Original Article

Impact of chronic obstructive pulmonary disease on lung cancer symptom burden: a population-based study in Ontario, Canada

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Background: Chronic obstructive pulmonary disease (COPD) and lung cancer commonly coexist and have significant symptom overlap. We sought to compare the symptom burden of lung cancer patients with COPD to those without COPD.

Methods: We conducted a retrospective, cross-sectional study of stage I–IV lung cancer patients in Ontario, Canada, who completed the Edmonton Symptom Assessment Scale (ESAS) within 90 days of diagnosis. COPD was ascertained using a validated algorithm and patients were grouped as: no COPD, previously diagnosed COPD (at least 90 days prior to lung cancer diagnosis), and newly diagnosed COPD (within 90 days of lung cancer diagnosis). The association between COPD status and any moderate to severe symptom (ESAS ≥4) and the number of moderate to severe symptoms was determined using multivariable modified Poisson regression analyses. Multivariable linear regression analysis was used to compare total symptom distress scores. Analyses were stratified by limited (I/II) and advanced stage (III/IV).

Results: Among 38,898 lung cancer patients, 53% had COPD (previously diagnosed 43%, newly diagnosed 10%). Collectively, those with previously diagnosed COPD had the most severe symptom burden. Across all stages, both COPD groups had a significantly higher risk of experiencing any (relative risk: 1.04 to 1.18) and multiple moderate to severe symptoms (RR 1.05 to 1.24), in addition to higher total symptom distress scores ($P<0.0001$). Differences in symptom burden between groups were most pronounced among early-stage patients.

Conclusions: Lung cancer patients with underlying COPD have worse symptom burden, indicating a need for interventions that effectively alleviate symptoms.

Keywords: Lung cancer; chronic obstructive pulmonary disease (COPD); symptoms

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Introduction

Chronic obstructive pulmonary disease (COPD) is very common among patients with lung cancer and is associated with poor prognosis (1). Even though these two diseases commonly co-occur and have a significant overlap in symptoms, little attention has been given as to how the additional disease burden of COPD impacts the severity, number, or type of symptoms that lung cancer patients experience. Prior studies among this population have focused on respiratory symptoms, demonstrating that dyspnea is negatively correlated with quality of life and functional status among lung cancer patients (2) and respiratory symptoms are more common among patients with COPD specifically (3,4). However, the generalizability of these studies is limited due to being conducted in single centres, with small sample sizes, and lack of a comprehensive symptom burden assessment which includes non-respiratory symptoms that are common among patients with COPD or lung cancer such as pain, fatigue, and poor mental health (5-10). Furthermore, little attention has been given to undiagnosed COPD, which can also be symptomatic (11,12). Undiagnosed COPD is very common among individuals at risk for (13,14) or with lung cancer (15,16). To better guide clinical care, it is pertinent to understand the symptom management needs of lung cancer patients with COPD, including those with undiagnosed or newly diagnosed disease. For example, patients with significant symptom burden may benefit from early integration of supportive care and optimization of their COPD-related care.

Understanding the prevalence of symptoms and various combinations thereof, is important to identify the need for symptom management among this population. This can be accomplished through the use of patient-reported outcome measures (PROMs). Cancer centres in Ontario, Canada, routinely assess symptoms via the Edmonton Symptom Assessment Scale (ESAS) which includes nine symptoms (17). Through combining these PROMs with health administrative data, we evaluated symptom burden in a large-scale population-based study. We aimed to determine if underlying COPD—previously diagnosed or newly diagnosed—increases the collective symptom burden in lung cancer patients, through examining the type, severity, number of symptoms, and total symptom distress scores. We hypothesized that lung cancer patients with COPD have more severe symptom burden compared to lung cancer patients without COPD. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-560/rc).

Highlight box

Key findings

- Lung cancer patients with underlying chronic obstructive pulmonary disease (COPD) have worse symptom burden compared to lung cancer patients without COPD.

What is known and what is new?

- COPD and lung cancer have a significant overlap in risk factors and symptoms.
- We found that the lung cancer patients with COPD were more likely to experience any moderate to severe symptom, multiple moderate to severe symptoms and have worse symptom distress scores.

What is the implication, and what should change now?

- Our findings support the need to develop and test interventions that can alleviate symptom burden and also support the consideration of and investigation for COPD among lung cancer patients.

Methods

Study design

We conducted a population-based cross-sectional study in Ontario, Canada, where the population exceeds 14 million people. This project was approved by the University of Toronto Health Sciences Research Ethics Board (protocol #40390) and individual consent for this retrospective analysis was waived. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Population

The cohort included all individuals aged 18 and over in Ontario who were diagnosed with lung cancer between January 1, 2009 and December 31, 2019 (International Classification of Diseases for Oncology (ICD-O) code C34, morphology codes available in Table S1) and had a complete the ESAS questionnaire within 90 days of diagnosis. We excluded individuals who had missing information on cancer stage or covariates, as well as those with stage 0 or occult lung cancer. Individuals were followed from the date of lung cancer diagnosis for up to 90 days to observe completion of the ESAS questionnaire, with a maximum follow-up date of March 31, 2020.

Data sources

Provincial health administrative databases and disease registries that capture information about Ontario residents were used in this study. These datasets were linked using unique encoded identifiers and analyzed at ICES. ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. Detailed information on the databases available and the procedures at ICES can be found here: https://www.ices.on.ca/.

