The Oncologist®

Lung Cancer

Province-Wide Analysis of Patient-Reported Outcomes for Stage IV Non-Small Cell Lung Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Non-small cell lung cancer • Stage IV • Edmonton Symptom Assessment System • Symptom burden • Patient-reported outcomes

Abstract

Background. In Ontario, Canada, patient-reported outcome (PRO) evaluation through the Edmonton Symptom Assessment System (ESAS) has been integrated into clinical workflow since 2007. As stage IV non-small cell lung cancer (NSCLC) is associated with substantial disease and treatment-related morbidity, this province-wide study investigated moderate to severe symptom burden in this population.

Materials and Methods. ESAS collected from patients with stage IV NSCLC diagnosed between 2007 and 2018 linked to the Ontario provincial health care system database were studied. ESAS acquired within 12 months following diagnosis were analyzed and the proportion reporting moderate to severe scores (ESAS ≥4) in each domain was calculated. Predictors of moderate to severe scores were identified using multivariable Poisson regression models with robust error variance.

Results. Of 22,799 patients, 13,289 (58.3%) completed ESAS (84,373 assessments) in the year following diagnosis. Patients with older age, with high comorbidity, and not receiving active cancer therapy had lower ESAS completion. The majority (94.4%) reported at least one moderate to severe symptom. The most prevalent were tiredness (84.1%), low well-being (80.7%), low appetite (71.7%), and shortness of breath (67.8%). Most symptoms peaked at diagnosis and, while declining, remained high in the following year. On multivariable analyses, comorbidity, low income, nonimmigrants, and urban residency were associated with moderate to severe symptoms. Moderate to severe scores in all ESAS domains aside from anxiety were associated with radiotherapy within 2 weeks prior, whereas drowsiness, low appetite and well-being, nausea, and tiredness were associated with systemic therapy within 2 weeks prior.

Conclusion. This province-wide PRO analysis showed moderate to severe symptoms were prevalent and persistent among patients with metastatic NSCLC, underscoring the need to address supportive measures in this population especially around treatments. ***The Oncologist*** 2021;26:e1800–e1811

Implications for Practice: In this largest study of lung cancer patient-reported outcomes (PROs), stage IV non-small cell lung cancer patients had worse moderate-to-severe symptoms than other metastatic malignancies such as breast or gastrointestinal cancers when assessed with similar methodology. Prevalence of moderate-to-severe symptoms peaked early and remained high during the first year of follow-up. Symptom burden was associated with recent radiation and systemic treatments. Early and sustained PRO collection is important to detect actionable symptom progression, especially around treatments. Vulnerable patients (e.g., older, high comorbidity) who face barriers in attending in-person clinic visits had lower PRO completion. Virtual PRO collection may improve completion.

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Introduction

Lung cancer is the most common cause of cancer-related death worldwide, including in Canada, where it accounts for 26% of cancer-related deaths [1, 2]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer [3]. Most patients with NSCLC present with incurable stage IV disease at diagnosis, historically with dismal 5-year survival of less than 10% according to a recent Surveillance, Epidemiology, and End Results study between 2013 and 2017 [3]. Even with newer therapies, such as immunotherapy and targeted therapy, by nature of the patient's incurable disease, the importance of symptom management remains crucial [4, 5]. Previous studies have demonstrated that lung cancer is associated with high symptom burden, which has strong implications on overall quality of life (QoL), caregiver burden, and health system resource utilization [6, 7]. It has been reported that depression is common among patients with stage IV NSCLC owing to its inherent high symptom burden and low survival [8]. In addition, patients with lung cancer may present with a unique constellation of symptoms as a consequence of local and regional tumor burden of structures within the thorax, such as dyspnea, hemoptysis, and chest pain [9].

Historically, the quantification of cancer-related symptoms and treatment toxicities were through health care providers recording adverse events in the medical record, as ascertained and graded from the provider perspective [10]. Recently, patient-reported outcome (PRO) measures have been increasingly used in the clinical setting to elicit patients' own response of symptoms resulting from disease or treatment. PROs present a unique opportunity to understand the patient-centered perspectives and areas where intervention might improve symptoms. Studies suggest that measuring and responding to PROs is associated with improved QoL, symptom management, and survival, while reducing emergency department visits among patients with advanced cancers [11, 12].

Our current understanding of PROs utility in patients with stage IV lung cancer is limited to smaller cohort studies [9, 13]. Quantification of patient-reported symptom burden and identification of factors associated with high symptom burden in a large population receiving routine cancer care are important to assess the unmet needs of patients with stage IV NSCLC and may aid decision-making on population-level health care resource allocation. To investigate these issues, the aim of this study was to analyze PRO utilization, as well as patient symptom burden and trajectory among patients with stage IV NSCLC in the 12 months following diagnosis from the entire province of Ontario, Canada. This study will then provide the basis for the development of strategies to address gaps in symptom management in this patient population.

Materials and Methods

Study Overview

In 2007, Cancer Care Ontario (CCO) implemented a province-wide program whereby all regional cancer centers systematically collected PROs via the Edmonton Symptom Assessment System (ESAS) questionnaire at outpatient cancer clinic visits. This study used these prospectively collected ESAS PROs linked to routinely collected administrative data acquired through patient interactions within the universal, single-payer health care system in Ontario (2018 population of 14.3 million), Canada. ESAS is a validated and reliable patient-reported outcome measure assessing the severity of nine common cancer-associated symptoms: anxiety, depression, drowsiness, lack of appetite, nausea, pain, shortness of breath, tiredness, and impaired well-being [14, 15]. Patients rate each symptom from 0 (no symptoms) to 10 (worst possible symptom) on the ESAS form during clinical encounters, which are collected as part of their records. The administrative data included all patients with a valid Ontario Health Insurance Plan (OHIP) number. The provincial ESAS data are consolidated and made available through the ICES (formally known as Institute for Clinical Evaluative Sciences) database. The study was approved by the Sunnybrook Health Sciences Centre research ethics board and adhered to data confidentiality and privacy policies of ICES. The study was conducted and reported following the Reporting of Studies Conducted Using Observational Routinely Collected Data statement [16].

