COPD: Journal of Chronic Obstructive Pulmonary Disease

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/icop20

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To cite this article: Enrico de Nigris, John Haughney, Amanda J. Lee, Mintu Nath, Hana Müllerová, Ulf Holmgren & Bo Ding (2023) Short- and Long-Term Impact of Prior Chronic Obstructive Pulmonary Disease Exacerbations on Healthcare Resource Utilization and Related Costs: An Observational Study (SHERLOCK), COPD: Journal of Chronic Obstructive Pulmonary Disease, 20:1, 92-100, DOI: 10.1080/15412555.2022.2136065

To link to this article: https://doi.org/10.1080/15412555.2022.2136065

COPD: JOURNAL OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE
2023, VOL. 20, NO. 1, 92–100
https://doi.org/10.1080/15412555.2022.2136065

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Short- and Long-Term Impact of Prior Chronic Obstructive Pulmonary Disease Exacerbations on Healthcare Resource Utilization and Related Costs: An Observational Study (SHERLOCK)

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ABSTRACT

The observational retrospective cohort Study on HEalthcare Resource utiLization (HCRU) related to exacerbatiOns in patients with COPD (SHERLOCK; D5980R00014) evaluated exacerbation-related HCRU and costs using the U.K. National Health Service Greater Glasgow and Clyde Health Board data. Patients (≥40 years) with COPD were stratified by exacerbations one year before the index date: Group A (none), B (1 moderate), C (1 severe) and D (≥2 moderate and/or severe). All-cause and COPD-related HCRU and costs were assessed over 36 months. Adjusted rate ratios (RRs) or relative costs versus Group A were estimated using generalized linear models with appropriate distributions and link functions. The study included 22 462 patients (Group A, $n=7788$; B, $n=5151$; C, $n=250$ and D, $n=9273$). At 12 months, RRs (95% CI) versus Group A for all-cause and COPD-related HCRU, respectively, were highest in Groups C (1.28 [1.18, 1.39] and 1.18 [1.09, 1.29]) and D (1.26 [1.23, 1.28] and 1.29 [1.26, 1.31]). General practitioner and outpatient visits, and general ward stays/days accounted for the greatest COPD-related HCRU. All-cause and COPD-related relative costs (95% CI) versus Group A at 12 months, respectively, were 1.03 (0.94, 1.12) and 1.06 (0.99, 1.13) in Group B; 1.47 (1.07, 2.01) and 1.54 (1.20, 1.97) in Group C; 1.47 (1.36, 1.58) and 1.63 (1.54, 1.73) in Group D. Increased HCRU and costs in patients with exacerbation histories persisted at 36 months, demonstrating the sustained impact of exacerbations. The study suggests the importance of management and prevention of exacerbations through intervention optimization and budgeting by payers for exacerbation-related costs.

ARTICLE HISTORY
Received 10 December 2021
Accepted 5 September 2022

KEYWORDS
Chronic obstructive pulmonary disease; exacerbation severity; healthcare resource utilization; healthcare costs; exacerbation history

Introduction

Chronic obstructive pulmonary disease (COPD) represents a significant global health challenge and forms part of the group of chronic respiratory diseases that ranked as the third leading cause of mortality worldwide between 2000 and 2019, and as a leading cause of disability [1]. Patients with COPD may exhibit an exacerbation, defined as the "acute worsening of respiratory symptoms that results in additional therapy" [2], which can be characterized by increased dyspnoea, cough, sputum production and sputum purulence [3]. Exacerbation severity is generally classified as mild (treated with short-acting bronchodilators only), moderate (treated with short-acting bronchodilators plus a prescription for antibiotics and/or corticosteroids), or severe (requiring a visit to the emergency room or hospitalization). Exacerbations are known to affect over 50% of patients with COPD [4, 5], with approximately 25% of patients with COPD experiencing multiple moderate-to-severe exacerbations per year [6].

COPD exacerbations negatively impact disease progression and a patient's health status [2] and can lead to an accelerated decline in lung function [7]. Previous studies have shown that patients who have had at least 1 moderate or severe exacerbation are at an increased risk of future exacerbation events [8]; thus, exacerbation history is considered to be a key predictor of future resource utilization and costs for healthcare systems [9].

Exacerbations are the leading respiratory cause of hospital admissions in patients with COPD [10] and a major contributor to primary care (PC) visits [11]. As a result, exacerbations of COPD account for a substantial proportion of the total COPD burden on healthcare systems [12] and make a major contribution to the estimated annual direct and indirect costs of COPD of approximately $50 billion in the United States and over €48 billion in the European Union [13, 14]. Therefore, preventing exacerbations is a key target for patient management and could reduce the healthcare costs associated with COPD [11].

