ORIGINAL RESEARCH

Clinical Impact and Healthcare Resource Utilization Associated with Early versus Late COPD Diagnosis in Patients from UK CPRD Database

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Purpose: Previous studies have shown that opportunities to diagnose chronic obstructive pulmonary disease (COPD) early are often missed in primary care. This retrospective study aimed to utilize secondary data from the United Kingdom (UK) healthcare system to understand the impact of early versus late diagnosis of COPD.

Patients and Methods: Newly diagnosed COPD patients were identified in the UK Clinical Practice Research Database from 2011 to 2014. Patients whose 5-year medical data before diagnosis revealed ≥3 counts of eight indicators of early COPD were deemed as late-diagnosed, whereas others were deemed as early-diagnosed. We assessed patients' characteristics; time-to-first, risk, and rates of exacerbation; and healthcare resource utilization (COPD-related clinic visits, Accident and Emergency visits, and hospitalizations) in late- versus early-diagnosed patients.

Results: Of 10,158 patients included in the study, 6783 (67%) were identified as late-diagnosed and 3375 (33%) as early-diagnosed. The median time-to-first exacerbation was shorter in late-diagnosed (14.5 months) versus early-diagnosed (29.0 months) patients, with a significant risk of exacerbation (hazard ratio 1.46 [95% confidence interval: 1.38–1.55]). Additionally, the exacerbation rate (per 100 person-years) over 3 years was higher in late (108.9) versus early (57.2) diagnosed patients. Late-diagnosed patients had a significantly higher rate of COPD hospitalizations (per 1000 patient years) compared with early-diagnosed patients during 2 and 3 years of follow-ups ($P = 0.0165$ and $P < 0.0001$, respectively).

Conclusion: Results showed that a significant percentage of COPD patients in UK primary care are diagnosed late. A late COPD diagnosis is associated with a shorter time-to-first exacerbation and a higher rate and risk of exacerbations compared with early diagnosis. Additionally, late diagnosis of COPD is associated with a higher rate of COPD-related hospitalizations compared with early diagnosis.

Keywords: chronic obstructive pulmonary disease, COPD, clinical practice research datalink, UK-CPRD, early diagnosis of COPD, late diagnosis of COPD, healthcare utilization

Introduction

Chronic obstructive pulmonary disease (COPD) is the second most common lung disease in the United Kingdom (UK), after asthma.[1,2] An estimated 1.2 million people in the UK are living with COPD, which constitutes around 2% of the overall population.[1,2] An earlier retrospective study conducted by Jones et al revealed that 85% of patients in the UK remain undiagnosed despite presenting COPD symptoms in

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the past 5 years.[3] Missing an opportunity to diagnose COPD translates to missing an opportunity to treat a patient early and potentially avoid adverse patient outcomes.[3,4] We hypothesized that early treatment of COPD is likely to lead to better control of the disease and reduced healthcare resource utilization (HCRU).[4] In this study, we have utilized data from the UK healthcare system to understand how the clinical and economic consequences are associated with the timing of COPD diagnosis in patients with COPD. Here, we report the clinical and economic outcomes associated with early versus late diagnosis of COPD in primary care.

Patients and Methods
Study Design
This was a retrospective cohort study conducted to compare the outcomes in patients with an early versus late diagnosis of COPD, among newly diagnosed COPD patients managed in primary care settings in the UK from 01 January 2006 through 31 March 2016 (Figure 1). Index date was the time of the first recorded physician's diagnosis of COPD during the identification time frame. The follow-up period for each patient was objective-specific with maximum 3 years. The study protocol was approved by the Clinical Practice Research Datalink (CPRD), Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research, UK (ISAC 17_213), and the study was conducted in accordance with the principles of the Declaration of Helsinki. The results of this study were reported adhering to the STROBE (Strengthening The Reporting of OBservational Studies in Epidemiology) guidelines.