Study Cohort

Patients diagnosed with stage IV lung cancer between January 2007 and September 2018 were identified in the Ontario Cancer Registry (OCR) using the International Classification of Disease for Oncology (ICD-O) topography codes (ICD-O-3 codes: C34.0–34.3, C34.8, and C34.9). ICD-O-3 histology codes were used to identify non-small cell histologies and to exclude carcinoid, mesothelioma, and small cell cancer histologies (supplemental online Appendix 1). OCR captures 95% of Ontario incident cancer diagnoses including the staging data since 1964, excluding nonmelanoma skin cancers [17]. Patients were excluded if they were aged <18 or > 99 years, if they had histology inconsistent with NSCLC, or if the follow-up period was less than 6 months with no confirmed death. Patients with additional cancer diagnosis between 5 years before and 1 year after NSCLC diagnosis were also excluded to eliminate noise due to symptoms related to additional cancer diagnosis and treatments. Follow-up was current to September 30, 2019, allowing a minimum follow-up of 1 year for all patients.

Data Sources

The following linked administrative data sets were used to capture baseline clinical characteristics, ESAS scores, and covariates: (a) OCR; (b) Cancer Activity Level Reporting (ALR); (c) OHIP database containing billing claims from clinicians, including physicians, laboratories, groups, and out-of-province health care providers; (d) CCO Symptoms Management Reporting Database; (e) Ambulatory Care Reporting System; (f) Canadian Institute of Health Information Discharge Abstract Database and Same Day Surgery; (g) Registered Persons Database (RPDB); (h) the 2006 Canadian Census; and (i) Permanent Resident Database of Immigration, Refugees, and Citizenship Canada (IRCC). Details on the use of each data source are contained in supplemental online Appendix 1.

Outcomes

The primary outcome of interest was the prevalence of moderate to severe symptoms, defined as an ESAS score ≥4 [18], reported each month within 1 year after diagnosis. Date of diagnosis was defined as the earlier between the recorded date of lung cancer diagnosis or the first day of delivery of cancer treatments. If more than one ESAS score was reported by a patient in a month, the highest score was used.

Covariates

All baseline characteristics were measured at the time of diagnosis. Age and sex were acquired from the RPDB. Rural residence was defined according to Rurality Index of Ontario [19] scored 0–100 based on the postal code of patients' primary home, which considers population size, population density, and health care resources of where patients primarily reside: major urban (0–9), non-major urban (10–44), or rural (≥45). Neighborhood income quintiles were categorized based on the median income of a patient's residential postal code using Canadian census data. Comorbidity was assessed using the Elixhauser comorbidity index, based on health service use in the 24 months prior to lung cancer diagnosis [20]. Elixhauser comorbidity indices were summed in a total score that was categorized as a dichotomous variable: low (0–3) and high (≥4) comorbidity burden, as per prior studies [20, 21]. From IRCC data, patients who immigrated to Canada (including refugees) were defined as immigrants; otherwise, they were defined as nonimmigrants.

Radiation (to any site) and systemic therapies received by a patient were identified from OHIP physician billing claims and ALR activity. To assess the associations between treatment delivery to peak symptom severities, the administrations of radiation and systemic therapies were included as time-dependent covariates, whereby ESAS scores within 2 weeks following the (onset of) therapy were examined. The year of diagnosis was a covariate as a continuous variable. To define number of months from diagnosis until the time of ESAS recording, timing of ESAS were categorized in 30-day intervals from the day of diagnosis.

Statistical Analysis

Of the patients with an ESAS score, proportions of patients reporting at least one moderate to severe (≥4) score in each ESAS domain within the 12-month follow-up period were then tabulated. Patients who received surgery were censored at the date of surgery, as they may represent patients with oligometastatic disease with better outcomes compared with the typically incurable patients with stage IV disease [22]. Symptom trajectories were plotted with line graphs depicting the proportion of patients with moderate to severe symptoms out of all patients with recorded ESAS in each month from diagnosis; median number of moderate to severe scores per patient was also reported each month. For each symptom, the highest monthly prevalence within 1 year was defined as "peak" and the lowest prevalence as "nadir." Sensitivity analyses of symptom trajectories were also performed for patients who survived 12 months after diagnosis.

Potential predictors of moderate to severe scores for each symptom were analyzed using multivariable modified Poisson regression models with robust error variance. As analyses were performed for nine ESAS domains, Bonferroni-correction α of 0.006 was used (familywise α of 0.05). The relevant variables were included a priori based on clinical relevance and existing literature [17, 23]; all variables were kept in the final model. Using a Bonferroni-adjusted α of 0.006, results are reported as relative risk (RR) with 99.4% confidence interval (99.4% CI). Results were considered statistically significant if $p < .006$.

Baseline characteristics were reported and stratified based on whether a patient completed at least one ESAS or none within 12 months after diagnosis. Categorical and ordinal variables were reported as frequencies and proportions. Continuous variables were reported as medians and interquartile ranges (IQRs). Characteristics of patients who completed and did not complete at least one ESAS score were compared using χ^2 tests for independence. Incomplete ESAS questionnaires were excluded from final analyses. All analyses were conducted using SAS, version 9.4 (SAS Institute, Cary, NC).

Results

Study Cohort and ESAS Completion

A total of 22,799 patients with stage IV lung cancer diagnosed between January 2007 and September 2018 were identified as meeting the study inclusion criteria. Among those, 13,289 (58.2%) had at least one completed ESAS (reported all nine symptom scores), with a total of 84,373 unique ESAS completed. Among patients with completed ESAS, 78.2% and 40.1% completed at least two and six ESAS, respectively.

The median follow-up period among patients with completed ESAS was 7.9 months (IQR: 3.7–12.2), and 63.3% died within 1 year of follow-up after diagnosis. Among patients with completed ESAS, median age was 68 (IQR: 60–75) years, and 48.2% were females. Of these, 127 (1.0%) underwent surgery. Details of patient characteristics based on ESAS completion are summarized in Table 1. Patients who did not complete any ESAS were more likely to be older, with higher comorbidity index, and from neighborhood with lower income quintile. ESAS completion was lower in patients not receiving active cancer treatments and diagnosed before 2013. Immigration status and residency rurality were similar between patients with and without completed ESAS.

