1.18)
- Other cancers excluding lung, OR 1.12 (1.08–1.16)
- Age (55–64 yrs vs 40–54 yrs), OR 1.11 (1.06–1.16)
- Age (>65 yrs vs 40–54 yrs), OR 1.09 (1.04–1.14)
- COPD complexity (severe vs low), OR 1.09 (1.04–1.15)
- Commercial payer type (vs non-commercial payers), OR 0.90 (0.87–0.92)
- Geographic region (South vs North), OR 0.90 (0.87–0.94)
- Lung cancer, OR 0.89 (0.84–0.94)
- Geographic region (Midwest vs North), OR 0.85 (0.82–0.88)
- Length of stay (4–7 vs 1–3 days), OR 0.82 (0.79–0.84)
- Asthma, OR 0.81 (0.79–0.84)
- COPD complexity (moderate vs low), OR 0.76 (0.72–0.79)

Multivariable analysis for 90 days:
- Charlson Index (2 vs 0), OR 1.46 (1.37–1.55)
- Charlson Index (3 vs 0), OR 2.18 (2.06–2.30)
- Length of stay (>10 vs 1–3 days), OR 1.55 (1.47–1.62)
- Renal failure, OR 1.41 (1.35–1.47)
- Charlson Index (1 vs 0), OR 1.23 (1.16–1.31)
- Length of stay (8–10 vs 1–3 days), OR 1.20 (1.14–1.27)
- COPD complexity (severe vs low), OR 1.17 (1.12–1.23)
- Pneumonia, OR 1.13 (1.10–1.16)
- Other cancers excluding lung, OR 1.10 (1.06–1.14)
- Ischemic heart disease excluding myocardial infarction, OR 1.05 (1.02–1.08)
- Age (>65 yrs vs 40–54 yrs), OR 1.05 (1.00–1.09)
- Commercial payer type (vs non-commercial payers), OR 0.91 (0.89–0.93)
- Geographic region (South vs North), OR 0.90 (0.87–0.93)
- Geographic region (Midwest vs North), OR 0.90 (0.87–0.93)
- Asthma, OR 0.88 (0.85–0.91)
- Length of stay (4–7 vs 1–3 days), OR 0.84 (0.82–0.87)
- COPD complexity (moderate vs low), OR 0.81 (0.78–0.85)

Univariate analysis:
NONE

Multivariable analysis:
- Male, OR 1.45 (1.38–1.52)
- Public assistance (yes vs no), OR 1.41 (1.36–1.46)
- Living in nursing home (yes vs no), OR 1.41 (1.34–1.47)

Univariate analysis:
- One or more hospitalisations for exacerbation in preceding year, yes/no, OR 14.4 (1.7–120.4)
- One or more days out of the house in week before hospitalisation, yes/no, OR 7.3 (1.8–30.2)
- Lower physical activity in Week 1 (defined as, <60 min/d > 3,000 Vector magnitude units) vs more, OR 6.7 (1.4–31.8)
- Two or more hospitalisations for exacerbation in preceding year, yes/no, OR 6.2 (1.7–23.2)
- Two or more outpatient-treated exacerbations in preceding year, yes/no, OR 4.6 (1.2–17.5)
- Renal disease, yes/no, OR 4.0 (1.1–14.7)
- Higher MRC dyspnea per unit on 0–4 scale, OR 2.53 (1.04–6.18)

Multivariable analysis:
- Lower physical activity in Week 1 (defined as, <60 min/d > 3,000 Vector magnitude units) vs more, OR 12.5 (1.9–79.8)
- One or more hospitalisations for exacerbation in preceding year, yes/no, OR 8.7 (1.3–56.5)

Univariate analysis:
- Eosinophil counts ≥200 cells/mL or ≥2% vs <200, OR 1.68 (0.85–3.31)

Multivariable analysis:
- Eosinophil counts ≥200 cells/mL or ≥2% vs <200, OR 2.32 (1.10–4.92)

Univariate analysis:
- Pseudomonas aeruginosa identification rate at admission, OR 4.74 (1.29–17.40)

Univariate analysis:
- Acidosis (pH < 7.35) before discharge, OR 2.04 (1.23–3.39)

Multivariable analysis:
Multivariable analysis:

- Frailty score was significantly associated with all-cause 30-day readmission in multi-variable analysis (F-ratio 6.47; P value=0.01).

Univariable analysis:

- Protein-calorie malnutrition, HR 1.54 (1.48–1.61)
- Heart failure, HR 1.52 (1.49–1.55)
- Renal failure, HR 1.45 (1.41–1.48)
- Acute myocardial infarction, HR 1.41 (1.37–1.45)
- Pulmonary fibrosis, HR 1.39 (1.28–1.51)
- Spinal cord or brain injury induced disability, HR 1.37 (1.32–1.43)
- Atrial fibrillation/flutter, HR 1.37 (1.34–1.40)
- Lung cancer, HR 1.34 (1.28–1.40)
- Dementia, HR 1.34 (1.30–1.38)
- Major psychiatric disorders, HR 1.34 (1.30–1.38)
- Pulmonary hypertension/heart disease, HR 1.31 (1.27–1.35)
- Long-term oxygen use, HR 1.31 (1.29–1.34)
- Pulmonary embolism, HR 1.28 (1.21–1.35)
- Pneumonia, HR 1.25 (1.23–1.28)
- Gastroesophageal reflux disease, HR 1.25 (1.22–1.28)
- Dual eligibility Medicare and Medicaid, HR 1.25 (1.22–1.28)
- Diabetes mellitus, HR 1.23 (1.21–1.26)
- Any malignancy, HR 1.20 (1.17–1.23)
- Age (≥80 years vs 65–69), HR 1.17 (1.14–1.21)
- Race (black vs white), HR 1.17 (1.12–1.21)
- Asthma, HR 1.15 (1.13–1.18)
- ICU on index admission, HR 1.15 (1.09–1.21)
- Use of continuous positive airway pressure, HR 1.11 (1.05–1.18)
- Age (75–79 vs 65–69), HR 1.07 (1.04–1.11)
- Alcohol use, OR 1.08 (1.04–1.11)
- Depression, OR 1.07 (1.05–1.09)
- Peripheral vascular disease, OR 1.07 (1.05–1.09)
- Valvular disease, OR 1.05 (1.03–1.08)
- Age (≥85 years vs 40–64 years), OR 1.02 (1.00–1.04)
- Quartiles for median household income (4 vs 1 "lowest"), OR 0.97 (0.96–0.98)
- Quartiles for median household income (3 vs 1 "lowest"), OR 0.96 (0.94–0.98)
- Quartiles for median household income (2 vs 1 "lowest"), OR 0.96 (0.95–0.98)
- Hispanics vs Non-Hispanic white, OR 0.95 (0.93–0.97)
- Obesity, OR 0.94 (0.92–0.96)
- Female, OR 0.91 (0.90–0.92)
- Patient residence (rural area vs urban area), OR 0.90 (0.89–0.92)
- Others vs non-Hispanic white, OR 0.90 (0.87–0.92)
- Missing vs non-Hispanic white, OR 0.86 (0.83–0.89)
- Health insurance (others vs Medicare), OR 0.78 (0.75–0.81)
- Health insurance (private vs Medicare), OR 0.71 (0.70–0.73)
- Health insurance (self-pay vs Medicare), OR 0.65 (0.63–0.68)
- Metastatic cancer, OR 1.99 (1.84–2.14)
- Number of prior ED visits (3 vs 0), OR 1.65 (1.59–1.72)
- Moderate or severe liver disease, OR 1.62 (1.32–1.99)
- Prior hospitalisation (<6 months prior vs >5 years or none) OR 1.58 (1.54–1.63)
- Number of prior ED visits (2 vs 0), OR 1.46 (1.41–1.51)
- Primary Cancer, OR 1.43 (1.37–1.50)
- Prior hospitalisation (6 months to 5 years prior vs >5 years or none) OR 1.31 (1.27–1.34)
- Discharge location (home with support services vs home), OR 1.30 (1.27–1.34)
- Renal disease, OR 1.24 (1.19–1.29)
- Heart failure, OR 1.22 (1.18–1.25)
- Number of prior ED visits (1 vs 0), OR 1.20 (1.17–1.24)
- Mild liver disease, OR 1.18 (1.08–1.31)
- Length of stay (≥14 vs 4 to 6), OR 1.18 (1.14–1.21)
- Length of stay, days (vs 4 to 6), OR 1.15 (1.04–1.26)
- COPD specialist care vs none, OR 1.15 (1.12–1.18)
- Diabetes with complications, OR 1.15 (1.12–1.19)
- Male, OR 1.15 (1.12–1.17)
- Myocardial infarction, OR 1.14 (1.09–1.19)
- Peripheral vascular disease, OR 1.14 (1.07–1.22)
- Length of stay, days (7 to 13 vs 4 to 6), OR 1.13 (1.10–1.16)
- Prior ICU stay, OR 1.11 (1.03–1.19)
- Duration of COPD (>5 vs <1 year), OR 1.09 (1.04–1.14)
- Residential instability (most marginalized vs lowest), OR 1.06 (1.02–1.11)
- Urban vs rural OR 1.05 (1.02–1.08)
- Respiratory failure on index admission, OR 1.05 (1.01–1.10)
- Discharge location (transfer to long term care/other vs home), OR 0.93 (0.90–0.97)

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<table>
<thead>
<tr>
<th>Univariate analysis:</th>
<th>Multivariable analysis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>The number of emergency visits in the last 6 months vs none, OR 1.25 (1.21–1.29)</td>
<td>NONE</td>
</tr>
</tbody>
</table>

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Hijawi et al. 2015 (394)

**Multivariable analysis:**
- Supplemental oxygen, OR 2.52 (1.18–5.38)
- Alcohol use, OR 2.17 (1.16–4.09)

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Jacobs et al. 2018 (395)

**Multivariable analysis:**
- No. of comorbidities (>9 vs ≤5), OR 1.46 (1.43–1.50)
- Discharge location (home healthcare vs home), OR 1.32 (1.30–1.35)
- Length of stay at index hospitalisation, days (>5 vs ≤5), OR 1.32 (1.29–1.34)
- No. of comorbidities (>7 vs ≤9), OR 1.30 (1.27–1.33)
- Heart failure, OR 1.28 (1.26–1.31)
- Discharge location (skilled nursing facility/another vs home), OR 1.28 (1.25–1.31)
- Renal failure, OR 1.19 (1.17–1.22)
- No. of comorbidities (>5 vs ≤7), OR 1.19 (1.16–1.21)
- Insurance type (Medicaid vs Medicare), OR 1.15 (1.12–1.18)
- Alcohol use, OR 1.13 (1.09–1.16)
- Median household income ($37,999 vs ≥$64,000), OR 1.08 (1.05–1.10)
- Length of stay at index hospitalisation, days (>2 vs ≤5), OR 1.06 (1.04–1.08)
- Median household income ($38,000–$47,999 vs ≥$64,000), OR 1.05 (1.03–1.08)
- Diabetes mellitus, OR 1.04 (1.02–1.06)
- Teaching status of hospital (nonmetropolitan vs metropolitan, nonteaching), OR 1.03 (1.01–1.04)
- Bed size of hospital (medium vs large), OR 0.95 (0.93–0.97)
- Teaching status of hospital (nonmetropolitan vs metropolitan, nonteaching), OR 0.89 (0.87–0.91)
- Age (65–74 vs 40–64), OR 0.88 (0.85–0.91)
- Female, OR 0.87 (0.85–0.88)
- Obesity, OR 0.87 (0.85–0.89)
- Insurance type (others vs Medicare), OR 0.80 (0.76–0.84)
- Age (≥75 vs 40–64), OR 0.78 (0.75–0.81)
- Insurance type (private vs Medicare), OR 0.70 (0.68–0.72)
- Insurance type (self-pay vs Medicare), OR 0.81 (0.78–0.84)

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Kon et al. 2015 (398)

**Univariate analysis in patients 65 years or older (166)**
- 4 m gait speed (4MGS) (1 median 0.32 m/s vs 4 median 0.91 m/s, OR 11.56 (3.08–43.35)
- 4 m gait speed (4MGS) (2 median 0.50 m/s vs 4 median 0.91 m/s, OR 4.38 (1.15–16.70)
- One or more admissions (last year), OR 3.37 (1.70–6.67)
- DECAF (2 vs 1), OR 1.55 (1.16–2.08)
- Charlon Index (2 vs 1), OR 1.50 (1.14–1.96)
- Gait speed continuous per 0.1 m/s decline, OR 1.37 (1.17–1.60)
- Exacerbations vs no exacerbations, OR 1.32 (1.13–1.54)
- Length of stay (4 vs 2), OR 1.10 (1.02–1.19)
- Katz Index (5–6 vs 1–4), OR 0.55 (0.36–0.83)

**Multivariable analysis in patients 65 years or older (166)**
- One or more admissions (last year), OR 6.75 (2.60–17.51)
- Exacerbations in the last year, OR 1.52 (1.20–1.92)
- Charlson Index (2 vs 1), OR 1.50 (1.07–2.09)
- Gait speed continuous per 0.1 m/s decline, OR 1.43 (1.13–1.80)
- Length of stay (4 vs 2 days), OR 1.14 (1.010–1.29)
<table>
<thead>
<tr>
<th>Reference</th>
<th>Univariable analysis:</th>
<th>Multivariable analysis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loh et al. 2017 (397)</td>
<td>- No significant association of peak inspiratory flow (PIF) group (optimal PIF or suboptimal PIF) with all-cause readmission (P=0.86) &lt;br&gt; - Days to all-cause readmission, suboptimal PIF (65.5 d) vs optimal PIF (101 d), (P= 0.009)</td>
<td>- Disposition (other/missing) vs. home, RR 3.13 (2.05–4.79) &lt;br&gt; - Length of stay ≥14 vs. 1–2 days, RR 2.70 (2.40–3.01) &lt;br&gt; - ED/ observational stay (yes vs. no), RR 1.66 (1.52–1.80) &lt;br&gt; - Anaemia (present on admission) vs. none, RR 0.93 (0.81–1.06) &lt;br&gt; - Charlson index score ≥3, RR 0.70 (0.58–0.85) &lt;br&gt; - Prior COPD hospitalisation, RR 0.75 (0.65–0.87)</td>
</tr>
<tr>
<td>Nguyen et al. 2014 (398)</td>
<td>- Length of stay ≥14 vs. 1–2 days, RR 2.79 (1.98–3.94) &lt;br&gt; - Disposition (other/missing) vs. home, RR 2.76 (1.90–210.61) &lt;br&gt; - ED/observational stay (yes vs. no), RR 2.23 (1.85–2.69) &lt;br&gt; - Anaemia (present on admission) vs. none, RR 1.94 (1.63–2.29) &lt;br&gt; - Charlson index score ≥3, RR 1.88 (1.55–2.28) &lt;br&gt; - Prior COPD hospitalisation, RR 1.82 (1.55–2.13) &lt;br&gt; - Prior non-COPD hospitalisation, RR 1.82 (1.53–2.17) &lt;br&gt; - Disposition (post-acute/hospital) vs. home, RR 1.65 (1.30–21.56) &lt;br&gt; - Length of stay 7–13 vs 1–2 days, RR 1.52 (1.21–1.91) &lt;br&gt; - Systemic corticosteroids vs. none, RR 1.49 (1.23–1.82) &lt;br&gt; - Pulmonary hypertension vs. none, RR 1.39 (1.14–1.68) &lt;br&gt; - Hypertension vs. none, RR 1.32 (1.09–1.61) &lt;br&gt; - Pneumovax within 5 yr. vs. none, RR 1.33 (1.15–1.55) &lt;br&gt; - New oxygen post index admission vs. none, RR 1.29 (1.05–1.58) &lt;br&gt; - Length of stay 4–6 days vs. 1–2 days, RR 1.29 (1.07–1.56) &lt;br&gt; - Smoking status (former vs never/passive), RR 1.27 (1.02–1.59) &lt;br&gt; - Marital status (unpartnered vs. partner), RR 1.20 (1.04–1.38) &lt;br&gt; - Insurance type (commercial/private pay vs. Medicare/Medicaid), RR 0.81 (0.69–0.96) &lt;br&gt; - ≥149 min/wk. moderate or vigorous physical activity, (insufficient) vs inactive, RR 0.67 (0.55–0.81) &lt;br&gt; - ≥150 min/wk. MVPA (active) vs inactive, RR 0.61 (0.47–0.80) &lt;br&gt; - Disposition (hospice) vs. home, RR 0.26 (0.13–0.50)</td>
<td>- Disposition (other/missing) vs. home, RR 3.13 (2.05–4.79) &lt;br&gt; - Length of stay ≥14 vs. 1–2 days, RR 2.93 (1.99–4.31) &lt;br&gt; - ED/observational stay (yes vs. no) RR 2.13 (1.76–2.59) &lt;br&gt; - Length of stay 7–13 vs 1–2 days, RR 1.66 (1.30–2.10) &lt;br&gt; - Prior non-COPD hospitalisation, RR 1.60 (1.31–1.94) &lt;br&gt; - Anaemia (present on admission) vs. none, RR 1.59 (1.33–1.90) &lt;br&gt; - Prior COPD hospitalisation, RR 1.53 (1.29–1.82) &lt;br&gt; - New oxygen post index admission vs. none, RR 1.52 (1.22–1.90) &lt;br&gt; - Charlson index score ≥3, RR 1.44 (1.17–1.78) &lt;br&gt; - Length of stay 4–6 days vs. 1–2 days, RR 1.37 (1.13–1.66) &lt;br&gt; - Pneumovax within 5 yr. vs. none, RR 1.20 (1.02–1.41) &lt;br&gt; - 1–149 min/wk. moderate or vigorous physical activity (MVPA) (insufficient) vs inactive, RR 0.67 (0.55–0.81) &lt;br&gt; - ≥150 min/wk. moderate or vigorous physical activity, (active) vs inactive, RR 0.66 (0.51–0.87) &lt;br&gt; - Disposition (hospice) vs. home, RR 0.25 (0.12–0.52)</td>
</tr>
<tr>
<td>Nguyen et al. 2015 (399)</td>
<td>- Length of stay (≥14 d vs ≤12), RR 2.85 (1.74–4.65) &lt;br&gt; - Disposition (other/missing vs home), RR 2.17 (1.17–4.04) &lt;br&gt; - Level of functioning within 74 h of discharge (Levels I–III (bed bound, able to sit or stand) vs Level V (walks more than 50 feet), RR 2.14 (1.62–2.84) &lt;br&gt; - ED/observational stay (yes vs. no), RR 2.11 (1.66–2.69) &lt;br&gt; - Prior non-COPD hospitalisation, RR 1.64 (1.29–2.09) &lt;br&gt; - Prior COPD hospitalisation, RR 1.56 (1.26–1.93) &lt;br&gt; - Anaemia (present on admission) vs. none, RR 1.56 (1.26–1.93) &lt;br&gt; - Chronic pain vs. none, RR 1.47 (1.14–1.89) &lt;br&gt; - New oxygen post index admission vs. none, RR 1.38 (1.06–1.80) &lt;br&gt; - Disposition (hospice vs home), RR 0.26 (0.12–0.58)</td>
<td></td>
</tr>
<tr>
<td>Rinne et al. 2017 (400)</td>
<td></td>
<td>- Follow-up visit (Medicare-only vs Veterans Affairs only care), OR 0.81 (0.72–0.91)</td>
</tr>
<tr>
<td>Rinne et al. 2017 (401)</td>
<td></td>
<td>- Patient length of stay (3–4 days vs &lt;3 days), OR 1.39 (1.18–1.63) &lt;br&gt; - Patient length of stay (≥4 days vs &lt;3 days), OR 2.03 (1.72–2.40)</td>
</tr>
<tr>
<td>Robert et al. 2015 (402)</td>
<td></td>
<td>- Hospitalised in previous 12 months, OR 5.70 (2.19–14.80) &lt;br&gt; - Pre-admission medication (SAMA), OR 6.69 (1.86–24.09) &lt;br&gt; - APR-DRG ≥ 3, OR 2.55 (1.03–6.33) &lt;br&gt; - Medication at discharge (oral corticosteroids), OR 0.28 (0.11–0.77)</td>
</tr>
</tbody>
</table>
### Multivariable analysis:
- Charlson score (≥5 vs 0), OR 2.25 (1.66–3.04)
- Charlson score (4 vs 0), OR 1.64 (1.52–1.77)
- Charlson score (3 vs 0), OR 1.61 (1.57–1.66)
- Charlson score (2 vs 0), OR 1.43 (1.41–1.46)
- Discharge destination (skilled nursing facility vs home), OR 1.42 (1.40–1.45)
- Discharge destination (home with home care vs home), OR 1.38 (1.34–1.38)
- Charlson score (1 vs 0), OR 1.22 (1.20–1.24)
- Dually enrolled in Medicare and Medicaid, OR 1.22 (1.20–1.24)
- Race (black vs white), OR 1.06 (1.04–1.08)
- Length of stay (5 vs 4 d), OR 1.03 (1.03–1.03)
- ICU use, OR 1.03 (1.02–1.05)
- Age (>80 y vs 65–80 y), OR 0.97 (0.96–0.99)
- Female, OR 0.89 (0.88–0.90)
- Discharge destination (other vs home), OR 0.84 (0.82–0.86)

### Multivariable analysis:
- Lung cancer (yes vs no), OR 1.6 (1.3–2.1)
- Anxiety (yes vs no), OR 1.5 (1.2–1.8)
- Depression (yes vs no), OR 1.3 (1.1–1.8)
- Osteoporosis (yes vs no), OR 1.3 (1.1–1.6)
- Length of stay (>7 vs 3–4 days), OR 1.3 (1.0–1.5)
- Length of stay (>7 vs. 3–4 days), OR 1.2 (1.1–1.5)
- Heart failure (yes vs No), OR 1.2 (1.0–1.5)
- Female, OR 0.9 (0.7, 0.9)
- Prescription of ACE inhibitors 12 months before index admission (yes vs no), OR 0.8 (0.6–0.9)
- Prescription of SABA/SAMA within 30 days of discharge (yes vs no), OR 0.8 (0.6–0.9)
- Prescription of any antibiotic within 30 days of discharge (yes vs no), OR 0.8 (0.6–0.9)
- Hospitalisation (two vs >3 admissions), OR 0.7 (0.6–0.9)
- Follow-up visit within 30 d (yes vs no), OR 0.7 (0.6–0.9)
- Prescription of oral steroid within 30 days of discharge (yes vs no), OR 0.7 (0.5–0.8)
- Hospitalisation (one vs >3 admissions), OR 0.6 (0.4–0.7)
- Prescription for statins 12 months before index admission (yes vs no), OR 0.6 (0.5–0.7)
- Hospitalisation (none vs >3 admissions), OR 0.4 (0.3–0.6)

### Multivariable analysis:
- Discharge (against medical advice vs home), OR 1.77 (1.66–1.90)
- Race (native American vs white), OR 1.75 (1.24–2.46)
- Metastatic cancer, OR 1.48 (1.35–1.61)
- Heart failure, OR 1.25 (1.22–1.29)
- Solid tumor, OR 1.24 (1.16–1.33)
- Race (black vs white), OR 1.20 (1.16–1.26)
- Psychoses, OR 1.19 (1.14–1.24)
- Patients on Medicare under the age of 65 with Medicaid Payer, OR 1.19 (1.10–1.29)
- Anaemia, OR 1.17 (1.13–1.29)
- Discharge (home health care vs home), OR 1.16 (1.12–1.20)
- Length of stay (>1 day), OR 1.16 (1.13–1.18)
- Liver disease, OR 1.13 (1.06–1.20)
- Month (Sep vs Jan), OR 1.12 (1.06–1.18)
- Drug abuse, OR 1.11 (1.05–1.17)
- Month (Aug vs Jan), OR 1.11 (1.05–1.18)
- Month (July vs Jan), OR 1.10 (1.04–1.16)
- Under age 65, OR 1.09 (1.04–1.15)
- Month (Nov vs Jan), OR 1.09 (1.3–115)
- Diabetes, OR 1.09 (1.06–1.12)
- Alcohol use, OR 1.08 (1.03–1.14)
- Weight loss, OR 1.08 (1.03–1.15)
- Month (Oct vs Jan), OR 1.07 (1.01–1.13)
- Inpatient mortality, OR 0.92 (0.90–0.94)
- Race (Hispanic vs white), OR 0.92 (0.89–0.96)
- Female, OR 0.91 (0.89–0.93)
- Payer (private vs Medicare), OR 0.90 (0.84–0.95)
- Patients on Medicare under the age of 65 with another payer, OR 0.77 (0.62–0.97)
- Race (other vs white), OR 0.73 (0.68–0.78)
- Patients on Medicare under the age of 65 with self-pay, OR 0.73 (0.55–0.96)
- Patients on Medicare under the age of 65 with Private Payer, OR 0.67 (0.61–0.73)
- Admission source (court/jail/low enforcement vs routine), OR 0.29 (0.12–0.72)

### Multivariable analysis:
- Length of stay, d (>7 vs 1), OR 1.47 (1.40–1.55)
- Anxiety, OR 1.43 (1.37–1.50)
- Depression, OR 1.34 (1.29–1.39)
- Alcohol use, OR 1.30 (1.15–1.47)
- Drug abuse, 1.29 (1.11–1.50)
- Year of discharge (2011 vs 2001), OR 1.24 (1.16–1.33)
- Length of stay, days (5–7 vs 1), OR 1.23 (1.18–1.28)
- Low socioeconomic status (Yes vs no), OR 1.22 (1.18–1.26)
- Male, OR 1.15 (1.12–1.19)
- ICU stay (yes vs no), 1.12 (1.08–1.15)
- Length of stay, days (3–5 vs 1), OR 1.07 (1.03–1.11)
<table>
<thead>
<tr>
<th>Spece et al. 2018 (406)</th>
<th>Multivariable analysis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Each one-point increase in Charlson index was associated with readmission and death, OR 1.24 (1.18–1.30)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tzy-Chyi Yu et al. 2015 (407)</th>
<th>Multivariable analysis:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anaemia, OR 1.60 (1.36–1.88)</td>
<td></td>
</tr>
<tr>
<td>• Heart failure, OR 1.51 (1.33–1.71)</td>
<td></td>
</tr>
<tr>
<td>• Chronic kidney disease, OR 1.42 (1.17–1.7)</td>
<td></td>
</tr>
<tr>
<td>• Pulmonary vascular disease, OR 1.33 (1.09–1.63)</td>
<td></td>
</tr>
<tr>
<td>• Depression, OR 1.30 (1.12–1.49)</td>
<td></td>
</tr>
<tr>
<td>• COPD severity score (units: 10), OR 1.27 (1.17–1.37)</td>
<td></td>
</tr>
<tr>
<td>• ICU in index hospitalisation, OR 1.19 (1.04–1.36)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: 4MGS: 4 m gait speed; ACP: Angiotensin-converting enzyme; APR-DRG: All Patient Refined™ Diagnosis-Related Groups; COPD: chronic obstructive pulmonary disease; CI: confidence interval; CODEX: (comorbidity, obstruction, dyspnea, and previous severe exacerbations); DECAF: Dyspnoea, Eosinopenia, Consolidation, Acidemia and atrial Fibrillation; ED: emergency department; HR: hazard ratio; ICU: intensive care unit; MI: myocardial infarction; MRC: medical research council; MVPA: moderate or vigorous physical activity; No.: number; OR: odd ratio; PEARL: (Previous admissions, eMRCD score, Age, Right-sided heart failure and Left sided heart failure), PIF: Peak Inspiratory Flow; RDW: red cell distribution width; RR: relative risk; SABA: short acting beta agonist; SAMA: short-acting muscarinic antagonist; SNF: skilled nursing facility; W/o: without.
4.3.3 Narrative Synthesis: risk factors for all-cause readmission at 30 days

4.3.3.1 Comorbidities

17/32 studies reported various comorbidities as significant risk factors for 30-day readmission, with heart failure, depression and renal failure included in our meta-analysis. Many other comorbidities were also reported (See Table 4). Four studies (275, 383, 398, 406) used the Charlson score to assess comorbidities. Space et al. (406) found that each one-point increase in Charlson score was associated with a 24% increased risk of readmission or death: OR 1.24 (1.18–1.30).

4.3.3.2 Previous COPD Exacerbations and Hospitalisations

Previous exacerbations and hospitalisations were risk factors for 30-day readmission in nine studies. Emergency room (ER) visits in the past six months (1 vs 0) was associated with increased readmission risk with OR of 1.90 (1.01–3.58) in the study by Bashir (380) and 1.25 (1.21–1.29) in Hakim (393). The risk of readmission increased with a greater number of previous ER visits (≥4 vs 0) with OR 4.37 (1.83–10.46) and OR 2.31 (2.23–2.39) (380, 392). Prior COPD and non-COPD hospitalisations in the previous year also significantly increased the risk for 30-day readmission by 53% to 56% and 60% to 64%, respectively (398, 399). Consistent with other studies, Goto et al. (391) found that frequent exacerbators (defined as 2 hospitalisations in the last year) had a 2.5-fold increase in odds of readmission compared to non-frequent exacerbators. Disease severity of COPD was also a risk factor for readmission and has been evaluated using
different tools. These included the LACE Index (380), the 3M™ All Patient Refined™ Diagnosis-Related Groups (APR-DRG) classification tool (381, 402) and a COPD complexity tool (383). Using long-term systemic corticosteroids was a risk factor for readmission, with 49% increased risk in one study (398). However, receiving oral corticosteroid at discharge decreased the odds of readmission by 72% and 30% (402, 403). The differences between use of corticosteroids in the immediate post-discharge period and longer term requires further study. The severity of an exacerbation is the composite of the severity of the insult and the severity of the underlying COPD. ICU admission was also associated with increased risk of re-admission in six studies. These patients are also likely to have longer lengths of stay.

4.3.3.3 Patient Demographics

Different age groups were found to be at different risk of readmission in six studies, but results were inconsistent. Older patients with COPD typically had a greater likelihood of being readmitted (see Table 4). Ethnicity was investigated in nine studies with results that were also inconsistent (see Table 4).

4.3.3.4 Behavioural Risk Factors

Physical activity was examined in four studies, which reported low activity to be a significant risk factor for 30-day readmission in three studies. Nguyen et al.(399), for example, reported that those with low level functioning within 24 hours of discharge (Levels I-III (bed bound, able to sit or can stand) vs Level V (walks more than 50 feet) were more likely to be
readmitted with a relative risk of 2.14 and that patients who engaged in moderate to strenuous exercise with 1–149 or ≥150 min/wk. post-discharge were at 33% to 34% less readmission risk compared to inactive patients (398). Alcohol use was the most frequently reported social risk factor in six papers (391, 394, 395, 403-405) and has been included in our meta-analysis. Singh et al. (405) and Gershon et al. (392) identified low socioeconomic status as a significant risk factor with a 22% and 6% increased risk of readmission.

4.3.3.5 Health System-related risk factors

Length of stay (LOS) was reported to be a significant risk factor for 30-day readmission; whilst in general a longer LOS was associated with increased risk of re-admission; some studies found the shortest lengths of stay were at higher risk than those slightly longer. For example, compared to 1-3 days, Candrilli et al. (383) found patients who stayed >10 days or from 8-10 days had increased odds of readmission by 64% and 25%, respectively, but there was 18% reduced odds of readmission for those who stayed 4-7 days. In Jacobs et al. (395), those hospitalised >5 vs ≤2 days had an OR of 1.32 (1.29–1.34). Furthermore, in two studies (398, 399), LOS ≥14 vs 1–2 days increased the relative risk of readmission 2.93 and 2.85-fold, respectively. Gershon et al. (392) found OR of 1.18 when LOS ≥14 compared to 4–6 days but that this risk decreased to 66% and 37% when the LOS was between 7-13 and 4-6 days (398). In Rinne et al. (401), those with LOS of 3-4 days or more showed higher odds of readmission at 39% and 2-fold, respectively, compared to less than three days. Simmering et al. (404) found OR of 1.16 with patients who stayed >1 day, and in Singh et al. (405), 160
the odds increased to 1.47 when LOS was >7 days. When >7 days was compared to 3-4 days in Sharif et al. (403), the readmission OR reduced to 1.20, but the odds increased to 1.30 when 1-2 days was compared to 3-4 days.

Discharge destination was found to be a significant risk factor for readmission in nine studies but is likely complex because of confounding with disease severity and co-morbidity. Compared to discharge to home with no home care, discharge to a skilled nursing facility increased readmission in three studies (275, 380, 395) by 3-fold, 42% and 28%, respectively. Only one study (405) reported this as a protective factor with an OR of 0.84. Additionally, when discharged to home with care, the odds of readmission increased by 30%, 36%, 32% and 16%, (275, 392, 395, 404) respectively, whereas other studies (398, 399, 405) found this to decrease the risk by 75%, 74% and 80% respectively.

Patients’ insurance was reported as a risk/protective factor in five studies: four in the US and one in Europe (380, 391, 395, 398, 400) (Table 3). Smaller hospital size (<100 beds) and fewer doctors were reported as significant readmission risk factors with 2.27-fold and 67% increased odds of readmission, respectively (382). Medium size hospitals compared to large decreased the odds of readmission by 5% (395). Those who had outpatient visits were 44% less likely to be readmitted (405).
4.3.4 Narrative Synthesis: Risk factors for 90-day all-cause COPD readmission

4.3.4.1 Comorbidities

Seven papers looked at risk factors for 90-day readmission (378, 379, 383, 387, 396, 397, 402). Five of them reported several comorbidities as significant risk factors for readmission such as heart failure, renal failure and liver disease (378, 379, 383, 387, 396) (see Table 4). Only two studies used the Charlson score as a tool to assess comorbidities. These studies found higher odds to readmission with a higher Charlson score, which ranged from 23% to 50% (383, 396).

