All-cause admissions following a first ever exacerbation-related hospitalisation in COPD

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Shareable abstract (@ERSpublications)
Nonrespiratory events are the predominant cause of hospital admission in patients with COPD following their first ever exacerbation-related hospitalisation. These findings challenge the current global post-exacerbation management goals. https://bit.ly/3AkC4QN

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Abstract

Background Hospital admissions are important contributors to the overall burden of chronic obstructive pulmonary disease (COPD). Understanding the patterns and causes of hospital admissions will help to identify targets for preventive interventions. This study aimed to determine the 5-year all-cause hospital admission trajectories of patients with COPD following their first ever exacerbation-related hospitalisation.

Methods Patients with COPD were identified from the Danish national registries. Patients experiencing their first ever exacerbation-related hospitalisation, defined as the index event, between 2000 and 2014 were included. All-cause hospital admissions were examined during a subsequent 5-year follow-up period, and categorised using the International Classification of Diseases, 10th revision.

Results In total, 82 964 patients with COPD were included. The mean±SD age was 72±10 years and 48% were male. Comorbidities were present in 58%, and 65% of the patients collected inhalation medication ⩽6 months prior to the index event. In total, 337 066 all-cause hospital admissions were identified, resulting in a 5-year admission rate of 82%. Most admissions were due to nonrespiratory causes (59%), amongst which cardiac events were most common (19%).

Conclusion Hospital admissions following a first exacerbation-related hospitalisation are common; nonrespiratory events constitute the majority of admissions. Besides the respiratory causes, treatment targeting the nonrespiratory causes of hospital admission should be considered to effectively decrease the burden of hospitalisation in COPD.

Introduction

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) play a central role in the clinical course and disease burden of the condition. Each event induces a decline in lung function, physical activity, mental health and overall quality of life, which enhances the risk of further and substantially earlier AECOPD, as well as death [1, 2]. Moreover, the degree of the disease severity contributes to the risk of AECOPD hospital admission. Indeed, the hospitalisation rate increases from 11% to 54% in patients with incrementing airflow limitation from moderate to very severe COPD, respectively [3]. The prognosis of patients hospitalised with AECOPD is poor. In-hospital mortality rates of up to 10% [4] and 2-year post-discharge mortality rates of 36% have been reported [5]. Furthermore, patients hospitalised due to AECOPD are significantly predisposed to hospital readmission. Approximately one-third of patients is

readmitted within 90 days [6]. As such, exacerbation-related hospitalisations contribute to the majority of COPD-related healthcare costs [7].

Patients with COPD often suffer from multiple comorbidities [8]. A recent systematic review and meta-analysis concluded that comorbidities were the most-commonly reported significant risk factor associated with 30- and 90-day all-cause hospital readmission following exacerbation-related hospitalisation [9]. Other major risk factors include prior exacerbations and hospitalisations, as well as prolonged length of hospital stay [9]. Whilst comorbidities may play a role in the susceptibility to readmission following exacerbation-related hospitalisation, AECOPD itself may also affect comorbidities. Exacerbation-related systemic manifestations, such as systemic inflammation, physical inactivity and pharmacological therapy with high-dose β_2-agonists, may result in the onset and/or aggravation of metabolic and cardiovascular comorbidities, both during and after AECOPD [1, 10–12]. Hence, whilst hospital readmissions for AECOPD are common, the causes of readmission following exacerbation-related hospitalisation may extend beyond the lungs [13].

To the best of our knowledge, the trajectories from first ever exacerbation-related hospitalisation to subsequent all-cause hospital admissions have not been studied to date. Therefore, the primary aim of this study was to explore the all-cause hospital admissions of patients with COPD in the first 5 years after their first exacerbation-related hospitalisation. Secondary aims were to study the differences between the short and long term, and frequently and less-frequently admitted patients.

Methods

Study design and ethical approval

This Danish nationwide observational population-based study used a retrospective follow-up design. Retrospective registry research does not require ethical approval by Danish law. Access to the data was granted by the Capital Region of Denmark (approval number P-2019–191). This study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study setting

All 5.33 million (*anno* 2000) Danish citizens have a unique civil personal registration number that is used as an identifier in the Danish registries. All citizens have access to free healthcare, which is financed through the Danish tax system. Medical doctors do not have financial incentives to admit patients within this system. The civil personal registration number was used to identify individuals across multiple different Danish registries [14].