Prevalence and Trajectories of Moderate to Severe Symptoms Reported on ESAS

Among patients who completed at least one ESAS, nearly all (94.4%) reported at least one moderate to severe score through ESAS within 12 months after diagnosis. The most prevalent moderate to severe ESAS symptoms within 12 months after diagnosis were tiredness (84.1%), lack of well-being (80.7%), low appetite (71.7%), and shortness of breath (67.8%; Fig. 1). Monthly peaks and nadirs of these symptoms were as follows: 67.6% (month 1) and

Table 1. Characteristics of patients with stage IV non-small cell lung cancer diagnosed in Ontario between January 2007 to September 2018 based on ESAS completion

Characteristics	No reported ESAS or incomplete ESAS surveys ($n = 9,510$)	Reported ESAS ($n = 13,289$)	Standardized difference
Sex			
Female	4,289 (45.1)	6,406 (48.2)	.06
Male	5,221 (54.9)	6,883 (51.8)	.06
Age, median (IQR), yr	71 (63-79)	68 (60-75)	.28
Elixhauser comorbidity index			
4 or more	1,306 (13.7)	1,288 (9.7)	.13
Less than 4	8,204 (86.3)	12,001 (90.3)	.13
Immigration status			
Immigrant	729 (7.7)	964 (7.3)	.02
Nonimmigrant	8,781 (92.3)	12,325 (92.7)	.02
Lung cancer treatments			
Systemic therapy and radiation	663 (7.0)	4,221 (31.8)	.66
Systemic therapy only	825 (8.7)	2,075 (15.6)	.21
Radiation only	2,674 (28.1)	4,815 (36.2)	.17
No active treatment	5,348 (56.2)	2,178 (16.4)	.91
Neighborhood income quintile			
Q1	2,411 (25.4)	2,868 (21.6)	.09
Q2	2,138 (22.5)	2,910 (21.9)	.01
Q3	1,876 (19.7)	2,610 (19.6)	.00
Q4	1,623 (17.1)	2,499 (18.8)	.05
Q5 (highest income)	1,417 (14.9)	2,370 (17.8)	.08
Unknown	45 (0.5)	32 (0.2)	.04
Residence			
Major urban	6,548 (68.9)	8,604 (64.7)	.09
Non-major urban	2,272 (23.9)	3,654 (27.5)	.08
Rural	690 (7.3)	1,031 (7.8)	.02
Diagnosis year			
2007–2012	5,109 (53.7)	5,221 (39.3)	.29
2013–2018	4,401 (46.3)	8,068 (60.7)	.29

Data are shown as *n* (%).
Abbreviations: ESAS, Edmonton Symptom Assessment Score; IQR, interquartile range.

47.0% (month 12) for tiredness; 64.6% (month 1) and 43.3% (month 10) for lack of well-being; 50.5% (month 1) and 33.1% (month 10) for low appetite; and 51.1% (month 1) and 35.8% (month 10) for shortness of breath (Fig. 2). Nausea was the least common moderate to severe symptom reported (12-month prevalence: 34.6%, monthly peak and nadir: 18.7% [month 2] and 11.0% [month 10]). In all nine ESAS domains, symptom severity peaked at 1 or 2 months after diagnosis and demonstrated downward trajectories in the subsequent months (Fig. 2). Symptoms with the largest prevalence change (from peak to nadir) during follow-up were anxiety (23.8%), lack of well-being (21.2%), tiredness (20.6%), and lack of appetite (17.3%). The smallest change was observed in nausea (7.7%). The median moderate to severe score was 5 for 1 to 3 months after diagnosis, and 4 in subsequent follow-up periods. Median time until first radiotherapy was 36 days (IQR: 21–64) from diagnosis, whereas median time until first systemic therapy was 57 days (IQR: 36–90) after diagnosis.

The symptom trajectory of the subset of patient surviving past 12 months ($n = 4,791$) after diagnosis is shown in Figure 3. Tiredness (84.1%), lack of well-being (75.7%), low appetite (65.0%), and shortness of breath (62.0%) were also the most prevalent symptoms in this subset of patients, whereas nausea (15.3%) was the least prevalent. Monthly peaks and nadirs of these symptoms were as follows: 54.6% (month 1) and 42.7% (month 10) for tiredness; 53.9% (month 1) and 38.3% (month 7) for lack of well-being; 37.2% (month 3) and 28.7% (month 10) for low appetite; 39.9% (month 1) and 31.1% (month 7) for shortness of breath; and 13.9% (month 2) and 9.0% (month 10) for nausea (Fig. 3). Among these, the median moderate to severe

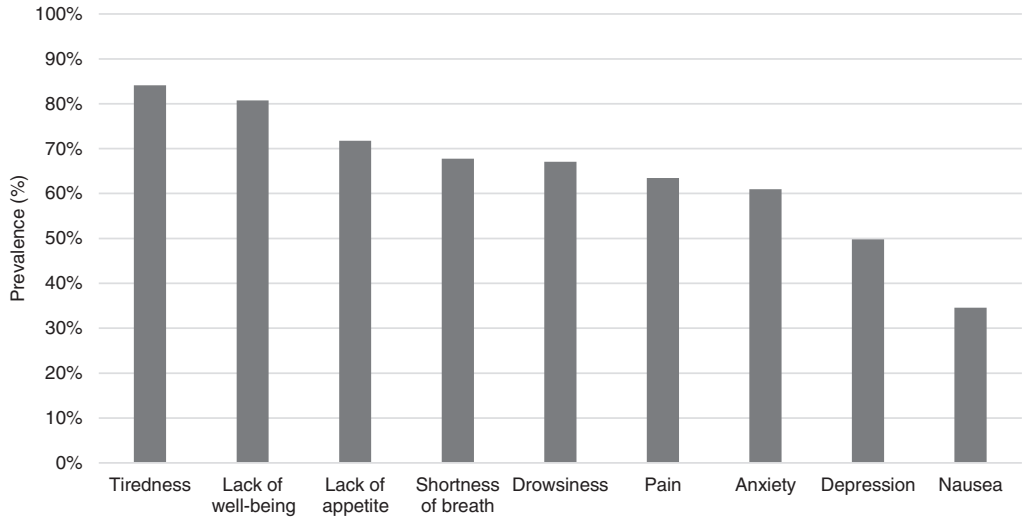

Figure 1. Bar graphs depicting prevalence of patients with stage IV NSCLC ($n = 13,289$) who reported at least one moderate to severe (≥4) score in each domain of the Edmonton Symptom Assessment Score within 12 months of the follow-up period. The symptom domains were ordered from the highest to lowest 12-month prevalence.

score was 4 in the months following diagnosis up to a year, aside from month 5 and 10, where the median was 3.