4.3.4.1 Previous Exacerbations and Hospitalisations, and COPD Severity

Previous exacerbations and hospitalisations were found to be a significant risk factor for readmission in five studies. Those previously hospitalised ≥2 versus 0 times had a 2.9-fold increased odds of readmission, whereas those with only one prior hospitalisation had an OR of 1.39 (379). In Kon et al. (396), those with one or more admissions in the last year had 6.75-fold increased odds of readmission. With any hospitalisation in the previous 12 months, readmission odds increased 3.99-fold in Roberts et al. (402).

Two studies (383, 402) found COPD disease severity (severe vs mild) increased odds of readmission by 17% and 2.70-fold. Baker et al. (379) reported patients who used systemic corticosteroids were 22% more likely to be readmitted. Two studies (378, 387) developed risk prediction tools
called CODEX and PEARL to predict 90-day readmission and found that higher scores were associated with a shorter time to readmission.

4.3.4.2 System-related risk factors

LOS was a significant risk factor for 90-day readmission in two studies (383, 396). Those who stayed 8-10 days were 20% more likely to be readmitted compared with 1-3 days. In Kon et al. (396), patients who stayed four days had 14% increased odds of readmission compared to two days. Kon et al. (396) reported a 9% reduction in readmission with commercial payer type vs non-commercial payers. Figure 21 shows the summary of risk factors associated with 30- and 90-day all-cause hospital readmission following a hospitalised exacerbation of COPD.
Figure 21. Summary of risk factors associated with 30- and 90-day all-cause hospital readmission following a hospitalised exacerbation of COPD.
Table 5. Summary of risk/predictive factors associated with 30- and 90-day all-cause hospital readmission

<table>
<thead>
<tr>
<th>Risk/predictive factors (Modifiable or non-modifiable)</th>
<th>Number of studies in which there was a significant finding (references)</th>
<th>Number of studies in which there was NOT a significant finding (references)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous exacerbations and hospitalisations (non-modifiable)</td>
<td>13 (378-380, 385, 387, 391-393, 396, 398, 399, 402, 403)</td>
<td>1 (380)</td>
</tr>
<tr>
<td>Length of stay (LOS) (modifiable)</td>
<td>Increased LOS 11 (275, 383, 392, 395, 396, 398, 399, 401, 403-405)</td>
<td>8 (380, 381, 387, 388, 393, 394, 399, 407)</td>
</tr>
<tr>
<td></td>
<td>Short LOS 4 (382, 383, 392, 403)</td>
<td></td>
</tr>
<tr>
<td>Sex (non-modifiable)</td>
<td>11 (275, 380, 382, 384, 390-392, 395, 403-405)</td>
<td>8 (381, 383, 388, 394, 398, 399, 402, 407)</td>
</tr>
<tr>
<td>COPD severity (non-modifiable)</td>
<td>9 (378, 380, 381, 383, 387, 392, 396, 402, 407)</td>
<td>2 (380, 381)</td>
</tr>
<tr>
<td>Discharge location (modifiable)</td>
<td>9 (275, 380, 387, 392, 395, 398, 399, 404, 405)</td>
<td>5 (380, 385, 398, 399, 404)</td>
</tr>
<tr>
<td>Risk Factor (modifiable)</td>
<td>Modifiable Codes</td>
<td>Non-modifiable Codes</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Behavioural and social risk factors (low socio-economic status, alcohol use, former smoking, living alone)</td>
<td>9 (382, 384, 391, 392, 394, 395, 398, 404, 405)</td>
<td>7 (387, 388, 394, 396, 398, 399, 403)</td>
</tr>
<tr>
<td>Age (non-modifiable)</td>
<td>8 (275, 382, 383, 387, 390, 391, 395, 404)</td>
<td>9 (380, 388, 390, 392, 398, 399, 403, 405, 407)</td>
</tr>
<tr>
<td>ICU admission (non-modifiable)</td>
<td>6 (275, 379, 390, 392, 405, 407)</td>
<td>0</td>
</tr>
<tr>
<td>Type of insurance (modifiable)</td>
<td>4 (275, 391, 395, 404)</td>
<td>6 (391, 394, 398-400, 404)</td>
</tr>
<tr>
<td>Oxygen use (at admission or at discharge) (modifiable)</td>
<td>4 (390, 394, 398, 399)</td>
<td>3 (381, 403, 407)</td>
</tr>
<tr>
<td>Physical activity (modifiable)</td>
<td>4 (385, 396, 398, 399)</td>
<td>1 (399)</td>
</tr>
<tr>
<td>Different ethnicity group (non-modifiable)</td>
<td>4 (275, 390, 391, 404)</td>
<td>5 (380, 382, 398, 399, 405)</td>
</tr>
<tr>
<td>Corticosteroid use (inhaled or oral) (modifiable)</td>
<td>4 (379, 398, 402, 403)</td>
<td>3 (381, 394, 398)</td>
</tr>
<tr>
<td>Hospital size and type (modifiable)</td>
<td>2 (382, 395)</td>
<td>1 (395)</td>
</tr>
<tr>
<td>Weather (non-modifiable)</td>
<td>1 (404)</td>
<td>1 (407)</td>
</tr>
<tr>
<td>Acidosis (pH&lt; 7.35 before discharge) (modifiable)</td>
<td>1 (388)</td>
<td>0</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa (modifiable)</td>
<td>1 (386)</td>
<td>0</td>
</tr>
</tbody>
</table>
Figure 22. Pooled adjusted ORs for heart failure.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Oddsratio (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baker et al. 2013</td>
<td>1.41 (1.11, 1.78)</td>
<td>3.97</td>
</tr>
<tr>
<td>Bottle et al. 2018</td>
<td>1.19 (1.12, 1.26)</td>
<td>14.95</td>
</tr>
<tr>
<td>Gershon et al. 2019</td>
<td>1.22 (1.18, 1.25)</td>
<td>16.52</td>
</tr>
<tr>
<td>Goto et al. 2018</td>
<td>1.41 (1.39, 1.43)</td>
<td>16.91</td>
</tr>
<tr>
<td>Jacobs et al. 2018</td>
<td>1.28 (1.26, 1.31)</td>
<td>16.80</td>
</tr>
<tr>
<td>Sharif et al. 2014</td>
<td>1.20 (1.00, 1.50)</td>
<td>6.02</td>
</tr>
<tr>
<td>Simmering et al. 2016</td>
<td>1.25 (1.22, 1.29)</td>
<td>16.52</td>
</tr>
<tr>
<td>Tzy-Chyi Yu et al. 2015</td>
<td>1.51 (1.33, 1.71)</td>
<td>8.29</td>
</tr>
<tr>
<td>Overall: (I² = 95.4%, P = 0.000)</td>
<td>1.29 (1.22, 1.37)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 23. Pooled adjusted ORs for renal failure.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Oddsratio (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bottle et al. 2018</td>
<td>1.21 (1.13, 1.28)</td>
<td>21.37</td>
</tr>
<tr>
<td>Candrilli et al. 2015</td>
<td>1.37 (1.32, 1.43)</td>
<td>24.08</td>
</tr>
<tr>
<td>Goto et al. 2018</td>
<td>1.27 (1.24, 1.29)</td>
<td>27.28</td>
</tr>
<tr>
<td>Jacobs et al. 2018</td>
<td>1.19 (1.17, 1.22)</td>
<td>27.28</td>
</tr>
<tr>
<td>Overall: (I² = 93%, P = 0.000)</td>
<td>1.26 (1.19, 1.33)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Figure 24. Pooled adjusted ORs for depression.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Oddsratio (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goto et al. 2018</td>
<td>1.27 (1.24, 1.29)</td>
<td>19.24</td>
</tr>
<tr>
<td>Jacobs et al. 2018</td>
<td>1.00 (0.98, 1.02)</td>
<td>19.28</td>
</tr>
<tr>
<td>Sharif et al. 2014</td>
<td>1.39 (1.10, 1.80)</td>
<td>8.89</td>
</tr>
<tr>
<td>Simmering et al. 2016</td>
<td>1.04 (1.00, 1.07)</td>
<td>19.13</td>
</tr>
<tr>
<td>Singh et al. 2016</td>
<td>1.34 (1.29, 1.39)</td>
<td>18.90</td>
</tr>
<tr>
<td>Tzy-Chyi Yu et al. 2015</td>
<td>1.39 (1.12, 1.49)</td>
<td>14.57</td>
</tr>
<tr>
<td>Overall: (I² = 98.7%, P = 0.000)</td>
<td>1.19 (1.05, 1.34)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Figure 25. Pooled adjusted ORs for alcohol use.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Oddsratio (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goto et al. 2018</td>
<td>1.08 (1.04, 1.11)</td>
<td>31.57</td>
</tr>
<tr>
<td>Hijjawi et al. 2015</td>
<td>2.17 (1.16, 4.09)</td>
<td>0.10</td>
</tr>
<tr>
<td>Jacobs et al. 2018</td>
<td>1.13 (1.09, 1.16)</td>
<td>31.57</td>
</tr>
<tr>
<td>Sharif et al. 2014</td>
<td>1.10 (0.90, 1.30)</td>
<td>4.76</td>
</tr>
<tr>
<td>Simmering et al. 2016</td>
<td>1.08 (1.03, 1.14)</td>
<td>25.03</td>
</tr>
<tr>
<td>Singh et al. 2016</td>
<td>1.30 (1.15, 1.47)</td>
<td>6.96</td>
</tr>
<tr>
<td>Overall: (I² = 59.9%, P = 0.029)</td>
<td>1.11 (1.07, 1.16)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
4.4 Discussion

This study is the first to systematically examine and summarise risk factors for all-cause hospital readmission following an initial admission for exacerbation of COPD. Other reviews (375) have only considered readmissions directly due to COPD, at variance with a patient-centred and holistic approach to health care and clinical outcomes. Our main findings indicate that comorbidities, previous exacerbations and hospitalisations, and increased LOS were the major risk factors for both 30- and 90-day readmission.

Our meta-analysis revealed that heart failure, renal failure, depression, and alcohol use were all associated with an increased risk of 30-day all-cause COPD readmission, whereas being female was a protective factor.
Many comorbidities were significant risk factors for 30- and 90-day readmission, including mental health disorders. A possible explanation for this might be a lack of adequate interventions that extend beyond COPD-specific treatment during the initial hospitalisation. There is an ongoing debate as to whether underlying comorbidities are the main reason for higher readmission rates (408); our results highlight that this is indeed a key risk.

Three comorbidities (heart failure, renal failure, and depression), and alcohol use were found to be frequently reported risks. This differs from the findings presented in a systematic review concerning readmission due only to COPD, in which no single comorbidity was reported to be associated with readmission risk (375). Focusing effort in addressing multi-morbidity and social determinants of health may be one method to reduce the burden of readmissions following a hospitalised exacerbation of COPD (408).

Consistent with the literature, our results show that previous exacerbations and hospitalisations are significantly associated with all-cause readmission (375). Exacerbations have been found to negatively affect health status, increase costs and ultimately increase the risk of death (409, 410). Indeed, frequent exacerbations have been reported as a distinct susceptibility phenotype, which may support the targeting of such patients with effective preventive strategies (411). There are many cost-effective interventions such as inhalers and PR that could reduce exacerbations and related hospitalisations. However, such interventions are not always effective due to inadequate inhaler technique or poor adherence (1). A recent meta-analysis found that the frequency of COPD exacerbations decreased over the past two decades, independent of major prognostic factors (412). This likely indicates health care improvements over
time have resulted in lower rates of exacerbation in the placebo groups of clinical trials. Adopting appropriate care and preventive approaches could also have a favourable effect on COPD readmissions.

Increased LOS was found to be a significant risk factor for readmission within 30 days in nine studies, and within 90 days in two studies. This may be because of increased severity of disease or, again, the presence of co-morbidities. LOS was not found to be a significant risk factor for COPD-related readmission in a previous systematic review that included 17 studies (375). LOS could be used to recognise patients with higher readmission risk and who may benefit from supported discharge, early COPD community support and/or earlier follow-up following initial discharge. We could not perform a meta-analysis on the LOS because the reporting comparisons across the studies were inconsistent.

Different tools have been used to assess COPD severity such as the LACE index, APR-DRG and COPD complexity tool (380, 381, 383). As expected, patients with increased disease severity had higher odds of 30-day readmission, independent of the method of measuring disease severity. There are other scores that have been developed to assess readmission risk in COPD, such as CODEX and PEARL (378, 387). However, there is no 30-day specific risk prediction tool to identify patients at high risk of all-cause COPD readmission. Thus far, there is one tool for 90-day COPD readmissions—the PEARL (Previous admissions, eMRCD score, Age, Right-sided and Left-sided heart failure) score and notably this does not include co-morbidities other than heart failure (387). According to a recent systematic review on models that predict exacerbations, no existing models meet the requirements for risk-
stratified treatment for personalised COPD care (413). In order to move personalised COPD medicine forward, a more harmonised approach to developing and validating high-quality predictions is needed.

We identified several patients, behavioural and social risk factors associated with an increased risk of 30-day readmission. Former smokers compared to those who had never smoked or were passive smokers, those with low socioeconomic status and unmarried patients were identified as at significant risk for 30-day readmission (391, 398, 405). Underweight patients and weight loss were also found to increase the risk of readmission in two studies (391, 404); being obese was reported to be a significant protective factor in two studies (391, 395). Six studies discussed alcohol use (391, 394, 395, 403-405), five of which found it as a significant risk factor for all-cause COPD readmission. This was not found to be an independent marker for COPD related readmission (375). Our results support previous finding that identified alcohol use as a significant predictor of COPD mortality (414).

Chronic use of systemic corticosteroids was a risk factor for both 30- and 90-day readmission (379, 398). This has been reported in Bahadori et al. (375) considering COPD-specific readmission. This might be explained by side effects such as muscle weaknesses or use of these drugs in people with more severe COPD. Low physical activity was found to be an important risk factor for 30-day readmission in three studies (385, 398, 399), with those who were more active being less likely to be readmitted. Indeed, physical inactivity has been associated with all-cause mortality and hospitalisation (415). Although there is a difference between physical activity and PR, existing research on early PR post-exacerbation did not show a reduction in readmission risk (416).
Further research considering interventions to improve or maintain physical activity in the immediate post-discharge period following COPD exacerbation is needed to test whether this can improve outcomes and reduce the risk of readmission.

Discharge destination was associated with 30-day readmission in nine studies. When patients were discharged to a skilled nursing facility or home with care, the odds of readmission increased in five studies (275, 380, 392, 395, 404). It is likely that those patients were more unwell or frail with more co-morbidity than those discharged home and thus more likely to be readmitted. However, the quality of care could affect readmission as demonstrated in other studies (398, 399, 405). In addition, we found that those with US Medicaid and Medicare cover had higher odds of readmission within 30 days than those with private insurance or self-funding; Medicaid and Medicare have more barriers to primary care than those with other types of insurance, which may also lead to increased readmissions (417).

Since the publication of our systematic review, we have updated our search and identified six additional studies (418-423). Generally, all the reported risk factors found in these additional studies were identified in our previous systematic review. Anbesse et al. conducted a prospective study and found that frequent admissions and the use of long-term oxygen to be associated with 30-day readmission (418). Similarly, another prospective study reported limitation in performing basic activities of daily living and frequent admissions for COPD exacerbations to be associated with risk of readmission at 30 and 90 days (419). A retrospective cohort study reported comorbidity and social factors (poverty) to be predictors for 30-day readmission (420). Another
retrospective cohort research found that patients with eosinophil levels of ≥ 300 cells/L had a higher 90-day readmission risk than those with values of < 300 cells/L (421). Regarding ethnicity, compared to black and Hispanic races, whites had a higher 30-day readmission rate (422). The last study we identified reported the dynamic increase of red blood cell distribution width as a predictor for 30-day all-cause readmission (423).

Our work has a number of distinguishing aspects from existing work, which had considered only COPD-related readmission (375). To our knowledge, the present study is the first to systematically evaluate existing literature with a focus on risk factors for all-cause readmissions. We conducted a meta-analysis using a random effects model to calculate the adjusted ORs on the most frequently reported risk/protective factors to account for observed heterogeneity among studies. This increased the generalisability of our findings, as heterogeneity was addressed by incorporating between-study variability of effect sizes.

This review has some limitations. First, we excluded two non-English studies. Second, study heterogeneity exists in location, setting, design and reported risk factors; therefore, our meta-analysis results were restricted to 14 studies in total, but these studies were representative of the target population. Third, we acknowledge the heterogeneity of the diagnosis of COPD exacerbations between studies. Exacerbation of COPD is a clinical diagnosis of exclusion, and all patients were being managed by their clinicians as having that diagnosis. Despite the limitations of this approach, it remains the gold standard diagnosis. As is common in studies of hospitalised COPD exacerbations, not all patients will have had confirmatory spirometry available to clinicians at the
time of management. Finally, our meta-analysis was conducted on summary data, not individual patient data.

Our review has important clinical implications. It summarises current evidence to inform guideline developers about the importance of carefully reviewing the discharge processes and to ensure that comorbidities are fully managed along with routine COPD management. Clinicians should devote more resources to identify and manage patients with COPD at a high risk of hospital readmission and to promote physical activity and follow-up in the immediate post-discharge period. Not all the risk factors for re-admission that we have identified are modifiable and therefore future research should focus on developing robust risk models to predict patients with COPD at high risk of potentially avoidable hospital readmission, with interventions tested to mitigate modifiable risk to improve outcomes for patients and health services.

4.5 Conclusion

Comorbidities, previous exacerbations and hospitalisation, and increased length of stay were significant risk factors for 30- and 90-day all-cause readmission after an index hospitalisation with an exacerbation of COPD.
5. Relationship between Forced Oscillation Technique (FOT) Parameters and Clinical Characteristics in Hospitalised COPD Exacerbation
5.1 Introduction

Pulmonary function testing has a vital role in the clinical assessment of chronic obstructive pulmonary disease (COPD) patients including diagnosis, monitoring and management. Thus far, spirometry is the gold standard test of lung function to assess airflow limitation over time (1). COPD severity is defined by GOLD based on persistent airflow limitation that spirometry demonstrates, combined with clinical reported symptoms and the frequency of exacerbations (3).

Nevertheless, spirometry has some drawback that limit its use in clinical practice. First, there is a weak relationship between spirometry indices and patient reported symptoms (424). Second, it has limited value in detecting early disease progression, which is a sign for developing chronic airway disease (1, 425). This could be justified because spirometry largely reflects the large airways flow. Although it has been established that COPD arises from small airways (426), COPD affects both small and large airways (427). Furthermore, spirometry is effort-dependent test and requires patients to forcefully exhale, which can be challenging to perform in children, frail and elderly patients, and patients who are acutely unwell for example at the time of an exacerbation.

Forced oscillation Technique (FOT) is a non-invasive, objective and effort-independent lung function test to assess respiratory impedance (resistance and reactance) (339). Dellacà et al. (2004) used FOT to detect expiratory limitation (EFL) in COPD patients and found that within-breath reactance ($\Delta X_{rs5Hz}$) provides an accurate, reliable and noninvasive technique to identify EFL (339). This technique is particularly useful in COPD to evaluate response
to interventions such as bronchodilator and continuous positive airway pressure (CPAP) titration, which offers monitoring of additional related variables than the spirometry (342). FOT has also been found to be feasible and has potential as a home telemonitoring tool to detect COPD exacerbations (349, 428). However, the clinical value of FOT for the assessment of EFL and other pulmonary mechanics in hospitalised COPD exacerbation patients is limited (306). Therefore, this chapter aims to determine the prevalence of EFL in upright and supine positions in a COPD population admitted to hospital due to exacerbation. In addition, we aim to identify whether there is an association between COPD airflow severity using spirometry and FOT indices as well as comparing the characteristics of patients who do and do not have EFL.

5.2 Research questions

- What is the prevalence of EFL in upright and supine positions among COPD patients who are hospitalised due to exacerbation?
- Does the degree of EFL change during the course of an admission?
- What is the relationship between FEV₁, a marker of COPD severity, and respiratory impedance (reactance and resistance)?

5.3 Study design

Prospective cohort single centre study.
5.4 Methodology

Over a period of one year (May 2019-March 2020), we approached 150 patients admitted to the Royal Free Hospital London NHS Foundation Trust, UK. We approached patients admitted to hospital because of COPD exacerbation.

Research outcomes

1. Explore the prevalence and change over time of EFL at exacerbation of COPD in upright and supine positions using FOT. EFL was defined as $\Delta X_{rs5Hz}$ of $\geq 2.8$ [cmH2O/(L/s)].

2. Assess the relationship between FEV\textsubscript{1}, a marker of COPD severity, and respiratory impedance including within breath reactance ($\Delta X_{rs5Hz}$) and resistance.

3. Compare the clinical characteristics of patients with COPD exacerbations between those who do and do not have EFL.

The baseline characteristics consist of:

- Spirometry (FEV\textsubscript{1}, FEV\textsubscript{1}/% predicted and FEV\textsubscript{1}/FVC ratio). Spirometry results defined as post-bronchodilator FEV\textsubscript{1}/VC $<$0.70 confirming COPD and an appropriate exposure history. Quality assured spirometry was performed according to ATS recommendations (429).

- Smoking history (pack years)

- Number of exacerbations in the past 12 months where the patient needed to take antibiotics or steroids (moderate exacerbations)
• Hospitalised due to COPD Exacerbations (<12 months, severe exacerbations)
• Attended Pulmonary rehabilitation (<12 months)
• Charlson Comorbidity Index
• Self-reported quality of life using CAT-score
• Dyspnoea using mMRC-score
• Anxiety and depression questionnaire (HADS)
• Body Mass Index (BMI) (calculated from height and weight)
• Peak inspiratory flow rate (PIFR)
• Reported Edmonton Frail Scale (REFS)
• Length of stay

Study procedure

Recruitment

A full description of recruitment is explained in the Methods chapter. Patients were approached during their admission on the wards by attending clinicians to introduce the study as soon as possible after admission. If a patient agreed, informed consent was obtained before demographic and relevant clinical information were gathered from the patients and their medical record. These measurements were repeated just prior to hospital discharge to assess changes between those who do and do not have EFL with recovery of the exacerbation. The methods of measuring FOT indices, spirometry and self-reported questionnaires are identical to those explained in the methods chapter.
5.5 Analysis

Data were inspected using histograms to look for outliers and tested for normality using a Kolmogorov–Smirnov test. If normally distributed (parametric), data were expressed as mean (SD) and if not normally distributed data were expressed as median (IQR) (non-parametric) as appropriate. Categorical variables were compared using the χ2 test or the Fisher exact test. For other comparisons, Wilcoxon signed-rank was used for non-parametric paired data and T-test (paired test) was used for parametric data. Relationships between variables were analysed using Spearman rank correlation coefficient test for non-parametric variables and for normally distributed variables we used the Pearson correlation. For the purposes of comparison, we divided patients into two groups according to their within breath reactance ($\Delta X_{rs5Hz}$) value (a marker of EFL) in the upright position. EFL was defined as $\Delta X_{rs5Hz}$ of ≥2.8 [cmH2O/(L/s)]. We analysed our data using the software Statistical Package for the Social Sciences (SPSS), Version 25.

5.6 Results

A total of 82 patients were recruited for the study and included in the main analysis (Figure 27; Consort diagram). The patients were older with mean age of 71 ±10.4 years. Most of the patients were ex-smokers 58 (71%) with median pack year of 42 (29-56). The admission characteristics of the patients are reported in Table 6. Range time from the admission to the assessment is 24-48 hours.
Table 6. Characteristics of the index admission between those with expiratory flow limitation and those without.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=82)</th>
<th>Patients with EFL (n=32)</th>
<th>Patients with no EFL (n=50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>40 (49%)</td>
<td>13 (41%)</td>
<td>27 (54%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Female</td>
<td>42 (51%)</td>
<td>19 (59%)</td>
<td>23 (46%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 ± 10.4</td>
<td>70.2 ± 10.2</td>
<td>72 ± 10.6</td>
<td>0.49</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>24 (20-29)</td>
<td>27 (21-36)</td>
<td>23 (19-26)</td>
<td>0.03</td>
</tr>
<tr>
<td>Current smoker</td>
<td>24 (29%)</td>
<td>10 (31%)</td>
<td>14 (28%)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>58 (71%)</td>
<td>22 (69%)</td>
<td>36 (72%)</td>
<td>0.68</td>
</tr>
<tr>
<td>Smoking history (Pack Years)</td>
<td>42 (29-56)</td>
<td>38 (27.5-53)</td>
<td>42.5 (29-61)</td>
<td>0.84</td>
</tr>
<tr>
<td>Number of Exacerbations (within past 12 months)</td>
<td>2 (1-4)</td>
<td>3 (1-4)</td>
<td>2 (1-4)</td>
<td>0.92</td>
</tr>
<tr>
<td>Number of hospitalised exacerbations (&lt;12 months)</td>
<td>2 (1-3)</td>
<td>1 (1-3)</td>
<td>2 (1-3)</td>
<td>0.61</td>
</tr>
<tr>
<td>Pulmonary rehabilitation (&lt;12 months)</td>
<td>28 (34%)</td>
<td>16 (50%)</td>
<td>12 (24%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>4.3 ± 1.6</td>
<td>4.1 ± 1.3</td>
<td>4.4 ± 1.7</td>
<td>0.23</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>0.86 ± 0.34</td>
<td>0.74 ± 0.30</td>
<td>0.94 ± 0.36</td>
<td>0.01</td>
</tr>
<tr>
<td>FEV₁%</td>
<td>34.3 ± 12.4</td>
<td>32 ± 12</td>
<td>36 ± 13</td>
<td>0.25</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.2 ± 2.3</td>
<td>1.7 ± 0.55</td>
<td>2.1 ± 0.63</td>
<td>0.009</td>
</tr>
<tr>
<td>FVC %</td>
<td>61 ± 16.7</td>
<td>59 ± 16.1</td>
<td>63 ± 17.5</td>
<td>0.45</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>43.5 ± 11</td>
<td>42 ± 11</td>
<td>44 ± 11</td>
<td>0.52</td>
</tr>
<tr>
<td>IC (L)</td>
<td>1.3 (1-1.8)</td>
<td>1.2 (1-1.8)</td>
<td>1.4 (1-1.8)</td>
<td>0.84</td>
</tr>
<tr>
<td>PIFR (L/m)</td>
<td>60 (50-85)</td>
<td>60 (50-88)</td>
<td>62 (50-85)</td>
<td>0.72</td>
</tr>
<tr>
<td>Length of stay in days</td>
<td>7 (4-10.3)</td>
<td>7.5 (4.2-11.5)</td>
<td>8 (5-10.7)</td>
<td>0.93</td>
</tr>
<tr>
<td>CAT Score</td>
<td>31 (27.7-34)</td>
<td>31 (27-34)</td>
<td>32 (28.5-34)</td>
<td>0.52</td>
</tr>
<tr>
<td>mMRC</td>
<td>4 (3.7-4)</td>
<td>4 (4-4)</td>
<td>4 (3-4)</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>REFS</td>
<td>Depression</td>
<td>Anxiety</td>
<td>WBC (10^9/L)</td>
</tr>
<tr>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td></td>
<td>10 (9-12.2)</td>
<td>10 (10-12)</td>
<td>10.5 (9-12)</td>
<td>0.54</td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td>10 (10-12)</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td></td>
<td>10.6 (7.9-14.5)</td>
</tr>
<tr>
<td>WBC (10^9/L)</td>
<td></td>
<td>10.5 (8-15)</td>
<td>11 (7.8-14)</td>
<td>0.70</td>
</tr>
<tr>
<td>Eosinophils</td>
<td></td>
<td></td>
<td></td>
<td>10.5 (8-15)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td></td>
<td>8 (5-12)</td>
<td>8 (6-11)</td>
<td>0.75</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>20 (6-62)</td>
<td>15 (6-70)</td>
<td>21 (5-70)</td>
<td>0.61</td>
</tr>
<tr>
<td>eGFR mL/min</td>
<td>85 (65-90)</td>
<td>70.5 (60-90)</td>
<td>90 (68-90)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

*Data are presented as n (%), mean±SD or median (IQR)

**Abbreviations:** BMI: Body Mass Index; CAT: COPD Assessment Test; CRP: C - reactive protein; eGFR: Estimated Glomerular Filtration Rate; FEV1%: Predicted Forced Expiratory Volume in 1 second; FEV1/FVC: calculated ratio between both measurements; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; IC: Inspiratory Capacity; mMRC: Modified Medical Research Council dyspnoea scale; PIFR: Peak Inspiratory Flow Rate; REFS: Reported Edmonton Frail Scale; WBC: White blood cell.

- **Prevalence of EFL at hospitalised COPD exacerbation:**

  The prevalence of EFL in the upright position was 39% (32/82), and this increased to 50% (41/82) when the measurement was taken supine. Median $\Delta Xrs_{5Hz}$ in the upright position was 2.1 (0.4-5.1) [cmH2O/(L/s)] with flow limitation percentage (FL%) of 20% and this went up to 3 (0.9-7) at supine position with FL% of 50%. At discharge, EFL had resolved in six out of the 39 subjects with flow-limited breathing in the upright position on admission, whilst EFL had resolved in nine out of 41 patients with flow-limited breathing in the supine position on admission. The measurements of FOT are presented in Table 7. There were no significant changes in $\Delta Xrs_{5Hz}$ in upright and supine positions from admission to discharge [2.1 (0.4-5.1) vs 2.7 (0.82-5.2), $p=0.51$] and [3 (0.9-7) vs 3.4 (1.3-7.3), $p=0.53$], respectively.
### Table 7. Forced Oscillation Technique indices at hospitalised COPD exacerbation

<table>
<thead>
<tr>
<th>Forced Oscillation Technique</th>
<th>All patients (n=82)</th>
<th>Patients with EFL (n= 32)</th>
<th>Patients with no EFL (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Delta X_{rs_{5Hz}} ) at upright position [cmH2O/(L/s)]</td>
<td>2.1 (0.4-5.1)</td>
<td>6.1 (4.4-8.1)</td>
<td>0.9 (0.07-1.75)</td>
</tr>
<tr>
<td>FL% at upright position</td>
<td>20 (0-91)</td>
<td>100 (85-100)</td>
<td>0 (0-20)</td>
</tr>
<tr>
<td>( \Delta X_{rs_{5Hz}} ) at supine position [cmH2O/(L/s)]</td>
<td>3 (0.9-7)</td>
<td>8.2 (4.3-11.3)</td>
<td>2.1 (0.7-3)</td>
</tr>
<tr>
<td>FL% at Supine position</td>
<td>50 (12-100)</td>
<td>100 (76-100)</td>
<td>29 (0-61)</td>
</tr>
<tr>
<td>( R_{rs_{5Hz}} ) at upright position [cmH2O/(L/s)]</td>
<td>4.7 (3.2-6.2)</td>
<td>6.1 (4.8-8.1)</td>
<td>3.9 (2.5-5.3)</td>
</tr>
<tr>
<td>( R_{rs_{5Hz}} ) at supine position [cmH2O/(L/s)]</td>
<td>5.3 (3.7-7.2)</td>
<td>6.4 (5.1-8.1)</td>
<td>4.8 (3.4-6.6)</td>
</tr>
</tbody>
</table>

*Data are presented as median IQR

**Abbreviations:**
- EFL: Expiratory flow limitation
- \( \Delta X_{rs_{5Hz}} \): Within Breath Reactance at 5 Hz
- FL\%: Flow limitation percentage
- \( R_{rs_{5Hz}} \): Resistance at 5 HZ.
Figure 27. Consort diagram.

Admitted due to COPD Exacerbation
(n=152)

Consented
(n=129)

Completed admission assessment
(n=82)

Analysed
(n=82)

Refused to take part
(n=23)

Excluded with reasons:
(n=47)
- Not COPD exacerbation (n=24)
- Cognitive impairment patients (n=6)
- Asthma (n=6)
- Bronchiectasis (n=4)
- Lung cancer (n=5)
- Not complying with the protocol (n=2)
➢ **Relationship between COPD airflow severity and FOT indices**

We explored the relation between FEV$_1$ and $\Delta$Xrs$_{5Hz}$ in upright and supine positions and found a weak but statistically significant negative correlations ($r= -0.25$, p=0.03; $r= -0.30$, p=0.01), respectively. Figure 28 illustrates that those with more severe airflow limitation (lower FEV$_1$) have greater EFL. We also investigated the relationship between FEV$_1$ and Rrs$_{5Hz}$ in the upright and supine positions and were statistically significant negative correlations also (R= -0.35, p=0.003; - 0.31, p=0.01), respectively (Figure 29.).

**Figure 28. Correlation between FEV$_1$ and EFL.**
Figure 29. Correlation between FEV$_1$ and Rrs$_{5\text{Hz}}$.

Relationship between baseline characteristics and FOT indices:

There were significant negative correlations between FVC and $\Delta Xrs_{5\text{Hz}}$ in the upright and supine positions ($r=-0.33$, $p=0.005$; $r=-0.36$, $p=0.002$), (Figure 30). Further, there were statistically significant positive correlations between BMI and $\Delta Xrs_{5\text{Hz}}$ in the upright and supine positions ($R=0.27$, $p=0.01$; $R=0.30$, $p=0.008$) respectively, in which those with higher BMI have greater EFL (Figure 31). There were no significant correlations between FOT indices and other clinical variables including age, smoking history, prior exacerbation and hospitalisation history, length of stay, comorbidity index, blood biomarkers and self-reported patient outcomes.
Figure 30. Correlation between FVC and EFL.