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/15412555.2022.2136065

The severity and frequency of exacerbations influence the costs associated with COPD [11, 15]. For example, the annual per-patient costs of COPD have been reported to increase substantially from £2108 for all patients to £3396 for patients who experienced ≥2 moderate-to-severe exacerbations, with general practitioner (GP) interactions accounting for almost half of these costs [11].

Although healthcare resource utilization (HCRU) and costs associated with exacerbations have been evaluated according to the frequency of prior exacerbations [8], data on the impact of a single recent prior moderate or severe exacerbation on clinical, HCRU, and/or cost outcomes compared with data from patients with no recent prior exacerbations are limited. Herein, we report HCRU and cost outcomes from the retrospective, observational Study on HEalthcare Resource utiLization related to exacerbatiOns in patients with COPD (SHERLOCK; D5980R00014). SHERLOCK evaluated the association between exacerbation history and the future rate and severity of exacerbations, and HCRU and related costs in patients with COPD from a UK database over a 3-year period. Clinical findings (exacerbation rate and severity) from this study are reported elsewhere and indicated that a recent history of even a single moderate exacerbation increased the risk of subsequent exacerbations compared with having no recent prior exacerbations [16].

Methods

Study design and population

The design of the SHERLOCK study has been previously described in [16]. In brief, SHERLOCK was a retrospective, observational cohort study that utilized data extracted from the National Health Service Greater Glasgow and Clyde (NHSGGC) Health Board Safe Haven database. The study included a baseline period (1 January 2013 to 31 December 2013), which was used to characterize a patient's exacerbation history, and a study period lasting until 31 December 2016, during which time patients were followed for a minimum of 12 months and up to 3 years. The index date was defined as 1 January 2014.

Patients with a historic Read or International Classification of Diseases, 10th Revision (ICD-10) code for COPD prior to the index date and not registered as deceased at the index date were included. The specific Read and ICD-10 codes used to identify patients for the SHERLOCK study have been previously published [16]. Patients were required to be aged ≥40 years at the index date and to have ≥1 COPD inhaled therapy prescription 1 year prior to the index date. Eligible patients were also required to have ≥1 year of data before and after the index date. Patients with significant pulmonary comorbidities (bronchiectasis, sarcoidosis, idiopathic pulmonary fibrosis, pleural disease, interstitial lung diseases, and extrinsic allergic alveolitis) were excluded.

For the current analyses, moderate exacerbations were defined as those which resulted in the patient being prescribed a course of oral corticosteroids and/or respiratory-related antibiotics (amoxicillin, clarithromycin, doxycycline and co-amoxiclav), and/or a visit to the emergency room with a primary diagnosis of any COPD-related event. Severe exacerbations were defined as those resulting in the patient being admitted to a hospital (general ward and/or inpatient care) with a primary diagnosis of a COPD-related event. Based on the history of exacerbations during the baseline period (1 year prior to the index date), patients were stratified into four groups: Group A (no exacerbations), Group B (1 moderate exacerbation), Group C (1 severe exacerbation), and Group D (≥2 moderate and/or severe exacerbations). To analyse patients who had experienced exactly 1 exacerbation (either moderate or severe), we also evaluated patients represented by Groups B and C, denoted here as Groups B + C.

Data source

The NHSGGC Health Board Safe Haven database is a large research resource that links health information datasets at the patient level, including routinely collected clinical primary and secondary activity such as HCRU, prescribing data, and laboratory values; it also links to the Scottish national register of deaths [17]. For the current analyses, research datasets were linked in-house prior to being released to investigators in a fully anonymized format. The full dataset was accessed remotely via NHSGGC Safe Haven by designated members of the Medical Statistics Team at the University of Aberdeen, UK. Therefore, ethical approval and patient informed consent for the SHERLOCK study were not required. Internal reviews and approvals were obtained (NHSGGC Project Number: GSH/19/RM/002).

Outcomes

The primary outcome (frequency and rate of exacerbations during follow-up) has previously been presented [16]. Secondary outcomes included all-cause and COPD-related HCRU and costs associated with COPD. Outcomes were assessed over 3 years at 12, 24, and 36 months of follow-up between 1 January 2014 and 31 December 2016. HCRU components included PC/GP visits, outpatient visits, emergency room visits, stays, and total days in the general ward, visits and total days in the intensive care unit. Among all-cause HCRU components, COPD-related HCRU events were identified when the primary diagnosis for the visit was matched with any COPD-related Read or ICD-10 code.