Factors Associated with Moderate to Severe Symptoms

There were significant associations between moderate to severe ESAS symptom scores and patient and treatment characteristics (Table 2). Older patients were less likely to report moderate to severe nausea (RR: 0.67–0.78 among patients ≥70 years) and pain (RR: 0.78–0.89 among patients ≥60 years); patients from age groups ≥80 years reported higher moderate to severe lack of appetite (RR: 1.13), whereas age groups ≥70 years reported higher shortness of breath (RR: 1.08–1.11) and tiredness (RR: 1.08–1.11).

Females were more likely than males to report moderate to severe anxiety (RR: 1.14; 99.4% CI: 1.09–1.19) and nausea (RR: 1.14; 99.4% CI: 1.06–1.23) and less likely to report moderate to severe pain (RR: 0.93; 99.4% CI: 0.89–0.97) and shortness of breath (RR: 0.88; 99.4% CI: 0.84–0.92). Moderate to severe shortness of breath, tiredness, and lack of well-being were more common among patients with high baseline Elixhauser comorbidity index (RR: 1.05–1.12). Immigrants were less likely to report moderate to severe drowsiness, shortness of breath, tiredness, and lack of well-being (RR: 0.85–0.94).

Compared with patients from neighborhoods with the highest income quintile, patients from neighborhoods with the lowest income quintile reported higher moderate to severe scores in depression, nausea, pain, shortness of breath, and tiredness (RR: 1.07–1.17); higher moderate to severe pain was observed among patients from three lower quintiles (RR: 1.09–1.15). Compared with major urban residents, rural residents reported lower depression and nausea (RR: 0.83 for both), whereas non-major urban residents reported lower depression and lack of well-being (RR: 0.90–0.94).

In terms of symptom prevalence over time, a lower prevalence of moderate to severe scores was observed within 2 months after diagnosis for anxiety, depression, pain, and lack of well-being; within 3 months for shortness of breath and tiredness; within 4 months for lack of appetite; and within 9 months for nausea. Aside from less drowsiness 6 months after diagnosis, this domain's prevalence seemed unchanged during follow-up. A later year of diagnosis was associated with a lower risk of moderate to severe scores in all ESAS domains but drowsiness (RR: 0.96–0.99 per 1-year increment).

There were significant associations between delivery of systemic or radiation treatments within 2 weeks prior to symptom peak and moderate to severe symptom scores. Higher drowsiness, lack of appetite, nausea, tiredness, and lack of well-being were associated with systemic therapy delivery within 2 weeks prior (RR: 1.03–1.25). Higher moderate to severe scores in all ESAS domains aside from anxiety were associated with radiotherapy delivered within 2 weeks prior (RR: 1.06–1.48).

Discussion

This province-wide analysis of ESAS from 22,799 patients with stage IV NSCLC reporting a total of 84,373 unique ESAS assessments represents, to our knowledge, the largest lung cancer PRO cohort published worldwide. Our cohort demonstrated high, persistent symptom burden among patients with stage IV NSCLC up to a year after diagnosis (Figs. 1–3). With nearly all patients who completed ESAS (94.4%) reporting at least one moderate to severe symptom within the 12 months of diagnosis, this population exhibited higher moderate to severe symptoms compared with other malignancies including breast, head and neck, central nervous system, and pancreatic cancers (Fig. 1) [17, 24]. In our population, nausea and drowsiness were the only symptoms in which prevalence increased after diagnosis (Fig. 2). Although difficult to distinguish with current data, these findings may relate to the side effects of cancer-directed

