RISK FACTORS FOR HOSPITAL READMISSION IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

by

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DECLARATION OF ORIGINALITY

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The research associated with this thesis abides by the Australian codes on human and animal experimentation, the guidelines by the Australian National Ethics and Institutional Biosafety Committees of the University. All research involving patients with chronic obstructive pulmonary disease was conducted under the approval of the Tasmanian Health and Medical Human Research Ethics Committee (Approval number H0017433).

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STATEMENT OF CO-AUTHORSHIP

Given that this thesis is presented as a sequence of papers, either published, in press or submitted, statement of co-authorship is provided for each chapter.

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PUBLICATIONS

All publications listed resulted from both work in collaboration with University of Central London (no 2) and those described in this thesis (no 1 and 3).

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Located in chapter 2: *Candidate is the primary author, who in conjunction with Authors 1, 2, 3 and 4 conceived and designed the study. Candidate undertook all data collection, analysis and drafting of the manuscript. Authors 5 and 6 provided input into the writing of the research article.*

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CONFERENCE ABSTRACTS

1. Chidiamara M. Njoku, Bonnie J. Bereznicki1, Barbara C. Wimmer, Gregory Peterson and Leigh Kinsman: Hospital readmission of patients with chronic obstructive pulmonary disease (COPD): risk factors, consequences, and preventability. Twelfth Annual Graduate Research Conference, University of Tasmania, Hobart, September 6-7, 2018 (poster presentation).
2. Chidiamara M. Njoku, Bonnie J. Bereznicki1, Barbara C. Wimmer, Gregory Peterson, Leigh Kinsman, Jaber S. Alqahtani and John R. Hurst: Risk factors and associated outcomes of hospital readmission in COPD: a systematic review. Australian Pharmaceutical Science Association (APSA), Melbourne, Australia, December 1-4, 2019 (oral and poster presentation).

We, the undersigned, endorse the above stated contribution of work undertaken for each of the published (or submitted) peer-reviewed manuscripts contributing to this thesis*:*

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Never grow tired of doing what is right.

LIST OF ABBREVIATIONS

6MWD	6-minute walking distance per day
95% CIs	95% Confidence intervals
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
ADO index	Age, MRC dyspnoea score and airflow obstruction measured by FEV_1
AIHW	Australian Institute of Health and Welfare
AUD	Australian dollars
ATSI	Aboriginal and Torres Strait Islander
APC-NMDS	Admitted patient care National Minimum Dataset
BMI	Body mass index
BODE	Body-mass index, airflow Obstruction, Dyspnea, and Exercise capacity
CAT	COPD Assessment Test
CCI	Charlson Comorbidity Index
CCMP	Comprehensive care management program
COPD	Chronic obstructive pulmonary disease
CODEX index	Comorbidity measured with Charlson comorbidity index score, airflow Obstruction measured by FEV_1, MRC Dyspnoea score and previous severe Exacerbation)
CRP	C-reactive protein
DOSE index	MRC Dyspnoea score, airflow Obstruction measured by FEV_1, Smoking status, and number of prior Exacerbations
ECOPD	Exacerbation of COPD
ED	Emergency Department
EKG	Electrocardiogram
FEV_1	Forced expiratory volume in one second

FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HADS	Hospital Anxiety and Depression Scale
HR	Hazard ratio
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification
ICS	Inhaled corticosteroid(s)
ICU	Intensive care unit
IHM	In-hospital mortality rate
IRSAD	Index of Relative Socio-economic Advantage and Disadvantage
IQR	Interquartile range
LABA	Long-acting $beta_2$ agonist
LACE index	Length of stay, Acuity of admission, Comorbidity measured with Charlson comorbidity index score and number of Emergency department visits in last 6 months)
LAMA	Long-acting muscarinic antagonist
LOS	Length of index hospital stay
LTOT	Long-term oxygen therapy
MRC	Medical Research Council breathless scale
mMRC	Modified MRC
NI	No information
ORs	Odds ratios
PaCO2	Partial pressure of oxygen
PEARL score	Previous admission, Extended MRC Dyspnoea score, Age, Right-sided heart failure and Left-sided heart failure)
PPH	Potentially preventable hospitalisation

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
SA2	Area of usual residence
SABA	Short-acting $beta_2$ agonist
SEIFA	Socio-Economic Indexes for Areas
SES	Socioeconomic status
SGRQ	St. George's Respiratory Questionnaire score
SPSS	Statistical Package for the Social Sciences
WBC	White blood cell
WHO	World Health Organisation

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is associated with deterioration in lung function, poor health status and high mortality, morbidity and healthcare costs. Globally, COPD is the third leading cause of death, accounting for 4.7 million annual deaths worldwide. In Australia, 14.5% of people aged 40 years and over have COPD, and it is the 5th leading cause of death. Furthermore, COPD is one of the most common chronic conditions associated with potentially preventable hospitalisation in Australia.

Acute exacerbation is one of the main reasons for hospital admission and readmission of patients with COPD, with severe negative impacts both for the patient and the healthcare system. Prevention of exacerbation of COPD has been recognised as an international priority to combat patients' deterioration and reduce associated healthcare costs. Twenty percent of patients admitted to hospital with an exacerbation of COPD will be readmitted within 30 days, and 50% will be readmitted within six months of hospital discharge. Several studies in Australia have addressed associated factors and trends in all-cause readmission for COPD, but none have explored readmission specifically for COPD. The work described in this thesis was aimed at identifying the prevalence of and risk factors for COPD-related hospital readmission. The specific objectives were to: (i) summarise and evaluate the published evidence on the prevalence of readmission for COPD and the risk factors and outcomes associated with readmission due to COPD, and (ii) investigate the prevalence of and risk factors for COPD readmission in Tasmania.

The last systematic review on risk factors for hospitalisation and all-cause readmission of COPD patients was published in 2007. There were no systematic reviews on risks factors for COPD-related readmission. Therefore, a systematic review of the literature was conducted to summarise the prevalence, risk factors and associated outcomes for COPD-related readmission. Fifty-seven

studies from 30 countries were included in the review. The prevalence of COPD-related readmission varied from 2.6-82.2% at 30 days, 11.8-44.8% at 31–90 days, 17.9-63.0% at 6 months, and 25.0-87.0% at 12 months post-discharge. The heterogeneity between studies precluded a meta-analysis. Hospitalisation in the previous year was the principal risk factor for COPD-related readmission. Variation in the prevalence and the reported factors associated with COPD-related readmission indicated that risk factors cannot be readily generalised, and interventions should be tailored to the local healthcare environment. Relative to those without readmissions, readmitted patients had higher in-hospital mortality rates, shorter long-term survival, poorer quality of life, longer hospital stay, increased recurrence of subsequent readmissions, and accounted for greater healthcare costs.

The second part of this thesis describes a five-year longitudinal retrospective study that utilised administrative hospital data from all four public hospitals in Tasmania. Patients ⩾40 years of age who had overnight COPD-related hospitalisation between 2011 and 2015 were followed up for 12 months post-index discharge. The study investigated the prevalence of hospital readmission for COPD at 30 days, 90 days and 12 months, and determined the risk factors for 30-day and 90-day readmission and time to COPD-related readmission within 12 months. Factors associated with readmission were identified using logistic and Cox regression. The rates of COPD-related readmission were 6.7% within 30 days, 12.2% within 90 days and 23.7% within 12 months. Being male (OR 1.49, 95% CI 1.06–2.09), Indigenous (OR 2.47, 95% CI 1.31–4.66) and living in the low socioeconomic North-West region (OR 1.80, 95% CI 1.20–2.69) were significant risk factors for 30-day readmission. Increased COPD-related (OR 1.48, 95% CI 1.22–1.80; OR 1.52, 95% CI 1.29–1.78) and non-COPD-related (OR 1.12, 95% CI 1.03–1.23; OR 1.11, 95% CI 1.03–1.21) Emergency Department (ED) visits in the previous six months were significant risk factors for 30-

day and 90-day readmissions. Being Indigenous (HR 1.61, 95% CI 1.10–2.37) and increased COPD-related ED visits in the previous six months decreased the time to readmission within 12 months (HR 1.30, 95% CI 1.21–1.39), while a higher Charlson Comorbidity Index increased time to readmission (HR 0.91, 95% CI 0.83–0.99).

In conclusion, the thesis summarised that hospitalisation in the previous year was the key predictor for COPD-related readmission reported in studies. Due to the differences in the reported factors associated with COPD-related readmissions, these factors should be considered in the light of locality due to variations in healthcare systems around the world. Some patient factors (being male, Indigenous, living in the lower socioeconomic North-West region) and system factors (recent ED visits) were identified to be associated with increased risk of COPD readmission in Tasmania.

The present work has the following public health implications. Males, Indigenous people, having recent ED visits and those in the lower socioeconomic areas are at increased risk of COPD-related readmission in Tasmania. Sustainable interventions (e.g. smoking cessation, education) directed at these people may avert and lessen COPD-related readmission. Embarking on community support frameworks that improve their access to health care may eradicate the barriers that influence the way they interact with healthcare system. Improving access to healthcare professionals within the communities, especially in the low socioeconomic areas, may also improve health outcomes, reduce ED visits and readmissions.

Table of Contents

1. CHAPTER 1: Introduction

1.1. Pathophysiology of COPD

Chronic obstructive pulmonary disease (COPD) is a progressive chronic condition that is mainly characterised by obstruction of airflow in the lungs that cannot be fully reversed [1,2]. Global Initiative for Chronic Obstructive Lung Disease (GOLD) defined COPD as a preventable and treatable disease characterised by persistent respiratory symptoms resulting from exposure to harmful particles or gases [1]. COPD comprises of a mixture of respiratory conditions such as emphysema, obstructive bronchiolitis, or a combination of both (Figure 1). Emphysema (parenchymal destruction) is a result of structural changes, narrowing and damaging of the air sacs in the lungs that lead to ineffective emptying of the lungs during expiration [1]. Parenchymal destruction results in hyperinflation of the lungs leading to shortness of breath. Chronic bronchitis is the persistent cough and sputum production (i.e. over three months); an outcome of tenacious irritation and inflammation of the lining of the airways (caused by cigarette smoke or other harmful agents).

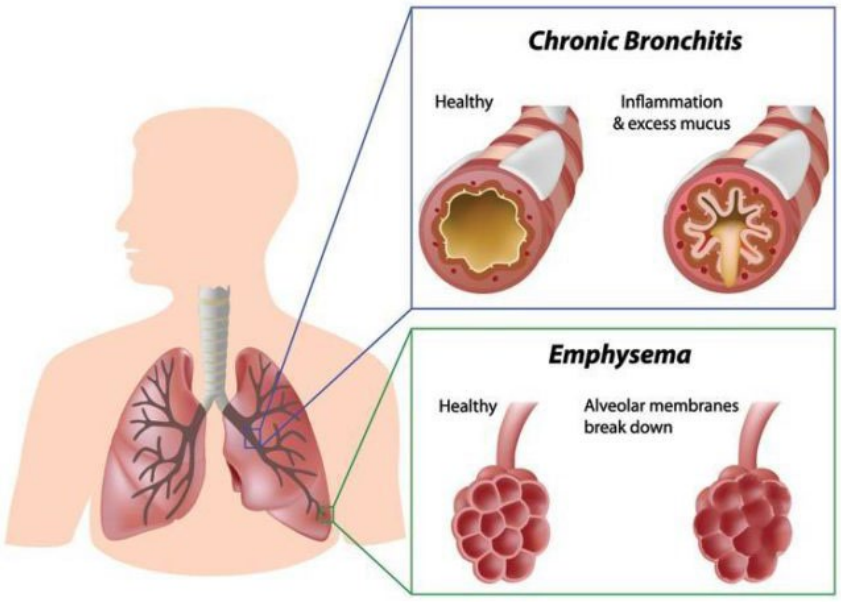

Figure 1. Illustrative representation of pathophysiological changes in COPD [3]

The obstruction of airways is often related to irregular inflammatory response of the lungs to injurious particles or gases such as tobacco smoke, chemicals at work or heavy pollution. Spirometry is the widely recognised and reproducible test of lung function used to measure airflow limitation. It is used to confirm diagnosis (i.e. the ratio of post-bronchodilator forced expiratory volume in one second to forced vital capacity (FEV_1/ FVC) < 0.70) of COPD. GOLD recommends that the diagnosis of COPD should be considered in anyone with dyspnoea, chronic cough or sputum production and/or a history of risk factors (e.g. smoking, occupation and pollution) [1]. GOLD states that assessment of COPD should involve assessment of airflow limitation, effect of disease condition on patient's health status, and risk of upcoming events such as exacerbation. Airflow limitation assessment is based on spirometry result (Table 1) [1].

Table 1. Classification of airflow limitation severity in COPD (based on post-bronchodilator FEV_1) [1]

In patients with FEV_1/FVC <0.70:	
GOLD Stages	**FEV_1 percent predicted**
GOLD Stage 1: mild	$FEV_1 \geq 80\%$ predicted
GOLD Stage 2: moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD Stage 3: severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD Stage 4: very Severe	$FEV_1 < 30\%$ predicted

Symptoms of breathless are usually based on the Modified British Medical Research Council (mMRC) Questionnaire (Table 2) [2], while other symptomatic effects of COPD are better

captured with a COPD Assessment Test (CAT) (Figure 2) [4]. Hence the assessment of COPD, according to the GOLD guidelines, is a combination of a patient's spirometry classification with symptomatic assessment and/or risk of exacerbations (Figure 3) [1].

Table 2. Modified MRC dyspnoea scale [1]

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 slightly 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 at my own pace on the level.
mMRC Grade 3	I stop for breath after walking about 100 metres 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.

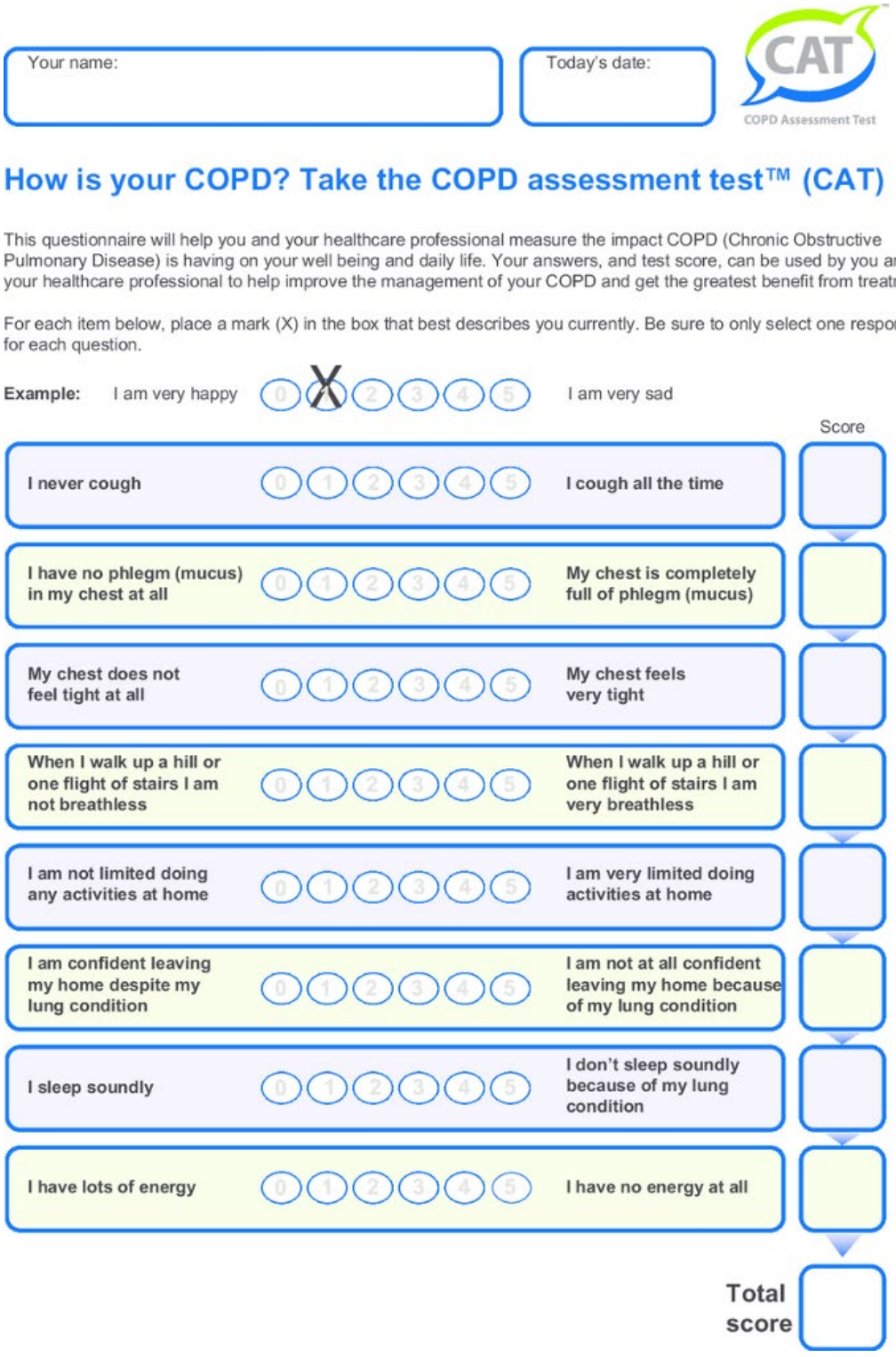

Figure 2. Evaluative questions from the COPD Assessment Test (CAT) [4] (logo is a trademark of the GlaxoSmithKline group of companies. © 2009 GlaxoSmithKline group of companies)

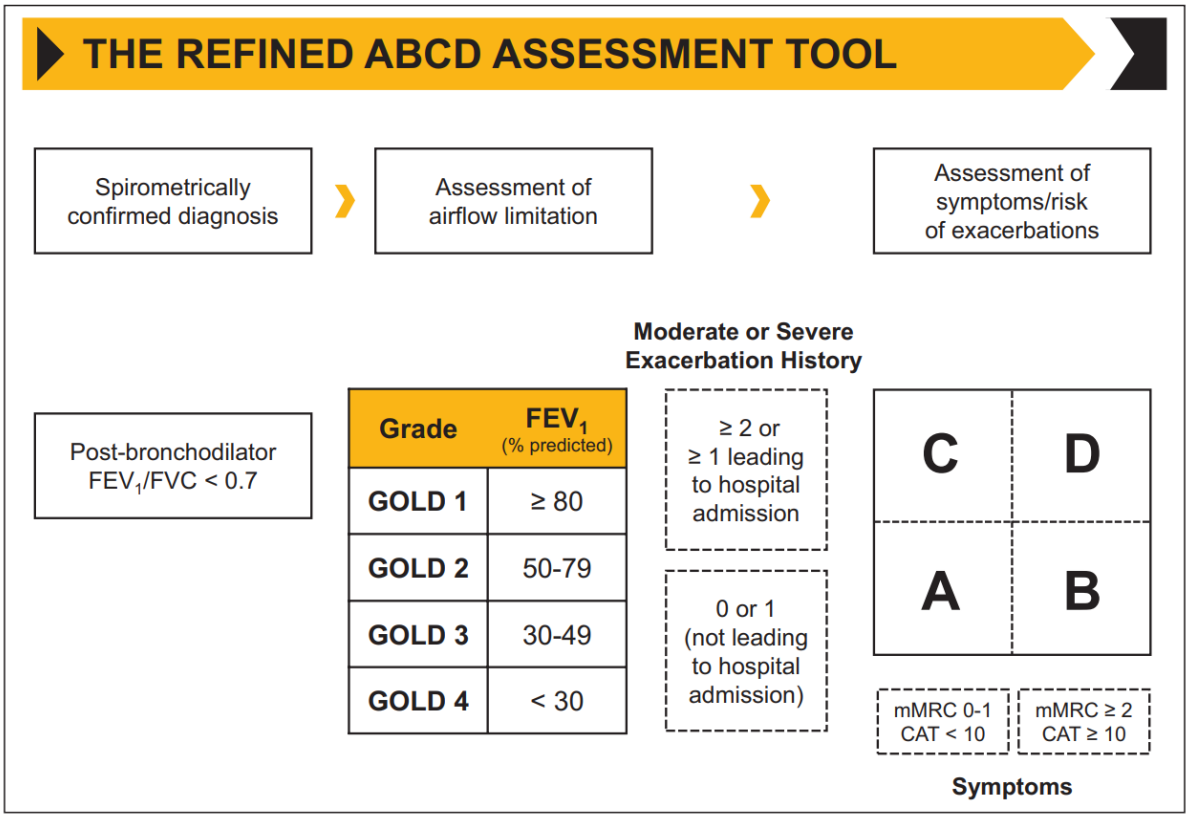

Figure 3. The ABCD assessment tool for COPD patients [1] (A, low exacerbation risk with less symptoms; B, low exacerbation risk with more symptoms; C, high exacerbation risk with less symptoms; D, high exacerbation risk with more symptoms; FEV_1, Forced expiratory volume in one second; FVC, Forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council breathless scale; CAT, COPD Assessment Test)

1.2. Prevalence

The prevalence of COPD occurs mainly in smokers and in people aged 40 years and over. Based on the Burden of Obstructive Lung Disease (BOLD) program, which assessed the prevalence and risk factors for COPD around the world, it is estimated that there were 384 million cases of COPD in 2010, a global prevalence of 11.7% (95% confidence interval [CI] 8.4%-15.0%) [5]. Estimation of COPD prevalence tends to vary depending on criteria used in defining COPD and who is reporting (i.e. self-reporting of respiratory symptoms will vary to when it is based on clinician

diagnosis). COPD is currently the 4th leading cause of death worldwide and is projected to 3rd by 2020 [2,6]. In Australia, COPD is the 5th leading cause of death [7]. Longevity with ageing populations, occupational/indoor air pollution and tobacco smoking are said to be major driving factors for the increase in prevalence [8,9]. It is still acknowledged that under-recognition and under-diagnosis of COPD decreases the accuracy of mortality data [10].

The economic and social burden associated with COPD are significant. The annual economic burden of COPD in 28 European countries in 2011 was 48.4 billion Euros [11]. This was 50% of the total cost for respiratory diseases. The financial cost of COPD in Australia in 2015-16 was $977 million (24.2%) of the total $4,044.21 million expenditure spent on respiratory disease [12]. COPD was the 5th leading cause of Disability-Adjusted Life Years (DALYs) lost across the world in 2013 [13].

In Australia, based on self-reported data in 2017-18, an estimate of 599,000 people (2.5%) were reported to have COPD [14]. This is estimated to be 464,000 people (4.8%) in Australians aged 45 years and over [15]. The prevalence of COPD GOLD Stage 2 or higher in Australia is said to be 7.5% among people aged ≥40 years and 29.2% among people aged ≥75 years [16]. Indigenous Australians (Aboriginal and Torres Strait Islander [ATSI]) bear an unequal burden of COPD disease (2.5 times higher prevalence of COPD, five times higher rate of hospitalisation from COPD and three times higher rate of death from COPD) compared to non-Indigenous Australians [17].

Data from the Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity Database reported that COPD was the principal diagnosis in the hospitalisation of 723.3 per 100,000 population in patients aged 45 years or more in 2015-16 compared to 689.6 per 100,000 population in 2014-15 (5% increase) [7]. AIHW National Hospital Statistics in 2015-2016 showed

that COPD was the most common chronic condition with potentially preventable hospitalisation (PPH) in all states and territories except in Victoria, Western Australia and the Australia Capital Territory [18]. COPD was the 3rd leading cause of PPH in Australia in 2015-16 with a rate of 260 admissions per 100,000 population and 218 admissions per 100,000 population in Tasmania [19]. PPH rate increased nationally from 246 per 100,000 population to 260 per 100,000 population from 2014-15 to 2015-16 (6% increase). In Tasmania, a 6% increase was also recorded from 2014-15 to 2015-2016 (206 vs 218 per 100,000 population) [19].

1.3. Risk factors for COPD

There are several factors that predispose people to COPD. These include genetic factors (such as deficiency of the serine protease α1 antitrypsin, parental lung function, etc.), tobacco smoke, environmental or occupational exposures to dusts, vapours or fumes, indoor air pollutants, outdoor air pollutant, malnutrition, ageing, infections, asthma, sex and low socioeconomic status (SES).

Some genetic factors have shown strong linkage to increased risk for COPD [20]. Low concentration of serine protease α1 antitrypsin in combination with environmental exposures leads to panlobular emphysema [20]. α1 antitrypsin deficiency is predicted to affect around one in 2,000-5,000 people and predisposes to lung disease (emphysema and bronchiectasis) and chronic liver disease (hepatitis, cirrhosis and hepatoma) [20]. There is also a significant correlation of parental lung function (i.e. familial risk of airflow limitation) of those who smoke to lung function of their children [21,22]. It has also been shown that different populations (i.e. current smokers, ex-smokers and non-smokers) have varying differences in the decline of their lung function over time [23,24]. There are also other genetic factors that have been implicated in COPD with inconsistent results (such as tumour necrosis factor α, microsomal epoxide hydrolase 1 etc.) [25].

Smoking is the biggest risk factor and one of the principal causes of COPD [1]. Approximately 75%-85% of COPD cases have been attributed to a history of smoking [26]. Lundback *et al*. reported lower prevalence of COPD attributable to smoking in the 46-77-year age group in Sweden (45%, [95% CI 29-58%]) based on GOLD criteria and 50% [95% CI 28-67%] based on British Thoracic Society criteria) [27] . This is similar to Australian population prevalence of ever smoking in ⩾40 years (53.6% [95% CI 52.3-54.9%]) [28]. Tasmania was reported to be the least to improve in the rate of adults' daily smoking between 2001 and 2016 (21% vs 16.9%) [29]. Tasmania had the second highest smoking rate (18.5%), highest proportion of people in their 20s, 30s and 40s who smoked daily in 2016 [29]. The highest prevalence of COPD mortality, respiratory symptoms, lung function abnormalities and rate of deterioration in FEV_1 are seen in cigarette smokers [30]. Passive smoking (such as living with a smoker) is also associated with a poorer quality of life and an increased risk of severe exacerbation in COPD patients [31].

Previously the prevalence of COPD was higher in males compared to females, but it is almost equal now with recent data from developed countries [25]. GOLD noted the change in smoking pattern in males and females could explain the almost equal rates of COPD in both genders [1]. In Australia, the rate of male and female daily smokers over the age of 18 years in 2016 were 14.6% and 11.6% respectively [29]. There was no difference in smoking rates in both males and females in those aged between 50-59 years (14.4% vs 14.1%).

As a condition common in the elderly, age has always been indicated as a risk factor for COPD. As the population lives longer, the risk of chronic disease such as COPD increases. There are also similarities found between the structural changes in COPD patients and that of aging airways and parenchyma [32]. Socioeconomic factors have a greater impact in the development of COPD. Poverty is recognised as an alternate measure for many factors that consequently increases risk of

COPD (such as poor nutrition, crowding, exposure to pollutants and high smoking rates, poor access to healthcare and early respiratory infections) [25].

