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Diagnostic and therapeutic gaps in Chronic Obstructive Pulmonary Disease management and their associations with 1-year survival after hospitalisation for acute exacerbations

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Summary

INTRODUCTION AND OBJECTIVES: Chronic Obstructive Pulmonary Disease (COPD) remains a leading cause of morbidity and mortality globally. Acute exacerbations of COPD (AE-COPD) significantly worsen patient outcomes; however, COPD is frequently underdiagnosed and undertreated despite established guidelines.This study aimed to assess (1) the characteristics of patients hospitalised for a first episode of AE-COPD, (2) the differences between patients who had received guideline-recommended inhalation therapy prior to their first AE-COPD hospitalisation and those who had not, and (3) the associations between patient characteristics, pre-hospital inhalation treatment status and 1-year all-cause mortality following the index hospitalisation.

METHODS: In this retrospective cohort study, 1855 consecutive patients admitted with clinically and spirometrically diagnosed AE-COPD to a secondary-level Swiss hospital between September 2016 and September 2024 were analysed. The primary outcome was 1-year all-cause mortality following the index hospitalisation. Survival was analysed using Kaplan-Meier estimates and Cox proportional hazards regression, with results reported as hazard ratios with 95% confidence intervals.

RESULTS: Overall, 50.6% (n = 938) of patients lacked documented spirometric GOLD staging and 82.6% (n = 1533) had no recorded risk classification. Patients were stratified based on pre-admission use of long-acting inhalation therapy: Group 1 (no therapy, n = 834 [45.0%]) and Group 2 (therapy, n = 1021 [55.0%]). Baseline characteristics were largely comparable between groups; however, patients receiving long-acting inhalation therapy (Group 2) had significantly more patients with spirometrically confirmed COPD. During 1-year follow-up, 236 deaths (12.7%) occurred, in 133 of the 834 (15.9%) Group 1 patients and 103 of the 1021 (10.1%) Group 2 patients (log-rank p <0.001). In multivariable Cox regression analysis, no long-acting inhalation therapy (Group 1) as a variable was independently associated with higher 1-year all-cause mortality (adjusted HR: 1.95, CI: 1.48–2.56, p <0.001).

CONCLUSION: Significant diagnostic and therapeutic gaps were observed in patients hospitalised for the first episode of AE-COPD. Guideline-recommended inhalation therapy prior to hospitalisation was independently associated with decreased 1-year all-cause mortality. Our findings suggest that guideline-recommended inhalation therapy reflects structured COPD care, earlier diagnosis and closer medical follow-up rather than a pharmacological effect alone. Hospitalisation for AE-COPD represents a critical opportunity to reassess the diagnosis and optimise long-term management, even within a well-resourced healthcare system.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death globally [1] and imposes a significant economic burden due to lost work productivity and healthcare costs [2]. Beyond the daily symptom burden, acute exacerbations of COPD (AE-COPD) substantially increase the overall impact of the disease on both patients and healthcare systems [3]. Exacerbations are

linked to accelerated lung function loss, particularly in those with mild disease [4]. COPD is a progressive respiratory condition that requires accurate diagnosis and classification to ensure appropriate treatment; diagnosis is based on spirometry and further categorized into risk classes based on the severity of symptoms and the history of exacerbations [5].

Primary care serves as the cornerstone of COPD management [6]. However, estimates from the year 2018 showed that approximately two-thirds of patients with COPD worldwide are underdiagnosed [7]. A population-based study conducted in Spain in the year 2000 involving over 4,000 participants reported an underdiagnosis rate of 78.2% among individuals with COPD, with only 71.1% of diagnosed cases receiving appropriate treatment [8]. Similarly, a 2023 study from Sweden found that more than 80% of COPD cases were underdiagnosed among a cohort of 128 patients [9]. Additionally, a United States analysis found higher mortality in undiagnosed COPD patients [10].

Despite significant advancements in pharmacological therapies and clinical guidelines, the persistent issues of underdiagnosis, undertreatment and poor adherence to inhalation therapies underscore the need for improved COPD management. Evidence strongly suggests that adherence to inhalation therapy reduces severe exacerbations [5]. However, most research has focused on outpatient populations, while data on inpatient management of AE-COPD remain scarce. Hospitalisation represents a critical stage in the disease course, associated with substantial healthcare costs and increased mortality and morbidity [11]. Previous national audits indicated gaps in inpatient COPD care and guideline adherence [12], further highlighting the need for studies in this setting.

The present study therefore assesses (1) the characteristics of patients hospitalised for a first episode of AE-COPD, (2) the differences between patients who had received guideline-recommended inhalation therapy prior to their first AE-COPD hospitalisation and those who had not, and (3) the associations between patient characteristics, pre-hospital inhalation treatment status and 1-year all-cause mortality following the index hospitalisation.

Methods

This was a non-randomised retrospective cohort study conducted at Buergerspital Solothurn, a secondary-level hospital in Switzerland. The study was conducted between September 2016 and September 2024 in a clinic for general internal medicine that cooperates with pulmonologists on an in- and outpatient basis. The study is reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [13].

Data collection

The patient sample was identified retrospectively from the electronic medical record system (KISIM, Cistec AG, Zurich, Switzerland) using a two-step automated search: (1) text entries of AE-COPD documented by treating physicians in discharge reports and (2) diagnostic codes for AE-COPD from the billing system (International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10): J44. Only primary diagnoses were included. Data quality was ensured by subsequent manual validation: all cases were reviewed for diagnosis, completeness and consistency. Missing variables were supplemented. All identified cases were exported into REDCap for data management.

ABBREVIATIONS
ACOS Asthma-COPD-Overlap Syndrome
AE-COPD acute exacerbation of COPD
COPD Chronic Obstructive Pulmonary Disease
GOLD Global Initiative for Chronic Obstructive Lung Disease
ICS inhaled corticosteroid
ICU intensive care unit
IQR interquartile range
LABA long-acting β_2-agonist
LAMA long-acting muscarinic antagonist
LTOT long-term oxygen therapy
PDE-4-I phosphodiesterase-4 inhibitor

The protocol was approved by the local ethics committee (Project-ID 2024-02509). No separate study protocol was prepared, as this was a retrospective cohort study. The predefined outcomes were specified in the ethics application. The study was not registered in a trial registry. The outcome was expanded from in-hospital mortality to 1-year follow-up on the basis of one reviewer's comments.

Inclusion / Exclusion criteria

Consecutive adult patients (≥18 years) admitted to the medical ward with clinically and spirometrically diagnosed AE-COPD as the main diagnosis between 1 September 2016 and 30 September 2024 were eligible for inclusion. Patients who had declined general consent and those identified through automated screening but found not to have AE-COPD as the primary diagnosis upon manual review were excluded.

Sample size calculation

We planned a sample size of at least 723 patients per group (totaling 1'446 patients) with 80% power, 5% level of significance, a mortality rate of 15% due to AE-COPD based on literature, and an estimated difference in mortality between groups of 5% [14–18]. The sample size was estimated based on an expected difference in 1-year all-cause mortality proportions between groups (fixed-time comparison at 365 days). Time-to-event analyses (Kaplan-Meier and Cox regression) were subsequently used to account for varying event times within the 1-year follow-up and to enable multivariable adjustment.