Data sources

Information on hospital admissions and pre-existing comorbidities was gathered from the Danish National Patient Registry using the 10th revision of the International Classification of Diseases (ICD-10) discharge diagnosis [14]. The Danish National Prescription Registry was used to gather information on medication use collected in the 6 months prior to the index admission. The Danish Cause of Death Registry was used to gather the date of death. Finally, information on age, sex and educational level was gathered from The Statistics of Denmark Registry.

Study population

Patients with COPD admitted to any Danish hospital for their first ever (*i.e.* lifetime) exacerbation-related hospitalisation, also referred to as the index event, between 1 January 2000, and 29 January 2014, were included in the current study. Therefore, all first time acute hospital episodes with a primary discharge diagnosis of COPD (J44), or a primary discharge diagnosis of acute respiratory failure (J96) or pneumonia (J13-J18) in combination with a secondary diagnosis of COPD were retrieved. These diagnostic criteria were previously validated with a predictive value ⩾90% [15]. Only admissions to a department with 24-h surveillance (therefore excluding emergency department contacts not leading to admission) were recorded to enhance the comparability of the current cohort. As such, emergency department visits without subsequent admission would include a number of moderate AECOPD. Furthermore, patients aged <40 or >90 years, and patients with chronic asthmatic bronchitis (J44.8B) or a (previous) diagnosis of asthma (J45) were excluded.

Outcomes and definitions

The primary outcome was all-cause hospital admission during a subsequent 5-year follow-up period after the first exacerbation-related hospitalisation. Mortality was explored during the same period. Admission causes were characterised according to their ICD-10 code: an overview is provided in supplementary table 1. Specific diagnoses were characterised using the first subsequent digit. As such, respiratory related

admissions were characterised using the ICD-10 code J, whereas specific diagnoses such as acute infections of the upper respiratory tract would be denoted by J0–J06. The diagnostic codes H, L, O–Q and Z were combined in the "other" cluster due to their low incidence. Short- and long-term outcomes were characterised by 30-day and 5-year time windows, respectively. Furthermore, frequently admitted patients were characterised by four or more admissions whereas less-frequently admitted patients were characterised by three or fewer admissions during follow-up.

Data collection

The following data were recorded from the index event: date of admission and discharge, discharge diagnosis, and time until discharge. Time till first readmission was calculated based on the time between discharge from the index event and the admission date of the first admission. Likewise, time till death was calculated based on the time between discharge from the index event and the date of death.

Basic characteristics included age, sex, educational level according to the International Standard of Education (ISCED) [16]: lower secondary education (0–2), upper secondary education (3), tertiary education or Bachelor's degree (5, 6) and Master's or Doctoral degree (7, 8). Please note that ISCED level 4 is not a part of the Danish education system. In addition, cohabitation status (*i.e.* living alone or together) and comorbidities ⩽5 years prior to the index admission (using the Charlson Comorbidity Index [17]) were collected. Of note, the comorbidities anxiety, depression and diabetes were defined using both the Danish National Patient Registry (for the corresponding ICD-10 codes) and the Danish National Prescription Registry for the corresponding medications (using the anatomic therapeutic chemical codes N05B, NO6A and A10, respectively). Furthermore, use of inhalation medication ⩽6 months prior to the index admission was recorded as the following exclusive categories: short-acting β_2-agonist; long-acting muscarinic agonist (LAMA); long-acting β_2-agonist (LABA); inhaled corticosteroid (ICS); LAMA/LABA; ICS/LAMA; ICS/LABA; triple therapy (LAMA/LABA/ICS); and no treatment.

Statistical analysis

Continuous variables are presented using mean±SD when normally distributed, otherwise using median (interquartile range (IQR)). Categorical data are presented using absolute counts and relative percentages. Admission and mortality rates are displayed using two distinct methods. First, cumulative incidence plots of first time all-cause hospital admission and mortality were created for the 5-year follow-up period. The Aalen–Johanson estimator was used to account for competing risk of death in the all-cause admissions curve. Secondly, admission and mortality trajectories after the index event are displayed irrespective of time using Sankey diagrams. Furthermore, mean cumulative counts are displayed using the mean cumulative function [18]. The 95% confidence interval was constructed assuming Poisson distribution. The median admission rate per patient was simultaneously calculated as:

$$((\text{Total admissions}/\text{days till death or end of follow-up period}))/(365.25 \times 5)$$

Corresponding IQRs were calculated. Data management and analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R (version 4.0.3).

Results

A total of 96 335 patients with COPD experienced their first ever exacerbation-related hospitalisation during 2000–2014 in Denmark. After excluding patients aged <40 or >90 years, patients with chronic asthmatic bronchitis (J44.8B) or a (previous) diagnosis of asthma (J45), a total of 82 964 patients were included (figure 1). An overview of the characteristics of these patients at the index event is provided in table 1. Briefly, the mean±SD age of the population was 72±10 years and there was no sex predominance. The majority collected any inhaled medication in the 6 months prior to the index event (65.2%) and had at least one pre-existing comorbidity (57.5%). Chronic heart failure, (complicated) diabetes and cerebrovascular disease were most prevalent.