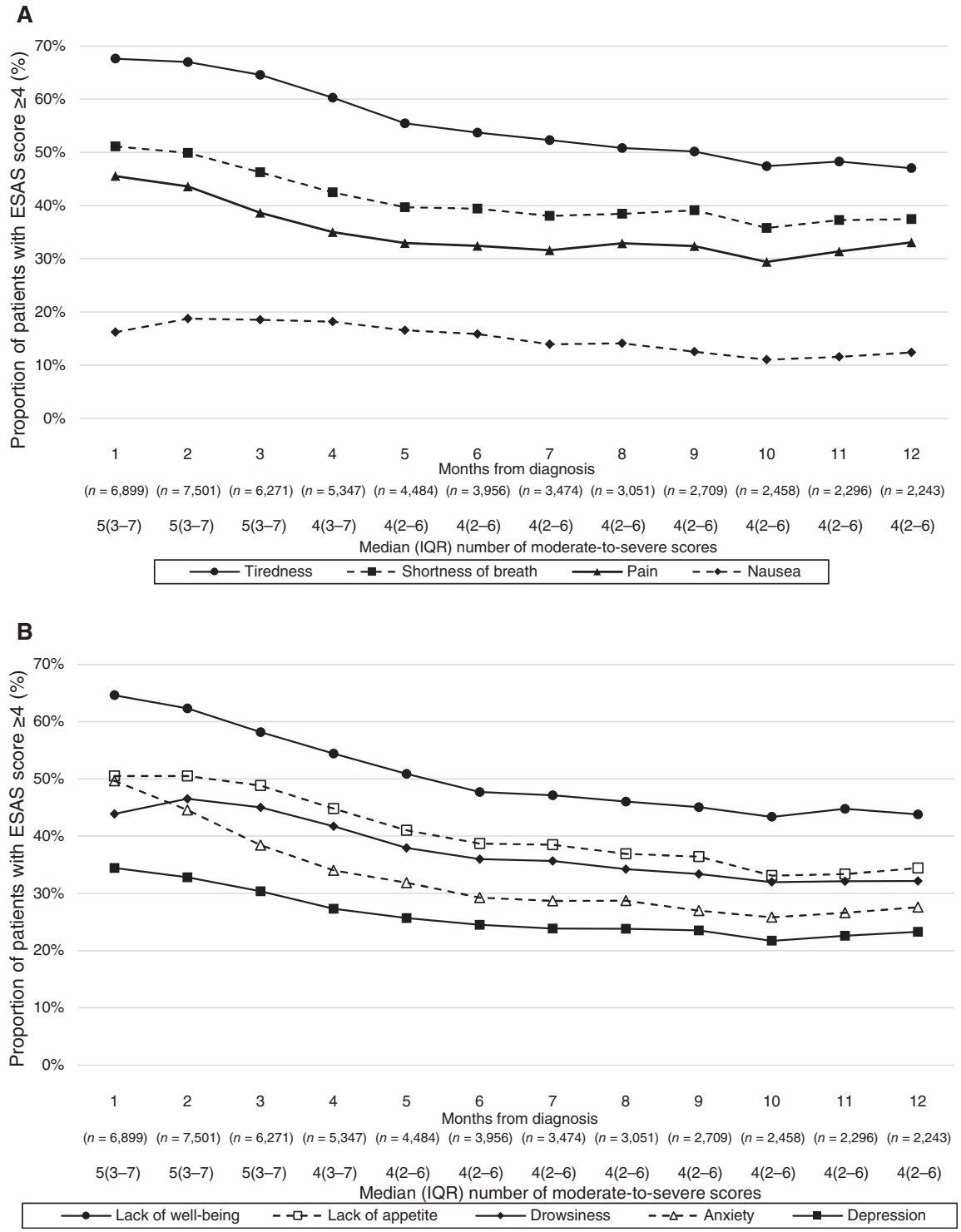

Figure 2. (A and B): Line graphs depicting trajectories of patient proportions reporting a moderate to severe (≥4) score in each domain of ESAS at each month up to 12 months after diagnosis of stage IV non-small cell lung cancer ($n = 13,289$). The median number of moderate to severe symptoms per patient each month was also reported.
Abbreviations: ESAS, Edmonton Symptom Assessment Score; IQR, interquartile range.

treatments, such as radiation and systemic therapy, as well as some supportive therapies such as opioids [25, 26].

Analysis of symptom trajectories among patients surviving at least 12 months after diagnosis demonstrated lower baseline moderate to severe symptom prevalence but less decrease of the prevalence over the 12-month period compared with the whole cohort (Figs. 2, 3). The decreasing moderate to severe symptom prevalence in the whole cohort over time may reflect the better symptom burden among longer surviving patients, who may have favorable cancer biology, less extensive metastatic disease, and better baseline performance status. This reflected the symptom persistence among patients with stage IV NSCLC.

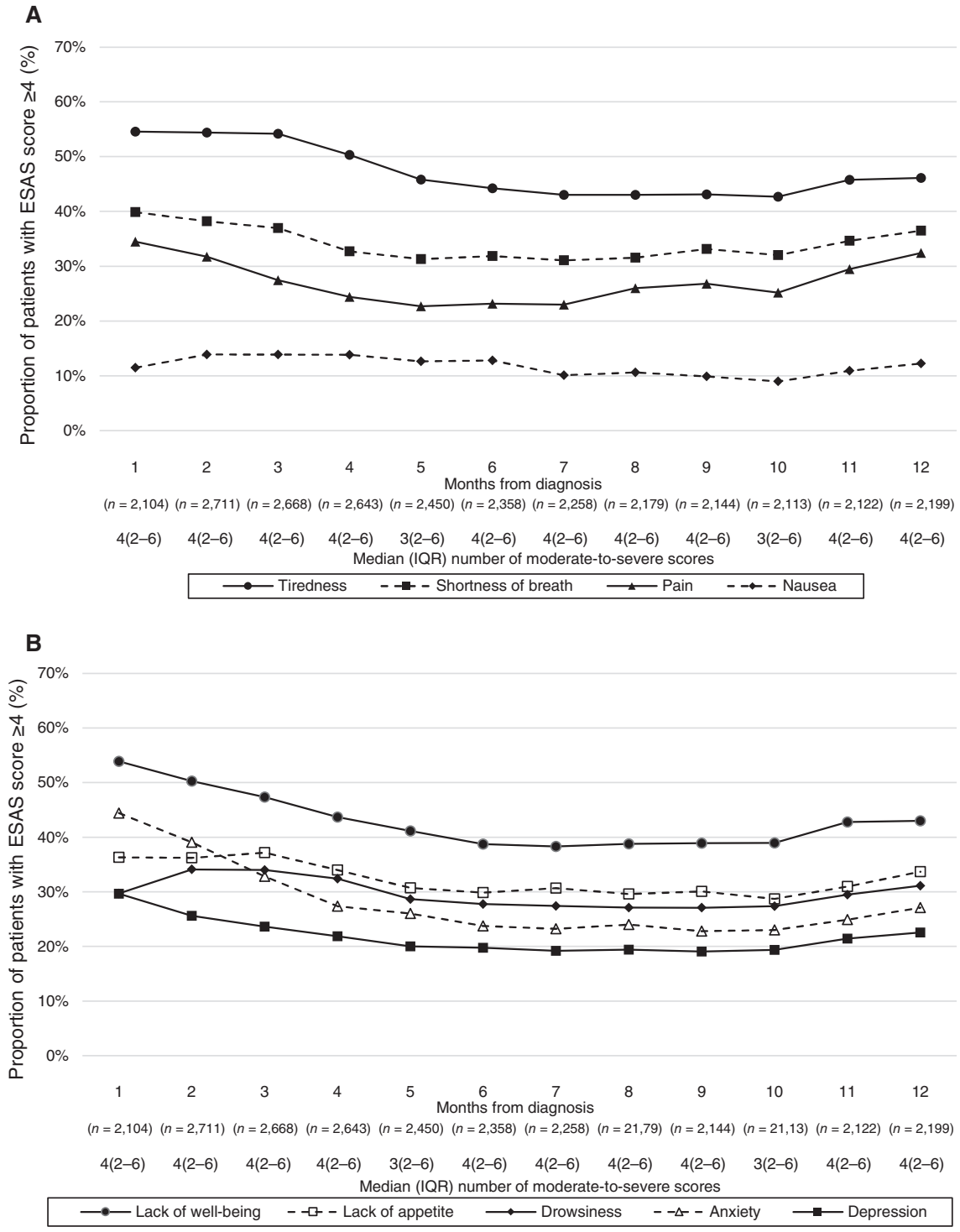

Figure 3. (A and B): Line graphs depicting trajectories of patient proportions reporting a moderate to severe (≥4) score in each domain of ESAS at each month among patients surviving at least 12 months after stage IV non-small cell lung cancer diagnosis ($n = 4,791$). The median number of moderate to severe symptoms per patient each month was also reported.
Abbreviations: ESAS, Edmonton Symptom Assessment Score; IQR, interquartile range.