Database
The data for this study were retrieved from the CPRD linked to the Hospital Episode Statistics (HES) database. The UK CPRD

is a high-quality clinical primary care database, whereas the HES database contains high-quality data from admitted patients, outpatients, and Accident and Emergency (A&E) records in England. Both databases are in part linked and we focused our investigation only on CPRD patients who are eligible for the linkage to evaluate acute and chronic outcomes most appropriately in primary and secondary care. CPRD is a longitudinal, anonymized research database derived from nearly 700 primary care practices in the UK.[5] By January 2015, CPRD contained more than 13 million research-quality patients registered at 684 practices.[6] Data include demographics, diagnoses, symptoms, investigations, referrals, and prescriptions. HES database contains details of all admissions, A&E attendances, and outpatient appointments at the National Health Service hospitals in England. Inpatient data are recorded in HES using the International Classification of Diseases 10th Revision (ICD-10) classification.[7]

Study Patients
Inclusion Criteria
Patients with a COPD diagnosis during the identification period,[6] eligible for data linkage to HES, age (≥40 years at index date) and gender information not missing, acceptable flag criterion in CPRD, and their practices flagged as up-to-standard during the pre-index period were included in the study. All patients were required to have a minimum of practice data of 5 years before and 1 year after their first COPD diagnosis. The registration date and a practice up-to-standard date 5 years prior to the index date were captured to ensure a minimum of 5 years of pre-index follow-up.

Exclusion Criteria
A diagnosis of both COPD and asthma in the pre-index period (as the respiratory signs and symptoms in a patient
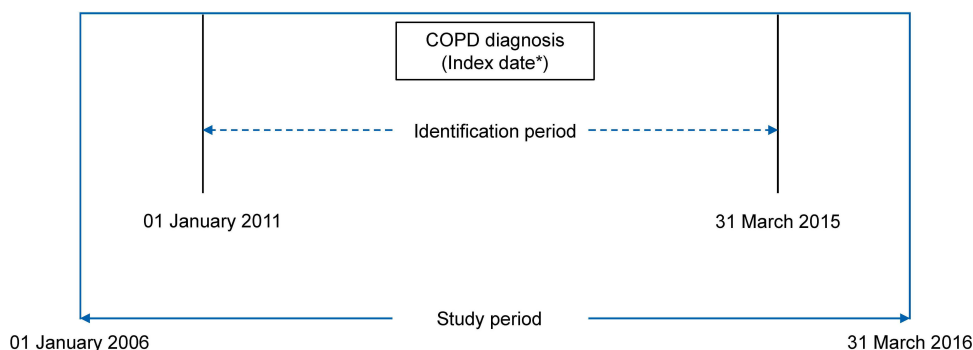

Figure 1 Study design. *Index date was the time of the first recorded physician's diagnosis of COPD during the identification time frame.
Abbreviation: COPD, chronic obstructive pulmonary disease.

with asthma would make the algorithm to identify early and late diagnosis in COPD invalid).

Early and Late-Diagnosed Cohorts

Patients who had fewer than three prior indicators of COPD within the 5-year pre-index period were included in the early diagnosis of COPD category. Patients who had three or more prior indicators of COPD within the 5-year pre-index period or had at least one prior indicator of COPD per year in the 2 years prior to the index date were included in the late diagnosis of COPD category. Selected indicators of COPD were pneumonia, respiratory diseases other than pneumonia, chest radiograph, prescription of oral steroids, prescription of antibiotics for airway or lung infections, prescriptions for respiratory disease targeted to relieve respiratory symptoms, and lung function measurements. Indicators recorded fewer than 28 days apart were considered as the same event and assigned to the earliest occurrence date. These indicators suggested possible early COPD respiratory signs, symptoms or exacerbations that patients experienced and led to prescriptions managing symptoms or diagnostic tests to investigate by their physicians.

Outcomes

Baseline characteristics were reported for these two cohorts, namely early- and late-diagnosed COPD patients. The clinical impact of early-diagnosed COPD compared with late-diagnosed COPD was assessed in terms of the time to, risk of, and rate of exacerbations. Economic burden was measured in terms of HCRU based on COPD-related clinic visits, A&E visits, and hospitalizations. To estimate both the clinical burden and HCRU, all patients were followed up for 3 years after the index date.

Diagnosis of Chronic Obstructive Pulmonary Disease

COPD diagnosis was defined by the presence of at least one specific code for COPD (ICD-10 code: J44), at least two prescriptions for a medication indicated for COPD within 4 weeks subsequent to the COPD diagnosis, and at least one spirometry exam within 18 months from the COPD diagnosis.[6] Severity of COPD was assessed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) updated in 2015 criteria presented in Supplementary Table S1.