In total, 56.0% (95% CI 55.6–56.3%) of patients had been admitted during the first 12 months after hospital discharge from the index event (figure 2a). After 5 years of follow-up, 81.8% (95% CI 81.6–82.1%) of patients had been admitted. Moreover, 5.5% (4554 out of 82 964) died during the index event. An additional 4029 patients died during the first 30 days post-discharge, resulting in a 30-day mortality rate of 10.4%. After 5 years of follow-up, 58.2% of patients had died (figure 2b).

The cumulative average of the total number of hospital admissions during the first 30 days post-discharge was 0.27 (95% CI 0.27–0.28) per patient (figure 3). A linear increase in the mean cumulative count was

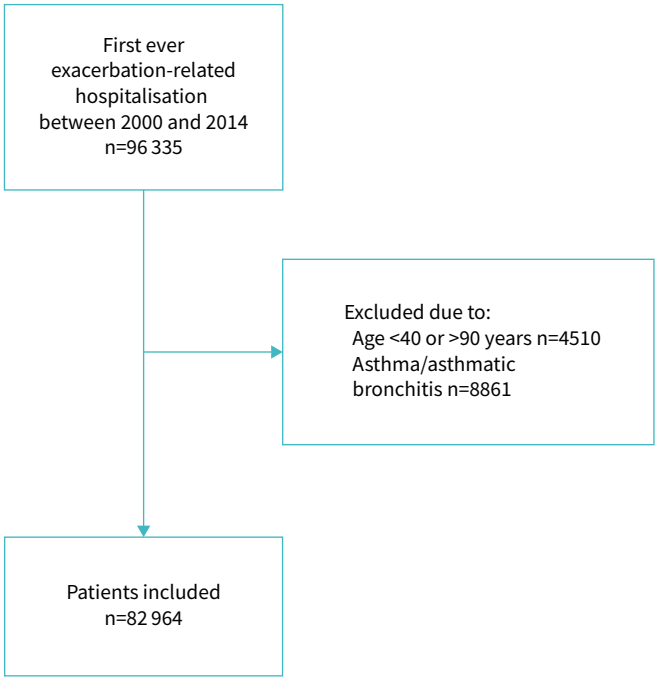

FIGURE 1 Flowchart of the study population.

observed over time. After 5 years of follow-up, the mean cumulative number of hospital admission was 6.4 (95% CI 6.4–6.4), which corresponds to the median admission rate of 6 (IQR 2–14) per patient.

Irrespective of time, 81.8% of patients (67 882 out of 82 964) had experienced at least one subsequent hospital admission, 7.0% of patients (5821 out of 82 964) had not been admitted and 11.2% of patients (9261 out of 82 964) had died (figure 4). Looking at the proportion of patients that had been admitted, nonrespiratory admissions accounted for 57.2% (38 852 out of 67 882) of the first hospital admission. Of these nonrespiratory causes, cardiac-related events were most common (21.0% (8174 out of 38 852)). Respiratory causes accounted for 42.8% (29 030 out of 67 882) of the first admission. Similar patterns were observed during subsequent admissions: nonrespiratory causes remained the main cause of a second and third hospital admission.

A similar distribution of the main diagnostic clusters was observed during the first 30 days post-discharge compared to 5 years post-discharge after the index event (table 2). Cardiac events remained the main nonrespiratory cause of hospital admission over time (18.5% (36 586 out of 337 066–139 272)). The specific diagnoses of the two most common diagnostic clusters are shown in figure 5.

At the end of follow-up, 80.9% of all admissions occurred in a group of frequently admitted patients experiencing four or more hospital admissions. Differences in baseline characteristics were observed between the frequently and less-frequently admitted patients (table 3). As such, the number of patients without pre-existing comorbidities surviving follow-up was higher in the less-frequently admitted patients compared to the frequently admitted patients. Moreover, the average age was highest in the less-frequently admitted patients not surviving follow-up. Regardless of the number of admissions, the patients not surviving follow-up were older, had more comorbidities and a longer hospital stay during the index event compared to the surviving patients.