Exposure

All enrolled patients were stratified into two groups according to their pre-admission inhalation therapy. Information on pre-admission therapy was obtained from the official medication lists documented at hospital entry, representing the current long-term outpatient treatment. Groups were defined as follows: Group 1 comprised patients who were not receiving long-acting inhalation therapy or only short-acting agents, while Group 2 included those who had been on guideline-recommended long-acting inhalation therapy. Guideline-recommended inhalation therapy was defined by the use of long-acting inhalation therapy, which included monotherapy with long-acting β2-agonists (LABA) or long-acting muscarinic antagonists (LAMA); dual-combination therapy with LABA/LAMA or LABA/inhaled corticosteroids (ICS); or triple-combination therapy with LABA/LAMA/ICS [19, 20].

Clinical management during hospitalisation

Acute exacerbations were managed according to local standards based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations [21] and national Swiss guidance [22]: systemic corticosteroids (oral prednisolone 40–50 mg once daily for up to 5 days), oxygen supplementation, short-acting bronchodilators and physiotherapy when feasible. Antibiotic therapy was initiated when Anthonisen criteria were met, in line with guideline recommendations [23].

Discharge management followed routine clinical practice. Patients were either continued on inpatient treatment or transitioned to an outpatient regimen once clinical improvement was achieved. Discharge medication was prescribed at the discretion of the treating physicians. Follow-up with the patient's general practitioner was routinely arranged, including written recommendations on further management and referral to a pulmonologist when indicated.

Measurements and variables

All included patients had a diagnosis of COPD recorded in the electronic health record. Whenever available, spirometry results were used; in patients without spirometry prior to the index hospitalisation, the diagnosis was based on clinical assessment by the treating physicians in accordance with GOLD recommendations, reflecting real-world clinical practice.

Comorbidities were recorded according to the GOLD report (heart failure, ischaemic heart disease, arrhythmias, arterial hypertension, pulmonary hypertension, peripheral vascular disease, obstructive sleep apnoea, diabetes mellitus, osteoporosis, anaemia, polycythaemia, depression, cognitive impairment, frailty and lung cancer) and, additionally, the Charlson Comorbidity Index (cerebrovascular disease, diabetes mellitus with end-organ damage, hemiplegia, connective tissue disease, liver disease, kidney disease, any tumour, leukaemia, lymphoma and metastatic cancer) [19, 24]. All variables were collected at hospital admission or events occurring during the index

hospitalisation. Additional variables collected included (1) smoking status, previous pulmonary rehabilitation, and already-established long-term oxygen therapy (LTOT), phosphodiesterase-4-inhibitor (PDE-4-i), theophylline, macrolides and spacer, and (2) occurrences during index hospitalisation or data from initial emergency presentation (pneumonia, antibiotic treatment, stay on the intensive care unit [ICU], white blood cells, C-reactive protein, acidosis, mean arterial pressure and oxygen saturation).

Outcomes and follow-up

The primary outcome was 1-year all-cause mortality following the index hospitalisation for AE-COPD. Mortality data were obtained from the electronic health record. Follow-up was complete for all patients, with censoring at day 365 after discharge from index hospitalisation to assess survival status. Secondary outcomes explored associations between patient characteristics, guideline-recommended inhalation therapy and 1-year all-cause mortality.

Statistical analysis

Baseline characteristics were summarised as means with standard deviations (SD) or medians with interquartile ranges (IQR) for continuous variables, and as counts with percentages for categorical variables. Group comparisons were performed using independent t-tests for continuous variables and chi-squared tests for categorical variables.

Time-to-event analyses were conducted for the primary outcome. Survival was described using Kaplan-Meier curves and compared between groups using the log-rank test. Univariable associations between variables and 1-year all-cause mortality were assessed using Cox proportional hazards regression models and are reported as hazard ratios (HR) with 95% confidence intervals (CI). A multivariable Cox proportional hazards regression model was performed adjusted for the following variables on 1-year all-cause mortality: age, sex, severe GOLD status (spirometrically diagnosed GOLD 3 and 4), heart failure, ischaemic heart disease, pulmonary hypertension, diabetes mellitus, moderate-severe kidney disease, lung cancer, pneumonia, antibiotic treatment, ICU, acidosis, C-reactive protein, mean arterial pressure and the grouping variable (Group 1: no long-acting inhalation therapy vs Group 2: long-acting inhalation therapy). Effect estimates from the multivariable model were reported as adjusted HRs with 95% CI.

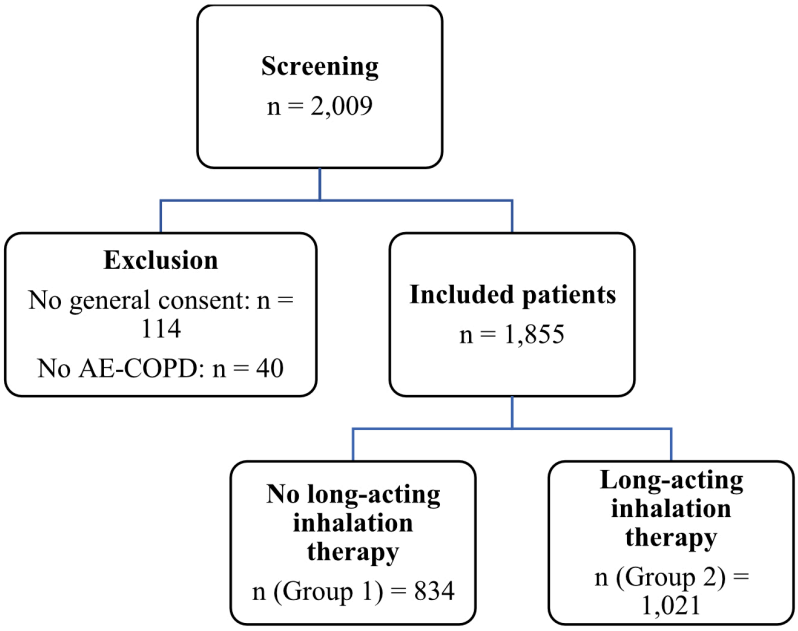
Missing data for baseline characteristics were reported. No imputation was performed for the multivariable survival analysis: only variables with complete-case data were used. In an exploratory analysis, we assessed the association between inhaled corticosteroid use, defined as a pre-admission inhalation regimen containing an inhaled corticosteroid component, and pneumonia incidence in a univariable analysis reported as an odds ratio (OR) with 95% CI. All statistical analyses were conducted using jamovi software (version 2.6.44, additional packages: *jsurvival* and *clinicopath*), with a two-sided significance threshold set at $p < 0.05$.

Results

Baseline characteristics

Overall, 1855 patients were included in the study (figure 1), with 834 (45.0%) patients without and 1021 (55.0%) patients with guideline-recommended long-acting inhalation therapy prior to hospitalisation. Baseline characteristics are listed in table S1 in the appendix. Patients were aged on average 72 years (SD: ±11.3) with a body mass index (BMI) of 25.6 kg/m^2 (IQR: 7.6, reported on available cases, missing values for 87 patients [4.7%]). In total, there were more male than female patients: 1058 (57.0%) vs 797 (43.0%). The GOLD stage was undocumented in 938 patients (50.6%), with a significantly higher proportion of missing data in Group 1 compared to Group 2 (66.5% vs 37.5%, $p < 0.001$). Advanced GOLD stages (3 and 4) were more frequently observed in Group 2 (29.5%) than in Group 1 (9.8%, $p < 0.001$). Similarly, risk classification was not documented in 1533 patients (82.6%), with a higher proportion of missing data in Group 1 (91.6% vs 75.3%, $p < 0.001$).