The population-based Ontario Cancer Registry (OCR) contains information on all cancers diagnosed in Ontario, including information on cancer stage and histological subtype. The Canadian Institute of Health Information (CIHI), Discharge Abstract Database (DAD), the National Ambulatory Care Reporting System (NACRS) Database, and the Ontario Health Insurance Plan (OHIP) Physician Claims database cover virtually all hospitalizations, emergency department, or outpatient physician visits in Ontario, Canada. The Registered Persons Database (RPDB) captures demographic information. The Immigration, Refugees and Citizenship Canada's (IRCC) permanent resident database captures immigration to Canada since 1985. The Symptom Management Reporting Database (SMRD) contains scores for the ESAS questionnaire, which is used in clinical practice at cancer centres in Ontario, Canada to measure symptom severity and distress in cancer patients. The Ontario Drug Benefit (ODB) database contains information on prescription medications for residents aged 65 or over.

Main exposure: COPD

A previously validated case definition was used to identify individuals with physician-diagnosed COPD using health administrative data. This case definition of at least one ambulatory claim or hospitalization for COPD based on ICD-9 codes 491, 492 or 496 and ICD-10 codes J41, J42, J43 or J44 (18) has been shown to have 85% sensitivity and 78% specificity compared to a clinical reference standard (18) and has been used previously to study COPD in population-based studies (19,20). People diagnosed with COPD >90 days prior to lung cancer were considered to have 'previously diagnosed COPD'. Individuals diagnosed with COPD within 90 days prior to, on the day of, or up to 90 days after lung cancer diagnosis, were considered to have 'newly diagnosed COPD'.

Outcomes

The ESAS (21-23) is self-administered via an electronic device. Patients rate the severity of nine symptoms; anxiety, depression, drowsiness, lack of appetite, nausea, pain, shortness of breath, tiredness, and wellbeing. The numerical rating scale ranges from 0 (none) to 10 (worst possible). If patients completed the ESAS more than once during the 90-day window, the earliest ESAS completion was used. A score of ≥4 was indicative of a moderate to severe rating (24). A total symptom distress score (out of 90) was also calculated by summing the individual ratings of the nine symptoms.

The primary outcome was the prevalence of moderate to severe symptoms. Secondary outcomes included the number of moderate to severe symptoms and the total symptom distress score.

Covariates

Demographic variables included: age, sex, residing in a rural area (<10,000 residents), neighbourhood income quintile for urban areas, immigration status [recent immigrants to Canada (≤10 years), long-term residents (>10 years) or non-immigrants since 1985], region of Ontario [five regions based on the Local Health Integration Networks (LHINs): Toronto, Central, East, North, and West]. The type of lung cancer [non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), or unspecified], and stage of lung cancer (early: I/II, advanced: III/IV). Stage of lung cancer was ascertained using the 'Best stage' variable in the OCR, which uses a collaborative method consistent with the tumour, lymph node, metastasis (TNM) international staging system (25). Comorbidities were ascertained from the John Hopkins ACG System® Version 10.0, using the Aggregated Diagnostic Groups (ADGs). Individuals were categorized as having high (≥10 ADGs) or low comorbidity (<10 ADGs). Additionally, validated algorithms were used to identify individuals with asthma (26) and dementia (since April 1996) (27), and congestive heart failure (28) and diabetes (29) (since April 1991).

Statistical analysis

An overall analysis that considered all stages of lung cancer was followed by stratified analyses for individuals with

early (I/II) or advanced (III/IV) stage. For the primary outcome, first descriptive statistics were used to compare the prevalence of moderate to severe symptoms among the disease groups. A standardized mean difference (SMD) >0.1 was considered statistically significant. Second, unadjusted and multivariable modified Poisson regression models were used to assess the impact of COPD (previously diagnosed and newly diagnosed) on the relative risk (RR) of reporting any moderate to severe symptom. Multivariable regression analyses were adjusted for the following covariates; sex, age, immigration status, rurality and urban income quintile, and comorbidities using the Hopkins ADGs.

In secondary analysis, unadjusted and multivariable negative binomial regression models were used to assess the impact of COPD on the relative rate of number of moderate to severe symptoms, and unadjusted and multivariable linear regression models were used to assess the impact of COPD on the total symptom distress score.

Additional analyses

Among individuals with COPD, we also further stratified by 'advanced COPD' and 'non-advanced COPD' to address the impact of disease severity on the risk of moderate to severe symptoms. Individuals were determined to have advanced COPD if they met one of the following criteria; one or more hospitalizations within the previous year or after index, with a most-responsible diagnosis for COPD-related respiratory disease (ICD-10 codes J10-18, J20, J22, J40, J42-J44) or receipt of long-term oxygen therapy (30). To account for the potential misclassification of COPD, we performed a sensitivity analysis using a stricter case definition (two or more outpatient claims or at least one hospitalization for COPD within a 2-year period prior to lung cancer diagnosis) which has higher specificity (91.5%) (18). We also assessed the impact of COPD medications on reporting any moderate to severe symptom through a sensitivity analysis of individuals with previously diagnosed COPD who were aged 66 or above. In Ontario, medication data is only available for individuals aged 65 and above and we included a look-back period to capture medications prescribed within one-year of lung cancer diagnosis. Individuals were considered to be taking COPD medications if they had a prescription claim for any of the following classes of medications: long-acting anti-cholinergic (LAAC), long-acting beta agonist (LABA), inhaled corticosteroid (ICS), combination LABA + LAAC, LABA + ICS.