Discussion

This study showed the 5-year all-cause hospital admission trajectories of >80 000 patients with COPD following their first ever exacerbation-related hospitalisation. The vast majority of patients had been admitted to the hospital for any cause 5 years after their first exacerbation-related hospitalisation. Whilst the causes of hospital admission varied widely, more than half of the admissions were nonrespiratory. Furthermore, more than half of the patients had died during follow-up. To the best of our knowledge, this

TABLE 1 Baseline characteristics of patients with COPD at their first exacerbation-related hospitalisation

Patients	82 964
Age, years, mean±SD	72.2±10.2
Sex	
Male	39 716 (47.9)
Female	43 248 (52.1)
Education[#]	
Lower secondary education	45 900 (61.0)
Upper secondary education	22 985 (30.6)
Tertiary education or Bachelor's degree	5246 (7.0)
Master's or Doctoral degree	1083 (1.4)
Cohabitation status[¶]	
Living alone	39 765 (53.8)
Living together	34 178 (46.2)
Inhaled medication	
SABA	7160 (8.6)
LAMA	4490 (5.4)
LABA	2704 (3.3)
ICS	8105 (9.8)
LAMA/LABA	1120 (1.3)
LAMA/ICS or LABA/ICS	17 031 (20.5)
Triple therapy	13 510 (16.3)
Total	54 120 (65.2)
No treatment	28 844 (34.8)
Comorbidities	
Chronic heart failure	13 692 (16.5)
(Complicated) diabetes	10 137 (12.2)
Cerebrovascular disease	9059 (10.9)
Peripheral vascular disease	8293 (10.0)
Cancer	7886 (9.5)
Myocardial infarction	6551 (7.9)
Depression	4334 (5.2)
Peptic ulcer disease	4264 (5.1)
Rheumatic diseases	3459 (4.2)
Chronic renal disease	2822 (3.4)
Dementia	2342 (2.8)
Anxiety	2310 (2.8)
(Severe) hepatic disease	1523 (1.8)
Metastatic cancer	1102 (1.3)
Hemiplegia	277 (0.3)
AIDS	82 (0.1)
Number of comorbidities	
0	35 256 (42.5)
1	20 499 (24.7)
2	12 901 (15.6)
⩾3	14 308 (17.2)
Characteristics of the index event	
Time until discharge, days, median (interquartile range)	4 (2–8)

Data are presented as n (%) unless otherwise stated. SABA: short-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; LABA: long-acting β_2-agonist; ICS: inhaled corticosteroid. [#]: n=75 214; [¶]: n=73 943.

is the first study to demonstrate the all-cause hospital admission trajectories of patients with COPD following their first ever exacerbation-related hospitalisation.

For many years, it has been well established that after an exacerbation-related hospitalisation, patients with COPD will be admitted for a subsequent AECOPD [2, 4, 6]. As such, the main goals in treating AECOPD are to minimise the negative impact of the current event and to prevent subsequent events [19]. In this study, we showed that, not surprisingly, respiratory admissions were most frequent. However, nonrespiratory admissions accounted for the majority of subsequent admissions, both in the short and long term. Indeed, we demonstrated the patterns of incidence over time. Hence, it could be observed that admissions related to cancer and the digestive and genitourinary tract became more incident over time.

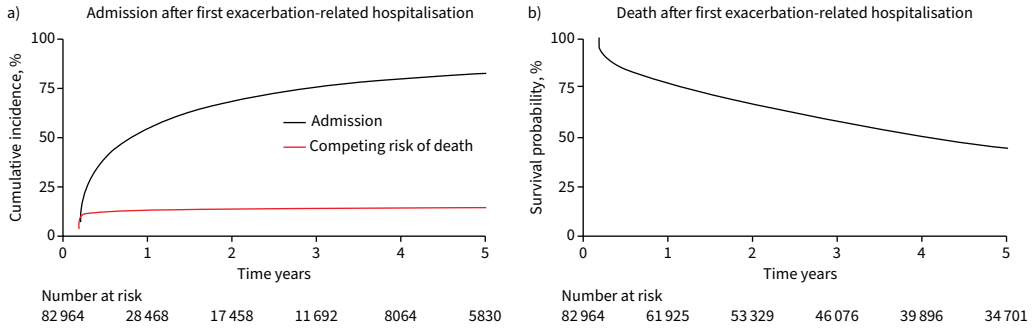

FIGURE 2 a) 5-year cumulative incidence of experiencing a first all-cause hospital admission after hospital discharge from the index event. b) 5-year survival probability.

These findings hold important implications for clinical practice, challenging the current global post-AECOPD management goals.