Figure 31. Correlation between BMI and EFL.
Clinical characteristics between those who do and do not have EFL:

There were no significant differences between those with and without EFL in gender, age, smoking history, comorbidity index and previous exacerbation and hospitalisation rates. However, subjects who have EFL at admission have greater BMI 27 (21-36) Vs 23 (19-26) kg/m2, p= 0.03. 50% of those with EFL had enrolled in PR within 12 months before their admission compared to only 12 (24%) in those without EFL, P= 0.02. There were significant differences between the two conditions in FEV1 (0.74 ± 0.30 vs 0.94 ± 0.36 L; p= 0.01) and FVC (1.7 ±0.55 vs 2.1 ±0.63 L; P= 0.009) respectively, which those with EFL have lower FEV1 and FVC compared to those without EFL. The results, as shown in Table 6, indicate no statistically significant differences between groups in the self-reported patients’ outcomes (breathlessness scale, CAT, HAD and frailty score), length of stay and blood biomarkers.

Comparing the two groups, it can be seen from Table 7 that ΔXrs5Hz in the upright and supine positions of the group with EFL was significantly higher than those with no EFL [6.1 (4.4-8.1) Vs 0.9 (0.07-1.75), 8.2 (4.3-11.3) Vs 2.1 (0.7-3) [cmH2O/(L/s)], p ≤ 0.001], respectively. This was also associated with significant differences in FL% in the upright and supine positions between groups, 100 (85-100) vs 0 (0-20); 100 (76-100) vs 29 (0-61) %, p ≤ 0.001, respectively. When we compared Rrs5Hz in the upright and supine positions between groups, statistically significant differences were found, which EFL group have a greater resistance than those with no EFL, 6.1 (4.8-8.1) vs 3.9 (2.5-5.3), 6.4 (5.1-8.1) vs 4.8 (3.4-6.6) [cmH2O/(L/s)], p ≤ 0.001, respectively.
➢ Admission to discharge changes between those who do and do not have EFL:

Table 8 shows the differences within and between groups between the admission and pre-discharge assessments. There were no significant differences between the groups in FOT indices except for $\Delta X_{rs5Hz}$ and FL% in the upright position (-35 (-2.4-0.96) vs 0.27 (-0.3-1.7), $p=0.009$; 0 (-22-0.9) vs 0 (-20-51), $p=0.02$), respectively. Within the EFL group, there were no statistically significant differences found in FOT indices, while there were significant differences in $\Delta X_{rs5Hz}$ and FL% in the upright position within patients in the group with no EFL.

There were statistically significant increases in PIFR between admission and discharge in the groups both with and without EFL 60 (50-88) vs 75 (50-100), $p=0.002$; 60 (50-85) vs 75 (55-100), $p=0.001$) respectively, while no difference was found between groups. Although there was an improvement trend in IC within the EFL group, no significant change was found, whereas within patients with no EFL group there was a significant change (1.2 (0.9-1.7) vs 1.4 (1-1.7) L, $p=0.02$). Generally, there were statistically significant differences in mMRC and CAT scores within both groups ($p=0.001$), but these changes were not significant between groups. Table 8 shows that there has been a significant improvement in most blood biomarkers within both groups from admission to discharge, with no statistically significant differences between the groups.

When we assessed the correlations in the EFL group, there were statistically positive correlations between median difference of EFL in upright and supine positions and median difference in mMRC, ($r=0.41$, $p=0.03$; $r=0.47$, $p=0.01$), respectively.
### Table 8. Changes from admission to discharge between both groups

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Patients with EFL (n= 32)</th>
<th>Patients with no EFL (n=50)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Admission</td>
<td>Discharge</td>
<td>Median difference</td>
</tr>
<tr>
<td>ΔXrs_{5Hz} at upright position</td>
<td>6.1 (4.4-8.1)</td>
<td>5.1 (3.9-6.5)</td>
<td>-0.35 (-2.4-0.96)</td>
</tr>
<tr>
<td>FL% at upright position</td>
<td>100 (85-100)</td>
<td>91 (63-100)</td>
<td>0 (-22-0.9)</td>
</tr>
<tr>
<td>ΔXrs_{5Hz} at supine position</td>
<td>8.2 (4.3-11.3)</td>
<td>7.4 (4.2-10.3)</td>
<td>0.1 (-2.1-1.7)</td>
</tr>
<tr>
<td>FL% at Supine position</td>
<td>100 (78-100)</td>
<td>91 (66-100)</td>
<td>0 (0-1.8)</td>
</tr>
<tr>
<td></td>
<td>Rs_{5Hz} at upright position [cmH2O/(L/s)]</td>
<td>Rs_{5Hz} at Supine position [cmH2O/(L/s)]</td>
<td>PIFR (L/m)</td>
</tr>
<tr>
<td>---------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td></td>
<td>6.1 (4.8-8.1)</td>
<td>6.2 (5.1-8.3)</td>
<td>0.05 (-1.1-0.6)</td>
</tr>
<tr>
<td></td>
<td>6.5 (5.2-8.1)</td>
<td>7.3 (5.5-8.8)</td>
<td>-0.1 (-0.9-1.7)</td>
</tr>
<tr>
<td></td>
<td>60 (50-88)</td>
<td>75 (50-100)</td>
<td>10 (-1.5-14.5)</td>
</tr>
<tr>
<td></td>
<td>1.2 (0.9-1.7)</td>
<td>1.3 (1-1.7)</td>
<td>0.04 (-0.14-0.19)</td>
</tr>
<tr>
<td></td>
<td>4 (4-4)</td>
<td>3 (2-3)</td>
<td>-1 (-1-0)</td>
</tr>
<tr>
<td></td>
<td>31 (27-34)</td>
<td>17.5 (14.2-22.7)</td>
<td>-10.5 (-15, -6)</td>
</tr>
<tr>
<td></td>
<td>10.5 (8-15)</td>
<td>8.5 (7-12)</td>
<td>-1.7 (-5.7-0.6)</td>
</tr>
<tr>
<td>Eosinophils (10^9/L)</td>
<td>Neutrophils (10^9/L)</td>
<td>CRP (mg/L)</td>
<td>eGFR mL/min</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------</td>
<td>------------</td>
<td>-------------</td>
</tr>
<tr>
<td>0.06 (0.02-0.17)</td>
<td>8 (5-12)</td>
<td>15 (6-70)</td>
<td>70.5 (60-90)</td>
</tr>
<tr>
<td>0.13 (0.05-0.25)</td>
<td>5.5 (5-8)</td>
<td>7 (4-47)</td>
<td>84 (63-90)</td>
</tr>
<tr>
<td>0.04 (-0.01-0.1)</td>
<td>-0.7 (-5.1-0.42)</td>
<td>-5 (-47-1)</td>
<td>0 (1.5-19)</td>
</tr>
<tr>
<td>0.05</td>
<td>0.009</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>0.1 (0.01-0.40)</td>
<td>8 (6-11)</td>
<td>21 (5-70)</td>
<td>90 (68-90)</td>
</tr>
<tr>
<td>0.13 (0.03-0.21)</td>
<td>7 (5-8)</td>
<td>11 (4-28)</td>
<td>90 (78-90)</td>
</tr>
<tr>
<td>0.01 (-0.11-0.14)</td>
<td>-1.5 (-4.6-0.91)</td>
<td>-8 (-52-1.5)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>0.91</td>
<td>0.002</td>
<td>0.003</td>
<td>0.25</td>
</tr>
<tr>
<td>0.39</td>
<td>0.76</td>
<td>0.89</td>
<td>0.23</td>
</tr>
</tbody>
</table>

*Data are presented as median IQR; *P value= median difference between groups

**Abbreviations:** EFL: Expiratory flow limitation; ∆Xrs5Hz: Within Breath Reactance at 5 Hz; FL%: Flow limitation percentage; Rrs5Hz: Resistance at 5 Hz; CAT: COPD Assessment Test; CRP: C - reactive protein; eGFR: Estimated Glomerular Filtration Rate; FEV1%: Predicted Forced Expiratory Volume in 1 second; FEV1/FVC: calculated ratio between both measurements; IC: Inspiratory Capacity; mMRC: Modified Medical Research Council dyspnoea scale; PIFR: Peak Inspiratory Flow Rate; WBC: White blood cell.
5.7 Discussion:

From this cohort of patients hospitalised due to COPD exacerbation, we have found that EFL measured by $\Delta X_{rs5Hz}$ is prevalent in both upright and supine positions, 39% and 50% respectively. EFL and resistance measured by $R_{rs5Hz}$ negatively correlated with FEV$_1$, a marker of airflow limitation. Those with EFL had lower FEV$_1$ and FVC and higher, $R_{rs5Hz}$ and BMI compared to those without EFL. During recovery from acute exacerbations, a reduction in EFL was observed in association with improvement in breathlessness.

We found higher prevalence of EFL during hospitalised COPD exacerbations in supine position 50% (41/82) than the upright position 39% (32/82). This was expected as the relaxation volume and end expiratory lung volume is reduced due to gravitational forces, associated with recumbency (430). Previous work in this area found a lower prevalence of EFL in seated position in which 31% (9/29) of the patients hospitalised due to exacerbation had EFL (306). However, this study was carried out on a small number of patients and did not present lung volume and inflammatory biomarkers measures. Our reported prevalence of EFL at seated position was consistent with that of Stevenson et al. (307) who found that 41% (9/22) of COPD patients showed EFL at admission. However, this was measured using NEP. In our cohort there were general improvements in those with EFL at discharge time, but complete resolution, defined as $\Delta X_{rs5Hz}$ of <2.8 [cmH2O/(L/s)] was only observed in 15% (6/29) at upright position and 22% (9/42) at supine position. This finding contrasted with Jetmalani et al. (306) and Stevenson et al. (307) in which 44% of the patients in each study had complete resolution from EFL. This could be attributed to the different factors including severity and physiology of COPD,
demographics data and hospital management and the fact they used NEP. Such finding indicates that when COPD patients recover from exacerbations, improvement in EFL happens but complete resolution from EFL is not universal.

We have provided detailed data demonstrating that those with severe airflow limitation (lower FEV₁) have greater EFL and resistance at hospital admission for exacerbation of COPD. EFL resulted owing to the double effects of permanent parenchymal destruction caused by emphysema and airway dysfunction in COPD. FEV₁ airflow severity reflects in turn reduced driving pressure for expiratory flow through constricted and frail airways in which airflow resistance is considerably increased, consequently EFL is increasing (431, 432). It has been found that EFL can predict patients-reported symptoms better than FEV₁ (322, 338). In stable COPD, EFL was associated with more severe airflow limitation and hyperinflation with reduced functional performance (346, 433). Indeed, the observed increase in ∆Xrs₅Hz and Rrs₅Hz at exacerbation can be attributed to several physiological changes that have poor correlation with spirometry. Further, respiratory reactance measured by FOT correlates with FEV₁ and can predict the rate of change in COPD patients over time (434). Given the ease with which EFL can be measured by FOT in patients hospitalised due to COPD exacerbation, measuring EFL can be more convenient and clinically relevant than spirometry to track disease recovery.

Concerning the relationship between baseline characteristics and FOT indices, we found significant negative correlations between FVC and within breath reactance (∆Xrs₅Hz) at upright and supine positions. This could be explained by presence of EFL and due to hyperinflation changing operating lung volumes
and increasing FRC (343). Those with higher BMI have higher EFL and this was expected because those patients usually breathe at low-lung volume, with the closing capacity increases above expiratory residual volume (ERV), therefore resulting in EFL (435, 436). There were no significant correlations between FOT indices and age, smoking history, exacerbation and hospitalisation history, length of stay, comorbidity index, inflammatory biomarkers, and self-reported patient outcomes.

When we compared EFL group to those with no EFL group, there were no statistically significant differences between groups in gender, age, smoking history, comorbidity index and previous exacerbation and hospitalisation rates and length of stay. This result agrees with similar study conducted with hospitalised COPD exacerbation patients (306). Nevertheless, Yamagami et al. (348) showed significant differences in respiratory impedance between those with frequent exacerbations and those with no exacerbation in the last two years. However, this study was limited by its retrospective design. There were significant differences between the two conditions in FEV\textsubscript{1} and FVC (P= 0.01; 0.009) respectively, in which those with EFL have lower FEV\textsubscript{1} and FVC compared to those without EFL. This outcome is contrary to that of Jetmalani et al. (306) who found similar spirometry values between those with EFL and those with no limitation; this could be due to their small sample size. Our findings show that there were significant differences between both groups in all FOT indices (∆Xrs\textsubscript{SHz}, FL\%, Rrs\textsubscript{SHz}), whereby EFL group had greater values compared to those with no EFL. We present for the first time, using inflammatory biomarker at admission, the relationship between COPD patients with and without EFL. Our results whilst preliminary, show no association in FOT and blood biomarkers between the groups.
The most important clinically relevant finding was that the improvement in EFL index values from admission to discharge is associated with an improvement in mMRC, CAT score, PIFR and blood inflammatory biomarkers in COPD patients. The observed improvement in these variables could be attributed to the improvement in $\Delta X_{rs5Hz}$. Indeed, the resting lung mechanics’ impairment is gradually resolved and not completely resolved at discharge time (307). Such findings have important clinical and research implications. Detecting EFL at COPD exacerbation could be used to identify those with more severe physiological disturbance and to assess their response to treatment during recovery. This could have a clinical value for patient monitoring and personalised treatment, by providing an effort-independent, objective test to measure lung function parameters during a COPD exacerbation requiring hospital admission. These findings raise intriguing research questions regarding the nature and extent of EFL impact on the patient’s recovery from COPD exacerbation and reducing hospital readmission, aiming to improve the clinical outcomes.

This study has some limitations. Firstly, we did not incorporate serial measurements which would have been valuable. Second, we looked at admission and discharge but would have been useful to look at follow-up, but this was beyond the scope of the study.
5.8 Conclusion:

Our study shows that during hospitalisation due to COPD exacerbation, those with more severe airflow limitation defined as a reduced FEV$_1$, have greater EFL. The severity of EFL increased when patients moved from a seated to a supine position. Improvement in EFL was associated with a reduction in breathlessness. Detecting EFL measured by FOT during COPD exacerbation could be used to identify those with more severe physiological disturbance and to assess their response to treatment during recovery. This could have a clinical value, by providing non-invasive, objective and effort-independent technique to measure lung function parameters during a COPD exacerbation requiring hospital admission.
6. Predictors of 30- and 90-day COPD Exacerbation Readmission: A Prospective Cohort Study
6.1 Introduction

As described in the introduction chapter, latest global estimates in 2017 found 3.2 million deaths have been reported worldwide caused by COPD (200), in which exacerbations of COPD remain a prevailing cause of death in COPD (188, 201). A five-year longitudinal study found that exacerbations requiring hospitalisation were independently associated with mortality and such risk increased with higher exacerbation frequencies (202). For COPD patients surviving hospitalisation due to COPD exacerbations, hospital readmission is a major clinical problem. COPD hospital readmissions contribute to a clinical and economic burden on society (268). Identifying and mitigating risk factors for readmission is, therefore, essential (206, 267).

Our recent systematic review and meta-analysis of nearly 4 million COPD patients found that all-cause readmission rate at 30 days ranged from 9% to 26% and from 17.5% to 39% at 90 days (220). We concluded that comorbidities, previous exacerbations and hospitalisations, and increased length of stay during the initial admission were the major risk factors for risk of all-cause readmission within 30 and 90 days (220). Latest finding from the European COPD Audit reported higher in-hospital mortality in those readmitted within 90 days compared to those patients who do not get readmitted (13.4% vs. 2.3%) (270).

Thus far, COPD readmission remains a debatable clinical measure as some (283) related readmissions to the severity of the disease, while others have considered readmissions as a marker of quality of care (272, 273). Despite global policy makers’ initiatives to apply financial penalties to hospitals with
higher readmission rates, a limited impact has been observed (437). Hence, there is an increasing need for prospective studies to identify biomarkers or phenotypes that can help to identify patients at greater risk of COPD readmission (438, 439). Therefore, our study aimed to prospectively identify the risk factors of COPD exacerbation recurrence within 30 and 90 days and find potential objective biomarkers that can be clinically translated into improvement in the readmission burden.

6.2 Research questions

➢ What are the factors that determine readmission to hospital within 30 days post discharge?
➢ What are the factors that determine readmission to hospital within 90 days post discharge?

6.3 Study design

Single centre prospective cohort study.

6.4 Methodology

Details about our methodology were described in the methods chapter. Ethical approval was obtained from the HRA (reference 19/EM/0080). Written informed consent was obtained for each participant before participating in the study. The trial was registered at ClinicalTrials.gov (NCT number): NCT04024735 (354).
6.4.1 Recruitment of participants

We approached patients admitted to Respiratory Ward in the Royal Free Hospital London NHS Foundation Trust, UK due to a COPD exacerbation. We identified patients from the COPD Audit list for the new COPD admission that updated every 24 hours. Over a period of one year started from May 2019 to March 2020 (I stopped recruitment due to COVID-19 pandemic), patients with a confirmed diagnosis of COPD (post-bronchodilator FEV₁/FVC <0.70 and appropriate exposure history) were recruited. Patients who agreed to partake were asked to sign a consent form.

6.4.2 Measurements

Demographic data and a complete medical history for each patient was collected. This included number of COPD exacerbations and previous hospitalisations due to COPD exacerbation in the past 12 months. Patients were asked to complete questionnaires that measure breathlessness (mMRC); health-related quality of life (CAT); anxiety and depression (HADs) and risk of frailty (REFS). For each patient, we collect spirometry, peak inspiratory flow rate, FOT indices and inflammatory blood biomarkers. All measurements were conducted at the recruitment assessment during admission and at discharge from hospital. Further details about all measurements are described in Chapter 3. Patients’ clinical progression during hospitalisation was recorded which included the length of stay in hospital.
Follow-up: At discharge, patients were followed-up for 30 days and 3 months to explore the risk factors for all-cause hospital readmission in patients with COPD. We used hospital dataset and follow-up calls to confirm information about the readmission within the follow-up period. Readmission was defined as any emergency (non-elective) readmission to hospital within the specified follow-up time.

6.4.3 Statistical analysis

Data were inspected using histograms to look for outliers and tested for normality using a Kolmogorov–Smirnov test. If normally distributed (parametric), data were expressed as mean (SD) and if not, normally distributed data were expressed as median (IQR) (non-parametric) as appropriate. Categorical variables were compared using the χ² test or the Fisher exact test. A univariate analysis was performed to identify variables associated with 30- and 90-days readmission (the dependent variable). A multivariable logistic analysis was applied in which re-admission at 30 and 90 days were the dependent variables, whilst the independent variables were identified from the univariate analysis to be associated with 30- and 90-days readmission. For other comparisons, Wilcoxon signed-rank was used for non-parametric paired data and T-test (paired test) was used for parametric data. Relationships between variables were analysed using Spearman rank correlation coefficient test for non-parametric variables and for normally distributed variables we used the Pearson correlation coefficient.
We constructed a receiver operating characteristic (ROC) curve to assess how the significant factors in univariate logistic regression predicted readmission. We found an optimum cut-off point for the best predictors (AUC >0.80) using the point on the curve with minimum distance from the left-upper corner of the unit square. We calculated the positive predictive value (PPV) and negative predictive value (NPV) for each cut-off.

We analysed our data using SPSS, Version 25. We sought statistical advice about our sample size calculation and data analysis from the Biostatistics Group at the JRO. It has been recommended to have 10 events as a minimum number of events per variable in a multivariable method of analysis as has been reported in the literature (355, 356). In our study, readmission is our event of interest, therefore having 30-40 readmitted patients will allow us to reliably examine 3 to 4 variables in the logistic regression model. As per the National COPD Audit in the UK, the national readmission rate for COPD patients is 24% within 30 days (206). Accordingly, we needed to recruit 125 to 166 patients to have 30 to 40 readmissions.

6.5 Results
➢ Baseline characteristics:

We approached 152 patients admitted due to COPD exacerbation. A total of 129 with a confirmed diagnosis of COPD (post-bronchodilator FEV₁/FVC <0.70 and appropriate exposure history) were recruited; 23 patients refused to take part. A total of 47 were excluded due to reasons described in
Consort Figure 32. Eventually, 82 patients were enrolled and reviewed at follow-up. Readmission rate within 30 days was 38% (31/82), and 56% within 90 days (46/82). The median time to readmission within 30 and 90 days were 11 (5-22) and 22 (10-57) days respectively. Table 9 describes the baseline characteristics of the patients categorised in those who had and hadn’t been readmitted within 30 days. The reasons for readmission within 30 and 90 days were mainly COPD-related, 52% and 55% respectively. Patients readmitted within 30 days had more exacerbations [3 (2-5) vs 2 (1-4), p=0.01], and hospitalisations [2 (1-4) vs1 (0-2), 0.006] in the last 12 months compared to those who were not readmitted.

➢ 30-day readmission

Length of stay was statistically significant between groups [8 (5-14) vs 6 (4-10) days, p=0.03], in which those who get readmitted within 30 days stayed more days in hospital. Readmitted patients had more depression [HAD: 12 (8-14) vs 9.5 (6-13), p=0.02] and frailty [REFS: 12 (11-14) vs 10 (8-11), p=0.001] scores compared to those with no readmission. Table 10 demonstrated no significant differences between groups in the spirometry and FOT values at the recruitment assessment. However, there was a statistically significant difference in PIFR [50 (40-60) vs 80 (55-90) L/m, p=0.001] between groups. Low PIFR (<60/min) was seen in 46% (38/82) at admission and 40% (33/82) at discharge.
Figure 32. Consort Diagram

Admitted due to COPD Exacerbation
(n=152)

Consented
(n=129)

Completed admission/discharge assessment
(n=82)

Analysed
(n=82)

Follow-up completed
(n=82)

Refused to take part
(n=23)

Excluded with reasons:
(n=47)
- Not COPD exacerbation (n=24)
- Cognitive impairment patients (n=6)
- Asthma (n=6)
- Bronchiectasis (n=4)
- Lung cancer (n=5)
- Not complying with the protocol (n=2)
Table 9. Characteristics of the index admission between those with 30 days readmission and those with no 30 days readmission.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=82)</th>
<th>Patients with 30 days readmission (n=31)</th>
<th>Patients who were not readmitted within 30 days (n=51)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>40 (49%)</td>
<td>18 (58%)</td>
<td>22 (43%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Female</td>
<td>42 (51%)</td>
<td>13 (42%)</td>
<td>29 (57%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 ± 10.4</td>
<td>71 ± 10</td>
<td>71.4 ± 11</td>
<td>0.85</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>24 (20-29)</td>
<td>23 (20-28)</td>
<td>25 (19-30)</td>
<td>0.59</td>
</tr>
<tr>
<td>Current smoker</td>
<td>24 (29%)</td>
<td>7 (23%)</td>
<td>17 (33%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>58 (71%)</td>
<td>24 (77%)</td>
<td>34 (67%)</td>
<td></td>
</tr>
<tr>
<td>Smoking history (Pack Years)</td>
<td>42 (29-56)</td>
<td>42 (27-63)</td>
<td>42 (29-54)</td>
<td>0.50</td>
</tr>
<tr>
<td>Percentage Living alone at home</td>
<td>39 (48%)</td>
<td>16 (52%)</td>
<td>23 (46%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Number of Exacerbations (within past 12 months)</td>
<td>2 (1-4)</td>
<td>3 (2-5)</td>
<td>2 (1-4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Number of hospitalised exacerbations (&lt;12months)</td>
<td>2 (1-3)</td>
<td>2 (1-4)</td>
<td>1 (0-2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Pulmonary rehabilitation (&lt;12 months)</td>
<td>28 (34%)</td>
<td>13 (42%)</td>
<td>15 (29%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Flu Vaccination (&lt;12months)</td>
<td>60 (73%)</td>
<td>24 (77%)</td>
<td>36 (71%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Pneumonia Vaccination (&lt;10 years)</td>
<td>26 (32%)</td>
<td>13 (42%)</td>
<td>13 (26%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Home Oxygen</td>
<td>7 (9%)</td>
<td>2 (6.5%)</td>
<td>5 (10%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Home NIV</td>
<td>7 (9%)</td>
<td>2 (6.5%)</td>
<td>5 (10%)</td>
<td>0.60</td>
</tr>
<tr>
<td>DECAF Score</td>
<td>2 (1-2)</td>
<td>1.7 ± 1</td>
<td>1.8 ± 0.9</td>
<td>0.70</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------</td>
<td>---------</td>
<td>-----------</td>
<td>------</td>
</tr>
<tr>
<td>SABA</td>
<td>69 (84%)</td>
<td>28 (90%)</td>
<td>41 (80%)</td>
<td>0.23</td>
</tr>
<tr>
<td>LABA/ICS</td>
<td>50 (61%)</td>
<td>21 (68%)</td>
<td>29 (57%)</td>
<td>0.32</td>
</tr>
<tr>
<td>LAMA</td>
<td>35 (43%)</td>
<td>15 (49%)</td>
<td>20 (39%)</td>
<td>0.41</td>
</tr>
<tr>
<td>LABA/LAMA</td>
<td>16 (20%)</td>
<td>4 (13%)</td>
<td>12 (24%)</td>
<td>0.24</td>
</tr>
<tr>
<td>LABA</td>
<td>4 (5%)</td>
<td>2 (7%)</td>
<td>2 (4%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Length of stay in days</td>
<td>7 (4-10.3)</td>
<td>8 (5-14)</td>
<td>6 (4-10)</td>
<td>0.03</td>
</tr>
<tr>
<td>CAT Score</td>
<td>31 (27.7-34)</td>
<td>31 (28-36)</td>
<td>32 (27-33)</td>
<td>0.50</td>
</tr>
<tr>
<td>mMRC</td>
<td>4 (3.7-4)</td>
<td>4 (3-4)</td>
<td>4 (4-4)</td>
<td>0.80</td>
</tr>
<tr>
<td>REFS</td>
<td>10 (9-12.2)</td>
<td>12 (11-14)</td>
<td>10 (8-11)</td>
<td>0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>11 (7-14)</td>
<td>12 (8-14)</td>
<td>9.5 (6-13)</td>
<td>0.02</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9 (6.7-11)</td>
<td>10 (7-11)</td>
<td>9 (6-11)</td>
<td>0.33</td>
</tr>
<tr>
<td>WBC (10^9/L)</td>
<td>10.6 (7.9-14.5)</td>
<td>10.5 (7-14)</td>
<td>10.7 (9-15)</td>
<td>0.50</td>
</tr>
<tr>
<td>Eosinophilis (10^9/L)</td>
<td>0.07 (0.02-0.24)</td>
<td>0.07 (0.03-0.4)</td>
<td>0.06 (0.01-0.2)</td>
<td>0.30</td>
</tr>
<tr>
<td>Neutrophils (10^9/L)</td>
<td>8 (5.1-11.6)</td>
<td>7.3 (5-10.4)</td>
<td>8.2 (6-12.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>20 (6-62)</td>
<td>30 (4-75)</td>
<td>19 (7.4-5.5)</td>
<td>0.80</td>
</tr>
<tr>
<td>eGFR mL/min</td>
<td>85 (65-90)</td>
<td>90 (66-90)</td>
<td>78 (60-90)</td>
<td>0.25</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>4.3 ± 1.6</td>
<td>4.4 ± 1.6</td>
<td>4.2 ± 1.5</td>
<td>0.71</td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td>32 (39%)</td>
<td>12 (39%)</td>
<td>20 (40%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>11 (13%)</td>
<td>6 (55%)</td>
<td>5 (45%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>19 (23%)</td>
<td>6 (19%)</td>
<td>13 (26%)</td>
<td>0.52</td>
</tr>
<tr>
<td>Heart failure</td>
<td>13 (16%)</td>
<td>6 (19%)</td>
<td>7 (14%)</td>
<td>0.50</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>13 (16%)</td>
<td>5 (16%)</td>
<td>8 (16%)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

*Data are presented as n (%), mean±SD or median (IQR)

**Abbreviations:** BMI: Body Mass Index; CAT: COPD Assessment Test; CRP: C-reactive protein; eGFR: Estimated Glomerular Filtration Rate; NIV: non-invasive ventilation; mMRC: Modified Medical Research Council dyspnoea scale; REFS: Reported Edmonton Frail Scale; WBC: White blood cell.
Table 10. Spirometry and Forced Oscillation Technique indices at recruitment assessment during admission.

<table>
<thead>
<tr>
<th>Forced Oscillation Technique</th>
<th>All patients (n=82)</th>
<th>Patients with 30 days readmission (n=31)</th>
<th>Patients with no 30 days readmission (n=51)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (L)</td>
<td>0.90 ± 0.34</td>
<td>0.90 ± 0.35</td>
<td>0.85 ± 0.34</td>
<td>0.60</td>
</tr>
<tr>
<td>FEV₁%</td>
<td>34.3 ± 12.4</td>
<td>34 ± 11</td>
<td>35 ± 13</td>
<td>0.67</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.2 ± 2.3</td>
<td>2.2 (1.7-2.5)</td>
<td>1.4 (2-2.4)</td>
<td>0.22</td>
</tr>
<tr>
<td>FVC %</td>
<td>61 ± 16.7</td>
<td>61 ±17</td>
<td>61±16.6</td>
<td>0.98</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>43.5 ± 11</td>
<td>42 ± 11</td>
<td>44 ± 11</td>
<td>0.56</td>
</tr>
<tr>
<td>IC (L)</td>
<td>1.3 (1-1.8)</td>
<td>1.40 (1-1.7)</td>
<td>1.20 (1-2)</td>
<td>0.77</td>
</tr>
<tr>
<td>PIFR (L/m)</td>
<td>60 (50-85)</td>
<td>50 (40-60)</td>
<td>80 (55-90)</td>
<td>0.001</td>
</tr>
<tr>
<td>ΔXrs&lt;sub&gt;5Hz&lt;/sub&gt; at upright position [cmH₂O/(L/s)]</td>
<td>2.1 (0.4-5.1)</td>
<td>1.7 (0.2-4.7)</td>
<td>2.2 (0.50-5)</td>
<td>0.60</td>
</tr>
<tr>
<td>FL% at upright position</td>
<td>20 (0-91)</td>
<td>20 (0-90)</td>
<td>2- (0-93)</td>
<td>0.98</td>
</tr>
<tr>
<td>ΔXrs&lt;sub&gt;5Hz&lt;/sub&gt; at supine position [cmH₂O/(L/s)]</td>
<td>3 (0.9-7)</td>
<td>2.6 (1.7-8)</td>
<td>3 (0.8-7)</td>
<td>0.73</td>
</tr>
<tr>
<td>FL% at Supine position</td>
<td>50 (12-100)</td>
<td>40 (27-90)</td>
<td>60 (7-100)</td>
<td>0.92</td>
</tr>
<tr>
<td>------------------------</td>
<td>------------</td>
<td>------------</td>
<td>------------</td>
<td>------</td>
</tr>
<tr>
<td>Rrs$_{5Hz}$ at upright position</td>
<td>4.7 (3.2-6.2)</td>
<td>4.8 (3-6.3)</td>
<td>4.8 (3.45-6.2)</td>
<td>0.53</td>
</tr>
<tr>
<td>Rrs$_{5Hz}$ at supine position</td>
<td>5.3 (3.7-7.2)</td>
<td>5.5 (3.5-6.6)</td>
<td>5.7 (3.8-7.4)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

*Data are presented as median IQR.

**Abbreviations**: EFL: Expiratory flow limitation; ∆Xrs$_{5Hz}$: Within Breath Reactance at 5 Hz; FL%: Flow limitation percentage; Rrs$_{5Hz}$: Resistance at 5Hz; FEV1%: Predicted Forced Expiratory Volume in 1 second; FEV1/FVC: calculated ratio between both measurements; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; IC: Inspiratory Capacity; PIIFR: peak inspiratory flow rate.
Changes from admission to discharge between both groups
We assessed the change from admission to discharge in FOT, lung volume, inspiratory flow, and blood inflammatory biomarkers between groups (Table 11). There were no significant differences within and between groups in FOT values. However, there was a trend to an overall increase in $\Delta X_{rs\,5Hz}$ in upright and supine positions among those who were readmitted within 30 days. There was no improvement in the PIFR from admission to discharge in readmitted patients, while statistically significant improvement was found in those with no readmission [80 (55-90) vs 95 (70-110) L, $p=0.001$]. Breathlessness within groups was improved with no statistically significant difference was found between groups. Generally, the symptoms improved within both groups as CAT sore decreased, but this was found with a statistically significant difference between readmitted and those with no readmission groups [-8 (-12, -3) vs -11 (-14, -7), $p=0.001$], respectively. Regarding inflammatory blood markers, there was an overall reduction within both groups, but this decline was with no significant differences between groups.