Results

Among 97,797 individuals diagnosed with lung cancer during the study period, 58,899 individuals were excluded (*Figure 1*). Among those excluded, 153 had stage 0 or occult cancer, 15,068 had missing stage information, 43,599 did not complete the ESAS within 90 days of diagnosis, and 79 had missing covariate information (*Figure 1*). There were notable differences between individuals who completed the ESAS within 90 days of diagnosis and individuals who did not complete the ESAS within 90 days of diagnosis (Table S2). Individuals who did not completed the ESAS within 90 days of diagnosis were, on average, older, more likely to have early-stage lung cancer or an unspecified type of lung cancer, live in the Toronto region, and have dementia or congestive heart failure. There was no difference in proportions of people by COPD status among those who did and did not complete the ESAS within 90 days of diagnosis.

A total of 38,898 lung cancer patients completed the ESAS within 90 days of diagnosis and were included in the study (*Figure 1*), most of whom were diagnosed with advanced stage lung cancer (77%, n=29,995). The median time from lung cancer diagnosis to completion of ESAS was 28 days [interquartile range (IQR), 16 to 48 days]. Overall, 47% of patients (n=18,271) did not have COPD, 43% (n=16,697) had previously diagnosed COPD, and 10% (n=3,930) had newly diagnosed COPD. On average, the time between COPD and lung cancer diagnosis was 9.7 years (IQR, 4.7 to 16.4 years) for people with previously diagnosed COPD, and +1 day (IQR, −20 to +36 days) for people with newly diagnosed COPD. *Table 1* depicts the characteristics of the study cohort.

Prevalence of moderate or severe symptoms

Most patients (80%, n=30,994) reported at least one moderate to severe symptom within 90 days of lung cancer diagnosis. More patients with advanced-stage lung cancer reported moderate to severe symptoms (82%, n=24,618), however many patients with early-stage disease also reported moderate to severe symptoms (72%, n=6,376). Among patients with previously diagnosed COPD, 82% reported at least one moderate or severe symptom, with tiredness (54%), poor wellbeing (49%) and shortness of breath (46%) being most common (*Figure 2A*). Similarly, 81% of patients with newly diagnosed COPD reported at least one moderate to severe symptom, with moderate to severe tiredness (53%),

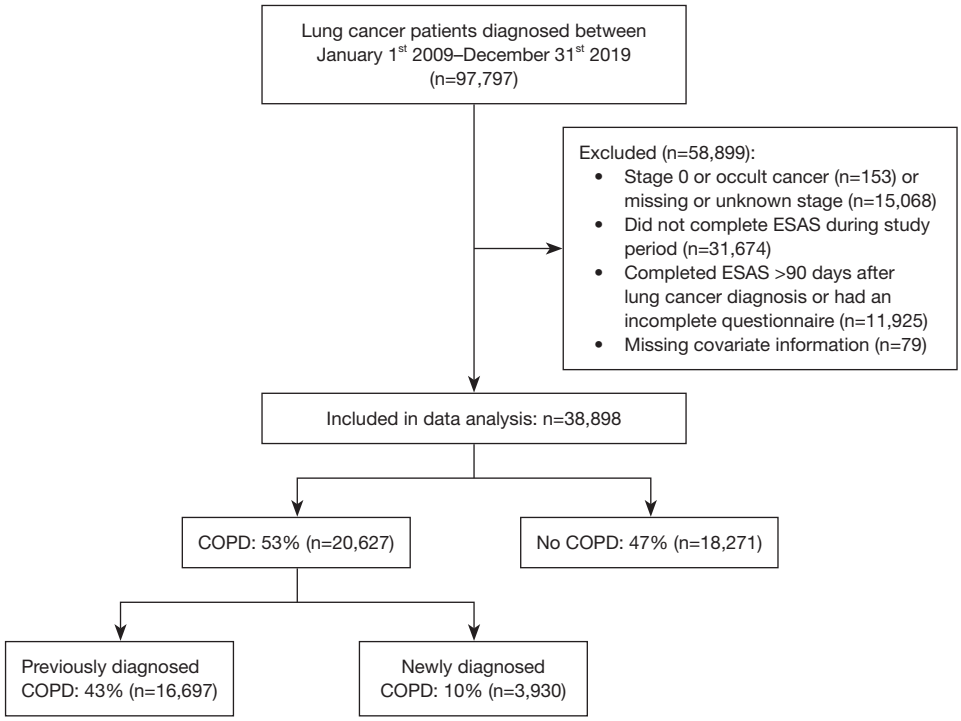

Figure 1 Flow diagram for study cohort. ESAS, Edmonton Symptom Assessment Scale; COPD, chronic obstructive pulmonary disease.

poor wellbeing (49%) and shortness of breath (43%) being the most common (*Figure 2A*). A total of 77% of patients without COPD reported at least one moderate to severe symptom. Moderate to severe tiredness (50%) and poor wellbeing (48%) were also common among patients without COPD and fewer patients reported moderate to severe shortness of breath (34%) (*Figure 2A*).

Differences in the prevalence of moderate to severe symptoms with respect to COPD status were greatest among early-stage patients (*Figure 2B*). Compared to early-stage patients without COPD, more patients with previously diagnosed COPD reported moderate to severe drowsiness, lack of appetite, pain, shortness of breath, tiredness, and poor wellbeing (SMD >0.1) (*Figure 2B*). Among early-stage patients with newly diagnosed COPD, only moderate to severe shortness of breath and tiredness were more common compared to patients without COPD (SMD >0.1) (*Figure 2B*). In advanced stage lung cancer, moderate to severe shortness of breath was the only symptom which was more prevalent among patients with COPD (previously diagnosed and newly diagnosed) compared to patients without COPD (SMD >0.1) (*Figure 2C*).