There is growing evidence that lower SES increases the risk of developing COPD [33]. Gershon *et al.* [34] demonstrated in their studies that lifetime risk of COPD was higher in individuals of lower SES than in those of higher status (32.1% vs 23.0%) and those who live in rural setting than those in urban setting (32.4% vs 26.7%). There is no clarification as to whether this is due to overcrowding or poor nutrition or other SES risk factors. There is strong evidence that people in the lowest SES group, unemployed and those who live in remote areas are more likely to smoke, and their quit attempts are highly unsuccessful [35]. The AIHW conducted a National Drug Strategy Household Survey in 2016 and confirmed that people living in the lowest SES areas (17.7%), unemployed (22.8%) and living in remote areas (20.7%) were more likely to smoke than those in highest SES areas (6.5%), employed (12.5%) and living in major cities (10.6%) [29]. The survey also reported that daily smokers aged 40 and over have increased from 2001 to 2016 (44% vs 57% respectively) [29].

1.4. Management of COPD

Treatment of COPD involves prevention of exacerbations (such as smoking cessation and vaccination), early detection of airflow limitation (especially in smokers to prevent impairment), pharmacological therapies (e.g. beta agonists, antimuscarinics, inhaled corticosteroids, antibiotics, oral corticosteroids, mucolytics etc.), oxygen therapy, pulmonary rehabilitation, education and self-management. The management of both stable and exacerbation of COPD lays emphasis on the importance of combination of preventative measures, pharmacological and non-pharmacological treatments, monitoring and follow-up.

The huge impact of comorbidity complicates the management of COPD as it cannot be treated in isolation without management of the other diseases. As the disease is progressive, there is also supportive, palliative, end-of-life and hospice care required at a later stage. Late-stage of COPD is chiefly marked by severe dyspnoea, cough, fatigue, anxiety, depression and social isolation [36]. These have immense impact on quality of life. Palliative care needs to be considered early by a multidisciplinary team with attention on symptom control, psychosocial and spiritual issues [37]. Early implementation of palliative care in the right group could prevent some hospital readmissions of patients at this stage.

1.4.1. COPD-X Guidelines

The COPD-X Guidelines is the Australian and New Zealand online management guideline for COPD developed jointly by the Lung Foundation and the Thoracic Society of Australia and New Zealand and is updated every quarter [37]. The main recommendations and level of evidence incorporated in the COPD-X Guidelines originated mainly from GOLD [37]. The main commendations of the COPD-X plan include:

- C - **C**onfirm diagnosis (via thorough history and examination, presence of airflow limitation etc.)
- O - **O**ptimise function (using stepwise pharmacotherapy approach, encourage physical activities, regular check on inhaler technique, pulmonary rehabilitation etc.)
- P - **P**revent deterioration (smoking cessation, vaccination, mucolytics and prevention of exacerbation)
- D - **D**evelop support network and self-management plan (support groups and other community services)

- X - Manage e**X**acerbations (inhaled bronchodilators, systematic corticosteroids and/or antibiotics).

The guidelines recommend a stepwise escalation of treatment depending on the severity of disease (based on assessment of lung function, history of exacerbations and comorbidities) (Figure 4) [36,37]. The aim of the stepwise approach recommended for pharmacotherapy is to ensure that symptoms are treated effectively, and exacerbations are prevented. The four key components of the non-pharmacological interventions are reduction of COPD risk factors, optimisation of lung function, consideration of comorbidities and appropriate referral. The Australian Therapeutic Guidelines specify that the goals of managing stable COPD are to decrease symptoms, decrease severity and occurrence of exacerbation and deterioration in lung function, increase exercise tolerance, increase health-related quality of life and slow disease advancement [36].

Typical symptoms	MILD • few symptoms • breathless on moderate exertion • recurrent chest infections • little or no effect on daily activities	MODERATE • breathless walking on level ground • increasing limitation of daily activities • cough and sputum production • exacerbations requiring corticosteroids and/or antibiotics	SEVERE • breathless on minimal exertion • daily activities severely curtailed • experiencing regular sputum production • chronic cough • exacerbations requiring corticosteroids
Typical Lung function	FEV_1 = 60 - 80% predicted	FEV_1 = 40 - 59% predicted	FEV_1 < 40% predicted
Non-pharmacological interventions	**RISK REDUCTION**: check smoking status, support smoking cessation, recommend annual influenza vaccine and pneumococcal vaccine according to immunisation handbook. **OPTIMISE FUNCTION**: encourage regular exercise and physical activity, review nutrition, provide education, develop GP management plan and written COPD action plan (and initiate regular review). **CONSIDER COMORBIDITIES**: especially osteoporosis, cardiovascular disease, lung cancer, anxiety and depression. **REFER** to pulmonary rehabilitation and consider psychosocial needs.		
		Consider oxygen therapy, surgery, bronchoscopic interventions, palliative care services and advanced care planning.	
Pharmacological interventions	Check inhaler device technique and adherence at each visit; up to 90% of patients use devices incorrectly. Short-acting reliever medication: short-acting bronchodilator (SABA or ipratropium).		
	Symptom relief: long-acting bronchodilator (LAMA and/or LABA). This may also help to prevent exacerbations.		
		Exacerbation prevention (when FEV_1 <50% predicted AND patient has had 2 or more exacerbations in the previous 12 months): consider commencing ICS+LABA combination therapy.	
			Consider low-dose theophylline.

Footnote: FEV_1, Forced expiratory volume in one second; SABA, Short-acting $beta_2$ agonist; LAMA, Long-acting muscarinic antagonist; LABA, Long-acting $beta_2$ agonist; ICS, Inhaled corticosteroid

Figure 4. Stepwise management of stable COPD [37]

1.4.2. Smoking cessation

Reduction of COPD risk factors is a priority in the management of the condition. Smoking cessation is the most cost-effective way to reduce the risk of developing COPD, and it also halts its advancement [38]. Smoking is an addiction with chronic relapsing, which makes quitting difficult. Combining pharmacotherapies (e.g. nicotine replacement products, varenicline, bupropion etc.) with behavioural interventions (i.e. advice and counselling delivered by health professionals) significantly increases smoking cessation rates [39]. GOLD emphasised that a successful smoking cessation strategy will involve incorporation of public policy and information propagation programs health education via media and schools [1].

1.4.3. Exacerbation of COPD

Another key factor for preventing deterioration in COPD patients is deterrence of exacerbation. Exacerbation of COPD (ECOPD) is marked by an acute onset of change in a patient's baseline dyspnoea, cough, and/or sputum (that is beyond the patient's normal daily variation), which leads to a change in regular medication or hospital admission [40]. GOLD classified exacerbation into three levels based on severity of treatment required [1]:

- Mild - managed only with short-acting bronchodilators
- Moderate - treated with short-acting bronchodilator as well as antibiotics and/or oral corticosteroids
- Severe - patients requiring admission or visit to ED or acute respiratory failure.

The American Thoracic Society/European Respiratory Society guidelines classified exacerbation into three levels based on operational grouping of the severity of clinical relevance of the episode and its outcome [41]:

- Level I - mild or moderate treated at home
- Level II- severe requiring hospitalisation
- Level III - severe leading to respiratory failure

The COPD-X guidelines however do not specify classification of ECOPD rather noted that an FEV_1 less than one litre (or < 40% predicted) is an indication of a severe exacerbation in patients with moderate COPD [37]. For severe COPD patients who are usually stable on FEV_1 <40% predicted, the vital signs for severe exacerbation are based on worsening hypoxaemia and/or respiratory acidosis [37]. Every ECOPD results in a loss of lung function especially in patients with mild disease where it has been shown to result in FEV_1 loss of 87mls/year (95% CI 23-151) [42]. Early diagnosis and management of exacerbations may inhibit hospitalisation and delay advancement of disease [43]. Although severe ECOPD is estimated to be <10% of all exacerbations [44], it has major socioeconomic impact with almost 60%-70% of healthcare cost associated with COPD [45].

1.5. Risk factors for readmission from ECOPD

ECOPD is one of the major risk factors for hospital admission and readmission, with a negative impact on health status and mortality [46]. ECOPD contributes to deterioration in lung function and decline in patients' quality of life [47,48]. Almost 50% of COPD patients will be readmitted at least once within six months of their initial hospitalisation [49,50]. The causes of readmission could be solely due to ECOPD or any respiratory disease or any other disease [46].

There have been conflicting definitions of readmission from COPD and a varied range of time intervals in published studies between early readmission (≤30 days) and late readmission (>30

days and up to 2 years) [46,51]. The variations in causes and time of readmission has implications on the ability to use these studies to predict and prevent readmission.

Recent evidence indicates that one in five patients admitted with ECOPD is readmitted within 30 days of discharge [52-54]. Many developed countries are aiming their policies to target reduction of early readmissions [51]. The aim of targeting these patients (i.e. 'high flyers') [55] who are the high users of clinical resources is to reduce health costs associated with hospitalisation as well as improve patients' quality of life. It is worth noting that 25% of patients are unable to recover their lung function by 35 days after an acute ECOPD [56]. This indicates that their readmission is likely expected. This is in line with a recent argument which states that 30-day readmission may not be the salient measure in relation to improvement of patient and clinical outcomes [57]. A broader approach involving consideration of local needs, healthcare policy, patient's ability to access inpatient and outpatient care while patient's health and socioeconomic issues should be the aim for effective outcomes.

Several factors have been recognised as major risk factors for ECOPD and readmission in COPD patients. These include reduced FEV_1, comorbidity, chronic mucus hypersecretion and lack of pulmonary rehabilitation [52,58]. Some factors are persistently connected with readmission of ECOPD patients such as poor lung function, previous admission for ECOPD, comorbidities and low SES [59-61]. Patients with severe disease, who have been initially hospitalised and have less social support are also more prone to COPD readmission [62]. Factors associated with readmission can be categorised under patient factors, provider factors and system factors (see Table 3) [63].

Table 3. Factors associated with readmission for COPD [63]

Patient factors	Provider factors	System factors
Increasing/older age	Prescription of respiratory-related medications	Previous admission and number of admissions in the past year
Sex (male)	Prescription of psychotropic drugs	Hospital length of stay (<2 or >5 days)
Poorer social determinants of health	Long-term oxygen therapy	Discharged to health/social institutions
Poor activity level	Use of ventilatory support	Discharged during winter season
Comorbidities	Lack of in-hospital tobacco cessation	Lack of pulmonologist follow-up after discharge
Nutritional factors		
Disease severity		
Decline in lung function		

There is evidence that more than 75% of all-cause readmissions do not have COPD as their primary diagnosis and 50% of readmissions in COPD patients are not mainly connected to respiratory illness but with their other comorbidities [54,63]. The implementation of Hospital Readmissions Reduction Penalty (HRRP) for COPD in 2014 by the Centres for Medicare and Medicaid Services in the USA was to reduce excess all-cause 30-day readmissions by penalising hospitals (3% payment reduction) with high rates [64]. However, the HRRP does not measure patient-centred outcomes (e.g. mortality, self-efficacy, patient satisfaction and exercise tolerance) [65], and there is still no evidence of any direct link between risk of 30-day readmission and quality of care [66].

There is still inconsistency in the reported literature on risk factors for COPD readmission with no systematic review that has summarised the risk factors specific for COPD-related

readmission. The only systematic review on all-cause readmission was undertaken in 2007 [67]. Improvement in identifying risk factors for COPD-related readmission and patients at high-risk of readmission are still being requested due to inconsistency in the quality of care delivered to hospitalised COPD patients across care continuum [68,69].

1.6. Clinical tools as prognosis indexes

The aim for identification of risk factors associated with readmission of ECOPD is to target patients with these factors and prevent readmission. Many approaches have been followed in relation to reducing and preventing readmission of ECOPD patients. Some have been focused on patients' factors such as socio-demographic characteristics [60,70] and others on clinical indicators such as FEV_1, duration of disease, hypercapnia at discharge, chronic use of steroids and comorbidities [55,60,71,72].

There has been a growing demand to utilise these risk factors in the development of various clinical tools as prognostic scores (see Table 4). Currently, there are:

- BODE index (Body mass index (BMI), airflow obstruction measured by FEV_1, dyspnoea score measure as per the Medical Research Council (MRC) dyspnoea score (MRC dyspnoea score) and exercise capacity measure by a 6-minute walk test) [41]
- ADO index (age, MRC dyspnoea score and airflow obstruction measured by FEV_1) [73]
- DOSE index (MRC dyspnoea score, airflow obstruction measured by FEV_1, smoking status, and number of prior exacerbations) [74]
- CODEX index (comorbidity measured with Charlson comorbidity index score, airflow obstruction measured by FEV_1, MRC dyspnoea score and previous severe exacerbation) [75]

- LACE index (length of stay, acuity of admission, comorbidity measured with Charlson comorbidity index score and number of emergency department [ED] visits in last 6 months) [76]
- PEARL score (previous admission, extended MRC Dyspnoea (eMRCD) score, age, right-sided heart failure and left-sided heart failure) [77]

Table 4. Prognostic tools [77,78]

Measured indices													
	Age	**BMI**	**Charlson comorbidity index score**	**FEV_1 % predicted**	**mMRC dyspnoea score**	**Exacerbation †**	**Severe Exacerbation ‡**	**Smoking status**	**Length of stay**	**Acuity of admission §**	**ED visits**	**Previous admissions**	**RHF[††] & LHF[‡‡]**
ADO	x			x	x								
BODEX		x		x	x		x						
CODEX[§§]			x	x	x		x						
DOSE				x	x	x		x					
LACE			x						x	x	x		
COTE			x										
PERL[¶]	x				x							x	x

†Patient-reported acute ECOPD in previous year; §Elective or emergency admission; ¶extended MRC Dyspnoea (eMRCD); ††RHF (right-sided heart failure); ‡‡LHF l(eft-sided heart failure); §§Age-adjusted Charlson Comorbidity Index (CCI)

The growing literature on the best predictor tool indicates that attention to COPD patients' comorbidities during admission could aid establishing patients at highest (and possibly modifiable) risk of readmission. There is still paucity of evidence of the most appropriate tool for predicting readmission for COPD. Four of the predictor tools are COPD specific (ADO, BODEX, CODEX, DOSE) but are not simple to use in clinical care. Despite the growing evidence of previous admission as a risk factor for readmission, PERL is the only predictor tool to include it in the measured indices (Table 4). LACE, though not specific to COPD, can be easily available as it uses patient characteristics that are easily available for clinicians and healthcare professionals. The heterogeneity of COPD disease may also explain the lack of a tool suitable for all patients. There is still no tool that has considered impact of SES status and health literacy in readmission for COPD. There is still paucity of evidence of the most appropriate tool for predicting COPD-related readmission.

1.7. Interventions to reduce readmission for COPD

Specific interventions have been identified to reduce early readmissions or reduce longer-term mortality in COPD patients such as patient self-management, pulmonary rehabilitation and follow up within 30 days of discharge from hospital [79]. Prieto-Centurion *et al.* [80] conducted a systematic review of five studies involving 1,393 participants, and identified five trials in six countries that evaluated interventions aimed to reduce readmission for COPD patients. Only two of the studies (Bourbeau *et al.* and Casas *et al.*) demonstrated significant reduction in all-cause readmission at 12 months (45% vs 67%, p = 0.028). The Bourbeau *et al.* study [81] conducted in Canada utilised post-discharged interventions that involved disease education, smoking cessation and health counselling, inhaler technique training, exercise program, development of action plan including medications, communication with primary care provider, home visits, follow-up telephone call and patient hotline. Casas *et al.* [82] utilised pre-discharge interventions (discharge planning, disease education, inhaler technique training), bridging interventions (transition

navigator), and post-discharge interventions (assessment of comorbidities, referral to social services, communication with patient's primary care provider, home visits, follow-up telephone call and patient hotline). None of the five studies examined 30-day and 90-day readmission as the primary outcome. Three of the studies implemented interventions post-discharge with only two utilising combination of pre-discharge and bridging (i.e. initiated while in hospital and continued after discharge) interventions. The differences in both the interventions as well as study population may have resulted in the variation in results.

Jennings *et al.* [83] conducted a clinical trial in 172 patients hospitalised for COPD exacerbations and assessed the effects of a four-intervention treatment bundle on rehospitalisation or emergency visits within 30 days of discharge. The treatment bundle consisted of inhaler training, smoking-cessation counselling, screening and referral for managing selected comorbid conditions (gastroesophageal reflux, depression, anxiety), and a follow-up telephone call after hospital discharge. There was no significant difference observed between the intervention (18/93 patients, 19%) and control (18/79, 23%) groups, respectively.

Fan *et al.* [84] conducted another trial in the United States which aimed to determine the efficacy of comprehensive care management program (CCMP) in the reduction of readmission for COPD patients. The CCMP comprised of COPD education during four individual sessions, an action plan for detecting and treating exacerbations and planned proactive telephone calls for case management. The study was terminated prematurely due to an increased risk of death in the intervention group compared to control group (28 deaths vs. 10 deaths [17% vs7%], $p = 0.003$).

The above illustrates the present conflicting outcomes on the best sets of interventions to reduce readmission due to ECOPD. It also highlights the inconsistency in the choice of risk factors targeted for intervention within the many risk factors reported to be associated with COPD readmission. Despite the vast literature on the various interventions attributed to reduction of readmission, there is an agreement that no one particular intervention on its own will prevent

readmission for COPD patients [80]. There is now the move to address the need of integrating evidence-based guidelines into practice with the use of clinical pathways [85]. Clinical pathways are clinical protocols used by healthcare professionals to adopt these guidelines in the management of their patients' conditions according to their local needs. There are indications of their value in the management of COPD patients to reduce readmission rates, but a recent systematic review was inconclusive due to limitations of the study designs [86]. Ongoing studies are addressing the evidence-based impact of clinical pathways in COPD [85,87].

1.8. Research gap and importance of research

The last systematic review on risk factors for hospitalisation and readmission for all-cause COPD patients was published in 2007 [67]. There is need to update this as there have been many new therapeutic interventions developed since. More importantly, there is no systematic review on risks/predictors of COPD-related readmission despite few literature reviews on this area [52,88]. Despite several calls for development of clinical tools specifically for COPD readmission, there is still no consensus on the key risk factors that are associated with readmission for COPD.

There is no clinical evidence to indicate what the independent risk factors of these readmissions resulting from COPD in Tasmania are in comparison with international literature. Australian data show that there is still a growing increase in all-cause readmissions for COPD and number of PPH from COPD. There is a lack of recent Australian research that has comprehensively investigated the epidemiology of these risk factors. Research focussing on the proportion of patients with a history of recurrent readmission from ECOPD is especially warranted in Australia where there is increase in PPH from COPD. Several studies in Australia have addressed associated factors and trend in all-cause readmission for COPD [89,90], but none has explored readmission specifically for COPD.

1.9. Aims and objectives

The overall aim of this thesis was to identify the prevalence of and risk factors, for COPD-related hospital readmission.

The specific objectives were to:

i. Summarise and evaluate the published evidence on the prevalence of readmission for COPD and the risk factors and outcomes associated with readmission due to COPD
ii. Investigate the prevalence of and risk factors for COPD readmission in Tasmania.

2. CHAPTER 2: Literature review (systematic review)

2.1. Risk factors and associated outcomes of hospital readmissions in COPD: A systematic review

Overview: This study addressed the first objective of the thesis. It summarises the prevalence of COPD-related readmission, identifies the risk factors, consequences and associated outcomes of readmission from COPD as reported in the literature.

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Review article

Risk factors and associated outcomes of hospital readmission in COPD: A systematic review

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a leading cause of unplanned readmission. There is need to identify risk factors for, and strategies to prevent readmission in patients with COPD.

Aim: To systematically review and summarise the prevalence, risk factors and outcomes associated with rehospitalisation due to COPD exacerbation.

Method: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. Five databases were searched for relevant studies.

Results: Fifty-seven studies from 30 countries met the inclusion criteria. The prevalence of COPD-related readmission varied from 2.6 to 82.2% at 30 days, 11.8–44.8% at 31–90 days, 17.9–63.0% at 6 months, and 25.0–87.0% at 12 months post-discharge. There were differences in the reported factors associated with readmissions, which may reflect variations in the local context, such as the availability of community-based services to care for exacerbations of COPD. Hospitalisation in the previous year prior to index admission was the key predictor of COPD-related readmission. Comorbidities (in particular asthma), living in a deprived area and living in or discharge to a nursing home were also associated with readmission. Relative to those without readmissions, readmitted patients had higher in-hospital mortality rates, shorter long-term survival, poorer quality of life, longer hospital stay, increased recurrence of subsequent readmissions, and accounted for greater healthcare costs.

Conclusions: Hospitalisation in the previous year was the principal risk factor for COPD-related readmissions. Variation in the prevalence and the reported factors associated with COPD-related readmission indicate that risk factors cannot be generalised, and interventions should be tailored to the local healthcare environment.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive, preventable and treatable chronic condition that is mainly characterised by obstruction of airflow in the lungs [1]. It is usually associated with an inflammatory reaction to inhaled tobacco smoke and toxic particles and gases [1]. COPD is associated with deterioration in lung function, poor health status and high mortality, morbidity and healthcare costs. The

Abbreviations: 6MWD, 6-minute walking distance per day; BMI, body mass index; BODE, Body-mass index, airflow Obstruction, Dyspnea, and Exercise capacity; CCI, Charlson Comorbidity Index Scores; COPD, Chronic obstructive pulmonary disease; CRP, C-reactive protein; ECOPD, exacerbation of COPD; EKG, electrocardiogram; FEV_1, Forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HADS, Hospital Anxiety and Depression Scale; ICS, inhaled corticosteroid; IHM, in-hospital mortality rate; LABA, Long-acting $beta_2$-agonists; LOS, length of index hospital stay; LTOT, Long-term oxygen therapy; MRC, Medical Research Council breathless scale; NI, no information; $PaCO_2$, partial pressure of oxygen; SGRQ, St. George's Respiratory Questionnaire score; WBC, white blood count.

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World Health Organization estimated that there were over 251 million cases of COPD globally in 2016, and that more than 3.2 million people died from COPD in 2015. Currently, COPD is the 4th leading cause of death worldwide [2] and is anticipated to become the 3rd leading cause of death by 2020 [3,4]. The global burden of COPD, expressed in disability-adjusted life years, ranked 8th out of the top 20 medical conditions in 2015 [5].

COPD is one of the leading causes of unplanned hospitalisation and readmission in the world [6,7]. Acute exacerbation is one of the main reasons for hospital admission and readmission of patients with COPD, with severe negative impacts both for the patient and the healthcare system. Prevention of exacerbation of COPD has been recognised as an international priority to combat patients' deterioration and reduce associated healthcare costs [7,8]. COPD is regarded as an ambulatory care sensitive condition, meaning that many hospital admissions are considered preventable through effective preventive care and management in the primary care setting [9].

A logical strategy to address readmission rates and healthcare costs is the identification and targeted care of high-risk patients with COPD [7,10]. There has been an increasing development of multicomponent predictor tools for assessing prognosis of severe exacerbation of COPD [11,12]. Previous studies have identified some patient and clinical factors as potential predictors of readmission due to COPD; including age, gender, comorbidities, low socioeconomic status, dyspnoea on admission and severe COPD disease [13–16]. Service level variables, such as previous hospitalisation, short (<2 days) or long (>5 days) length of index hospital stay (LOS), an absence of follow-up, and the discharge destination (i.e. home without care), have also been associated with readmission [17,18].

There is no recent comprehensive systematic review of the literature summarising the prevalence and risk factors implicated in readmission for COPD, and associated outcomes. The only available systematic review of risk factors for readmission from COPD was published in 2007 [19]. Over the last 10 years, the body of knowledge in the area of risk factors for readmission in COPD has grown substantially. In addition, recent literature has investigated socioeconomic factors. Hence, this systematic review aims to provide an update by examining the prevalence of, and identified risk factors for, recurrent COPD exacerbation hospitalisations and the associated outcomes of readmission.

2. Methods

2.1. Study design

A comprehensive systematic review of the literature was conducted based on the current guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols-2015 (PRISMA-P 2015) [20] (Supplement A). The protocol was registered with the international prospective register of systematic reviews (PROSPERO; CRD42018102931).

2.2. Eligibility criteria

Studies published between January 2000 and June 2019 were included based on the following inclusion criteria:

- readmission/rehospitalisation of COPD clearly defined as more than one admission (as an inpatient and not including emergency department attendance) due to COPD/exacerbation of COPD (ECOPD), where COPD was the primary diagnosis for the readmission/rehospitalisation; and
- included the analysis of the contribution of risk factors or predictors or causes (and/or their associated outcomes) for ECOPD leading to readmission/rehospitalisation.

Studies were excluded if they:

- examined a single factor related to readmission in isolation, without analysing and presenting data on a range of potential risk factors;
- described the implementation of interventions or programs beyond normal care;
- were conference abstracts, editorial reports and letters, theses, reviews, randomised control trials, or qualitative studies;
- were published in any language other than English; or
- were undertaken in developing countries, according to the International Monetary Fund classification [21].

2.3. Information sources

Five databases (Medline, Scopus, Embase, Cumulative Index to the Nursing and Allied Literature [CINAHL] and International Pharmaceutical Abstracts [IPA]) were searched for relevant papers. Additional articles were sourced via Google, Google Scholar and manual screening of reference lists.

2.4. Search strategy

We developed a step-wise detailed search strategy. Four main key terms (COPD, readmission, risk factors and consequences) were developed as 'concepts' based on reviewing the previous systematic review and studies relevant to the topic [19,22]. Detailed alternative terms and synonyms for each of the key concepts were also identified as free-text terms and used to search in the databases as title and abstract. The databases were also searched using database-specific controlled vocabulary/subject headings (Supplement B). Further alternative words were obtained from scanning titles and abstracts of relevant studies related to the topic, in collaboration with a research librarian.

Each concept was separately searched as a free-text term and subject heading/sub-heading in the databases. The free-text search and subject heading/MeSH terms were combined with the Boolean operator "OR". The search results for each concept were combined with the Boolean operator "AND". Detailed information on the search strategy can be found in a supplement table (Supplement C).

2.5. Study selection and data extraction

Following the removal of duplicates using EndNote X8 (Thomson Reuters, USA), the studies were exported into the Covidence online systematic review platform (Veritas Health Innovation, Australia). The initial screening of titles and abstracts was undertaken by the first author and then independently checked by other authors. Articles approved following the preliminary screening of titles and abstracts underwent full-text screening independently by two reviewers. Disagreements between independent reviewers were resolved following group discussions.

Risk factors were classified as patient, provider and system factors. The patient factors were grouped into socioeconomic- and clinical-related factors, while the provider (including prescriber) factors were grouped into pharmacological and non-pharmacological factors. We conveyed the effect of both individual comorbidities and number of comorbidities by classifying individual comorbidities in accordance with the International Classification of Disease, 10th Revision, Clinical Modification code [23], while reporting comorbid burden using Charlson Comorbidity Index Scores (CCI) [24].

2.6. Quality assessment and hierarchy of evidence

The methodological quality of each included study was evaluated independently by two authors using the coding manual of the Newcastle-Ottawa Scale [25]. This tool was developed and is mainly used for the appraisal of non-randomised studies, while assessing three aspects of the study (selection, comparability, and outcome). The scale utilises a 'star' system with a maximum of nine stars for each study.

