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Full Title: Risk factors and associated outcomes of hospital readmission in COPD: a systematic review

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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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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 2.6-82.2% 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.

Keywords: COPD, readmission, risk factors, consequences

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)

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 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] (Figure 1).

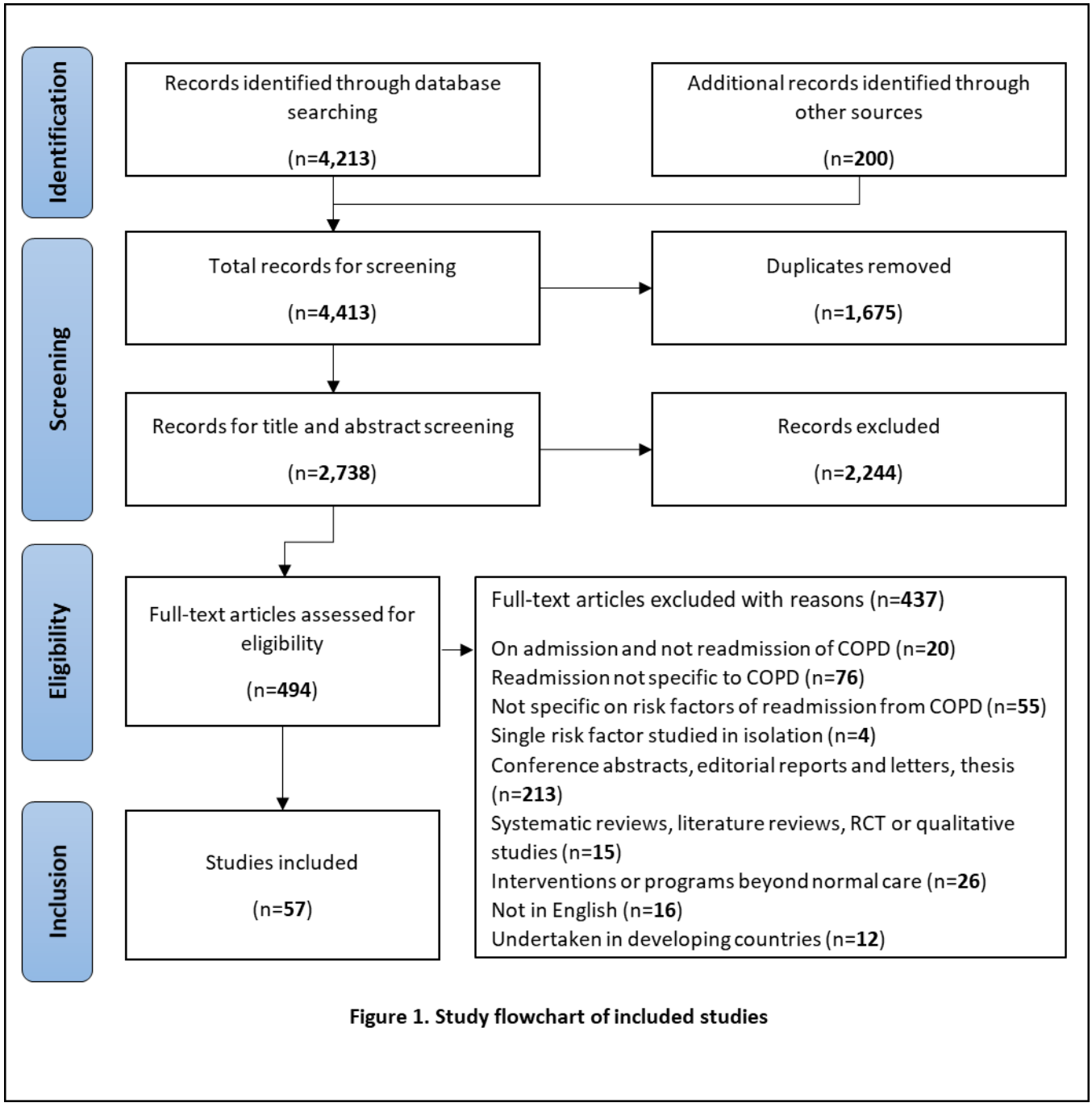

Figure 1. Study flowchart of included studies

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 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% to 44.8% for 31 to 90 days, 17.9% to 63.0% for 6 months, and 25.0% to 87.0% for 12 months post-discharge. The number of readmissions within one year was also reported as 9.0% to 47.0% for ≥2 readmissions, 3.8% to 23.0% for ≥3 readmissions, 2.4% to 17.6% for ≥4 readmissions and 5.2% to 8.6 % for ≥10 readmissions (Table 1).