Figure 1: Study design.



For comorbidities, heart failure (40.3% vs 35.6%, p = 0.038), pulmonary hypertension (10.1% vs 13.5%, p = 0.026), obstructive sleep apnoea (12.2% vs 16.3%, p = 0.014), moderate-severe kidney disease (10.0% vs 15.7%, p <0.001) and Asthma-COPD-Overlap Syndrome (ACOS) (1.8% vs 7.8%, p <0.001) were significantly less frequently observed in Group 1 than in Group 2. In contrast, cognitive impairment (9.2% vs 4.6%, p <0.001), cerebrovascular disease (6.8% vs 4.1%, p = 0.012) and moderate-severe liver disease (1.3% vs 0.4%, p = 0.035) were significantly more frequently reported in Group 1 than in Group 2. There were no significant differences for the following comorbidities: arterial hypertension, ischaemic heart disease, arrhythmia, peripheral vascular disease, lung cancer, diabetes mellitus with and without end-organ damage, osteoporosis, anaemia, polycythaemia, anxiety and depression, frailty, connective tissue disease, mild liver disease, hemiplegia, any tumour, leukaemia, lymphoma and metastatic cancer.

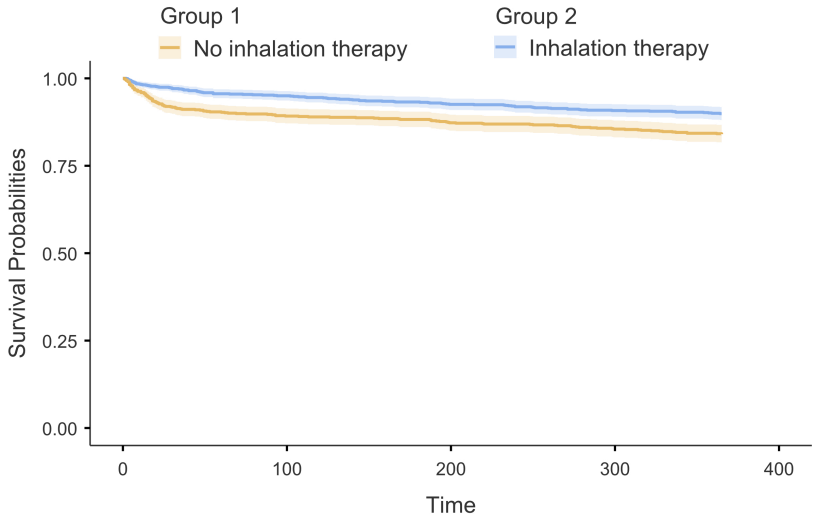
Further, no significant differences were observed between groups in terms of pulmonary rehabilitation, pack-years (reported on available cases, missing values for 836 patients [45.1%]), use of theophylline, macrolides or spacers. However, significant differences were found in the use of LTOT, smoking cessation support, PDE-4-i and long-acting inhaled corticosteroids.

During the index hospitalisation, there were fewer cases with prescribed antibiotic treatment in Group 1 than in Group 2 (20.6% vs 26.3%, p = 0.004). There were no significant differences between groups for: pneumonia, ICU, white blood cells, C-reactive protein, acidosis, mean arterial pressure and oxygen saturation.

Outcomes

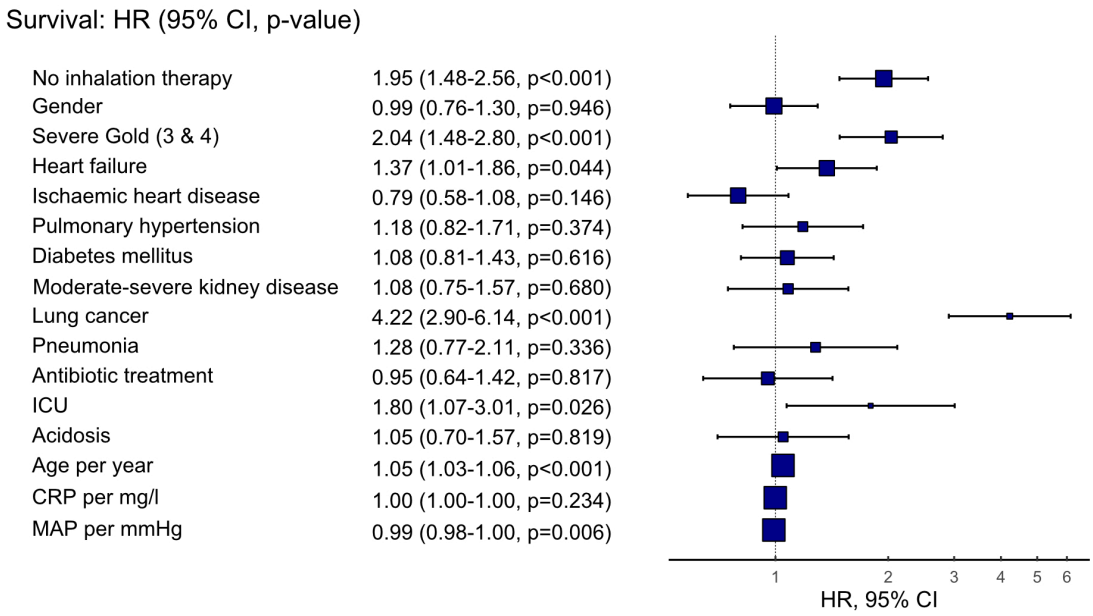
The Kaplan-Meier survival curves (figure 2) demonstrate a significantly higher survival probability in patients receiving guideline-recommended inhalation therapy (Group 2) compared to those without guideline-recommended inhalation therapy (Group 1) throughout the 1-year follow-up period. In total, 236 deaths (12.7%) occurred: in 133 of the 834 (15.9%) patients in Group 1 and 103 of the 1021 (10.1%) patients in Group 2. The difference between groups was statistically significant in the log-rank test (χ^2 = 15.0, df = 1; p <0.001).

Figure 2: Kaplan-Meier survival curve. X-axis denotes time in days (censored at day 365). Y-axis denotes survival probability. Group 1: no inhalation therapy. Group 2: inhalation therapy. A total of 236 events (12.7%) occurred: 133 among the 834 patients (15.9%) in Group 1 and 103 among the 1021 patients (10.1%) in Group 2. The difference between groups was statistically significant in the log-rank test (χ^2 = 15.0, df = 1; p <0.001).