The most common nonrespiratory cause of hospital admission included cardiac events: ischaemic and pulmonary heart diseases were most common, followed by myocarditis, cardiomyopathy and arrhythmias. Indeed, cardiac diseases remain the leading cause of death worldwide [20]. With an estimated prevalence ranging from 30% to 60%, COPD and cardiac diseases frequently co-occur [21, 22]. This relationship is likely to be due to shared risk factors, such as smoking and low physical activity, as well as persistent low-grade pulmonary and systemic inflammation [21]. Additionally, cardiac-related conditions are important differential diagnoses of AECOPD, underlining the challenges associated with the current AECOPD definition [19]. Indeed, the question may arise as to what extent the index AECOPD may have been affected by pre-existing or concurrent cardiovascular diseases, and whether such cardiovascular diseases were misclassified as AECOPD during the index admission. The current real-world data reflect the diagnostic difficulties clinicians are faced with. Nevertheless, it is unlikely that such single misclassifications have had an impact on the outcomes of the current study, given its substantial cohort size. More so, we believe that these results are a true reflection of the impact of cardiac comorbidities on the need for hospitalisation in patients with COPD.

Research has pointed out that comorbidities, previous AECOPD and hospitalisations as well as an increased length of hospital stay are major risk factors for all-cause hospital readmission following exacerbation-related hospitalisation [9]. In line with previous studies [23], more than half of the patients in the current study had one or more pre-existing comorbidity. One might question whether these comorbidities, rather than the AECOPD *per se*, were the major driver of the observed subsequent hospital admission(s). Yet, previous research in patients with COPD showed that AECOPD confer an increased risk

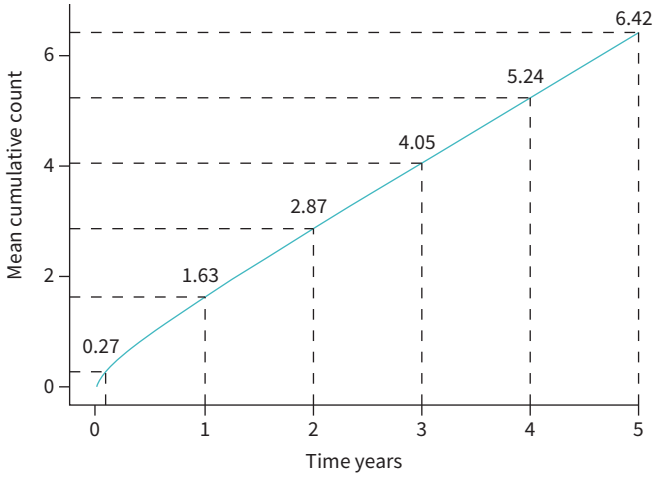

FIGURE 3 Mean cumulative count of subsequent hospital admissions during the 5-year follow-up.