Healthcare resource uses were valued in British pound sterling at the time of analysis using sources based on 2017 and 2018 cost values (Supplementary Table 1). Medication costs were obtained from the 2018 National Health Service Drug Tariff and the 2019 British National Formulary (Supplementary Table 2). The overall cost of drugs, including COPD-specific drugs and drugs used for the management of exacerbations, was calculated for each patient within specified time points. COPD-specific drugs included in the analysis were inhaled corticosteroids (ICS), short-acting muscarinic antagonists, short-acting β_2-agonists (SABA),

long-acting muscarinic antagonists (LAMA), long-acting β_2-agonists (LABA), theophyllines, bronchodilator tablets and nebulizers, and phosphodiesterase-4 inhibitors. Drugs included for the treatment of moderate exacerbations were oral corticosteroids and antibiotics commonly prescribed for respiratory conditions, including amoxicillin, clarithromycin, doxycycline, and co-amoxiclav. The cost of each drug at each prescription date was calculated by multiplying the quantity with the unit cost. The HCRU-related cost per patient was calculated by assigning unit costs to resource use for each patient. Total costs were calculated by summing all costs due to HCRU components, drug costs and associated costs.

Statistical analysis

Sample size calculations for the primary outcome were based on estimates from 2 UK-based COPD cohorts [8, 18]. For the current study, it was estimated that a baseline population of approximately 25 000 patients would include 19% of patients in Group A (no prior exacerbations) and 19.5% of patients in Group B (1 moderate exacerbation within 12 months of follow-up). Under this assumption, the study had 90% power to detect a mean difference in number of exacerbations in the first year of follow-up of at least 0.13 at a two-sided 5% significance level. The study was not specifically powered for assessment of HCRU and cost outcomes described in this report as these were secondary endpoints of the study.

Baseline patient characteristics and unadjusted outcomes were summarized for the total population and each exacerbation history group. Censored patients (those who died during follow-up or those who moved out of the geographical boundary of the NHSGGC Health Board) were included in the statistical models up to the point at which they were censored.

Unadjusted all-cause and COPD-related HCRU at 12, 24 and 36 months of follow-up among Groups A, B, C and D are presented using descriptive statistics (means with standard deviation [SD]). To model all-cause and COPD-related HCRU rates for PC visits and total HCRU components (sum of PC, outpatient, emergency room visits and general ward stays), a generalized linear model (GLM) with a negative binomial distribution and log link function was used. Outpatient visits and total hospitalization visits (emergency room visits, general ward stays and intensive care stays) were modelled using a hurdle GLM that incorporated a negative binomial distribution with log link function for positive counts and binomial distribution with logit link functions for zero counts. The final adjusted GLMs included the following baseline characteristics: sex, age, smoking status, cardiovascular disease, cerebrovascular disease, depression and Medical Research Council (MRC) dyspnoea score; the models did not incorporate interaction terms. Differences in HCRU for each group versus Group A are presented as an adjusted rate ratio (RR) with a 95% confidence interval (CI).

Unadjusted mean all-cause and COPD-related HCRU were used as the basis for calculating HCRU data. GLMs with gamma distributions and log link function were used to model costs; data are reported as relative costs for each group versus Group A.

Results

Study population

Patient flow in the SHERLOCK study has previously been described [16]. In brief, of 31 418 patients identified with a historic diagnostic code for COPD at index date, 22 462 fulfilled eligibility criteria and were included in the study. All patients were followed up for 3 years; however, as of 31 December 2016, 153 patients were lost to follow-up (152 had died and 1 had moved out of the catchment area). The number of patients included in each exacerbation history group was as follows: 7788 in Group A, 5151 in Group B, 250 in Group C and 9273 in Group D.

Baseline demographics and clinical characteristics by exacerbation history group have been published [16]. In the overall population, mean (SD) age was 65.7 (10.7) years, 59.4% ($n = 13\,332$) of patients were female and 51.0% ($n = 11\,456$) were current smokers. The median (quartile 1 [Q1], quartile 3 [Q3]) number of COPD-related GP consultations during the year prior to the index date was 11 (7, 15). Cardiovascular disease, including heart failure, and depression were the most common comorbidities at baseline. The majority of patients ($n = 20\,458$; 91.1%) were receiving SABA; for maintenance of COPD, patients were prescribed LAMA and LABA with and without ICS (LAMA: $n = 5221$ [23.2%]; LABA: $n = 1677$ [7.5%]; LABA with ICS: $n = 3243$ [14.4%]); no patients were receiving dual LAMA/LABA therapy.

HCRU

Unadjusted mean (SD) all-cause and COPD-related HCRU data are reported in Supplementary Table 3. Across all groups, the greatest mean all-cause HCRU at 12 months of follow-up were observed for PC/GP visits (range: 13.3 – 16.8), outpatient visits (range: 1.9 – 3.0), and general ward total days (range: 1.6 – 4.9). The unadjusted mean number of all-cause PC/GP visits, outpatient visits, emergency room visits, general ward stays and total days in the general ward was numerically greater for patients in Group C and D than for patients in Group B and Group A at 12 months of follow-up. Similar observations were made for COPD-related HCRU at 12 months of follow-up.