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	
Adeyemi, 2013[66]	UK	696,385	NI	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[97]	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[70]	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[72]	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)
de Miguel-Diez, 2016[46]	Spain	301,794	74.8	89.0	17.5				Good (9)
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[76]	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 50.3 at 12 months	15.8 with 1 readmission at 12 months 17.0 with 2 readmissions at 12 months 8.8 with 3 readmissions at 12 months 8.8 with ≥3 readmissions at 12 months	Good (9)
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 18.2 at 90 days	26.7 at 6 months 37.0 at 12 months	21.8 with 1 readmission at 12 months 9.0 with 2 readmissions at 12 months 3.8 with 3 readmissions at 12 months 2.4 with ≥4 readmissions at 12 months	Good (9)
Kim, 2010[68]	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[98]	Hong Kong	243	74.2	85.6			76.5 at 3 years		Good (9)
Lau, 2001[75]	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)
Nantsupawat, 2012[39]	USA	81	73.9	46.9	13.6				Good (7)
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[69]	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

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[26,27,51,68], two studies defined it as >2 readmissions[31,62], while another used ≥4 readmissions[69]. 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 (Table 2a and Table 2b).

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[70]			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[72]	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[97]		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)			
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[97]		OR 0.56 (0.33-0.97)		
Dependent on self-care activities (vs independent)	Lau[75]			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[69]			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/m² (vs normal)	Hunter[73]			HR 0.87 (0.76-0.99)	
BMI <18.5 kg/m² (vs ≥18.5)	Kim[68]				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 >22.7g 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					

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[28,29,38,52,62,66,70] while six associated increased risk of readmission with the age range of 40-84 years[33,35,36,46,71,72].

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[68] indicated that patients with low BMI were more likely to be readmitted, while four studies[46,52,68,73] 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).

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[72]	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[70]			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[69]				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)	
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[70]			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[69]			HR 1.03 (1.01-1.05)	
Baseline BODE scores (quartile 4 vs 1)	Ko[98]			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[75]			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)	
Admission WBC count, per 1x109/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[75]			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[68]				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 one second; 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

Comorbidities: The presence of comorbid conditions was associated with increased risk of readmission in nine studies[16,28,33,43,46,52,57,61,72]. Comorbidities (categorised according to the International 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[14,70] 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[26,28,63,68,74].

3.5.2. Provider factors

Provider factors associated with readmission included the prescribed use of respiratory-related medications (n=7)[16, 17,32,40,57,58,67,75] and non-pharmacological therapies (n=6)[28,34,46,48,53,69,71] (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.

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 ≥1000g beclomethasone/day for ≥3months pre-admission	Lau[75]			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[69]			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

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[28,46,69,71] and home noninvasive ventilation[69] with readmission while four other studies[32,41,63,75] 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[13,17,28,38,44,59,62,71,73,75,76] while others reported the number of hospitalisations in the previous year[14,17,40,49,50,59,66,69,71] (Table 4). Any hospital admission in the previous 12 months[75], and one admission for exacerbation in the previous 12 months[70], were associated with a shorter time to the first readmission.

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[75]			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[76]		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[69]			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[75]			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)			
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[75]			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[76]		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					

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 17 found no association. Four of the nine studies associated hospital LOS of >5 days with increased risk of readmission[33,59,71,75] 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[76] had higher risk of readmission.

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**[28,33,35,36,38,46,52,62,66,70-72]		**38**[10,13,14,16,17,26,27[a],31,32,34,37,39-41,43,45,47[a],48,49,51[a],53-55,57-61,63,64,67-69,73-76,97]	51
Sex (male)	**10**[35,36,38,42[a],43,46,59,60,62,97]	**2**[52,71]	**36**[10,13,14,16,17,26,27[a],28,29,31-34,37,39,40,41,45,53,54,55,57,58,61,63,64,66,67[a],68-70,72-76]	48
Social determinants of health				
Smoking status		**1**[52]	**28**[13,14,16,26,27[a],28,29,31,34,39,40,43,45,47[a],48,49,51[a],53,57,61,63,67[a],68,69,70,73,74,97]	29
Marital status (single)	**1**[16]		**5**[13,27[a],57,75,97]	6
Ethnicity	**2**[35,36]	**4**[35,36,38,66]	**5**[27[a],32,34,37,97]	10
Living in deprived area	**6**[10,35,59,71,73,75]		**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**[97]		**3**[45,53,69]	4
Dependency on self-care activities	**1**[75]		**2**[13,53]	3
SGRQ score	**3**[13,14,29]		**2**[69,70]	5
6-minute walk distance (per 10-metre increase)	**1**[69]		**2**[29,51[a]]	3
Nutritional factors				
Obesity		**2**[46,52]	**2**[36,62]	4
BMI	**1**[68]	**1**[73]	**18**[13,16,26,27[a],28,29,34,37,45,47[a],48,51[a],53,57,63,64,67[a],69]	20
Malnutrition	**3**[43,46,52]			3
Cured meat intake >22.7g per day	**1**[45]			1
Comorbidities				
Charlson score	**8**[16,28,33,43,46,52,57,72]	**1**[61]	**14**[13,27[a],37,40,45,51[a],53,55,58,60,64,66,69,74]	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**[14,17,26,34,46,47[a],48,53,61,62,63,67[a],74,75]	21
Mental and behavioural disorders (F00-F99)				
Depression	**7**[34-36,40,41,62,70]		**8**[13,14,27[a],29,31,68,69,97]	15
Anxiety	**2**[40, 69]		**5**[14,27[a],34,68,70]	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],46,53,55,59,75]	12
Congestive heart failure	**6**[40,41,43,52,55,59]		**12**[17,26,34-36,46,50,53,61-63,75]	17
Cerebrovascular disease	**1**[59]			1
Atrial fibrillation	**1**[43]	**1**[33]	**4**[34,39,62,75]	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**[73,74]	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**[17,34,36,41,42[a],43,46,59,63]	9
Disease severity and complexity				
Severity (GOLD stage 1-4)	**1**[16]		**5**[26,28,63,68,74]	6
Decline in lung function (FEV_1 %)	**6**[26,27[a],29,50,67[a],73]	**4**[14,16,45,70]	**17**[13,26,28,31,34,37,39,47[a],48,49,51[a],53,64,68,69,74,76]	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**[69]		**1**[37]	2
Higher baseline BODE scores	**1**[98]		**3**[29,51[a],69]	4
Suboptimal peak inspiratory flow	**1**[37]			1
Chronic cough and sputum production	**1**[26]		**2**[28,29]	3
Dyspnoea/difficult breathing	**3**[40,50,57]		**11**[13,27[a],28,29,37,41,45,49,51[a],67[a],69]	15
Pressure-time index[b]	**2**[47[a],48]			2
Right heart strain pattern on EKG	**1**[75]			1
Emphysema >5% by radiology	**1**[29]			1
Duration of COPD	**2**[27[a],59]		**2**[68,76]	4
Laboratory findings				
Respiratory acidosis	**1**[46]		**1**[61]	2
Arterial blood gas testing	**1**[57]			1