Our analyses demonstrated notable associations between patient baseline characteristics and the occurrence of moderate to severe symptoms (Table 2). Similar to patients with stage I–III NSCLC, the most prevalent symptoms were tiredness, lack of well-being, low appetite, and shortness of breath [23]. Older patients were at higher risk of low appetite, shortness of breath, and tiredness but at lower risk of nausea and pain. Females reported higher anxiety and nausea but lower shortness of breath and pain. High comorbidity index, major urban residence, and nonimmigrants are associated with higher moderate to severe symptoms in some ESAS domains such as shortness of

Table 2. Multivariable modified Poisson regression analysis of the association between patient and treatment characteristics and moderate to severe ESAS scores in the 12 months after stage IV non-small cell lung cancer diagnosis for all symptoms

	Relative Risk (Bonferroni-corrected [99.4%] confidence interval)								
Characteristic	**Anxiety**	**Depression**	**Drowsiness**	**Lack of appetite**	**Nausea**	**Pain**	**Shortness of Breath**	**Tiredness**	**Lack of well-being**
Age group, yr									
18–49	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]
50–59	1.11 (0.98–1.25)	1.11 (0.95–1.29)	1.06 (0.95–1.18)	1.03 (0.94–1.14)	1.03 (0.87–1.23)	1 (0.9–1.11)	1.09 (0.97–1.23)	1.04 (0.96–1.12)	1.02 (0.94–1.1)
60–69	1.03 (0.91–1.15)	0.99 (0.85–1.14)	1.01 (0.9–1.12)	1.03 (0.94–1.13)	0.85 (0.72–1.01)	0.89 (0.8–0.98)[a]	1.10 (0.99–1.23)	1.03 (0.96–1.11)	0.98 (0.91–1.06)
70–79	1.01 (0.89–1.13)	0.99 (0.86–1.15)	1.04 (0.94–1.16)	1.07 (0.98–1.18)	0.78 (0.66–0.93)[a]	0.85 (0.77–0.95)[a]	1.18 (1.06–1.32)[a]	1.08 (1.01–1.16)[a]	1.01 (0.94–1.09)
80 and older	0.97 (0.85–1.1)	1 (0.86–1.18)	1.06 (0.95–1.19)	1.13 (1.02–1.25)[a]	0.67 (0.54–0.82)[a]	0.78 (0.7–0.88)[a]	1.19 (1.05–1.34)[a]	1.11 (1.03–1.2)[a]	1.05 (0.96–1.14)
Sex									
Male	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]
Female	1.14 (1.09–1.19)[a]	1.01 (0.95–1.07)	0.97 (0.93–1.01)	1.02 (0.98–1.05)	1.14 (1.06–1.23)[a]	0.93 (0.89–0.97)[a]	0.88 (0.84–0.92)[a]	1 (0.97–1.02)	1 (0.97–1.03)
Elixhauser Comorbidity Index									
Low (<4)	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]
High (≥4)	1.03 (0.95–1.11)	1.08 (0.98–1.19)	1.05 (0.98–1.13)	1.04 (0.97–1.11)	1.08 (0.95–1.24)	1.07 (0.99–1.15)	1.12 (1.05–1.19)[a]	1.06 (1.01–1.1)[a]	1.05 (1–1.11)[a]
Immigration status									
Nonimmigrant	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]
Immigrant	0.91 (0.82–1)	1.03 (0.92–1.15)	0.85 (0.78–0.94)[a]	0.93 (0.86–1.01)	0.92 (0.79–1.07)	0.98 (0.9–1.07)	0.87 (0.79–0.95)[a]	0.94 (0.89–0.99)[a]	0.93 (0.88–0.99)[a]
Income quintile									
Q5 (highest income)	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]
Q1	1.08 (0.99–1.16)	1.13 (1.03–1.24)[a]	1.1 (1.03–1.18)	1.04 (0.98–1.11)	1.17 (1.04–1.32)[a]	1.15 (1.07–1.23)[a]	1.12 (1.05–1.19)[a]	1.07 (1.02–1.12)[a]	1.04 (0.99–1.09)
Q2	1.03 (0.96–1.11)	1.06 (0.96–1.16)	1.05 (0.98–1.13)	1.05 (0.99–1.12)	1.09 (0.97–1.23)	1.12 (1.04–1.2)[a]	1.06 (0.99–1.13)	1.03 (0.98–1.08)	1.02 (0.97–1.07)
Q3	1.04 (0.96–1.12)	1.07 (0.97–1.18)	1.05 (0.98–1.12)	1.05 (0.99–1.12)	1.12 (0.99–1.27)	1.09 (1.01–1.18)[a]	1.02 (0.96–1.1)	1.04 (0.99–1.08)	1.03 (0.98–1.08)
Q4	1.04 (0.97–1.13)	1.05 (0.95–1.16)	1.02 (0.95–1.1)	1.01 (0.94–1.07)	1.04 (0.92–1.18)	1.04 (0.96–1.12)	1.03 (0.96–1.1)	1.01 (0.97–1.06)	1.01 (0.96–1.07)
Rurality									
Major urban	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]
Non-major urban	0.97 (0.92–1.02)	0.9 (0.84–0.96)[a]	0.98 (0.93–1.03)	0.98 (0.94–1.02)	0.97 (0.89–1.05)	0.95 (0.9–1)	1.01 (0.96–1.06)	0.97 (0.94–1)	0.94 (0.91–0.97)[a]
Rural	0.94 (0.86–1.03)	0.83 (0.74–0.94)[a]	0.98 (0.9–1.06)	0.97 (0.91–1.05)	0.83 (0.71–0.97)[a]	0.96 (0.88–1.05)	1.01 (0.94–1.09)	0.96 (0.9–1.01)	0.97 (0.91–1.03)