Exacerbations

Episodes of COPD exacerbation treated in primary care were defined according to a validated algorithm that takes into account the drug codes and diagnosis codes in the CPRD database[8] and integrated with in-hospital data from the HES database. Moderate exacerbations were defined as treatment with oral corticosteroids (OCS) and antibiotics on the same day (but no hospitalization) or a lower respiratory tract infection except pneumonia, or exacerbation symptoms and prescription of OCS or oral antibiotics on the same day. Severe exacerbations were defined as COPD-related hospitalizations (Admitted Patient Care) or emergency visits (Emergency and Admission) or an episode of acute exacerbation recorded by a general practitioner (details of the exacerbation symptoms, algorithm, read codes, and definition are provided in Supplementary Section S1). Recurrent exacerbations occurring within 14 days were considered as a unique event.

Comorbidities

Comorbidities were defined based on the diagnosis codes in the primary or secondary care setting and by medications according to the National Prescription Register.[9]

Statistical methods

Categorical data for baseline characteristics are presented as counts (n) and proportions (%). Continuous data are presented as summary statistics (mean, standard deviation, median, interquartile range, minimum, maximum). A Kaplan–Meier cumulative incidence curve was calculated to estimate the time and risk of first exacerbation. Adjusted hazard ratios and 95% confidence intervals (CIs) for the time-to-first exacerbation were estimated using a multivariable Cox model. A negative binomial regression model was used to calculate unadjusted and adjusted rate ratios of exacerbations between the early and late-diagnosed COPD patients. The models were adjusted for all "a priori" variables that would provide the best Akaike information criterion in the model, which is an estimator of the relative quality of statistical models for a given set of data. The "a priori" variables were age, Charlson Comorbidity Index (CCI), body mass index (BMI), smoking status, GOLD severity, and adherence to COPD treatment. Severity of the disease and adherence to medication were included as covariates in this analysis to avoid the lead-time bias.

Results
Baseline Characteristics

A total of 135,739 HES-eligible patient data of acceptable research quality were identified in CPRD. After applying inclusion and exclusion criteria, 10,158 patients were remaining for the evaluation, of which 6783 (67%) were identified as late-diagnosed and 3375 (33%) as early-

diagnosed. Attrition of patients is presented in Supplementary Figure S1. The baseline characteristics were comparable and are presented in Table 1. Early-diagnosed patients were relatively younger and more often male and current smokers compared with late-diagnosed patients ($P < 0.001$). Patients with late-diagnosed COPD had more comorbidities than those with early-diagnosed COPD. The most commonly recorded comorbidity was hypertension in both the cohorts.

Clinical Burden
Time-to-First Exacerbation
The median (95% CI) time-to-first exacerbation from the index date in the late-diagnosed COPD patients was 14.5 months (13.80–15.10) compared with 29.0 months (27.40–30.70) in the early-diagnosed COPD patients ($P < 0.0001$; Figure 2). The hazard ratio for the first exacerbation was significantly higher (1.46; $P < 0.0001$) in late-diagnosed COPD patients compared with early-diagnosed COPD patients (Table 2). Patients aged 40–64 years who were adherent to their COPD medication were less likely to have an exacerbation compared with patients who were non-adherent. Patients in GOLD group D had a hazard ratio of 1.83 for the first exacerbation compared with patients in GOLD group A (Table 2).

Rate of Exacerbation
The rate of exacerbations was consistently higher in the late-diagnosed patients versus early-diagnosed patients when compared over a 3-year period (Table 3).

Healthcare Resource Utilization
COPD-Related Clinic Visits
The rate of clinic visits (per 1000 person-years) in late-diagnosed patients was lower than that of early-diagnosed patients during 1 and 2 years of follow-up. However, comparable rates of clinic visits were observed in both the early- and late-diagnosed patients during 3 years of follow-up (Table 4).

COPD-Related A&E Visits
The rate of A&E visits was numerically higher in the late-diagnosed patients than in the early-diagnosed patients during all 3 years of follow-up (Table 4).

COPD-Related Hospitalization
The rate of hospitalization was higher in patients in the late-diagnosed COPD patients than in the early-diagnosed patients during all 3 years of follow-up (Table 4).