Factors associated with the readmission within 30 days
In univariate logistic-regression analysis, we assessed factors associated with 30 days readmission following exacerbation, using all significant variables we found between groups. The best predictor of readmission within 30 days was the frailty score (OR, 1.72; 95% CI, 1.32 to 2.29; $p<0.001$). Table 12 shows other variables that associated with 30 days readmission.
Table 11. Changes from admission to discharge between patients with 30-day readmission vs. no readmission.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Patients with 30-day readmission (n= 31)</th>
<th>Patients with no readmission (n=51)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Admission</td>
<td>Discharge</td>
<td>Median difference</td>
</tr>
<tr>
<td>ΔXrs5Hz at upright position [cmH2O/(L/s)]</td>
<td>1.7 (0.2-4.7)</td>
<td>2.6 (0.4-5)</td>
<td>0.2 (-2.4-2.2)</td>
</tr>
<tr>
<td>FL at upright position</td>
<td>38 (0-91)</td>
<td>34 (0-100)</td>
<td>0 (-24-9.3)</td>
</tr>
<tr>
<td>ΔXrs5Hz at supine position [cmH2O/(L/s)]</td>
<td>2.6 (1.7-8)</td>
<td>4.7 (1.3-7.5)</td>
<td>0.2 (-2.37-2.22)</td>
</tr>
<tr>
<td>FL at Supine position</td>
<td>40 (27-90)</td>
<td>48 (7-100)</td>
<td>0.4 (-31-20)</td>
</tr>
<tr>
<td>Rs5Hz at upright position [cmH2O/(L/s)]</td>
<td>4.7 (3-6)</td>
<td>4.9 (3-6)</td>
<td>0.1 (-0.9-0.7)</td>
</tr>
<tr>
<td>Rs5Hz at Supine position [cmH2O/(L/s)]</td>
<td>5.5 (3.5-7)</td>
<td>5 (4-6.5)</td>
<td>-0.4 (-0.9-1)</td>
</tr>
<tr>
<td>PIFR (L/m)</td>
<td>50 (40-60)</td>
<td>50 (45-55)</td>
<td>5 (-10-8.5)</td>
</tr>
<tr>
<td>IC (L)</td>
<td>1.3 (1-1.7)</td>
<td>1.4 (0.9-1.7)</td>
<td>0.05 (-0.18-0.5)</td>
</tr>
<tr>
<td>Variable</td>
<td>mMRC</td>
<td>CAT score</td>
<td>WBC (10^9/L)</td>
</tr>
<tr>
<td>------------</td>
<td>-----------</td>
<td>-----------</td>
<td>--------------</td>
</tr>
<tr>
<td>4 (3-4)</td>
<td>3 (2-4)</td>
<td>-1 (-1, 0)</td>
<td>0.00</td>
</tr>
<tr>
<td>3 (2-4)</td>
<td>-1 (-1, 0)</td>
<td>0.00</td>
<td>10.5 (7-14)</td>
</tr>
<tr>
<td>-1 (-1, 0)</td>
<td>-8 (-12, -3)</td>
<td>0.00</td>
<td>8.4 (7-11.4)</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.03</td>
</tr>
<tr>
<td>1</td>
<td>0.00</td>
<td>0.00</td>
<td>10.7 (9-15)</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>10 (8-12)</td>
</tr>
<tr>
<td>1</td>
<td>0.00</td>
<td>0.00</td>
<td>-1.4 (-3.7-1.1)</td>
</tr>
<tr>
<td>0.001</td>
<td>0.01</td>
<td>0.004</td>
<td>0.05</td>
</tr>
<tr>
<td>0.21</td>
<td>0.85</td>
<td>0.08</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*Data are presented as median IQR; P value = median difference between group; *P value = median difference between groups.

**Abbreviations:** EFL: Expiratory flow limitation; ∆Xrs5Hz: Within Breath Reactance at 5 Hz; FL%: Flow limitation percentage; Rrs5Hz: Resistance at 5 Hz; CAT: COPD Assessment Test; CRP: C-reactive protein; eGFR: Estimated Glomerular Filtration Rate; FEV1%: Predicted Forced Expiratory Volume in 1 second; FEV1/FVC: calculated ratio between both measurements; IC: Inspiratory Capacity; mMRC: Modified Medical Research Council dyspnoea scale; PIFR: Peak Inspiratory Flow Rate; WBC: White blood cell.
Table 12. Univariate analysis for predictors of readmission within 30 days of index hospitalisation.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Exacerbations (&lt;12 months)</td>
<td>1.27</td>
<td>1.03-1.6</td>
<td>0.027</td>
</tr>
<tr>
<td>Number of hospitalised exacerbations (&lt;12 months)</td>
<td>1.39</td>
<td>1.05-1.8</td>
<td>0.021</td>
</tr>
<tr>
<td>CAT at discharge</td>
<td>1.14</td>
<td>1.04-1.24</td>
<td>0.004</td>
</tr>
<tr>
<td>Frailty Score</td>
<td>1.72</td>
<td>1.32-2.29</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>1.12</td>
<td>1.01-1.24</td>
<td>0.038</td>
</tr>
<tr>
<td>PIFR at admission (L/m)</td>
<td>0.94</td>
<td>0.92-0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PIFR at discharge (L/m)</td>
<td>0.93</td>
<td>0.90-0.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay (day)</td>
<td>1.08</td>
<td>1.01-1.16</td>
<td>0.034</td>
</tr>
<tr>
<td>ΔPIFR (L/m)</td>
<td>0.93</td>
<td>0.89-0.97</td>
<td>0.001</td>
</tr>
<tr>
<td>ΔCAT</td>
<td>1.12</td>
<td>1.02-1.22</td>
<td>0.019</td>
</tr>
</tbody>
</table>

**Abbreviations:** CAT: COPD Assessment Test; FEV1%: Predicted Forced Expiratory Volume in 1 second; PIFR: Peak Inspiratory Flow Rate, OR: odd ratio; CI: confidence interval.
We constructed a ROC curve to assess how the significant predictors in univariate logistic regression predicted the readmission, as shown in the combined Figure 33 below. The area under the ROC curve (AUC) is a measure of how well a parameter can distinguish between two diagnostic groups (in this case, readmission within 30 days vs no-readmission).

We found that PIFR at discharge and frailty score values had the highest prediction ability than other variables in AUC (AUC 0.86, 95%CI 0.78 to 0.95, p<0.001), (AUC 0.81, 95%CI 0.71 to 0.90, p<0.001), respectively. This indicates an excellent ability to predict readmission, defined an AUC ≥0.80. The highest AUC for CAT score was found when it is measured at discharge (AUC 0.68, 95%CI 0.55 to 0.81, p=0.006).

Figure 33. ROC curve of the significant predictors in the univariate logistic regression.
ROC Curve (Number of hospitalised exacerbations <12months)

(AUC 0.67, 95%CI 0.55 to 0.79, p= 0.008)

ROC Curve (CAT at discharge)

(AUC 0.68, 95%CI 0.56 to 0.81, p= 0.006)
(AUC 0.81, 95% CI 0.71 to 0.90, p = 0.001)

(AUC 0.65, 95% CI 0.53 to 0.77, p = 0.02)
(AUC 0.77, 95%CI 0.67 to 0.88, p<0.001)

(AUC 0.88, 95%CI 0.78 to 0.95, p<0.001)
ROC Curve (Length of hospital stay)

(AUC 0.64, 95% CI 0.52 to 0.76, p = 0.03)

ROC Curve (ΔPIFR)

(AUC 0.76, 95% CI 0.65 to 0.87, p<0.001)
Next, we undertook a multivariable analysis includes the top three predictive variables found in the ROC analysis, specifically (PIFR at discharge, frailty score, CAT at discharge). We selected only three because we have only 31 readmissions, thus we should only include one variable per ten patients meeting the outcome. Among all the three variables, only PIFR showed statistically significant odds to predict readmission with 30 days (OR 0.94, 95% CI 0.91-97, p<0.001). Thus, those with lower PIFR values were at higher risk to get readmitted (Table 13).
Table 13. Multivariable analysis for predictors of readmission within 30 days of index hospitalisation.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frailty score</td>
<td>1.31</td>
<td>0.96-1.80</td>
<td>0.08</td>
</tr>
<tr>
<td>PIFR at discharge</td>
<td>0.94</td>
<td>0.91-0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CAT at discharge</td>
<td>1.01</td>
<td>0.91-1.13</td>
<td>0.77</td>
</tr>
</tbody>
</table>

We finally assessed the combined predictive ability of these three variables together, which showed an excellent predictive performance (AUC 0.89, CI 0.81 to 0.96, p<0.001) as presented in Figure 34.

**Figure 34. ROC curve of the combined variables for readmission within 30 days.**
Sensitivity and specificity of the best predictors (AUC >0.80)

We find an optimum scale cut-off point for the best predictors that maximising the true positive and true negative detection rates. According to the ROC analysis, the optimal cut-off for PIFR was 62.5 L/m that 82% sensitive and 83% specific. When we selected specificity of 90%, the cut-off decreased to 54 L/m on sensitivity of 58%. In contrast, on 90% sensitivity, a cut of 82.5 L/m was 67% specific. The calculated PPV and NPV for each cut-off presented in Table 14.

Regarding the frailty, the best cut-off score was 10.5 and this was 81% sensitive and 73% specific. More details about other cut-off values with their PPV and NPV were described in Table 14.

Table 14. Sensitivity and specificity (PPV and NPV) of the best predictors for 30 days readmission.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIFR at discharge</td>
<td>62.5</td>
<td>82%</td>
<td>83%</td>
<td>70%</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>58%</td>
<td>90%</td>
<td>78%</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>82.5</td>
<td>90%</td>
<td>67%</td>
<td>64%</td>
<td>91%</td>
</tr>
<tr>
<td>Frailty Score</td>
<td>10.5</td>
<td>81%</td>
<td>73%</td>
<td>46%</td>
<td>70%</td>
</tr>
<tr>
<td></td>
<td>12.5</td>
<td>45%</td>
<td>90%</td>
<td>50%</td>
<td>66%</td>
</tr>
<tr>
<td></td>
<td>9.5</td>
<td>93%</td>
<td>44%</td>
<td>45%</td>
<td>79%</td>
</tr>
</tbody>
</table>

Abbreviations: PIFR: peak inspiratory flow rate; PPV: positive predictive value; NPV: negative predictive value.
Factors associated with the readmission within 90 days

Using univariate logistic-regression analysis, we found those with flow limitation in supine position had the greatest odds of 90-day readmission among all variables (OR 3.02, 95% CI 1.17-7.83, p=0.022), followed by frailty score (OR 1.65, 95% CI 1.27-2.13, p=0.022). Length of stay was not found to be a significant predictor for 90 days readmission (OR 1.03, 95% CI 0.96-1.10, p=0.96 (Table 15).
Table 15. Predictors of readmission within 90 days of index hospitalisation.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Exacerbations (within past 12 months)</td>
<td>1.44</td>
<td>1.11-1.87</td>
<td>0.005</td>
</tr>
<tr>
<td>Number of hospitalised exacerbations (within past 12 months)</td>
<td>1.57</td>
<td>1.13-2.18</td>
<td>0.007</td>
</tr>
<tr>
<td>CAT at discharge</td>
<td>1.16</td>
<td>1.06-1.28</td>
<td>0.002</td>
</tr>
<tr>
<td>Frailty Score</td>
<td>1.65</td>
<td>1.27-2.13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>1.14</td>
<td>1.02-1.27</td>
<td>0.013</td>
</tr>
<tr>
<td>PIFR at admission (L/m)</td>
<td>0.94</td>
<td>0.92-0.97</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PIFR at discharge (L/m)</td>
<td>0.93</td>
<td>0.91-0.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay (day)</td>
<td>1.03</td>
<td>0.96-1.10</td>
<td>0.37</td>
</tr>
<tr>
<td>ΔPIFR (L/m)</td>
<td>0.94</td>
<td>0.91-0.98</td>
<td>0.002</td>
</tr>
<tr>
<td>ΔCAT (L/m)</td>
<td>1.05</td>
<td>0.96-1.16</td>
<td>0.25</td>
</tr>
<tr>
<td>Flow Limited in supine position (Yes vs No)</td>
<td>3.02</td>
<td>1.17-7.83</td>
<td>0.022</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>0.94</td>
<td>0.89-0.99</td>
<td>0.031</td>
</tr>
</tbody>
</table>
Next, we developed a ROC analysis of all the included variables in the univariate logistic regression to assess these variables' abilities to predict readmission within 90 days. PIFR at discharge had the highest AUC (0.86, CI 0.77 to 0.95, p<0.001), which showed an excellent ability to predict readmission. Table 16 presents the ROC analysis for predictors of 90 days readmission, which were statistically significant for all variables, except length of stay.

Table 16. ROC curve (AUC) of the variables for readmission within 90 days.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>AUC 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Exacerbations (&lt;12 months)</td>
<td>0.72 (0.61-0.84)</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of hospitalised exacerbations (&lt;12 months)</td>
<td>0.71 (0.59-0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>CAT at discharge</td>
<td>0.72 (0.61-0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>Frailty Score</td>
<td>0.78 (0.67-0.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>0.67 (0.55-0.79)</td>
<td>0.007</td>
</tr>
<tr>
<td>PIFR at admission</td>
<td>0.81 (0.71-0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PIFR at discharge</td>
<td>0.86 (0.77-0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay</td>
<td>0.55 (0.43-0.68)</td>
<td>0.38</td>
</tr>
<tr>
<td>ΔPIFR</td>
<td>0.73 (0.60-0.84)</td>
<td>0.001</td>
</tr>
<tr>
<td>ΔCAT</td>
<td>0.76 (0.65-0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Flow Limited in supine position (Yes vs No)</td>
<td>0.63 (0.51-0.76)</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI</td>
<td>0.65 (0.53-0.77)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Further, we applied a multivariable analysis included the (PIFR at discharge, frailty score, CAT at discharge and exacerbations within past 12 months). We found PIFR at discharge was the only predictor for 90 days readmission among other variables, (OR 0.95, 95% CI 0.92-0.97, p=0.001). Table 17 shows the multivariable logistic regression for readmission within 90 days.

**Table 17. Multivariable analysis for predictors of readmission within 90 days of index hospitalisation.**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frailty score</td>
<td>1.17</td>
<td>0.85-1.61</td>
<td>0.32</td>
</tr>
<tr>
<td>PIFR at discharge</td>
<td>0.95</td>
<td>0.92-97</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>CAT at discharge</td>
<td>1.05</td>
<td>0.92-1.19</td>
<td>0.44</td>
</tr>
<tr>
<td>Exacerbations within past 12 months</td>
<td>1.36</td>
<td>0.95-1.95</td>
<td>0.76</td>
</tr>
</tbody>
</table>

Next, to assess the predictive performance of all these variables, we combined them using ROC analysis. This shows an excellent combined predictive performance (AUC 0.89, CI 0.81 to 0.96, p<0.001) as presented in Figure 35.
We assessed sensitivity, specificity, PPV and NPV for the best predictor of 90 days readmission: PIFR at discharge. We found that a cut off 72.5 was the optimum value that 78% sensitive and 88% specific. This has a PPV of 77.5%, which indicates a good clinical ability to predict readmission (Table 18).

**Table 18. Sensitivity and specificity (PPV and NPV) of the best predictor for 90 days readmission.**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Cut-off</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIFR at discharge (L/m)</td>
<td>72.5</td>
<td>78%</td>
<td>88%</td>
<td>77.5%</td>
<td>64%</td>
</tr>
<tr>
<td></td>
<td>92.5</td>
<td>89%</td>
<td>67%</td>
<td>75%</td>
<td>77%</td>
</tr>
<tr>
<td></td>
<td>77.5</td>
<td>78%</td>
<td>92%</td>
<td>76%</td>
<td>65%</td>
</tr>
</tbody>
</table>

**Abbreviations:** PIFR: peak inspiratory flow rate; PPV: positive predictive value; NPV: negative predictive value.
6.6 Discussion

This is the first prospective cohort study in the UK to determine the risk factors for 30 and 90-day all-cause readmission following hospitalisation for an exacerbation of COPD. The findings show that 30-day and 90-day hospital readmission rates were 38% and 56%, respectively. We found that previous exacerbations, higher CAT score at discharge, frailty, sub-optimal PIFR and increased length of stay were significantly associated with 30-day COPD readmission. Furthermore, 90-day COPD readmission were significantly associated with previous exacerbations and hospitalisations, higher CAT score at discharge, frailty, depression, sub-optimal PIFR and EFL in supine position defined as $\Delta X_{rs5Hz}$ of ≥2.8 [cmH2O/(L/s)]. The best predictive variable in the multivariable analysis for both 30- and 90-day COPD readmission was PIFR at discharge.

The observed 30-day and 90-day readmission rates were higher than readmission rates in the previous UK COPD audit, 24% and 43% respectively (206). This finding was also greater compared to those of other studies (379, 383, 395). Our study’s high readmission rates can be explained by the relatively higher exacerbations, and frailty burden.

We identified several disease severity factors associated with an increased risk of early readmission. Consistent with literature, we found that previous COPD exacerbations and hospitalisations are significantly associated with all-cause readmission (440, 441). Hospitalisations due to COPD exacerbation can lead to a huge economic and clinical burden (442), which can be 60 times more expensive than mild and moderate exacerbations.
managed by community services (443). Such frequent exacerbations are linked with increased mortality rate (444). Thus, early detection of exacerbation symptoms and timely management may reduce the likelihood of hospitalisation and ultimately readmission.

Discharge assessment is the key to assess readmission risk, we found that higher CAT score at discharge was associated with COPD readmission, in which those who get readmitted had greater CAT scores at discharge compared to those with no readmission. This indicates that those patients who get readmitted were more symptomatic at discharge and their exacerbations not recovered. A potential explanation of this finding would be that earlier intervention to these exacerbations was not established, eventually they will take longer time to recover (445). Further and for the first time, we reported that PIFR at discharge can detect both 30- and 90-day readmission risk with an excellent AUC value of 0.86 for both 30- and 90-day readmission. This was also reflected in the multivariable logistic regression, which was found to be the best predictor after adjustment for age, airflow severity and comorbidities index. Similarly, Loh et al. 2017 (397) conducted a retrospective study and showed that suboptimal PIF was the only variable that predict days to COPD readmission, but this was not statistically significant in predicting 30- and 90-days COPD readmission. However, Sharma et al. (364) found no association between PIFR and all-cause readmission up to six months follow-up period. We reported for the first time the prevalence of sub-optimal PIFR at admission due to COPD exacerbation and at discharge, unlike others (364, 397). Our reported 46% and 40% prevalence of sub-optimal PIFR during hospitalisation was greater
than 31% prevalence reported by Sharma et al. (29). In contrast, Loh et al. 2017 (28) found higher prevalence of sub-optimal PIFR at 52%. However, this study used 60 L/min or less as a cut off to define sup-optimal PIFR, dissimilar to us and others in which we used less than 60 L/min to define it (364).

To our knowledge this is the first study to report frailty defined by the REFS as an independent risk factor for 30 days COPD readmission following exacerbation of COPD. There is only one study conducted in Spain had tested this and found frailty as defined by the REFS to be a risk factor for 90 days COPD readmission (446). They reported that those with higher frailty scores were five times more likely to get readmitted compared to non-frail patients. The Short Physical Performance Battery is another tool used to assess lower limb function, which consists of three individual sub-tests: standing balance, 4-meter gait speed and 5-repetition sit-to-stand (447). The sub-test 4-meter gait speed has been found to be an independent predictor for 90-day all-cause readmission following hospitalisation for acute exacerbation of COPD (396). However, this study had only a small number of younger patients, which could limit generalisation of such results to younger population. Certainly, assessing acutely unwell patients during hospitalisation using multidimensional frailty tool such as REFS may be beneficial to stratify patients who are at higher readmission risk. This would facilitate personalised disease management, aiming to improve the outcomes of those vulnerable patients.
Increased length of stay was found to be a significant risk factor for readmission within 30 days but not with 90 days. This finding was consistent with other studies included in our recent systematic review (220). Thus, length of stay can be used as a potential indicator for patients who may benefit from COPD community support and earlier follow-up following initial discharge. Moreover, depression was associated with 90 days COPD readmission in this study. This finding broadly supports the work of other studies in this area linking depression with COPD readmission (220, 448). Despite the high prevalence of depression in COPD patients (449), thus far, there is no evidence to support the efficiency of antidepressants in reducing readmission risk (450).

No previous studies had tested whether using FOT with objective measurements of resting lung function during hospitalisation can predict COPD readmission. For the first time, we found EFL measured by $\Delta X_{rs5Hz}$ in supine position at discharge to be a significant predictor for 90 days readmission. Thus, using FOT during hospitalisations may support clinicians in earlier detection of patients at higher risk of readmission and reduce dependence on the patient’s self-reported symptoms. According to the Walker et al. (451), using FOT to measure lung function in COPD patients was practical, well tolerated, and acceptable, allowing it to be incorporated into clinical service.

This study findings have important clinical implications. It emphasises the important value of discharge assessments in predicting COPD readmission risk that incorporating patient’s reported symptoms and objective measurements. Clinicians should check PIFR at discharge to guide COPD
treatment options, ultimately reduce COPD readmission risk. In addition to the assessment of symptoms using CAT, FOT could be used as a complimentary option to categorise those patients with EFL at discharge who can benefit from additional therapy and early follow-up, aiming to mitigate symptoms and unresolved EFL, and reduce readmission rate. Identifying patients with severe frailty at time of hospitalisation would facilitate potential rehabilitation programmes following discharge that could decrease early readmission for COPD patients.

Our study was limited by not having a separate validation cohort; thus, our results might not be extrapolated to all COPD population. We did not collect chest imaging data, and this would have been valuable. Our follow up was 90 days but would have been useful to look at long term outcomes such as readmission within 12 months and mortality but this was beyond the scope of the study. Our study required informed consent from patients, and this could lead to consent bias.

6.7 Conclusion:

Our study shows that previous exacerbations, higher CAT score at discharge, frailty, sub-optimal PIFR and increased length of stay were found significant predictors for 30-day COPD readmission. Patients with EFL in supine position were significantly associated with 90-day readmission. This finding supports clinicians in identifying COPD patients at higher readmission risk to improve their outcomes by delivering effective personalised interventions as most of the reported risk factors are modifiable.
7. Changes in inspiratory and expiratory flow limitation, and physical activity following discharge from hospital after acute exacerbation of COPD
7.1 Introduction:

In the previous chapter, I reported the predictors for 30- and 90-day COPD readmission following hospitalisation due to COPD exacerbation. Following hospital discharge for COPD exacerbation there is no detailed information available on the changes in physical activity, PIFR limitation and EFL (measured by FOT) and how these changes relate to the recovery time for symptoms. Therefore, we offered a follow-up for patients to explore such measures throughout the recovery period at 30-day post hospitalisation. We hypothesised that an improvement in breathlessness and symptoms following hospitalisation may associate with an improvement in lung function and flow measures (spirometry, FOT, PIFR) and physical activity.

7.2 Methods:

This study was part of the previous study described in Chapter six. Ethical approval was obtained from the HRA (reference 19/EM/0080).

7.2.1 Participants

Patients who agreed to take part in the previous study were asked to attend 30-day follow-up after hospital discharge for re-assessment. Those patients who agreed to have follow-up were given a step-counter pedometer and asked to record their daily steps following hospitalisation for 30 consecutive days, they were informed not to wear the step-counter during showering.
and sleeping. At the follow-up visit, patients had a re-assessment of the same measures described in the previous chapter and methods.

### 7.2.2 Measurements

Full detail of all measurements taken was described in the Methods chapter. Figure 36 demonstrates a summary of the methods used for this chapter.

**Figure 36. A summary of the used methods in this chapter.**

**Discharge Measurements**

- Full medical history (including exacerbations, readmission post discharge)
- FOT
- Spirometry
- PIFR
- Physical activity using the step counter Pedometer
- Questionnaires (mMRC / CAT / HADS).
7.2.3 Statistical analysis

We assessed data for normality using visual inspection of the histogram, and the Kolmogorov-Smirnov test. We compared the baseline characteristics between those patients who attended the 30-day follow-up after hospital discharge and those who did not attend. Next, we compared discharge and 30-day measurements to assess pattern of improvements. Correlations between outcomes were assessed using the Spearman rank correlation coefficient test. For comparisons, an independent t-test was applied to assess differences between two groups for normally distributed data and a Mann-Whitney U test was used for non-normally distributed data. For parametric data, we used T-test (paired test) to assess changes in measurements between discharge and follow-up and Wilcoxon signed-rank for non-parametric paired data. Data for physical activity (step count) were averaged over the duration of follow-up time. The (SPSS), Version 25 (IBM Corp, Armonk, USA) software was used to analyse our data.

7.3 Results

Baseline characteristics

Figure 37 describes the recruitment process from admission to follow-up. Consecutively we approached 152 patients, 82 patients completed the pre-discharge assessment, and 12 patients attended the follow-up assessment at 30 days post hospital discharge. Table 19 shows the admission characteristics between those who attended and did not attend the 30-day follow-up. In general, there were no significant differences between groups in the measurements. However, those who attended follow-up had a shorter
hospital length of stay compared to those who did not attend, 5 (3-8) vs 8 (5-12) days, p= 0.03, respectively. Further, those who did not attend follow-up had higher depression scores than those who attended follow-up, 12 (7-14) vs 8 (6-10), p= 0.02, respectively. Within breath reactance (ΔXrs5Hz) in supine position was significantly different between the groups 2.4 (0.8-5.6) vs 3.8 (3-12) [cmH2O/(L/s)], p=0.03, in which those who attended the follow-up have a greater value during admission (Table 20).

**Figure 37. Consort diagram of the study.**

Admitted due to COPD Exacerbation 
(n=152)

Consented 
(n= 125)

Completed admission assessment 
(n= 82)

Completed discharge assessment 
(n= 82)

Attended 30 days follow-up 
(n= 12)

Refused to take part 
(n= 23)

Excluded with reasons: 
(n= 47) 
- Not COPD exacerbation 
(n= 24) 
- Cognitive impairment patients (n= 6) 
- Asthma (n= 6) 
- Bronchiectasis (n= 4) 
- Lung cancer (n= 5) 
- Not complying with the protocol (n= 2)

Did not attend 30 days follow-up 
(n= 70)
Table 19. Characteristics of the index admission between those who attend and did not attend the 30 days follow-up.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=82)</th>
<th>Did not attend F/U (n=70)</th>
<th>Did attend F/U (n=12)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>40 (49%)</td>
<td>32 (46%)</td>
<td>8 (67%)</td>
<td>0.18</td>
</tr>
<tr>
<td>Female</td>
<td>42 (51%)</td>
<td>38 (54%)</td>
<td>4 (33%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>71 ± 10.4</td>
<td>71 ±10</td>
<td>73 ±11</td>
<td>0.56</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24 (20-29)</td>
<td>24 (20-30)</td>
<td>26 (21-27)</td>
<td>0.88</td>
</tr>
<tr>
<td>Current smoker</td>
<td>24 (29%)</td>
<td>21 (30%)</td>
<td>3 (25%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>58 (71%)</td>
<td>49 (70%)</td>
<td>9 (75%)</td>
<td></td>
</tr>
<tr>
<td>Smoking history (Pack Years)</td>
<td>42 (29-56)</td>
<td>44 (29-60)</td>
<td>38 (23-46)</td>
<td>0.20</td>
</tr>
<tr>
<td>Number of Exacerbations (within past 12 months)</td>
<td>2 (1-4)</td>
<td>2 (1-4)</td>
<td>1 (1-4)</td>
<td>0.34</td>
</tr>
<tr>
<td>Number of hospitalised exacerbations (&lt;12months)</td>
<td>2 (1-3)</td>
<td>2 (1-3)</td>
<td>1 (0-4)</td>
<td>0.65</td>
</tr>
<tr>
<td>Pulmonary rehabilitation (&lt;12 months)</td>
<td>28 (34%)</td>
<td>48 (68%)</td>
<td>6 (50%)</td>
<td>0.21</td>
</tr>
<tr>
<td>Charlson Comorbidity Index</td>
<td>4.3 ± 1.6</td>
<td>4.3 ±1.6</td>
<td>4.2 ±1.1</td>
<td>0.74</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>0.86 ± 0.34</td>
<td>0.86 ± 0.35</td>
<td>0.86 ± 0.32</td>
<td>0.95</td>
</tr>
<tr>
<td>FEV₁%</td>
<td>34.3 ± 12.4</td>
<td>33 ±11.3</td>
<td>39 ±17</td>
<td>0.30</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.2 ± 2.3</td>
<td>1.95 ± 0.6</td>
<td>2 ± 0.6</td>
<td>0.65</td>
</tr>
<tr>
<td>FVC %</td>
<td>61 ± 16.7</td>
<td>59±16</td>
<td>67±17</td>
<td>0.14</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>43.5 ± 11</td>
<td>44 ±11</td>
<td>43 ±10</td>
<td>0.89</td>
</tr>
<tr>
<td>IC (L)</td>
<td>1.30 (1-1.8)</td>
<td>1.39 (0.9-1.8)</td>
<td>1.24 (1.1-1.7)</td>
<td>0.91</td>
</tr>
<tr>
<td>PIFR (L/min)</td>
<td>60 (50-85)</td>
<td>60 (50-90)</td>
<td>63 (50-80)</td>
<td>0.82</td>
</tr>
<tr>
<td>Length of stay in days</td>
<td>7 (4-10.3)</td>
<td>8 (5-12)</td>
<td>5 (3-8)</td>
<td>0.03</td>
</tr>
<tr>
<td>CAT Score</td>
<td>31 (27.7-34)</td>
<td>32 (28-34)</td>
<td>28 (24-34)</td>
<td>0.08</td>
</tr>
<tr>
<td>mMRC</td>
<td>4 (3.7-4)</td>
<td>4 (3.7-4)</td>
<td>4 (3-4)</td>
<td>0.99</td>
</tr>
<tr>
<td>REFS</td>
<td>10 (9-12.2)</td>
<td>11 (9-13)</td>
<td>10 (7-11)</td>
<td>0.07</td>
</tr>
<tr>
<td>Depression</td>
<td>11 (7-14)</td>
<td>12 (7-14)</td>
<td>8 (6-10)</td>
<td>0.02</td>
</tr>
<tr>
<td>Anxiety</td>
<td>9 (6.7-11)</td>
<td>9 (7-11)</td>
<td>9 (4-15)</td>
<td>0.95</td>
</tr>
<tr>
<td>WBC (10^9/L)</td>
<td>10.6 (7.9-14.5)</td>
<td>10 (8-14)</td>
<td>12 (9-17)</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>All patients (n=82)</td>
<td>Did not attend F/U (n= 70)</td>
<td>Did attend F/U (n=12)</td>
<td>P value*</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------</td>
<td>----------------------------</td>
<td>-----------------------</td>
<td>----------</td>
</tr>
<tr>
<td>∆Xrs&lt;sub&gt;5Hz&lt;/sub&gt; at upright position [cmH2O/(L/s)]</td>
<td>2.1 (0.4-5.1)</td>
<td>1.6 (0.2-4.7)</td>
<td>3.6 (1.5-6.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>FL% at upright position</td>
<td>20 (0-91)</td>
<td>19 (0-81)</td>
<td>80 (5-100)</td>
<td>0.12</td>
</tr>
<tr>
<td>∆Xrs&lt;sub&gt;5Hz&lt;/sub&gt; at supine position [cmH2O/(L/s)]</td>
<td>3 (0.9-7)</td>
<td>2.4 (0.8-5.6)</td>
<td>3.8 (3-12)</td>
<td>0.03</td>
</tr>
<tr>
<td>FL% at Supine position</td>
<td>50 (12-100)</td>
<td>40 (9-90)</td>
<td>91 (60-100)</td>
<td>0.01</td>
</tr>
<tr>
<td>Rrs&lt;sub&gt;5Hz&lt;/sub&gt; at upright position [cmH2O/(L/s)]</td>
<td>4.7 (3.2-6.2)</td>
<td>4.7 (3.2-6.3)</td>
<td>5.1 (4.2-6.1)</td>
<td>0.70</td>
</tr>
<tr>
<td>Rrs&lt;sub&gt;5Hz&lt;/sub&gt; at supine position [cmH2O/(L/s)]</td>
<td>5.3 (3.7-7.2)</td>
<td>5.3 (3.7-7.1)</td>
<td>5.5 (3.4-7.4)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

*Data are presented as median IQR, *p value= did vs. did not attend follow-up.

**Abbreviations:** EFL: Expiratory flow limitation; ∆Xrs<sub>5Hz</sub>: Within Breath Reactance at 5 Hz; FL%: Flow limitation percentage; Rrs<sub>5Hz</sub>: Resistance at 5 Hz.
Changes from discharge to follow-up

Table 21 presents the changes in spirometry, FOT indices, PIFR, and questionnaires from hospital discharge to 30-day follow-up among those who attended. Although there were no statistical differences between discharge and follow-up data, there was a trend towards improvement in the most measurements. EFL defined as \( \Delta X_{rs5Hz} > 2.8 \ [\text{cmH}_2\text{O}/(\text{L/s})] \) generally improved from discharge to follow-up in upright position (10 vs 5, patients) and supine position (9 vs 6, patients), respectively. Only the depression score significantly increased post discharge from 7 (4-10) to 9 (6-11), p= 0.02. Average physical activity over 30-day post discharge was 1343 (419-2552) step/day, in which 473 (162-1151) step/day have been recorded over the first seven days post discharge. We found a significant positive correlation between step-counts recorded over the first 7 days and these recorded over 30-day post discharge, in which those with higher steps in first week post discharge have higher overall physical activity within 30 days, \( r= 0.84, p=0.001 \).

Correlations between breathlessness, symptoms and change in other outcomes from discharge to follow-up

First, we investigated the relationship between change in breathlessness and change in other outcomes from discharge to follow-up (Table 22). We found significant negative correlations between \( \Delta m\text{MRC} \) and \( \Delta FEV_1 \) \( (r= -0.85, p=0.004) \), \( \Delta FEV_1 \% \) \( (r= -0.77, p=0.01 \) and \( \Delta IC \) \( (r= -0.68, p=0.04) \), respectively. This indicates the greater the improvement in the breathlessness, the greater the improvement in lung function values. In contrast, there were no significant relationships between change in
breathlessness and other variables including FOT, PIFR and physical activity.

Next, we assessed the relationships between change in symptoms and change in other variables from discharge to follow-up (Table 23). There was a significant negative correlation between change in CAT and ∆FEV₁ (r= -0.68, p=0.04). Also, we found a positive correlation between change in symptoms and depression scale (r= 0.68, p=0.04), which indicates an improvement in symptoms is associated with lower depression scores.

Table 21. Change from hospital discharge to 30 days follow-up among those who attended the follow-up.