Unadjusted, univariable results between variables and 1-year all-cause mortality are reported in table S2 in the appendix. In the multivariable Cox regression analysis between variables and 1-year all-cause mortality with reported adjusted HRs (see figure 3 and table S2 in the appendix), the treatment group independently showed a significant association with 1-year all-cause mortality (HR: 1.95; 95% CI: 1.48–2.56; p <0.001). Further variables with independent significant associations with 1-year all-cause mortality in adjusted analyses were:severe GOLD stage (GOLD 3 or 4, HR: 2.04; 95% CI: 1.48–2.80; p <0.001), heart failure (HR: 1.37; 95% CI: 1.01–1.86, p = 0.044), lung cancer (HR: 4.22; 95% CI: 2.90–6.14; p <0.001), ICU (HR: 1.80, 95% CI: 1.07–3.01; p = 0.026) and higher age per year (HR: 1.05; 95% CI: 1.03–1.06; p <0.001). Higher mean arterial pressure per point mmHg was significantly associated with lower 1-year all-cause mortality (HR: 0.99; 95% CI: 0.98–1.00, p = 0.006). There was no significant association found for sex, ischaemic heart disease, pulmonary hypertension, diabetes mellitus, moderate-severe kidney disease, pneumonia, antibiotic treatment, acidosis and C-reactive protein.

Figure 3: Forest plot for multivariable Cox regression analysis with listed variables on 1-year all-cause mortality after index hospitalisation for AE-COPD, reported as adjusted hazard ratio. Variable 1: Grouping variable where Group 1 = no inhalation therapy (reference), Group 2 = inhalation therapy (comparator). Interpretation: The reference group (Group 1) shows a significantly higher HR than the comparator group (Group 2). CI: confidence interval; CRP: C-reactive protein; HR: hazard ratio; ICU: intensive care unit; MAP: mean arterial pressure.



Incidence of pneumonia and inhaled corticosteroids

Among patients with inhaled corticosteroid-based therapy (n = 521), the incidence of pneumonia was 10.8% (56 cases) compared to 12.0% (160 cases) in patients without inhaled corticosteroid use (n = 1334). In the univariable analysis, the odds ratio of pneumonia was not significantly different between groups (OR: 0.88; 95% CI: 0.6–1.2; p = 0.47).

Table 1: Univariable analysis including odds ratio between use of inhaled corticosteroids and pneumonia incidence.

Variables (n, [%])	Pneumonia (+)	Pneumonia (-)	Pneumonia incidence (%)	Univariable analysis		
				OR	CI	p-value
ICS users	56 [3.0%]	465 [25.1%]	10.8%	0.88	(0.6;1.2)	0.47
Non-ICS users	160 [8.5%]	1174 [63.3%]	12.0%			

CI: confidence interval; ICS: inhaled corticosteroid; OR: odds ratio.

Subgroup analysis

In a subgroup analysis restricted to patients with spirometrically confirmed COPD, the Kaplan-Meier survival curves showed a comparable separation between groups (see figure S1 in the appendix). The association between prior inhalation therapy and improved 1-year survival remained consistent.

Discussion

This study characterises patients at their first recorded hospitalisation for AE-COPD in a real-world, single-centre cohort in Switzerland, which operates in a well-developed healthcare system [25]. We found that 50.6% and 82.6% of patients admitted with AE-COPD had no documented GOLD stage or risk classification, respectively. Further, 45.0% of patients did not have any guideline-recommended inhalation therapy prior to admission. These findings highlight ongoing diag-

nostic and therapeutic challenges in the management of COPD, though it remains unclear whether these deficits stem from provider practices or patient adherence. The burden of comorbidities was high, particularly cardiovascular disease and malignancy, which is consistent with previous reports describing COPD as a multimorbid condition [19, 26]. These findings suggest that a considerable proportion of patients enter the hospital system with insufficient prior diagnostic work-up and incomplete disease characterisation, limiting risk stratification and potentially delaying appropriate management.

Patients with guideline-recommended long-acting inhalation therapy prior to hospitalisation differed only modestly in baseline characteristics from those without prior inhalation therapy, supporting overall comparability between groups. Patients receiving inhalation therapy tended to have more advanced COPD, yet showed lower 1-year all-cause mortality. This apparent paradox argues against a simple confounding by disease severity and suggests that prior inhalation therapy may serve as a surrogate marker for better integration into structured COPD care due to the healthy adherer effect [27]. Such patients are more likely to have established diagnoses, and higher adherence and physician awareness, rather than benefiting solely from the pharmacological effect of inhalation therapy.

The Kaplan-Meier survival curves showed higher early mortality during the one-year follow-up among patients without prior inhalation therapy. The early divergence suggests that the risk is concentrated in and around the hospitalisation phase, aligning with literature describing AE-COPD as a critical event [19, 28]. The curves then become parallel, potentially indicating intensified follow-up and an improvement in diagnostic and therapeutic management after hospitalisation. In our cohort, prior inhalation therapy remained independently associated with lower one-year all-cause mortality, alongside established prognostic factors such as age, severe GOLD stages, ICU admission, and relevant comorbidities [19]. These findings confirm the concept that AE-COPD is not merely an acute event but a marker of vulnerability, where post-discharge management and continuity of care may be decisive for survival.

Despite the advantages of a highly accessible healthcare infrastructure, continued efforts to reduce smoking and advancements in COPD care, the disease remains underdiagnosed and undertreated, with a substantial burden of comorbidity. It is likely that these gaps may be even more pronounced in countries with less developed healthcare systems. Our data further indicate that guideline-based care, particularly regarding routine spirometry and stepwise intensification of inhalation therapy, is not yet fully integrated into daily clinical practice. The findings further suggest a heterogeneous patient population: some with confirmed spirometric diagnoses but poor treatment adherence, and others with clinically diagnosed COPD managed by primary care, yet receiving guideline-recommended inhalation therapy.

Comparison with existing literature

Our findings are consistent with previous studies that have highlighted the underdiagnosis and the undertreatment of COPD [7-9]. However, whereas prior research has primarily focused on outpatient populations, our study extends these observations to the inpatient setting. A significant proportion of hospitalised patients lacked documented GOLD staging, had no recorded risk classification, or were documented in risk categories (A or B) that are inconsistent, as hospitalisation for AE-COPD inherently places patients into Group E since GOLD 2023 revision (formerly GOLD Group C/D). Inadequate disease stratification in this context may have significant consequences for both therapeutic decision-making and patient prognosis [29].

Our findings align with Diab et al., who reported significant underdiagnosis and poor documentation in real-world settings, especially in primary care [7]. Patients with prior guideline-recommended inhalation therapy had a significantly lower one-year all-cause mortality rate, despite having more advanced disease stages and comparable comorbidities. This protective association is supported by Suissa et al., who demonstrated that inhalation therapy reduces mortality and severe exacerbations [30]. The decision to add antibiotic treatment to AE-COPD was significantly higher in Group 2, yet the cofactors during hospitalisation remained similar. Rello et al. showed that COPD patients are more likely to receive antibiotics, independent of pneumonia diagnosis [31]. We explain this phenomenon by a higher level of clinical vigilance; however, the possibility of overtreatment remains. Interestingly, despite concerns in previous studies [32] about an increased pneumonia risk with inhalation ICS use, our findings did not demonstrate any association between ICS-based regimens and pneumonia incidence in univariable analysis. Compared with previous Swiss audits, our documentation rate was lower than in the recent single-centre audit [12], but higher

than in the Swiss subset of the European COPD Audit [33]. This likely reflects a higher proportion of first COPD diagnoses or clinically suspected cases without prior spirometric confirmation in our cohort. The comorbidity rates are comparable to those in national registries [33].