Ratings of the quality of studies are categorised as either good (7–9 stars), fair (4–6 stars) or poor (1–3 stars). Each paper was independently assessed by two authors and discrepancies were resolved via group discussion. Every step of the data processing and extraction was documented and saved in EndNote and Covidence.

3. Results

3.1. Study selection

The initial search yielded 4,213 hits with an additional 200 from other resources (Google Scholar search), of which 1,675 were duplicates and removed. From 2,738 titles and abstracts, 494 articles were selected for full-text review and 57 studies were finally included. The results of the study search, indicating excluded studies (with reasons) and included studies, are reported in the PRISMA flowchart [20] (Fig. 1).

3.2. Study characteristics

The characteristics of the included studies are displayed in Table 1. Of the 57 studies, 37 (64.9%) were retrospective studies, and 20 (35.1%) were prospective studies, of which two were cross-sectional studies [26,27]. The studies were conducted in 30 different countries, with three in multiple countries [14,28,29]. The majority of studies were conducted in the USA (n = 15) [17,29–42], Spain (n = 13) [13,28,29,43–52] and Canada (n = 9) [16,53–59], with 44 (77.2%) studies undertaken in the last 11 years (2008–2019). Fifty-four (94.7%) studies reported risk factors for COPD readmission, nine (16.0%) reported both risk factors and outcomes associated with readmission [14,28,35,38,46,49,60–62] and three (5.4%) reported only patient-related outcomes of readmission [63–65]. Study sample sizes varied from 17 [65] to 696,385 [66] patients, with a total of 2,822,486 patients across all studies. Most studies reported the mean age of their patients which ranged from 56.6 [41] to 76.8 [60] years.

3.3. Study quality

After comprehensive assessment, study quality was identified as being good for most studies (n = 50), with seven studies rating as fair [27,30,42,47,51,65,67] (Supplement D). The main area of weakness was lack of clarity in the definition and representativeness of readmitted patients. In the case of uncertainty regarding the cause of readmission (i.e. all-cause or COPD-related), study authors were contacted and asked for clarification. There was also a lack of clarity on the comparability of cohorts, as variables controlled for in the studies were often not clearly indicated. Most studies clearly defined their inclusion criteria and

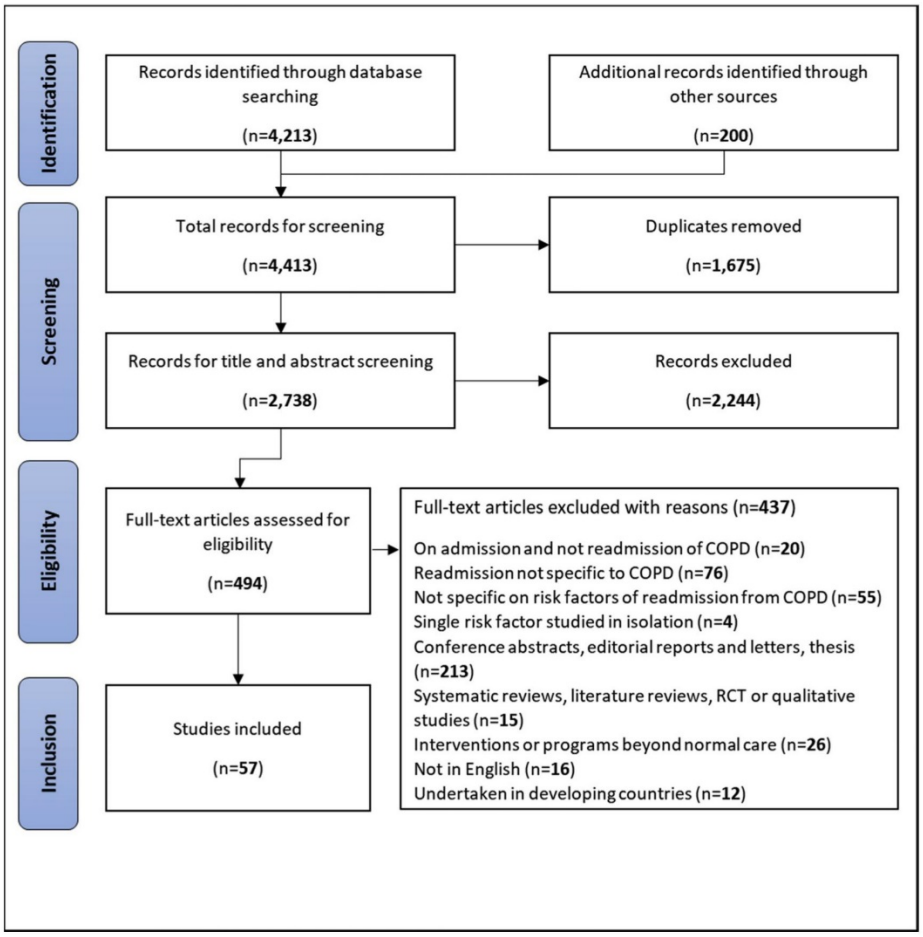

Fig. 1. Study flowchart of included studies.

Table 1
Characteristics of included studies.

First author, year	Country/region	Number of patients	Mean age (years)	Gender (male %)	Readmission rate (%)				Quality assessment score
					30 days	31–90 days	>90 days	Frequency	
				53.0		Median 29.5 at 36 days			Good (8)
Almagro, 2006 [13]	Spain	129	72.0	93.0	16.3	34.9 at 90 days	41.1 at 6 months 58.1 at 12 months		Good (9)
Amalakuhan, 2011 [30]	USA	106	NI	NI				47.0 with ≥2 readmissions at 12 months	Fair (6)
Bahadori, 2009 [53]	Canada	310	74.0	54.0			38.0 at 20 months	22.0 with 1 readmission at 20 months 9.0 with 2 readmissions at 20 months 7.0 with ≥3 readmissions at 20 months	Good (9)
Baker, 2013 [17]	USA	6,095	NI	NI	5.6	11.8 at 90 days	27.6 at 12 months	12.6 with ≥2 readmissions at 12 months	Good (9)
Barba, 2012 [43]	Spain	275,521	72.3	70.0	15.6				Good (9)
Bhatt, 2008 [31]	USA	100	71.9	43.0	25.0	43.0 at 90 days	63.0 at 6 months 87.0 at 12 months	44.0 with 1 readmission at 12 months 21.0 with 2 readmissions at 12 months 23.0 with ≥3 readmissions at 12 months	Good (7)
Bishwakarma, 2017 [32]	USA	6,066	NI	32.7	7.8				Good (9)
Bourbeau, 2003 [54]	Canada	1,742	76.2	63.9			48.6 at 12 months		Good (8)
Burgel, 2009 [26]	France	433	65.0	82.6	NI				Good (9)
Candrilli, 2015 [33]	USA	264,526	67.6	49.0	7.0	12.0 at 90 days			Good (9)
Cao, 2006 [27]	Singapore	186	NI	83.0			67.2 at 12 months	45.7 with ≥2 readmissions at 12 months 8.6 with ≥10 readmissions at 12 months	Fair (4)
Carneiro, 2010 [63]	Portugal	45	68.3	84.4			33.3 at 66 weeks		Good (7)
Chan, 2011 [60]	Hong Kong	65,497	76.8	77.0	24.2				Good (8)
Chen, 2006 [68]	Taiwan	145	72.2	73.1	21.4 at 14 days 32.4 at 30 days	41.4 at 60 days 44.8 at 90 days			Good (8)
Chen, 2009 [55]	Canada	108,726	72.3	54.5			49.1 at 12 months		Good (8)
Couillard, 2017 [56]	Canada	167	71.4	51.5			32.3 at 12 months		Good (9)
Coventry, 2011 [69]	UK	79	65.3	56.0		33.0 at 90 days	76.0 at 12 months		Good (8)
Crisafulli, 2015 [44]	Spain	125	69.2	93.6	23.0				Good (9)
Crockett, 2000 [70]	Australia	520	72.4	49.6	40.1 at 28 days				Good (9)
de Batlle, 2012 [45]	Spain	274	68.0	93.0			35.4 at 2.6 median years	12.5 with 1 readmission at 2.6 median years 10.2 with 2 readmissions at 2.6 median years 12.8 with ≥3 readmissions at 2.6 median years	Good (9)
	Spain	301,794	74.8	89.0	17.5				Good (9)

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Table 1 (*continued*)

First author, year	Country/region	Number of patients	Mean age (years)	Gender (male %)	Readmission rate (%)				Quality assessment score
					30 days	31–90 days	>90 days	Frequency	
de Miguel Diez, 2016 [46]									
Epstein, 2018 [61]	Israel	539	69.2	60.3		41.6 at 60 days			Good (9)
Fuhrman, 2016 [71]	France	58,144	72.6	61.4	7.2	14.9 at 90 days	31.1 at 12 months		Good (9)
Gavish, 2015 [72]	Israel	195	66.0	95.2		18.3 at 90 days			Good (9)
Gershon, 2019 [59]	Canada	126,013			12.0				Good (9)
Gonzalez, 2008 [48]	Spain	112	69.3	100.0			32.1 at 12 months		Good (7)
González, 2004 [47]	Spain	90	69.3	100.0	8.8	14.4 at 90 days			Fair (6)
Groenewegen, 2003 [64]	Netherlands	171	70.6	60.8	14.0	21.1 at 90 days	29.8 at 6 months	15.8 with 1 readmission at 12 months 17.0 with 2 readmissions at 12 months	Good (9)
							50.3 at 12 months	8.8 with 3 readmissions at 12 months 8.8 with ≥3 readmissions at 12 months	
Gudmundsson, 2005 [14]	Sweden, Norway, Finland, Iceland and Denmark	406	69.2	51.2			60.6 at 12 months		Good (9)
Guerrero, 2016 [49]	Spain	378	71.4	84.0	18.0				Good (9)
Harries, 2017 [10]	UK	20,932	72.4	52.2	10.2	17.8 at 90 days	32.2 at 12 months		Good (9)
Hartl, 2015 [28]	13 European countries[a]	16,016	70.8	67.8		35.1 at 90 days			Good (9)
Hunter, 2015 [73]	UK	1,756	NI	51.2	13.4 at 14 days		45.2 at 4.5 median years		Good (9)
Iyer, 2015 [34]	USA	422	64.8	50.1			31.3 at 12 months		Good (9)
Jiang, 2018 [35]	USA	268,084	NI	45.0	7.6–8.0				Good (9)
Johannesdottir, 2013 [62]	Denmark	3,176	71.1	55.2	9.4	14.7 at 60 days	26.7 at 6 months	21.8 with 1 readmission at 12 months 9.0 with 2 readmissions at 12 months	Good (9)
						18.2 at 90 days	37.0 at 12 months	3.8 with 3 readmissions at 12 months 2.4 with ≥4 readmissions at 12 months	
Kim, 2010 [74]	Korea	77	69.2	83.1			54.6 at 12 months	45.4 with ≥2 readmissions at 12 months 5.2 with >10 readmissions at 12 months	Good (8)
Ko, 2010 [75]	Hong Kong	243	74.2	85.6			76.5 at 3 years		Good (9)
Lau, 2001 [76]	Hong Kong	551	73.8	77.3			59.4 at 12 months		Good (8)
Lau, 2017 [36]	USA	597,502	NI	44.5	6.7				Good (9)
Liu, 2007 [67]	Taiwan	100	73.8	85.0	NI				Fair (6)
Loh, 2017 [37]	USA	123	64.9	52.8	7.3	21.1 at 90 days			Good (9)
McGhan, 2007 [38]	USA	51,353	69.0	97.2			25.0 at 12 months 44.0 at 5 years		Good (9)
Müllerova, 2015 [29]	12 countries[b]	670	64.0	65.0			46.7 at 3 years		Good (8)
	USA	81	73.9	46.9	13.6				Good (7)

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Table 1 (*continued*)

First author, year	Country/region	Number of patients	Mean age (years)	Gender (male %)	Readmission rate (%)				Quality assessment score
					30 days	31–90 days	>90 days	Frequency	
Nantsupawat, 2012 [39]									
Pitta, 2006 [65]	Belgium	17	69.0	94.0			64.7 at 12 months		Fair (5)
Quintana, 2014 [50]	Spain	1,537	72.3	90.7		19.5 at 60 days			Good (9)
Renom, 2009 [51]	Spain	116	70.6	94.0	NI				Fair (6)
Rezaee, 2018 [57]	Canada	1,574	72.6	56.8	82.2				Good (9)
Roberts, 2016 [40]	USA	3,612	66.6	32.8	4.8		17.9 at 6 months		Good (7)
Sin, 2001 [58]	Canada	22,620	75.1	56.5			25.0 at 12 months		Good (9)
Tsui, 2016 [77]	Hong Kong	250	76.7	90.4			73.2 at 12 months	17.6 with ≥4 readmissions at 12 months	Good (9)
Wong, 2008 [16]	Canada	109	63.0	61.5			39.4 at 6 months		Good (9)
Yu, 2015 [41]	USA	18,282	56.6	37.6	2.6				Good (9)
Zapatero, 2013 [52]	Spain	313,233	73.9	70.3	16.7				Good (9)
Zhong, 2017 [42]	USA	114	NI	NI	21.0				Fair (6)

Footnote : NI no information.

[a] Austria, Belgium, Croatia, Greece, Ireland, Malta, Poland, Romania, Slovakia, Spain, Switzerland, Turkey and UK.

[b] Bulgaria, Canada, Czech Republic, Denmark, Netherlands, New Zealand, Norway, Slovenia, Spain, Ukraine, UK and USA.

evaluated readmission risk predictors for either time to the first readmission, rate or number of readmissions.

3.4. Prevalence of readmission

All studies, except for three [26,51,67], reported the readmission rate. Reported readmission rates ranged from 2.6% to 82.2% for 30 days, 11.8%–44.8% for 31–90 days, 17.9%–63.0% for 6 months, and 25.0%–87.0% for 12 months post-discharge. The number of readmissions within one year was also reported as 9.0%–47.0% for ≥2 readmissions, 3.8%–23.0% for ≥3 readmissions, 2.4%–17.6% for ≥4 readmissions and 5.2% to 8.6% for ≥10 readmissions (Table 1).

3.5. Risk factors for COPD readmission

The risk factors for COPD readmission were categorised into patient factors (Table 2a and Table 2b), provider factors (Table 3) and system factors (Table 4). Twenty-two studies reported risk factors within 30 days, 12 reported within 31–90 days, 22 reported over 90 days and seven reported on frequency of readmission within 12 months. The definition of readmission frequency varied in the latter seven studies. Four studies defined frequent readmission as ≥2 readmissions [26,27,51,74], two studies defined it as >2 readmissions [31,62], while another used ≥4 readmissions [77]. Two studies did not report parameter estimates (likelihood ratios) [30,42], one study [51] reported univariate analysis, and two studies reported only p values for the multivariate analysis [37,67]. Table 5 outlines all the studies that considered any of the variables in relation to association or no association with readmission. This table presents both the direction of the association found and highlights studies that did investigate various variables but found no association with COPD-related readmission.

3.5.1. Patient-related risk factors

Forty-nine (86.0%) of the 57 studies reported patient-related risk factors for readmission from COPD. These risk factors were sub-grouped into socioeconomic factors and clinical factors (Tables 2a and 2b).

3.5.1.1. Patient-related socioeconomic risk factors. Increasing/older age: Despite 13 studies indicating increasing age as a risk factor for readmission, 38 studies that included age in their analysis did not find any significant relationship with readmission. Seven of the 13 studies indicated increasing age as a risk factor for readmission [28,29,35,38,52,62,66,69,71] while six associated increased risk of readmission with the age range of 40–84 years [33,36,46,70].

Sex: Of 47 studies that reported sex as predictor of readmission, nine studies associated male sex with higher risk of readmission while one study found male patients 25% less likely to be readmitted within 30 days of discharge [52]. Another study associated female sex with lower risk of readmission from COPD [71]. Thirty-six other studies did not find any correlation between sex and readmission from COPD.

Social determinants of health: The risk of readmission varied depending on the insurance type in some countries, with increased risk in patients with public health care coverage [17,35,36,60], while those with private care coverage [33,35,41] were less likely to be readmitted. Other socioeconomic factors reported in the studies to be associated with increased risk of readmission from COPD were living in deprived areas (6 out of 7), residing in urban or large metropolitan areas with at least one million residents (n = 2), marital status (single) (1 out of 6) and ethnicity (4 out of 9).

Nutritional factors: Three large retrospective studies with 790,548 patients undertaken in Spain described malnutrition as being highly associated with an increased risk of readmission within 30 days of discharge [43,46,52]. Zapatero et al. associated malnutrition with a 29% increase in 30-day readmission and a 73% increase in in-hospital mortality [52]. One study [74] indicated that patients with low BMI were more likely to be readmitted, while four studies [46,52,73,74] found that obese patients were less likely to be readmitted than non-obese patients. Eighteen other studies found no association between readmission and BMI.

Smoking status: Of 29 studies that investigated association of smoking status of patients and readmission, 28 did not find any association between smoking status of patients and readmission.

3.5.1.2. Patient-related clinical factors. The patient-related clinical variables associated with readmission were increasing number/presence of comorbidities (n = 26), disease severity and complexity (n = 22), and certain laboratory findings (n = 15) (Table 2b).

Comorbidities: The presence of comorbid conditions was associated with increased risk of readmission in nine studies [16,28,33,43,46,52,57,61,70]. Comorbidities (categorised according to the International

Table 2a
Patient-related socioeconomic risk factors for COPD readmission.

Patient factors	Authors	≤30 day readmission adjusted analysis (95% CI)	>30–90 day readmission adjusted analysis (95% CI)	>90 day readmission adjusted analysis (95% CI)	12 month readmission frequency adjusted analysis (95% CI)
Age					
Age (years)	Hartl [28]		OR 1.01 (1.01–1.02)		
Age (years)	McGhan [38]			HR 1.01 (1.00–1.01)	
Age (years)	Zapatero [52]	OR 1.001 (1.000–1.001)			
Age (years)	Adeyemi [66]		[a]OR 1.0004 (1.000–1.0006)		
Age (years)	Coventry [69]			OR 1.09 (1.01–1.18)	
Per 10-year increase	Johannesdottir [62]			OR 1.10 (1.00–1.20)	OR 1.40 (1.00–1.80)
Per 10-year increase	Müllerova [29]			HR 1.29 (1.13–1.46)	
40–64 years (vs ≥ 65)	Lau [36]	OR 1.22 (1.17–1.28)			
45–64 years (vs 18–44)	Jiang [35]	OR 1.91 (1.70–2.14)			
>50 years (vs < 50)	Crockett [70]	OR 1.04 (1.02–1.09)			
55–64 years (vs 40–54)	Candrilli [33]	OR 1.37 (1.26–1.48)	OR 1.27 (1.19–1.35)		
≥65 years (vs 40–54)	Candrilli [33]	OR 1.59 (1.47–1.72)	OR 1.58 (1.48–1.68)		
55–64 years (vs 40–54)	de Miguel-Diez [46]	OR 0.94 (0.89–0.99)			
65–84 years (vs 40–54)	de Miguel-Diez [46]	OR 1.07 (1.02–1.13)			
75–84 years (vs 25–44)	Fuhrman [71]			RR 1.65 (1.45–1.87)	
Sex					
Male	Barba [43]	OR 1.33 (1.30–1.36)			
Male	Chan [60]	OR 1.45 (1.38–1.52)			
Male	de Miguel-Diez [46]	OR 1.34 (1.30–1.37)			
Male	Gershon [59]	OR 1.17 (1.14–1.21)			
Male	Jiang [35]	OR 1.14 (1.10–1.17)			
Male	Johannesdottir [62]			OR 1.10 (1.00–1.30)	OR 1.70 (1.10–2.90)
Male	Lau [36]	OR 1.19 (1.15–1.23)			
Male	McGhan [38]			HR 1.28 (1.13–1.45)	
Male	Chen [68]		OR 3.00 (1.17–7.68)		
Male	Zapatero [52]	OR 0.75 (0.73–0.77)			
Female	Fuhrman [71]			RR 0.84 (0.81–0.86)	
Social determinants of health					
Marital status (single)	Wong [16]			OR 4.18 (1.03–17.02)	
Ethnicity					
African American (vs Caucasian)	Lau [36]	OR 1.08 (1.02–1.14)			
Other (vs Caucasian)	Lau [36]	OR 0.82 (0.77–0.87)			
Asian (vs black)	Adeyemi [66]		[a]OR 0.69 (0.57–0.82)		
Hispanic (vs black)	Jiang [35]	OR 0.89 (0.83–0.96)			
Hispanic (vs white)	McGhan [38]			HR 0.86 (0.76–0.98)	
White (vs black)	Jiang [35]	OR 1.09 (1.03–1.15)			
White (vs back)	Adeyemi [66]		[a]OR 0.83 (0.79–0.87)		
Living in deprived area (quintile 5 vs 1)	Fuhrman [71]			RR 1.06 (1.01–1.11)	
Living in deprived area (quintile 5 vs 1)	Hunter [73]			HR 0.80 (0.65–0.98)	
Median household income quartile (1st vs 4th)	Jiang [35]	OR 1.18 (1.12–1.24)			
Median household income quartile (1st vs 4th)	Lau [36]	OR 1.15 (1.09–1.21)			
Median household income quartile (2nd vs 4th)	Lau [36]	OR 1.08 (1.02–1.14)			
Residential instability (most marginalized vs lowest)	Gershon [59]	OR 1.09 (1.04–1.15)			
Large metropolitan areas with ≥1 million residents (vs small metropolitan area)	Jiang [35]	OR 1.10 (1.06–1.13)			
Living in urban areas (vs rural)	Gershon [59]	OR 1.08 (1.04–1.12)			
Alcohol abuse (yes vs no)	Lau [36]	OR 1.09 (1.01–1.17)			
Drug abuse (yes vs no)	Lau [36]	OR 1.41 (1.29–1.55)			
Basic health insurance coverage					
Health maintenance organisation (vs comprehensive)	Baker [17]		OR 1.62 (1.17–2.23)		
Public assistance (yes vs no)	Chan [60]	OR 1.41 (1.36–1.46)			
Medicaid (vs medicare beneficiary)	Jiang [35]	OR 1.28 (1.21–1.35)			
Medicaid (vs private insurance)	Lau [36]	OR 2.24 (2.07–2.42)			
Medicare (vs private insurance)	Lau [36]	OR 1.80 (1.68–1.93)			
Commercial (vs non-commercial payers)	Candrilli [33]	OR 0.87 (0.83–0.90)	OR 0.90 (0.87–0.93)		
Private insurance (vs medicare beneficiary)	Jiang [35]	OR 0.57 (0.53–0.61)			

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Table 2a (*continued*)

Patient factors	Authors	≤30 day readmission adjusted analysis (95% CI)	>30–90 day readmission adjusted analysis (95% CI)	>90 day readmission adjusted analysis (95% CI)	12 month readmission frequency adjusted analysis (95% CI)
Fee for service (vs health maintenance organisation)	Yu [41]	OR 0.64 (0.50–0.81)			
Self-pay (vs medicare beneficiary)	Jiang [35]	OR 0.71 (0.65–0.78)			
No charge (vs medicare beneficiary)	Jiang [35]	OR 0.74 (o.64–0.85)			
Activity level					
Little/no difficulty in undertaking daily activity (multi-component assessment) (vs greater difficulty)	Chen [68]		OR 0.56 (0.33–0.97)		
Dependent on self-care activities (vs independent)	Lau [76]			HR 1.40 (1.06–1.84)	
SGRQ score at discharge ≥50 points (vs < 50)	Almagro [13]			OR 2.18 (1.03–5.41)	
SGRQ score per 4-units increase	Gudmundsson [14]			HR 1.06 (1.02–1.10	
SGRQ score per 4-point increase	Müllerova [29]			HR 1.05 (1.02–1.09)	
6-minute walk distance at baseline (per 10-metre increase)	Tsui [77]			HR 0.98 (0.97–0.99)	
Nutritional factors					
Obesity (yes vs no)	Zapatero [52]	OR 0.87 (0.85–0.92)			
Obesity (yes vs no)	de Miguel-Diez [46]	OR 0.81 (0.78–0.84)			
BMI ≥25 kg/m^2 (vs normal)	Hunter [73]			HR 0.87 (0.76–0.99)	
BMI <18.5 kg/m^2 (vs ≥ 18.5)	Kim [74]				OR 5.31 (1.25–22.45)
Malnutrition (no vs yes)	Barba [43]	OR 1.27 (1.20–1.35)			
Malnutrition (no vs yes)	Zapatero [52]	OR 1.29 (1.22–1.38)			
Malnutrition (no vs yes)	de Miguel-Diez [46]	OR 1.77 (1.62–1.94)			
Cured meat intake >22.7 g per day (yes vs no)	de Batlle [45]			HR 2.02 (1.31–3.12)	

Footnote :

[a] Antilog result; BMI body mass index; SGRQ St. George's Respiratory Questionnaire score.

Classification of Diseases, 10th Revision, Clinical Modification code) were the most highly reported predictors (47.4%) of readmission, although with many inconsistencies. While some studies associated several comorbidities with readmission, it was often the case that other studies reported no association for these same comorbidities (Table 5). For example, 12 studies found diseases of the circulatory system were associated with readmission, while 21 studies reported no association. Mental and behavioural disorders were associated with readmission in eight studies, while ten studies found no association. Diseases of the respiratory system was the only comorbidity associated with readmission (n = 9) with fewer studies (n = 4) reporting no association. Asthma was the only relatively consistent comorbidity associated with readmission. Five large (total of 448,680 patients) retrospective studies conducted in the USA (n = 3) [33,38,40], Canada (n = 1) [59] and Denmark (n = 1) [62] demonstrated that the presence of asthma significantly increased the risk of readmission, while another study (268,084 patients) [35] undertaken in the USA found patients with asthma were 39% less likely to be readmitted.

Disease severity and complexity: Lower lung function, measured by a post-bronchodilator FEV_1/forced vital capacity (FVC) ratio <70% (i.e. airflow limitation), at baseline [50,73] and post-discharge [27] were associated with an increased risk of readmission. Other studies reported less likelihood of readmission with baseline [16,45] and post-discharge [14,69] FEV_1% prediction. Only ten out of 27 studies associated decline in FEV_1% predicted measurement with readmission. Dyspnoea, chronic cough and sputum production were associated with increased readmissions in four (out of 17) studies [26,40,50,57]. Similarly, five (out of six) studies found no association between disease severity (defined using GOLD stage 1–4 classification) and readmission [26,28,56,63,74].

3.5.2. Provider factors

Provider factors associated with readmission included the prescribed use of respiratory-related medications (n = 7) [16,17,32,40,57,58,67,76] and non-pharmacological therapies (n = 6) [28,34,46,48,53,71,77] (Table 3). Despite several respiratory-related medications used before and at admission indicating increased risk of readmission, a greater number of studies found no association.