The results of the modified Poisson regression analyses are reported in *Table 2*. After adjusting for confounders, patients with previously diagnosed COPD had a higher risk of experiencing any moderate to severe symptom compared to patients without COPD (RR: 1.08, 95% CI: 1.07 to 1.09). The effect was greatest among patients with early-stage lung cancer (RR: 1.18, 95% CI: 1.15 to 1.22). The risk of experiencing any moderate to severe symptom was also slightly elevated for patients with newly diagnosed COPD compared to patients without COPD (RR: 1.05, 95% CI: 1.03 to 1.07).

Number of moderate to severe symptoms

Patients experienced a median of three moderate to severe symptoms (IQR, 1 to 5) which was consistent among the exposure groups. The results of the negative binomial regression analyses are provided in *Table 3*. Across all stages and after adjusting for confounding variables, the rate of moderate to severe symptoms was higher among lung cancer patients with COPD compared to patients without COPD. The greatest relative rate was among early-stage patients with previously diagnosed COPD (RR: 1.24, 95% CI: 1.19 to 1.30).

Table 1 Baseline characteristics of study cohort (n=38,898)

Characteristics	No COPD (n=18,271)	Previously diagnosed COPD (n=16,697)	Newly diagnosed COPD (n=3,930)	SMD
Stage, n (%)				0.252
Early (I/II)	3,356 (18.40)	4,791 (28.70)	756 (19.20)	
Advanced (III/IV)	14,915 (81.60)	11,906 (71.30)	3,174 (80.80)	
Type of lung cancer, n (%)				
NSCLC	15,383 (84.20)	13,278 (79.50)	3,207 (81.60)	0.081
SCLC	2,164 (11.80)	2,579 (15.40)	572 (14.60)	0.07
Unspecified	724 (4.00)	840 (5.00)	151 (3.80)	0.039
Age, mean (SD)	67.4 (11.0)	70.8 (9.1)	67.7 (9.6)	0.231
Sex, n (%)				0.033
Male	9,268 (50.70)	8,517 (51.00)	2,091 (53.20)	
Female	9,003 (49.30)	8,180 (49.00)	1,839 (46.80)	
Region of Ontario, n (%)				
Toronto	1,026 (5.60)	757 (4.50)	172 (4.40)	0.038
Central	4,327 (23.70)	2,879 (17.20)	783 (19.90)	0.107
East	5,613 (30.70)	5,295 (31.70)	1,041 (26.50)	0.077
North	1,609 (8.80)	1,978 (11.80)	473 (12.00)	0.071
West	5,696 (31.20)	5,788 (34.70)	1,462 (37.20)	0.084
Immigration status, n (%)				
Recent immigrant (≤10 years)	374 (2.00)	51 (0.30)	46 (1.20)	0.111
Long-term resident (>10 years)	1,152 (6.30)	402 (2.40)	142 (3.60)	0.129
Non-immigrant	16,745 (91.60)	16,244 (97.30)	3,742 (95.20)	0.167
Rurality & urban income quintile, n (%)				
Urban 1 (lowest)	3,057 (16.70)	3,598 (21.50)	753 (19.20)	0.082
Urban 2	3,359 (18.40)	3,259 (19.50)	782 (19.90)	0.026
Urban 3	3,056 (16.70)	2,710 (16.20)	620 (15.80)	0.017
Urban 4	3,128 (17.10)	2,215 (13.30)	576 (14.70)	0.072
Urban 5	2,977 (16.30)	1,954 (11.70)	511 (13.00)	0.088
Rural	2,694 (14.70)	2,961 (17.70)	688 (17.50)	0.054
Comorbidities, n (%)				
Median number of ADGs (IQR)	8 (5 to 10)	9 (7 to 12)	8 (5 to 10)	0.297
High (>10 ADGs)	5,710 (31.30)	7,877 (47.20)	1,185 (30.20)	0.236
Asthma	1,475 (8.10)	4,136 (24.80)	369 (9.40)	0.309
Dementia	377 (2.10)	541 (3.20)	59 (1.50)	0.077
Diabetes	4,238 (23.20)	4,811 (28.80)	878 (22.30)	0.099
Congestive heart failure	1,069 (5.90)	2,486 (14.90)	290 (7.40)	0.201

COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SD, standard deviation; ADGs, Aggregated Diagnosis Groups; IQR, interquartile range.