The inpatient setting represents both a challenge and an opportunity in COPD care. Hospitalisation for AE-COPD is associated with high short-term mortality but also offers a key moment to reassess diagnosis, optimise inhalation therapy, and initiate supportive measures such as smoking cessation or referral to rehabilitation [34, 35]. Structured inpatient pathways showed trends for improving guideline-conform care [36]. We argue that several factors may explain the high rate of undocumented GOLD staging and risk classification at the time of the index hospitalisation. Outpatient diagnostic pathways seem to be insufficiently established, meaning that many patients are hospitalised for the first time without prior spirometry or risk assessment. During the index hospitalisation, which is dominated by acute management, comprehensive diagnostics such as spirometry are frequently not feasible, particularly in severely ill patients. On the provider side, poor adherence by patients in the outpatient setting may contribute to underutilisation of long-acting inhalation therapy. We therefore argue that hospitalisation has to serve as a turning point to efficiently address these gaps.

Implications for research and clinical practice

The high proportions of patients without documented GOLD staging, risk classification or guideline-recommended inhalation therapy at the time of first AE-COPD hospitalisation highlight substantial diagnostic and therapeutic inadequacies in routine clinical care. Systematic use of spirometry and structured disease management should be reinforced in the outpatient setting and, where feasible, referrals initiated during hospitalisation. Clinical efforts should not only focus on prescribing guideline-recommended inhalation, but also on ensuring continuity of care, treatment escalation when indicated and adherence over time. Additionally, the high prevalence of comorbidities in COPD patients highlights the need for integrated care models that address multimorbidity in COPD management.

Future clinical research needs to strengthen patient adherence to therapy by addressing misconceptions, knowledge gaps and barriers to adherence. Further, the role of comorbidities in COPD patients and the barriers to treatment adherence from the patient's point of view need to be explored.

Strengths and limitations

The large sample size and the real-world setting enhance the generalisability of the findings. The potential for missing data concerning spirometric COPD diagnosis was considered low due to the hospital's geographical location (catchment area) and due to close collaboration with regional pulmonologists with regular transfer of patient information: the hospital routinely admits all patients with AE-COPD (usually no transfer to e.g. tertiary hospital necessary); and for AE-COPD patients, referral pathways are well established without competing hospitals within the immediate geographic area.

However, the retrospective observational design limits causal inference, and all results should be interpreted as associations. Although standardised data extraction with predefined protocols and manual record validation were applied to minimise information bias, reliance on routine clinical documentation may have resulted in misclassification. Residual confounding cannot be excluded. Furthermore, false-negative cases of COPD not captured by electronic queries could not be systematically quantified. Detailed information on discharge medication, structured follow-up, duration of pre-admission inhalation therapy and treatment adherence was not available: medication status at admission reflected current outpatient prescriptions but did not permit conclusions regarding long-term use or adherence. Outcomes may be confounded due to missing data for smoking status and pack-years; however, the extent of missingness for these variables paralleled missing GOLD classifications, suggesting that incomplete documentation primarily occurred in patients without spirometric confirmation of COPD, in whom disease severity and related parameters were generally less comprehensively recorded.

Finally, patients receiving guideline-recommended inhalation therapy had more advanced COPD yet demonstrated better outcomes. This apparent paradox, as previously prescribed, likely reflects differences in healthcare utilisation and medical supervision rather than a pharmacological effect alone, and may partially explain the observed survival advantage.

Conclusion

In this study, we found that 45.0% of patients hospitalised with AE-COPD had no prior guideline-recommended inhalation therapy, 50.6% had no documented GOLD staging and 82.6% had not undergone formal risk stratification. Overall, we saw a high comorbidity burden and a 1-year all-cause mortality of 12.7% with a significantly worse outcome for undertreated patients in and around the index hospitalisation for AE-COPD. Our study suggests that guideline-recommended inhalation therapy reflects structured COPD care, earlier diagnosis and closer medical follow-up rather than a pharmacological effect alone. These findings highlight that deficiencies in COPD management may persist even in well-resourced healthcare settings and that hospitalisation for AE-COPD represents a critical opportunity to reassess diagnosis and optimise long-term treatment. Addressing these gaps will require coordinated efforts among general practitioners, hospital-based physicians, pulmonologists and patients to ensure comprehensive and continuous care for individuals with COPD.

Data sharing statement

The datasets generated and analysed during the current study are not publicly available due to patient privacy and institutional restrictions. Deidentified data (including a data dictionary) can be made available from the corresponding author upon reasonable request, subject to approval by the local ethics committee. The dataset includes patient demographics (age, sex), treatment group allocation, GOLD stage, risk classification, comorbidities, smoking status, additional COPD therapies and clinical variables (mortality, antibiotic use, ICU admission, pneumonia). Data will be available from the date of publication for five years. Access will be granted to researchers with a legitimate scientific interest for purposes such as meta-analyses, validation studies or secondary research related to COPD care and hospital outcomes. Requests should be directed to the corresponding author and will be reviewed by the study team; data will be shared via secure transfer following a data use agreement.

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Author contributions: JF and SJ designed the study. JF wrote the first draft. All authors made significant contributions to the development of the protocol and approved the final version.

Financial disclosure

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest related to the content of this manuscript was disclosed.

References

1. Mathers CD , Loncar D . Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006 Nov;(11):e442. https://doi.org/10.1371/journal.pmed.0030442
2. Rehman AU , Hassali MA , Muhammad SA , Harun SN , Shah S , Abbas S . The economic burden of chronic obstructive pulmonary disease (COPD) in Europe: results from a systematic review of the literature. Eur J Health Econ. 2020 Mar;(2):181–94. https://doi.org/10.1007/s10198-019-01119-1
3. Vogelmeier CF , Román-Rodríguez M , Singh D , Han MK , Rodríguez-Roisin R , Ferguson GT . Goals of COPD treatment: focus on symptoms and exacerbations. Respir Med. 2020 May;:105938. https://doi.org/10.1016/j.rmed.2020.105938
4. Dransfield MT , Kunisaki KM , Strand MJ , Anzueto A , Bhatt SP , Bowler RP , et al.; COPDGene Investigators . Acute Exacerbations and Lung Function Loss in Smokers with and without Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2017 Feb;(3):324–30. https://doi.org/10.1164/rccm.201605-1014OC
5. Guay CA , Maltais F , Beaudoin C , Carmichael PH , Laouan Sidi EA , Perreault L , et al. Trends in COPD severe exacerbations, and all-cause and respiratory mortality, before and after implementation of newer long-acting bronchodilators in a large population-based cohort. BMC Pulm Med. 2024 Sep;(1):450. https://doi.org/10.1186/s12890-024-03277-2
6. Sandelowsky H , Weinreich UM , Aarli BB , Sundh J , Høines K , Stratelis G , et al. COPD - do the right thing. BMC Fam Pract. 2021 Dec;(1):244. https://doi.org/10.1186/s12875-021-01583-w
7. Diab N , Gershon AS , Sin DD , Tan WC , Bourbeau J , Boulet LP , et al. Underdiagnosis and Overdiagnosis of Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2018 Nov;(9):1130–9. https://doi.org/10.1164/rccm.201804-0621CI
8. Peña VS , Miravitlles M , Gabriel R , Jiménez-Ruiz CA , Villasante C , Masa JF , et al. Geographic variations in prevalence and underdiagnosis of COPD: results of the IBERPOC multicentre epidemiological study. Chest. 2000 Oct;(4):981–9. https://doi.org/10.1378/chest.118.4.981
9. Axelsson M , Backman H , Nwaru BI , Stridsman C , Vanfleteren L , Hedman L , et al. Underdiagnosis and misclassification of COPD in Sweden - A Nordic Epilung study. Respir Med. 2023 Oct;:107347. https://doi.org/10.1016/j.rmed.2023.107347
10. Martinez CH , Mannino DM , Jaimes FA , Curtis JL , Han MK , Hansel NN , et al. Undiagnosed Obstructive Lung Disease in the United States. Associated Factors and Long-term Mortality. Ann Am Thorac Soc. 2015 Dec;(12):1788–95. https://doi.org/10.1513/AnnalsATS.201506-388OC
11. Halpin DM , Miravitlles M , Metzdorf N , Celli B . Impact and prevention of severe exacerbations of COPD: a review of the evidence. Int J Chron Obstruct Pulmon Dis. 2017 Oct;:2891–908. https://doi.org/10.2147/COPD.S139470
12. Boesing M , Ottensarendt N , Lüthi-Corridori G , Leuppi JD . The Management of Acute Exacerbations in COPD: A Retrospective Observational Study and Clinical Audit. J Clin Med. 2023 Dec;(1):19. https://doi.org/10.3390/jcm13010019