Respiratory-related medicines: Bronchodilators (3 out of 10), ICS (6 out of 15), oral corticosteroids (3 out of 14), vaccination (2 out of 6) and antimicrobials post-discharge (1 out of 5) were associated with increased risk of readmission.

Non-pharmacological therapies: Two retrospective studies [53,71] and one prospective study [48] all associated the use of home long-term oxygen therapy (LTOT) to readmission. Eleven other studies found no association of LTOT with COPD readmission. Four studies associated any hospital ventilatory support [28,46,71,77] and home noninvasive ventilation [77] with readmission while four other studies [32,41,63,76] found no correlation. Iyer et al. showed that tobacco cessation counselling was associated with 66% reduced risk of one-year readmission despite a low percentage (11%) of patients receiving tobacco cessation education [34].

3.5.3. System factors

Hospitalisations in the previous year: Hospitalisations in the previous year were the second most commonly reported independent risk factor (35.1% of studies). Some studies reported any hospitalisation in the previous year [13,17,28,38,44,59,62,71–73,76] while others reported the number of hospitalisations in the previous year [14,17,40,49,50,59,66,71,77] (Table 4). Any hospital admission in the previous 12 months [76], and one admission for exacerbation in the previous 12 months [70], were associated with a shorter time to the first readmission.

LOS: Of the 26 studies that analysed the impact of LOS on COPD readmission, nine reported that readmitted patients had a significantly longer index LOS compared to patients who were not readmitted, while

Table 2b
Patient-related clinical risk factors for COPD readmission.

Patient factors	Authors	≤30 day readmission adjusted analysis (95% CI)	>30–90 day readmission adjusted analysis (95% CI)	>90 day readmission adjusted analysis (95% CI)	12 month readmission frequency adjusted analysis (95% CI)
Comorbidities					
Charlson score					
Every one unit increase	Zapatero [52]	OR 1.20 (1.18–1.23)			
Every one unit increase	Crockett [70]	OR 1.13 (1.01–1.26)			
Every one unit increase	Hartl [28]		OR 1.09 (1.07–1.12)		
Every one unit increase	Wong [16]			OR 1.47 (1.10–1.97)	
Every one unit increase	Rezaee [57]	OR 3.60 (2.90–4.40)			
>2 (vs ≤ 2)	Barba [43]	OR 1.19 (1.15–1.22)			
>2 (vs 0)	de Miguel-Diez [46]	OR 1.55 (1.49–1.62)			
≥3 (vs 0)	Candrilli [33]	OR 1.22 (1.12–1.34)	OR 1.30 (1.21–1.40)		
>5 (vs < 5)	Epstein [61]		OR 0.47 (0.27–0.84)		
Neoplasms (C00–C97)					
Any cancer	Baker [17]	OR 2.26 (1.21–4.25)	OR 1.82 (1.08–3.10)		
Any cancer	Barba [43]	OR 1.53 (1.48–1.58)			
Any cancer	Gershon [59]	OR 1.10 (1.04–1.17)			
Metastatic	Gershon [59]	OR 1.19 (1.07–1.33)			
Any cancer except lung cancer	Candrilli [33]	OR 0.91 (0.86–0.97)	OR 0.89 (0.85–0.94)		
Any cancer except lung cancer	Johannesdottir [62]				OR 2.50 (1.20–5.30)
Any cancer except lung cancer	Zapatero [52]	OR 1.54 (1.49–1.58)			
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)					
Anaemia	Barba [43]	OR 1.25 (1.21–1.29)			
Anaemia	Lau [36]	OR 1.06 (1.01–1.10)			
Anaemia	Yu [41]	OR 1.43 (1.09–1.88)			
Endocrine, nutritional and metabolic diseases (E00-E90)					
Diabetes	Barba [43]	OR 1.09 (1.06–1.12)			
Diabetes	Crisafulli [44]	OR 11.03 (1.77–68.54)			
Diabetes	Lau [36]	OR 1.06 (1.02–1.09)			
Diabetes	Roberts [40]	OR 1.45 (1.06–1.97)		OR 1.30 (1.07–1.59)	
Diabetes	Hartl [28]		OR 0.90 (0.82–0.99)		
Complicated diabetes	McGhan [38]			HR 0.76 (0.63–0.91)	
Uncomplicated diabetes	McGhan [38]			HR 0.86 (0.81–0.90)	
Uncomplicated diabetes	Gershon [59]	OR 0.94 (0.90–0.98)			
Mental and behavioural disorders (F00–F99)					
Depression	Coventry [69]			OR 1.30 (1.06–1.60)	
Depression	Iyer [34]	OR 3.83 (1.84–7.96)	OR 2.47 (1.34–4.55)	OR 2.67 (1.59–4.47)	
Depression	Jiang [35]	OR 1.09 (1.03–1.15)			
Depression	Lau [36]	OR 1.16 (1.11–1.22)			
Depression	Roberts [40]			OR 1.47 (1.14–1.90)	
Depression	Yu [41]	OR 1.28 (1.02–1.61)			
Depression	Johannesdottir [62]			OR 1.60 (1.00–2.50)	
Anxiety	Roberts [40]	OR 1.68 (1.17–2.41)		OR 1.75 (1.37–2.23)	
HADS ≥8 score	Tsui [77]				OR 3.97 (1.49–10.57)
Psychosis	Lau [36]	OR 1.19 (1.13–1.25)			
Diseases of the circulatory system (I00–I99)					
Pulmonary heart disease and diseases of circulation					
Pulmonary heart disease	Chen [55]			HR 1.36 (1.29–1.44)	
Cor pulmonale	González [47]		OR 2.20 (1.20–4.20)		
Cor pulmonale	Gonzalez [48]			OR 2.20(1.20–4.20)	
Pulmonary circulation disorders	Jiang [35]	OR 1.12 (1.01–1.25)			
Pulmonary vascular disease	Roberts [40]			OR 1.68 (1.23–2.28)	
Hypertension	Roberts [40]			OR 1.62 (1.31–2.01)	
Uncomplicated hypertension	McGhan [38]			HR 0.95 (0.91–0.98)	
Complicated hypertension	McGhan [38]			HR 0.77 (0.66–0.90)	
Pulmonary hypertension	McGhan [38]			HR 1.24 (1.14–1.35)	
Ischemic heart disease	Johannesdottir [62]				OR 2.60 (1.30–5.40)
Ischemic heart disease	Jiang [35]	OR 1.06 (1.02–1.10)			
Ischemic heart disease	Roberts [40]	OR 1.73 (1.26–2.38)		OR 1.54 (1.26–1.89)	
Ischemic heart disease	Nantsupawat [39]	OR 6.4 (1.10–37.42)			
Congestive heart failure	Barba [43]	OR 1.04 (1.01–1.06)			
Congestive heart failure	Chen [55]			HR 1.20 (1.17–1.23)	
Congestive heart failure	Roberts [40]			OR (1.50 (1.21–1.87)	
Congestive heart failure	Zapatero [52]	OR 1.08 (1.06–1.12)			
Congestive heart failure	Gershon [59]	OR 1.08 (1.05–1.12)			
Congestive heart failure	Yu [41]	OR 1.53 (1.25–1.88)			
Atrial fibrillation	Barba [43]	OR 1.19 (1.16–1.22)			
Atrial fibrillation	Jiang [35]	OR 0.96 (0.92–0.99)			
Arrhythmias	Chen [55]			HR 1.03 (1.00–1.06)	

(*continued on next page*)

Table 2b (*continued*)

Patient factors	Authors	≤30 day readmission adjusted analysis (95% CI)	>30–90 day readmission adjusted analysis (95% CI)	>90 day readmission adjusted analysis (95% CI)	12 month readmission frequency adjusted analysis (95% CI)
Pulmonary unilateral infiltrate	Nantsupawat [39]	OR 12.8 (1.89–86.44)			
Cerebrovascular disease	Gershon [59]	OR 0.83 (0.75–0.93)			
Diseases of the respiratory system (J00 J99)					
Respiratory failure	Gershon [59]	OR 1.18 (1.13–1.24)			
Other chronic respiratory disease	Bahadori [53]			OR 1.78 (1.06–2.99)	
Other chronic respiratory disease	Baker [17]	OR 2.52 (1.56–4.05)			
Other chronic respiratory disease	Hartl [28]		OR 1.13 (1.04–1.24)		
Pneumonia	Candrilli [33]	OR 1.15 (1.10–1.20)	OR 1.14 (1.10–1.18)		
Pneumonia in the year prior to admission	Roberts [40]	OR 1.75 (1.25–2.43)		OR 1.77 (1.42–2.20)	
History of lung infection	Bahadori [53]			OR 1.73 (1.01–2.97)	
Asthma	Candrilli [33]		OR 1.05 (1.01–1.10)		
Asthma	Jiang [35]	OR 0.61 (0.55–0.67)			
Asthma	McGhan [38]			HR 1.11 (1.04–1.18)	
Asthma	Roberts [40]	OR 1.57 (1.14–2.16)		OR 1.66 (1.35–2.05)	
Asthma	Johannesdottir [62]			OR 1.30 (1.10–1.60)	
Asthma	Gershon [59]	OR 1.07 (1.04–1.10)			
Diseases of the digestive system (K00–K93)					
Moderate or severe liver disease	Baker [17]		OR 2.79 (1.23–6.34)		
Gastroesophageal reflux disease	Iyer [34]			OR 2.15 (1.07–4.32)	
Ulcers of the digestive system	Gershon [59]	OR 0.73 (0.57–0.92)			
Diseases of the musculoskeletal system and connective tissue (M00-M99)					
Osteoporosis	Jiang [35]	OR 1.16 (1.09–1.24)			
Osteoporosis	Roberts [40]			OR 1.56 (1.15–2.14)	
Osteoporosis	Johannesdottir [62]			OR 1.50 (1.10–1.90)	
Diseases of the genitourinary system (N00–N99)					
Renal failure	Candrilli [33]	OR 1.09 (1.02–1.17)	OR 1.19 (1.13–1.26)		
Disease severity and complexity					
Severity (GOLD stage 1–4) at admission	Wong [16]			OR 6.23 (2.47–15.72)	
Decline in lung function (FEV_1% predicted)					
Post-discharge	Coventry [69]			OR 0.96 (0.93–0.99)	
At index admission	de Batlle [45]			HR 0.97 (0.96–0.98)	
Per 10% increase of predicted at discharge	Gudmundsson [14]			HR 0.83 (0.76–0.91)	
Prior to admission	Liu [67]	[a]0.04			
At index admission	Wong [16]			OR 0.87 (0.80–0.95)	
<30 (very severe vs mild)	Hunter [73]			HR 1.75 (1.39–2.19)	
<30 (vs ≥ 50) at index admission	Quintana [50]		OR 1.88 (1.19–2.95)		
<50 (vs ≥ 50) post discharge	Cao [27]				OR 2.60 (1.18–5.74)
Per 5% decrease	Müllerova [29]			HR 1.11 (1.06–1.16)	
Per 10% decrease	Burgel [26]				OR 1.75 (1.36–2.26)
≥2 ECOPD in the past year	Guerrero [49]	HR 2.47 (1.51–4.05)			
COPD severity score (high vs low)	Yu [41]	OR 1.30 (1.16–1.46)			
Severe complexity (vs low)	Candrilli [33]	OR 2.26 (2.05–2.48)	OR 2.32 (2.15–2.51)		
Baseline COPD Assessment Test score	Tsui [77]			HR 1.03 (1.01–1.05)	
Baseline BODE scores (quartile 4 vs 1)	Ko [75]			HR 1.12 (1.05–1.20)	
Suboptimal vs optimal peak inspiratory flow (63.5 vs 144) days to readmission	Loh [37]	[a]0.04			
Presence of chronic cough and sputum production >3 months in past 2 years pre-index admission (yes vs no)	Burgel [26]				OR 4.08 (1.18–14.09)
Dyspnoea at index admission (yes vs no)	Roberts [40]	OR 1.63 (1.17–2.27)		OR 1.61 (1.31–1.98)	
Difficulty breathing (yes vs no)	Rezaee [57]	OR 1.70 (1.10–2.60)			
MRC scale 5 (vs 1)	Quintana [50]		OR 2.57 (1.10–6.01)		
Very severe/severe dyspnoea 1 week after index visit (vs none/very slight)	Quintana [50]		OR 2.15 (1.44–3.23)		
Pressure-time index >25 (vs < 25)[b]	Gonzalez [48]			OR 2.70 (1.40–5.30)	
Pressure-time index >25 (vs < 25)[b]	González [47]		OR 2.70 (1.40–5.30)		
Right heart strain pattern on EKG (yes vs no)	Lau [76]			HR 1.56 (1.19–2.04)	
Emphysema > 5% by radiology	Müllerova [29]			HR 1.56 (1.23–1.97)	
Duration of COPD >5 years (vs < 5 years)	Cao [27]				OR 2.32 (1.09–4.92)
>5 years (vs < 1 year)	Gershon [59]	OR 1.45 (1.36–1.54)			
Laboratory findings					
Respiratory acidosis (yes vs no)	de Miguel-Diez [46]	OR 1.06 (1.01–1.12)			
Arterial blood gas testing at admission (yes vs no)	Rezaee [57]	OR 4.40 (1.30–15.10)			
Admission WBC count	Wong [16]			OR 1.25 (1.02–1.54)	

(*continued on next page*)

Table 2b (*continued*)

Patient factors	Authors	≤30 day readmission adjusted analysis (95% CI)	>30–90 day readmission adjusted analysis (95% CI)	>90 day readmission adjusted analysis (95% CI)	12 month readmission frequency adjusted analysis (95% CI)
Admission WBC count, per 1 × 109/L	Müllerova [29]			HR 1.15 (1.07–1.24)	
Eosinophilia ≥200 (vs < 200) cells/μL and/or ≥2% WBC	Couillard [56]			OR 3.59 (1.65–7.82)	
Red cell distribution width at admission (>14.5%)	Epstein [61]		OR 2.11 (1.17–3.83)		
CRP at discharge ≥7.6 mg/L	Crisafulli [44]	OR 7.41 (1.34–40.91)			
B-type natriuretic peptide testing at admission (yes vs no)	Rezaee [57]	OR 2.20 (1.40–3.50)			
Low serum magnesium level (1.77 ± 0.19 mEq/L)	Bhatt [31]				OR 0.003 (<0.001–0.55)
Higher serum sodium level (137.4 mMol/L)	Iyer [34]			OR 1.14 (1.03–1.25)	
Actual bicarbonate >25 mMol/L (vs ≤25)	Lau [76]			HR 1.351 (1.062–1.720)	
$PaCO_2$ >45 mmHg at discharge	Almagro [13]			OR 2.18 (0.84–5.63)	
$PaCO_2$ >40 mmHg	Kim [74]				OR 4.21 (1.19–14.88)
Hypoxia pre index admission (yes vs no)	Roberts [40]	OR 1.67 (1.06–2.63)		OR 1.59 (1.16–2.17)	

Footnote : HADS Hospital Anxiety and Depression Scale.

[a] Only p-value reported; FEV_1 Forced expiratory volume in 1 s; MRC Medical Research Council breathless scale; CRP C-reactive protein; $PaCO_2$ partial pressure of oxygen; WBC white blood count; BODE Body-mass index, airflow Obstruction, Dyspnea, and Exercise capacity; GOLD Global Initiative for Chronic Obstructive Lung Disease; EKG electrocardiogram.

[b] Indicator of respiratory muscle efficiency.

17 found no association. Four of the nine studies associated hospital LOS of >5 days with increased risk of readmission [33,59,71,76] while another four studies found readmitted patients to have longer index LOS compared to non-readmitted patients [33,35,43,46].

Discharge destination, discharge season and follow-up: There was strong association of living in or discharged to nursing homes (5 out of 6), with readmission. Patients who self-discharged against medical advice [35,59] or were discharged to or living in health/social institutions [35,46,59] and home health care [35,59] were more likely to be readmitted. A study conducted in the USA found patients discharged during winter to have 59% increased risk of being readmitted within 30 days compared to those discharged during summer [35]. Another study found no association between being hospitalised during winter season and readmission [41]. Patients who were under the care of a COPD specialist [59] or unable to attend follow-up visits with a pulmonologist [72] had higher risk of readmission.

3.6. Outcomes associated with COPD readmission

Twelve studies reported patient and healthcare-related outcomes associated with readmission (Table 6). Of these studies, three examined these outcomes in relation to readmission [63–65] while nine examined both the risk factors and the outcomes [14,28,35,38,46,49,60–62].

3.6.1. Patient-related outcomes

Eleven studies reported patient-related outcomes of readmission from COPD, which included increased inpatient mortality (n = 11) [14,28,38,46,49,60–64,71], shorter survival period (n = 1) [49] and poorer functional status (n = 1) [65] (Table 6). Mortality was defined in different ways: in-hospital mortality (IHM) [14,28,38,46,49,60–64,71], and up to 30 days [49,62], 2 months [61,62], 3 months [28,62,64,71], 6 months [49,62,64], 1 year [38] and 5 years [38] post-discharge. The mortality rates of readmitted patients were reported to be higher than non-readmitted patients. Seven studies reported a higher IHM rate in comparison to overall mortality rates at various time periods [28,38,61–64,71] (Table 6). In a prospective study conducted in 13 European countries, the mortality rate of readmitted patients was six-times higher than in non-readmitted patients (13.4% vs 2.3%) 90-day post-discharge [28]. There was no indication that readmitted and non-readmitted patient mortality rates were standardised to account for confounding variables before these rates were aggregated. Therefore, it is not clear whether these factors impacted the different mortality rates observed in readmitted and non-readmitted patients, even in the different participating countries. Furthermore, the robustness of the process was not evaluated in participating hospitals and countries as this was considered an audit.

A long-term observational study of good quality associated shorter survival period with readmission across the three follow-up periods (6 months, 1 year and 3 years). Patients who were readmitted had shorter survival periods of 109 days, 124 days, and 250 days, compared to non-readmitted patients with 162 days, 209 days and 445 days in the 6-month, 1-year and 3-year follow-up periods, respectively [49].

3.6.2. Healthcare utilisation

Two large retrospective studies with 569,887 patients undertaken in Spain and the USA associated readmission with increased cost [35,46]. There was a 5.9% increase in mean cost for readmission compared to the index admission in the USA study in 2014 ($40,611 vs $38,337) [35]. The study conducted in Spain showed a 1.7% increase in the cost of readmission compared to the admission cost [46].

Recurrence of readmission reduced the time to the next readmission in a retrospective study of 3,176 patients in Denmark [62]. Readmission rate at 30 days post-discharge increased from first admission (9.4%) to 2nd, 3rd and 4th readmission (19.3%, 26.6% and 30.8%), respectively [62]. A longer LOS for 30-day and 12-month readmissions compared to the index admission were reported in three studies (mean 5.2 days vs mean 4.6 days [35]; median 9 days vs median 7 days [49]; and 10 days vs 8 days [46], respectively).

4. Discussion

This systematic review provides a summary of the COPD-related readmission studies concerning risk factors and associated outcomes, published between 2000 and 2019. Uniquely, we report factors both associated with and not associated with rehospitalisation from ECOPD. Hospitalisation in the previous year was the main risk factor for readmission. Comorbidity (asthma), socioeconomic status (inadequate health insurance and living in a deprived area) and living or discharged to nursing home were also associated with readmission. Increased IHM, shorter survival period, poorer quality of life, increased cost, longer LOS and frequent readmissions were outcomes of rehospitalisation from COPD.

The varied reported rates of readmission could be attributed to several factors. There were variations in the study populations (e.g. USA

Table 3
Provider-related risk factors for COPD readmission.

Provider factors	Authors	≤30 day readmission adjusted analysis (95% CI)	>30–90 day readmission adjusted analysis (95% CI)	>90 day readmission adjusted analysis (95% CI)	12 month readmission frequency adjusted analysis (95% CI)
Medications prescribed					
Use of bronchodilators pre-admission	Baker [17]		OR 1.21 (1.02–1.45)		
Albuterol prescribed post-discharge	Rezaee [57]	OR 4.10 (2.60–6.40)			
Use of albuterol pre-admission	Roberts [40]	OR 1.40 (1.02–1.91)		OR 1.52 (1.25–1.86)	
Use of levalbuterol pre-admission	Roberts [40]			OR 1.49 (1.08–2.05)	
Use of salmeterol pre-admission	Roberts [40]			OR 1.51 (1.23–1.84)	
Tiotropium prescribed post-discharge	Rezaee [57]	OR 1.80 (1.00–3.20)			
Use of tiotropium pre-admission	Roberts [40]	OR 1.61 (1.16–2.23)			
Use of ipratropium pre-admission	Roberts [40]			OR 1.47 (1.19–1.82)	
Use of ipratropium + albuterol pre-admission	Roberts [40]			OR 1.47 (1.16–1.86)	
Oral theophylline post discharge	Sin [58]			RR 1.20 (1.20–1.27)	
ICS ≥1000 g beclomethasone/day for ≥3months pre-admission	Lau [76]			HR 1.35 (1.02–1.80)	
ICS prescribed post-discharge	Rezaee [57]	OR 3.80 (1.30–10.70)			
ICS prescribed post-discharge	Sin [58]			RR 0.76 (0.71–0.80)	
Use of fluticasone pre-admission	Roberts [40]			OR 1.69 (1.38–2.06)	
Use of LABA + ICS prior and post discharge	Bishwakarma [32]	OR 1.48 (1.18–1.86)			
Fluticasone + salmeterol prescribed post-discharge	Rezaee [57]	OR 2.30 (1.30–4.20)			
Use of fluticasone + salmeterol pre-admission	Roberts [40]			OR 1.51 (1.23–1.85)	
Use of oral corticosteroid post-discharge	Sin [58]			RR 2.09 (1.97–2.20)	
Long term use of ≥15 mg/day prednisolone pre-admission	Liu [67]	[a]0.01			
Previous steroid therapy pre-admission	Wong [16]			OR 2.98 (1.21–7.33)	
Use of prednisolone pre-admission	Roberts [40]	OR 1.70 (1.25–2.31)		OR 1.78 (1.46–2.17)	
Use of methylprednisolone pre-admission	Roberts [40]			OR 1.41 (1.11–1.81)	
At least one claim for an oral corticosteroid within 30 days post-discharge	Roberts [40]			OR 1.50 (1.21–1.87)	
Use of montelukast pre-admission	Roberts [40]	OR 1.59 (1.10–2.30)		OR 1.76 (1.38–2.24)	
Antimicrobials use post-discharge	Sin [58]			RR 1.17 (1.10–1.23)	
Total no of prescription claims pre-admission (in units of 10)	Roberts [40]	OR 1.03 (1.00–1.05)		OR 1.02 (1.00–1.04)	
% of the pre-index period when prescription COPD medications available	Roberts [40]			OR 1.01 (1.01–1.01)	
Use of psychotropic drugs pre-admission	Cao [27]				OR 13.47 (1.48–122.92)
Vaccination status at index admission	Cao [27]				OR 3.27 (1.12–9.57)
Vaccination pre-admission	Roberts [40]	OR 1.50 (1.08–2.09)			
Non-pharmacological therapies					
Ventilation					
Non-invasive (yes vs no)	de Miguel-Diez [46]	OR 1.16 (1.11–1.22)			
Invasive or non-invasive (yes vs no)	Fuhrman [71]			RR 1.14 (1.05–1.18)	
Any ventilatory support (yes vs no)	Hartl [28]		OR 1.13 (1.04–1.24)		
Previous acute non-invasive (yes vs no)	Tsui [77]			HR 1.56 (1.08–2.26)	
LTOT before hospitalisation (yes vs no)	Fuhrman [71]			RR 1.83 (1.78–1.89)	
Home LTOT use before admission (yes vs no)	Bahadori [53]			OR 2.55 (1.47–4.42)	
Home LTOT use before admission (yes vs no)	Gonzalez/2008 [48]			OR 2.30 (1.20–4.40)	
Tobacco cessation counselling in the hospital (yes vs no)	Iyer [34]			OR 0.34 (0.18–0.66)	

Footnote :
[a] Only p-value reported; ICS inhaled corticosteroid; LTOT Long-term oxygen therapy; LABA Long-acting beta$_2$-agonists.

Medicare/Medicaid population, Spanish national hospital database), healthcare systems (e.g. UK public healthcare system, Canadian single-payer healthcare), type of hospitals, locality factors (e.g. access to primary care and secondary care), socioeconomic factors (e.g. living in deprived or urban areas), and statistical analyses. The research was dominated by studies from the USA, with its insurance-based approach to healthcare, and Spain, where most healthcare is publicly funded. The rate of patient readmission and the severity of their condition will differ according to the presence of support frameworks in different localities. A study undertaken in Christchurch, New Zealand illustrates this line of reasoning [78]. The study demonstrated that the diversion of patients with mild and moderate COPD from hospital to non-hospital settings (community acute care services, community GP-manned facilities, or at home with appropriate support) resulted in a 48% decrease in bed-day

Table 4
System-related risk factors for COPD readmission.