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Discharge</th>
<th>Follow-up</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV₁ (L)</td>
<td>0.95 ± 0.20</td>
<td>1.13 ±0.38</td>
<td>0.19</td>
</tr>
<tr>
<td>FEV₁%</td>
<td>44 ± 16.1</td>
<td>48 ±17.4</td>
<td>0.42</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>2.06 ± 0.33</td>
<td>2.08 ± 0.50</td>
<td>0.86</td>
</tr>
<tr>
<td>FVC %</td>
<td>68 ±18</td>
<td>69 ±14</td>
<td>0.80</td>
</tr>
<tr>
<td>FEV₁/FVC (%)</td>
<td>48 ±9</td>
<td>51 ±11</td>
<td>0.23</td>
</tr>
<tr>
<td>IC (L)</td>
<td>1.47 (1.2-1.6)</td>
<td>1.60 (1.2-2.1)</td>
<td>0.40</td>
</tr>
<tr>
<td>PIFR (L/m)</td>
<td>85 (77-105)</td>
<td>100 (62-110)</td>
<td>0.67</td>
</tr>
<tr>
<td>CAT Score</td>
<td>15 (15-19)</td>
<td>15 (8-24)</td>
<td>0.99</td>
</tr>
<tr>
<td>mMRC</td>
<td>3 (2-3)</td>
<td>3 (2-3.5)</td>
<td>0.33</td>
</tr>
<tr>
<td>Depression</td>
<td>7 (4-10)</td>
<td>9 (6-11)</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Anxiety</td>
<td>6 (4-14)</td>
<td>7 (5-11)</td>
<td>0.86</td>
</tr>
<tr>
<td>∆Xrs 5Hz in upright position [cmH2O/(L/s)]</td>
<td>3.8 (2.8-5.8)</td>
<td>2.9 (0.2-5.5)</td>
<td>0.31</td>
</tr>
<tr>
<td>FL% in upright position</td>
<td>64 (50-91)</td>
<td>50 (0-91)</td>
<td>0.11</td>
</tr>
<tr>
<td>Number of patients with EFL in upright position</td>
<td>10 (83%)</td>
<td>5 (42%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Measurements</td>
<td>Correlation</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>-------------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>ΔCAT</td>
<td>0.61</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>ΔDepression</td>
<td>0.56</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>ΔFEV(_1) (L)</td>
<td>-0.85</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>ΔFEV(_1)%</td>
<td>-0.77</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>ΔIC (L)</td>
<td>-0.68</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>ΔXrs(_{Shz}) in upright position [cmH(_2)O/(L/s)]</td>
<td>-0.06</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>ΔXrs(_{Shz}) in supine position [cmH(_2)O/(L/s)]</td>
<td>0.01</td>
<td>0.96</td>
<td></td>
</tr>
</tbody>
</table>

Table 22. Correlations between change in mMRC (breathlessness) and change in other outcomes from discharge to follow-up.
\[ \Delta \text{Rrs}_{5Hz} \text{ in upright position} \] [cmH2O/(L/s)]
- 0.56
0.11

\[ \Delta \text{Rrs}_{5Hz} \text{ in supine position} \] [cmH2O/(L/s)]
- 0.47
0.19

\[ \Delta \text{PIFR} \]
- 0.39
0.29

Average physical activity- step/day over 30-day post discharge
- 0.15
0.68

Average physical activity- step/day over 7 days post discharge
0.08
0.82

\[ \Delta \text{mMRC} \] 0.61
0.08

\[ \Delta \text{Depression} \] 0.68
0.04

\[ \Delta \text{FEV}_1 \text{(L)} \] - 0.68
0.04

\[ \Delta \text{FEV}_1\% \] - 0.48
0.18

\[ \Delta \text{IC} \text{(L)} \]
- 0.61
0.07

\[ \Delta \text{Xrs}_{5Hz} \text{ in upright position [cmH2O/(L/s)]} \] - 0.06
0.87

\[ \Delta \text{Xrs}_{5Hz} \text{ in supine position [cmH2O/(L/s)]} \] 0.20
0.60

\[ \Delta \text{Rrs}_{5Hz} \text{ in upright position [cmH2O/(L/s)]} \] - 0.18
0.63

\[ \Delta \text{Rrs}_{5Hz} \text{ in supine position [cmH2O/(L/s)]} \] - 0.13
0.74

\[ \Delta \text{PIFR} \] 0.26
0.49

Average physical activity- step/day over 30-day post discharge
- 0.52
0.14

Average physical activity- step/day over 7 days post discharge
0.18
0.63

\[ \Delta \]: delta between discharge and 30 days follow-up.

Table 23. Correlations between change in CAT and change in other outcomes from discharge to follow-up.

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Correlation</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ \Delta \text{mMRC} ]</td>
<td>0.61</td>
<td>0.08</td>
</tr>
<tr>
<td>[ \Delta \text{Depression} ]</td>
<td>0.68</td>
<td>0.04</td>
</tr>
<tr>
<td>[ \Delta \text{FEV}_1 \text{(L)} ]</td>
<td>- 0.68</td>
<td>0.04</td>
</tr>
<tr>
<td>[ \Delta \text{FEV}_1% ]</td>
<td>- 0.48</td>
<td>0.18</td>
</tr>
<tr>
<td>[ \Delta \text{IC} \text{(L)} ]</td>
<td>-</td>
<td>0.07</td>
</tr>
<tr>
<td>[ \Delta \text{Xrs}_{5Hz} \text{ in upright position [cmH2O/(L/s)]} ]</td>
<td>- 0.06</td>
<td>0.87</td>
</tr>
<tr>
<td>[ \Delta \text{Xrs}_{5Hz} \text{ in supine position [cmH2O/(L/s)]} ]</td>
<td>0.20</td>
<td>0.60</td>
</tr>
<tr>
<td>[ \Delta \text{Rrs}_{5Hz} \text{ in upright position [cmH2O/(L/s)]} ]</td>
<td>- 0.18</td>
<td>0.63</td>
</tr>
<tr>
<td>[ \Delta \text{Rrs}_{5Hz} \text{ in supine position [cmH2O/(L/s)]} ]</td>
<td>- 0.13</td>
<td>0.74</td>
</tr>
<tr>
<td>[ \Delta \text{PIFR} ]</td>
<td>0.26</td>
<td>0.49</td>
</tr>
<tr>
<td>Average physical activity- step/day over 30-day post discharge</td>
<td>- 0.52</td>
<td>0.14</td>
</tr>
<tr>
<td>Average physical activity- step/day over 7 days post discharge</td>
<td>0.18</td>
<td>0.63</td>
</tr>
</tbody>
</table>

\[ \Delta \]: delta between discharge and 30 days follow-up.
7.4 Discussion

In this pilot study we studied changes in spirometry, FOT and physical activity from discharge to 30-day follow-up, aiming to explore whether there are relationships between such changes and recovery from symptoms. We found no significant changes at 30-day follow-up between variables. Physical activity steadily increased, in which those patients with higher steps in first seven days post discharge had greater overall steps at 30-day follow-up. When we assessed the relationship between change in breathlessness and symptoms and change in other outcomes from discharge to follow-up, we found that improvement in breathlessness and symptoms were associated with improvement in spirometry values and depression scores, but not with other variables including FOT, PIFR and physical activity.

The current study re-evaluated patients’ recovery at 30-day following discharge from hospital after acute exacerbation of COPD by assessing the physiological variables including spirometry, FOT, PIFR and physical activity. Stevenson et al. has investigated changes in both airflow and lung volumes at 42 days following hospitalisation due to exacerbation and found significant changes in FVC, IC with no significant differences in FEV₁ and resistance and reactance (307). In our study we also found no significant changes in CAT, breathlessness, PIFR and anxiety sores, but depression was significantly increased at 30-day follow-up. Such findings also accord with earlier observations, which showed that recovery at 90-day was incomplete in a significant proportion of COPD exacerbations (290). Nonrecovery from exacerbations could be related to non-resolution of
systemic inflammation and frequent exacerbations (164). Interestingly, a longitudinal study shows an association between systemic inflammation and increased depression symptoms over time (452).

We report low physical activity within 30-day in those who attended the follow-up, 1343 (419-2552) step/day. In other studies the daily step-count of stable COPD were reported to be 4154 ±2586 and such steps decreased to 3673 ±2258 during non-hospitalised exacerbation (453). The low step-count we found, indicates that unrecovered respiratory symptoms during the recovery following discharge may reduce physical activity. According to Marilyn et al. (454), COPD patients with lower daily-physical activity have greater rates of exacerbation and hospitalisation, independent of airflow severity. Our data was in agreement with a study measuring physical activity during COPD hospitalisation and after 1 month of discharge, which found that COPD was less active during and after hospitalisation for COPD exacerbation (455). It has been found that stable COPD patients were noticeably less active in their day-to-day lives, in which most of them spent their day sitting or lying down (456). Hence, attempts and strategies to boost physical activity are crucial and should be incorporated with the discharge disease management plan to improve patients’ prognosis. A Cochrane systematic review shows that post exacerbation PR has positive effects on patients' quality of life and exercise capacity, suggesting PR as an effective intervention post exacerbation and can be promoted to improve patients’ prognosis (113).
When we assessed change in breathlessness from discharge to 30-day follow-up and other physiological measurements, we observed significant relationship with change in FEV$_1$, FEV$_1$% and IC. This indicates when airflow limitation and lung volumes improved, the breathlessness improved. Other variables including FOT, PIFR and physical activity were not associated with improvement in breathlessness. This could be attributed to both breath-to-breath variation in such measures and COPD heterogeneity (457, 458). We also reported that change in symptoms as measured by CAT was associated with improvement in FEV$_1$% and depression from discharge to 30-day follow-up. This indicates the importance of using CAT to quantify exacerbation severity and recovery (459, 460). Due to our limited sample size, there was no significant correlation between change in breathlessness and CAT ($r=0.61$, $p=0.08$).

Several difficulties were encountered in conducting this study. First, it was challenging to achieve high follow-up rate with our cohort patients because of the severity variation and the tendency to relapse within 30-day following discharge as has been described in the previous chapter. Second, we could not offer follow-up to all patients because of the COVID-19 pandemic and related governmental measures such as lockdown, quarantine, and social distancing. Therefore, we were limited by small sample size and high dropout rate. However, in general, there were no major differences in physiological measures between those who attended follow-up and those who did not attend follow-up.
7.5 Conclusion:

At 30-day follow-up following discharge, we found that improvements in breathlessness and symptoms were associated with improvement in spirometry values and depression, but not with other variables including FOT, PIFR and physical activity. Physical activity following hospitalised exacerbation was found low and was not correlated with an improvement in physiological and symptom measures.
My primary research project had to be stopped early because of the COVID-19 pandemic. Therefore, I conducted a rapid systematic review and meta-analysis to evaluate COVID-19 burden on COPD patients and those with a history of smoking. The results of this analysis have been published in PLOS One Journal (461) and have been highly cited.

### 8.1 Introduction

The emergence in Wuhan City, Hubei Province of China of a novel pneumonia of unknown origin on the 31\textsuperscript{st} of December, 2019 was the start of an outbreak which would later be declared a pandemic by the WHO (462). The name COVID-19 (acronym for “coronavirus disease 2019”) was coined on the 11\textsuperscript{th} of February 2020 to describe presentation with severe acute respiratory disease (463). COVID-19 is caused by a novel strain of coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus belongs to the family of single stranded RNA viruses some of which have been previously described to be responsible for the severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) (464, 465). Although the symptoms and clinical presentation of COVID-19 is similar to SARS and MERS, the rate of spread is greater (466). As of 25\textsuperscript{th} of March 2020, the total number of confirmed case of COVID-19 stands at 459,419 with 20,818 deaths globally and the number is projected to increase (467).

COPD is a common, persistent, and preventable dysfunction of the lung associated with limitation in airflow. COPD is a complex disease associated with abnormalities of the airway and/ or alveoli which is predominantly
caused by exposure to noxious gases and particulates over a long period (1). With a global prevalence of 251 million cases in 2016, and 3.17 million (5%) deaths in 2015 alone, COPD was ranked by the WHO as the third leading cause of death especially with a particular burden in low- and middle-income countries (468, 469). This burden is predicted to grow due mainly to increased global exposure to tobacco, aging populations, poor awareness and inadequate access to diagnosis (470). COPD exacerbations are a major event in the natural history of the disease associated with worsening of symptoms often resulting in hospitalisation and poor prognosis (138). Various factors have been described to contribute to acute worsening of COPD, however, viral infection remains the main trigger, including seasonal coronaviruses (6, 156, 471).

Since the emergence of COVID-19, scientists around the world continue to better understand the clinical, diagnostic and prognostic characteristic of the disease. While over 150 papers, editorials and comments have been written about COVID-19 as of 24th of March 2020, there is none dedicated to the specific risk posed to patients with a previous history of COPD. This review addresses this gap in knowledge with the aim of assisting clinicians to assess the prognosis of COVID-19 infection in patients with COPD and those with smoking history.

8.2 Methods:

This systematic review was conducted in accordance with the PRISMA guidelines (376). We prospectively registered this review to Prospero (registration number is: CRD42020175518).
We searched MEDLINE and Google scholar from inception date to March 16, 2020. The search was updated on March 24, 2020. We used an extensive search strategy developed by a specialist librarian for retrieving this type of evidence, which included the reference list of eligible papers and published pre-print papers (see appendix 12). All retrieved studies were exported into EndNote to remove duplicates. The remaining studies were exported to Rayyan software for title, abstracts and full text screening by two independent reviewers.

➢ **Inclusion and exclusion Criteria**

Eligible studies were those that investigated: epidemiological, clinical characteristics and features of COVID-19 and prevalence of chronic diseases specifically COPD in their analysis. We excluded the following: studies that did not report COPD, studies that included respiratory diseases but did not specifically analyse COPD, only children, editorials, correspondence letters, reviews, qualitative studies, theses, non-English language and non-full text articles.

➢ **Data Collection**

Two authors (JSA and TO) independently screened titles and abstracts of potential studies and conflicts were resolved through discussion between the two. Full-text articles of potential studies were then independently read by two authors (JSA and TO) to identify studies meeting the inclusion criteria. The reference lists from all identified studies and reviews were scrutinized for eligible articles. Disagreement on selected papers was resolved through discussion with a third author (AA).
➢ **Quality Assessment**

Two authors independently evaluated the methodological quality of included studies using a modified version of the Newcastle-Ottawa Scale (377). It includes seven domains, each one of these domains was scored from 0 (high risk of bias) to 3 (low risk of bias) and we took a mean of the domains to result in a score between 0 and 3, where a higher score represents a lower risk of bias. Any disagreement in the quality assessment was resolved by discussion with a third author.

➢ **Data Synthesis**

We completed meta-analysis to calculate the pooled prevalence of COPD and current smokers among those patients with confirmed COVID-19. The output was generated using the Stata procedure Metaprop. Owing to heterogeneity within and between studies, we used the random-effects model in Stata/SE 15. Data were displayed using forest plots. We examined between-study heterogeneity using the I² statistic. A narrative synthesis of the results was conducted considering the prevalence, disease severity and mortality among COVID-19 COPD patients and smoking status. We defined COVID-19 severity as those who were admitted to ICU, had severe, oxygenation, and needed mechanical ventilation or death.

➢ **Pre-Print**

As this is a rapidly evolving area, we also searched pre-print literature and whilst not incorporating such data in the formal analysis, provide narrative synthesis where such pre-print data are relevant to our main findings.
8.3 Results:

An initial search generated 123 potentially relevant papers, of which two were immediately excluded due to duplication. After the first screening of title and abstracts, 61 papers were potentially relevant according to the inclusion criteria. An additional 46 papers were excluded after full-text review, which resulted in 15 studies that satisfied all criteria. The reference list of the relevant papers was also examined (see Figure 38, PRISMA flow diagram).

➢ Description of included studies

A summary of the included studies is presented in Table 24, which included a total of 2473 confirmed COVID-19 patients. Of those patients, only 58 (2.3%) had COPD as a comorbidity. The sample size of the included studies ranged from 21 to 1099 patients. Most of the studies were retrospectively conducted and all were studied in China, except one in the United States. The risk of bias ranged from 0.4 to 2.7; nine studies scored ≥ 2, which indicates low risk of bias (see, appendix 12). The overall crude mortality rate for COVID-19 was 7.4% (184/2473). There were no reports of the baseline characteristics of the 58 COPD patients that described their age, or severity of COPD airflow limitation. Smoking status was reported in eight studies, in which 193 confirmed COVID-19 cases were current smokers.
Figure 38. PRISMA flow diagram

Records identified through databases searching (n = 123)

Records after duplicates removed (n = 121)

Records screened (n = 121)

Records excluded (n = 60)

Full-text articles assessed for eligibility (n = 61)

Full-text articles excluded, with reasons (n = 46)
  - Not reporting COPD as a comorbidity (46)

Studies included in qualitative synthesis (n = 15)

Studies included in quantitative synthesis (n = 15)
Table 24. Characteristics of the included studies.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Country/ Type of study</th>
<th>Sample size</th>
<th>Age mean ±SD or median, range</th>
<th>Current Smokers</th>
<th>COPD patients</th>
<th>COPD Survived</th>
<th>COPD Non-Survived</th>
<th>Mortality rate for study/COPD</th>
<th>Severe cases for study/ severe COPD Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arentz M et al. 2020</td>
<td>United states/ Washington Retrospective study from February 20, 2020, and March 5, 2020</td>
<td>21</td>
<td>70 (43-59)</td>
<td>NA</td>
<td>7 (33.3%)</td>
<td>NA</td>
<td>NA</td>
<td>11 (52.4%)</td>
<td>NA</td>
</tr>
<tr>
<td>Guan et al. 2020</td>
<td>China/ 30 provinces Retrospective study from December 11, 2019, and January 29, 2020</td>
<td>1099</td>
<td>47 (35–58)</td>
<td>137 (12.5%)</td>
<td>12 (1.1%)</td>
<td>NA</td>
<td>NA</td>
<td>15 (1.4%)</td>
<td>173 (15.7%)/ 6 (3.4%)</td>
</tr>
<tr>
<td>Huang Y et al. 2020</td>
<td>China /Hubei province Retrospective study from December 2019 to January 2020</td>
<td>34</td>
<td>56.24 ± 17.14</td>
<td>NA</td>
<td>3 (8.82%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Huang et al. 2020</td>
<td>China/Wuhan Prospective study from Dec 16, 2019, to Jan 2, 2020</td>
<td>41</td>
<td>49 (41–58)</td>
<td>3 (7%)</td>
<td>1 (2%)</td>
<td>NA</td>
<td>NA</td>
<td>6 (15%)</td>
<td>29 (70.7%)/ 1 (3.44%)</td>
</tr>
<tr>
<td>Liu et al. 2020</td>
<td>China/Hubei province Retrospective study from December 30, 2019 to January 24, 2020</td>
<td>137</td>
<td>57 (20–83)</td>
<td>NA</td>
<td>2 (1.5%)</td>
<td>NA</td>
<td>NA</td>
<td>16 (11.7%)</td>
<td>NA</td>
</tr>
<tr>
<td>Study</td>
<td>Location</td>
<td>Description</td>
<td>N</td>
<td>M</td>
<td>F</td>
<td>Range</td>
<td>ICU (n=36)</td>
<td>Non-ICU (n=102)</td>
<td>Survived</td>
</tr>
<tr>
<td>-------</td>
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<td>-------------</td>
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<td>----------</td>
</tr>
<tr>
<td>Mo et al. 2020 (477)</td>
<td>China/Wuhan</td>
<td>Retrospective study from January 1st to February 5th</td>
<td>155</td>
<td>M= 86 (55.5%)</td>
<td>F= 69 (45.5%)</td>
<td>54 (42-66)</td>
<td>6 (3.9%)</td>
<td>5 (3.2%)</td>
<td>NA</td>
</tr>
<tr>
<td>Wang et al. 2020 (478)</td>
<td>China/Wuhan</td>
<td>Retrospective, single-center case series from January 1 to January 28, 2020</td>
<td>138</td>
<td>M= 75 (54.3%)</td>
<td>F= 63 (45.7%)</td>
<td>56 (42-68)</td>
<td>NA</td>
<td>4 (2.9%)</td>
<td>NA</td>
</tr>
<tr>
<td>Wu et al. 2020 (479)</td>
<td>China/Wuhan</td>
<td>Retrospective study from December 25, 2019, and January 26, 2020</td>
<td>201</td>
<td>M=128 (63.7%)</td>
<td>F=73 (36.3%)</td>
<td>51 (43-60)</td>
<td>NA</td>
<td>5 (2.5%)</td>
<td>NA</td>
</tr>
<tr>
<td>Wu J et al. 2020 (480)</td>
<td>China/ outside of the Wuhan area</td>
<td>Prospective study from January to February 2020</td>
<td>80</td>
<td>M= 42 (52%)</td>
<td>F= 38 (48%)</td>
<td>44 (11)</td>
<td>26 (33%)</td>
<td>3 (4%)</td>
<td>NA</td>
</tr>
<tr>
<td>Xu X et al. 2020 (481)</td>
<td>China/Guangzhou</td>
<td>Retrospective study from January 23, 2020, and February 4, 2020</td>
<td>90</td>
<td>M=39 (43%)</td>
<td>F= 51 (57%)</td>
<td>50 (18–86)</td>
<td>NA</td>
<td>1 (1%)</td>
<td>NA</td>
</tr>
<tr>
<td>Xu XW et al. 2020 (482)</td>
<td>China/Zhejiang province</td>
<td>Retrospective study from 10 January 2020 to 26 January 2020</td>
<td>62</td>
<td>M= 35 (56%)</td>
<td>F= 27 (44%)</td>
<td>41 (32-52)</td>
<td>NA</td>
<td>1 (2%)</td>
<td>NA</td>
</tr>
<tr>
<td>Yang et al. 2020 (483)</td>
<td>China/Wuhan</td>
<td>Retrospective study from late December 2019, and Jan 26, 2020.</td>
<td>52</td>
<td>M= 35 (67%)</td>
<td>F= 17 (33%)</td>
<td>59.7 (13.3)</td>
<td>2 (4%)</td>
<td>Survived=2 (10%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Study</td>
<td>Region</td>
<td>Study Design</td>
<td>Dates</td>
<td>Cases Total</td>
<td>Males</td>
<td>Females</td>
<td>Severe Cases</td>
<td>Survivors</td>
<td>Non-Survivors</td>
</tr>
<tr>
<td>---------------</td>
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<td>-----------------------------------</td>
<td>-------------------------------</td>
<td>-------------</td>
<td>-------</td>
<td>---------</td>
<td>--------------</td>
<td>------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Zhang et al. 2020 (484)</td>
<td>China/Wuhan</td>
<td>Retrospective study from January 16 to February 3, 2020</td>
<td>140</td>
<td>M=71 (50.7%)</td>
<td>69 (49.3%)</td>
<td>2 (1.4%)</td>
<td>Severe cases= 2 (3.4)</td>
<td>2 (1.4)</td>
<td>NA</td>
</tr>
<tr>
<td>Zhou et al. 2020 (485)</td>
<td>China/Wuhan</td>
<td>Retrospective cohort study from Dec 29, 2019 to Jan 31, 2020</td>
<td>191</td>
<td>M= 119 (62%)</td>
<td>72 (38%)</td>
<td>11 (6%)</td>
<td>Non-survivor= 5 (9%)</td>
<td>2 (1%)</td>
<td>4 (7%)</td>
</tr>
<tr>
<td>Zhu et al. 2020 (486)</td>
<td>China/Anhui province</td>
<td>Retrospective study from 24 January 2020 and 20 February 2020</td>
<td>32</td>
<td>M= 15 (47%)</td>
<td>17 (53%)</td>
<td>6 (18.7%)</td>
<td>2 (6%)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
➢ **Prevalence of COPD in confirmed COVID-19 cases:**

The pooled prevalence of COVID-19 patients who had COPD from all studies was 2% (95% CI, 1%–3%), Figure 39. The overall $I^2$ was 41.90%, $p$ 0.04.

**Figure 39. Pooled prevalence of COPD with confirmed COVID-19, (ES: effect size).**
➢ **Disease severity and mortality among COVID-19 COPD patients:**

Seven studies that included 35 COPD patients reported COVID severity in their analysis. With 63% (22/35) patient reported as severe compared to 37% (13/35) non-severe, this shows that COPD patients are at a higher risk of more severe COVID-2019 compared to patients without COPD 33.4% (409/1224) [calculated risk ratio (RR), 1.88 (95% CI, 1.4–2.4)]. Data from two studies (483, 485) including COPD patients with confirmed COVID-19 demonstrate 60% (6/10) mortality rate compared to mortality rate in patients without COPD 55% (86/157), [calculated RR, 1.10 (95% CI, 0.6–1.8)].

➢ **Smoking history and risk of COVID-19**

Smoking exposure including (current and ex-smokers) was reported in eight studies, with 221 confirmed COVID-19 cases. We assessed the prevalence of current smokers in all studies using meta-analysis of proportions of current smokers that had confirmed COVID-19. There was a pooled prevalence of 9%, (95% CI, 4%–14%), Figure 40. The overall $I^2$ was 92.49%, $p$ 0.001. Indeed, 22.30% (31/139) of current smokers and 46% (13/28) of ex-smokers had severe complications. Calculating the RR from these two studies showed that current smokers (31/108) were 1.45 times more likely [RR=1.45, 95% CI: 1.03–2.04] to have severe complications compared to former and never smokers (147/808) patients (473, 484). A higher mortality rate of 38.5% (5/13) was also seen among current smokers.
Figure 40. Pooled prevalence of current smokers with confirmed COVID-19, (ES: effect size).
8.3 Discussion:

To the best of our knowledge, this was the first systematic review and meta-analysis to develop an informed understanding of the prevalence, severity and mortality of COPD patients diagnosed with COVID-19. We provide an updated report in relation to smokers (487). Our main outcomes show that the prevalence of COPD in COVID-19 patients was low, but that the risk of severity (63%) and mortality (60%) were high, which indicates COPD patients with confirmed COVID-19 are at a greater risk of severe complications and death. Furthermore, the prevalence of current smokers in COVID-19 patients was 9% (95% CI, 4%–14%), and this was also associated with greater severity (22.30%) and mortality (38.5%).

We report a low prevalence of COPD patients in COVID-19 case series compared to the latest COPD prevalence rate in China, which was 13.6% (95% CI 12.0-15.2) and the global prevalence of COPD (9-10%) (69, 488). There was a low heterogeneity among the studies, which was 41.90%, p 0.04. This is expected since clinical and methodological diversity always occur in a meta-analysis. We speculate that patients may have not been diagnosed. Having a reliable estimate of the prevalence of COPD in COVID-19 cases, and likely outcomes, is crucial to ensure specific successful global preventive and treatment strategies for COPD patients. Bearing this in mind, in the included studies there was no report on COPD severity data and COPD-related comorbidities, which prevents us from assessing the impact of such essential information.
Although the COPD prevalence was not high in the included confirmed COVID-19 cases, COVID-19 causes a substantial burden on COPD patients with increased disease severity. This summary agrees with other results currently available only in pre-print (489, 490). Viral infections in COPD patients increase systemic inflammation with slow recovery of reported symptoms (491, 492). In addition to the effects of COVID-19, patients with COPD have various comorbidities, some of which are associated with increased risk of hospitalisation (209, 493, 494). According to recent systematic reviews, the prevalence of comorbidities in COVID-19 patients was high and these comorbidities were associated with increased disease severity (495, 496). Most of the studies that reported COPD severity defined severe cases as those who were admitted to ICU, had severe oxygenation, needed mechanical ventilation or death (473, 474, 477, 478, 482, 484). These studies did not give details about the underlying COPD. It would have been interesting to know if the frequency of previous exacerbations was linked to increased complications in COPD patients diagnosed with COVID-19. In general, those with severe case of COVID-19 were older and had more coexisting comorbidities than those with mild illness.

Data from two studies (483, 485) describing COPD patients with confirmed COVID-19 show a higher mortality rate at 60%. This concurs with pre-print studies that found similarly high mortality rates (489, 497-500). Despite the small number of patients that were analysed, this increases concerns about the prognosis of this vulnerable population. However, this high mortality rate could be attributed to several factors. The majority of COPD patients have
various comorbidities that may also be associated with mortality and related conditions may have been underreported because of the difficulties finding the specific cause of mortality (253). Moreover, in patients with severe COPD, respiratory failure is the principal cause of mortality, and this demands ICU intervention. It is possible that limited access to respiratory support as part of COVID-19 management may be contributing to this mortality, dependent on critical care capacity in each hospital or region. According to a recent COVID-19 report from Italy, the surge in patients requiring intensive care has been unmanageable, with 12% of positive cases requiring ICU admission (501), more than that reported in China (473, 483). As a consequence, patients were dying because mechanical ventilation could not be offered, on top of acute shortage of clinicians who were able to manage those patients (502, 503). Until now, the mechanisms of how COVID-19 increases COPD severity and mortality is unknown, and undoubtedly more research is needed to find the possible mechanisms that linked COVID-19 and increased severity and mortality of COPD patients.

Concerning smoking and COVID-19, our data showed a pooled prevalence of 9% current smokers, (95% CI, 4%–14%), lower than the reported prevalence of smoking in China that was 25.2% (25.1–25.4) (504). The overall I² was 92.49% among the studies, which indicates considerable heterogeneity. However, this was address by using random effect model to incorporate between-study variability of effect sizes. Such heterogeneity is expected due to different study designs, regions, and outcomes. Interestingly, we found that 22.30% (31/139) of current smokers and 46% (13/28) of ex-smokers had severe complications associated and greater
mortality reaching 38.5% in current smokers. The calculated RR from two studies showed that current smokers were 1.45 times more likely [RR=1.45, 95% CI: 1.03–2.04] to have severe complications compared to former and never smokers (473, 484). The impact of smoking history on vulnerability to COVID-19 has been explored but there is limited data on the contribution of tobacco smoking to the spread of and poor outcome in COVID-19. A recent systematic review on COVID-19 and smoking including five studies found that smoking was most likely associated with the negative outcomes. This recommended further research to explore this in more detail due to limited studies (487). Evidence from other respiratory viruses, respiratory syncytial virus, has shown that inhaled tobacco smoke raises the transmission rate and severity of viral respiratory tract infections (505). It seems there is underlying mechanisms behind this prevalence, as smoking has been related to higher expression of angiotensin converting enzyme 2 (ACE2) (the receptor for SARS-CoV-2) (pre-print) (506). However, as more reports globally from diverse racial and genetic contexts become available, differences in the production of ACE2 can be further evaluated and linked to how they lead to COVID-19 vulnerability in different groups (507).

Since the publication of our systematic review, several further systematic reviews have been published on COPD, smoking and COVID-19 (508-511) with results that are generally similar. The recent systematic review published in February 2021, on the association between smoking and negative outcomes among COVID-19 patients found that both current and former smoking significantly increased risk of COVID-19 severity and death (508). However, a different living systematic review and meta-analysis on
smoking and COVID-19 (searches up to 16th February 2021) reported that current smokers seem to be at a lower risk of SARS-CoV-2 infection than never smokers, but former smokers tend to be at higher risk of hospitalisation, increased disease severity, and death from COVID-19 (512). However, whether these relationships are causative remains unknown. Regarding the relationship between COPD and COVID-19, Gerayeli et al. conducted an updated systematic review and meta-analysis (511). They included 59 studies and found that COPD increased odds of hospitalisation (OR 4.23, 95% CI 3.65-4.90), ICU admission (OR 1.35, 95% CI 1.02-1.78), and death (OR 2.47, 95% CI 2.18-2.79). This was similar to what we had reported in our rapid, early systematic review.

To our knowledge, the present study is the first to systematically evaluate existing literature with a focus on risk of COVID-19 on COPD. For the first time, we conducted a meta-analysis using a random effects model to calculate the pooled prevalence of COPD in confirmed COVID-19 and examined outcomes. This increased the generalisability of our findings, as heterogeneity was addressed by incorporating between-study variability of effect sizes. We showed that COPD and smoking in COVID-19 were associated with greater disease severity and higher mortality. This review has some limitations. Few studies were eligible for inclusion and most of them come from China. Second, heterogeneity exists in location, setting, and design. The reported clinical characteristics were not available in most of the studies at the time of analyses. This work has several clinical and research implications. It highlights the global prevalence and the clinical effects of COVID-19 on COPD patients and smokers. As COPD patients
are at an increased risk of severe outcomes if they became infected with COVID-19, it is recommended that patients and clinicians establish effective plans for ensuring prevention, such as using tele-medicine to ensure that COPD receive the best care (513, 514). We strongly advocate public awareness campaigns concentrating on ways to achieve smoking cessation among smokers, and it is possible that an improvement in cessation rates will help to reduce the spread of SARS-CoV-2. Future studies should investigate the mechanisms between COPD, smoking and COVID-19 infection.

8.4 Conclusion

Though COPD prevalence in reported COVID-19 cases is low, COVID-19 infection is associated with significant severity and mortality in COPD. There was also increased risk of severe disease and mortality in current smokers. Effective preventive measures are urgently required to reduce COVID-19 risk on COPD patients and current smokers.
9.1 Introduction

COPD affects 251 people around the world (68). In addition to daily symptoms such as breathlessness and cough, and associated functional limitation, many people living with COPD are susceptible to acute deteriorations in respiratory health termed ‘exacerbations’ (214). Most exacerbations are driven by airway infection. People living with COPD say that exacerbations are the most disruptive aspect of their disease (515) and frequent exacerbations are associated with more rapid disease progression (191), impaired quality of life (516) and excess mortality (517). Exacerbations therefore cause most of the costs associated with COPD: personal cost to those affected, but also financial costs to health services (518) and to society more broadly. Preventing exacerbations is a major goal in COPD care, and guidelines summarise the evidence in support of a range of exacerbation reduction interventions (1), both pharmacological and non-pharmacological. Despite development of new interventions, and better targeting of older interventions, exacerbation prevention is incompletely effective even when optimally deployed. Moreover, there has not been a single new class of drugs licenced to treat exacerbations in more than 30 years. The transformation that is required in prevention and treatment of COPD exacerbations demands robust research (519). However, respiratory research has been neglected in relation to disease burden (520). There is a strong argument for prioritising research that addresses the questions most important to those living with the condition and research agendas set by academics or the pharmaceutical industry do not necessarily reflect the priorities of patients and health-services (521). Completed robustly, such
joint patient-clinician PSPs can themselves be more successful in supporting requests for funding. Despite the high burden of COPD exacerbations, there is no existing research prioritisation exercise specific to this area.