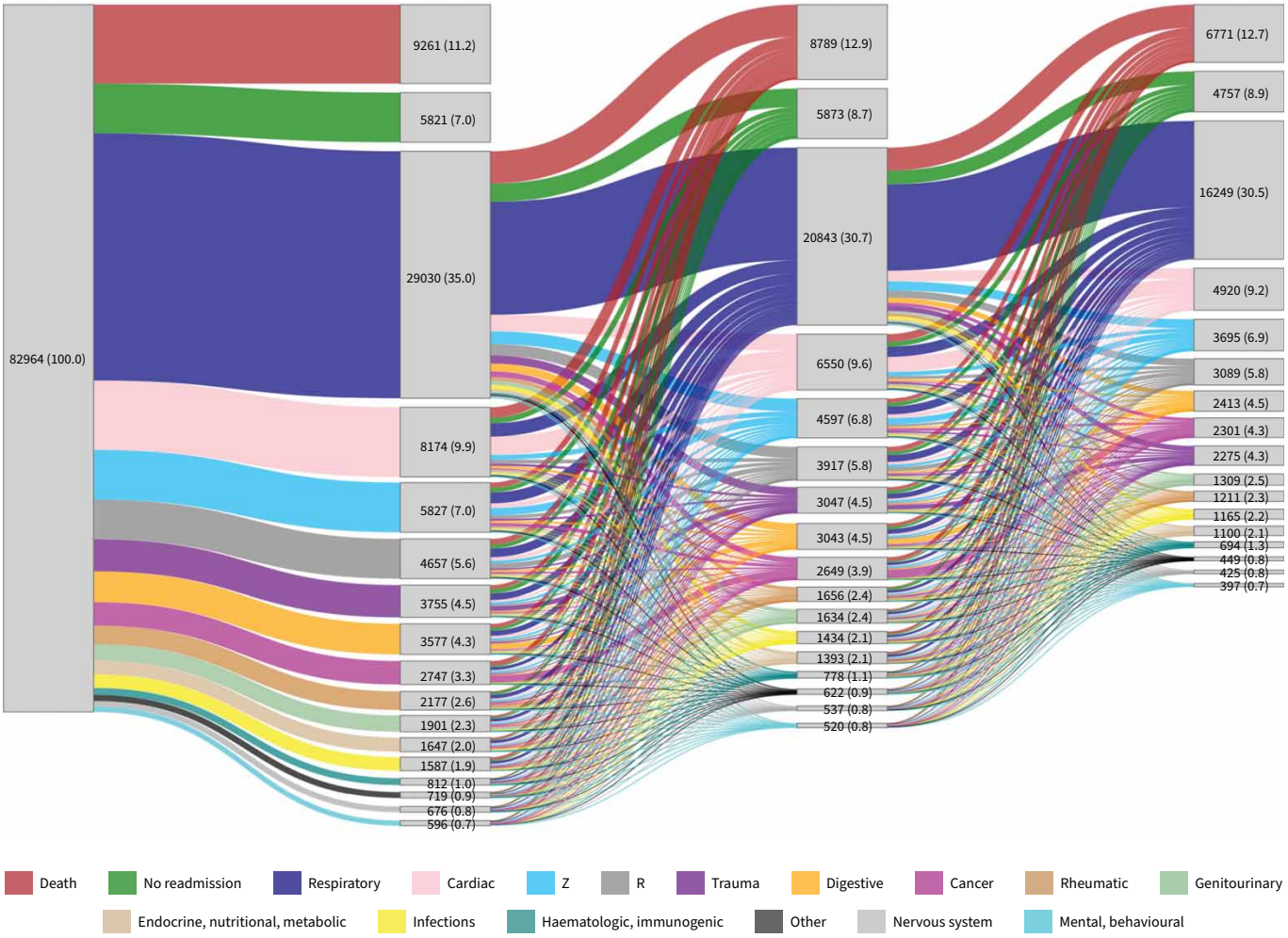

FIGURE 4 Sankey diagram displaying the diagnoses of the first three hospital admissions after the index event. Data are presented as n (%).

TABLE 2 Short-term (30 days post-discharge) *versus* long-term (5 years post-discharge) diagnoses of subsequent hospital admissions

	30-day	5-year
Total number of admissions	20 894	337 066
Respiratory	10 194 (48.8)	139 272 (41.3)
Cardiac	2419 (11.6)	36 586 (10.9)
Other	1900 (9.1)	33 149 (9.8)
Symptoms and signs not elsewhere classified	1406 (6.7)	25 551 (7.6)
Cancer	963 (4.6)	16 751 (5.0)
Digestive	854 (4.1)	18 621 (5.5)
Trauma	648 (3.1)	16 915 (5.0)
Infections	548 (2.6)	9180 (2.7)
Endocrine, nutritional, metabolic	544 (2.6)	8834 (2.6)
Genitourinary	530 (2.5)	10 655 (3.2)
Musculoskeletal or connective tissue	262 (1.3)	8917 (2.6)
Mental or behavioural	209 (1.3)	3678 (1.1)
Haematologic or immunogenic	245 (1.2)	5674 (1.7)
Nervous system	172 (0.8)	3283 (1.0)

Data are presented as n (%).