System factors	Authors	≤Another chronic respiratory disease readmission adjusted analysis (95% CI)	>30–90 day readmission adjusted analysis (95% CI)	>90 day readmission adjusted analysis (95% CI)	12 month readmission frequency adjusted analysis (95% CI)
Hospitalisation					
Hospital stay in resuscitation or intensive care (yes vs no)	Fuhrman [71]			RR 0.95 (0.90–0.99)	
Prior intensive care stay	Gershon [59]	OR 1.12 (1.03–1.22)			
No of intensive care days in index admission	Baker [17]	OR 1.05 (1.00–1.10)	OR 1.04 (1.00–1.08)		
Hospitalisation in the previous year					
COPD-related (yes vs no)	Almagro [13]			OR 4.27 (1.51–12.04)	
COPD-related (yes vs no)	Hunter [73]			HR 1.32 (1.20–1.45)	
COPD-related (yes vs no)	Johannesdottir [62]			OR 3.20 (2.60–3.90)	OR 2.30 (1.40–4.00)
COPD-related (yes vs no)	Roberts [40]	OR 2.20 (1.35–3.59)		OR 3.64 (2.65–4.99)	
Any (yes vs no)	Roberts [40]	OR 1.67 (1.23–2.27)		OR 2.10 (.72–2.55)	
Any (yes vs no)	Lau [76]			HR 1.55 (1.22–2.00)	
Any (yes vs no)	McGhan [38]			HR 1.23 (1.22–1.24)	
Any (yes vs no)	Gavish [72]		OR 2.24 (1.57–3.19)		
Any (yes vs no)	Hartl [28]		OR 2.48 (2.30–2.67)		
Respiratory related (yes vs no)	Roberts [40]	OR 1.94 (1.38–2.72)		OR 2.81 (2.26–3.50)	
<6 months (vs > 5 year or none)	Gershon [59]	OR 2.39 (2.30–2.49)			
>6 months–5 years (vs > 5 years or none)	Gershon [59]	OR 1.66 (1.61–1.72)			
No. of hospitalisations in the previous year					
1 COPD-related (vs 0)	Tsui [77]			HR 1.11 (1.06–1.16)	OR 1.96 (1.54–2.50)
1 COPD-related (vs 0)	Müllerova [29]			HR 2.71 (2.24–3.29)	
1 (vs 0)	Baker [17]	OR 1.39 (1.02–1.90)	OR 1.61 (1.14–2.26)		
1 (vs 0)	Roberts [40]	OR 1.23 (1.13–1.33)		OR 1.25 (1.17–1.33)	
Respiratory-related (1 vs 0)	Roberts [40]	OR 1.46 (1.28–1.65)		OR 1.70 (1.50–1.91)	
>1 COPD-related (vs 0)	Crisafulli [44]	OR 8.04 (1.61–40.17)			
1 COPD-related (vs 0)	Fuhrman [71]			RR 1.97 (1.89–2.05)	
2 COPD-related (vs 0)	Fuhrman [71]			RR 2 63 (2.47–2.81)	
≥2 COPD-related (vs 0)	Quintana [50]		OR 2.51 (1.74–3.62)		
>3 COPD-related (vs 0)	Fuhrman [71]			RR 4.08 (3.79–4.38)	
>2 (vs 0)	Baker [17]	OR 3.20 (2.24–4.58)	OR 3.92 (2.95–5.20)		
>2 (vs 0)	Gudmundsson [14]			HR 1.98 (1.42–2.76)	
Out-patient visits in pre-index					
2 (vs 0)	Gershon [59]	OR 1.33 (1.28–1.39)			
>2 (vs 0)	Baker [17]		OR 1.61 (1.29–2.01)		
3 (vs 0)	Gershon [59]	OR 1.48 (1.40–1.55)			
>4 (vs 0)	Gershon [59]	OR 2.02 (1.93–2.11)			
>3 (vs 0)	Adeyemi [66]		[a]OR 0.51 (0.49–0.54)		
Hospital LOS during index admission					
1 (vs 4–6) days	Gershon [59]	OR 1.20 (1.07–1.35)			
>1 day	Zapatero [52]	OR 1.01 (1.01–1.02)			
5 (vs 4) days	Jiang [35]	OR 1.01 (1.01–1.02)			
>5 (vs ≤ 5) days	Lau [76]			HR 1.40 (1.11–1.77)	
7-13 (vs 4–6) days	Gershon [59]	OR 1.08 (1.05–1.12)			
8 (vs 11) days	Bahadori [53]			OR 0.44 (0.26–0.74)	
>10 (vs 1–3) days	Candrilli [33]	OR 3.09 (2.82–3.21)	OR 2.507 (2.36–2.66)		
9-13 (vs < 6) days	Fuhrman [71]			RR 1.13 (1.09–1.18)	
11 (vs 9) days	Barba [43]	OR 1.014 (1.013–1.014)			
≥14 (vs < 6) days	Fuhrman [71]			RR 1.16 (1.11–1.21	
30 days: 3–5 (vs ≤ 2) days 90 days: >9 (vs ≤ 2) days	Harries [10]	OR 0.87 (0.77–0.99)	OR 1.17 (1.05–1.30)		
Discharge Destination, time and follow-up					
Left against medical advice	Jiang [35]	OR 1.86 (1.71–2.03)			
Left against medical advice	Gershon [59]	OR 2.11 (1.90–2.34)			
Health/social institutions (yes vs no)	de Miguel-Diez [46]	OR 1.41 (1.34–1.49)			
Intermediate care/skilled nursing facility (vs routine discharge)	Jiang [35]	OR 1.16 (1.11–1.22)			
Long term care/other (vs home)	Gershon [59]	OR 0.89 (0.85–0.93)			
Home health care (vs routine discharge)	Jiang [35]	OR 1.21 (1.16–1.26)			
Home with support services (vs home)	Gershon [59]	OR 1.28 (1.24–1.32)			

(continued on next page)

Table 4 (*continued*)

System factors	Authors	≤Another chronic respiratory disease readmission adjusted analysis (95% CI)	>30–90 day readmission adjusted analysis (95% CI)	>90 day readmission adjusted analysis (95% CI)	12 month readmission frequency adjusted analysis (95% CI)
Home health care (vs routine discharge)	Jiang [35]	OR 1.21 (1.16–1.26)			
Living in nursing homes (yes vs no)	Chan [60]	OR 1.41 (1.34–1.47)			
Living in nursing homes (yes vs no)	Lau [76]			HR 1.72 (1.17–2.53)	
Winter (vs summer)	Jiang [35]	OR 1.59 (1.52–1.66)			
Autumn (vs summer)	Jiang [35]	OR 0.61 (0.58–0.65)			
No pulmonary follow-up visit post-discharge	Gavish [72]		OR 2.91 (1.06–8.01)		
COPD specialist care (vs none)	Gershon [59]	OR 1.14 (1.10–1.17)			

Footnote :

[a] Antilog result; LOS length of stay.

occupancy for COPD patients. These findings are consistent with previous studies where patient population, resources and place of healthcare provision were drivers of readmission [79]. Similarly, differences in the reported patient, provider and system factors associated with readmissions may reflect variations in the local context, such as the availability of community-based services to care for exacerbations of COPD.

The previous systematic review noted three main predictors (previous hospitalisation, dyspnoea and oral corticosteroids) of readmission from COPD [19]. Our results are consistent with the first variable. One study identified having two or more prior exacerbations as independently associated with readmission within 30 days [49]. Exacerbation is known to result in hospitalisation of COPD patients with damaging effects on health and mortality of COPD [18]. The findings of our review support the concept of 'frequent exacerbation phenotypes' who are susceptible to readmission, irrespective of the severity of their disease [80]. Again, another explanation points to the variation of care within and between countries regarding pre- and post-discharge from COPD exacerbations [10,28,36,81]. It is possible that in areas where healthcare systems do not practice community-based strategies for managing mild-to-moderate COPD patients, patients may be more likely to be admitted and readmitted to hospital for care that could be managed appropriately outside hospitals [82,83].

This is the first review to detail inconsistencies across several risk factors previously reported as being associated with readmission. These inconsistencies and the heterogeneity of the studies resulted in the inability to undertake a meta-analysis. However, Table 5 provides information on both associated and non-associated risk factors for COPD readmission. Apart from asthma, which consistently increased the risk of readmission, there was variation in most of the comorbidities reported to be association with readmission. Five studies of good quality in 448,680 patients found that comorbid asthma increased the risk of readmission from 5% [33] up to 66% [40]. There is the overlapping spectrum of some patients having a distinct phenotype of COPD and some features of asthma, and it has been reported that patients with this overlapping spectrum have higher exacerbation frequency and hospitalisations [29,84,85]. Asthma flare-ups in these patients could result in exacerbation of COPD and further rehospitalisation. One study excluded asthma and other respiratory comorbidities because of their significant effects of overshadowing other factors [76].

Interestingly, some socioeconomic factors (lack of health insurance, living in a deprived area and urban area, alcohol and drug abuse) and living in or discharged to a nursing home were highlighted as patient risk factors for COPD readmission. These results support the observation that most hospital readmissions are driven by patient factors that are outside hospital control [86]. In some countries, public health insurance could indicate financial hardship, which may result in inadequate access to preventive health care and procurement of medications.

Several studies associated living in a deprived area with increased risk of readmission [33,34,59,71]. These findings are similar to a prior study that found COPD patients with a low socioeconomic status had a 22% higher all-cause readmission rate [87]. Nursing home residents are generally frail and burdened with complications and comorbidities that can result in unavoidable readmissions [60,88]. There is also the issue of nursing home staff, who may lack the necessary skills in the management of mild-moderate ECOPD to prevent progression into severe exacerbation. This sort of admission could be reduced through outreach programmes, such as a respiratory home care service, access health crisis team or community specialised nurses.

Malnutrition was one of the modifiable factors reported in small number of good quality studies to be associated with readmission. Nutritional supplements promoted gain in fat-free mass in malnourished patients with COPD, enhanced their exercise capacity and health status [89]. Despite limited evidence regarding malnutrition intervention resulting in exacerbation reduction, nutritional supplements can prevent body wasting and improve prognosis for COPD patients [46]. Preventive measures such as healthy living, education, and general wellbeing awareness can be promoted across healthcare sectors for lasting impact on patient wellbeing [83,90–92].

Our review found readmissions to be associated with increased IHM, shorter survival period, poorer quality of life, increased cost, longer LOS and frequent recurrence of readmission. One possible explanation for increase in IHM could be that COPD patients with frequent exacerbation are likely to have severe underlying disease. Hence, there may be confounding by indication as sicker patients will require extensive and complex medication management. Severity of acute illness predisposes COPD patients to IHM, while severity and duration of disease are predictors of post-discharge long-term mortality [93]. Respiratory acidosis on admission and the need for ventilatory support were found to be independent predictors of both IHM and post-discharge mortality in COPD patients [28]. Respiratory acidosis is modifiable in hospital setting. Appropriate and effective use of ventilatory support with oxygen in a randomised trial reduced readmission and mortality in COPD patients [94].

The finding of longer LOS in readmitted patients was similar to the literature [95]. This increase in LOS could explain the increased cost of readmission compared to the index admission. Similar to our review, the mean cost of readmission was 18% higher than index hospitalisation in another study [96]. This review demonstrated the high burden of COPD readmission on patients and the health system, indicating that reducing readmissions is a vital area for potential savings.

The review contains some limitations. The literature search was limited to research published in developed countries and available in English. We restricted the review to developed countries to minimise heterogeneity. Yet, the variation between studies and health system contexts made comparison of readmission rates and risk factors challenging, and prevented a meta-analysis. Despite these limitations, the study has the following strengths: firstly, it included a large number of studies and provided comprehensive information on COPD-related

Table 5
Risk factors associated and not associated with COPD readmission.

Patient factors	Association		No association	Total
	Positive association	Negative association		
Demographic factors				
Age	13 [28,33,35,36,38,46,52,62,66,69–71]		38 [10,13,14,16,17,26,27,[a]31,32,34,37,39–41,43,45,47[a]–49,51,[a],53–61,63,64,67[a],68,72–74,76,77]	51
Sex (male)	10 [35,36,38,42,[a]43,46,59,60,62,68]	2 [52,71]	36 [10,13,14,16,17,26–29,31–34,37,39–41,45,53–58,61,63,64,66,67[a],69,70,72–74,76,77]	48
Social determinants of health				
Smoking status		1 [52]	28 [13,14,16,26–29,31,34,39,40,43,45,47[a]–49,51[a],53,56,57,61,63,67[a]–69,73,74,77]	29
Marital status (single)	1 [16]		5 [13,27[a],57,68,76]	6
Ethnicity	2 [35,36]	4 [35,36,38,66]	5 [27[a],32,34,37,68]	10
Living in deprived area	6 [10,35,59,71,73,76]		1 [13]	7
Large metropolitan/urban areas	2 [35,59]			2
Alcohol abuse	1 [36]			1
Drug abuse	1 [36]			1
Health insurance coverage	8 [17,31,33,35,36,39,41,60]		2 [32,57]	10
Activity level				
Daily activity (multi-component assessment)	1 [68]		3 [45,53,77]	4
Dependency on self-care activities	1 [76]		2 [13,53]	3
SGRQ score	3 [13,14,29]		2 [69,77]	5
6-min walk distance (per 10-m increase)	1 [77]		2 [29,51,[a]]	3
Nutritional factors				
Obesity		2 [46,52]	2 [36,62]	4
BMI	1 [74]	1 [73]	18 [13,16,26–29,34,37,45,47[a],48,51[a],53,57,63,64,67[a],77]	20
Malnutrition	3 [43,46,52]			3
Cured meat intake >22.7g per day	1 [45]			1
Comorbidities				
Charlson score	8 [16,28,33,43,46,52,57,70]	1 [61]	14 [13,27,[a]37,40,45,51[a],53,55,56,58,60,64,66,77]	23
Neoplasms (C00–C97)				
Cancer	5 [17,43,52,59,62]	1 [33]	5 [35,36,46,61,63]	11
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (D50-D89)				
Anaemia	3 [36,41,43]		3 [35,49,61]	6
Endocrine, nutritional and metabolic diseases (E00-E90)				
Diabetes	4 [36,40,43,44]	3 [28,38,59]	14 [14,17,26,34,46–48,53,56,61–63,67[a],76]	21
Mental and behavioural disorders (F00–F99)				
Depression	7 [34–36,40,41,62,69]		8 [13,14,27[a]29,31,68,74,77]	15
Anxiety	2 [40,77]		5 [14,27[a],34,69,74]	7
Psychosis	1 [36]			1
Diseases of the circulatory system (100–199)				
Pulmonary heart disease and diseases of circulation	5 [35,40,47,[a]48,55]		5 [17,36,41,46,62]	10
Hypertension	2 [38,40]		9 [26,34,36,39,47,[a]48,61,62,67[a]]	11
Ischemic heart disease	4 [35,39,40,62]		8 [17,33,34,42,[a]46,53,55,59,76]	12
Congestive heart failure	6 [40,41,43,52,55,59]		12 [17,26,34–36,46,50,53,61–63,76]	17
Cerebrovascular disease	1 [59]			1
Atrial fibrillation	1 [43]	1 [33]	4 [34,39,62,76]	6
Arrhythmias	1 [55]			1
Pulmonary unilateral infiltrate	1 [39]			1
Diseases of the respiratory system (J00-J99)				
Respiratory failure	1 [59]			1
Other chronic respiratory disease	3 [17,28,53]		1 [73]	4
Pneumonia	2 [33,40]		1 [41]	3
History of lung infection	2 [17,53]			2
Asthma	5 [33,38,40,59,62]	1 [35]	2 [56,73]	8
Diseases of the digestive system (K00–K93)				
Moderate or severe liver disease	1 [17]		4 [36,46,59,63]	5
Gastroesophageal reflux disease	1 [34]			1
Ulcer of the digestive system	1 [59]			1
Diseases of the musculoskeletal system and connective tissue (M00-M99)				
Osteoporosis	3 [35,40,62]			3
Diseases of the genitourinary system (N00–N99)				
Renal failure	1 [33]		8 [17,34,36,41–43,46,59,63]	9
Disease severity and complexity				
Severity (GOLD stage 1–4)	1 [16]		5 [26,28,56,63,74]	6
Decline in lung function (FEV_1%)	6 [26,27,[a]29,50,67[a],73]	4 [14,16,45,69]	17 [13,26,28,31,34,37,39,47[a]–49,51[a],53,56,64,72,74,77]	27
≥2 exacerbations in the past year	1 [49]			1
COPD severity score	1 [41]		1 [49]	2
Severe complexity	1 [33]			1
COPD Assessment Test	1 [77]		1 [37]	2
Higher baseline BODE scores	1 [75]		3 [29,51[a],77]	4
Suboptimal peak inspiratory flow	1 [37]			1
Chronic cough and sputum production	1 [26]		2 [28,29]	3

(continued on next page)

Table 5 (*continued*)

Patient factors	Association		No association	Total
	Positive association	Negative association		
Dyspnoea/difficult breathing	3 [40,50,57]		11 [13,27[a]–29,37,41,45,49,51[a],67[a],77]	15
Pressure-time index[b]	2 [47,[a]48]			2
Right heart strain pattern on EKG	1 [76]			1
Emphysema >5% by radiology	1 [29]			1
Duration of COPD	2 [27[a],59]		2 [72,74]	4
Laboratory findings				
Respiratory acidosis	1 [46]		1 [61]	2
Arterial blood gas testing	1 [57]			1
Admission WBC count	2 [16,29]		5 [34,39,56,61,76]	7
Eosinophilia ≥200 cells/μL and/or ≥2% WBC	1 [56]			1
Red cell distribution width (>14.5%)	1 [61]			1
CRP at discharge ≥7.6 mg/L	1 [44]		1 [29]	2
B-type natriuretic peptide testing	1 [57]		2 [31,39]	3
Low serum magnesium level (1.77 ± 0.19 mEq/L)	1 [31]			1
Higher serum sodium level (137.4 mMol/L)	1 [34]			1
Actual bicarbonate >25 mMol/L	1 [76]		1 [34]	2
$PaCO_2$ >45 mmHg	2 [13,74]		11 [16,28,45–49,61,63,64,76]	13
Hypoxia	1 [40]		4 [45,47,[a]48,64]	5
Medications prescribed				
Bronchodilators	3 [17,40,57]		7 [14,26,39,54,56,58,63]	10
Oral theophylline	1 [58]		1 [49]	2
ICS	5 [32,40,57,67[a],76]	1 [58]	9 [14,17,26,31,39,45,54,56,63]	15
Oral corticosteroid	3 [16,40,58]		11 [14,17,28,31,39,54,56,63,64,74,76]	14
Montelukast	1 [40]			1
Antimicrobials	1 [58]		4 [28,39,54,56]	5
Psychotropic drugs	1 [27a]			1
Vaccination	2 [27,[a]40]		4 [31,39,41,77]	6
Non-pharmacological therapies				
Ventilation	4 [28,46,71,77]		4 [32,41,63,76]	8
LTOT	3 [48,53,71]		11 [13,14,17,26,31,41,56,63,76,77]	14
Tobacco cessation counselling in the hospital		1 [34]		1
Hospitalisation				
Hospital stay in resuscitation or intensive care		1 [71]	2 [41,64]	3
Hospitalisations in the previous year	12 [13,17,28,29,38,44,62,71–73,76]		6 [47,[a]48,50,55,56,69]	18
No. of hospitalisations in the previous year				7
	7 [14,17,50,59,66,71,77]			
Hospital LOS during index admission	9 [10,33,35,43,52,53,59,71,76]		17 [13,14,31,32,37,39,41,46–49,55,61,64,68,70]	26
Discharge destination	2 [35,46]			3
Living in or discharged to nursing homes	5 [35,46,59,60,76]		1 [53]	6
Winter	1 [35]		1 [41]	2
Autumn		1 [35]		1
COPD specialist/ pulmonologist follow-up visit	2 [59,72]		1 [53]	3

Footnote : SGRQ St. George's Respiratory Questionnaire score.

[a] indicates study with fair quality assessment; GOLD Global Initiative for Chronic Obstructive Lung Disease; FEV_1 Forced expiratory volume in one second; BODE Body-mass index, airflow Obstruction, Dyspnea, and Exercise capacity.

[b] Indicator of respiratory muscle efficiency; CRP C-reactive protein; PaCO2 partial pressure of oxygen; WBC white blood count; ICS inhaled corticosteroid; LTOT Long-term oxygen therapy.

readmission. Secondly, it is the first of its kind to report and summarise both associated and non-associated risk factors for COPD readmission.

In conclusion, the incidence of readmission from ECOPD varied substantially across all studies and timepoints. Hospitalisation in the previous year and comorbidity (asthma) were the most consistent predictors of ECOPD readmission. Readmitted patients had a higher in-hospital mortality rate, shorter long-term survival period, poorer quality of life, longer hospital stay and increased recurrence of readmission, and accounted for greater healthcare costs. Variation in the incidence of COPD-related readmissions and the reported factors associated with readmission could reflect diversity in local context and healthcare systems between studies, meaning that risk factors cannot be readily generalised, and interventions should be tailored to the local healthcare environment. The identified socioeconomic factors (e.g. living in deprived areas) should also guide the targeting of local intervention strategies.

Authors contributions

CN, BB, BW, GP and LK were responsible for the conceptualisation, identification, quality assessment of potential studies and interpretation of data. CN prepared and drafted the manuscript. All co-authors critically revised and approved the final manuscript. BB, BW, GP and LK provided oversight and mentorship.

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Declaration of competing interest

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Table 6
Outcomes associated with COPD readmission.

System factors	Authors	≤30 day readmission	>30–90 day readmission	>90 day readmission	12 month readmission
Patient-related outcomes					
Increased mortality rate	Carneiro, 2010 [63]			4.4% IHM and 15.5% overall mortality at 66 weeks	
	Chan, 2011 [60]	3.4% mortality in readmitted and 2.9% in non-readmitted patients			
	de Miguel-Diez, 2015 [46]				8.5% readmission IHM and 4.3% index admission IHM
	Epstein, 2018 [61]		4.4% IHM and 5% overall mortality at 60 days		
	Groenewegen, 2003 [64]		8.0% IHM and 16.0% overall mortality at 90 days		
	Gudmundsson, 2005 [14]				10.3% mortality in readmitted patients and 2.2% in non-readmitted patients
	McGhan, 2007 [38]				3.5% IHM and 21% overall mortality
	Johannesdottir, 2013 [62]	5.6% IHM and 4.2% overall mortality			
	Hartl, 2015 [28]		13.4% mortality in readmitted patients and 2.3% in non-readmitted patients at 90 days 4.9% IHM and 5.9% mortality at 90 days post-discharge follow-up		
	Guerrero, 2016 [49]	5% mortality in readmitted patients and 1% in non-readmitted patients	27% mortality in readmitted patients and 10% in non-readmitted patients at 6 months	67% mortality in readmitted patients and 43% in non-readmitted patients at 3 years	37% mortality in readmitted patients and 17% in non-readmitted patients
Shorter survival period			Median 109 days in readmitted patients and median days of 162 in non-readmitted patients at 6 months	Median 250 days in readmitted patients and median 445 days in non-readmitted patients at 3 years	Median 124 days in readmitted patients and median 209 days in non-readmitted patients
Functional status	Pitta, 2006 [65]	Median 9 min/d walking time at 1-month post-discharge in patients with one or more hospitalisation in the year before inclusion to study and median 26 min/d in non-hospitalised patients Median 200 m 6MWD at day 8 of rehospitalisation in readmitted patients and 351 m in non-readmitted patients Median 12 min/d walking time at 1 month in readmitted patients and 30 min/d in non-readmitted patients			
Healthcare utilisation					
Cost	de Miguel-Diez, 2015 [46]				Readmission mean cost €3921 and admission mean cost €3855
	Jiang 2018 [35]	Readmission mean cost US $40,611 and admission mean cost $38,337			
Subsequent readmission	Johannesdottir, 2013 [62]	1st readmission rate of 9.4% at 30 days from discharge and 19.4%, 29.6% and 30.8% at 2nd, 3rd and 4th subsequent readmissions			
Treatment		Use of mechanical ventilation rate of 0.7% at 30 days from discharge	Use of mechanical ventilation rate of 1.3% and 1.8% at 60 days and 90 days from discharge respectively	Use of mechanical ventilation rate 2.8% at 180 days from discharge	
		Antibiotics and steroid prescription rate of 5.7% at 30 days from discharge	Antibiotics and steroid prescription rate of 9.6% and 12.8% at 60 days and 90 days from discharge, respectively	Antibiotics and steroid prescription rate of 19.9% at 180 days from discharge	
Length of stay	Jiang, 2018 [35]	Mean 5.2 days in readmitted patients and mean 4.6 days in non-readmitted patients at 30 days			
	Guerrero, 2016 [49]	Median 9 days in readmitted patients and median 7 days in non-readmitted patients at 30 days			
	de Miguel-Diez, 2015 [46]				Mean 10 days in readmitted patients and mean 8 days in non-readmitted patients at 12 months
	Jiang, 2018 [35]	Mean 5.2 days in readmitted patients and mean 4.6 days in non-readmitted patients at 30 days			

Footnote : IHM in-hospital mortality rate; 6MWD 6-minute walking distance per day.

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Appendix A. Supplementary data

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Summary:

Fifty-seven studies from 30 countries were included in the review. The prevalence of readmission from COPD varied from 2.6-82.2% at 30 days, 11.8-44.8% at 31-90 days, 17.9-63.0% at 6 months, and 25.0-87.0% at 12 months post-discharge. The heterogeneity between studies precluded a meta-analysis. Hospitalisation in the previous year was the key predictor for COPD-related readmission. Comorbidities (in particular asthma), living in a disadvantaged area and living in or discharged to a nursing home were also significantly associated with increased readmission. Comparative to those without readmissions, readmitted patients had higher in-hospital mortality rates, shorter long-term survival, poorer quality of life, extended hospital stay, increased recurrence of subsequent readmissions, and accounted for greater healthcare costs. Difference in the prevalence and the reported factors associated with COPD-related readmission suggest that risk factors may not be generalised, and interventions should be tailored to the local healthcare environment.

3. CHAPTER 3: Prevalence of and risk factors for hospital readmission due to chronic obstructive pulmonary disease in Tasmania: a five-year longitudinal study

Abstract

Objective: To investigate the prevalence of hospital readmission for chronic obstructive pulmonary disease (COPD) at 30 days, 90 days and 12 months, and to determine risk factors for 30-day and 90-day readmission and time to COPD-related readmission within 12 months.

Methods: Patients ≥40 years admitted for COPD between 2011 and 2015 were identified using administrative data from all major public hospitals in Tasmania, Australia. Factors associated with readmission and time to readmission were identified using logistic and Cox regression, respectively.

Results: The rates of COPD-related readmission were 6.7% within 30 days, 12.2% within 90 days and 23.7% within 12 months. Being male (OR 1.49, CI 1.06–2.09), Indigenous (OR 2.47, CI 1.31–4.66) and living in the lower socioeconomic North-West region of Tasmania (OR 1.80, CI 1.20–2.69) were risk factors for 30-day readmission. Increased COPD-related (OR 1.48, CI 1.22–1.80; OR 1.52, CI 1.29–1.78) and non-COPD-related (OR 1.12, CI 1.03–1.23; OR 1.11, CI 1.03–1.21) emergency department (ED) visits in the preceding six months were risk factors for both 30-day and 90-day readmissions. Being Indigenous (HR 1.61, CI 1.10–2.37) and previous COPD-related ED visits (HR 1.30, CI 1.21–1.39) decreased, while a higher Charlson Comorbidity Index (OR 0.91, CI 0.83–0.99) increased the time to readmission within 12 months.

Conclusion: Being male, Indigenous, living in the North-West region and previous ED visits were associated with increased risk of COPD readmission in Tasmania. Interventions to improve access to primary healthcare for these groups may reduce COPD-related readmissions.

Keywords: COPD, Patient readmission, Prevalence, Risk factors

Key Messages:

1. Implications for policy-makers

- Being male, Indigenous, having recent ED visit and living in the lower socioeconomic region of Tasmania were significant predictors of COPD-related readmission.
- Improving patient-centred access to healthcare within the community, especially for Indigenous people, male patients and those living in lower socioeconomic areas, may reduce COPD-related readmissions.
- Future studies focused on improving patient-centred access to healthcare within the community and providing community support framework may divert mild and moderate cases of COPD from hospital.

2. Implications for public

Hospital readmission for COPD places a substantial burden on patients and healthcare systems around the globe. In the present study, we aimed to investigate the prevalence of hospital readmission for COPD at 30 days, 90 days, and 12 months and to determine the risk factors for 30-day and 90-day readmission and time to COPD-related readmission within 12 months. Our findings indicated that male patients, Indigenous people, and those living in the lower socioeconomic region were more likely to be readmitted for COPD in Tasmania.

3.1. Introduction

Chronic obstructive pulmonary disease (COPD) places a substantial burden on patients and healthcare systems around the globe. COPD is the third leading cause of death, accounting for 4.7 million annual deaths worldwide [91,92]. It was the fifth leading cause of disability-adjusted life years lost across the world in 2013 [93]. Based on the Global Initiative for Obstructive Lung Disease criteria, 14.5% of Australians aged 40 years and over had COPD in 2010 [94]. COPD

was the most common chronic condition associated with potentially preventable hospitalisation in four of the eight states and territories of Australia in 2015-16 [18]. Tasmania is the only Australian island state, with a population of 530,000 [95], predominantly regional and rural [96]. In Tasmania, COPD was the third leading cause of potentially preventable hospitalisation in 2015-16, with 218 admissions per 100,000 population, which increased by 9% in 2016-17 [97].