Table 1 Baseline Characteristics of Early- versus Late-Diagnosed COPD Patients

Characteristics	Early Diagnosis of COPD (N = 3375)	Late Diagnosis of COPD (N = 6783)	P-value
Age			
Mean ± SD	67.28 ± 10.21	69.32 ± 10.55	<0.0001
Age, ≥40 to <65 years	1297 (38.4%)	2160 (31.8%)	
Age, ≥65 years	2078 (61.6%)	4623 (68.2%)	
Gender, Male	2132 (63.2%)	3516 (51.8%)	<0.0001
BMI, mean ± SD	27.01 ± 6.16	27.5 ± 6.16	0.0009
Smoking status			
Never smoker	137 (4.1%)	360 (5.3%)	0.0078
Ex-smoker	1637 (48.5%)	3752 (55.3%)	
Current smoker	1593 (47.2%)	2649 (39.1%)	
Missing	8 (0.2%)	22 (0.3%)	
mMRC score			
<2	1823 (54.0%)	3280 (48.4%)	<0.0001
≥2	897 (26.6%)	2514 (37.1%)	
Missing	655 (19.4%)	989 (14.6%)	
Lung function			
FEV$_1$ (L)[a], mean ± SD	1.88 ± 0.78	1.77 ± 0.72	<0.0001
Percentage predicted FEV$_1$[b], mean ± SD	61.07 ± 18.76	62.78 ± 19.38	0.0011
FEV$_1$/FVC (%)[c], mean ± SD	58.04 ± 16.94	59.40 ± 17.72	0.0014
FEV$_1$/FVC ≥ 70% predicted	483 (19.5%)	1164 (24.4%)	<0.0001
FEV$_1$/FVC < 70% predicted	1999 (80.5%)	3614 (75.6%)	
Comorbidities in the pre-index period[d]			
Hypertension	1759 (52.1%)	3919 (57.8%)	<0.0001
Depression	878 (26.1%)	2197 (32.4%)	<0.0001
Anxiety	730 (21.6%)	1985 (29.3%)	<0.0001
Hyperlipidemia	751 (22.3%)	1757 (25.9%)	<0.0001
Diabetes	344 (10.2%)	931 (13.7%)	<0.0001
Pneumonia	188 (5.6%)	903 (13.3%)	<0.0001
Atrial fibrillation or other cardiac arrhythmias	280 (8.3%)	856 (12.6%)	<0.0001
Acute myocardial infarction	238 (7.1%)	642 (9.5%)	<0.0001
Stroke	208 (6.2%)	568 (8.4%)	<0.0001
Osteoporosis	142 (4.2%)	497 (7.3%)	<0.0001
Heart failure	109 (3.2%)	395 (5.8%)	<0.0001
Lung cancer	13 (0.4%)	95 (1.4%)	<0.0001
CCI score in the pre-index period, mean ± SD	2.19 ± 1.6	2.7 ± 1.91	<0.0001
Eosinophils (cells/µL)			
<150	717 (33.57%)	1461 (32.68%)	0.0313
≥150 and <300	725 (33.94%)	1575 (35.23%)	
>300	694 (32.49%)	1434 (32.08%)	