(continued)

Table 2. (continued)

Characteristic	Relative Risk (Bonferroni-corrected [99.4%] confidence interval)								
	Anxiety	Depression	Drowsiness	Lack of appetite	Nausea	Pain	Shortness of Breath	Tiredness	Lack of well-being
Diagnosis year									
2007–2018	0.98 (0.98–0.99)[a]	0.99 (0.98–0.99)[a]	0.99 (0.99–1)	0.96 (0.96–0.97)[a]	0.97 (0.96–0.98)[a]	0.99 (0.98–0.99)[a]	0.99 (0.98–0.99)[a]	0.99 (0.99–0.99)[a]	0.99 (0.98–0.99)[a]
Systemic therapy within 2 weeks prior to highest monthly ESAS score									
Yes	0.97 (0.93–1.01)	1.01 (0.97–1.06)	1.08 (1.05–1.12)[a]	1.06 (1.02–1.09)[a]	1.25 (1.17–1.34)[a]	1.02 (0.98–1.06)	1.01 (0.98–1.05)	1.05 (1.02–1.07)[a]	1.03 (1–1.06)[a]
No	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]
Radiation within 2 weeks prior to highest monthly ESAS score									
Yes	1.03 (0.99–1.08)	1.11 (1.06–1.17)[a]	1.28 (1.23–1.33)[a]	1.17 (1.12–1.21)[a]	1.48 (1.38–1.6)[a]	1.2 (1.16–1.25)[a]	1.06 (1.02–1.1)[a]	1.15 (1.12–1.18)[a]	1.1 (1.07–1.14)[a]
No	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]
Months from diagnosis									
1	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]	1 [Ref.]
2	0.9 (0.86–0.93)[a]	0.94 (0.89–0.99)[a]	1.04 (0.99–1.09)	0.99 (0.95–1.03)	1.09 (0.99–1.19)	0.94 (0.9–0.99)[a]	0.97 (0.94–1.01)	0.98 (0.95–1)	0.96 (0.93–0.99)[a]
3	0.78 (0.74–0.82)[a]	0.9 (0.84–0.95)[a]	1.04 (0.99–1.09)	0.97 (0.93–1.02)	1.08 (0.98–1.19)	0.86 (0.82–0.91)[a]	0.92 (0.88–0.96)[a]	0.97 (0.94–0.99)[a]	0.91 (0.88–0.94)[a]
4	0.71 (0.67–0.75)[a]	0.85 (0.79–0.9)[a]	1.02 (0.97–1.07)	0.93 (0.88–0.98)[a]	1.11 (0.99–1.23)	0.82 (0.77–0.86)[a]	0.86 (0.82–0.91)[a]	0.93 (0.9–0.96)[a]	0.88 (0.84–0.91)[a]
5	0.68 (0.64–0.72)[a]	0.82 (0.76–0.87)[a]	0.96 (0.91–1.02)	0.88 (0.83–0.92)[a]	1.04 (0.93–1.16)	0.8 (0.75–0.84)[a]	0.84 (0.8–0.88)[a]	0.89 (0.85–0.92)[a]	0.84 (0.81–0.88)[a]
6	0.63 (0.6–0.68)[a]	0.79 (0.74–0.85)[a]	0.94 (0.89–0.99)[a]	0.85 (0.8–0.9)[a]	1.01 (0.9–1.13)	0.8 (0.75–0.85)[a]	0.85 (0.81–0.89)[a]	0.87 (0.84–0.91)[a]	0.81 (0.77–0.84)[a]
7	0.64 (0.6–0.69)[a]	0.8 (0.75–0.87)[a]	0.97 (0.91–1.03)	0.87 (0.82–0.92)[a]	0.92 (0.81–1.04)	0.8 (0.75–0.85)[a]	0.85 (0.81–0.9)[a]	0.87 (0.83–0.9)[a]	0.81 (0.78–0.85)[a]
8	0.64 (0.6–0.68)[a]	0.81 (0.75–0.87)[a]	0.94 (0.89–1)	0.85 (0.8–0.91)[a]	0.94 (0.83–1.07)	0.85 (0.79–0.9)[a]	0.87 (0.82–0.92)[a]	0.86 (0.82–0.9)[a]	0.81 (0.77–0.85)[a]
9	0.62 (0.58–0.66)[a]	0.81 (0.75–0.88)[a]	0.95 (0.89–1.01)	0.86 (0.81–0.91)[a]	0.86 (0.75–0.99)[a]	0.86 (0.8–0.92)[a]	0.89 (0.84–0.95)[a]	0.86 (0.82–0.9)[a]	0.8 (0.76–0.85)[a]
10	0.62 (0.58–0.67)[a]	0.8 (0.74–0.87)[a]	0.95 (0.89–1.02)	0.82 (0.77–0.88)[a]	0.8 (0.7–0.93)[a]	0.82 (0.77–0.88)[a]	0.87 (0.82–0.92)[a]	0.85 (0.81–0.89)[a]	0.8 (0.76–0.85)[a]
11	0.64 (0.59–0.69)[a]	0.83 (0.76–0.9)[a]	0.97 (0.9–1.04)	0.84 (0.79–0.9)[a]	0.85 (0.74–0.99)[a]	0.88 (0.82–0.94)[a]	0.9 (0.85–0.96)[a]	0.86 (0.82–0.9)[a]	0.83 (0.79–0.88)[a]
12	0.66 (0.62–0.71)[a]	0.85 (0.79–0.93)[a]	1 (0.94–1.07)	0.89 (0.83–0.95)[a]	0.93 (0.8–1.07)	0.93 (0.87–0.99)[a]	0.92 (0.87–0.98)[a]	0.87 (0.82–0.91)[a]	0.84 (0.79–0.88)[a]

[a]Statistically significant using Bonferroni correction ($p < .006$).
Abbreviations: ESAS, Edmonton Symptom Assessment System; Ref., reference.

breath or pain, which could be alleviated with supportive therapies. Ensuring PRO completion for symptom identification will be especially important for these high-risk patients. Understanding patient characteristics that may be associated with increased risk of certain symptom constellations may aid in devising strategic supportive care initiatives. As an example, higher depression, nausea, pain, shortness of breath, and tiredness is increased in patients with lower income. To address this barrier, upstream referrals to the relevant care providers and creation of frameworks to systematically improve access are examples of initiatives that could be piloted to address patient-centered needs [27].