9.2 Methods

The JLA has pioneered robust and transparent methodology to bring together patients, carers, and clinicians as equal partners in PSPs to systematically collect ‘uncertainties’ and prioritise resulting research questions. The JLA was established as a non-profit organisation in 2004, sitting within the NIHR – the research arm of the UK NHS. More than 50 PSPs have now been completed. The final output is a list of top-ten questions that patients and clinicians want the research community to address. We have completed a JLA PSP in Exacerbations of COPD, using the stages described below. Further detail on the Methodology applied can be found in the JLA Guidebook, and in the Method Chapter. In brief, there are five stages: 1) establishing the PSP and agreeing project scope, 2) gathering and identifying ‘uncertainties’ using a survey, 3) summarising and processing uncertainties to develop over-arching research questions, 4) interim prioritisation of these questions using a Web survey, 5) a final priority setting workshop to reach consensus on the top-ten questions. The work was funded by the British Lung Foundation. Ethics permission was not required. The steering group agreed and published the PSP protocol and scope [https://www.jla.nihr.ac.uk/priority-setting-partnerships/copd-](https://www.jla.nihr.ac.uk/priority-setting-partnerships/copd-).
**Figure 41.** Five-stage James Lind Alliance Priority Setting Partnership for Exacerbations of COPD: a summary.

**Stage 1: Establishing the Priority Setting Partnership and Agreeing the Project Scope**
- From February 2019 to April 2019
- 14 participants (3 patients, 9 clinicians, 1 information specialist and 1 JLA advisor).

**Stage 2: Gathering and identifying questions (first survey)**
- 18th April 2019–12th July 2019
- 1,548 registered
- 571 respondents
- 1912 total raw submissions identified [patients (n=1238), Carer/relative (n=139), HCPs (n= 508), others (n= 27)].

**Stage 3: Summarising the responses and processing ‘uncertainties’**
- Processing responses August 2019 - March 2020
- Removed 1121 "out of scope" responses
- In scope responses: 791 reworded into 59 indicative questions.
- Prevention (226 reduced to 26), Diagnosis (326 to 15) and Treatment (239 to 18)
- One of the indicative questions was removed by the steering group because it covered ‘miscellaneous other interventions’ and could not be searched.
- Existing evidence checked in Cochrane database, GOLD and NICE guidelines
- Seven indicative questions answered
- 51 questions go forward to interim prioritisation

**Stage 4: Interim prioritisation (second survey)**
- From 29th July 2020 – 15th September 2020
- 236 participants registered to complete online survey
- 191 were respondents
- Rankings created separately for lay and clinician responders, then combined with equal weight
- Top 15 ranks identified to go forward to final workshop (=16 questions)

**Stage 5: Priority setting workshop**
- April 1st 2021, full-day online workshop
- 20 participants
- Top ten question rank agreed
9.3 Results:

9.3.1 Gathering and identifying questions (first survey)
A total of 1,548 participants registered on the first survey and 571 completed the online survey and proposed one or more questions. A total of 1912 raw submissions were identified from 571 responses (sometimes more than one question was asked by a participant). The characteristics of the respondents to the first survey are summarised in Table 25. They included 418 people living with COPD, 39 carers and 110 healthcare professionals. Respondents took part from across the UK and 47% were aged 50-69 years.

9.3.2 Summarising the responses and processing ‘uncertainties’
The 1912 individual statements submitted in the first survey were reviewed and re-categorised into three major themes: diagnosis, prevention, and treatment. A total of 1121 statements were out of scope leaving 791 questions in scope. Out of scope questions included requests for specific advice, and questions about COPD that were not related to exacerbations. Using thematic analysis, the 791 questions were re-formulated by reviewing similarity, combining, and rephrasing to create 59 overarching questions. At the evidence checking stage, seven had been adequately answered by evidence, and one question was removed by the steering committee because it covered ‘miscellaneous other interventions’ that could not be further assessed (Figure 41). This left a total of 51 unanswered research questions which went forward to the interim prioritisation stage.
Table 25. Demographic characteristics of respondents to the JLA COPD Exacerbation PSP.

<table>
<thead>
<tr>
<th>Participant Characteristics</th>
<th>First survey</th>
<th>Second survey</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL PARTICIPANTS REGISTERED</td>
<td>1,548</td>
<td>236</td>
</tr>
<tr>
<td>➢ Respondents</td>
<td>571</td>
<td>191</td>
</tr>
<tr>
<td>GENDER</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Male</td>
<td>138 (24.3%)</td>
<td>124 (65.0%)</td>
</tr>
<tr>
<td>➢ Female</td>
<td>430 (75.0%)</td>
<td>64 (33.5%)</td>
</tr>
<tr>
<td>➢ Prefer not to say</td>
<td>3 (0.5%)</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>AGE (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ 18-29</td>
<td>16 (2.8%)</td>
<td>5 (2.5%)</td>
</tr>
<tr>
<td>➢ 30-49</td>
<td>97 (17.0%)</td>
<td>67 (35.0%)</td>
</tr>
<tr>
<td>➢ 50-69</td>
<td>269 (47.1%)</td>
<td>70 (37.0%)</td>
</tr>
<tr>
<td>➢ 7-79</td>
<td>165 (28.9%)</td>
<td>42 (22.0%)</td>
</tr>
<tr>
<td>➢ ≥ 80</td>
<td>23 (4.0%)</td>
<td>6 (3.0%)</td>
</tr>
<tr>
<td>➢ Prefer not to say</td>
<td>1 (0.2%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Race and Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Any other Mixed/Multiple ethnic background</td>
<td>6 (1.05%)</td>
<td>5 (2.5%)</td>
</tr>
<tr>
<td>➢ Arab</td>
<td>1 (0.17%)</td>
<td>3 (1.5%)</td>
</tr>
<tr>
<td>➢ Asian-Asian British</td>
<td>13 (2.27%)</td>
<td>13 (7%)</td>
</tr>
<tr>
<td>➢ Black / Black British</td>
<td>1 (0.17%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>➢ White</td>
<td>548 (95.9%)</td>
<td>164 (86%)</td>
</tr>
<tr>
<td>➢ Prefer not to say</td>
<td>2 (0.35%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Experience</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Lived experience of COPD</td>
<td>418 (73.29%)</td>
<td>74 (39%)</td>
</tr>
<tr>
<td>➢ Carer/Partner/Relative of someone with COPD or who died with COPD</td>
<td>39 (6.8%)</td>
<td>9 (5.0%)</td>
</tr>
<tr>
<td>➢ Health or social care practitioner</td>
<td>110 (19.26%)</td>
<td>101 (53%)</td>
</tr>
<tr>
<td>➢ Others</td>
<td>4 (0.70%)</td>
<td>7 (3.0%)</td>
</tr>
<tr>
<td>Primary HCPs work setting.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>➢ Community Care</td>
<td>39 (39.0%)</td>
<td>42 (41.5%)</td>
</tr>
<tr>
<td>➢ Primary care</td>
<td>25 (22.7%)</td>
<td>13 (13.0%)</td>
</tr>
<tr>
<td>➢ Secondary care</td>
<td>46 (41.8%)</td>
<td>46 (45.5%)</td>
</tr>
</tbody>
</table>
9.3.3 Summarising the responses and processing ‘uncertainties’

The 1912 individual statements submitted in the first survey were reviewed and re-categorised into three major themes: diagnosis, prevention, and treatment. A total of 1121 statements were out of scope leaving 791 questions in scope. Out of scope questions included requests for specific advice, and questions about COPD that were not related to exacerbations. Using thematic analysis, the 791 questions were re-formulated by reviewing similarity, combining, and rephrasing to create 59 overarching questions. At the evidence checking stage, seven had been adequately answered by evidence, and one question was removed by the steering committee because it covered ‘miscellaneous other interventions’ that could not be further assessed (Figure 41). This left a total of 51 unanswered research questions which went forward to the interim prioritisation stage.

9.3.4 Interim prioritisation (second survey)

A total of 236 participants registered for the interim prioritisation survey and 191 completed the survey. The characteristics of the respondents are also presented in Table 25. Compared to the initial survey there was a higher proportion of men 124 (65.0%) and a greater proportion of health-care professionals 101 (53%). Delivery of care for people with COPD during COVID-19 has not changed top priorities list in 138 (72.3%) respondents. Table 26 shows the 51 questions with overall ranking, and rankings categorised by patient/carer and clinicians’ groups separately. As there were two questions ranked 15th, 16 questions went forward to the final priority setting workshop.
Table 26. Ranked 51 questions, with joint rank giving equal weight to Lay and HCP ranks. The top 15 questions that went forward to the final workshop are shaded green.

<table>
<thead>
<tr>
<th>Joint Rank</th>
<th>Research Question</th>
<th>Lay rank</th>
<th>HCP rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>What is the best way to tell the difference between an exacerbation and a different cause of changing symptoms in a person with COPD?</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>=2</td>
<td>What is the best way to treat breathlessness during a COPD exacerbation?</td>
<td>=2</td>
<td>=8</td>
</tr>
<tr>
<td>=2</td>
<td>What is the best way to tell the start of an exacerbation from day-to-day variation in symptoms?</td>
<td>=7</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>What can prevent exacerbations of COPD?</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>=5</td>
<td>What is the optimal combination of treatments at COPD exacerbations and what is the best way to decide this for individual patients?</td>
<td>=13</td>
<td>6</td>
</tr>
<tr>
<td>=5</td>
<td>Why do some exacerbations recur following treatment?</td>
<td>11</td>
<td>=8</td>
</tr>
<tr>
<td>7</td>
<td>What is the value of integrated respiratory teams in preventing COPD exacerbations and COPD admissions?</td>
<td>=20</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Question</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------------------------------------------------</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>8</td>
<td>How does the presence of anxiety and depression affect the prevention, diagnosis and treatment of COPD exacerbations?</td>
<td>=20</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>What factors determine whether someone with a COPD exacerbation can be managed at home or needs admission to hospital?</td>
<td>=7</td>
<td>19</td>
</tr>
<tr>
<td>10</td>
<td>Does regular exercise reduce the risk of having an exacerbation (and to what level of exercise)?</td>
<td>=13</td>
<td>=16</td>
</tr>
<tr>
<td>11</td>
<td>When should a COPD exacerbation be treated with steroids alone, antibiotics alone or both?</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>11</td>
<td>Which palliative care regimes should be used to treat an exacerbation, in which circumstances, and what are the potential benefits? ('Palliative care' is defined by the World Health Organisation as an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering).</td>
<td>=14</td>
<td>=16</td>
</tr>
<tr>
<td>13</td>
<td>What are the risks and benefits of 'rescue packs' used to prevent COPD exacerbations, and how should they be best used?</td>
<td>=11</td>
<td>21</td>
</tr>
<tr>
<td>14</td>
<td>What are the risks and benefits of long-term antibiotics to prevent COPD exacerbations, and how should they be best used?</td>
<td>9</td>
<td>=25</td>
</tr>
<tr>
<td>14</td>
<td>What is the role of nutrition in the prevention and treatment of exacerbations?</td>
<td>=20</td>
<td>14</td>
</tr>
<tr>
<td>=14</td>
<td>What are the associations between co-morbidity and risk of COPD exacerbations?</td>
<td>24</td>
<td>=10</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>=17</td>
<td>Which biomarkers can be used to help diagnose a COPD exacerbation and how reliable are they?</td>
<td>34</td>
<td>1</td>
</tr>
<tr>
<td>=17</td>
<td>If a patient suspects a COPD exacerbation, when should they start their own treatment ('rescue pack') for exacerbation?</td>
<td>=2</td>
<td>33</td>
</tr>
<tr>
<td>19</td>
<td>Is the best approach to diagnosis of exacerbations to use a COMBINATION of symptoms, biomarkers and physiology?</td>
<td>=34</td>
<td>=6</td>
</tr>
<tr>
<td>=20</td>
<td>If a patient suspects a COPD exacerbation, when should they contact a health-care professional?</td>
<td>=2</td>
<td>40</td>
</tr>
<tr>
<td>=20</td>
<td>Are there different types of exacerbations, and what is the best way to classify exacerbations into different types?</td>
<td>32</td>
<td>=10</td>
</tr>
<tr>
<td>=20</td>
<td>What are the risk factors for having COPD exacerbations?</td>
<td>=13</td>
<td>29</td>
</tr>
<tr>
<td>23</td>
<td>Which environmental factors (such as weather, pollution, allergens and temperature) affect the risk of exacerbation and what should I do about it?</td>
<td>=13</td>
<td>31</td>
</tr>
<tr>
<td>=24</td>
<td>What are the risks and benefits of oral and inhaled steroids to prevent COPD exacerbations, and how should they be best used?</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>=24</td>
<td>Does singing prevent or reduce the severity of COPD exacerbations?</td>
<td>=14</td>
<td>=33</td>
</tr>
<tr>
<td></td>
<td>Question</td>
<td>=32</td>
<td>=16</td>
</tr>
<tr>
<td>---</td>
<td>-------------------------------------------------------------------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>26</td>
<td>Which airway clearance regimes should be used to treat an exacerbation and what are the potential benefits and side-effects?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>How can recovery from an exacerbation be best assessed and monitored?</td>
<td>=34</td>
<td>15</td>
</tr>
<tr>
<td>28</td>
<td>How do the family of medicines called ‘macrolides’ prevent exacerbations?</td>
<td>29</td>
<td>22</td>
</tr>
<tr>
<td>29</td>
<td>What is the role of the bacteria that live on and in us (our ‘microbiome’) in determining the risk of exacerbation</td>
<td>45</td>
<td>=10</td>
</tr>
<tr>
<td>30</td>
<td>What is the benefit of taking a sputum sample during an exacerbation of COPD?</td>
<td>=24</td>
<td>=33</td>
</tr>
<tr>
<td>31</td>
<td>What is the best way to treat cough during a COPD exacerbation?</td>
<td>=24</td>
<td>=33</td>
</tr>
<tr>
<td>32</td>
<td>What are the risks and benefits of the family of medicines called ‘statins’ to prevent COPD exacerbations, and how should they be best used?</td>
<td>=24</td>
<td>38</td>
</tr>
<tr>
<td>33</td>
<td>What can a person with COPD do to reduce the risk of picking up an infection from other people?</td>
<td>=13</td>
<td>49</td>
</tr>
<tr>
<td>34</td>
<td>What is the best way to choose the right prevention strategy for a particular person?</td>
<td>=34</td>
<td>=29</td>
</tr>
<tr>
<td>35</td>
<td>How should patients with a clinical diagnosis of a COPD exacerbation be looked after if there is no ‘official diagnosis’ with spirometry?</td>
<td>42</td>
<td>=22</td>
</tr>
<tr>
<td></td>
<td>Question</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------------------------------------------------</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>36</td>
<td>What are the risks and benefits of, and which complementary/alternative medicine approaches prevent COPD exacerbations, and how should they be best used?</td>
<td>=20</td>
<td>45</td>
</tr>
<tr>
<td>37</td>
<td>What is the value of assessing physiology at an exacerbation of COPD?</td>
<td>=45</td>
<td>=22</td>
</tr>
<tr>
<td>38</td>
<td>What are the risks and benefits of the family of medicines called ‘monoclonals’ to prevent COPD exacerbations, and how should they be best used?</td>
<td>40</td>
<td>28</td>
</tr>
<tr>
<td>39</td>
<td>Which psychological support regimes can be used to prevent exacerbations, in which circumstances, and what are the potential benefits?</td>
<td>49</td>
<td>=19</td>
</tr>
<tr>
<td>40</td>
<td>What are the risks and benefits of the family of medicines called 'phosphodiesterase inhibitors' to prevent COPD exacerbations, and how should they be best used?</td>
<td>=29</td>
<td>=40</td>
</tr>
<tr>
<td>41</td>
<td>What are the risks and benefits of the family of medicines called 'bronchodilators', alone and in combination, used to prevent COPD exacerbations, and how should they be best used?</td>
<td>=24</td>
<td>=49</td>
</tr>
<tr>
<td>42</td>
<td>Which oral/inhaled steroid regime (drug, dose, length; first line, second line) should be used to treat an exacerbation and what are the potential benefits and side-effects?</td>
<td>=34</td>
<td>=40</td>
</tr>
<tr>
<td>43</td>
<td>What is the relationship between loneliness and COPD exacerbations?</td>
<td>=49</td>
<td>=25</td>
</tr>
<tr>
<td>Question</td>
<td>Value1</td>
<td>Value2</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
<td>--------</td>
<td>--------</td>
<td></td>
</tr>
<tr>
<td>What are the risks and benefits of oxygen to prevent COPD exacerbations, and how should it be best used?</td>
<td>≈29</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>Which psychological support regimes should be used to treat an exacerbation, in which circumstances, and what are the potential benefits?</td>
<td>≈49</td>
<td>≈31</td>
<td></td>
</tr>
<tr>
<td>Which mucolytic regime (drug, dose, length; first line, second line) should be used to treat an exacerbation and what are the potential benefits and side-effects?</td>
<td>44</td>
<td>≈38</td>
<td></td>
</tr>
<tr>
<td>What is the value of starting exacerbation treatment as soon as possible?</td>
<td>≈34</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>What is the value of medical imaging at an exacerbation of COPD?</td>
<td>≈40</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Which antibiotic regime (drug, dose, length; first line, second line) should be used to treat an exacerbation and what are the potential benefits and side-effects?</td>
<td>≈45</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>Which bronchodilator regime (drug, dose, length, and route) should be used to treat an exacerbation and what are the potential benefits and side-effects?</td>
<td>≈42</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>How does the presence of anaemia affect the diagnosis and treatment of COPD exacerbations?</td>
<td>48</td>
<td>≈46</td>
<td></td>
</tr>
</tbody>
</table>
9.3.5 Priority setting workshop

The agreed top ten research questions are presented as Table 27, including the final rank of all 16 questions discussed at the workshop. Six were included in the top ten ranked questions in the interim prioritisation survey. Two questions address diagnosis, five address prevention and two address treatment. Table 27 includes the final rank of all 16 questions discussed in the final workshop.

Table 27. The final top ten research priorities for COPD exacerbations, and rank of all sixteen questions discussed at the final workshop.

<table>
<thead>
<tr>
<th>Rank</th>
<th>Top 10 research priorities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>What can prevent exacerbations of COPD?</td>
</tr>
<tr>
<td>2</td>
<td>What is the best way to tell the start of an exacerbation from day-to-day variation in symptoms?</td>
</tr>
<tr>
<td>3</td>
<td>What is the best way to tell the difference between an exacerbation and a different cause of changing symptoms in a person with COPD?</td>
</tr>
<tr>
<td>4</td>
<td>What is the optimal combination of treatments at COPD exacerbations and what is the best way to decide this for individual patients?</td>
</tr>
<tr>
<td>5</td>
<td>What are the associations between co-morbidity and risk of COPD exacerbations?</td>
</tr>
<tr>
<td>6</td>
<td>Which palliative care regimes should be used to treat an exacerbation, in which circumstances, and what are the potential benefits?</td>
</tr>
<tr>
<td>7</td>
<td>Why do some exacerbations recur following treatment?</td>
</tr>
<tr>
<td>8</td>
<td>What are the risks and benefits of 'rescue packs' used to prevent COPD exacerbations, and how should they be best used?</td>
</tr>
<tr>
<td>9</td>
<td>How does the presence of anxiety and depression affect the prevention, diagnosis, and treatment of COPD exacerbations?</td>
</tr>
<tr>
<td>10</td>
<td>What are the risks and benefits of long-term antibiotics to prevent COPD exacerbations, and how should they be best used?</td>
</tr>
<tr>
<td>11</td>
<td>What is the best way to treat breathlessness during a COPD exacerbation?</td>
</tr>
<tr>
<td>12</td>
<td>When should a COPD exacerbation be treated with steroids alone, antibiotics alone or both?</td>
</tr>
<tr>
<td></td>
<td>Question</td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>13</td>
<td>What is the value of integrated respiratory teams in preventing COPD exacerbations and COPD admissions?</td>
</tr>
<tr>
<td>14</td>
<td>What is the role of nutrition in the prevention and treatment of exacerbations?</td>
</tr>
<tr>
<td>15</td>
<td>What factors determine whether someone with a COPD exacerbation can be managed at home or needs admission to hospital?</td>
</tr>
<tr>
<td>16</td>
<td>Does regular exercise reduce the risk of having an exacerbation (and to what level of exercise)?</td>
</tr>
</tbody>
</table>

### 9.4 Discussion

We have completed the first research prioritisation exercise for COPD exacerbations, with an equal voice to patient and clinicians’ preferences using the well-established, robust, and transparent JLA methodology. This has produced a top ten list of research priorities in COPD exacerbations that can be used by both researchers and funders to shape future research in diagnosis, prevention, and treatment of COPD exacerbation. Our findings demonstrate important uncertainties and gaps in the existing evidence, pinpointing the main unanswered areas for future investigations. There is considerable unmet need in the prevention, diagnosis and management of COPD exacerbations and research is known not to reflect disease burden (522). Research is of greatest value where it meets the priorities of those directly affected by the condition, both patients and clinicians.

Prioritising research questions using rigorous methodology will position the COPD community to submit commissioned and investigator-led research calls in the knowledge that these have been transparently co-developed via a multi-professional team, in partnership with patients and carers, and that they are considered both relevant to people living with COPD and practice changing. Research proposals developed in this way are much more likely
to be funded. In 2007, for example, a Research Prioritisation was conducted in asthma (6), resulting in a successful NIHR (HTA) funding and an answer to the question of whether breathing exercises improve quality of life (373). Co-producing research priorities is also advocated by the US Patient-Centred Outcomes Research Institute, and priorities developed in this way have a track-record of successful funding (523).

The highest rated question was to identify better ways to prevent exacerbations. Despite the availability of many pharmacological and non-pharmacological interventions to reduce exacerbations, these are incompletely effective even when optimally deployed and our results highlight the importance of developing and testing novel approaches. Specific questions relating to prevention focused on understanding links between co-morbidity and exacerbation risk including optimal ways to manage anxiety and depression and COPD, and optimal use of antibiotic prophylaxis which whilst known to be effective is associated with adverse effects including the development of bacterial resistance. One question sought to better understand exacerbation recurrence (with the ultimate aim to intervene and prevent recurrent exacerbations). Exacerbation recurrence is a particular problem following hospitalised exacerbations with around one in four people re-admitted within a month (195).

Regarding diagnosis, two questions relate to the important point that a COPD exacerbation is a clinical diagnosis of exclusion without a diagnostic test. One seeks to find ways to assist patients and clinicians to differentiate the start of an exacerbation from day-to-day symptoms variation in COPD, whilst a second aims to assist differentiation of exacerbation from other
causes of symptom deteriorations that may mimic (or complicate) COPD exacerbations – for example cardiac dysfunction, pneumonia and pulmonary embolus.

Questions relating to treatment focused on the role of ‘rescue packs’, which treatments to use to treat exacerbation in which people (stratified medicine) and – notably – a question on the optimal use of palliative care approaches in COPD. These top ten priorities will require diverse methods to study complimentary, and it is important to note that the longer list of 51 questions contains important uncertainties worthy of further study.

The key strength of our study is the use of robust JLA methods for establishing and supporting Priority Setting in transparent processes lead by a broad range of experience and expertise in the steering group supervised by JLA methodological experts. Such JLA methods are well established and conducted across different diseases. Whilst we had a large sample size, we had fewer people from BAME backgrounds. People mostly responded online which could risk excluding those without access to such resource. The study was conducted in the UK and whilst likely to be of relevance in other high-income settings, our work does not address priorities for COPD exacerbation research in low- and middle-income countries.

In the UK, we will now lobby for research commissioned on these top ten priorities. Indeed, a question on developing ways to better support COPD patients to tell the difference between an exacerbation and day-to-day symptom variation has already been included as a theme of interest in an NIHR call (391).
9.5 Conclusion:

To conclude we have rigorously identified and prioritised major research priorities relating to exacerbations of COPD, as a partnership between patients and clinicians, therefore positioning researchers to apply for investigator-led awards, and lobby for commissioned calls, to address these prioritised topics.
10. Discussion, conclusion, and suggested future studies
The major findings of this PhD thesis are summarised in this chapter, along with recommendations for future research.

The following are the main results of this PhD:

1. **Risk factors for all-cause hospital readmission following exacerbation of COPD: a systematic review and meta-analysis**
   - Comorbidities, previous exacerbations and hospitalisations, and increased length of stay were the major risk factors for both 30- and 90-day readmission.
   - Our meta-analysis revealed that heart failure, renal failure, depression, and alcohol use were all associated with an increased risk of 30-day all-cause COPD readmission, whereas being female was a protective factor.
   - The review summarises current evidence to inform guideline developers about the importance of carefully reviewing the discharge processes and to ensure that comorbidities are fully assessed as part of routine COPD management.
   - Not all risk factors for re-admission that we identified are modifiable and therefore future research should focus on developing robust risk models to predict patients with COPD at high risk of potentially avoidable hospital readmission, with interventions tested to mitigate modifiable risk to improve outcomes for patients and health services.
2- Relationship between FOT Parameters and Clinical Characteristics in Hospitalised COPD Exacerbation

➢ We have found that EFL measured by $\Delta X_{rs_{5Hz}}$ is prevalent at COPD exacerbation hospitalisations, in both upright and supine positions, 39% and 50% respectively.

➢ EFL and resistance measured by $R_{rs_{5Hz}}$ negatively correlated with FEV$_1$, the gold-standard marker of airflow limitation.

➢ Those with EFL had lower FEV$_1$ and FVC and higher $R_{rs_{5Hz}}$ and BMI compared to those without EFL.

➢ During recovery from acute exacerbations, a reduction in EFL was observed in association with improvement in breathlessness.

➢ Detecting EFL using FOT during COPD exacerbations could be used to identify those with more severe physiological disturbance and to assess their response to treatment during recovery. FOT has advantages over spirometry.

3- Predictors of 30- and 90-day COPD Exacerbation Readmission: A Prospective Cohort Study

➢ The 30-day and 90-day hospital readmission rates were 38% and 56%, respectively.

➢ Previous exacerbations, higher CAT score at discharge, frailty, low PIFR and increased length of stay were significantly associated with 30-day COPD readmission.
➢ 90-day COPD readmission were significantly associated with previous exacerbations and hospitalisations, higher CAT score at discharge, frailty, depression, and low PIFR.

➢ For the first time, we found EFL measured by $\Delta X_{rs5Hz}$ in the supine position at discharge was a significant predictor for 90 days readmission.

➢ The best predictive variable in the multivariable analysis for both 30- and 90-day COPD readmission was PIFR at discharge.

➢ Sub-optimal PIFR (<60/min) was seen in 46% (38/82) at admission and 40% (33/82) at discharge.

➢ Our findings help determine people at highest risk of readmission and support optimisation of COPD care prior to discharge.

4- Pilot study: Changes in inspiratory and expiratory flow limitation, and physical activity following discharge from hospital after acute exacerbation of COPD

➢ We found no significant changes from discharge to 30-day follow-up in CAT, breathlessness, spirometry, FOT, PIFR and anxiety scores.

➢ Physical activity steadily increased, in which those patients with higher steps in first seven days post discharge had greater overall steps at 30-day follow-up.

➢ An improvement in breathlessness and symptoms (CAT score) was associated with improvement in spirometry values and depression scores, but not with other variables including FOT, PIFR and physical activity.
➢ It was challenging to achieve follow-up with our cohort of patients because of the tendency to relapse within 30-day following discharge as well as because of the COVID-19 pandemic and related governmental measures such as lockdown, quarantine, and social distancing.

5- Prevalence, Severity and Mortality associated with COPD and Smoking in patients with COVID-19: A Rapid Systematic Review and Meta-Analysis

➢ This was the first systematic review and meta-analysis to develop an informed understanding of the prevalence, severity and mortality of COPD patients diagnosed with COVID-19.

➢ The prevalence of COPD in COVID-19 patients was lower than expected at 2% (95% CI, 1%–3%).

➢ The risk of severity and mortality were high, which indicates COPD patients with confirmed COVID-19 were at a greater risk of severe complications and death.

➢ The prevalence of current smokers in COVID-19 patients was 9% (95% CI, 4%–14%), and this was also associated with greater severity and mortality.
6- Research Priorities in Exacerbations of COPD: results of a James Lind Alliance Priority Setting Partnership

➢ We completed the first research prioritisation exercise for COPD exacerbations, with an equal voice to patient and clinicians’ preferences using the well-established, robust, and transparent JLA methodology.

➢ Our findings demonstrate important uncertainties and gaps in the existing evidence, determining the main unanswered areas for future investigations.

➢ We reported a longer list of 51 questions contains important uncertainties worthy of further study.

➢ This project produced a top ten list of research priorities in COPD exacerbations that can be used by both researchers and funders to shape future research in diagnosis, prevention, and treatment of COPD exacerbation.

➢ The top priority was to identify better approaches to prevent exacerbations.
Discussion:
In brief, my PhD thesis has identified existing risk factors for all-cause COPD readmission in previous studies, prospective predictors of COPD exacerbation readmission within 30 and 90 days, changes in lung function measures (spirometry, FOT and PIFR) and physical activity following discharge from hospital and research priorities in COPD exacerbations. Given the increasing number of people diagnosed with COPD around the world, and the fact that exacerbations are a leading cause of hospitalisation and death in COPD patients, identifying better solutions to prevent such clinical burden, particularly better prevention strategies for COPD exacerbation and their recurrence are urgently needed.
People with COPD have been let down by the respiratory community's failure to address the problem of high re-admission rates after hospitalisation for COPD exacerbations. Patients with COPD who had frequent hospitalisations are at a higher risk of death, with a five-year survival rate of just 20% (202). Despite evidence showing exacerbations, especially hospitalised exacerbations, cause much of the health-care burden and expenses associated with COPD, we continue to ignore re-admissions. The cost of a hospitalised exacerbation is eight times that of a community-treated event (524). Therefore, more research into the mechanism of re-admissions and exacerbation recurrence, as well as better strategies to avoid exacerbations, is needed.
Our review of the current literature identified that co-morbidities, previous exacerbations and hospitalisation, and increased length of stay were significant risk factors for all-cause readmission. Particularly, heart failure, renal failure, depression, and alcohol use were all associated with an increased risk of 30- and 90-day re-admission. These findings highlight inadequate identification and management of co-morbidities at discharge which can inform guideline developers about the importance of carefully reviewing the discharge processes to ensure that comorbidities are fully managed along with routine COPD management. As not all the risk factors for re-admissions that we found are modifiable, future research should focus on conducting prospective studies to predict patients with COPD who are at high risk of hospital readmission.

To address risk factors for readmission prospectively, we conducted a cohort study to identify predictors of COPD exacerbation readmission within 30 and 90 days. We concluded that previous exacerbations, higher CAT score at discharge, frailty, low PIFR and increased length of stay were significantly associated with 30- and 90-day COPD readmission. Furthermore, we found EFL measured by ΔXrs5Hz in supine position at discharge to be a significant predictor for 90 days readmission. Such findings are important because we identified potential predictors (PIFR, CAT, frailty and EFL index) of readmission that would support optimisation of care prior to discharge by highlighting factors that can be modified. Our findings emphasise the value of discharge assessments in predicting COPD readmission risk. Clinicians should assess PIFR at discharge to guide
COPD treatment options, which may reduce readmission risk. In addition to the assessment of symptoms using CAT, FOT could be used as a complimentary option to categorise those patients with EFL at discharge who may benefit from additional therapy and early follow-up, aiming to mitigate symptoms and unresolved EFL, and reduce readmission. FOT is of potential clinical value by providing a non-invasive, objective, and effort-independent technique to measure lung function parameters during exacerbations requiring hospital admission, as has been discussed in Chapter 4. Identifying patients with severe frailty would facilitate potential rehabilitation programmes following discharge that could decrease readmission, such as post-exacerbation PR (525). The result of this thesis highlighted the need for more work to optimise care prior discharge and implement evidence-based interventions to reduce COPD exacerbation readmissions.

Discharge from hospital represents a critical time for sickest COPD patients as evidence indicates that people living COPD are at most risk of COPD recurrence in the time immediately after an initial exacerbation, even when that first event has fully recovered (526). In our pilot study that re-evaluated patients' recovery at 30-day following discharge, we found no significant changes from discharge to 30-day follow-up in CAT, breathlessness, spirometry, FOT, PIFR and anxiety sores. This finding indicates nonrecovery of the previous exacerbation at 30-day follow-up. This is also reflected in the low step-count [1343 (419-2552) step/day] we found at 30-day follow-up, which indicates unrecovered respiratory symptoms during
the recovery following discharge may reduce physical activity. However, we were limited by total number of patients who attended the follow-up, that resulted because of the tendency to relapse within 30-day following discharge as well as we could not offer follow-up to all patients because of the COVID-19 pandemic.

Given that the majority of readmissions to hospital will be COPD related, respiratory tools to identify which patients are at highest readmission risk will assist in reducing the burden on health care systems (527). In my clinical studies I identified three simple tools (FOT, PIFR and frailty score) that could be used during hospitalisation to determine the likelihood of readmission. There are advantages for these tools including that they are cheap and simple to perform, and all multidisciplinary teams can be trained to interpret them and stratify those who might be at higher risk of hospital readmission. Although administering FOT is generally easy, potential causes of error and variances include changes in breathing, bacterial filters, artificial airways, equipment hardware and data processing techniques. Although I did incorporate serial FOT measurements, these were not at standardised timepoints, such that additional measurements would have been valuable to look at the recovery trajectory. Regarding PIFR, we instructed patients to inhale from FRC, and it would be interesting to investigate the values at discharge from both FRC and RV to see which point would have more prediction ability for readmission. Moreover, comparing the readmission prediction ability of both our frailty self-reported questionnaire and the short physical performance battery measure would
add interesting data. Although a comprehensive assessment was conducted at admission and discharge, we were limited by not having a separate validation cohort and conducting the study at one site, which therefore requires independent confirmation of results to confirm the generalisability of our findings. Our follow up was complete at 90 days but it would have been useful to look at longer term outcomes such as readmission within 12 months and mortality, but this was beyond the scope of the present study.