Notes: Data presented as n (%) unless otherwise stated. [a]Early (n = 2693) versus late (n = 5337) diagnosed patients. [b]Early (n = 1966) versus late (n = 3909) diagnosed patients. [c]Early (n = 2482) versus late (n = 4778) diagnosed patients. [d]Prior to the date of the first COPD diagnosis during the identification period.
Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council; SD, standard deviation.
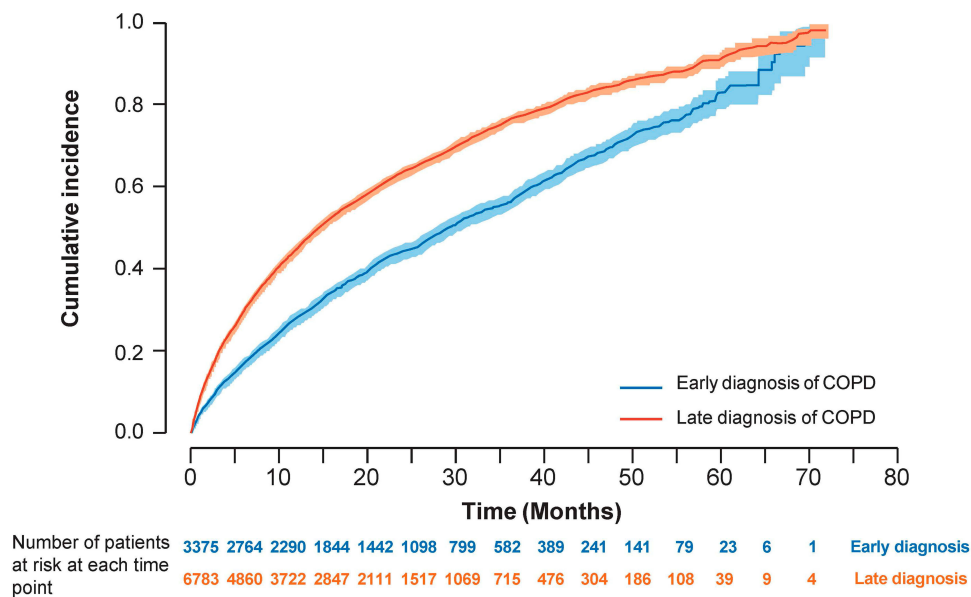
Figure 2 Time-to-first exacerbation in the early and late-diagnosed COPD patients.
Abbreviation: COPD, chronic obstructive pulmonary disease.

Overall Healthcare Resource Utilization

Overall, the HCRU in terms of annual rates of COPD-related clinic visits, A&E visits, and hospitalizations was higher in the late-diagnosed patients in all 3 years of follow-up compared with the early diagnosed patients.

Table 2 Hazard Ratio of First Exacerbation for Early versus Late COPD Diagnosis

Variables	Adjusted[a] HR (95% CI)
Late versus early diagnosis of COPD	1.46 (1.38–1.55); $P < 0.0001$
Age, ≥ 65 years versus ≥ 40 to < 65 years	0.92 (0.87–0.98)
CCI score 0 versus ≥ 1 to ≤ 2	1.00 (0.68–1.46)
CCI score 0 versus > 2	1.09 (0.74–1.59)
Underweight versus normal weight[b]	1.13 (0.99–1.28)
Overweight versus normal weight[b]	0.98 (0.91–1.05)
Obese versus normal weight[b]	0.90 (0.83–0.96)
Ex-smoker versus never smoker	1.02 (0.90–1.15)
Current smoker versus never smoker	1.13 (1.00–1.28)
GOLD B versus GOLD A	1.23 (1.11–1.37)
GOLD C versus GOLD A	1.54 (1.41–1.67)
GOLD D versus GOLD A	1.83 (1.68–1.99)
Adherence[c] to COPD medication versus non-adherence	0.07 (0.07–0.08)
Patients with depression versus without depression	1.18 (1.09–1.27)
Patients with pneumonia versus without pneumonia	1.12 (1.06–1.18)
Patients with osteoporosis versus without osteoporosis	1.10 (1.00–1.22)

Notes: *P*-value from the Wald test obtained from an adjusted Cox model. [a]Adjusted for depression and the "a priori" variables, namely age, CCI, BMI, smoking status, GOLD severity, and adherence to COPD treatment. [b]Weight was measured based on BMI. [c]Calculated based on MPR. The number of patients with good adherence versus poor adherence was very low, especially in patients not having an exacerbation. This may be attributed to the difficulties around recording of medication in the CPRD database. **Abbreviations:** BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; MPR, medicine possession ratio.

However, for clinical visits the HCRU was lower in patients in the late-diagnosed patients versus early diagnosed patients during year 1 and year 2 of follow-up.

Medication Use in Post-Index Period

Overall, the proportion of patients receiving GOLD appropriate therapy after 2 years of follow-up was low in both late- (55.7%) and early (46.2%) diagnosed COPD patients (Supplementary Table S2). The median time-to-first inhaled corticosteroid-long-acting β_2-agonist-long-acting muscarinic antagonist (ICS-LABA-LAMA) combination therapy was slightly lower in patients with late-diagnosed COPD (60.1 months) compared with those with early-diagnosed COPD (63.5 months; Supplementary Figure S2). Short-acting β_2-agonist (SABA) was most commonly prescribed in combination in both the early (57.5%) and late (59.3%) diagnosed COPD cohorts; however, it was not possible to discriminate whether SABA was administered as rescue medication or as maintenance therapy. In the late-diagnosed patients, ICS was prescribed in combination with 50.9% compared with 43% in the early-diagnosed patients. The combination of ICS-LABA-LAMA was prescribed in 17.1% of early-diagnosed patients compared to 22.5% of late-diagnosed patients during the follow up (Supplementary Table 3).