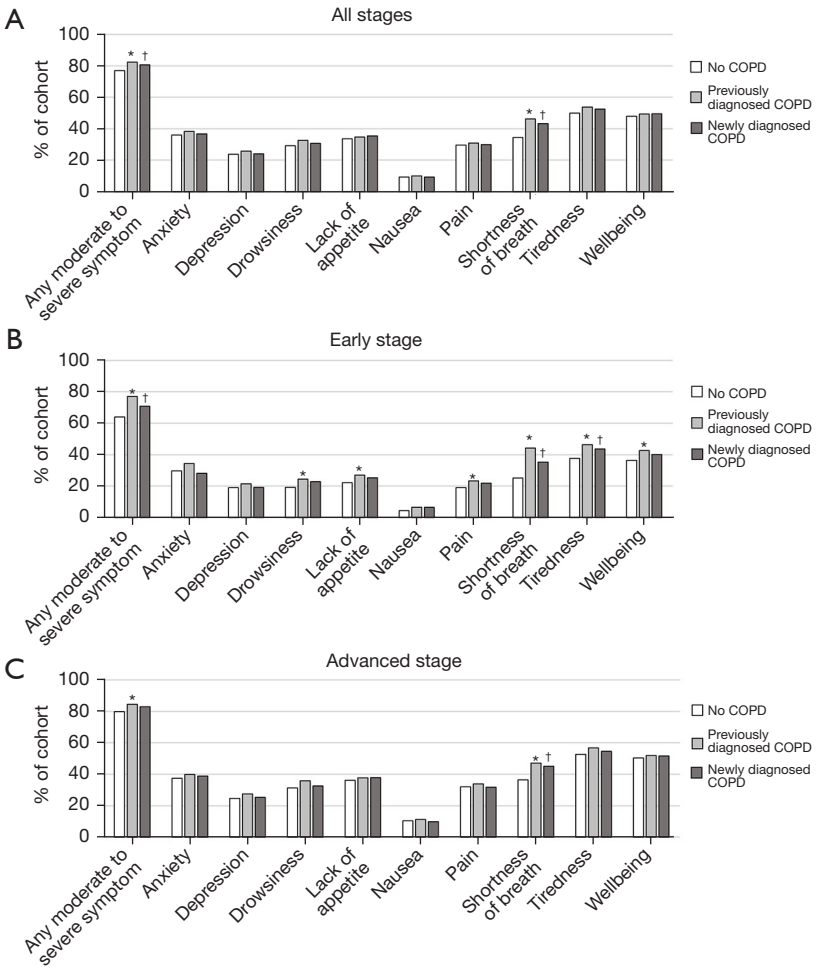

Figure 2 Prevalence of moderate to severe symptoms by COPD status. Symptoms were assessed within 90 days of lung cancer diagnosis with an Edmonton Symptom Assessment Scale score ≥4 indicating moderate to severe symptoms. Results for all stages (A), early stage (B) and advanced stage (C) are depicted. *, a SMD >0.1 between no COPD and previously diagnosed COPD groups; †, a SMD >0.1 between no COPD and newly diagnosed COPD groups. COPD, chronic obstructive pulmonary disease; SMD, standardized mean difference.

Total symptom distress

Lung cancer patients with previously diagnosed COPD had a median total symptom distress score of 24 (IQR, 12 to 38). Patients with newly diagnosed COPD had a median total symptom distress score of 23 (IQR, 11 to 38) and the median score for patients without COPD was 21 (IQR, 10 to 36). Results of the linear regression analyses are provided in *Table 4*. The greatest difference in total symptom distress scores was observed among the early-stage cohort, where patients with previously diagnosed COPD scored, on average, 3.60 points higher (95% CI: 2.88 to 4.31) compared to patients without COPD (*Table 4*).

Additional analyses

Among individuals with COPD, 23% (n=4,726) met the criteria for advanced COPD (24% of patients with previously diagnosed COPD and 18% of patients with previously undiagnosed COPD). The vast majority of patients with advanced COPD reported at least one moderate to severe symptom (91%, n=4,286). Overall, patients with advanced COPD had a higher risk of reporting any moderate to severe symptom compared to

Table 2 Results of the modified Poisson regression analyses for the association between COPD status and reporting any moderate to severe symptom

Variables	Relative risk (95% CI)	
	Unadjusted	Adjusted*
Overall (all stages)		
Previously diagnosed COPD	1.07 (1.06 to 1.08)	1.08 (1.07 to 1.09)
Newly diagnosed COPD	1.05 (1.03 to 1.07)	1.05 (1.03 to 1.07)
No COPD	Reference	Reference
Early stage		
Previously diagnosed COPD	1.21 (1.17 to 1.24)	1.18 (1.15 to 1.22)
Newly diagnosed COPD	1.11 (1.05 to 1.16)	1.10 (1.04 to 1.15)
No COPD	Reference	Ref Reference
Advanced stage		
Previously diagnosed COPD	1.06 (1.05 to 1.07)	1.04 (1.03 to 1.06)
Newly diagnosed COPD	1.04 (1.02 to 1.06)	1.04 (1.02 to 1.05)
No COPD	Reference	Reference

*, model adjusted for age, sex, type of lung cancer, rurality & urban income quintile, immigration status, region of Ontario, and comorbidity (John Hopkins Aggregated Diagnostic Groups). The overall analysis was also adjusted for lung cancer stage. COPD, chronic obstructive pulmonary disease; CI, confidence interval.

Table 3 Results of the negative binomial regression analyses for the association between COPD status and the number of moderate to severe symptoms

Variables	Relative rate (95% CI)	
	Unadjusted	Adjusted*
Overall (all stages)		
Previously diagnosed COPD	1.10 (1.08 to 1.12)	1.13 (1.11 to 1.15)
Newly diagnosed COPD	1.06 (1.03 to 1.09)	1.07 (1.04 to 1.11)
No COPD	Reference	Reference
Early stage		
Previously diagnosed COPD	1.27 (1.21 to 1.33)	1.24 (1.19 to 1.30)
Newly diagnosed COPD	1.14 (1.05 to 1.24)	1.13 (1.04 to 1.22)
No COPD	Reference	Reference
Advanced stage		
Previously diagnosed COPD	1.10 (1.08 to 1.12)	1.08 (1.06 to 1.11)
Newly diagnosed COPD	1.05 (1.02 to 1.09)	1.05 (1.02 to 1.08)
No COPD	Reference	Reference

*, model adjusted for age, sex, type of lung cancer, rurality & urban income quintile, immigration status, region of Ontario, and comorbidity (John Hopkins Aggregated Diagnostic Groups). The overall analysis was also adjusted for lung cancer stage. COPD, chronic obstructive pulmonary disease; CI, confidence interval.