Adjusted RRs (95% CI) for all-cause and COPD-related HCRU for each exacerbation history group relative to Group A are presented in Table 1. Adjusted RRs (95% CI) for all-cause total HCRU at 12 months of follow-up relative to Group A were 1.04 (1.01, 1.06) in Group B, 1.28 (1.18, 1.39) in Group C, 1.05 (1.02, 1.07) in Groups B + C and 1.26 (1.23, 1.28) in Group D. Adjusted RRs for COPD-related HCRU were comparable to the corresponding estimates for all-cause HCRU (Table 1).

Table 1. Adjusted rate ratios versus Group A (no exacerbations) for all-cause and COPD-related HCRU by exacerbation history[a] at 12, 24, and 36 months of follow-up.

	Group B ($n = 5151$)		Group C ($n = 250$)		Groups B + C ($n = 5401$)		Group D ($n = 9273$)	
Adjusted[b] RR (95% CI)	All-cause	COPD-related	All-cause	COPD-related	All-cause	COPD-related	All-cause	COPD-related
12 months of follow-up								
PC/GP visits	1.02 (1.00, 1.05)	1.03 (1.01, 1.06)	1.21 (1.11, 1.31)	1.14 (1.05, 1.24)	1.03 (1.01, 1.06)	1.04 (1.02, 1.06)	1.20 (1.18, 1.22)	1.24 (1.22, 1.27)
Outpatient visits[c]	1.05 (0.99, 1.12)	1.04 (0.87, 1.23)	1.31 (1.07, 1.61)	1.14 (0.75, 1.74)	1.06 (1.00, 1.13)	1.04 (0.88, 1.23)	1.27 (1.21, 1.34)	1.23 (1.07, 1.41)
Total hospitalizations	0.98 (0.88, 1.10)	0.82 (0.60, 1.11)	1.29 (0.95, 1.76)	1.10 (0.59, 2.03)	0.99 (0.89, 1.11)	0.83 (0.61, 1.12)	1.41 (1.28, 1.54)	1.47 (1.15, 1.87)
Total HCRU components[d]	1.04 (1.01, 1.06)	1.04 (1.02, 1.06)	1.28 (1.18, 1.39)	1.18 (1.09, 1.29)	1.05 (1.02, 1.07)	1.05 (1.02, 1.07)	1.26 (1.23, 1.28)	1.29 (1.26, 1.31)
24 months of follow-up								
PC/GP visits	1.02 (1.00, 1.04)	1.04 (1.01, 1.06)	1.17 (1.08, 1.27)	1.12 (1.03, 1.21)	1.03 (1.01, 1.05)	1.04 (1.02, 1.06)	1.20 (1.17, 1.22)	1.24 (1.22, 1.27)
Outpatient visits[c]	1.05 (0.99, 1.10)	1.01 (0.88, 1.14)	1.18 (0.99, 1.40)	1.08 (0.78, 1.51)	1.05 (1.00, 1.11)	1.01 (0.89, 1.15)	1.27 (1.22, 1.33)	1.31 (1.19, 1.45)
Total hospitalizations	0.98 (0.90, 1.07)	0.97 (0.79, 1.20)	1.54 (1.21, 1.98)	1.74 (1.09, 2.77)	1.00 (0.92, 1.09)	1.00 (0.81, 1.23)	1.44 (1.34, 1.54)	1.74 (1.48, 2.06)
Total HCRU components[d]	1.03 (1.01, 1.05)	1.04 (1.02, 1.06)	1.24 (1.14, 1.34)	1.16 (1.08, 1.26)	1.04 (1.02, 1.06)	1.04 (1.02, 1.07)	1.25 (1.23, 1.27)	1.28 (1.26, 1.31)
36 months of follow-up								
PC/GP visits	1.02 (1.00, 1.05)	1.04 (1.02, 1.06)	1.16 (1.07, 1.26)	1.11 (1.03, 1.20)	1.03 (1.01, 1.05)	1.04 (1.02, 1.06)	1.19 (1.17, 1.22)	1.24 (1.22, 1.26)
Outpatient visits[c]	1.04 (0.99, 1.09)	1.01 (0.90, 1.13)	1.13 (0.96, 1.33)	1.23 (0.90, 1.67)	1.05 (1.00, 1.10)	1.02 (0.91, 1.14)	1.28 (1.23, 1.33)	1.37 (1.25, 1.51)
Total hospitalizations	1.02 (0.95, 1.10)	1.07 (0.91, 1.26)	1.82 (1.47, 2.27)	1.67 (1.16, 2.40)	1.05 (0.98, 1.12)	1.09 (0.93, 1.28)	1.51 (1.42, 1.60)	1.85 (1.62, 2.11)
Total HCRU components[d]	1.03 (1.01, 1.05)	1.04 (1.02, 1.07)	1.23 (1.14, 1.33)	1.17 (1.08, 1.26)	1.04 (1.02, 1.06)	1.05 (1.03, 1.07)	1.24 (1.22, 1.26)	1.28 (1.26, 1.31)

Notes: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HCRU, healthcare resource utilization; MRC, Medical Research Council; n, number of patients; PC/GP, primary care/general practitioner; RR, rate ratio.