We identified 51 research priorities in a joint patient-clinician research prioritisation exercise for exacerbations of COPD. Our findings demonstrate important uncertainties and gaps in the existing evidence, determining the main unanswered questions for future investigations. The top ten priorities will require various approaches to study. Such priorities are focus on prevention, diagnosis, and treatment. Prioritising research questions using rigorous methodology places the COPD community to submit commissioned and investigator-led research calls confident that these have been transparently co-created via a multi-disciplinary team, in partnership with patients and carers, such that questions can be considered relevant to people living with COPD and practice changing. However, our PSP does not address COPD exacerbation research priorities in low- and middle-income countries. This could be investigated in the future and see how that differs from the current findings in high-income settings.
To conclude, this thesis has summarised current evidence concerning risk factors for all-cause COPD, prospectively highlighted novel and simple predictors that help identify factors that can be modified, and finally, it has shed light on important research priorities for COPD exacerbations that need to be addressed in the future. COPD re-admissions are a challenging problem, in which we do not yet have all the answers to find a solution. Eventually, more future research is needed in this field, in order to find new and simple therapies that are successful and practical in scale. That is the only way we can lessen the COPD readmission burden. There's nothing less that our patients deserve.
Future work suggestions:

1- Does optimisation of inhaled drug prescription and delivery prior to hospital discharge for a COPD exacerbation will reduce all-cause readmission and death at 90 days?

We have demonstrated that low PIFR at discharge was associated with 30- and 90-day all-cause readmission in patients admitted due to a COPD exacerbation. DPI is a popular inhaler device to deliver drugs to COPD patients, but an adequate inspiratory flow is required to effectively disperse the drug. It is critically important that an inhaler can be used appropriately, and inhaler testing is part of the ‘discharge bundle’. However, assessing PIFR in clinical practice at hospital discharge is not routine. Thus, patients with the most severe COPD and lowest inspiratory flows are likely being discharged on devices that they cannot use correctly, and we believe this can contribute to increased risk of re-admissions. This question can be addressed by conducting a multicentre interventional RCT to assess the effect of optimisation of drug prescription and delivery prior hospital discharge versus usual clinical practice on all-cause readmission and mortality at 90 days.

The suggested PICO framework to conduct the study as follows: P: population (COPD patients admitted due to COPD exacerbation); I: intervention (assessment of inspiratory flow and optimisation of inhalers accordingly); C: comparison (regular practice); O: outcome (all-cause readmissions and mortality at 90 days).
2- What is the effect of rescue packs on all-cause readmission at 90 days following hospitalisation for COPD exacerbations?

COPD exacerbations are a major cause of unplanned hospital admissions. Patients consider exacerbations, especially hospitalised exacerbations, as the most disruptive aspect of living with COPD. Most re-admissions are respiratory related and there is evidence that there is an increased risk of recurrent exacerbation in the period following a first. There is evidence that earlier therapy of exacerbations can decrease the severity of the event and risk of hospitalisation. One way to achieve earlier intervention is to offer patients with a ‘rescue pack’ of treatment to have at home, which can be used at the start of an exacerbation. However, use of ‘recue packs’ is controversial. Overuse risks anticipated adverse effects from oral corticosteroids, as well as contributing to antimicrobial resistance from antibiotics (most exacerbations are caused by viruses). Underuse risks missing out on the potential benefit of early therapy, which might reduce the severity of the exacerbation and the risk of hospitalisation. Therefore, an appropriately powered, multicentre RCT compering rescue pack issued at discharge versus no rescue pack on 90-day all-cause readmission is needed to address this question.

The suggested PICO framework to conduct the study as follows: P: population (COPD patients admitted due to COPD exacerbation); I: intervention (Rescue pack issued on discharge with education on how to use it and support in decision to use); C: comparison (No rescue pack on discharge); O: outcome (all-cause readmissions at 90 days).
References:

2. Celli BR, Agustí AJEor. COPD: time to improve its taxonomy? 2018;4(1).
29. Gayle AV, Quint JK, Fuertes EIJERoRM. Understanding the relationships between environmental factors and exacerbations of COPD. 2020.


44. Gan WQ, Man SFP, Postma DS, Camp P, Sin DD. Female smokers beyond the perimenopausal period are at increased risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respiratory Research. 2006;7(1):52.


67. Torres-Duque CA. Poverty cannot be inhaled and it is not a genetic condition. How can it be associated with chronic airflow obstruction? The European respiratory journal. 2017;49(6).


130. Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, et al. The Registry of the International Society for Heart and


239. Jørgensen NR, Schwarz P, Holme I, Henriksen BM, Petersen LJ, Backer V. The prevalence of osteoporosis in patients with chronic


review and meta-analysis about clinical outcomes prediction and classification of patients into GOLD stages. 2016;149(2):413-25.


386. Choi J, Oh JY, Lee YS, Hur GY, Lee SY, Shim JJ, et al. Pseudomonas aeruginosa infection increases the readmission rate of COPD patients. (1178-2005 (Electronic)).


392. Gershon ASA-OhooX, Thiruchelvam D, Aaron S, Stanbrook M, Vozoris N, Tan WCA-Ohoo, et al. Socioeconomic status (SES) and 30-day hospital readmissions for chronic obstructive pulmonary (COPD) disease: A population-based cohort study. (1932-6203 (Electronic)).


Organization WH. Chronic obstructive pulmonary disease (COPD) 2020 [Available from: https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)]


laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel medicine and infectious disease. 2020;101623.


527. Alqahtani JS, Mandal S, Hurst JR. The Impact of Re-Admissions in COPD. Archivos de Bronconeumologia. DOI: 10.1016/j.arbres.2021.06.006
Appendices
List of Appendices

Appendix 1: HRA approval letter.
Appendix 2: Patient information sheet.
Appendix 3: Consent form.
Appendix 4: Main project participant’s assessment sheet.
Appendix 5: Daily step counts sheet after discharge.
Appendix 6: MRC dyspnoea scale form.
Appendix 7: COPD Assessment Test (CAT).
Appendix 8: Hospital anxiety and depression score (HADs) questionnaire.
Appendix 9: Reported Edmonton Frail Scale (REFS).
Appendix 10: COPD exacerbations PSP protocol.
Appendix 11: Databases search strategies and quality assessment of the systematic review.
Appendix 12: Medline search strategy and quality assessment of the smoking and COPD systematic review.
Appendix 13: Systematic review and Meta-analysis (Conference Abstract).

Appendix 14: Risk factors for all-cause hospital readmission following exacerbation of COPD: a systematic review and meta-analysis.

Appendix 15: Relationship Between FEV₁ and Expiratory Flow Limitation at Hospitalised COPD Exacerbation (Abstract).

Appendix 16: Limitation of Inspiratory and Expiratory Flow and Re-Admission Risk at Exacerbation of COPD (Abstract).

Appendix 17: Frailty and Risk of COPD Readmission within 30 Days Following Exacerbation of COPD (Abstract).


Appendix 19: Research priorities for exacerbations of COPD.

Appendix 20: The impact of re-admissions in COPD (Editorial).
Appendix 1: HRA approval letter.

Professor John Hurst  
Royal Free Hospital - UCL Respiratory  
London  
NW3 2PF

15 March 2019

Dear Professor Hurst

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

Study title: Mechanisms of COPD Exacerbation Recurrence  
IRAS project ID: 259010  
REC reference: 19/EM/0080  
Sponsor: University College London

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

How should I continue to work with participating NHS organisations in England and Wales? You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should formally confirm their capacity and capability to undertake the study. How this will be confirmed is detailed in the “summary of assessment” section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a ‘green light’ email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
Appendix 2: Patient Information Sheet

Mechanisms of COPD Exacerbation Recurrence (Student Study)

You are being invited to take part in a research study. Please take the time to read the following information carefully and discuss it with others. Please ask us if there is anything that you do not understand or if you would like more information.

What is the study about? Why is it being done?

COPD (chronic obstructive pulmonary disease) is a very common lung condition. In addition, to symptoms such as breathlessness and cough, people living with COPD are prone to developing periods when their symptoms get worse. These are called exacerbations, ‘flare ups’ or ‘lung attacks’. They are sometime bad enough that people need to be admitted to hospital. After discharge, we know that around 1 in 4 people, will be re-admitted to hospital within the next 30 days. The study aims to explore the reasons that lead to hospital readmission.

If you agree to take part in this study, we will collect information about your clinical condition during the hospital admission, at discharge, and 30 and 90 days later. This will help us to understand the reasons for re-admission. We will not give any new treatment as part of this study.

What Happens in The Study?

During the admission, we will ask you to fill in some questionnaires and have some lung function tests. We will also collect a blood and sputum sample. We will try to do the blood sample when you are having routine blood tests on the ward to avoid an extra test.
Just before you go home you will have the same tests and we will give you a step counter that measures how active you are, together with a diary to record the steps over the next 30 days. We will invite you back for re-assessment at 30 days and do a telephone follow-up at 90 days. If you are re-admitted to hospital we will do the tests at the re-admission instead.

**Why Have I Been Invited?**

You have been invited to join this study because you have COPD and you have been admitted to hospital.

**Do I Have to Take Part?**

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive. If you decide to withdraw at any time, the data already collected with consent would be used in the study, unless you refused.

**What Does The Study Involve?**

During your hospital stay we will collect information including age, home support, and medical history. We will give you some questionnaires to fill in. Then, we will measure your lung function (by using tests called “spirometry” and “forced oscillation” described below), and collect a small sample of blood and sputum. Just before you go home, the same tests will be repeated. In addition, we will provide you with a step counter (“pedometer”) and a diary card to measure how active you are for the next 30 days. We will do the same tests if you do get readmitted to hospital, or ask you to come back to see us 30 days later if you have not been re-admitted. We will do a telephone follow-up at 90 days to see how you are getting on at that time. If you agree to take part, the total study time will be 3 months. The actual study will only involve one visit at 30 days following discharge (if there is
no readmission). Unfortunately, we are not able to pay you for travel costs to this visit.

**How does the forced oscillation technique (FOT)?**

FOT device is a lung function test but unlike the ‘spirometry’ test you will be familiar with this one does not need any effort. The test is done sitting. Your cheeks and the base of the mouth should be firmly supported using your hands to prevent mouth leaks. We will also ask you to wear a nose clip, as shown in the photo below. You will be instructed to breathe in and out normally for 10-20 breaths into the device.

![Picture 1. FOT](image1.png) ![Picture 2. Spirometry](image2.png)

**How to use the pedometer?**

We will ask you to wear the step counter pedometer on the left side of your body all the time, except when sleeping or showering. It is best put on a belt or waistband, in line with the middle of your thigh. At the end of the day, we will ask you to record the number of steps on a diary card.

**What are the possible risks of taking part?**

We are not changing any of your treatment; therefore we do not expect any harm or risk to you if you take part. You may experience bruising while collecting a blood sample, however all blood will be taken by the researchers or clinical staff who are trained.
**What are the potential for benefit to research participants?**

There is no direct benefit to you if you take part in this study. We hope that being part of the research project will be a positive experience for you. Everyone taking part in the study will have access to specialist advice during the study. It can be rewarding to be involved in developing new knowledge that may improve future care for people with COPD and which could lead to a better understanding of ways to prevent exacerbation recurrence.

**Participation**

It is up to you whether you want to be part of this study. If you do not want to be in this study, that is okay and you’re usual NHS care will continue as normal. You can stop during the study at any time without giving a reason. Your doctor will still look after you as normal. We hope, though, that you will tell us why you wish to stop the study. Any information collected to the point of withdrawal will be used in the study but no further data would be collected or any other research procedures carried out.

**Confidentiality**

If you join the study, some parts of your medical records and data collected for the study will be looked at by researchers who are not part of your direct healthcare team. The sponsoring organisation and the NHS Trust may also check these records to ensure that the study is being carried out correctly. All will have a duty of confidentiality to you. The researchers will also need to keep a record of your telephone number and address to contact you. This information will be kept securely on UCL computers with password access and will not be disclosed to anyone outside of the research team. A study code and number will be used for storing confidential information. Original paper questionnaires, assessment forms and participants' contacts will be collected from patients in accordance with the patient consent form and patient information sheet. UCL is the data controller and Professor John Hurst will act as the data custodian for the study. Only the investigators involved with this study will have the original code for patient
identifiable data. Mr. Jaber Alqahtani (Student researcher), University College London will process, store and dispose of original paper questionnaires assessment forms and participants' contact details in accordance with all applicable legal and regulatory requirements under supervision of the Chief Investigator/Academic Supervisor. This project is covered by the UCL Data Protection Registration, reference No Z6364106/2019/01/113 health research.

Data Privacy Notice

UCL is the sponsor for this study. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. UCL will keep identifiable information about you for 3 years after the study has finished.

Your rights to access change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information please visit [http://www.ucl.ac.uk/jro/who-are-we/data-protection](http://www.ucl.ac.uk/jro/who-are-we/data-protection) or email data-protection@ucl.ac.uk

NHS will collect information from you and your medical records for this research study in accordance with our instructions. Royal Free Hospital will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from UCL and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Royal Free Hospital will pass these details to UCL along with the
information collected from you and your medical records. The only people in UCL who will have access to information that identifies you will be people who need to contact you to check the accuracy of the research study or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details. Royal Free Hospital will keep identifiable information about you from this study for 3 years after the study has finished until 01/05/2025 after which it will be destroyed.

**What will happen to the samples I provide?**

The samples will be transferred to UCL for further analysis. The blood and sputum samples will be analysed to identify markers of inflammation, types of infection and antibiotic resistance patterns. No names will be included. The samples will be processed and stored at UCL in line with all applicable legal and regulatory requirements, including the Human Tissue Act 2004 and any amendments thereafter. The analysed data will be used in the result section of the final report of this project. It will not be possible to identify any individual participant from these reports or publications. The samples will be disposed of at the end of the study.

**What happens when the research study stops?**

Written reports of the study findings will be available from the primary researcher and if you wish, a copy of the report can be requested from Mr. Jaber Alqahtani at the address given at the end.

**What will happen to the results of the research study?**

The data will be analysed and will be available to a range of people, including the research team, health professionals and researchers through open access and searchable written reports, established website reports, presentations and journal publications. However, it will not be possible to identify any individual participant from these reports or publications.
Who is organizing and funding the study?

This research is being funded by the Saudi Ministry of Higher Education as part of a PhD award to Mr. Alqahtani to study at UCL. The study is sponsored by University College London (UCL).

Who has reviewed the study?

The Health Research Authority (HRA) have reviewed the study and was given a favorable ethical opinion for conduct in the NHS by the xxxx REC.

What if there is a problem” or “What happens if something goes wrong?

If you are concerned about any aspect of this study, please speak to the researchers who will do their best to answer your questions. Please contact: 020 7794 0500 Extension 34301. If you remain unhappy, you can make a formal complaint through the National Health Service (NHS) complaints procedure. Details can be obtained through the Royal Free Hospital Patient Advice and Liaison Service (PALS) on 020 7472 6445, email: rf.pals@nhs.net, address: PALS, Patient Affairs Department Executive Offices 2nd Floor, Pond Street London NW3 2QG.

University College London (UCL) holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. University College London does not accept liability for any breach in the hospital’s duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Thank you for taking time to consider this study. Please ask any questions and let us know if there are things that you do not understand, or would like more information about.
Please address any further questions to:

Academic Supervisor Dr. John Hurst, Respiratory Consultant, Royal Free Hospital
j.hurst@ucl.ac.uk

Student Researcher Mr. Jaber Alqahtani. PhD student at University College London.
Tel: 020 7794 0500 extension 34301.
Mobile: 07846713703
jaber.alqahtani.18@ucl.ac.uk

Thank you for taking the time to read this information sheet.
CONSENT FORM

Mechanisms of COPD Exacerbation Recurrence (student study)

1. I confirm that I have read the information sheet dated (version 2.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University College London, the respiratory research team from the Royal Free Hospital, and from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.

5. I understand that the information held and maintained by the respiratory research team (chief investigator, researcher, and research assistants) from Royal Free Hospital and other central UK NHS bodies may be used to help contact me or provide information about my health status.

6. I agree to take part in the study.

7. I wish to receive a summary of the results from the study.

Name of Participant ___________________ Date _____________ Signature ___________________

Name of Person taking consent ___________________ Date _____________ Signature ___________________
**Appendix 4: Main project participant’s assessment sheet.**

<table>
<thead>
<tr>
<th>General information</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFH number:</td>
</tr>
<tr>
<td>Gender:  c Male  c Female</td>
</tr>
<tr>
<td>Date of admission:</td>
</tr>
</tbody>
</table>

Has the patient admitted due to exacerbation previously?  c Yes  c No  c Not known

**Clinical information**

![UCL logo]

Smoking status  c Current smoker  c Ex-smoker  c Never smoked

If current or ex-smoker:

- Age started:  
- Age stopped:  
- Maximum number/day:  

Smoke anything else other than cig: Yes/No

Have you ever had pneumonia vaccine?  c Yes  c No
If yes what:  

Have you ever had flu vaccination?  c Yes  c No
If yes when:  

Have you ever received flu shots?  c Yes  c No
If yes when:  

Do you receive Oxygen therapy at home?  c Yes  c No
If yes how long and hrs/d:  

Do you receive IV or NIV at home?  c Yes  c No
If yes please specify:  

Does the patient take any respiratory medication before admission (GABA, LABA, LAMA, ICS, Nebulizers or other vasoactive, mental health drugs)?  c Yes  c No  c Not known
If yes please specify:

- Drug:  Dose:  Frequency:  
- Drug:  Dose:  Frequency:  
- Drug:  Dose:  Frequency:  

Medical records if possible:

- No other medical conditions  
- Myocardial infarction  
- CHF  
- Peripheral vascular disease  
- Hyperlipidemia  
- Lung volume surgery  
- Osteoporosis  
- Connective tissue disease  
- Liver disease  
- Solid tumor  
- Lymphoma  
- Stroke (CVA)  
- Chronic kidney disease  
- Atrial fibrillation  
- Diabetes mellitus  
- Rheumatoid arthritis  
- Anemia  
- Depression  
- Alcohol abuse  
- Pneumonia  
- Angina  
- Pulmonary hypertension  
- Hypertension  
- Systemic hypertension

Other personal records if any:

How often do you drink?  c Every day  c 1-3 times a week  c Once a week  c Only on weekends
Do you engage in binge drinking? (5 or more drinks in a sitting)  c Yes  c No
Number of drinks:  

Drug:  Dose:  Frequency:  
Drug:  Dose:  Frequency:  
Drug:  Dose:  Frequency:  

350
**COPD Exacerbation (acute infection)**

<table>
<thead>
<tr>
<th>No of exacerbations ≤ 1 year:</th>
<th>Hospitalisation due to exacerbation ≤ 1 year apart from the current one:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes/no if yes, how many...</td>
</tr>
</tbody>
</table>

**When was last COPD exacerbation apart from the current one?**

**Were you admitted to hospital?** Yes/no

**Is the patient on any antibiotic and/or steroid?**

**Assessment questionnaire**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>At admission</th>
<th>At discharge</th>
<th>At readmission or 30 days</th>
<th>If followed-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mMRC grade:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CAT</td>
<td></td>
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</tr>
</tbody>
</table>

**Pulmonary function**

**Outcomes:**

<table>
<thead>
<tr>
<th>Previous test if available from MR</th>
<th>FEV1:</th>
<th>FEV1 %:</th>
<th>FVC:</th>
<th>FVC%:</th>
<th>FEV1/FVC:</th>
<th>IC:</th>
</tr>
</thead>
<tbody>
<tr>
<td>At discharge</td>
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<td>At readmission</td>
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<tr>
<td>At follow-up</td>
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<tr>
<td></td>
<td>Respiratory (mmHg/L)</td>
<td>Respiratory (mmHg/L)</td>
<td>Respiratory (mmHg/L)</td>
<td>PIF (%)</td>
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<tr>
<td>At admission</td>
<td>Upright seated</td>
<td>supine</td>
<td>Upright seated</td>
<td>supine</td>
<td>Upright seated</td>
<td>supine</td>
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<tr>
<td>At discharge</td>
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<tr>
<td>At readmission</td>
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<tr>
<td>Follow-up</td>
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</tbody>
</table>

**Body composition**

<table>
<thead>
<tr>
<th>Outcomes:</th>
<th>during admission</th>
<th>At discharge</th>
<th>If followed up</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td></td>
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</table>

**Other outcomes:**

<table>
<thead>
<tr>
<th>Outcomes:</th>
<th>during admission</th>
<th>At readmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOS</td>
<td></td>
<td></td>
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<tr>
<td>ICU admission</td>
<td></td>
<td></td>
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<tr>
<td>Use of NIV</td>
<td></td>
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<tr>
<td>History of anaphylaxis</td>
<td></td>
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<tr>
<td>Use of Oxygen</td>
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<tr>
<td>Use of HFNOT</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood test</th>
<th>Admission</th>
<th>Discharge</th>
<th>At readmission</th>
<th>Follow-up</th>
<th>ABG</th>
<th>Admission</th>
<th>Discharge</th>
<th>At readmission</th>
<th>Follow-up</th>
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</thead>
<tbody>
<tr>
<td>White Cell Count (WCC)</td>
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<td>Leukocytes</td>
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<td>Neutrophils</td>
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<td>Hemoglobin (Hb)</td>
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<td>C-reactive protein (CRP)</td>
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<td>Brain natriuretic peptide (BNP)</td>
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<td>DECAF score</td>
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<tr>
<td>Dyspnea (1 or 2)</td>
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<td>Eosinopenia (&gt;0.05 x10^9/L)</td>
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<tr>
<td>Consolidation</td>
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<td>Acidemia (pH &lt;7.3)</td>
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<td>AFibillation</td>
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</tbody>
</table>

(Too breathless to leave the house unassisted but independent in washing and/or dressing (1) if require help (2)

- **Presence of Emphysema on CT scan:** Yes/No date if ____________________________

- **PA/A ratio:** ____________________________

- **Diffusion test:** type of test ____________________________ Date ____________________________ normal = abnormal
<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seen within 24 hours of admission by a respiratory specialist?</td>
<td>✔ Yes □ No</td>
</tr>
<tr>
<td>Had a Discharge Bundle?</td>
<td>✔ Yes □ No</td>
</tr>
<tr>
<td>Ever had ECHOCARDIOGRAM. If YES, date</td>
<td>✔ Yes □ No If yes please Specify date: …………………………………</td>
</tr>
<tr>
<td></td>
<td>□ NORMAL</td>
</tr>
<tr>
<td></td>
<td>□ ABNORMAL VENTRICULAR FUNCTION</td>
</tr>
<tr>
<td>Discharge location</td>
<td>□ Own home with no support</td>
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<tr>
<td></td>
<td>□ Own home with support</td>
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<td></td>
<td>□ Home with professional care</td>
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<tr>
<td></td>
<td>□ Nursing home</td>
</tr>
<tr>
<td></td>
<td>□ Residential home</td>
</tr>
<tr>
<td>Does the patient agreed to be followed-up?</td>
<td>✔ Yes □ No</td>
</tr>
<tr>
<td>Does the patient agreed to wear the step counter pedometer?</td>
<td>✔ Yes □ No</td>
</tr>
<tr>
<td>Date of follow up</td>
<td></td>
</tr>
<tr>
<td>If followed up, does any of the routine care has changed including medication, smoking status, or others?</td>
<td>✔ Yes □ No If yes please Specify: …………………………………</td>
</tr>
<tr>
<td>Did you have any chest infection? If you have, did you take antibiotic or steroid? If yes how long and when?</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 5: Daily step counts sheet after discharge.

<table>
<thead>
<tr>
<th>Date</th>
<th>Number of steps</th>
<th>Date</th>
<th>Number of steps</th>
<th>Date</th>
<th>Number of steps</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>
Appendix 6: MRC dyspnoea scale form.

| mMRC Grade 0 | I only get breathless with strenuous exercise. |
| mMRC Grade 1 | I get short of breath when hurrying on the level or walking up a slight hill. |
| mMRC Grade 2 | I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level. |
| mMRC Grade 3 | I stop for breath after walking about 100 meters or after a few minutes on the level. |
| mMRC Grade 4 | I am too breathless to leave the house or I am breathless when dressing or undressing. |
Appendix 7: COPD assessment (CAT)

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

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 [X] 0 2 3 4 5 I am very sad

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>I never cough</td>
<td></td>
</tr>
<tr>
<td>I cough all the time</td>
<td></td>
</tr>
<tr>
<td>I have no phlegm (mucus) in my chest at all</td>
<td></td>
</tr>
<tr>
<td>My chest is completely full of phlegm (mucus)</td>
<td></td>
</tr>
<tr>
<td>My chest does not feel tight at all</td>
<td></td>
</tr>
<tr>
<td>My chest feels very tight</td>
<td></td>
</tr>
<tr>
<td>When I walk up a hill or one flight of stairs I am not breathless</td>
<td></td>
</tr>
<tr>
<td>When I walk up a hill or one flight of stairs I am very breathless</td>
<td></td>
</tr>
<tr>
<td>I am not limited doing any activities at home</td>
<td></td>
</tr>
<tr>
<td>I am very limited doing activities at home</td>
<td></td>
</tr>
<tr>
<td>I am confident leaving my home despite my lung condition</td>
<td></td>
</tr>
<tr>
<td>I am not at all confident leaving my home because of my lung condition</td>
<td></td>
</tr>
<tr>
<td>I sleep soundly</td>
<td></td>
</tr>
<tr>
<td>I don't sleep soundly because of my lung condition</td>
<td></td>
</tr>
<tr>
<td>I have lots of energy</td>
<td></td>
</tr>
<tr>
<td>I have no energy at all</td>
<td></td>
</tr>
</tbody>
</table>

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Last Updated: February 21, 2012
## Appendix 8: Hospital anxiety and depression score

**Hospital Anxiety and Depression Score (HADS)**

This questionnaire helps your physician to know how you are feeling. Read every sentence. Place an “X” on the answer that best describes how you have been feeling during the LAST WEEK. You do not have to think too much to answer. In this questionnaire, spontaneous answers are more important.

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th></th>
<th>D</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I feel tense or ‘wound up’</td>
<td></td>
<td>I feel as if I am slowed down</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Most of the time</td>
<td>3</td>
<td>Nearly all the time</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>A lot of the time</td>
<td>2</td>
<td>Very often</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>From time to time (occ.)</td>
<td>1</td>
<td>Sometimes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>0</td>
<td>Not at all</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>I still enjoy the things I used to enjoy:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Definitely as much</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not quite as much</td>
<td>1</td>
<td>Occasionally</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Only a little</td>
<td>2</td>
<td>Quite often</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Hardly at all</td>
<td>3</td>
<td>Very often</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>I get a sort of frightened feeling as if something awful is about to happen:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very definitely and quite badly</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes, but not too badly</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A little, but it doesn’t worry me</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I can laugh and see the funny side of things:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>As much as I always could</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not quite so much now</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Definitely not so much now</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Worrying thoughts go through my mind:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A great deal of the time</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>A lot of the time</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>From time to time, but not often</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Only occasionally</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I feel cheerful:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not often</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sometimes</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Most of the time</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I can sit at ease and feel relaxed:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Definitely</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Usually</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not often</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I get sort of frightened feeling like “butterflies” in the stomach:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occasionally</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quite often</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very often</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I have lost interest in my appearance:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Definitely</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I don’t take as much care as I should</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I may not take quite as much care</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I take just as much care</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I feel restless as I have to be on the move:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very much indeed</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quite a lot</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not very much</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I look forward with enjoyment to things:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>As much as I ever did</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rather less than I used to</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Definitely less than I used to</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hardly at all</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I get sudden feelings of panic:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very often indeed</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quite often</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not very often</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not at all</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>I can enjoy a good book or radio/TV program:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Often</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sometimes</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not often</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very seldom</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 9: Reported Edmonton Frail Scale (REFS)

<table>
<thead>
<tr>
<th>Frailty Domain</th>
<th>Item</th>
<th>0 Point</th>
<th>1 Point</th>
<th>2 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognition</td>
<td>Please imagine this pre-drawn circle is a clock. I would like you to place the numbers in the correct positions, then place the hands to indicate a time of ‘ten after eleven’.</td>
<td>No errors</td>
<td>Minor spacing errors</td>
<td>Other errors</td>
</tr>
<tr>
<td>General Health Status</td>
<td>In the past year, how many times have you been admitted to a hospital?</td>
<td>0</td>
<td>1-2</td>
<td>≥ 2</td>
</tr>
<tr>
<td></td>
<td>In general, how would you describe your health?</td>
<td>Excellent/Very Good/Good</td>
<td>Fair</td>
<td>Poor</td>
</tr>
<tr>
<td>Functional Independence</td>
<td>With how many of the following activities do you require help?</td>
<td>0-1</td>
<td>2-4</td>
<td>5-8</td>
</tr>
<tr>
<td></td>
<td>meal preparation / shopping / transportation / telephone / housekeeping / laundry / managing money / taking medications</td>
<td>Always</td>
<td>Sometimes</td>
<td>Never</td>
</tr>
<tr>
<td>Social Support</td>
<td>When you need help, can you count on someone who is willing and able to meet your needs?</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Medication Use</td>
<td>Do you use five or more different prescription medications on a regular basis?</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>At times, do you forget to take your prescription medications?</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td>Have you recently lost weight such that your clothing has become looser?</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Mood</td>
<td>Do you often feel sad or depressed?</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Continence</td>
<td>Do you have a problem with losing control of urine when you don’t want to?</td>
<td>No</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Self Reported Performance</td>
<td>Two weeks ago, were you able to:</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1) Did heavy work around the house like washing windows, walk, or floors without help?</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2) Walk up and down stairs to the second floor without help?</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3) Walk 1 km without help?</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

**Scoring for the Reported Edmonton Frail Scale (/18):**

- **Not Frail:** 0-5
- **Apparently Vulnerable:** 6-7
- **Mildly Frail:** 8-9
- **Moderate Fraility:** 10-11
- **Severe Fraility:** 12-18


COPD Exacerbation PSP Protocol

Published: 12/03/2020
Read Time: 11 minutes
Version: 2
Print this document

Purpose of the PSP and background

The purpose of this protocol is to clearly set out the aims, objectives and commitments of the COPD Exacerbations Priority Setting Partnership (PSP) in line with James Lind Alliance (JLA) principles. The Protocol is a JLA requirement and will be published on the PSP’s page of the JLA website. The Steering Group will review the Protocol regularly and any updated version will be sent to the JLA.

The JLA is a non-profit making initiative, established in 2004. It brings patients, carers and clinicians together in PSPs. These PSPs identify and prioritise the evidence uncertainties, or ‘unanswered questions’, that they agree are the most important for research in their topic area. Traditionally PSPs have focused on uncertainties about the effects of treatments, but some PSPs have chosen to broaden their scope beyond that. The aim of a PSP is to help ensure that those who fund health research are aware of what really matters to patients, carers and clinicians. The National Institute for Health Research (NIHR – www.nihr.ac.uk) coordinates the infrastructure of the JLA to oversee the processes for PSPs, based at the National Evaluation Trials and Studies Coordinating Centre (NETSCC), University of Southampton.

This PSP was originally developed by a group of clinical academic whose overarching aim is to improve the outcomes and experience for people affected by exacerbations of COPD. A proposal was submitted to the British Lung Foundation and we were notified of successful funding in late 2015. We subsequently approached additional representation from people affected by COPD.

Aims, objectives and scope of the PSP

The aim of the COPD Exacerbations PSP is to identify the unanswered questions about exacerbations of COPD from patient, carer and clinical perspectives and then prioritise those that patients, carers and clinicians agree are the most important for research to address.

The objectives of the PSP are to:

- work with patients, carers and clinicians to identify uncertainties about the management and prevention of exacerbations in people with COPD

Contents

1. Purpose of the PSP and background
2. Aims, objectives and scope of the PSP
3. The Steering Group
   1. Patient and carer representative(s)
   2. Clinical representative(s)
4. Partners
   1. Exclusion criteria
5. The methods the PSP will use
   1. Step 1: Identification and invitation of potential partners
   2. Step 2: Awareness raising
   3. Step 3: Identifying evidence uncertainties
   4. Step 4: Refining questions and uncertainties
   5. Step 5: Prioritisation – interim and final stages
6. Dissemination of results
• to agree by consensus a prioritised list of those uncertainties, for research
• to publicise the results of the PSP and process
• to take the results to research commissioning bodies to be considered for funding.

The scope of the COPD Exacerbations PSP is defined as:

The main themes are in relation to diagnosis, prevention, and management of exacerbations incorporating treatment. These can be conceptualised as:

Why did this event happen? What causes exacerbations?

How can we treat exacerbations while they are happening? This includes self-care, additional support e.g., physiotherapy, occupational therapy, psychological support and clinician led support.

What can we do to prevent them from happening in the future, both self-care and multi-disciplinary clinical support?

The PSP has agreed that this PSP cannot cover all elements of COPD. Therefore it is agreed that the PSP would concentrate on exacerbations in people with COPD. The group recognised the need to include those who may refer to their disease using alternative terms such as emphysema or chronic bronchitis. This will be reflected in the survey when we ask who is completing the survey.

Included in the COPD Exacerbation PSP scope:

- Any participant above 18 years of age (adult)
- We will only consider responses from the UK,
- Excluded from the COPD Exacerbation PSP scope:
  - Asthma
  - Responses from industry or pharmaceutical companies.

The Steering Group is responsible for discussing what implications the scope of the PSP will have for the evidence-checking stage of the process. Resources and expertise will be put in place to do this evidence checking.