Previous research from the United States showed that 20% of patients admitted with an exacerbation of COPD (ECOPD) were readmitted within 30 days [52], and 50% were readmitted within six months [49] of hospital discharge. A recent systematic review highlighted inconsistencies across several risk factors previously reported as being associated with readmission for COPD [98]. This review demonstrated that hospitalisation in the previous year was the key predictor of readmission [98]. Patients living in deprived areas and in nursing homes were also at increased risk of readmission for COPD. However, there were variations in the reported factors associated with risk of readmission, which may reflect differences in the local context, such as the availability of community-based services to prevent and care for ECOPD. It was recommended that risk factors for COPD-related readmissions should be considered in the light of locality due to variations in healthcare systems around the world [98].

A few Australian studies have addressed risk factors for all-cause readmission following a COPD index admission [89,90], but none have explored readmission specifically for COPD. As an island state, Tasmania has minimal interstate hospital visits for patients in the community, making it an ideal setting for longitudinal research. This study aimed to measure the prevalence of 30-day, 90-day and 12-month COPD-related readmission in Tasmania. Additional aims were to identify the risk factors associated with 30-day and 90-day COPD-related readmission, and time to readmission within 12 months.

3.2. Methods

3.2.1. Study design and setting

In this longitudinal study, a retrospective cohort of patients admitted with COPD to any of the four main hospitals in Tasmania between January 1, 2011 and December 31, 2015 were reviewed. Data were collected until December 31, 2016, to allow 12-month follow-up for each patient. These hospitals (Royal Hobart Hospital, Launceston General Hospital, North West Regional Hospital and Mersey Community Hospital) collectively account for 95% of all public hospital admissions [99]. The population of Tasmania is dispersed across three regions: Hobart (South; 271,214 persons), Launceston (North; 145,033 persons) and the North-West Coast (111,954 persons), where these hospitals are located [95]. Socioeconomic status across the three regions of Tasmania varies. Within the socioeconomic ranking across Australia, Southern Tasmania ranks among the highest, followed by the North, with the North-West ranking lowest [101]. Four per cent of Tasmanian residents identfiy as Indigenous [100].

3.2.2. Data source

The study utilised the anonymised administrative admitted patient care National Minimum Dataset from the Department of Health and Human Services, Tasmania. The dataset provided access to de-identified demographic, administrative and clinical information pertaining to all COPD-related admissions and readmissions from January 1, 2011 to December 31, 2016. Mortality records of admitted patients were linked to the dataset.

3.2.3. Study participants

The study comprised patients aged 40 years and over, who had an overnight hospitalisation with a primary diagnosis of COPD between January 1, 2011 and December 31, 2015 (index admission). The diagnosis of COPD was determined using the International Statistical

Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) codes (J40–J44).

3.2.4. Measures

All patients with an index admission were followed up for 12 months post-index discharge except in the case of death occurring first. COPD-related readmissions following the index admission within 30 days, 90 days, and 12 months were analysed for all patients. COPD-related readmissions were subsequent admissions with a primary diagnosis of COPD. Non-readmitted patients were those who had an index admission but did not have a subsequent COPD-related readmission within the follow-up period. Those who died were identified from the mortality records that were linked to the dataset.

Based on well-established evidence on the relationship between previous emergency department (ED) visits and COPD-related readmission, the numbers of COPD-related and non-COPD-related ED visits in the six months preceding the index admission were both recorded as covariates [98]. Socioeconomic status (SES) of patients was estimated from their residential address using the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD) for areas [102]. Based on the Australian Bureau of Statistics recommendation, deciles were used in ranking the index of IRSAD [102]. Patients' usual residence was also used to group participants into the three main geographical regions (South, North and North-West) in Tasmania. Other covariates that were considered included age at index admission, sex, country of birth (Australia or overseas) and Indigenous status. Variables related to patients' index admission included discharge destination, admission to intensive care, length of stay, weekday or weekend admission and season of admission. The Charlson Comorbidity Index (CCI) [103] was used to determine the level of comorbidity.

3.2.5. Ethical approval

The study was approved by the Tasmania Human Research Ethics Committee (H0017433).

3.2.6. Statistical analysis

Data were analysed using STATA version 16.1 (StataCorp LLC, College Station, TX, USA). Descriptive analyses were used to report the prevalence of COPD-related readmission. Demographic and clinical characteristics of patients who were and were not readmitted during the follow-up periods were compared. Chi-square tests were used to compare categorical variables, and Mann-Whitney U-tests were used to compare continuous variables, between patients who were and were not readmitted.

Multiple logistic regression was performed to determine the factors independently associated with 30-day and 90-day readmission. Based on previous studies [98], age and sex, together with variables with p values of ≤ 0.1 in the univariate analyses, qualified for entry into the logistic regression models. Prior to performing logistic regression, variables were tested for inter-correlation. Categorical variables were assessed for collinearity against continuous variables using the Mann-Whitney U test and included in the logistic regression model if $p \geqslant 0.05$. Continuous or ordinal variables were assessed for collinearity against other continuous variables using a correlation test and included if the Spearman rho <0.4.

Cox proportional hazards regression was used to identify independent factors associated with time to first COPD readmission within 12 months. Bivariate analyses (i.e. simple Cox regression) were performed for each variable. Age, sex, and variables with p values of ≤ 0.1 were included in the multiple Cox proportional hazard regression. The end of follow-up was set at 12 months after hospital discharge or date of death, whichever occurred first. Proportional hazards assumption was assessed for each variable by visual inspection of the log-minus-log plots across

the covariate categories and by analysing residuals. Proportional hazard assumptions were confirmed using the test for parallel lines.

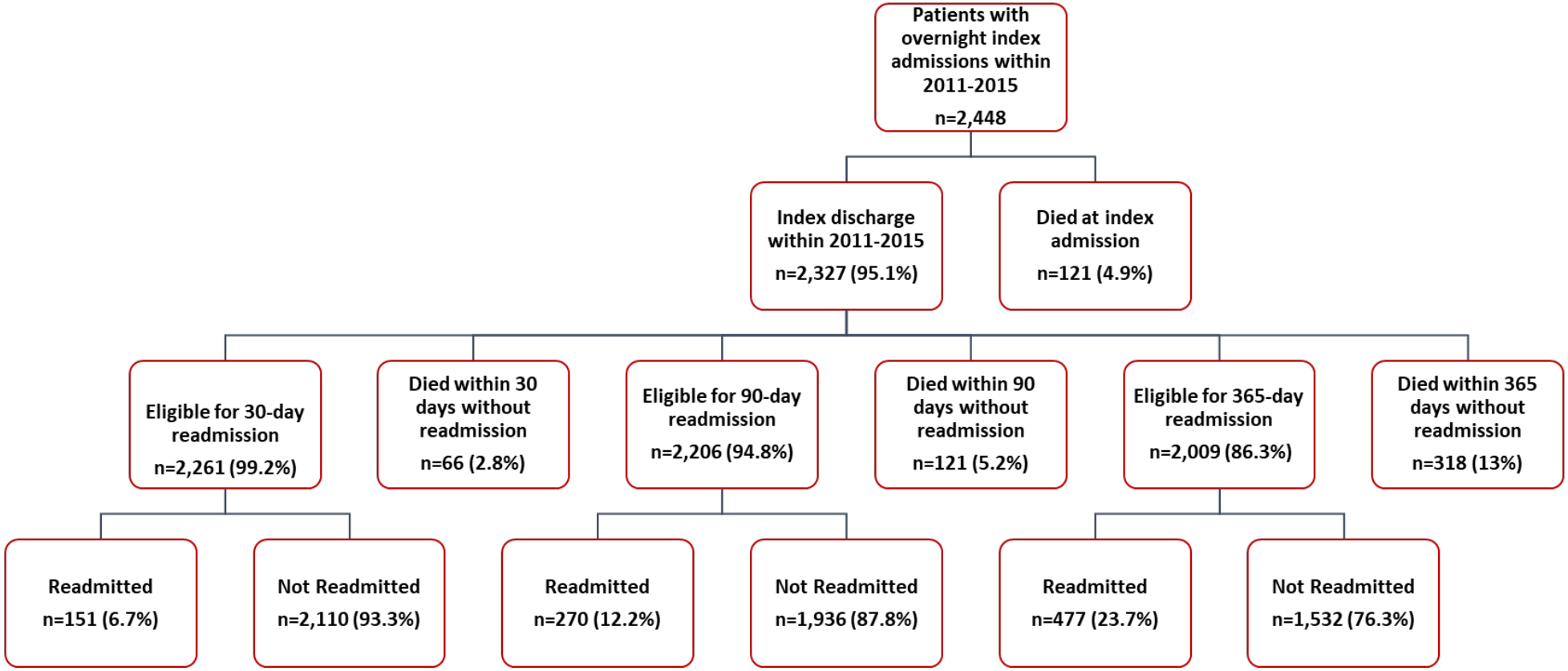
3.3. Results

3.3.1. Prevalence of COPD-related readmission in Tasmania

Between January 1, 2011 and December 31, 2015, there were 2,448 patients ⩾40 years who had an overnight index admission with COPD as the primary diagnosis and were followed up for subsequent COPD-related readmissions. The rate of COPD-related readmission was 6.7% within 30 days, 12.2% within 90 days and 23.7% within 12 months (Figure 6).

3.3.2. Factors associated with COPD-related readmissions

Table 5 shows the factors associated with 30-day and 90-day readmissions. Seven variables were included in the 30-day and the 90-day readmission multivariate models (Table 6). Five variables (sex, Indigenous status, Tasmanian region, COPD- and Non-COPD related ED visits) and two variables (COPD and Non-COPD related ED visits) significantly predicted 30-day ($F(7, 2209) = 10.35$, $p < 0.001$, adjusted $R^2 = 0.029$) and 90-day ($F(7, 2154) = 8.18$, $p < 0.001$, adjusted $R^2 = 0.023$) COPD readmission, respectively. There was significant intercorrelation between the Tasmanian region and IRSAD deciles (Kruskal-Wallis H test $\chi 2 = 106.68$, $p < 0.001$), which resulted in the exclusion of IRSAD decile from the multivariate analyses.



Figures 6. Prevalence of 30 days, 90 days and 12 months COPD readmission in the 4 main Tasmanian hospitals

Table 5. Demographic characteristics of patients at index admission, 30 days and 90 days

Characteristics	30-day readmission				90-day readmission			
Variables	**Total (n=2,261)**	**Yes (n=151)**	**No (n=2,110)**	**p**	**Total (n=2,206)**	**Yes (n=270)**	**No (n=1,936)**	**p**
Age (years), median (IQR)	72 (64–80)	72 (64–79)	72 (64–80)	0.28	72 (64–80)	73 (65–80)	72 (64–80)	0.76
Sex, n (%)								
Male	1117 (49.4)	89 (8.0)	1028 (92.0)		1083 (49.1)	148 (13.7)	935 (86.3)	
Female	1144 (50.6)	62 (5.4)	1082 (94.6)	**0.02**	1123 (50.9)	122 (10.9)	1001 (89.1)	**0.05**
Country of birth, n (%)								
Australian born	1989 (88.0)	137 (6.9)	1852 (93.1)	0.28	1939 (87.9)	235 (12.1)	1704 (87.9)	0.64
Overseas born	272 (12.0)	14 (5.1)	258 (94.9)		267 (12.1)	35 (13.1)	232 (86.9)	
Indigenous status, n (%)								
Indigenous	89 (4.0)	14 (15.7)	75 (84.3)	**<0.01**	88 (4.0)	16 (18.2)	72 (81.8)	0.08
Non-Indigenous	2161 (95.6)	137 (6.3)	2024 (93.7)		2107 (95.5)	253 (12.0)	1854 (88.0)	
Missing data	11 (0.4)				11 (0.5)			
Tasmanian region, n (%)								
South	906 (40.1)	48 (5.3)	858 (94.7)	**0.01**	889 (40.9)	108 (12.1)	781 (87.9)	0.09
North	651 (28.8)	42 (6.5)	609 (93.5)		625 (28.8)	66 (10.6)	559 (89.4)	

North-West	671 (29.7)	61 (9.1)	610 (90.9)		659 (30.3)	96 (14.6)	563 (85.4)	
Interstate patients	33 (1.5)				33 (1.5)			
IRSAD decile, median (IQR)	3 (2–5)	3 (2–4)	3 (2–5)	0.26	3 (2–5)	3 (2–4)	3 (2–5)	**0.02**
CCI, median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	0.74	1 (1–2)	1 (1–2)	1 (1–2)	0.38
Length of index stay (days), median (IQR)	4 (2–7)	4 (2–7)	4 (2–7)	0.65	4 (2–6)	4 (2–7)	4 (2–6)	0.33
Intensive care admission at index, n (%)								
Yes	111 (4.9)	5 (4.5)	106 (95.5)	0.35	109 (4.9)	8 (7.3)	101 (92.7)	0.11
No	2150 (95.1)	146 (6.8)	2004 (93.2)		2097 (95.1)	262 (12.5)	1835 (87.5)	
Discharge destination, n (%)								
Home	2043 (90.4)	135 (6.6)	1908 (93.4)		1998 (90.6)	246 (12.3)	1752 (87.7)	
Nursing home	42 (1.9)	3 (7.1)	39 (92.9)	0.92	40 (1.8)	4 (10.0)	36 (90.0)	0.90
Other[†]	176 (7.8)	13 (7.4)	163 (92.6)		168 (7.6)	20 (11.9)	148 (88.1)	
Number of ED visits in previous 6 months, median (IQR)								
COPD-related	1 (0–1)	1 (0–1)	1 (0–1)	**<0.01**	1 (0–1)	1 (0–1)	1 (0–1)	**<0.01**
Non-COPD-related	1 (0–1)	1 (0–2)	1 (0–1)	**0.02**	1 (0–1)	1 (0–2)	1 (0–1)	**0.02**
Admission day of the week, n (%)								

Weekend	589 (26.1)	38 (6.5)	551 (93.5)	0.80	576 (26.1)	68 (11.8)	508 (88.2)	0.71
Weekday	1672 (73.9)	113 (6.8)	1559 (93.2)		1630 (73.9)	202 (12.4)	1428 (87.6)	
Australian season of admission, n (%)								
Spring	620 (27.4)	42 (6.8)	578 (93.2)		607 (27.5)	70 (11.5)	537 (88.5)	
Summer	453 (20.0)	30 (6.6)	423 (93.4)	0.99	441 (20.0)	49 (11.1)	392 (88.9)	0.13
Autumn	426 (18.8)	27 (6.3)	399 (93.7)		415 (18.8)	65 (15.7)	350 (84.3)	
Winter	762 (33.7)	52 (6.8)	710 (93.3)		743 (33.7)	86 (11.6)	657 (88.4)	

IQR, interquartile range; ED, Emergency Department; CCI, Charlson Comorbidity Index; IRSAD, Index of Relative Socioeconomic Advantage and Disadvantage; [†]Other: welfare institutions, prisons, mental and rehabilitation centres, private and rural hospitals.

Being male (OR 1.49, 95% CI 1.06–2.09), Indigenous (OR 2.47, 95% CI 1.31–4.66), living in the North-West region (OR 1.80, 95% CI 1.20–2.69), and increased COPD-related (OR 1.48, 95% CI 1.22–1.80) and non-COPD-related (OR 1.12, 95% CI 1.03–1.23) ED visits in the previous six months were significant risk factors for 30-day readmission. Increased COPD-related (OR 1.52, 95% CI 1.29–1.78) and non-COPD-related (OR 1.11, 95% CI 1.03–1.21) ED visits in the previous six months significantly increased the risk of 90-day readmission. The most common reasons for non-COPD related ED visits were pneumonia (1,614/15,421; 10.5%), pain in the throat and chest (881/15,421; 5.7%) and heart failure (714/15,421; 4.6%).

Table 6. Logistic regression for predictors of COPD-related readmission within 30 days and 90 days

Variables	30-day readmission Adjusted ORs (95% CIs)	90-day readmission Adjusted ORs (95% CIs)
Age (years)	0.99 (0.98–1.01)	1.00 (0.99–1.02)
Male (vs female)	**1.49 (1.06–2.09)**	1.24 (0.95–1.61)
Indigenous (vs non-indigenous)	**2.47 (1.31–4.66)**	1.52 (0.85–2.73)
Tasmanian region (vs South)		
North	1.25 (0.81–1.92)	0.82 (0.59–1.14)
North-West	**1.80 (1.20–2.69)**	1.21 (0.89–1.64)
Number of ED visits in previous 6 months		
COPD-related to	**1.48 (1.22–1.80)**	**1.52 (1.29–1.78)**
Non-COPD-related	**1.12 (1.03–1.23)**	**1.11 (1.03–1.21)**

ORs, odd ratios; CIs, confidence intervals; ED, Emergency Department.

3.3.3. Independent predictors of shorter time to readmission

The median time to the first COPD-related hospital readmission within 12 months was 75 days (interquartile range [IQR] 59–84). Seven variables were included in the multivariate Cox proportional hazard regression analysis (Table 7). Being Indigenous (HR 1.61, 95% CI 1.10–2.37) and a higher number of COPD-related ED visits in the previous six months (HR 1.30, 95% CI 1.21–1.39) were associated with shorter time to readmission within 12 months, while a higher CCI was associated with longer time to readmission (HR 0.91, 95% CI 0.83–0.99).

Table 7: Cox proportional hazards regression for factors associated with time to readmission within 12 months

Variables	Unadjusted HRs (95% CIs)	Adjusted HRs (95% CIs)
Age (years)	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Male (vs female)	1.05 (0.88–1.26)	1.03 (0.86–1.24)
Australian born (vs oversea born)	0.99 (0.76–1.31)	
Indigenous (vs non-Indigenous)	**1.91 (1.34–2.74)**	**1.61 (1.10–2.37)**
Tasmanian region (vs South)		
North	0.88 (0.71–1.11)	
North-West	1.04 (0.84–1.29)	
CCI	**0.88 (0.81–0.96)**	**0.91 (0.83–0.99)**
Australian season of admission (vs winter)		
Spring	0.91 (0.71–1.15)	0.88(0.69–1.11)
Summer	1.24 (0.97–1.58)	1.12 (0.88–1.44)
Autumn	1.03 (0.79–1.33)	1.02 (0.79–1.33)
Weekend admission (vs weekday)	0.95 (0.77–1.17)	
Number of ED visits in previous 6 months		
COPD-related	**1.35 (1.27–1.45)**	**1.30 (1.21–1.39)**

Non-COPD-related	1.04 (0.98–1.11)	
Length of index stay (days)	1.01 (1.00–1.02)	
Intensive care admission during index (vs no)	0.86 (0.56–1.33)	
Discharge destination (vs home)		
Nursing home	0.42 (0.16–1.13)	0.44 (0.16–1.17)
Other†	0.93 (0.66–1.32)	0.99 (0.70–1.41)

HR, hazard ratio; CI, confidence interval; ED, Emergency Department; CCI, Charlson Comorbidity Index; †Other: welfare institutions, prisons, mental and rehabilitation centres, private and rural hospitals.

3.4. Discussion

To our knowledge, this is the first Australian study to assess risk factors for COPD-related readmission. The rates of COPD-related readmission within 30 days (6.7%), 90 days (12.2%) and 12 months (23.7%) were comparable to those reported in studies from other countries, such as the United States [104], Spain [105] and France [106]. There are also studies that reported lower [107] or higher [108] rates.

Patients who were male, Indigenous and living in a lower socieconomic region (North-West) were at significantly increased risk of 30-day COPD-related readmission. COPD-related and non-COPD related ED visits in the previous six months increased the risk of 30-day and 90-day readmission. Being Indigenous and having more COPD-related ED visits in the past six months were associated with shorter time to readmission while higher CCI was related to longer time to readmission within 12 months.

Patients living in the North-West region of Tasmania were 80% more likely to be readmitted within 30 days compared to those living in the South. Several studies have demonstrated an increased risk of readmission for COPD among people living in deprived areas [109,110]. The

North-West region is Tasmania's poorest region and, according to national data, people in lower socioeconomic areas are more inclined to have poorer health status, higher smoking rates, poorer access to primary healthcare and are less able to pay for medication [100,111]. A UK study found that disadvantaged communities have low ratios of general practitioners (GPs) per 1,000 population [112]. This finding is similar in Tasmania, with its lower number of full-time equivalent GPs in the North-West compared with Southern Tasmania (64.2 vs 78.7 per 100,000 population, respectively in 2012) [113]. This disparity in provision and access of healthcare services to the socioeconomically disadvantaged communities may expain their higher readmission risks.

Being Indigenous was the strongest risk factor for 30-day readmission and significantly decreased time to readmission within 12 months. National data indicates that Indigenous Australians are about three times more likely to be daily smokers, and have a 2.5 times higher prevalence of COPD and five times higher rate of hospitalisation for COPD [17].

There have been conflicting results regarding the association of sex and COPD-related readmission in the literature. Zapatero *et al.* [114] reported male patients were 25% less likely to be readmitted, another study found no such association [115], while another demonstrated male patients were 45% more likely to be readmitted within 30 days [116]. We found that male patients were 49% more likely to be readmitted within 30 days. A potential reason for this observation in Tasmania could be the higher rate of current male smokers (19.3%) compared to females (15.7%) [117]. There is also the possibility of more men having higher occupational exposure to dust and fume chemicals [118]. Male patients are also less likely to seek health advice during illness [119]. This could delay management of mild/moderate symptoms before escalation to more severe symptoms requiring hospitalisation and then frequent readmission.

The number of COPD-related and non-COPD-related ED visits in the six months prior to the index admission were associated with an increased risk of readmission within 30 and 90 days, as well as a significantly shorter time to COPD readmission. These findings are similar to prior studies that found a significant correlation between COPD readmission and previous ED visits [110,120]. One explanation points to patients with frequent exacerbation phenotype, who may be more likely to be readmitted [121]. Patients with severe COPD may be more susceptible to frequent ED visits and admission to hospital [104,123].

Frequent ED visits, leading to hospital admission, place an enormous burden on patients and the healthcare system. A previous study in Tasmania reported a 2.5 times higher per capita rate of ED visits in the North-West compared to the South [122]. An Australian study that targeted older adults with complex health needs and disadvantaged socioeconomic communities demonstrated a significant reduction in the average number of ED visits via the creation of a comprehensive community care programme There is a possibility that lack of community support frameworks that divert mild and moderate cases of COPD from hospital to settings in the community may increase the risk of readmission.

Our results show that patients with higher CCI have longer time to readmission within 12 months. Some studies have demonstrated that higher CCIs increase the risk of readmission [114,123], while another has shown a decreased risk of readmission with higher CCI [124]. There is the possibility that COPD patients with numerous comorbidities may be consulting their GP more often, resulting in closer monitoring and longer time to COPD-related readmission.

The findings of this study are in line with the findings of Australia's most recent national health report, which highlighted that social determinants of health are contributing to inequalities in health between population groups [125]. The present study has the following public health

implications. It has identified that male patients, Indigenous people, patients with recent ED visits and those living in the lower socioeconomic North-West area of Tasmania are at increased risk of COPD-related readmission. Trials on sustainable interventions (e.g. smoking cessation, care pathways, education) aimed at these people may prevent and reduce COPD-related readmission. Future studies focused on improving patient-centred access to healthcare within the community, especially in the lower socioeconomic areas, may improve health outcomes, and reduce ED visits and hospital readmissions.

The main limitation of this study is the inherent shortcomings related to the retrospective design using administrative data, such as missing and incomplete data. However, missing and incomplete data accounted for only 1.5% of the dataset. There is also the possibility of inaccurate or inconsistent coding, the extent of which is unknown. Futhermore, individual smoking status and several clinical factors (e.g. previous exacerbations of COPD, the severity of the disease, decline in lung function, etc.) were not available from the data source.

Despite the limitations, our study is the first to investigate COPD-related readmission in Australia and has identified the prevalence and key risk factors for readmissions due to COPD. This five-year logitudinal study comprised all patients admitted with COPD to the four main public hospitals in Tasmania with minimal interstate hospital visits. Further studies are required to assess clinical risk factors, such as lung function and smoking status, that are not available in the National Minimum Dataset for a broader understanding of determinants of COPD-related readmissions.

3.5. Conclusion

The prevalence of 30-day, 90-day and 12-month COPD-related readmissions in Tasmania were 6.7%, 12.2% and 23.7%, respectively. Being male, Indigenous and living in the North-West

region were significant predictors of COPD-related readmission. Previous ED visits were associated with increased risk of 30-day and 90-day COPD-related readmissions and shorter time to readmision within 12 months. Studies on interventions aimed at providing and improving access to community-based healthcare services to males, Indigenous people and those living in disadvantaged socioeconomic areas may reduce COPD-related readmissions.

4. CHAPTER 4: General discussion and conclusion

COPD readmission has become a global public health challenge with significant consequences for patients, their families and healthcare systems. It is one of most common chronic conditions associated with potentially preventable hospitalisation in Australia. The work described in this thesis included initial systematic review to summarise and evaluate the published evidence on the prevalence, the risk factors and outcomes associated with readmission due to COPD. An original research study was then undertaken to investigate the prevalence of and risk factors for COPD-related readmission in Tasmania.

The key finding of this work is that despite several calls for development of specific predictor tools for identification of COPD-related readmission, reported prevalence and risk factors associated with COPD-related readmission vary between countries and healthcare settings. Therefore, determinants of COPD readmission are not readily generalisable, and so interventions should be adapted to local healthcare environments.

The systematic review identified hospitalisation in the previous year as a key predictor of COPD-related readmission [98]. Comorbidity (asthma), living in a deprived area and living in or discharged to a nursing home were also associated with increased risk of COPD readmission [98]. Similar to the review, the five-year longitudinal study also showed that ED visits in the previous six months and living in the low socioeconomic North-West region of the state were associated with increased risk for COPD readmission in Tasmania. Within the Tasmanian locality, male patients and Indigenous people were also at increased risk of COPD-related readmission. Despite the review associating increased risk of readmission to living in or discharge to nursing home, the Tasmanian study did not find such significant correlation.

The 2015 White paper (One State, One Health System, Better Outcomes) on delivering safe and sustainable clinical services in Tasmania underpinned the work in this thesis. The paper outlines the Government's vision for Tasmanians to have the healthiest population in Australia by 2025 while ensuring patient-centred care at the appropriate time and place [126]. The paper outlines strategies to improve safety and quality of services through more services to the community while improving patient support to enable access to the improved services. Our work endorses the important of addressing patients' health issues close to home and away from hospital. The White paper emphasised the provision of vital community services for patients with chronic and complex conditions such as COPD. It also noted that Tasmanians expect their health care services to be patient-centred, outcome-focused, affordable, acknowledge the risks of poor health especially literacy, and provide coherent 'patient journey' via effective linkages and appropriate communication processes [126]. This resonates with our study population especially the vulnerable groups (Indigenous people and those living in low socioeconomic areas) who may require support with cost of treatment and improvement in health literacy for effective communication.