[a]Exacerbation history groups: Group B, 1 moderate exacerbation only; Group C, 1 severe exacerbation only; Group D, ≥2 prior moderate and/or severe exacerbations.

[b]Adjustment for the following baseline sociodemographic and clinical characteristics: sex, age, smoking status, cardiovascular disease, cerebrovascular disease, depression, and MRC dyspnoea score.

[c]COPD-related outpatient visits are defined as visits to a respiratory medicine clinic.

[d]Total HCRU components (sum of PC, outpatient, emergency room, intensive care visits, and general ward stays).

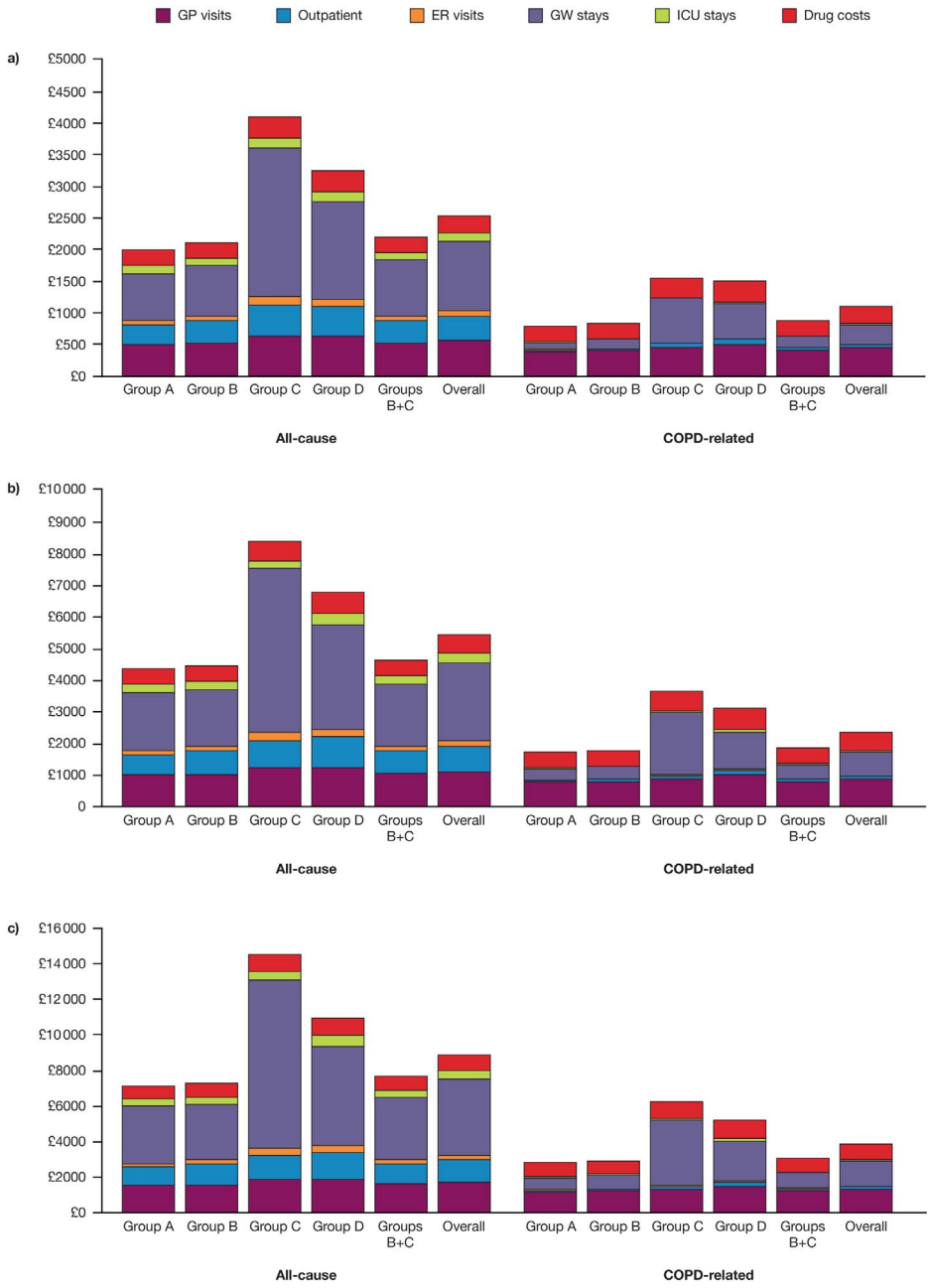

Figure 1. All-cause and COPD-related unadjusted mean cumulative costs by exacerbation history group[a] at (a) 12, (b) 24 and (c) 36 months of follow-up. COPD, chronic obstructive pulmonary disease; ER, emergency room; GP, general practitioner; GW, general ward; ICU, intensive care unit. [a]Exacerbation history groups: Group A, no prior exacerbations; Group B, 1 prior moderate exacerbation only; Group C, 1 prior severe exacerbation only; and Group D, ≥2 prior moderate and/or severe exacerbations.