Discussion

In this retrospective study, we showed that the opportunity for an early diagnosis of COPD was missed in two-thirds of the patients in the UK primary care setting, despite the

Table 3 Annual Rate of Exacerbations in the 1-, 2-, and 3-Year Periods Following the Index Date

Variable	Number of Exacerbations	Person-Years	Exacerbation Rate (Per 100 Person-Years)	Unadjusted* Rate Ratio (95% CI); P-Value	Adjusted† Rate Ratio (95% CI); P-Value
1-year follow-up after the index date					
Late COPD diagnosis	6052	6430.72	94.11	1.99 (1.84–2.15); P < 0.0001	1.67 (1.56–1.80); P < 0.0001
Early COPD diagnosis	1513	3163.26	47.83		
2-year follow-up after the index date					
Late COPD diagnosis	11,521	11,406.45	101.00	1.96 (1.84–2.09); P < 0.0001	1.68 (1.58–1.79); P < 0.0001
Early COPD diagnosis	2924	5560.81	52.58		
3-year follow-up after the index date					
Late COPD diagnosis	15,715	14,425.96	108.94	1.95 (1.83–2.07); P < 0.0001	1.68 (1.59–1.79); P < 0.0001
Early COPD diagnosis	4013	7011.69	57.23		

Notes: P-value from the Wald test obtained from both the adjusted and unadjusted negative binomial regression model. *Used only late/early as independent variable. †Adjusted for pneumonia, depression, baseline eosinophil levels, osteoporosis, atrial fibrillation, and the "a priori" variables, which include age, CCI, BMI, smoking status, GOLD severity, and adherence to COPD treatment.
Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

previous reports.[3,10,11] Our results also showed that late diagnosis of COPD was associated with worse clinical outcomes and higher HCRU compared with an early diagnosis. Our findings are in agreement with the outcomes of a retrospective study in UK primary care conducted by Jones et al[3] which showed that majority of the patients (85%) presented symptoms of COPD during the past 5 years leading to diagnosis of the disease. The fact that the missed opportunity for COPD diagnosis was present in a smaller proportion of patients (67%) in our study may be due to the differences in the study period and the indicators used to identify COPD. However, the characteristics of patients evaluated in our analysis were consistent with those of the previous reports.[10,11]

In our study, we have observed that the time-to-first exacerbation was shorter in late-diagnosed patients compared with early-diagnosed patients, which was expected. The overall rate per 100-person years within the 3-year period for late-diagnosed patients was higher versus early-diagnosed patients. A similar analysis using the same definitions for early and late diagnosis in the ARCTIC study also showed that earlier diagnosis and treatment of COPD could substantially improve overall health outcomes compared with late diagnosis in a Swedish population. The study reported that 69.5% of patients who were diagnosed late incurred higher annual direct costs than patients with an early diagnosis.[11] In addition, late-diagnosed patients were

more likely to be admitted as inpatients for COPD-related hospitalization, which was also comparable with the outcomes of the ARCTIC study.[11] Results of the previous studies imply that late COPD diagnosis appears to be a common characteristic in primary care settings regardless of the country studied.

Overall, the treatment pattern observed in our study was comparable with the previous findings, with some differences. In our study, prescriptions in UK primary care were as per the GOLD strategy document and aligned with an earlier report.[10] However, the use of ICS-LABA-LAMA combination therapy was slightly lower in our study compared with previous report.[12]

Although, the large sample size of COPD patients and the robust outcomes of this study provide data that are highly representative of the general population, there are acknowledged drawbacks of observational studies that use electronic health record data. The data used in this analysis were restricted to those of patients who were HES eligible and therefore limited to England-based patients only, and findings of this study may not be generalizable to the entire UK population and population of other countries. Further, lead-time bias may exist among the COPD patients included in our study and influence the results, as patients with early diagnosed COPD may demonstrate an apparent improvement in the time-to-first COPD exacerbation and may remain the same without changing the eventual disease course.