The work undertaken in this thesis highlighted the differences on the rates of patient readmission which seems to be based on the presence or absence of support frameworks in different localities. Hence, the possibility that areas where the healthcare system are lacking community-based strategies for the management of mild-to-moderate COPD patients may be at increased risk of readmission for care that could be managed outside hospital [127,128]. Management of mild-to-moderate COPD patients within their community may divert potentially preventable hospitalisations and readmission. The success of diverting patients with mild and moderate COPD from hospital to community-based care may be based on several factors such as altering the health system response to exacerbation via correlated care process between ambulances, community care and hospitals [129]. There may also be an opportunity

to use community services in educating patients on available services and when/how to engage. Community based programs may improve communication across healthcare providers and patients making the care provided patient-centred and appropriate.

This is the first study in Australia to associate males, previous ED visits, Indigenous people and living in low socioeconomic area to increased risk of COPD-related readmission. There is currently no evidence that these risk factors will be predictors of COPD readmission in the other states of Australia. Hence the need for further research to investigate if these risk factors are also associated with COPD readmission across the other Australian states is vital. However, our results have provided direction to policy makers and stakeholders in Tasmania on areas where initiatives and interventions for COPD-related readmission reduction is required.

In Australia, Indigenous people and those living in low socioeconomic areas are classified among the most vulnerable population groups [100]. They are at greater risk of health inequity because of social and economic disadvantages [130]. The Australian Government has recently initiated the "tackling Indigenous smoking" program aimed at improving the life expectancy among Indigenous people via reduction of tobacco use [131]. This program aims to breach the 23% gap in health burden between Indigenous and non-Indigenous Australians associated to tobacco smoking [131]. Although our study confirmed that Indigenous people were more likely to be readmitted for COPD compared to non-Indigenous, we were unable to evaluate smoking status of patients.

Despite our study finding previous ED visits as predictors of COPD readmission, we do not know the causality of ED visits on COPD readmission. However, Government reports have shown that people from lower socioeconomic areas, and people living in the regional or remote areas are more likely to visit the ED [132,133]. A previous study in Tasmania reported a 2.5

times higher per capita rate of ED presentations in the low socioeconomic North-West region compared to the South [122].

The findings of this thesis are in line with the White paper [126] and the Australian Health 2020 [125] principles on adopting a person-centred and population health approach while addressing health inequity. Person-centred approach simply means putting the patient at the centre of their health and wellbeing while healthcare services are powered with outcomes that are appropriate to the patient. Levesque *et al.* conceptualised five dimensions that will make access to healthcare patient-centred: approachability, acceptability, availability and accommodation, affordability and appropriate [134]. Five corresponding abilities are required of patients for effective patient-centred access to healthcare: ability to perceive, ability to seek, ability to reach, ability to pay and ability to engage [134]. These abilities highlight the complexity faced by COPD patients in the process of accessing healthcare services.

Healthcare services within Tasmania that target males, Indigenous, people living in the North-West region and people with recent ED visits will need to address these five dimensions to enable reduction of COPD readmission. These groups of patients should also be educated to ensure that they have competent health literacy to perceive their health need, seek it, reach where it is being provided, pay for it, and engage. Although availability of healthcare services is vital in the community, improving the health literacy of males, Indigenous people and those living in the North-West region of Tasmania may improve self-assessment of healthcare need and better understanding of the health system. Lower health literacy worsens underlying access and equity issues already experienced by these groups [135]. Policy makers however may have to consider addressing the access and affordability of healthcare in Indigenous people and those with poor socioeconomic status to improve access to the services and reduce out-of-pocket expenses incurred by patients.

Low health literacy though not evaluated in this work, may play a vital role in health inequity within the Indigenous people and those living in low socioeconomic areas. Lower socioeconomic groups are disproportionally affected by limited health literacy [135]. According to the U.S. Department of Health and Human Services (HSS), health literacy is "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions [135]". Low health literacy was reported in 59% of Australian adults and 37% in Tasmanian adults in a national survey undertaken in 2006 [136]. Recent report indicated that 44.9% (95% CI 43.1%-46.6%) Tasmanians (51.3% [95% CI 48.5%-54.1%] in North-West region) have significantly more difficulty in accessing the healthcare providers they need [137]. Patients with low health literacy rates are less likely to seek preventive care, less able to cope with chronic conditions, and have a higher rate of hospitalisation and use of health care services [138]. The importance of improving health literacy is vital in COPD patients with complex treatment regimens, necessitating various consultations with different clinicians. COPD patients will require health literacy for effective self-management, accessing and utilising healthcare, interacting with health service providers, participating in decision making regarding their health and caring for their own health and that of others [139].

Despite identifying the risk factors for COPD readmission in Tasmania using the National minimum Dataset, these identified risk factors may be specific to Tasmanian population especially in relation to Indigenous people. We do not know if they will be relevant in other Australia states. There was also a limited number of Indigenous people in the study population. The study was unable to evaluate smoking status, health literacy and other clinical factors associated with COPD readmission.

4.1. Recommendation and future direction

Risk factors for COPD readmission need to be identified within health locality for effective prevention and reduction. Testing the provision of community-based health services to treat mild to moderate COPD patients may give better understanding of strategies to utilise in reducing readmission. These healthcare services should be made accessible and affordable. Healthcare professionals should be utilising every visit/contact with COPD patients to assess their knowledge and understanding of their health and self-care. Care should be taken to ensure that information being provided are appropriate, simple, and easy to understand. Management of COPD patients should incorporate knowledge assessment at every opportunity to identify knowledge gap and design appropriate interventions to address patient's healthcare needs.

As patient-related factors play vital role in readmission for COPD, national data is required to determine risk factors for COPD readmission in other Australian states and territories. Future studies should focus on determining the best approach for improving health inequity within Indigenous people and those living in lower socioeconomic areas to reduce COPD readmission. Future studies are also required to assess smoking status, health literacy and clinical risk factors (decline in lung function, biomarkers, severity of disease) that were not available from the data source for a broader comprehension of determining factors for COPD-related readmission.

4.2. Conclusion

Risk factors associated with COPD readmission may not be readily generalisable and should be evaluated within local healthcare environment. The factors associated with increased risk for COPD-related readmission in Tasmania are being male, Indigenous, living in poor socioeconomic North-West region and ED visits in the previous six months. Patient-centred interventions to provide and improve affordability of and better access to healthcare services

to males, Indigenous people, and those living in disadvantaged socioeconomic areas in their community may reduce COPD-related readmissions and improve patients' health outcomes in Tasmania. Policy makers and stakeholders should also ensure that healthcare services provided within the community are patient-centred, affordable, appropriate, and accessible for COPD patients to reduce readmission.

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6. Appendices

6.1. Ethics application approval Letter

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

03 August 2018

Dr Bonnie Bereznicki
C/- University of Tasmania

Sent via email

Dear Dr Bereznicki

REF NO: H0017433
TITLE: Retrospective evaluation of COPD readmission risk factors profile in Tasmania

Document	***Version***	***Date***
Low Risk Application Form	Version 4	2 Aug 2018
Privacy Form	Version 1	12 June 2018

The Tasmanian Health and Medical Human Research Ethics Committee considered and approved the above documentation on **02 August 2018** to be conducted at the following site(s):

University of Tasmania

Please ensure that all investigators involved with this project have cited the approved versions of the documents listed within this letter and use only these versions in conducting this research project.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approvals of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2014).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC. Please note that all requests for changes to approved documents must include a version number and date when submitted for review by the HREC.

(3) Section 5.5.3 of the National Statement states:

Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested. http://www.utas.edu.au/research-admin/research-integrity-and-ethics-unit-rieu/human-ethics/human-research-ethics-review-process/health-and-medical-hrec/managing-your-approved-project

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for four years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due 3 August 2019**.** You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 2764.

Yours sincerely

Alison Gulliver-Davies
Administration Officer

6.2. Tasmanian Health and Medical Human Research Ethics Committee Low Risk Application Form

UNIVERSITY of TASMANIA | DIVISION OF RESEARCH

Tasmanian Health and Medical Human Research Ethics Committee Low Risk Application Form

To submit this application:
An electronic version of this Low Risk Form and attachments must be emailed to human.ethics@utas.edu.au.
For queries contact 03 6226 6254

LOW AND NEGLIGIBLE RISK RESEARCH

The National Statement on Ethical Conduct in Human Research defines low risk and negligible research in the following manner:

Low Risk Research is research with no foreseeable harm or risk other than discomfort. If the risk exceeds this, then it cannot be defined as low risk research and a full application will be required.

Negligible Risk Research is research where there is no foreseeable risk of harm or discomfort other than the potential for inconvenience. If the risk exceeds this definition, then it cannot be called negligible risk research. (Chapter 5.1.18)

Audit Applications with a research output should be completed on a different form. Low Risk Audit Application can be found here.

1. PROJECT DETAILS

Project title:
Retrospective evaluation of COPD readmission risk factors profile in Tasmania

Period for which approval is sought:
01/06/2018 to 31/05/2019

What is the main purpose of this project?
Research for Publication ☐ Teaching ☐ Research for Thesis ☒

2. APPLICANTS

A Chief Investigator **cannot** be a student. If the project is to be undertaken by an Honours, Masters or PhD student, then the primary supervisor must be listed as the Chief Investigator.

All correspondences will be addressed to the Chief Investigator. The Chief Investigator is responsible for ensuring that all coinvestigators are fully informed of communications from the HREC.

Chief Investigator/Supervisor:	**Name:** Dr Bonnie Bereznicki
Position:	Lecturer in Pharmacological Sciences, Division of Pharmacy, School of Medicine, UTAS
Phone:	**Work:** 03 6226 4624
Email:	Bonnie.Bereznicki@utas.edu.au
Other Investigator:	**Name:** Prof Greg Peterson
Position:	Professor of Pharmacy and Director, Health Services Innovation Tasmania, School of Medicine, UTAS

Phone:	**Work:** 03 6226 2197
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Other Investigator:	**Name:** Dr Barbara Wimmer
Position:	Lecturer
Phone:	**Work:** 03 6226 1067
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Other Investigator:	**Name:** Professor Leigh Kinsman
Position:	Professor of Healthcare Improvement, School of Health Sciences, UTAS
Phone:	**Work:** 03 6324 3770 **Mobile:** 04
Email:	leigh.kinsman@utas.edu.au

UTas Student Investigator Details (if applicable)

Student Name	Student ID No.	Date of birth	Honours, PhD etc.
Maria Chidiamara Njoku	477528	26/08/1974	PhD
Student email address: SrChidi.Njoku@utas.edu.au		Phone:	Mobile: 0450899819

3. PEER REVIEW

Has the research proposal, including design and methodology, undergone a peer review process? Yes ☐ No ☒

Please provide details of the review process:

Who reviewed the proposal and when was it reviewed?

What did the review process involve?

What were the recommendations (if any), and how were these acted upon?

4. CONFLICTS OF INTEREST

Do any of the researchers have a conflict of interest, or what could be perceived as a conflict of interest? (NS 5.4) Yes ☐ No ☒

If **YES –** please provide details:
Please describe the nature of the conflict.

Please describe how the conflict will be managed.

5. FUNDING

Under the National Statement (2.2.6) a researcher must disclose:

- the amount and sources or potential sources of funding for the research; and
- financial or other relevant declarations of interest of researchers, sponsors or institutions

Do the investigators have any financial interest in this project? No ☒ Yes ☐

If this Application relates to a Grant(s) and/or Consultancies, please indicate the title and Number relating to it:

Funding Body:	Amount:
Funding Body:	Amount:

If no external funding has been obtained, please indicate how any costs of research will be met:
There is no cost associated with obtaining the data and any other minimal costs will be borne by UTAS as part of Chidi's PhD; hence funding not required.

6. BRIEF OUTLINE OF PROPOSAL

Please provide a brief synopsis of the study. HREC members come from a variety of backgrounds and expertise but may not be familiar with your specialist area and therefore a straightforward explanation of your project is requested.

Overview:

This is the initial part of Chidi's PhD thesis that will be looking at the risk factors, consequences and possible solutions to hospital readmission of chronic obstructive pulmonary disease (COPD) patients in Tasmania.

This project will investigate the profile presentation of re-hospitalised COPD patients in Tasmania. The project will focus on identification of risk factors relevant to readmission of COPD patients and identifying any clinical and demographic characteristics specific to frequent readmission in COPD patients. The study aims to determine predictors of COPD readmission and will also examine the variation in risk of COPD readmission between the four major public hospitals in Tasmania (i.e. Royal Hobart Hospital, Launceston General Hospital, Mersey Community Hospital, and North West Regional Hospital). The study will describe the risk factors for readmission of COPD patients registered at all four Tasmanian hospitals between 2010 and 2017.

The project will utilise the Admitted Patient Care National Minimum Dataset for (APC-NMDS) for Tasmanian patients. The dataset contains a core set of clinical and administrative data elements that are subject to mandatory collection and reporting by all Australian hospitals. The Tasmanian Department of Health and Human Services (DHHS) maintains the APC-NMDS dataset. APC-NMDS data contains demographic, administrative and clinical information of all admissions. All records from the seven financial years, 2010-11 to 2016-17 will be extracted.

The APC-NMDS dataset will be reviewed to identify eligible patients and their baseline index admission, defined as their earliest acute admission for COPD from 1st January 2010 to 31st December 2015. The post-index period will be set as subsequent COPD-related readmission(s) following the baseline index admission until 30th June 2017. Any post-index admission within 30 days of the index admission will be referred to as the early cohort while those after 30 days will be referred to as the late cohort. All patients will be followed up until 30th June 2017 to identify any subsequent admissions and to ensure that all patients have a minimum 2 years follow up. Two time periods will be used to evaluate COPD-related readmissions based on the discharge date from the index

admission; 1-30 days post discharge and >30 days post discharge to the end of the post index period. Recorded diagnoses will be assessed to identify COPD, based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM) codes J40-44 and recorded comorbidities.

The study will explore recurrent COPD admissions whereby patients may return to hospital due to COPD or exacerbation of COPD during the follow-up period (up to end of study).

The study will focus on:

- Rates of recurrent COPD admissions at the end of the study (30th June 2017).
- Rates of COPD readmissions <30 days and >30 days post discharge from the Index Admission.
- The cohort of patients who experienced multiple recurrent COPD admissions by the end of the study - the demographic characteristics of patients who were readmitted for COPD (e.g. age, gender, region, comorbidities) and outcomes (e.g. mortality and length of hospital stay) associated with COPD readmissions.
- The timing between recurrent COPD admissions.
- Utilise the published LACE index (23) in COPD patients in Tasmania to test for the prediction of 30-day all-cause hospital readmission of COPD patients.

The results of this study will highlight the specific readmission profile of COPD patients in Tasmania. This will also help in comparing Tasmania data to the international literature in relation to these risk factors for readmission.

Aims:

Please give a concise description of the main objectives and/or hypothesis of the study.

To investigate risk factors, consequences and possible solutions to hospital readmission of COPD patients in Tasmania.

Please give a concise description of the main objectives and/or hypothesis of the study.

- To identify any patient risk factors related to readmission of COPD patients in Tasmania.
- To assess the prevalence and patterns of recurrent readmission of COPD patients in Tasmania.
- To identify any pattern and prevalence in patients with highest risk of recurrent readmission (i.e. 'high flyers') or any sub-group in relation to demographic characteristics.
- To compare Tasmania to the international literature in relation to risk factors for readmission of COPD.

Justification:

Explain why this particular study is worth doing; and the main advantages to be gained from it.

Chronic obstructive pulmonary disease (COPD) is a progressive chronic condition that is mainly characterised by obstruction of airflow in the lungs and cannot be fully reversed (1, 2). COPD is currently the 4th leading cause of death worldwide, and is projected to 3rd by 2020 (2, 3). In Australia COPD is the 5th leading cause of death (4). The financial cost of COPD in Australia in 2008/09 was $929 million spent mainly on hospital

admissions (58%) and prescription medicines (23%) (5). National Hospital Statistics in 2015-2016 showed that COPD was the most common chronic condition with PPH in all states and territories except in Victoria, Western Australia and the Australia Capital Territory (6). COPD was the 3rd leading cause of potentially preventable hospitalisations (PPH) in Australia in 2015-16 with a rate of 260 admissions per 100,000 population and 218 admissions per 100,000 population in Tasmania (6). The PPH rate for COPD increased by six percent nationally and in Tasmania from 2014-15 to 2015-16 (246 vs 260 per 100,000 population and 206 vs 218 per 100,000 population) respectively (6).

Almost 50% of COPD patients will be readmitted at least once within six months of their initial hospitalisation (7, 8). Exacerbation of COPD (ECOPD) is one of the major risk factors of hospital admission and rehospitalisation with a negative impact on health status and mortality (9). Some factors are persistently connected with readmission of ECOPD patients such as older age, poor lung function, previous admission for ECOPD, comorbidities and low socioeconomic status (SES), hospital length of stay (<2 or >5 days) (10-13). Recent evidence indicates that one in five patients admitted with exacerbation of COPD is readmitted within 30 days of discharge (13-15). The LACE index (length of stay, acuity of admission, comorbidity measured with Charlson comorbidity index score and number of emergency department [ED] visits in last 6 months) measures risk of unplanned readmission and death within 30 days post discharge from hospital (16). This will be an opportunity to apply the LACE index to COPD patients in Tasmania and compare the result to the previous study in Sydney (17).

There is no clinical evidence to indicate what the independent risk factors of these readmissions resulting from COPD in Tasmania are, in comparison with international literature despite the growing increase in readmissions from COPD patients and number of PPH from COPD. There is a lack of recent Australian research that has comprehensively investigated the epidemiology of these risk factors. Research focussing on the proportion of patients with a history of recurrent readmission from ECOPD is especially warranted in Australia where there is increase in PPH from COPD. Knowing more about risk factors readmission due to ECOPD will help to develop an algorithm or clinical pathway for patients with a high predictive score being flagged to clinicians at the point of care. This will aid healthcare professionals in stratifying/personalising interventions and target the appropriate level of treatment to the high flyers, and hence prevent/reduce readmission. The starting point to achieving this will be exploring first the specific risk factors for readmission of ECOPD patients in Tasmania.

Relevant literature review Please list the most relevant and recent literature references, both by the investigator and/or by others, that support the justification for the study.

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17. Hakim MA, Garden FL, Jennings MD, Dobler CC. Performance of the LACE index to predict 30-day hospital readmissions in patients with chronic obstructive pulmonary disease. Clin Epidemiol. 2018;10:51-9.

6A. REVIEW OF ETHICAL CONSIDERATIONS

Your research may still be considered low risk should you answer in the affirmative to either of these questions.

- Is your research a clinical trial? (Clinical Trial decision aid)	No ☒ Yes ☐
Does your research involve the administration of medication or placebo beyond the normal routine care of the participant (if under medical care)?	No ☒ Yes ☐
- Does your research involve an innovation in clinical practice or complementary medicine? (*An innovation is defined as a new diagnostic or therapeutic method that aims to improve health outcomes but which has not yet been fully assessed for safety and/or efficacy. The spectrum of innovations may range widely from minor variations or extensions of existing methods to new indications, through to completely novel technologies*)	No ☒ Yes ☐

- Does your research involve the collection of human tissue samples beyond the normal routine care of the participant (if under medical care)? Human tissue samples include blood and other bodily fluids (See National Statement Chapter 3.4.8 (a) regarding biospecimens)	No ☒ Yes ☐
- Does your research involve the use of gametes and/or human embryos?	No ☒ Yes ☐
- Does your research involve the use of human stem cells?	No ☒ Yes ☐
- Does you research involve genetic testing?	No ☒ Yes ☐
- Does your research involve the deception of participants, including concealing the purposes of research, covert observation and/or audio or visual recording without consent?	No ☒ Yes ☐
- Does your research involve the participation of people without their prior consent other than access to or use of medical records or the use or personal data obtained from a Commonwealth or State agency, or an organisation in the private sector?	No ☒ Yes ☐
- Does your research involve withholding from one group specific treatments or methods of learning from which they may benefit?	No ☒ Yes ☐
- Does your research involve the use of ionising radiation?	No ☒ Yes ☐
- Does your research **specifically target** any of the following groups of people; (specifically target means they are the central group of participants, as opposed to potentially being incidentally recruited as part of the general population) For further information refer: (NS: Section 4) • Women who are pregnant and the human foetus • Children and young people • Those highly dependent on medical care who are unable to give consent • People with a cognitive impairment, intellectual disability or mental illness • People who may be involved in illegal activities or residents of custodial institutions • Aboriginal and Torres Strait Islander Peoples • People in other countries • People who are unable to give informed consent because of difficulties in understanding an information sheet (i.e. non English speakers etc) • People in dependant or unequal relationships	No ☒ Yes ☐
- Does your research pose any risks for participants under medical care beyond those of their routine care? (Risks include not only physical risks but also psychological, spiritual and social harm or distress eg stigmatisation or discrimination)	No ☒ Yes ☐

- Does your research involve the in depth discussion of any of the following topics whether by interview or as part of a questionnaire or survey; • Parenting practices, • Sensitive personal issues, • Sensitive cultural issues, • Grief death or serious traumatic loss, • Depression mood states or anxiety, • Gambling, • Eating disorders, • Illicit drug taking or substance abuse, • Psychological disorders, • Suicide, • Gender identity and/or sexuality, • Race and/or ethnic identity, • Fertility and/or termination of pregnancy	No ☒ Yes ☐
- Does your research involve the potential disclosure of illegal activities or criminal behaviour?	No ☒ Yes ☐
- Are there any specific risks to the researcher (i.e. will the research involve the use of hazardous materials or be undertaken in a politically unstable area)?	No ☒ Yes ☐
- If your research will take place in an overseas setting do any of the following apply: is the research to be undertaken in a politically unstable area? Does it involve sensitive cultural issues? And/or: will the research take place in a country in which criticism of the government and institutions might put participants and/or researchers at risk?	No ☒ Yes ☐
- Does your research explore potentially confidential business practices or seek to elicit potentially confidential commercial information from participants?	No ☒ Yes ☐

6B. REVIEW OF ETHICAL CONSIDERATIONS

Your research may still be considered low risk should you answer in the affirmative to either of these questions. However, you may be required to complete a Privacy Form. Please refer to Section 8 below.

Does your research involve the access or use of medical records where participants can be identified or linked to their records in some way?	No ☐ Yes ☒
Does your research involve the use of personal data obtained from a Commonwealth or State Government Department/Agency without the consent of the participants e.g. getting a list of addresses from the Australian Electoral Commission?	No ☐ Yes ☒

6C. RISK REVIEW

What is the level and nature of the risk to the participants in this research? There is no risk to participants as this is a retrospective study of high-level dataset.
What is the likelihood of this risk occurring and the severity of this risk? Not applicable
Who might the risks affect (participants and/or others)? Not applicable as there is no risk to 'participants'.

What means/techniques have been established to manage this risk?

Not applicable as there is no risk to 'participants'.

7. PROCEDURES

Alternatively, you may submit a separate study protocol with your application.

Design

Specify which type of quantitative design, mixed methods or qualitative. Clearly define the intervention and control groups (if relevant). For qualitative studies, include information as to framework/approach for data analysis.

This is a quantitative study that will utilise descriptive statistics to report and analyse some of the risk factors for readmission of COPD patients in Tasmanian hospitals over seven financial years. Descriptive statistics will be used to identify patterns from COPD readmissions in Tasmania and compare the result across the three Tasmanian regions (South, North and North-West). Appropriate unadjusted and adjusted regression analyses will be conducted such as quantile regression to compare the demographic and clinical characteristics of 'high flyers' with those of patients with less frequent readmissions during 24 months of their index hospitalisation.

Setting

Description of sites/centres where participants will be recruited

Not applicable as this is a retrospective study that will be analysing available data.

Inclusion/Exclusion of Participants

Characteristics of source population relevant to study and characteristics of persons unsuitable for study

- Admission to a Tasmanian hospital between 1st January 2010 and 31st December 2015 with COPD.
- Tasmanian Area of Usual Residence (SA2) (i.e. a geographical classification used by the Australian Bureau of Statistics that usually comprises multiple postcodes of a similar socioeconomic status)

Sample size and justification

Statistical justification for quantitative data, appropriate form of justification for pilot and qualitative studies.

The data will be for the whole seven financial years (2010-2017) and all qualified patients admitted for COPD will be included in the study. There will be approximately 6000 admissions for COPD over that time period. No hypothesis will be tested, therefore no sample size calculation has been performed.

Recruitment

How, when, by whom. Clearly describe the experimental and, where relevant, control groups. Include details of number of subjects, sex, age range, special characteristics. Give a justification for your choice of subject group/s.

If your research involves the use of data from medical records, please provide details as what criteria will be applied to the inclusion or exclusion of records.

The project will utilise the APC-NMDS for Tasmanian patients. The dataset contains a limited core set of demographic, clinical and administrative data elements that are subject to mandatory collection and reporting by all Australian hospitals. All records from the seven financial years, 2010-11 to 2016-17 will be extracted. The APC-NMDS will be reviewed to identify eligible patients and their index admission, defined as their

earliest acute admission commencing from 1st January 2010 up to 31st December 2015 (i.e. five years window for the index event). These patients will all be followed up for at least 2 years post-index event. The International Statistical Classification of Diseases and Related Health Problems, Australian modification coding system (ICD-10-AM), is a medical classification system managed by the World Health Organisation (WHO) that has been modified for Australian purposes. This coding system will be used to record patient diagnoses in the APC-NMDS. Admissions where the primary reason for admission was related to COPD will be identified where an ICD-10-AM code is between J40-44 (chronic lower respiratory disease, including 'bronchitis not specified as acute or chronic' (J40), 'simple and mucopurulent chronic bronchitis' (J41), 'unspecified chronic bronchitis' (J42), 'emphysema' (J43) and 'other chronic obstructive pulmonary disease' (J44).

Inclusive criteria:

- Admission to a Tasmanian hospital between 1st January 2010 and 31st December 2015 with COPD.
- Tasmanian Area of Usual Residence (SA2) (i.e. a geographical classification used by the Australian Bureau of Statistics that usually comprises multiple postcodes of a similar socioeconomic status).

Measures

Describe, justify choice with psychometric data where relevant, attach copies of self-report/interview questions

Details of the demographic factors (i.e. region, postcode, age, sex) will be recorded to identify potential risk factors of COPD readmissions in Tasmania.

Data Collection

How, when, by whom. A flow chart/diagram may be of use. Include information as to data collection timeframes.

Data will be provided to researchers by the DHHS for the seven financial years 2010 to 2017 and relevant information will be recorded by the researchers.

Quality control and feasibility

Steps taken to ensure quality data collection and achievement of nominated sample size. Include information regarding peer or internal review procedures (if relevant).

Not relevant – all patients hospitalised with COPD during the study period will be captured.