Adjusted RRs for all-cause and COPD-related HCRU in Groups C and D were higher for all HCRU components compared with Groups B and B+C at 12 months, with adjusted RRs relative to Group A for total hospitalizations (all-cause and COPD-related HCRU, respectively) being greater in Group D (1.41 [1.28, 1.54] and 1.47 [1.15, 1.87]) than in Group C (1.29 [0.95, 1.76] and 1.10 [0.59, 2.03]). Estimates for all-cause and COPD-related HCRU components demonstrated consistent trends at 24 and 36 months of follow-up for both unadjusted analyses (Supplementary Table 3) and adjusted analyses (Table 1).

HCRU-related costs

In the overall population, unadjusted mean (SD) all-cause and COPD-related total costs at 12 months of follow-up were £2561 (£5362) and £1101 (£2416), respectively (Figure 1a and Supplementary Table 4). Unadjusted mean (SD) HCRU-related costs were lowest in Group A for both all-cause and COPD-related costs: £1992 (£4316) and £779 (£1529), respectively. In contrast, patients in Group C had the greatest all-cause and COPD-related HCRU-related costs (£4095 [£7582] and £1549 [£2376], respectively). Patients in

Table 2. Relative all-cause and COPD-related costs (£) versus Group A by exacerbation history[a] group at 12, 24 and 36 months of follow-up.

	Group B ($n=5151$)		Group C ($n=250$)		Groups B + C ($n=5401$)		Group D ($n=9273$)	
	All-cause	COPD-related	All-cause	COPD-related	All-cause	COPD-related	All-cause	COPD-related
Adjusted[b]*model: relative cost*[c] (95% CI)								
12 months of follow-up	1.03 (0.94, 1.12)	1.06 (0.99, 1.13)	1.47 (1.07, 2.01)	1.54 (1.20, 1.97)	1.04 (0.96, 1.14)	1.08 (1.01, 1.15)	1.47 (1.36, 1.58)	1.63 (1.54, 1.73)
24 months of follow-up	1.03 (0.96, 1.11)	1.03 (0.97, 1.09)	1.47 (1.12, 1.91)	1.61 (1.28, 2.03)	1.05 (0.98, 1.13)	1.05 (0.99, 1.12)	1.39 (1.31, 1.48)	1.56 (1.48, 1.65)
36 months of follow-up	1.02 (0.96, 1.08)	1.04 (0.98, 1.11)	1.53 (1.20, 1.93)	1.67 (1.33, 2.09)	1.04 (0.97, 1.10)	1.07 (1.01, 1.13)	1.37 (1.29, 1.45)	1.60 (1.51, 1.68)

CI, confidence interval; COPD, chronic obstructive pulmonary disease; MRC, Medical Research Council; n, number of patients.
[a]Exacerbation history groups: Group A, no prior exacerbations; Group B, 1 prior moderate exacerbation only; Group C, 1 prior severe exacerbation only; and Group D, ≥2 prior moderate and/or severe exacerbations.
[b]Adjusted model included the following baseline sociodemographic and clinical characteristics: sex, age, smoking status, cardiovascular disease, cerebrovascular disease, depression, and MRC dyspnoea score.
[c]Costs relative to Group A.

Group B accumulated substantial all-cause and COPD-related costs at 12-months of follow-up (£2102 [£4414] and £841 [£1178], respectively). Similar trends in all-cause and COPD-related total costs were observed at 24 and 36 months of follow-up (Figure 1b and 1c, and Supplementary Table 4).

Differences in general ward stay costs were notable across groups, while other HCRU component costs were generally comparable (Figure 1 and Supplementary Table 4). Mean (SD) cumulative costs (all-cause and COPD-related, respectively) for general ward stays were higher in Group C (£2369 [£7143] and £701 [£2226] at 12 months, £5187 [£10859] and £1988 [£5382] at 24 months, and £9467 [£15595] and £3631 [£7701] at 36 months of follow-up) than in all other exacerbation history groups, with the next highest general ward costs observed in Group D.

Relative costs (95% CI) for all-cause and COPD-related costs for each exacerbation history group compared with Group A are presented in Table 2. At 12 months of follow-up, relative costs (95% CI) for all-cause and COPD-related costs relative to Group A, respectively, were 1.03 (0.94, 1.12) and 1.06 (0.99, 1.13) in Group B, 1.47 (1.07, 2.01) and 1.54 (1.20, 1.97) in Group C, 1.04 (0.96, 1.14) and 1.08 (1.01, 1.15) in Groups B + C, and 1.47 (1.36, 1.58) and 1.63 (1.54, 1.73) in Group D. Observations were similar at 24 and 36 months of follow-up (Table 2).