Our results suggest that patients with metastatic NSCLC exhibited worse symptom burden when compared with other advanced, incurable malignancies such as metastatic breast, gastric, and esophageal cancers [28–30]. The degree of early symptom burden from our results suggests that almost all patients with stage IV NSCLC would benefit from supportive interventions such as psychosocial or palliative care referral soon after diagnosis. Indeed, a randomized trial showed QoL improvement and survival prolongation with early palliative care for patients with stage IV NSCLC [4]. Nonetheless, although referral to palliative care after a diagnosis of metastatic NSCLC may be helpful in the management of symptom and side effects, this strategy is not feasible in broader practice owing to the limited availability of specialized palliative care services (especially in lower resource settings), as well as patient/provider hesitancy for early involvement [31, 32]. Instead, clinician-initiated palliative referrals guided by institutional criteria and/or identification of patients who may best benefit on the basis of symptom burden thresholds warrants additional evaluation [31].

A recent study investigating ESAS among patients with cancer in Ontario indicated that a high symptom burden was a predictor of adverse events such as unplanned hospitalizations and emergency room visits [33]. We would suggest that early PRO completion (e.g., ESAS) may help with timely symptom detection and thus alert clinicians about the need for specific supportive measures in this population. For instance, a worsening dyspnea score serves as an early indicator for actionable diagnoses such as pleural effusion or pneumonitis needing further investigations with chest x-ray and routine blood work.

The rate of ESAS completion has increased since 2013 compared with prior, indicating its increasing use since the program implementation in 2007. A study in 2019 reported increasingly uniform rates of ESAS completion between Ontario regions since its deployment [34]. Encouragingly, there are also significant associations between year of diagnosis and lower reported moderate to severe symptoms in all ESAS domains, which may reflect progress in the awareness and effectiveness of supportive managements and treatments for patients with stage IV NSCLC [35]. Importantly, an Ontario study showed that more documentations and clinical actions such as addition of symptom-directed medications or referrals are triggered by high ESAS symptom scores [36].

Nonetheless, patients who are older, with higher comorbidity, or not receiving active cancer treatment were less likely to complete ESAS (Table 1); these patients may have fewer visits to cancer centers where ESAS are systematically collected. The surge in virtual health care adoption due to the COVID-19 pandemic may present an opportunity to implement PRO collection without in-person clinic visits [37]. Systematic verbal collection of the ESAS scores during these virtual encounters may be a method to address a particularly vulnerable patient population within the current evolving clinical workflow.

There were significant associations between patient-reported moderate to severe scores across multiple ESAS domains and the administration of radiotherapy 2 weeks prior to peak symptoms (Table 2). Several factors may contribute to these associations. These patients commonly received radiotherapy early after diagnosis, corresponding to the period of highest symptom burden in this population (Fig. 2). Radiotherapy in this setting is often used to palliate symptoms such as hemoptysis, pain, and shortness of breath [38]. The effect of radiotherapy can take weeks to manifest [39], which, in addition to its associated side effects, highlights the need for heightened supportive care during this period. Regarding systemic therapy, its delivery 2 weeks prior to peak symptoms was associated with higher drowsiness, lack of appetite, tiredness, and lack of well-being but lower anxiety (Table 2). Nausea is a common side effect of platinum-based chemotherapies used in stage IV NSCLC, which can be effectively managed with modern antiemetics [40]. A key caveat of these associations is that it does not necessarily infer causality between symptoms and treatment, a topic our group plans to investigate in more detail in future work.

Additional limitations of our study warrant mention. First, more than 40% of the population did not complete any ESAS, representing a substantial data loss. These nonrespondents were more likely to be older, to be of higher comorbidity, and to not receive any active cancer treatment, all features that may be particularly associated with vulnerability. Patients who do not complete PROs may have their symptoms unaddressed and experienced delay in accessing treatments, which may lead to cessation of therapies and worse clinical outcomes [13]. Second, administrative documentation processes involved in the large databases used for the analysis may introduce random error to the results. Third, the rates of ESAS collection may not be uniform between centers within the study period, reflecting differential rates of ESAS uptake in Ontario since its province-wide implementation in 2007. Lastly, our current data set lacks information on tumor biomarkers such as epidermal growth factor receptor mutations or ALK rearrangements, which guide the choice of systemic therapy in the modern era [41, 42]. Despite these limitations, a major strength of our study lies in its large size in the context of a province-wide PRO implementation within routine clinical care, improving its generalizability. Future studies are planned to investigate the frequency of focused symptom-specific interventions, health care resource utilization, and the patient stakeholder perspective of our PRO research.

Conclusion

This province-wide study of PRO cohort data of patients with stage IV NSCLC demonstrated that moderate to severe

symptoms were high and persistent and peaked early after diagnosis. This supports the importance of early and sustained PRO collection for identification of symptoms that may be amenable to intervention in these patients. Characteristics of patients less likely to complete any ESAS were identified; considerations to address this can include remote ESAS collection through telemedicine or virtual clinics, which are increasingly being used within our health system.

Acknowledgments

This research was funded by an Ontario Institute of Cancer Research Grant. N.G.C. receives salary support from the Sherif and MaryLou Hanna Chair in Surgical Oncology Research and is the Clinical Lead for Patient-Reported Outcomes and Symptom Management for Ontario Health-Cancer Care Ontario.

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Disclosures

Mark Doherty: Merck, AstraZeneca, Eisai, Boehringer Ingelheim, Roche, Takeda (C/A), Merck, AstraZeneca (RF); **Julie Hallet:** Ipsen, Advanced Accelerator Applications (H); **Biniam Kidane:** AstraZeneca (SAB); **Natalie G. Coburn:** AstraZeneca (H); **Alexander V. Louie:** RefleXion, Varian Medical Systems Inc., AstraZeneca (H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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