ABSTRACT

Introduction: To evaluate whether and the degree to which patients with advanced NSCLC (aNSCLC) receiving lung cancer treatments will experience functional disability or have resilience and to identify characteristics associated with functional disability.

Methods: We evaluated longitudinal data of patients with aNSCLC receiving treatment in the Beating Lung Cancer in Ohio prospective cohort study. Disability versus resilience in functional status (usual activities, mobility, and self-care) was measured monthly for 8 months using the EuroQol-5D-5L. Data captured included baseline demographics (Eastern Cooperative Oncology Group performance status), comorbidities, cancer and depressive symptoms (Patient Health Questionnaire-9), anxiety (Generalized Anxiety Disorder-7 scale), and cancer stress (impact of events). Group-based latent class trajectory modeling was used to determine clinically distinct functional disability trajectories jointly with attrition probability (death or withdrawal) in the study period.

Results: Among 207 participants, the mean age was 63.5 years (range: 34–92 y), 58.9% were male, 6.8% were African American or Black, 73.3% were former smokers, and 35% resided in rural areas. At baseline, participants had adenocarcinoma histological subtype (74.9%), 40.3% had brain metastases, and 46.1% had bone metastases. Participants received chemotherapy plus immunotherapy (46.9%), immunotherapy single agent (21.7%), targeted treatments (18.8%), or no treatment (12.6%). Three distinct functional trajectory groups were identified, as follows: none/mild (n = 79, 38.2%), moderate (n = 99, 47.8%), and severe disability (n = 29, 14.0%). Characteristics associated with severe disability included baseline Eastern Cooperative Oncology Group performance status greater than 1, worse dyspnea and pain, and higher Patient Health Questionnaire-9 and Generalized Anxiety Disorder-7 scale scores. At month 8, 95 participants (45.9%) displayed resilience, 11 (5.3%) experienced functional decline, and 69 (33.3%) were deceased.

Conclusions: We identified three distinct functional trajectories among patients with aNSCLC. Risk stratification tools and targeted interventions designed to target these three groups are needed to improve functional resilience and prevent disability.
Introduction

Many older adults with cancer consider the maintenance of functional status as equally or more important than overall survival. Functional status is a person’s ability to perform basic activities of daily living (ADLs, e.g., bathing), instrumental ADLs (e.g., managing medication), and mobility. Few cancer studies have incorporated repeated measures of functional status as defined by ADLs, instrumental ADLs, and mobility. This is also true for measures of resiliency. Resilience has multiple meanings but can be defined as the ability to maintain functional status over time or to recover from functional decline and disability after an intervening health care event, for example, cancer treatment. This is different from psychological resilience, which has been defined as an individual’s ability to recover, cope, or adapt to considerable difficulties such as trauma, tragedy, threats, or significant sources of stress. Currently, clinical trials for newer lung cancer treatments such as immunotherapy or combinations of chemotherapy and immunotherapy do not characterize functional status or resiliency as longitudinal outcomes. There are studies on quality of life, symptoms, and function over time, but they focus on cancer survivors, which traditionally have excluded patients with advanced lung cancer. As a result, clinicians have little information about how immunotherapy or targeted treatments affect functional status over time. Understanding functional trajectories and resiliency phenotypes is valuable, as it may facilitate the identification of patients at risk for functional decline and thus allow for the development of risk stratification tools and targeted supportive care interventions during cancer treatment.

Which patients with lung cancer will experience disability and when remains unclear. Some patients may have poor functional status before diagnosis but improve after treatment has started; others may experience worsening functional status (functional decline) during treatment. Thus far, only cross-sectional data—often containing sample sizes and typically restricted to patients with earlier stage (I–III) disease only—or studies evaluating outdated treatments are available. Some studies on functional status trajectories have excluded patients with lung cancer, perhaps owing to a lower percentage of long-term survivorship compared with other cancers. Because of this knowledge gap, clinicians treating patients with advanced lung cancer are not able to determine which patients may experience functional decline versus resiliency.