Discussion

This retrospective, 3-year, observational cohort study examined HCRU and associated costs based on history of exacerbations in patients with COPD from the NHSGGC Health Board Safe Haven database. The key finding of this report is that a recent history of exacerbations was associated with increased all-cause and COPD-related HCRU and costs, relative to having no exacerbations in the previous year. The observed increases in HCRU and costs were greatest in patients with a recent history of 1 severe exacerbation (Group C) or a history of ≥2 moderate and/or severe exacerbations (Group D). Outpatient visits, PC/GP visits, and total days in the general ward were associated with the greatest all-cause and COPD-related HCRU across all exacerbation history groups. Similar trends were observed for HCRU-related costs, with the highest all-cause and COPD-related costs occurring in patients with the recent history of 1 severe exacerbation or ≥2 moderate and/or severe exacerbations at all-time points up to 36 months of follow-up. The key driver for increased HCRU-related costs was general ward stays. Relative to patients with no prior history of exacerbations, all-cause and COPD-related costs for general ward stays, respectively, were approximately 3-fold and 6-fold greater in patients with 1 prior severe COPD exacerbation and approximately 2-fold and 5-fold greater in patients with a history of ≥2 moderate and/or severe exacerbations at 12 months of follow-up; these cost differences were generally similar at 24 months and decreased slightly at 36 months of follow-up.

The increased HCRU and associated costs observed in patients with a recent history of 1 severe or ≥2 moderate and/or severe exacerbations are consistent with previously published studies [11, 19–21]. In a retrospective cohort of 58 589 patients with COPD identified in the UK Clinical Practice Research Datalink (CPRD) database, patients with ≥2 moderate-to-severe exacerbations accumulated greater total annual per-patient COPD costs (£3396) compared with patients with 1 exacerbation (£2405) or no exacerbations (£1523), with GP interactions being the main contributor to these costs [11], although this study did not differentiate between moderate and severe exacerbations. A secondary analysis of Italian healthcare administrative databases comprising 15 857 patients hospitalized for a severe COPD exacerbation during 2006 demonstrated that patients with at least 1 severe exacerbation in a 3-year pre-index period had significantly higher total healthcare costs per patient than those with ≥1 moderate exacerbation and those with no exacerbations in the same period [20], with differences in costs being attributable to hospitalizations. Similarly, Pasquale et al [21] reported that COPD-associated HCRU was greatest in patients with ≥2 exacerbations compared with patients with ≥1 exacerbations in a US population of 8554 predominantly Medicare patients with chronic bronchitis; inpatient hospitalizations contributed most to total COPD-related costs. In the same study, patients with severe exacerbations had higher mean annual COPD-related costs per patient ($12 765) than patients with moderate exacerbations ($3356) [21]. The current study demonstrates that a single exacerbation (moderate or severe) is associated with

increased HCRU and associated costs over a 36-month follow-up period, confirming that COPD exacerbations place a substantial burden on a patient's health and daily life [4], as well as on HCRU and associated costs [20].

Compared with patients without a history of exacerbations, patients with any prior COPD exacerbation are more likely to develop new exacerbations [6, 8, 20, 22, 23]. A post hoc analysis over a 10-year period using data from the UK CPRD found that patients who experienced 1 prior moderate exacerbation had a 70% and 20% increased risk of future moderate or severe exacerbations, respectively, in the first year of follow-up compared with patients with no prior exacerbations [8]. This finding is also supported by clinical data from the SHERLOCK study [16]. In the SHERLOCK study, rates of moderate or severe exacerbations (per patient, per year) were 0.69 in patients with no prior exacerbations, 1.20 in patients with 1 prior moderate exacerbation, 1.27 in patients with 1 prior severe exacerbation, and 3.11 in patients with ≥2 prior moderate and/or severe exacerbations over the initial 12 months of follow-up [16]. Although moderate exacerbations are often managed in PC [2], the SHERLOCK study demonstrated that a single moderate exacerbation is associated with an increased risk of the future severe exacerbation [16]. The current analyses indicate that having at least 1 prior moderate exacerbation was associated with only moderate increases in HCRU and costs; however, the increased risk of having additional exacerbations after a single moderate exacerbation could translate into substantially greater costs to the healthcare system over a longer period if these patients progress to having more frequent and/or more severe exacerbations. As a higher risk of exacerbations and the subsequent hospitalizations are associated with late diagnosis of COPD [24], emphasizing early diagnosis and treatment of COPD for the prevention of exacerbations could also reduce COPD-related HCRU and costs.