Admission WBC count	**2**[16,29]		**5**[34,39,61,74,75]	7
Eosinophilia ≥200 cells/µL and/or ≥2% WBC	**1**[74]			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**[75]		**1**[34]	2
$PaCO_2$ >45 mmHg	**2**[13,68]		**11**[16,28,45,46,47[a],48,49,61,63,64,75]	13
Hypoxia	**1**[40]		**4**[45,47[a],48,64]	5
Medications prescribed				
Bronchodilators	**3**[17,40,57]		**7**[14,26,39,54,58,63,74]	10
Oral theophylline	**1**[58]		**1**[49]	2
ICS	**5**[32,40,57,67[a],75]	**1**[58]	**9**[14,17,26,31,39,45,54,63,74]	15
Oral corticosteroid	**3**[16,40,58]		**11**[14,17,28,31,39,54,63,64,68,74,75]	14
Montelukast	**1**[40]			1
Antimicrobials	**1**[58]		**4**[28,39,54,74]	5
Psychotropic drugs	**1**[27[a]]			1
Vaccination	**2**[27[a],40]		**4**[31,39,41,69]	6
Non-pharmacological therapies				
Ventilation	**4**[28,46,69,71]		**4**[32,41,63,75]	8
LTOT	**3**[48,53,71]		**11**[13,14,17,26,31,41,63,69,74,75]	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**[13,17,8,29,38,44,62,71,73,75,76]		**6**[47[a],48,50,55,70,74]	18
No. of hospitalisations in the previous year	**7**[14,17,50,59,66,69,71]			7
Hospital LOS during index admission	**9**[10,33,35,43,52,53,59,71,75]		**17**[13,14,31,32,37,39,41,46,47[a],48,49,55,61,64,72,97]	26
Discharge destination	**2**[35,46,59]			3
Living in or discharged to nursing homes	**5**[35,46,59,60,75]		**1**[53]	6
Winter	**1**[35]		**1**[41]	2
Autumn		**1**[35]		1
COPD specialist/pulmonologist follow-up visit	**2**[59,76]		**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

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].

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 metres 6MWD at day 8 of rehospitalisation in readmitted patients and 351 metres in non-readmitted patients Median 12 min/d walking time at 1 month in readmitted patients and 30min/d in non-readmitted patients			
Healthcare utilisation					
Cost	de Miguel-Diez, 2015[46]				Readmission mean cost €3,921 and admission mean cost €3,855
	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					

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 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[77]. 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 occupancy for COPD patients. These findings are consistent with previous studies where patient population, resources and place of healthcare provision were drivers of readmission[78]. 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[79]. Again, another explanation points to the variation of care within and between countries regarding pre- and post-discharge from COPD exacerbations[10,28,36,80]. 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[81,82].

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[29,83,84]. 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[75].

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[85]. 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[86]. Nursing home residents are generally frail and burdened with complications and comorbidities that can result in unavoidable readmissions[60,87]. 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[88]. 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[82,89-91].

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[92]. 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[93].

The finding of longer LOS in readmitted patients was similar to the literature[94]. 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[95]. 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 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.

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