Data analysis

Describe variables for analysis and how they will be used in your chosen quantitative and/or qualitative analytic strategies Please provide detailed procedures:

Details of the potential risk factors (i.e. length of stay, readmission rate, comorbidities), demographic (i.e. region, age, sex) of COPD readmission in Tasmania will be recorded in Microsoft Excel, and a descriptive analysis will be conducted using SPSS statistical software. Appropriate unadjusted and adjusted regression analyses will be conducted such as quantile regression to compare the demographic and clinical characteristics of 'high flyers' with those of patients with less frequent readmissions during 24 months of their index hospitalisation.

The LACE index (length of stay, acuity of admission, comorbidities [based on the Charlson comorbidity index], and emergency visits within the last 6 months) will be used to calculate a score for each patient. The predictive ability of the LACE index will be assessed using receiver operator characteristic (ROC) curves. The outcomes

to be tested includes readmission within 30 days and death during index hospitalization combined and 30-day readmission alone.

Results, Outcomes and Future Plans

- *Plans for return of results of research to participants*
- *Plans for dissemination and publication of project outcomes*
- *Other potential uses of the data at the end of the project*
- *Project closure processes*
- *Plans for sharing and/or future use of data and/or follow-up research*
- *Anticipated secondary use of data*

The outcome of the research will be published and will aid in identifying any patterns in hospital readmissions from COPD in Tasmania. All data will be pooled and no identifying data will be published.

Where is this project to be conducted?

Applicants should attach a letter of agreement/support to participate from any organisation or department whose resources will be accessed as part of this project.

Not applicable

7A. Data Identifiability

The National Statement on Ethical Conduct in Human Research (2007, updated May 2015), published by the NHMRC has three mutually exclusive definitions of data identifiability:

- Individually identifiable data
- Re-identifiable data
- Non-identifiable data

The National Statement avoids the term 'de-identified data' as its meaning is unclear, and could refer to both re-identifiable and non-identifiable data. Please refer to the Australian National Data Service for guidance

Information about subjects

Which of the following best describes the identifiability of the data (including tissues) to be used and or collected?

Non-identifiable data (which has never been labelled with individual identifiers, or from which identifiers have been permanently removed, and by means of which no specific individual can be identified)	☐
Re-Identifiable (from which identifiers have been removed and replaced by a code, but it remains possible to re-identify a specific individual by, for example, using the code or linking different data sets)	☐
Identifiable (where the identity of a specific individual can reasonable be ascertained. Examples of identifiers include the individuals name, image, date of birth or address).	☒

If the information is Re-Identifiable or Identifiable, please give details of the information that will be collected. Also indicate how the confidentiality and anonymity of the participants will be protected:

Data in each patient's record will include a unique patient identifier, as well as the patient's date of birth and SA2 code (a geographical classification used by the Australian Bureau of Statistics, usually comprising multiple postcodes), but not name. This raw data will be stored in a database on a password-protected server managed by the Faculty of Health, University of Tasmania. Only the researchers listed on this application will have access to this database. No identifiable or re-identifiable data will be printed. Only aggregate, population-wide

results will be reported. No individual findings or identifying details will be included in any reports or publications generated from this research and as such patient confidentiality will be protected.

7B. USE OF DATA FROM MEDICAL RECORDS

If you propose to use data from medical records without the consent of the patient, please provide the following information:

1. Please provide an outline of the search criteria to be applied by the Medical Records Department in order to generate the data report.

Individual medical records will not be accessed. All eligible records based on the coding system utilised to record patient diagnosis in the APC-NMDS from Tasmanian public hospitals for the study period will be extracted. Admissions where the primary reason for admission was related to COPD will be identified where an ICD-10-AM code is between J40-44 (chronic lower respiratory disease, including 'bronchitis not specified as acute or chronic' (J40), 'simple and mucopurulent chronic bronchitis' (J41), 'unspecified chronic bronchitis' (J42), 'emphysema' (J43) and 'other chronic obstructive pulmonary disease' (J44).

2. Will the data in the report be identifiable, re-identifiable or de-identified

The data in the report will be potentially identifiable as it contains unique patient identifiers, dates of birth and residential SA2 codes (a geographical classification used by the Australian Bureau of Statistics, usually comprising multiple postcodes).

3. Following receipt of the report, do the investigators intend to access the patient's medical record? If so, by whom will this record be accessed? If it is proposed that an investigator (for example a student) who is not a member of DHHS staff will have access to the medical records, please provide details as to how this access will be granted and monitored.

Not for this specific study.

8. DATA

A. Collection, use or disclosure of personal information

Does the proposed research involve the collection, use or disclosure of personal information (including medical records) held by a Commonwealth or State agency, or an organisation in the private sector?

☒ Yes If yes, please complete & submit the Privacy Form along with your application.

☐ No

A. Storage

All raw data (including blood and/or tissue) must be held by the responsible institution (i.e. UTas, DHHS, AMC) for a period of at least five (5) years from the date of the first publication (This includes the publication of the thesis). The data may be kept for longer than five (5) years. Please include details on hard and electronic data.

1. Where will the data be kept?

UTAS College of Health and Medicine IT Server

2. How will the data be kept secure?

The data will be password protected and stored on the UTAS College of Health and Medicine IT Server. Only the researchers listed on this application will have access to the data.

3. How and when will the data be destroyed?

All copies of the data will be destroyed after a minimum of five years from the date of the final publication reporting the findings of this research. Data will be deleted from the server.

9. CONSENT

Chapter 2.2 of the National Statement provides guidelines on the requirements for consent in human research. With few exceptions, participation must be voluntary and based on sufficient information and an adequate understanding of the proposed research. In general, an information sheet and consent form is used to provide potential participants with necessary information about study and to obtain their consent should they choose to participate.

Does the research involve:

☐	An opt-out approach (*National Statement* 2.3.5). **Please complete section 12A below.**
☒	A waiver of consent (*National Statement* 2.3.9). **Please complete 12B below.**
☐	Obtaining consent from participants prior to their involvement or the use of their data (including medical records, tissues etc). **Please complete section 12C below.**

9A. Opt-out approach

Why is explicit consent neither practical nor feasible? (*National Statement* 2.3.5)

How does the public interest in the proposed activity substantially outweigh the public interest in the protection of privacy? (*National Statement* 2.3.6(b))

Why is near-complete data on outcomes required? (*National Statement* 2.3.6(c))

Provide details on the information provided to the participants including the nature of the data to be collected, the purpose for collecting it, and the procedure to decline participation or withdraw. (*National Statement* 2.3.6 (d)).

How much time has been allowed between the participant receiving information and the use of the data? (*National Statement* 2.3.6(e))

What mechanism(s) are there for participants to obtain further information and register for non-participation? (*National Statement* 2.3.6(f))

Provide details on the governance process in place. Including the process that delineates specific responsibility for the project and the appropriate management of the data in accordance with relevant security standards. (*National Statement* 2.3.6(g) and (h))

9B. Waiver of Consent

Please note, this application must be reviewed by the **full Health and Medical HREC** in accordance with section 2.3.9 of the National Statement.

Why do the benefits of the research justify any risks of harm associated with not seeking consent? (*National Statement* 2.3.10(b))

The benefits achieved from accurate profile of the prevalence and patterns of predictors for readmissions from COPD will impact the whole of Tasmania. This will hopefully be a starting point in addressing the future accurate individualised-targeted management of COPD patients. There is no risk of harm associated with waiving consent to access data. Data will be aggregated in order to investigate admissions across the whole population.

Why is it impracticable to obtain consent? (*National Statement* 2.3.10(c))

This study is a retrospective study that will involve large number of patient records and there will not be any direct contact with participants.

Is there any reason for thinking that participants would not consent if they were asked? (*National Statement* 2.3.10(d)) (Note, an explanation is required)

No. We are interested in the epidemiology and demographic characteristics of readmissions from COPD across Tasmania. Data at an individual level is not a focus of this study and as such there is no reason to expect that participants would not consent if given the opportunity

Will the results of the research have significance for the participants' welfare?

☐ Yes	If yes, how will the information arising from the research be made available to the participants? (*National Statement* 2.3.10(g))
☒ No	

How will the participant's privacy be protected? (*National Statement* 2.3.10(e))

The data will be password protected and stored on the UTAS College of Health and Medicine IT Server. Only the researchers listed on this application will have access to the data.

Explain how confidentiality of participants and their data will be protected in the dissemination of research results? (*National Statement* 2.3.10(f))

Only aggregate, population-wide results will be reported. No individual findings or identifying details will be included in any reports or publications generated from this research and as such patient confidentiality will be protected

9C. Information Sheet and Consent Form

How will potential participants be informed about the purpose, methods, demands, risks and potential benefits of the proposed research prior to deciding to participate? (please refer to 2.2.2 & 2.2.6 of the *National Statement* for a list of information to be communicated to participants)

☐ Information Sheet – Please attach to the application

☐ Other – Please describe:

How will participants provide consent for participating in the proposed research?

☐ Consent Form – Please attach to the application

☐ Other – Please describe:

10. STUDENT INVOLVEMENT

For projects in which a student will be involved, please complete the following questions.
How does this project relate to the student's education? (i.e. part of their Master's thesis, fifth year medicine rotation, Honour's thesis).

This project is part of Chidi's PhD thesis

What training/induction has the student been given regarding research ethics issues, such as confidentiality and privacy?

The student has completed the Research Integrity Unit at the University of Tasmania (RIEU101) to further develop her understanding of research ethics.

11. APPROVALS FROM OTHER DEPARTMENTS/INSTITUTIONS

Does this project need the approval of any institution other than the University of Tasmania and/or the Department of Health and Human Services (i.e. Department of Education, particular wards in hospitals, prisons, government institutions, or businesses)?

Please note: projects that are conducted using the resources of UTAS and DHHS (including the involvement of staff as researchers) must be signed off by both the Head of School and Head of Department.

If 'YES', Please indicate below what Institutions are involved and what the status of the Approval.

No ☒ Yes ☐ (please detail):

Name of Other Institution(s): Status:

Does this project need the approval of any other HREC? If 'YES', Please indicate below which HREC and the status of the application.	No ☒ Yes ☐ (please detail): Other HREC(s): Status:

12. DECLARATIONS

The Head of School or the Head of Department is required to certify that:

- He or she is familiar with this project and endorses its undertaking;
- The resources required to undertake this project are available;
- The researchers have the skill and expertise to undertake this project appropriately or will undergo appropriate training as specified in this application.

***If the Head of School/Department is one of the investigators/research personnel, this statement must be signed by an appropriate person. This will normally be the Head of School/Department in a related area or by the Dean**.

Please note: this declaration is only required on the final approved application, not at the initial application submission stage.

Name	**Prof Ben Canny**
Position	**Head of School, School of Medicines**
Signature	
Date	08/06/2018

Conformity with NHMRC Guidelines

The **Chief Investigator** is required to sign the following statement:

I, Bonnie Bereznicki , certify that:

- All information in this application and supporting documentation is correct and as complete as possible;
- I have read and addressed in this application the requirements of the National Statement and any other relevant guidelines;
- I have familiarised myself with, considered and addressed in this application any relevant legislation, regulations, research guidelines and organisational policies;
- All relevant financial and non-financial interests of the project team have been disclosed; and
- In the capacity of a supervisor, as applicable, I have reviewed this application and I will provide appropriate supervision to the student(s) in accordance with the arrangements specified in this application and those associated with the student's educational program

Name of Chief Investigator	**Dr Bonnie Bereznicki**
Signature	
Date	6th June 2018

Signatures of Other Investigators / Research Personnel and Students		
(Name) Dr Barbara Wimmer	(Signature)	(Date) 7th June 2018
(Name) Prof Gregory Peterson	(Signature)	(Date) 6th June 2018
(Name) Prof Leigh Kinsman	(Signature)	(Date) 6th June 2018
(Name) Maria Chidiamara Njoku	(Signature)	(Date) 6th June 2018

6.3. Appendix A: Risk factors and associated outcomes of hospital readmission in COPD: a systematic review (Chapter Two)

6.3.1. Supplement A1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4

Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8

Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097

6.3.2. Supplement A2. List of database search concepts

	Concept 1	**Concept 2**		**Concept 3**
Key concepts	COPD	Risk factor OR Consequences		Readmission
Free-text terms (titles and abstracts)	Chronic obstructive pulmonary disease COPD Chronic obstructive lung disease Chronic obstructive airway disease Bronchitis Emphysema	Risk factor* Risk assessment Patient risk Recurrence risk Contributing factors Predisposing factors Protective factor* Predictors Harmful effects	Consequences Aftereffect Aftermath Repercussion Ramification Outcomes Outcome assessment Disease association Impact	Rehospitali?ation* Re-hospitali?ation* Readmission* Re-admission* Multiple admission Repeat admission
	Controlled vocabulary terms / Subject terms (MeSH terms, Emtree terms)			
Medline via Pubmed: [MeSH]	Lung diseases, obstructive (no exp) Bronchitis (no exp) Pulmonary disease, chronic Obstructive (exp) Emphysema (no exp)	Risk Risk factors Risk assessment Protective factors	Outcome assessment	Patient readmission
Embase via Ovid: (Emtree terms)	Chronic obstructive lung disease (no exp) Emphysema (no exp) Lung emphysema (no exp) Chronic bronchitis (no exp) Bronchitis (no exp)	Risk factors (no exp) Risk assessment (no exp) Risk reduction (no exp) Patient risk (no exp) Attributable risk (no exp) Recurrence risk (no exp)	Outcome assessment Disease association	Hospital readmission
CINAHL: [MH "Terms"]	Pulmonary disease, chronic obstructive (exp) Lung diseases, obstructive (exp) Bronchitis (no exp) Bronchitis, chronic (no exp) Emphysema (no exp)	Risk factors (no exp) Risk assessment (no exp)	Outcome assessment Outcomes (health care)	Readmission (no exp)
Scopus: *No medical headings (title/abstract*)	COPD Chronic obstructive pulmonary disease Bronchitis	"Risk factor*" "contributing factors" "predisposing factors"	Outcome assessment Outcomes (health care)	"Readmission*" "Re-admission*" "Rehospitali?ation*"

	Emphysema Lung emphysema Chronic obstructive lung disease	"protective factor*" "Predictor*" "Patient risk" "Risk assessment" "Recurrence risk" "Harmful effect"	Consequences Aftereffect/Aftermath Repercussion Ramification Outcomes Outcome assessment Disease association Impact	"Re-hospitali?ation*" "Patient admission*" "Multiple admission" "Repeat admission"
IPA: No medical headings (title/abstract)	Chronic obstructive pulmonary disease COPD Chronic obstructive lung disease Chronic obstructive airway disease Bronchitis Emphysema	Risk factors Risk assessment Patient risk Recurrence risk Contributing factors Predisposing factors Protective factors Predictors Harmful effects	Outcome assessment Outcomes (Health Care) Consequences Aftereffect Aftermath Repercussion Ramification Outcomes Outcome assessment Disease association Impact	Rehospitali?ation* Re-hospitali?ation* Readmission* Re-admission* Multiple admission Repeat admission

6.3.3. Supplement A3. Search strategy of the electronic databases

Search	Search terms
Scopus	
#1	TITLE-ABS (copd) OR TITLE-ABS ("chronic obstructive pulmonary disease") OR TITLE-ABS (bronchitis) OR TITLE-ABS (emphysema) OR TITLE-ABS ("chronic obstructive lung disease") OR TITLE-ABS ("chronic obstructive airway disease")
#2	TITLE-ABS ("risk factor*") OR TITLE-ABS ("contributing factors") OR TITLE-ABS ("predisposing factors") OR TITLE-ABS ("protective factors") OR TITLE-ABS (predictor*) OR TITLE-ABS ("patient risk") OR TITLE-ABS ("risk assessment") OR TITLE-ABS ("recurrence risk") OR TITLE-ABS ("harmful effect")
#3	TITLE-ABS (consequences) OR TITLE-ABS ("aftereffect") OR TITLE-ABS ("aftermath") OR TITLE-ABS (repercussion) OR TITLE-ABS (ramification) OR TITLE-ABS (outcome* OR TITLE-ABS ("outcome assessment") OR TITLE-ABS ("disease association") OR TITLE-ABS (impact)
#4	#2 OR #3
#5	TITLE-ABS (readmission*) OR TITLE-ABS ("re-admission*") OR TITLE-ABS (rehospitali?ation*) OR TITLE-ABS ("re-hospitali?ation*") OR TITLE-ABS ("patient admission*") OR TITLE-ABS ("multiple admission") OR TITLE-ABS ("repeat admission")
#6	#1 AND #4 AND #5
Embase via Ovid	
1	chronic obstructive lung disease/
2	emphysema/
3	lung emphysema/
4	chronic bronchitis/
5	bronchitis/
6	chronic obstructive pulmonary disease.ab,ti.
7	COPD.ab,ti.
8	chronic obstructive lung disease.ab,ti.
9	chronic obstructive airway disease.ab,ti
10	bronchitis.ab,ti.
11	emphysema.ab,ti.
12	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13	risk factor/
14	risk assessment/
15	patient risk/
16	attributable risk/
17	recurrence risk/
18	risk factor$1.ab, ti.

19	risk assessment.ab,ti.
20	patient risk.ab,ti.
21	recurrence risk.ab,ti.
22	predictor$1.ab, ti.
23	protective factor$1.ab, ti.
24	contributing factor$1.ab,ti.
25	predisposing factor$1.ab,ti.
26	harmful effect$1.ab,ti.
27	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28	outcome assessment/
29	disease association/
30	consequences.ab,ti.
31	aftereffect.ab,ti.
32	aftermath.ab,ti.
33	repercussion.ab,ti.
34	ramification.ab,ti.
35	outcome$1.ab,ti
36	outcome assessment.ab,ti.
37	disease association.ab,ti.
38	impact.ab,ti.
39	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40	27 or 39
41	hospital readmission/
42	re-hospitali?ation$1.ab,ti.
43	rehospitali?ation$1.ab,ti.
44	readmission$1.ab,ti.
45	re-admission$1.ab,ti.
46	multiple admission$1.ab,ti.
47	repeat admission$1.ab,ti.
48	41 or 42 or 43 or 44 or 45 or 46 or 47
49	12 and 40 and 48

CINAHL via EBSCOhost	
S1	(MH "Pulmonary Disease, Chronic Obstructive+") OR (MH "Lung Diseases, Obstructive+") OR (MH "Bronchitis") OR (MH "Emphysema")
S2	(MH "Bronchitis, Acute") OR (MH "Bronchitis")
S3	(MH "Emphysema")
S4	"chronic obstructive pulmonary disease" OR COPD OR "chronic obstructive lung disease" OR "chronic obstructive airway disease" OR bronchitis OR emphysema
S5	S1 OR S2 OR S3 OR S4
S6	(MH "Risk Factors")
S7	(MH "Risk Assessment")
S8	"risk factor*" OR "risk assessment" OR "patient risk" OR "recurrence risk" OR "contributing factor*" OR "predisposing factor*" OR "protective factor*' OR predictor* OR "harmful effect*"
S9	S6 OR S7 OR S8
S10	(MH "Outcomes (Health Care)") OR (MH "Outcome Assessment")
S11	(outcomes or impacts or consequences) OR aftermath OR aftereffect OR repercussion OR outcome assessment OR disease association OR ramification
S12	S10 OR S11
S13	S9 OR S12
S14	(MH "Readmission")
S15	"rehospitali?ation*" OR "re-hospitali?ation*" OR readmission* OR "re-admission*" OR "multiple admission*" OR "repeat admission*"
S16	S14 OR S15
S17	S5 AND S13 AND S16
Medline via PubMed	
#1	"Bronchitis"[Mesh:NoExp]) OR "Lung Diseases, Obstructive"[Mesh:NoExp]) OR "Emphysema"[Mesh:NoExp]) OR "Pulmonary Disease, Chronic Obstructive"[Mesh]
#2	chronic obstructive pulmonary disease[Title/Abstract]) OR COPD[Title/Abstract]) OR chronic obstructive lung disease[Title/Abstract]) OR chronic obstructive airway disease[Title/Abstract]) OR bronchitis[Title/Abstract]) OR emphysema[Title/Abstract]
#3	#1 OR #2
#4	"Risk"[Mesh:NoExp]) OR "Risk Factors"[Mesh:NoExp]) OR "Risk Assessment"[Mesh]) OR "Protective Factors"[Mesh:NoExp]
#5	risk factor*[Title/Abstract]) OR risk assessment[Title/Abstract]) OR patient risk[Title/Abstract]) OR recurrence risk[Title/Abstract]) OR contributing factor*[Title/Abstract]) OR predisposing factor*[Title/Abstract]) OR protective factor*[Title/Abstract]) OR predictor*[Title/Abstract]) OR harmful effect*[Title/Abstract]
#6	#4 OR #5
#7	"Outcome Assessment (Health Care)"[Mesh]
#8	consequences[Title/Abstract]) OR aftereffect[Title/Abstract]) OR aftermath[Title/Abstract]) OR repercussion[Title/Abstract]) OR ramification[Title/Abstract]) OR outcome[Title/Abstract]) OR outcome assessment[Title/Abstract]) OR disease association[Title/Abstract]) OR impact[Title/Abstract]

#9	#7 OR #8
#10	#6 OR #9
#11	"Patient Readmission"[Mesh]
#12	rehospital*[Title/Abstract]) OR re-hospital*[Title/Abstract]) OR readmission*[Title/Abstract]) OR re-admission*[Title/Abstract]) OR multiple admission*[Title/Abstract]) OR repeat admission[Title/Abstract]
#13	#11 OR #12
#14	#3 AND #10 AND #13
International Pharmaceutical Abstracts	
S1	chronic obstructive pulmonary disease OR COPD OR chronic obstructive lung disease OR chronic obstructive airway disease OR bronchitis OR emphysema
S2	risk factor* OR risk assessment OR patient risk OR recurrence risk OR contributing factor* OR predisposing factor* OR protective factor* OR predictor* OR harmful effect*
S3	consequences OR aftermath OR aftereffect OR repercussions OR ramifications OR outcomes OR disease association OR impact OR outcome assessment
S4	S2 OR S3
S5	rehospitali?ation* OR re-hospitali?ation* OR readmission* OR re-admission* OR multiple admission* OR repeat admission*
S6	S1 AND S4 AND S5

6.3.4. Supplement A4. Quality scores of studies using the Newcastle-Ottawa Scale

	Selection (max 4 points)				Comparability (max 2points)		Outcome (max 3 points)			
Author, year	Representativeness of exposed cohort	Controls from the same cohort	Ascertainment of readmission from COPD	Outcome of interest not present at the start of study	Comparability of cohorts	Assessment of outcome	Adequate follow-up duration	Adequate follow-up rate	Score	Quality
Adeyemi, 2013[66]	1	1	1	1	1	1	1	1	8	Good
Almagro, 2006[13]	1	1	1	1	2	1	1	1	9	Good
Amalakuhan, 2011[30]	1	1	1	1	0	1	1	0	6	Fair
Bahadori, 2009[53]	1	1	1	1	2	1	1	1	9	Good
Baker, 2013[17]	1	1	1	1	2	1	1	1	9	Good
Barba, 2012[43]	1	1	1	1	2	1	1	1	9	Good
Bhatt, 2008[31]	0	1	1	1	2	1	1	0	7	Good
Bishwakarma, 2017[32]	1	1	1	1	2	1	1	1	9	Good
Bourbeau, 2003[54]	0	1	1	1	2	1	1	1	8	Good
Burgel, 2009[26]	1	1	1	1	2	1	1	1	9	Good
Candrilli, 2015[33]	1	1	1	1	2	1	1	1	9	Good
Cao, 2006[27]	0	1	0	1	1	0	1	0	4	Fair
Carneiro, 2010[63]	0	1	1	1	1	1	1	1	7	Good
Chan, 2011[60]	0	1	1	1	2	1	1	1	8	Good
Chen, 2009[55]	1	1	1	1	1	1	1	1	8	Good
Chen, 2006[97]	0	1	1	1	2	1	1	1	8	Good
Couillard, 2017[56]	1	1	1	1	2	1	1	1	9	Good
Coventry, 2011[70]	0	1	1	1	2	1	1	1	8	Good
Crisafulli, 2015[44]	1	1	1	1	2	1	1	1	9	Good
Crockett, 2000[72]	1	1	1	1	2	1	1	1	9	Good

de Battle 2012[45]	1	1	1	1	2	1	1	1	9	Good
deMiguel-Diez, 2016[46]	1	1	1	1	2	1	1	1	9	Good
Epstein, 2018[61]	1	1	1	1	2	1	1	1	9	Good
Fuhrman, 2016[71]	1	1	1	1	2	1	1	1	9	Good
Gavish, 2015[76]	1	1	1	1	2	1	1	1	9	Good
Gershon, 2019[59]	1	1	1	1	2	1	1	1	9	Good
Gonzalez, 2004[47]	0	1	1	1	1	1	1	0	6	Fair
González, 2008[48]	0	1	1	1	2	1	1	0	7	Good
Groenewegen, 2003[64]	1	1	1	1	2	1	1	1	9	Good
Gudmundsson, 2005[14]	1	1	1	1	2	1	1	1	9	Good
Guerrero, 2016[49]	1	1	1	1	2	1	1	1	9	Good
Harries, 2017[10]	1	1	1	1	2	1	1	1	9	Good
Hartl, 2015[28]	1	1	1	1	2	1	1	1	9	Good
Hunter, 2015[73]	1	1	1	1	2	1	1	1	9	Good
Iyer, 2015[34]	1	1	1	1	2	1	1	1	9	Good
Jiang, 2018[35]	1	1	1	1	2	1	1	1	9	Good
Johannesdottir, 2013[62]	1	1	1	1	2	1	1	1	9	Good
Kim, 2010[68]	1	1	1	1	2	1	1	0	8	Good
Ko, 2010[98]	1	1	1	1	2	1	1	1	9	Good
Lau, 2001[75]	1	1	1	1	1	1	1	1	8	Good
Lau, 2017[36]	1	1	1	1	2	1	1	1	9	Good
Liu, 2007[67]	0	0	1	1	1	1	1	1	6	Fair
Loh, 2017[37]	1	1	1	1	2	1	1	1	9	Good
McGhan, 2007[38]	1	1	1	1	2	1	1	1	9	Good
Müllerova, 2015[29]	1	1	0	1	2	1	1	1	8	Good

Nantsupawat, 2012[39]	1	1	1	1	0	1	1	1	7	Good
Pitta, 2006[65]	0	1	1	1	0	1	1	0	5	Fair
Quintana, 2014[50]	1	1	1	1	2	1	1	1	9	Good
Renom, 2009[51]	0	1	1	1	0	1	1	1	6	Fair
Rezaee, 2018[57]	1	1	1	1	2	1	1	1	9	Good
Roberts, 2016[40]	1	1	1	1	0	1	1	1	7	Good
Sin, 2001[58]	0	1	1	1	2	1	1	1	9	Good
Tsui, 2016[69]	1	1	1	1	2	1	1	1	9	Good
Wong, 2008[16]	1	1	1	1	2	1	1	1	9	Good
Yu, 2015[41]	1	1	1	1	2	1	1	1	9	Good
Zapatero, 2013[52]	1	1	1	1	2	1	1	1	9	Good
Zhong, 2017[42]	0	1	1	1	1	1	1	0	6	Fair