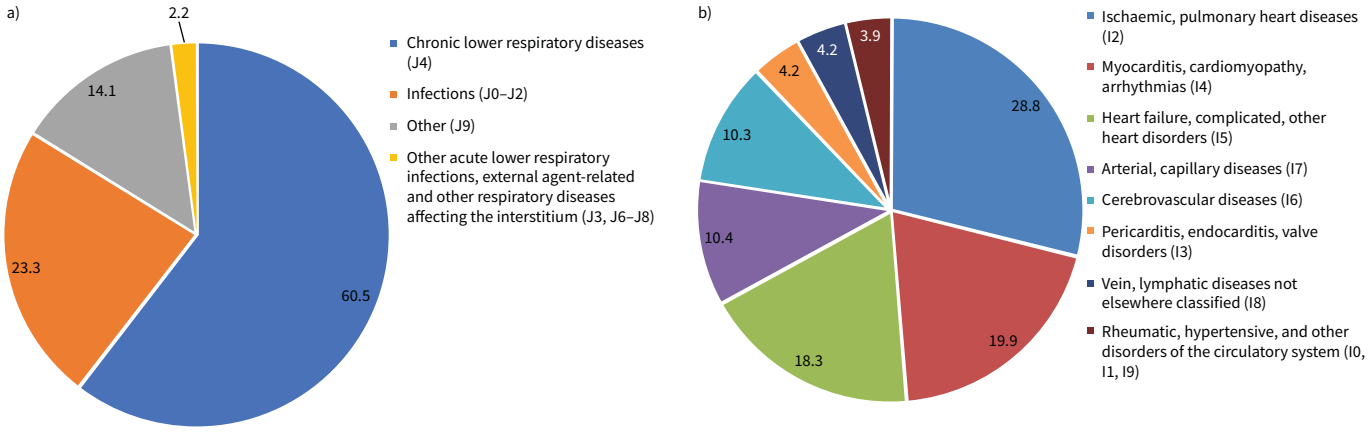

FIGURE 5 Specific diagnoses of the two most common causes of hospital admission at the end of the 5-year follow-up. Relative percentages of the total number of admissions are presented. a) Specific diagnoses of the 139 272 respiratory-related admissions. b) Specific diagnoses of the 36 586 cardiac-related admissions. International Classification of Diseases (10th Revision) codes are given in parentheses.

TABLE 3 Baseline characteristics of the frequently (four or more admissions) and less-frequently (three or fewer admissions) admitted patients during the 5-year follow-up period

	⩽3 admissions		⩾4 admissions		Total
	Alive	Dead	Alive	Dead	
Patients	**20 200**	**29 937**	**14 466**	**18 361**	**82 964**
Age, years, mean±SD	67.5±10.5	76.3±8.7	68.7±10.1	73.5±9.1	72.2±10.2
Sex					
Male	8484 (42.0)	15 173 (50.7)	6459 (44.6)	9600 (52.3)	39 716 (47.9)
Female	11 716 (58.0)	14 764 (49.3)	8007 (55.4)	8761 (47.7)	43 248 (52.1)
Education					
Lower secondary education	11 053 (58.0)	16 520 (63.6)	8097 (59.6)	10 230 (61.7)	45 900 (61.0)
Upper secondary education	6182 (32.4)	7376 (28.4)	4365 (32.1)	5062 (30.5)	22 985 (30.6)
Tertiary education or bachelor's degree	1540 (8.1)	1668 (6.4)	970 (7.1)	1068 (6.4)	5246 (7.0)
Master's or Doctoral degree	295 (1.5)	397 (1.5)	162 (1.2)	229 (1.4)	1083 (1.4)
Total	19 070	25 961	13 594	16 589	75 214
Cohabitation status					
Living alone	9473 (47.0)	13 305 (62.1)	7204 (49.8)	9783 (54.6)	39 765 (53.8)
Living together	10 677 (53.0)	8111 (37.9)	7253 (50.2)	8137 (45.4)	34 178 (46.2)
Total of cohabitation status	20 150	21 416	14 457	17 920	73 943
Inhaled medication					
SABA	2033 (10.1)	2363 (7.9)	1264 (8.7)	1500 (8.2)	7160 (8.6)
LAMA	987 (4.9)	1746 (5.8)	722 (5.0)	1035 (5.6)	4490 (5.4)
LABA	705 (3.5)	909 (3.0)	495 (3.4)	595 (3.2)	2704 (3.3)
ICS	2306 (11.4)	2562 (8.6)	1511 (10.4)	1726 (9.4)	8105 (9.8)
LAMA/LABA	231 (1.1)	382 (1.3)	216 (1.5)	291 (1.6)	1120 (1.3)
LAMA/ICS or LABA/ICS	4112 (20.4)	5705 (19.0)	3306 (22.8)	3908 (21.3)	17 031 (20.5)
Triple therapy	2582 (12.8)	4764 (15.9)	2510 (17.4)	3654 (19.9)	13 510 (16.3)
Total	12 956 (64.1)	18 431 (61.6)	10 024 (69.3)	12 709 (69.2)	54 120 (65.2)
No treatment	7244 (35.9)	11 506 (38.4)	4442 (30.7)	5652 (30.8)	28 844 (34.8)
Number of comorbidities					
0	12 843 (63.6)	9597 (32.1)	6683 (46.2)	6133 (33.4)	35 256 (42.5)
1	4400 (21.8)	7594 (25.4)	3855 (26.6)	4650 (25.3)	20 499 (24.7)
2	1825 (9.0)	5675 (19.0)	2064 (14.3)	3337 (18.2)	12 901 (15.6)
⩾3	1132 (5.6)	7071 (23.5)	1864 (12.9)	4241 (23.1)	14 308 (17.2)
Characteristics of the index event, median (interquartile range)					
Time until discharge, days	3 (1–7)	6 (2–10)	4 (1–7)	5 (2–8)	4 (2–8)
Time until death, days		177 (20–656)		969 (566–1379)	

Data are presented as n (%) unless otherwise stated. SABA: short-acting β_2-agonist; LAMA: long-acting muscarinic antagonist; LABA: long-acting β_2-agonist; ICS; inhaled corticosteroid.

of subsequent cardiovascular events, regardless of pre-existing cardiac comorbidities [24]. The current findings may therefore substantiate the previously identified increased risk of cardiovascular events following AECOPD.