Table 4 Results of the linear regression analyses for the association between COPD status and the ESAS total symptom distress score (out of 90)

Variables	Unadjusted		Adjusted*	
	β (SE)	95% CI	β (SE)	95% CI
Overall (all stages)				
Previously diagnosed COPD	2.08 (0.19)	1.71 to 2.45	2.75 (0.19)	2.37 to 3.12
Newly diagnosed COPD	1.49 (0.31)	0.88 to 2.10	1.74 (0.30)	1.14 to 2.33
No COPD	Reference		Reference	
Early stage				
Previously diagnosed COPD	4.04 (0.36)	3.33 to 4.74	3.60 (0.37)	2.88 to 4.31
Newly diagnosed COPD	2.00 (0.64)	0.74 to 3.27	1.71 (0.64)	0.46 to 2.96
No COPD	Reference		Reference	
Advanced stage				
Previously diagnosed COPD	2.43 (0.22)	2.00 to 2.86	2.03 (0.23)	1.59 to 2.47
Newly diagnosed COPD	1.45 (0.35)	0.77 to 2.14	1.40 (0.35)	0.72 to 2.08
No COPD	Reference		Reference	

*, model adjusted for age, sex, type of lung cancer, rurality & urban income quintile, immigration status, region of Ontario, and comorbidity (John Hopkins Aggregated Diagnostic Groups). The overall analysis was also adjusted for lung cancer stage. COPD, chronic obstructive pulmonary disease; ESAS, Edmonton Symptom Assessment Scale; SE, standard error; CI, confidence interval.

patients without COPD (RR: 1.16, 95% CI: 1.14 to 1.18) (*Table 5*). The impact of advanced COPD was greatest among patients with early-stage lung cancer (RR: 1.30, 95% CI: 1.24 to 1.35), yet still evident among patients with advanced-stage lung cancer (RR: 1.14, 95% CI: 1.12 to 1.16).

Among individuals with previously diagnosed COPD, 11,902 were aged 66 and over and had medication data available, of which 60.2% were prescribed COPD medication in the year prior to lung cancer diagnosis. Among this subgroup, individuals prescribed COPD medication had a higher risk of reporting any moderate to severe symptom compared to patients who were not prescribed COPD medication (RR: 1.09, 95% CI: 1.07 to 1.10) (*Table 5*).

When using a case definition with higher specificity to account for potential misclassification of COPD, our findings were similar to the primary analysis (*Table 5*).

Discussion

In this population-based study, we utilized PROMs to understand the impact of underlying COPD on symptom burden among lung cancer patients. We found that lung cancer patients with COPD experienced more severe symptom burden. This association was most evident among patients with early-stage lung cancer, and not as pronounced in patients with advanced stage lung cancer. Previously diagnosed COPD had the greatest impact on symptom burden, however even individuals with newly diagnosed COPD had worse symptom burden compared to individuals without COPD. These findings speak to the importance of considering comorbid respiratory disease when caring for lung cancer patients and the need for interventions that can effectively alleviate symptom burden for patients with underlying COPD.

Our findings were largely driven by differences in symptoms with the greatest overlap between lung cancer and COPD (e.g., tiredness and shortness of breath). Even patients with newly diagnosed COPD had worse shortness of breath and, in the early-stages, worse tiredness compared to patients without COPD. This finding supports the consideration of and investigation for COPD among lung cancer patients who are symptomatic. It is important to note that patients with 'newly diagnosed COPD' were likely diagnosed with COPD due to the clinical assessment for lung cancer and presumably their COPD may have remained undiagnosed otherwise. It is commonly assumed that 'undiagnosed' COPD is mild and not clinically meaningful. However, our findings show that individuals with 'undiagnosed' COPD (or in our case, 'newly diagnosed' COPD) are symptomatic, which is consistent

Table 5 Results of the sensitivity analyses: modified Poisson regression analyses to assess the impact of COPD severity, COPD management, and potential misclassification of COPD on the risk of reporting any moderate to severe symptom

Variables	Relative risk (95% CI)	
	Unadjusted	Adjusted*
Advanced COPD		
Overall (all stages)		
Advanced COPD (n=4,726)	1.18 (1.16 to 1.20)	1.16 (1.14 to 1.18)
Non-advanced COPD (n=15,901)	1.03 (1.02 to 1.04)	1.05 (1.03 to 1.06)
No COPD (n=18,271)	Reference	Reference
Early stage		
Advanced COPD (n=939)	1.33 (1.28 to 1.39)	1.30 (1.24 to 1.35)
Non-advanced COPD (n=4,608)	1.16 (1.13 to 1.20)	1.14 (1.11 to 1.18)
No COPD (n=3,356)	Reference	Reference
Advanced stage		
Advanced COPD (n=3,787)	1.15 (1.13 to 1.17)	1.14 (1.12 to 1.16)
Non-advanced COPD (n=11,293)	1.02 (1.01 to 1.03)	1.01 (1.00 to 1.02)
No COPD (n=14,915)	Reference	Reference
Previously diagnosed COPD (age ≥66)		
Overall (all stages)		
COPD medication (n=7,161)	1.08 (1.06 to 1.10)	1.09 (1.07 to 1.10)
No COPD medication (n=4,741)	Reference	Reference
Early stage		
COPD medication (n=2,457)	1.13 (1.08 to 1.17)	1.12 (1.08 to 1.16)
No COPD medication (n=1,299)	Reference	Reference
Advanced stage		
COPD medication (n=4,704)	1.08 (1.06 to 1.10)	1.07 (1.05 to 1.09)
No COPD medication (n=3,442)	Reference	Reference
COPD case definition with higher specificity		
Overall (all stages)		
COPD (n=11,104)	1.08 (1.07 to 1.09)	1.09 (1.08 to 1.10)
No COPD (n=27,794)	Reference	Reference
Early stage		
COPD (n=3,506)	1.20 (1.17 to 1.23)	1.18 (1.15 to 1.21)
No COPD (n-5,397)	Reference	Reference
Advanced stage		
COPD (n=7,598)	1.06 (1.05 to 1.08)	1.05 (1.04 to 1.06)
No COPD (n=22,397)	Reference	Reference