13. Strengthening the reporting of observational studies in epidemiology. STROBE Checklists: STROBE; 2024 [04.02.2025]. Available from: https://www.strobe-statement.org/checklists/
14. Chen PK , Hsiao YH , Pan SW , Su KC , Perng DW , Ko HK . Independent factors associate with hospital mortality in patients with acute exacerbation of chronic obstructive pulmonary disease requiring intensive care unit admission: focusing on the eosinophil-to-neutrophil ratio. PLoS One. 2019 Jul;(7):e0218932. https://doi.org/10.1371/journal.pone.0218932
15. Groenewegen KH , Schols AM , Wouters EF . Mortality and mortality-related factors after hospitalization for acute exacerbation of COPD. Chest. 2003 Aug;(2):459–67. https://doi.org/10.1378/chest.124.2.459
16. Gunen H , Hacievliyagil SS , Kosar F , Mutlu LC , Gulbas G , Pehlivan E , et al. Factors affecting survival of hospitalised patients with COPD. Eur Respir J. 2005 Aug;(2):234–41. https://doi.org/10.1183/09031936.05.00024804
17. Montagnani A , Mathieu G , Pomero F , Bertù L , Manfellotto D , Campanini M , et al.; FADOI-Epidemiological Study Group . Hospitalization and mortality for acute exacerbation of chronic obstructive pulmonary disease (COPD): an Italian population-based study. Eur Rev Med Pharmacol Sci. 2020 Jun;(12):6899–907.
18. Statulator. Sample Size Calculator for Comparing Two Independent Proportions 2023 [Available from: https://statulator.com/SampleSize/ss2P.html
19. Global Initiative for Chronic Obstructive Lung Disease 2025 Report. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: GOLD 2025 Report; 2024 [04.02.2025]. Available from: https://goldcopd.org/2025-gold-report/
20. Calverley PM , Anderson JA , Celli B , Ferguson GT , Jenkins C , Jones PW , et al.; TORCH investigators . Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007 Feb;(8):775–89. https://doi.org/10.1056/NEJMoa063070
21. Patel N . An update on COPD prevention, diagnosis, and management: The 2024 GOLD Report. Nurse Pract. 2024 Jun;(6):29–36. https://doi.org/10.1097/01.NPR.0000000000000180
22. Stolz D , Barandun J , Borer H , Bridevaux PO , Brun P , Brutsche M , et al. Diagnosis, Prevention and Treatment of Stable COPD and Acute Exacerbations of COPD: the Swiss Recommendations 2018. Respiration. 2018;(4):382–98. https://doi.org/10.1159/000490551
23. Anthonisen NR , Manfreda J , Warren CP , Hershfield ES , Harding GK , Nelson NA . Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med. 1987 Feb;(2):196–204. https://doi.org/10.7326/0003-4819-106-2-196
24. Charlson ME , Pompei P , Ales KL , MacKenzie CR . A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;(5):373–83. https://doi.org/10.1016/0021-9681(87)90171-8
25. De Pietro C , Camenzind P , Sturny I , Crivelli L , Edwards-Garavoglia S , Spranger A , et al. Switzerland: Health System Review. Health Syst Transit. 2015;17, 4 .doi:2015;17(4):1-288.
26. Yin HL , Yin SQ , Lin QY , Xu Y , Xu HW , Liu T . Prevalence of comorbidities in chronic obstructive pulmonary disease patients: A meta-analysis. Medicine (Baltimore). 2017 May;(19):e6836. https://doi.org/10.1097/MD.0000000000006836
27. Ladova K , Vlcek J , Vytrisalova M , Maly J . Healthy adherer effect - the pitfall in the interpretation of the effect of medication adherence on health outcomes. J Eval Clin Pract. 2014 Apr;(2):111–6. https://doi.org/10.1111/jep.12095
28. Lindenauer PK , Dharmarajan K , Qin L , Lin Z , Gershon AS , Krumholz HM . Risk Trajectories of Readmission and Death in the First Year after Hospitalization for Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2018 Apr;(8):1009–17. https://doi.org/10.1164/rccm.201709-1852OC
29. Ehteshami-Afshar S , Merchant N . The underappreciated role of documentation in improving COPD care. Cleve Clin J Med. 2022 May;(5):249–51. https://doi.org/10.3949/ccjm.89a.21044
30. Suissa S , Dell'Aniello S , Ernst P . Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. Thorax. 2012 Nov;(11):957–63. https://doi.org/10.1136/thoraxjnl-2011-201518
31. Rello J , Rodriguez A , Torres A , Roig J , Sole-Violan J , Garnacho-Montero J , et al. Implications of COPD in patients admitted to the intensive care unit by community-acquired pneumonia. Eur Respir J. 2006 Jun;(6):1210–6. https://doi.org/10.1183/09031936.06.00139305
32. Lodise TP , Li J , Gandhi HN , O'Brien G , Sethi S . Intraclass Difference in Pneumonia Risk with Fluticasone and Budesonide in COPD: A Systematic Review of Evidence from Direct-Comparison Studies. Int J Chron Obstruct Pulmon Dis. 2020 Nov;:2889–900. https://doi.org/10.2147/COPD.S269637
33. Buess M , Schilter D , Schneider T , Maurer M , Borer H , Thurnheer R , et al. Treatment of COPD Exacerbation in Switzerland: Results and Recommendations of the European COPD Audit. Respiration. 2017;(4):355–65. https://doi.org/10.1159/000477911
34. Amin AN , Cornelison S , Woods JA , Hanania NA . Managing hospitalized patients with a COPD exacerbation: the role of hospitalists and the multidisciplinary team. Postgrad Med. 2022 Mar;(2):152–9. https://doi.org/10.1080/00325481.2021.2018257
35. Reis AJ , Alves C , Furtado S , Ferreira J , Drummond M , Robalo-Cordeiro C ; GI DPOC-Grupo de Interesse na Doença Pulmonar Obstrutiva Crónica . COPD exacerbations: management and hospital discharge. Pulmonology. 2018;(6):345–50. https://doi.org/10.1016/j.pulmoe.2018.06.006
36. Kim N , Teng W , Akande O , Rhodes D , Rochester CL . Impact of an Inpatient COPD Care Pathway on Hospital Care Process and Outcome Metrics. Chronic Obstr Pulm Dis (Miami). 2025 Jul;(4):304–16. https://doi.org/10.15326/jcopdf.2024.0585