COPD-related resource use predicted future exacerbation rates and HCRU in a 1-year study of 88 548 patients with COPD from multiple Swedish registries [9]. High resource use (defined as patients with ≥2 respiratory-related hospitalizations in the previous year and consistent use of ICS plus a LAMA and/or LABA at baseline) was associated with an 8.3-fold increase in severe exacerbation rates and a 1.8-fold increase in HCRU rates in the following year [9]. These findings, taken together with observations from the current study, provide additional evidence of a relationship between exacerbation rates and HCRU and associated costs. They also suggest that identifying and managing patients with any exacerbation history, even a single moderate prior exacerbation, may help reduce overall HCRU and associated healthcare costs.

Strengths and limitations

The main strengths of the SHERLOCK study included its large patient population (entirely inclusive of the population from the geographical area covered by the NHSGGC Health Board) and its use of a limited number of exclusion criteria, which make the findings generalizable to the broader population of patients with COPD. Data from both primary and secondary care settings were also evaluated, and patients were followed up for 36 months, allowing for long-term evaluation of cumulative HCRU and costs, and changes in HCRU and costs over time. However, there are also limitations to consider. The primary limitations are those inherent to retrospective studies in general and to observational studies that utilize databases designed for clinical use and not for research. One such limitation is the need to rely on a large and disparate group of clinicians to make diagnoses and record data accurately. In addition, missing data (especially for home visits and out-of-hours care) and the inability to extract some data in electronic form are limitations. The exclusion of patients with significant pulmonary comorbidities may introduce bias against patients with more severe respiratory illness, who are at an increased risk of hospitalization [25, 26]. Mean patient age tended to be lower compared with those in other similar cohort studies [11, 27], which could limit generalizability. It should also be acknowledged that the definition for Group D (≥2 prior moderate and/or severe exacerbations) in this analysis encompasses a range of patients with widely varying exacerbation histories. Future analyses should examine this group in a more granular fashion (i.e. as a function of the number of total exacerbations) to better reflect the profiles of patients who have experienced multiple exacerbations.

Future clinical and/or real-world studies of patients experiencing symptomatic breakthroughs that qualify as mild exacerbations requiring self-medication (indicated by increased use of SABA) would also provide valuable insight into whether early intervention before moderate or severe exacerbations arise can help to further reduce HCRU and associated costs.

Conclusions

The primary findings from the SHERLOCK study highlight that having a history of exacerbations, even 1 single moderate exacerbation, increases the risk of subsequent exacerbations compared with having no recent prior exacerbations [16]. The current report expands those findings to HCRU and costs, demonstrating that patients with a history of greater exacerbation severity or higher exacerbation frequency have increased HCRU and associated healthcare costs over a period of 3 years compared with those without prior exacerbations. The highest HCRU across exacerbation history groups was associated with PC/GP visits, while costs in patients with 1 prior severe or ≥2 prior moderate and/or severe exacerbations were driven by general ward use. Taken together, these findings suggest patients with a history of exacerbations should be monitored in both primary and specialty care settings to reduce HCRU and associated costs.

Compared with a history of no exacerbations in the previous year, even a recent history of a single moderate exacerbation was associated with the modest increases in HCRU and healthcare costs over 3 years. This indicates that the clinical management of COPD should focus on minimizing

the risk of any type of exacerbation, regardless of severity, to maintain patient health status and reduce the overall burden of COPD on the healthcare system.

Acknowledgments

Medical writing support, under the direction of the authors, was provided by Sara Cameron, MPhil, CMC Connect, a division of IPG Health Medical Communications, funded by AstraZeneca in accordance with Good Publication Practice (GPP 2022) guidelines [28]. All authors were involved in the design and conduct of the study and in the interpretation of the data. All authors were involved in the writing of the manuscript and the final decision to submit to *COPD: Journal of Chronic Obstructive Pulmonary Disease*.

Data availability statement

Remote access to this dataset was provided to the study statisticians via Safe Haven. Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data are not available.

Declaration of interest

Enrico de Nigris was an employee of AstraZeneca at the time this study was conducted. Bo Ding is an employee of AstraZeneca. John Haughney reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Circassia and Teva unrelated to the conduct of the study. Amanda Lee and Mintu Nath have no conflicts to disclose. Hana Müllerová and Ulf Holmgren are employees and hold stock and/or stock options in AstraZeneca.

Previous presentation

These data were reported at the 2020 International Society for Pharmacoeconomics and Outcomes Research European Virtual Congress (16 – 19 November 2020). Data reporting the associations between exacerbation history and rates of the subsequent COPD exacerbations from this study were presented at the 2020 European Respiratory Society International Virtual Congress (5 – 9 September 2020).

Funding

This study was sponsored by AstraZeneca. AstraZeneca authors were involved in the design of the study; in the analysis, and interpretation of the data; in the writing of the report; and in the decision to submit the article for publication.

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