*, models adjusted for age, sex, type of lung cancer, rurality & urban income quintile, immigration status, region of Ontario, and comorbidity (John Hopkins Aggregated Diagnostic Groups). The overall analysis was also adjusted for lung cancer stage. COPD, chronic obstructive pulmonary disease; CI, confidence interval.

with prior studies (11-13). Given that nearly half of patients with newly diagnosed COPD reported moderate to severe shortness of breath and tiredness, it is pertinent to ensure that these patients are receiving COPD-related care in addition to their lung cancer treatment. For lung cancer patients with comorbid COPD, integrating respirology care has been shown to improve guideline-based management of COPD (31), however, the impact of this approach on symptom burden remains unclear. When compared to usual care, integrated respirologist management for lung cancer patients with COPD, with an emphasis on inhaled therapy, showed non-significant trends towards improvement in dyspnea and fatigue with no difference in global quality of life scores (32). The results of our sensitivity analysis suggest COPD medication heightened the risk of reporting any moderate to severe symptom however this may be a reflection of inappropriate treatment, or simply that individuals with more severe COPD were more likely to be prescribed COPD medication. Further studies are needed to determine whether integrated approaches to caring for patients with lung cancer and COPD can improve patient-oriented outcomes. Additional comorbidities should also be considered when designing interventions to alleviate symptom burden among this population.

A higher comorbidity index is associated with reporting moderate to severe symptoms among lung cancer patients (9,10). In our study, individuals with previously diagnosed COPD had a higher comorbidity index and were more likely to have asthma and congestive heart failure compared to individuals with newly diagnosed COPD or individuals without COPD, which may have contributed to their collective symptom burden. Additionally, lung cancer treatment or medications for other chronic diseases can elicit symptoms such as drowsiness or lack of appetite and this may have influenced our results. To our knowledge, only two studies (3,4) have reported on non-respiratory symptoms among lung patients with and without COPD and did not find any significant differences in the prevalence of pain or fatigue, however these studies did not consider the symptom severity or stratify by stage which may explain our conflicting results. Regardless of the complex relationship between lung cancer symptoms and comorbidities, our findings suggest that attention should also be given to non-respiratory symptoms, such as drowsiness, lack of appetite, pain, and tiredness when caring for early-stage lung cancer patients with comorbid COPD. Their overall well-being should also be considered.

Since COPD has the greatest impact on symptom burden in the early-stages of lung cancer, our findings support the need for early and ongoing symptom monitoring and management of symptoms among this population. Prior research has shown that symptoms continue to persist over time among lung cancer patients (9,10), emphasizing the need for routine symptom monitoring among this population. Since the implementation of routine symptom monitoring with the ESAS questionnaire by Cancer Care Ontario in 2007, the proportion of cancer patients being screened for symptoms has been steadily increasing (33). Yet differences between ESAS completers and non-completers are evident (9,10,34). In our study, regional differences were apparent among ESAS completers and non-completers, but there were also additional disparities, including fewer patients with early-stage disease. This emphasizes the need for earlier integration of symptom monitoring in lung cancer care. Routine symptom monitoring with the ESAS in Ontario has been associated with reduced healthcare utilization and improved survival among cancer patients (35,36). Additional benefits of PROM feedback interventions include improved physician-patient communication and quality of life, albeit there appears to be no impact on symptom burden (37). However, PROMs can still be implemented successfully into clinical practice and serve as indicators of when to escalate care. In Ontario, efforts should be undertaken to have universal completion of symptom screening by all cancer patients, early in their disease trajectory. Cancer centres or hospitals outside of this province should also consider early implementation of symptom screening to quickly identify and manage patient's needs.

Among the strengths of this study, the most notable is the large sample size and inclusive, population-based, real-world approach. We assessed symptom burden using a validated questionnaire, including reporting the prevalence of specific symptoms as well as using regression analyses to account for potential confounders impacting symptom burden. Additionally, we stratified by previously diagnosed COPD and newly diagnosed COPD to provide insights into the needs of these unique populations.

Although our sample size was very large, the generalizability of our findings is limited by the exclusion of lung cancer patients with missing stage information and those who did not complete the ESAS within 90 days of lung cancer diagnosis, which was a significant proportion of the population. We chose to focus on symptoms within 90 days of diagnosis to compare symptoms at a similar time point for all patients and because early identification of

symptoms can be used to guide clinical decisions. We also restricted the population to those with stage information which allowed us to identify important differences in symptom burden with respect to lung cancer stage. Patients with missing stage information were on average, older, more likely to live in Central Ontario, had a higher comorbidity index and were more likely to have dementia, congestive heart failure. Individuals with missing stage were also more likely to have previously diagnosed COPD but less likely to have newly diagnosed COPD. If individuals with more severe COPD, and subsequently more severe symptom burden, were excluded, this means our study may underestimate the impact of COPD on symptom burden. Another limitation of our study was the inability to ascertain smoking status or history and thus we could not address its impact on symptom burden. Additionally, we were unable to stratify by the severity of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (38) due to a lack of spirometry results in our databases. However, we stratified by advanced and non-advanced COPD with a definition used previously by our team to identify individuals in need of palliative care (30). Findings were consistent in this stratified analysis and suggested that advanced COPD had an even greater impact on symptom severity. Our results also reflect a real-world population since spirometry is widely underutilized (39) and there are significant barriers to spirometry testing (39,40). Using health administrative data to identify individuals also introduces the possibility of misclassification of COPD. We also addressed this limitation by using a case definition with higher specificity and found consistent results with our primary analysis.