Table 4 Annual Rate of COPD-Related Clinic Visits, A&E Visits, and Hospitalizations After 1, 2, and 3 Years from the Index Date

Variable	Number of Visits	Person-Years	Rate (Per 1000 Person-Years)	Adjusted[a]	
				Rate Ratio (95% CI)	P-value
Clinic visits[b]					
Within 1 year after the index date					
Late COPD diagnosis Early COPD diagnosis	10,253 5544	6431 3163	159.44 175.26	0.91 (0.87–0.94)	<0.0001
Within 2 years after the index date					
Late COPD diagnosis Early COPD diagnosis	19,229 9614	11,406 5561	168.58 172.89	0.99 (0.96–1.02)	0.5024
Within 3 years after the index date					
Late COPD diagnosis Early COPD diagnosis	25,712 12,453	14,426 7012	178.23 177.60	1.03 (1.00–1.06)	0.0687
A&E visits					
Within 1 year after the index date					
Late COPD diagnosis Early COPD diagnosis	325 127	6431 3163	5.05 4.01	1.03 (0.79–1.33)	0.8488
Within 2 years after the index date					
Late COPD diagnosis Early COPD diagnosis	706 254	11,406 5561	6.19 4.57	1.11 (0.91–1.35)	0.3140
Within 3 years after the index date					
Late COPD diagnosis Early COPD diagnosis	999 345	14,426 7012	6.93 4.92	1.19 (1–1.42)	0.0482
Hospitalizations					
Within 1 year after the index date					
Late COPD diagnosis Early COPD diagnosis	3241 1196	6431 3163	50.40 37.81	1.05 (0.93–1.19)	0.3916
Within 2 years after the index date					
Late COPD diagnosis Early COPD diagnosis	7192 2476	11,406 5561	63.05 44.53	1.12 (1.02–1.23)	0.0165
Within 3 years after the index date					
Late COPD diagnosis Early COPD diagnosis	10,606 3538	14,426 7012	73.52 50.46	1.18 (1.08–1.28)	0.0001

Notes: *P*-value from the Wald test obtained from an adjusted negative binomial regression model. [a]Adjusted for the "a priori" variables plus for each parameter presented in the table. Clinic visits: depression, lung cancer, and diabetes. A&E visits: pneumonia, acute myocardial infarction, depression, and atrial fibrillation. Hospitalizations: baseline eosinophil groups, pneumonia, atrial fibrillation, hypertension, heart failure, and hyperlipidemia. Overall model: pneumonia, baseline eosinophil group, atrial fibrillation, depression, heart failure, and diabetes. [b]Each occurrence of a COPD-related clinic visit at different dates from the clinical or referral CPRD dataset with the COPD code.
Abbreviations: A&E, accident and emergency; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPRD, clinical practice research database.

Thus, we have included severity of COPD and adherence to medication as covariates to reduce the impact of this lead-time bias; however, it is not possible to completely rule this out.

Conclusion

This retrospective study demonstrated that about two-thirds of patients with COPD from UK primary care are diagnosed late despite presenting with respiratory

symptoms or other potential disease manifestations. Late diagnosis was associated with a shorter time to and higher risk of first exacerbation as well as increased exacerbation rate, which was reflected in the increased rate of hospitalizations in late-diagnosed patients versus early-diagnosed patients with COPD.

Abbreviations

A&E, accident and emergency; BMI, body mass index; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HES, Hospital Episode Statistics; HCRU, healthcare resource utilization; ICD-10, International Classification of Diseases 10th Revision; ICS, inhaled corticosteroids; ISAC, Independent Scientific Advisory Committee; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroid; SABA, short-acting β_2-agonist.

Data Sharing Statement

Novartis is committed to sharing with qualified external researchers' access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudyda tarequest.com.

Ethics Approvals

The study protocol was approved by the CPRD, Independent Scientific Advisory Committee for Medicines and Healthcare products Regulatory Agency database research, UK (ISAC 17_213), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for Publication

All authors approved the final version and provided consent to publish this manuscript.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, drafting the manuscript, revising the manuscript critically, read and approve the final draft of the manuscript for submission, gave final approval of the manuscript version to be published and agreed to be accountable for every step of the work.

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Disclosure

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