The Steering Group

The Steering Group includes membership of patients and carers and clinicians, as individuals or representatives from a relevant group.

The COPD Exacerbations PSP will be led and managed by a Steering Group involving the following:

Patient and carer representative/s:

Teresa BURGOYNE, Patient and Carer Representative; BLF Trustee
Clinical representatives:

- John HURST, Professor of Respiratory Medicine, University College London
- Tom WILKINSON, Professor of Respiratory Medicine, University of Southampton
- Charlotte BOLTON, Professor of Respiratory Medicine, University of Nottingham
- Jennifer QUINT, Reader in Respiratory Epidemiology, Imperial College London
- Elizabeth SAPEY, Reader in Respiratory Medicine, University of Birmingham
- Mona BAFADHEL, Associate Professor in Respiratory Medicine, University of Oxford
- Heidi RIDSDALE, Service Lead and Specialist Physiotherapist, Camden COPD and Home Oxygen Service
- Joanne KING, Consultant Respiratory Nurse, Clinical Lead for the Adult Integrated Respiratory Team
- Steve HOLMES, General Practitioner, Park Medical Practice, Shepton Mallet

Project coordinator: Jaber Alcahtani, PhD student, University College London

James Lind Alliance Adviser and Chair of the Steering Group: Ms Sheela Upadhyaya, JLA

The Steering Group will agree the resources, including time and expertise that they will be able to contribute to each stage of the process, with input and advice from the JLA.

Partners

Organisations and individuals will be invited to be involved with the PSP as partners. Partners are organisations or groups who will commit to supporting the PSP, promoting the process and encouraging their represented groups or members to participate. Organisations which can reach and advocate for these groups will be invited to become involved in the PSP. Partners represent the following groups:

- people who have had COPD Exacerbations
- carers of people who have had COPD Exacerbations
- health and social care professionals – with experience of COPD Exacerbations.

Exclusion criteria

Some organisations may be judged by the JLA or the Steering Group to have conflicts of interest. These may be perceived to
potentially cause unacceptable bias as a member of the Steering Group. As this is likely to affect the ultimate findings of the PSP, those organisations will not be invited to participate. It is possible, however, that interested parties may participate in a purely observational capacity when the Steering Group considers it may be helpful.

The methods the PSP will use

This section describes a schedule of proposed steps through which the PSP aims to meet its objectives. The process is iterative and dependent on the active participation and contribution of different groups. The methods used in any step will be agreed through consultation between the Steering Group members, guided by the PSP’s aims and objectives. More details of the method are in the Guidebook section of the JLA website at www.jlaihri.ac.uk where examples of the work of other JLA PSPs can be seen.

Step 1: Identification and invitation of potential partners

Potential partner organisations will be identified through a process of peer knowledge and consultation, through the Steering Group members’ networks. Potential partners will be contacted and informed of the establishment and aims of the COPD Exacerbations PSP.

Step 2: Awareness raising

PSPs will need to raise awareness of their proposed activity among their patient, carer and clinician communities, in order to secure support and participation. Depending on budget, this may be done by a face-to-face meeting, or there may be other ways in which the process can be launched, e.g. via social media. It may be carried out as part of steps 1 and/or 3. The Steering Group should advise on when to do this. Awareness raising has several key objectives:

- to present the proposed plan for the PSP
- to generate support for the process
- to encourage participation in the process
- to initiate discussion, answer questions and address concerns

Step 3: Identifying evidence uncertainties

The COPD Exacerbations PSP will carry out a consultation to gather uncertainties from patients, carers and clinicians. A period of 2-3 months will be given to complete this exercise (which may be revised by the Steering Group if required).

The COPD Exacerbations PSP recognises that the following groups may require additional consideration:

- BAME Populations
- Those living with mental health problems
Existing sources of evidence uncertainties may also be searched. These will include existing evidence synthesis and clinical guidelines, and a search of ongoing research studies.

**Step 4: Refining questions and uncertainties**

The consultation process will produce ‘raw’ questions and comments indicating patients’, carers’ and clinicians’ areas of uncertainty. These raw questions will be categorised and refined by Mr Jaber Alqahtani into summary questions which are clear, addressable by research, and understandable to all. Similar or duplicate questions will be combined where appropriate. Out-of-scope and ‘answered’ submissions will be compiled separately. The Steering Group will have oversight of this process to ensure that the raw data is being interpreted appropriately and that the summary questions are being worded in a way that is understandable to all audiences. The JLA Adviser will observe to ensure accountability and transparency.

This will result in a long list of in-scope summary questions. These are not research questions and to try and word them as such may make them too technical for a non-research audience. They will be framed as researchable questions that capture the themes and topics that people have suggested.

The summary questions will then be checked against evidence to determine whether they have already been answered by research. This will be done by Mr Jaber Alqahtani. The PSP will complete the JLA Question Verification Form, which clearly describes the process used to verify the uncertainty of the questions, before starting prioritisation. The Question Verification Form includes details of the types and sources of evidence used to check uncertainty. The Question Verification Form should be published on the JLA website as soon as it has been agreed to enable researchers and other stakeholders to understand how the PSP has decided that its questions are unanswered, and any limitations of this.

Questions that are not adequately addressed by previous research will be collated and recorded on a standard JLA template by Mr Jaber Alqahtani. This will show the checking undertaken to make sure that the uncertainties have not already been answered. The data should be submitted to the JLA for publication on its website on completion of the priority setting exercise, taking into account any changes made at the final workshop, in order to ensure that PSP results are publicly available.

The Steering Group will also consider how it will deal with submitted questions that have been answered, and questions that are out of scope.

**Step 5: Prioritisation – interim and final stages**

The aim of the final stage of the priority setting process is to prioritise through consensus the identified uncertainties about COPD Exacerbations. This will involve input from patients, carers and clinicians. The JLA encourages PSPs to involve as wide a range of people as possible, including those who did and did not contribute to the first consultation. There are
usually two stages of prioritisation.

1. Interim prioritisation is the stage where the long list of questions is reduced to a shorter list that can be taken to the final priority setting workshop. This is aimed at a wide audience, and is done using similar methods to the first consultation. With the JLA’s guidance, the Steering Group will agree the method and consider how best to reach and engage patients, carers and clinicians in the process. The most highly ranked questions (around 25) will be taken to a final priority setting workshop. Where the interim prioritisation does not produce a clear ranking or cut off point, the Steering Group will decide which questions are taken forwards to the final prioritisation.

2. The final priority setting stage is generally a one-day workshop facilitated by the JLA. With guidance from the JLA and input from the Steering Group, up to 30 patients, carers and clinicians will be recruited to participate in a day of discussion and ranking, to determine the top 10 questions for research. All participants will declare their interests. The Steering Group will advise on any adaptations needed to ensure that the process is inclusive and accessible.

**Dissemination of results**

The Steering Group will identify audiences with which it wants to engage when disseminating the results of the priority setting process, such as researchers, funders and the patient and clinical communities. They will need to determine how best to communicate the results and who will take responsibility for this. Previous PSPs’ outputs have included academic papers, lay reports, infographics, conference presentations and videos for social media.

It should be noted that the priorities are not worded as research questions. The Steering Group should discuss how they will work with researchers and funders to establish how to address the priorities and to work out what the research questions are that will address the issues that people have prioritised. The dissemination of the results of the PSP will be led by Professor John Hurst.

The JLA encourages PSPs to report back about any activities that have come about because of the PSP, including funded research. Please send any details to jla@soton.ac.uk.

**Agreement of the Steering Group**

The COPD Exacerbations PSP Steering Group agreed the content and direction of this Protocol on 15th March 2019.
**Appendix 11: Databases search strategies**

- **Medline Search Strategy**

<table>
<thead>
<tr>
<th>#</th>
<th>Searches</th>
<th>Results</th>
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<td>1</td>
<td>exp Pulmonary Disease, Chronic Obstructive/</td>
<td>51742</td>
</tr>
<tr>
<td>2</td>
<td>chronic airway obstruction.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]</td>
<td>333</td>
</tr>
<tr>
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<td>(obstructive adj3 (lung or pulmonary or respiratory or bronchopulmonary)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]</td>
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<td>569</td>
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21 14 or 15 or 16 or 17 or 18 or 19 or 20 (74121)

22 risk/ or risk factor/ (1360649)

23 risk assessment/ (510172)

24 patient risk/ (5588)

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26 recurrence risk/ (66618)

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Quality assessment of the systematic review.

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<td>Nguyen, Chu, Liu, et al. 2014</td>
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<td>1</td>
<td>1</td>
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<td>8</td>
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</tr>
<tr>
<td>Rinne, S. T et al. (1) 2017</td>
<td>0</td>
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</tr>
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<td>1</td>
<td>9</td>
<td>Good</td>
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<tr>
<td>Goto et al. 2018</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>1</td>
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<td>Good</td>
</tr>
<tr>
<td>Bottle A. et al. 2018</td>
<td>1</td>
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<td>1</td>
<td>1</td>
<td>2</td>
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<td>9</td>
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<td>Choi et al. 2018</td>
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<td>1</td>
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<td>1</td>
<td>7</td>
<td>Good</td>
</tr>
<tr>
<td>Ehsani et al. 2019</td>
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<td>1</td>
<td>1</td>
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<td>Gershon et al.2019</td>
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<td>Almagro et al. 2014</td>
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<td>1</td>
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<td>1</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>Good</td>
</tr>
</tbody>
</table>
Appendix 12: Medline search strategy and quality assessment of the smoking and COPD systematic review.

➢ Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to March 16, 2020>

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<th>24-03-2020</th>
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</tr>
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</tr>
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</tr>
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<td>concept word, rare disease supplementary concept word, unique identifier, synonyms</td>
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<td>15</td>
<td>limit 14 to dt=20200316-20200323 [March 16th, 2020 - March 24th, 2020]</td>
<td>18</td>
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</table>

Abstract

Background

Coronavirus disease 2019 (COVID-19) is an evolving infectious disease that dramatically spread all over the world in the early part of 2020. No studies have yet summarized the potential severity and mortality rates caused by COVID-19 in patients with chronic obstructive pulmonary disease (COPD), and we update information in smokers.

Methods

We systematically searched electronic databases from inception to March 24, 2020. Data were extracted by two independent authors in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Study quality was assessed using a modified version of the Newcastle-Ottawa Scale. We synthesized a narrative from eligible studies and conducted a meta-analysis using a random-effects model to calculate pooled prevalence rates and 95% confidence intervals (95%CI).

Results

In total, 123 abstracts were screened and 81 full-text manuscripts were reviewed. A total of 16 studies met the inclusion criteria, which included a total of 2473 confirmed COVID-19 patients. All studies were included in the meta-analysis. The crude case fatality rate of COVID-19 was 7.4%. The pooled prevalence rates of COPD patients and smokers in COVID-19 cases were 2% (95% CI, 1%-3%) and 9% (95% CI, 4%-14%), respectively. COPD patients were at a higher risk of more severe disease (risk of severity = 0.53, 95%CI) compared to patients without COPD (23.4% (95%CI 1.0-4.3)). This was associated with higher mortality (80%). Our results showed that 22% (95%CI 1.0-2.3) of current smokers and 45% (95%CI) of ex-smokers had severe complications. The calculated RR showed that current smokers were 4.45 times more likely (95% CI, 1.05-2.04) to have severe complications compared to former and never smokers. Current smokers also had a higher mortality rate of 39.6%.

Conclusion

Although COPD prevalence in COVID-19 cases was low in current smokers, COVID-19 infection was associated with substantial severity and mortality rates in COPD. Compared to former and never smokers, current smokers were at greater risk of severe complications and higher mortality rate. Effective preventive measures are required to reduce COVID-19 risk in COPD patients and current smokers.
Impact

In this systematic review and meta-analysis of 15 studies including a total of 473 confirmed COVID-19 patients, COVID-19 was associated with greater severity and mortality in COPD patients and current smokers. Despite the low prevalence of COPD and smoking in COVID-19 cases, this result emphasizes attention to effective preventive measures to support reducing the burden of COVID-19 in these vulnerable populations. This has the potential to improve outcomes for patients and lessen the burden on health services.

Introduction

The emergence in Wuhan City, Hubei Province of China of a novel pneumonia of unknown origin on the 31st of December, 2019 was the start of an outbreak which would later be declared a pandemic by the World Health Organization (WHO) [1]. The name COVID-19 (acronym for "coronavirus disease 2019") was coined on the 11th of February 2020 to describe presentation with severe acute respiratory disease [2]. COVID-19 is caused by a novel strain of coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This virus belongs to the family of single stranded RNA viruses some of which have been previously described to be responsible for the Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [3, 4]. Although the symptoms and clinical presentation of COVID-19 is similar to SARS and MERS, the rate of spread is greater [5]. As of 25th of March 2020, the total number of confirmed case of COVID-19 stands at 4,59,419 with 20,818 deaths globally and the number is projected to increase [6].

Chronic Obstructive Pulmonary Disease (COPD) is a common, persistent and preventable dysfunction of the lung associated with limitation in airflow. COPD is a complex disease associated with abnormalities of the airway and/or alveoli which is predominantly caused by exposure to noxious gases and particulates over a long period [7]. With a global prevalence of 251 million cases in 2016, and 3.17 million (5%) deaths in 2015 alone, COPD was ranked by the WHO as the third leading cause of death especially with a particular burden in low- and middle-income countries [8, 9]. This burden is predicted to grow due mainly to increased global exposure to tobacco, aging populations, poor awareness and inadequate access to diagnosis [10]. COPD exacerbations are a major event in the natural history of the disease associated
with worsening of symptoms often resulting in hospitalization and poor prognosis [11]. Various factors have been described to contribute to acute worsening of COPD, however, viral infection remains the main trigger, including seasonal coronaviruses [12–14].

Since the emergence of COVID-19, scientists around the world continue to better understand the clinical, diagnostic and prognostic characteristics of the disease. While over 150 papers, editorials and comments have been written about COVID-19 as of 24th of March 2020, there is none dedicated to the specific risk posed to patients with a previous history of COPD. This review addresses this gap in knowledge with the aim of assisting clinicians to assess the prognosis of COVID-19 infection in patients with COPD and those with smoking history.

Methods

This systematic review was conducted in accordance with the Preferred Reporting in Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15]. We prospectively registered this review in Prospero (registration number: CRD42020175518).

We searched MEDLINE and Google Scholar from inception date to March 16, 2020. The search was updated on March 24, 2020. We used an extensive search strategy developed by a specialist librarian for retrieving this type of evidence, which included the reference list of eligible papers and published pre-print papers (see S1 Table in S1 Appendix). All retrieved studies were exported into EndNote to remove duplicates. The remaining studies were exported to Rayyan software for title, abstracts and full text screening by two independent reviewers.

Inclusion and exclusion criteria

Eligible studies were those that investigated: epidemiological, clinical characteristics and features of COVID-19 and prevalence of chronic diseases specifically COPD in their analysis. We excluded the following studies that did not report COPD, studies that included respiratory diseases but did not specifically analyze COPD, only children, editorials, correspondence letters, reviews, qualitative studies, theses, non-English language and non-full text articles.

Data collection

Two authors (JS and TO) independently screened titles and abstracts of potential studies and conflicts were resolved through discussion between the two. Full-text articles of potential studies were then independently read by two authors (JS and TO) to identify studies meeting the inclusion criteria. The reference lists from all identified studies and reviews were scrutinized for eligible articles. Disagreement on selected papers was resolved through discussion with a third author (AA).

Quality assessment

Two authors independently evaluated the methodological quality of included studies using a modified version of the Newcastle-Ottawa Scale (NOS) [16]. It includes seven domains, each one of these domains was scored from 0 (high risk of bias) to 3 (low risk of bias) and we took a mean of the domains to result in a score between 0 and 3, where a higher score represents a lower risk of bias. Any disagreement in the quality assessment was resolved by discussion with a third author.

Data synthesis

We completed meta-analysis to calculate the pooled prevalence of COPD and current smokers among those patients with confirmed COVID-19. The output was generated using the Stata
procedure Metaprop. Owing to heterogeneity within and between studies, we used the random-effects model in Stata/SE 15. Data were displayed using forest plots. We examined between-study heterogeneity using the $I^2$ statistic. A narrative synthesis of the results was conducted considering the prevalence, disease severity and mortality among COVID-19 COPD patients and smoking status. We defined COVID-19 severity as those who were admitted to intensive care unit (ICU), had severe, oxygenation needed mechanical ventilation or death. Since our meta-analysis was performed to estimate the pooled prevalence and not assessing treatment effects, the assessment for potential risk of bias that could affect the results was not indicated.

Pre-print
As this is a rapidly evolving area, we also searched pre-print literature and whilst not incorporating such data in the formal analysis, provide narrative synthesis where such pre-print data are relevant to our main findings.

Results
An initial search generated 123 potentially relevant papers, of which two were immediately excluded due to duplication. After the first screening of title and abstracts, 61 papers were potentially relevant according to the inclusion criteria. An additional 46 papers were excluded after full-text review, which resulted in 15 studies that satisfied all criteria. The reference list of the relevant papers was also examined (see Fig 1, PRISMA flow diagram).

Description of included studies
A summary of the included studies is presented in Table 1, which included a total of 2473 confirmed COVID-19 patients. Of those patients, only 58 (2.3%) had COPD as a comorbidity. The sample size of the included studies ranged from 21 to 1699 patients. Most of the studies
Table 1. Characteristics of the included articles.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Country/Type of study</th>
<th>Sample size (M= male, F= female)</th>
<th>Age mean ±SD or Median, range</th>
<th>Current Smokers</th>
<th>COPD patients</th>
<th>COPD Survived</th>
<th>COPD Non-Survived</th>
<th>Mortality rate for study/COPD Cases</th>
<th>Severe cases for study/COPD Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arentz M et al. 2020</td>
<td>United States/Washington Retrospective study from February 1, 2020 to March 5, 2020</td>
<td>2. M= 11 (22%), F= 10 (8%)</td>
<td>72 (28-59)</td>
<td>NA</td>
<td>7 (33.3%)</td>
<td>NA</td>
<td>NA</td>
<td>11 (52.6%)</td>
<td>NA</td>
</tr>
<tr>
<td>Gao et al. 2020</td>
<td>China/30 provinces Retrospective study from December 11, 2019, and January 20, 2020</td>
<td>199 M = 62 (31%), F = 69 (17%)</td>
<td>47 (35-58) Severe 52 (40-65) Non-severe 49 (34-57)</td>
<td>137 (12.5%)</td>
<td>12 (1.1%)</td>
<td>NA</td>
<td>15 (1.4%)</td>
<td>171 (15.7%)</td>
<td>6 (3.4%)</td>
</tr>
<tr>
<td>Huang Y et al. 2020</td>
<td>China/Hubei province Retrospective study from December 2019 to January 2020</td>
<td>3N=14 (1.2%), F= 30 (19.8%)</td>
<td>562 (37.34)</td>
<td>NA</td>
<td>5 (8.3%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Huang et al. 2020</td>
<td>China/Wuhan Prospective study from December 30, 2019, to January 2, 2020</td>
<td>4. M = 39 (27%), F = 11 (17%)</td>
<td>69 (41-58)</td>
<td>NA</td>
<td>1 (2%)</td>
<td>NA</td>
<td>6 (15%)</td>
<td>29 (70.7%)</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>Liu et al. 2020</td>
<td>China/Hubei province Retrospective study from December 30, 2019 to January 24, 2020</td>
<td>177 M = 61 (45.8%), F = 76 (55.5%)</td>
<td>57 (36-83)</td>
<td>NA</td>
<td>2 (1.5%)</td>
<td>NA</td>
<td>16 (11.7%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mo et al. 2020</td>
<td>China/Wuhan Retrospective study from January 14 to February 5, 2020</td>
<td>165 M = 86 (52.8%), F = 69 (43%)</td>
<td>54 (42-66)</td>
<td>6 (3.9%)</td>
<td>NA</td>
<td>5 (3.2%)</td>
<td>NA</td>
<td>NA</td>
<td>85 (54.8%)</td>
</tr>
<tr>
<td>Wang et al. 2020</td>
<td>China/Wuhan Retrospective, single-center case series from January 1 to January 28, 2020</td>
<td>118 M = 75 (64.3%), F = 63 (53.7%)</td>
<td>56 (42-68) ICU patients (n= 58) Non-ICU (n = 10)</td>
<td>NA</td>
<td>4 (2.9%)</td>
<td>NA</td>
<td>6 (4.3%)</td>
<td>3 (1.9%)</td>
<td>NA</td>
</tr>
<tr>
<td>Wu et al. 2020</td>
<td>China/Wuhan Retrospective study from December 25, 2019, and January 16, 2020</td>
<td>281 M = 128 (45.7%), F = 73 (45.7%)</td>
<td>51 (42-60)</td>
<td>NA</td>
<td>5 (2.5%)</td>
<td>NA</td>
<td>44 (21.9%)</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Wu J et al. 2020</td>
<td>China/Outside of the Wuhan area) Prospective study from January to February 2020</td>
<td>89 M = 42 (47.2%), F = 38 (42.6%)</td>
<td>44 (11)</td>
<td>26 (31%)</td>
<td>3 (4%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Xu K et al. 2020</td>
<td>China/Guangzhou retrospective study from January 3, 2020, and February 4, 2020</td>
<td>99 M = 39 (40%), F = 51 (51%)</td>
<td>50 (18-86)</td>
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<td>1 (1%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>Xu et al. 2020</td>
<td>China/Zhejiang province Retrospective study from October 2019 to February 2020</td>
<td>132 M = 35 (26.9%), F = 27 (20.1%)</td>
<td>41 (32-52)</td>
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<td>NA</td>
<td>NA</td>
<td>0</td>
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</tr>
<tr>
<td>Yang et al. 2020</td>
<td>China/Wuhan Retrospective study from December 25, 2019, and January 26, 2020</td>
<td>52 M = 35 (66.3%), F = 17 (33.7%)</td>
<td>58 (27-87)</td>
<td>2 (4%)</td>
<td>4 (8%)</td>
<td>2 (4%)</td>
<td>32 (61%)/2 (50%)</td>
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<td>NA</td>
</tr>
<tr>
<td>Zhang et al. 2020</td>
<td>China/Wuhan Retrospective study from January 16 to February 3, 2020</td>
<td>110 M = 71 (64.6%), F = 49 (44.5%)</td>
<td>57 (25-87)</td>
<td>2 (1.8%)</td>
<td>4 (3.6%)</td>
<td>2 (1.4%)</td>
<td>NA</td>
<td>NA</td>
<td>38 (41.4%)/2 (1.8%)</td>
</tr>
</tbody>
</table>

(Continued)
Table 1. (Continued)

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Country/Type of study</th>
<th>Sample size (M = male, F = female)</th>
<th>Age mean ±SD or median, range</th>
<th>Current Smokers</th>
<th>COPD patients</th>
<th>COPD Survived</th>
<th>COPD Non-Survived</th>
<th>Mortality rate for study/COPD</th>
<th>Severe cases for study/severe COPD Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou et al., 2020 [30]</td>
<td>China/Wuhan retrospective cohort study from Dec 29, 2019 to Jan 31, 2020</td>
<td>191 M = 110 (62%) F = 72 (38%)</td>
<td>56 (46–67)</td>
<td>11 (6%) Non-survivor = 5 (5%) Survivors = 6 (6%)</td>
<td>6 (36%)</td>
<td>2 (13%)</td>
<td>4 (7%)</td>
<td>51 (28.3%)/4 (66.7%)</td>
<td>NA</td>
</tr>
<tr>
<td>Zhu et al., 2020 [31]</td>
<td>China/Anhui province retrospective study from 24 January 2020 to 20 February 2020</td>
<td>32 M = 15 (47%) F = 17 (53%)</td>
<td>68 (33–52)</td>
<td>6 (18.7%)</td>
<td>2 (68%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Prevalence of COPD in confirmed COVID-19 cases

The pooled prevalence of COVID-19 patients who had COPD from all studies was 2% (95% CI, 1%–3%). Figure 2. The overall $I^2$ was 41.90%, p<0.04.

Disease severity and mortality among COVID-19 COPD patients

Seven studies that included 35 COPD patients reported COVID severity in their analysis. With 63% (22/35) patient reported as severe compared to 37% (13/35) non-severe, this shows that COPD patients are at a higher risk of more severe COVID-19 compared to patients without COPD 33.4% (49/147) calculated RR, 1.88 (95% CI, 1.4–2.4). Data from two studies [28, 30] including COPD patients with confirmed COVID-19 demonstrate 60% (6/10) mortality rate compared to mortality rate in patients without COPD 55% (6/117), [calculated RR, 1.10 (95% CI, 0.6–1.8)].

Smoking history and risk of COVID-19

Smoking exposure including (current and ex-smokers) was reported in eight studies, with 221 confirmed COVID-19 cases. We assessed the prevalence of current smokers in all studies using meta-analysis of proportions of current smokers that had confirmed COVID-19. There was a pooled prevalence of 9%, (95% CI, 4%–14%), Figure 3. The overall $I^2$ was 92.4%, p<0.00. Indeed, 22.3% (31/139) of current smokers and 46% (13/28) of ex-smokers had severe complications. Calculating the RR from these two studies showed that current smokers (31/108) were 1.45 times more likely [RR = 1.45, 95% CI: 1.03–2.04] to have severe complications compared to former and never smokers (13/808) patients [18, 27]. A higher mortality rate of 38.3% (5/13) was also seen among current smokers.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to develop an informed understanding of the prevalence, severity and mortality of COPD patients...
diagnosed with COVID-19. We provide an updated report in relation to smokers [33]. Our main outcomes show that the prevalence of COPD in COVID-19 patients was low, but that the risk of severity (63%) and mortality (66%) were high, which indicates COPD patients with confirmed COVID-19 are at a greater risk of severe complications and death. Furthermore, the prevalence of current smokers in COVID-19 patients was 9% (95% CI, 4%–14%), and this was also associated with greater severity (22%–30%) and mortality (38.5%).

We report a low prevalence of COPD patient in COVID-19 case series compared to the latest COPD prevalence rate in China, which was 15.6% (95% CI 12.6–18.2) and the global prevalence of COPD (9–10%) [33, 34]. There was a low heterogeneity among the studies, which was 41.90%, p 0.04. This is expected since clinical and methodological diversity always occur in a meta-analysis. We speculate that patients may have not been diagnosed. Having a reliable estimate of the prevalence of COPD in COVID-19 cases, and likely outcomes, is crucial to ensure specific successful global preventive and treatment strategies for COPD patients. Bearing this in mind, in the included studies there was no report on COPD severity data and COPD-related comorbidities, which prevents us from assessing the impact of such essential information.

Although the COPD prevalence was not high in the included confirmed COVID-19 cases, COVID-19 carries a substantial burden on COPD patients with increased disease severity. This
<table>
<thead>
<tr>
<th>Study</th>
<th>Name</th>
<th>ES (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guan et al. 2020</td>
<td></td>
<td>0.12 (0.11, 0.15)</td>
<td>15.26</td>
</tr>
<tr>
<td>Huang et al. 2020</td>
<td></td>
<td>0.07 (0.03, 0.19)</td>
<td>10.92</td>
</tr>
<tr>
<td>Mo et al. 2020</td>
<td></td>
<td>0.04 (0.02, 0.06)</td>
<td>14.73</td>
</tr>
<tr>
<td>Wu et al. 2020</td>
<td></td>
<td>0.32 (0.23, 0.43)</td>
<td>9.11</td>
</tr>
<tr>
<td>Yang et al. 2020</td>
<td></td>
<td>0.04 (0.01, 0.13)</td>
<td>13.29</td>
</tr>
<tr>
<td>Zhang et al. 2020</td>
<td></td>
<td>0.01 (0.00, 0.05)</td>
<td>15.25</td>
</tr>
<tr>
<td>Zhou et al. 2020</td>
<td></td>
<td>0.06 (0.03, 0.10)</td>
<td>14.57</td>
</tr>
<tr>
<td>Zhu et al. 2020</td>
<td></td>
<td>0.15 (0.09, 0.35)</td>
<td>6.96</td>
</tr>
<tr>
<td>Overall (I² = 92.48%, p = 0.00)</td>
<td></td>
<td>0.05 (0.04, 0.14)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Fig 3. Pooled prevalence of current smokers with confirmed COVID-19. (ES: Effect size).

Viral infections in COPD patients increase systemic inflammation with slow recovery of reported symptoms [37, 38]. In addition to the effects of COVID-19, patients with COPD have various comorbidities, some of which are associated with increased risk of hospitalization [33–35]. According to recent systematic reviews, the prevalence of comorbidities in COVID-19 patients was high and these comorbidities were associated with increased disease severity [42, 43]. Most of the studies that reported COPD severity defined severe cases as those who were admitted to intensive care unit (ICU), had severe oxygenation, needed mechanical ventilation or death [18, 19, 22–23, 27, 28]. These studies did not give details about the underlying COPD. It would have been interesting to know if the frequency of previous exacerbations was linked to increased complications in COPD patients diagnosed with COVID-19. In general, those with severe case of COVID-19 were older and had more coexisting comorbidities than those with mild illness.

Data from two studies [28, 36] describing COPD patients with confirmed COVID-19 show a higher mortality rate at 60%. This concurs with pre-print studies that found similarly high mortality rates [35, 44–47]. Despite the small number of patients that were analyzed, this increases concerns about the prognosis of this vulnerable population. However, this high...
mortality rate could be attributed to several factors. The majority of COPD patients have various comorbidities that may also be associated with mortality and related conditions may have been underreported because of the difficulties finding the specific cause of mortality [48]. Moreover, in patients with severe COPD, respiratory failure is the principal cause of mortality and this demands ICU intervention. It is possible that limited access to respiratory support as part of COVID-19 management may be contributing to this mortality, dependent on critical care capacity in each hospital or region. According to a recent COVID-19 report from Italy, the surge in patients requiring intensive care has been unmanageable, with 12% of positive cases requiring ICU admission [49], more than that reported in China [18, 28]. As a consequence, patients were dying because mechanical ventilation could not be offered on top of acute shortage of clinicians who were able to manage those patients [50, 51]. Until now, the particular mechanisms of how COVID-19 increases COPD severity and mortality is unknown, and undoubtedly more research is needed to find the possible mechanisms that linked COVID-19 and increased severity and mortality of COPD patients.

Concerning smoking and COVID-19, our data showed a pooled prevalence of 9% current smokers (95% CI, 4%–14%), lower than the reported prevalence of smoking in China that was 25.2% (25.1–25.4) [52]. The overall I² was 92.48% among the studies, which indicates considerable heterogeneity. However, this was addressed by using random effect model to incorporate between-study variability of effect sizes. Such heterogeneity is expected due to different study designs, regions and outcomes. Interestingly, we found that 22.30% (31/139) of current smokers and 46% (13/28) of ex-smokers had severe complications associated and greater mortality reaching 38.5% in current smokers. The calculated RR from two studies showed that current smokers were 1.45 times more likely [RR = 1.45, 95% CI 1.03–2.04] to have severe complications compared to former and never smokers [18, 29]. The impact of smoking history on vulnerability to COVID-19 has been explored but there is limited data on the contribution of tobacco smoking to the spread of and poor outcome in COVID-19. A recent systematic review on COVID-19 and smoking including five studies found that smoking was most likely associated with the negative outcomes. This recommended further research to explore this in more detail due to limited studies [32]. Evidence from other respiratory viruses, respiratory syncytial virus, has shown that inhaled tobacco smoke raises the transmission rate and severity of viral respiratory tract infections [53]. It seems there is underlying mechanisms behind this prevalence, as smoking has been related to higher expression of ACE2 (the receptor for SARS-CoV-2) (pre-print) [54]. However, as more reports globally from diverse racial and genetic contexts become available, differences in the production of ACE2 can be further evaluated and linked to how they lead to COVID-19 vulnerability in different groups [55].

To our knowledge, the present study is the first to systematically evaluate existing literature with a focus on risk of COVID-19 on COPD. For the first time, we conducted a meta-analysis using a random effects model to calculate the pooled prevalence of COPD in confirmed COVID-19 and examined outcomes. This increased the generalizability of our findings, as heterogeneity was addressed by incorporating between-study variability of effect sizes. We showed that COPD and smoking in COVID-19 is associated with greater disease severity and higher mortality. This review has some limitations. Few studies were eligible for inclusion and most of them come from China. Second, heterogeneity exists in location, setting, and design. The reported clinical characteristics were not available in most of the studies at the time of analyses. This work has a number of clinical and research implications. It highlights the global prevalence and the clinical effects of COVID-19 on COPD patients and smokers. As COPD patients are at an increased risk of severe outcomes if they become infected with COVID-19, it is recommended that patients and clinicians establish effective plans for ensuring prevention, such as using tele-medicine to ensure that COPD receive the best care [46, 57]. We strongly
advocate public awareness campaigns concentrating on ways to achieve smoking cessation among smokers, and it is possible that an improvement in cessation rates will help to reduce the spread of SARS-CoV-2. Future studies should investigate the mechanisms between COPD, smoking and COVID-19 infection.

**Conclusion**

Though COPD prevalence in reported COVID-19 cases is low, COVID-19 infection is associated with significant severity and mortality in COPD. There was also increased risk of severe disease and mortality in current smokers. Effective preventive measures are urgently required to reduce COVID-19 risk among COPD patients and current smokers.

**Supporting information**

**SI Appendix.**

(DOCX)

**SI Checklist. PRISMA 2009 checklist: Prevalence, severity and mortality associated with COPD and smoking in patients with COVID-19: A rapid systematic review and meta-analysis.**

(DOC)

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**Project administration:** Jaber S. Alqahtani.

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**Supervision:** Swapna Mandal, John R. Hurst.

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**Writing – original draft:** Jaber S. Alqahtani.

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References


Appendix 19: Research priorities for exacerbations of COPD

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Research priorities for exacerbations of COPD

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