Other nonrespiratory causes of hospital admission included cancer, digestive and genitourinary disorders. Close to one-third of the cancer-related admissions were driven by malignancies of the respiratory and intrathoracic organs. Indeed, patients with COPD are at high risk of lung cancer, irrespective of smoking status [25]. However, digestive and genitourinary related admissions are unreported in the current literature. Future studies are indicated to explore the mechanisms linking these types of admissions to AECOPD.

Respiratory-related admissions contributed to less than half of the observed admissions. The majority could be attributed to chronic lower respiratory diseases followed by acute respiratory infections. It is well recognised that a history of AECOPD predisposes patients to subsequent AECOPD [3] and that respiratory infections trigger these events [26]. Indeed, the majority of the observed respiratory admissions was exacerbation related.

Besides their cause, it is essential to understand the timing and rates of hospital admissions whilst striving to reduce their occurrence. The current study showed that most patients experienced their first hospital admission within the first year after hospital discharge from the index event. A linear increase in the cumulative average of the total number of admissions was observed over time. By the end of follow-up, the average number of admissions was six per patient. These findings underline the need for close monitoring, especially in the first year after AECOPD hospital discharge.

We noted an in-hospital mortality rate of 5.5% during the index event. This is in line with previously reported in-hospital mortality rates of first ever hospitalised AECOPD [27, 28]. Importantly, although mortality rates are heterogeneous across studies, similar in-hospital mortality rates were reported among patients with a (severe) AECOPD history [4]. Moreover, the observed long-term mortality rates are in accordance with previous reports [29, 30], underlining the external validity of our findings. Thus, the prognosis of patients with COPD at their first exacerbation-related hospitalisation may be as poor as during subsequent events, both during and after hospitalisation.

A substantial part of the population had died after fewer than four subsequent admissions. We noted that, consistent with the general population [31], the worst prognosis (*i.e.* death) was not necessarily related to the number of admissions but rather to an older age, a higher number of comorbidities and a longer duration of hospital stay during the index event. These findings highlight the need to incorporate these well recognised risk factors of mortality after exacerbation-related hospitalisation in discharge planning [32]. Moreover, >30% of patients did not use inhaled medication prior to the index event. This group includes patients without a prior diagnosis of COPD and nonadherent patients, indicating a need for earlier diagnosis and improved adherence. It may also represent a group of patients with mild disease, who have not received treatment for COPD. The likelihood of another respiratory admission may therefore be less likely, which could have contributed to the observed high number of nonrespiratory admissions. However, our findings do underline that morbidity in COPD may not only be contributed to the disease itself.

Several strengths and limitations should be noted. A major strength of the current study was its unique national hospital dataset covering all first-time exacerbation-related hospitalisations in Denmark between 2000 and 2014. The substantial sample size and follow-up period allowed us to study the nationwide all-cause hospital admission trajectories following this index event. At the same time, the dataset presented important limitations. First, the dataset was administrative and did not include certain clinical data (*e.g.* spirometry). The current definition used to characterise a (first) exacerbation-related hospitalisation has been widely used in Danish registry research and was previously validated (*i.e.* >90% positive predictive value) [15]. Yet, some inaccuracy is introduced, which should be taken into consideration when interpreting the results. Furthermore, this study did not differentiate between less severe and very severe hospital admissions. To limit this bias, only admissions to a department with 24-h surveillance were counted. Moreover, ∼10% of patients had died after each hospital admission, which may indicate that these events likely were less severe. In this view, whilst a control population was missing, the prognosis of more severe procedures is worse for patients with COPD than for patients without COPD [33].

Taken together, we showed that all-cause hospital admissions following a first exacerbation-related hospitalisation are common and predominantly caused by nonrespiratory events. Hence, besides the respiratory causes, treatment targeting the nonrespiratory causes of hospital admission should be considered in order to effectively decrease the burden of hospitalisation in COPD. Awareness amongst clinicians

should be raised to screen patients proactively and comprehensively before hospital discharge, and to monitor patients accordingly post-discharge. The current findings show that, particularly, cardiac comorbidities should be monitored. This knowledge should be included in the patient's written action plans.

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