Appendix 1: Baseline characteristics

Table S1: Baseline characteristics of patients hospitalised with AE-COPD, stratified by pre-admission inhalation therapy

Variables	All patients (n=1,855)	No long-acting inhalation therapy (Group 1, n=834)	Long-acting inhalation therapy (Group 2, n=1,021)	P-value
Age in years (mean, [SD])	72 [11.3]	71.5 [11.7]	72.4 [10.9]	0.099
BMI* (median, [IQR])	25.6 [7.6]	25.7 [7.5]	25.6 [7.8]	0.288
Gender				
Male (n, [%])	1,058 [57.0%]	491 [58.9%]	567 [55.5%]	
Female (n, [%])	797 [43.0%]	343 [41.1%]	454 [44.5%]	0.148
GOLD stage				
GOLD 1 (n, [%])	107 [5.8%]	65 [7.8%]	42 [4.1%]	
GOLD 2 (n, [%])	427 [23.0%]	132 [15.8%]	295 [28.9%]	
GOLD 3 (n, [%])	261 [14.1%]	61 [7.3%]	200 [19.6%]	
GOLD 4 (n, [%])	122 [6.6%]	21 [2.5%]	101 [9.9%]	
GOLD unknown (n, [%])	938 [50.6%]	555 [66.5%]	383 [37.5%]	<0.001
Risk category				
Risk class A (n, [%])	63 [3.4%]	22 [2.6%]	41 [4.0%]	
Risk class B (n, [%])	133 [7.2%]	20 [2.4%]	113 [11.1%]	
Risk class C (n, [%])	21 [1.1%]	4 [0.5%]	17 [1.7%]	
Risk class D (n, [%])	93 [5.0%]	20 [2.4%]	73 [7.1%]	
Risk class E (n, [%])	12 [0.6%]	4 [0.5%]	8 [0.8%]	
Risk class unknown (n, [%])	1,533 [82.6%]	764 [91.6%]	769 [75.3%]	<0.001
Smoking status				
No smoking cessation (n, [%])	797 [43.0%]	369 [44.2%]	428 [41.9%]	
Smoking cessation (n, [%])	538 [29.0%]	192 [23.0%]	346 [33.9%]	
Unknown smoking (n, [%])	520 [28.0%]	273 [32.7%]	247 [24.2%]	<0.001
Pack-years* (median, [IQR])	50 [30]	50 [29.5]	50 [25.5]	0.440
Therapy				
Pulmonary rehabilitation (n, [%])	53 [2.9%]	17 [2.0%]	36 [3.5%]	0.056
LTOT (n, [%])	142 [7.7%]	37 [4.4%]	105 [10.3%]	<0.001
PDE-4-i (n, [%])	30 [1.6%]	4 [0.5%]	26 [2.5%]	<0.001
Theophylline (n, [%])	7 [0.4%]	1 [0.1%]	6 [0.6%]	0.102
Macrolide (n, [%])	15 [0.8%]	5 [0.6%]	10 [1.0%]	0.363
Spacer (n, [%])	9 [0.5%]	2 [0.2%]	7 [0.7%]	0.169
ICS (n, [%])	521 [28.1%]	26 [3.1%]	495 [48.5%]	<0.001
Comorbidities				
Heart failure (n, [%])	699 [37.7%]	336 [40.3%]	363 [35.6%]	0.038
Ischaemic heart disease (n, [%])	706 [38.1%]	304 [36.5%]	402 [39.4%]	0.211
Arrhythmia (n, [%])	489 [26.4%]	220 [26.4%]	269 [26.3%]	1.000
Arterial hypertension (n, [%])	1275 [68.7%]	555 [66.5%]	720 [70.5%]	0.070
Pulmonary hypertension (n, [%])	222 [12.0%]	84 [10.1%]	138 [13.5%]	0.026

Peripheral vascular disease (n, [%])	247	[13.3%]	110	[13.2%]	137	[13.4%]	0.891
Cerebrovascular disease (n, [%])	99	[5.3%]	57	[6.8%]	42	[4.1%]	0.012
ACOS (n, [%])	95	[5.1%]	15	[1.8%]	80	[7.8%]	<0.001
Obstructive sleep apnea (n, [%])	268	[14.4%]	102	[12.2%]	166	[16.3%]	0.014
Diabetes mellitus (n, [%])	543	[29.3%]	239	[28.7%]	304	[29.8%]	0.608
Diabetes with end-organ damage (n, [%])	119	[6.4%]	57	[6.8%]	62	[6.1%]	0.507
Osteoporosis (n, [%])	238	[12.8%]	102	[12.2%]	136	[13.3%]	0.530
Anemia (n, [%])	532	[28.7%]	236	[28.3%]	296	[29.0%]	0.757
Polycythemia (n, [%])	38	[2.0%]	15	[1.8%]	23	[2.3%]	0.515
Depression (n, [%])	427	[23%]	201	[24.1%]	226	[22.1%]	0.319
Cognitive impairment (n, [%])	124	[6.7%]	77	[9.2%]	47	[4.6%]	<0.001
Frailty (n, [%])	245	[13.2%]	118	[14.1%]	127	[12.4%]	0.301
Hemiplegia (n, [%])	10	[0.5%]	5	[0.6%]	5	[0.5%]	0.761
Connective tissue disease (n, [%])	15	[0.8%]	10	[1.2%]	5	[0.5%]	0.118
Mild liver disease (n, [%])	61	[3.3%]	30	[3.6%]	31	[3.0%]	0.515
Moderate-severe liver disease (n, [%])	15	[0.8%]	11	[1.3%]	4	[0.4%]	0.035
Moderate-severe kidney disease (n, [%])	243	[13.1%]	83	[10.0%]	160	[15.7%]	<0.001
Lung cancer (n, [%])	87	[4.7%]	40	[4.8%]	47	[4.6%]	0.912
Any tumor (n, [%])	582	[31.4%]	273	[32.7%]	309	[30.3%]	0.269
Leukemia (n, [%])	8	[0.4%]	6	[0.7%]	2	[0.1%]	0.151
Lymphoma (n, [%])	13	[0.7%]	6	[0.7%]	7	[0.7%]	1.000
Metastatic cancer (n, [%])	250	[13.5%]	114	[13.7%]	136	[13.3%]	0.827
Index hospitalisation							
Pneumonia (n, [%])	216	[11.6%]	94	[11.3%]	122	[11.9%]	0.663
Antibiotic treatment (n, [%]	441	[23.8%]	172	[20.6%]	269	[26.3%]	0.004
ICU (n, [%])	81	[4.4%]	32	[3.8%]	49	[4.8%]	0.361
WBC (median, [IQR])	9.1	[4.8]	9	[4.7]	9.1	[4.8]	0.319
CRP (median, [IQR])	11.8	[53.8]	11.45	[56.4]	12.2	[52.7]	0.501
Acidosis (n, [%])	223	[12.0%]	92	[11.0%]	131	[12.8%]	0.251
MAP (median, [IQR])	98	[22.0]	98	[23.0]	98	[23.0]	0.454
Oxygen saturation (median, [IQR])	94	[4.0]	94	[4.0]	94	[5.0]	0.130

Group 1 includes COPD patients not receiving long-acting inhalation therapy at the time of hospital admission. Group 2 includes COPD patients receiving long-acting inhalation therapy at the time of hospital admission. Missing values are reported separately in their own group to be accounted for ("Unknown") or marked by *. For BMI, 1'768 cases were available (87 missing values); for pack-years, 1'019 cases were available for summary statistics (836 missing values). ACOS = asthma-COPD-overlap syndrome, BMI = body mass index, CRP = C-reactive protein, ICS = inhaled corticosteroid, ICU = intensive care unit, IQR = interquartile range, LTOT = long-term oxygen therapy, MAP = mean arterial pressure, PDE-4-i = Phosphodiesterase-4-inhibitor, SD = standard deviation, WBC = white blood cells.