The findings of our cohort study suggest differences in symptom burden among patients with and without COPD around the time of lung cancer diagnosis in a real-world setting. However, given that time of ESAS completion was not uniform among the population, we cannot comment on whether these differences are affected by lung cancer treatment or persist in the survivorship stage. It is also difficult to ascertain the cause of the symptoms (e.g., lung cancer, COPD, other comorbidities or life situations). We also cannot comment on the impact of symptom burden on the quality of life for lung cancer patients with and without COPD or the impact on healthcare utilization or mortality, which are important directions that should be explored further. Future studies should also consider incorporating the patient experience, since the symptom which is rated as most severe on the ESAS does not always correlate with what patients perceive to be the most bothersome symptom (41). Our findings also support the need for early symptom monitoring among lung cancer patients and evaluating interventions which integrate respiratory care for patients with comorbid COPD to alleviate symptom burden.

Conclusions

Symptom burden is worse among lung cancer patients with underlying COPD. There is a need to develop and test interventions that aim to alleviate symptom burden among this population.

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Footnote

Reporting Checklist: The authors have completed the

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This project was approved by the University of Toronto Health Sciences Research Ethics Board (protocol #40390) and individual consent for this retrospective analysis was waived. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Supplementary

Table S1 Lung cancer morphology codes

Type of lung cancer	Morphology codes
Non-small cell lung cancer	
Adenocarcinoma	80503, 80523, 81303, 81403, 81406, 82503, 82513, 82523, 82533, 82543, 82553, 82563, 82573, 82603, 82653, 84803, 84813, 85503, 85513, 85713, 85723, 85743, 85753, 85763
Squamous cell carcinoma	80703, 80713, 80723, 80733, 80743, 80763, 80833, 80843
Large cell carcinoma	80033, 80043, 80123, 80133, 80143, 80303, 80313, 80323, 80343, 80353, 82463
Adenosquamous	85603, 85623
Not otherwise specified	80103, 80203, 80463, 81233
Small cell lung cancer	80023, 80413, 80423, 80443, 80453
Unspecified	80003, 80013, 82303

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Table S2 Characteristics of individuals who completed the ESAS within 90 days of diagnosis and individuals who did not complete the ESAS within 90 days of diagnosis (n=82,576)

Characteristics	Did not complete ESAS within 90-days of diagnosis (n=43,478)	Completed ESAS within 90-days of diagnosis (n=38,898)	SMD
COPD status, n (%)			
Previously diagnosed COPD	20,333 (46.8)	16,697 (42.9)	0.077
Newly diagnosed COPD	4,447 (10.2)	3,930 (10.1)	0.004
No COPD	18,698 (43.0)	18,271 (47.0)	0.08
Stage, n (%)			0.222
Early (I/II)	14,259 (32.8)	8,903 (22.9)	
Advanced (III/IV)	29,219 (67.2)	29,995 (77.1)	
Type of lung cancer, n (%)			
NSCLC	32,381 (74.5)	31,868 (81.9)	0.182
SCLC	4,146 (9.5)	5,315 (13.7)	0.128
Unspecified	6,951 (16.0)	1,715 (4.4)	0.39
Age, mean (SD)	71.6 (10.5)	68.9 (10.2)	0.261
Sex, n (%)			0.016
Male	22,569 (51.9)	19,876 (51.1)	
Female	20,909 (48.1)	19,022 (48.9)	
Rurality & income quintile, n (%)			
Rural	6,187 (14.2)	6,343 (16.3)	0.058
1 (lowest)	9,740 (22.4)	7,408 (19.0)	0.083
2	8,491 (19.5)	7,400 (19.0)	0.013
3	7,111 (16.4)	6,386 (16.4)	0.002
4	6,296 (14.5)	5,919 (15.2)	0.021
5 (highest)	5,653 (13.0)	5,442 (14.0)	0.029
Region of Ontario, n (%)			
Central	10,638 (24.5)	7,989 (20.5)	0.094
East	12,006 (27.6)	11,949 (30.7)	0.07
North	3,291 (7.6)	4,060 (10.4)	0.101
West	13,677 (31.5)	12,945 (33.3)	0.038
Toronto	3,866 (8.9)	1,955 (5.0)	0.154
Immigration status, n (%)			
Recent immigrant (≤10 years)	585 (1.3)	471 (1.2)	0.012
Long-term resident (>10 years)	2,146 (4.9)	1,696 (4.4)	0.028
Non-immigrant	40,747 (93.7)	36,731 (94.4)	0.031
Comorbidity by John Hopkins Aggregated Diagnostic Groups, n (%)			0.073
High (≥10)	18,061 (41.5)	14,772 (38.0)	
Low (<10)	25,417 (58.5)	24,126 (62.0)	
Specific comorbidities, n (%)			
Asthma	7,387 (17.0)	5,980 (15.4)	0.044
Congestive heart failure	6,295 (14.5)	3,845 (9.9)	0.141
Diabetes	12,215 (28.1)	9,927 (25.5)	0.058
Dementia	2,689 (6.2)	977 (2.5)	0.181

ESAS, Edmonton Symptom Assessment Scale; SMD, standardized mean difference; COPD, chronic obstructive pulmonary disease; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SD, standard deviation.

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