Appendix 2: Multivariable analysis model

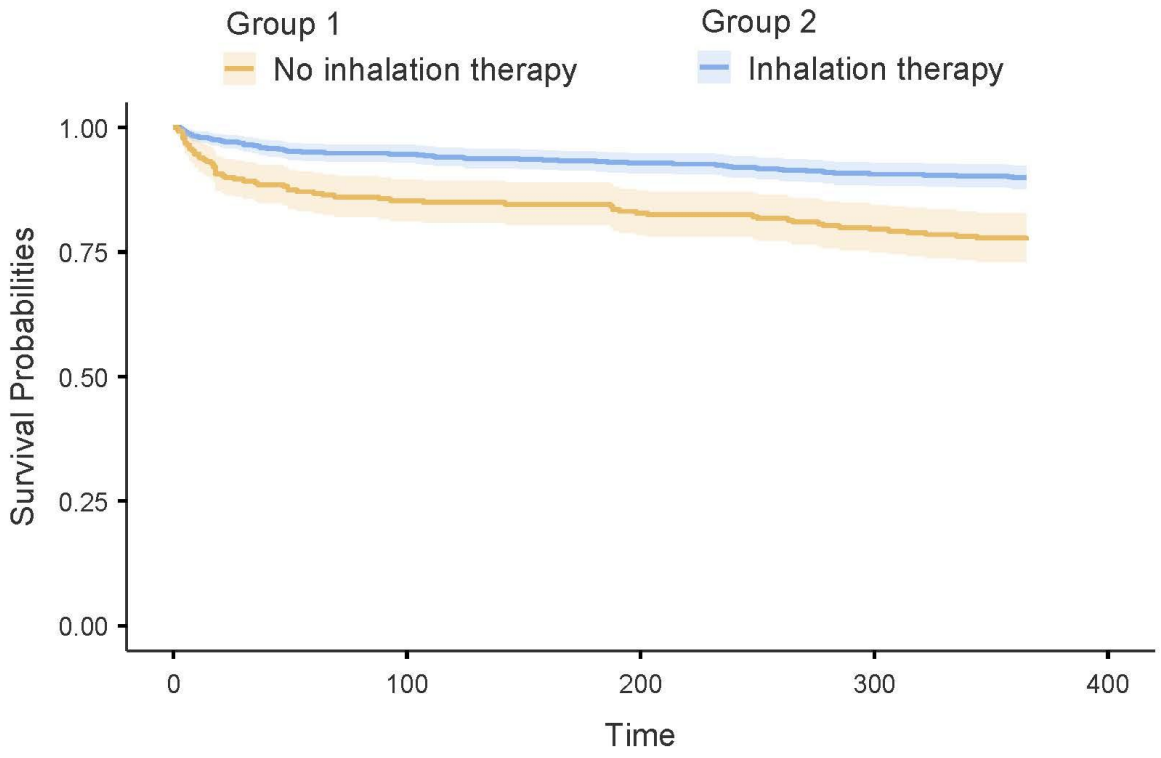
Table S2: Univariable and multivariable survival analyses. Association of listed covariables with one-year all-cause mortality

Covariable	Univariable Analysis			Multivariable Analysis		
	HR	CI	P-value	HR	CI	P-value
Inhalation therapy	1.65	1.28-2.14	< 0.001	1.95	1.48-2.56	< 0.001
Gender	0.98	0.75-1.26	0.859	0.99	0.76-1.30	0.946
Severe GOLD (3 & 4)	1.38	1.03-1.84	0.032	2.04	1.48-2.80	< 0.001
Heart failure	1.53	1.19-1.98	0.001	1.37	1.01-1.86	0.044
Ischaemic heart disease	1.04	0.80-1.35	0.759	0.79	0.58-1.08	0.146
Pulmonary hypertension	1.31	0.91-1.87	0.141	1.18	0.82-1.71	0.374
Diabetes mellitus	1.07	0.81-1.41	0.639	1.08	0.81-1.43	0.616
Moderate-severe kidney disease	1.12	0.78-1.61	0.534	1.08	0.75-1.57	0.680
Lung cancer	3.68	2.55-5.31	< 0.001	4.22	2.90-6.14	< 0.001
Pneumonia	1.21	0.84-1.76	0.306	1.28	0.77-2.11	0.336
Antibiotic treatment	1.15	0.86-1.54	0.343	0.95	0.64-1.42	0.817
ICU	1.90	1.17-3.07	0.009	1.80	1.07-3.01	0.026
Acidosis	1.03	0.70-1.51	0.900	1.05	0.70-1.57	0.819
Age per year	1.04	1.03-1.06	< 0.001	1.05	1.03-1.06	< 0.001
CRP per mg/l	1.00	1.00-1.00	0.280	1.00	1.00-1.00	0.234
MAP per mmHg	0.99	0.98-1.00	0.014	0.99	0.98-1.00	0.006

HR (95% CI) from univariable and from multivariable analysis adjusted for treatment group, age, gender, severe GOLD stages (3 & 4), heart failure, ischaemic heart disease, pulmonary hypertension, diabetes mellitus, lung cancer, pneumonia, ICU, CRP, acidosis, MAP. Outcome: one-year all-cause mortality. Interpretation: HR > 1 indicated worse outcome (one-year all-cause mortality) in patients treated without long-acting inhalation therapy (reference=Group 1) compared to those with long-acting inhalation therapy (comparison=Group 2). CI: confidence interval, CRP: C-reactive protein, HR: hazard ratio, ICU: intensive care unit, MAP: mean arterial pressure.

Appendix 3: Kaplan-Meier survival curve for subgroup analysis

Figure S1: Kaplan-Meier survival curve for subgroup analysis including only patients with spirometrically diagnosed COPD



Kaplan-Meier survival curve for subgroup analysis – patients with spirometrically diagnosed COPD only (GOLD 1, 2, 3 and 4). X-axis time in days (censored at day 365). Y-axis survival probability. In total, 917 patients (of 1,855 (= 49.4%) had a spirometrical diagnosis of COPD. Group 1: spirometrically diagnosed COPD GOLD stages 1-4 without inhalation therapy (n=279). Group 2: spirometrically diagnosed COPD GOLD stages 1-4 with inhalation therapy (n=638). 127 events (13.9%) occurred: 63 of 279 patients (22.6%) in Group 1, and 64 of 638 patients (10.0%) in Group 2. The difference between groups was statistically significant in the log-rank test ($\chi^2 = 26.8$, df = 1; $p < 0.001$)