Our previous work revealed that it is possible to characterize functional trajectories among older adults with a new cancer diagnosis (all cancer types). Of the participants in that study, 40% were unable to regain baseline functional status within the 12 months after diagnosis. Importantly, clinical factors associated with worsening functional status were poor physical performance as measured by the Short Physical Performance Battery and the presence of depressive symptoms.

Though immunotherapy and targeted treatments are improving overall survival, recent data suggest that functional disability is common among patients with advanced NSCLC (aNSCLC). For example, within 40 days of treatment initiation for aNSCLC, 23.1% of patients had functional disability with self-care, 69.8% with usual activities, and 51.6% with mobility.

Thus, the present study was designed to determine functional trajectories and resiliency phenotypes among adults with aNSCLC within the immunotherapy and targeted treatment era. We hypothesized that patients would fall into distinct disability groups, with some participants maintaining or improving functional status (resilient), some experiencing modest functional decline, and others experiencing significant disability throughout the study period.

Materials and Methods

Sample

Participants were enrolled from June 2017 to October 2019 into the Beating Lung Cancer in Ohio ongoing prospective cohort study (Clinicaltrials.gov: NCT03199651) at the Thoracic Oncology Center at The Ohio State University, a National Cancer Institute–designated Comprehensive Cancer Center. Participants were eligible if they were aged more than or equal to 18 years, had newly diagnosed aNSCLC (stage IV) confirmed by pathological report in the medical record and imaging, within 30 days of first-line treatment regimen start (average time to treatment start), English speaking, and were willing to provide biospecimens, access to medical records, and respond to self-report measures either in-person or by telephone interview. Participants could have any Eastern Cooperative Oncology Group performance status (ECOG PS). Participants were excluded if they received treatment with concurrent chemoradiotherapy for stage III NSCLC, received treatment for longer than 30 days, and/or had disabling hearing, vision, or psychiatric impairment preventing consent or completion of self-report
measures. Of 394 patients approached, 294 were consented and enrolled and completed the baseline assessment. Of the 100 patients who declined study enrollment, 77% was because of lack of interest. Only 3% stated that they were too tired or too sick to participate. The analytical sample was restricted to 207 participants as described in Supplementary Figure 1.

**Data Collection**

The Ohio State University Institutional Review Board approved the study, and all procedures were in accordance with the ethical standards of the Declaration of Helsinki. All participants completed written informed consent. Within two weeks of enrollment, patients were contacted by telephone by independent, trained interviewers to conduct assessments, which included demographics (age, sex, ZIP code to determine urban/rural living), patient-reported assessments, which included demographics (age, sex, ZIP code to determine urban/rural living), patient-reported depressive symptoms (Patient Health Questionnaire—9 [PHQ-9]19), anxiety symptoms (Generalized Anxiety Disorder—7 Scale [GAD-7]26), lung cancer-specific symptoms (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer—13 [EORTC-QLQ-LC13]21), cancer-specific stress (Impact of Events Scale [IES]—Revised22,23), and functional status (EuroQol-5D-5L [EQ-5D-5L]24). All baseline assessments which included the psychological surveys and documented ECOG PS were performed either before treatment start or within 30 days of treatment start. Study personnel abstracted the presence of brain and/or bone metastases from participants’ baseline imaging reports. Because persons from rural settings report disability at higher rates than those from urban settings,25 2013 Rural-Urban Continuum Codes26 were used to categorize patients into a rural or urban living setting.

**Outcome Variables**

**Disability.** Functional status was assessed monthly for 8 months using the validated EQ-5D-5L survey.27 Each item was rated by participants on a 5-point Likert scale, as follows: 0 (no problems), 1 (slight problems), 2 (moderate problems), 3 (severe problems), and 4 (unable to do). The EQ-5D-5L has been mapped to the EORTC-QLQ-C30,27 specifically among patients with aNSCLC.28 The EQ-5D-5L consists of a 5-item and a 1-item visual analogue scale (VAS). Two of the five items, pain and anxiety/depression, were captured but excluded from the disability score as previously described.18 The average inter-item correlation of the three items is 0.43, indicating good internal consistency reliability. Summing the three self-reported function-related items—self-care, usual activities, and mobility—the total disability score ranged from 0 to 12; a higher score indicates greater disability,29 similar to previous analytical approaches.12

**Resilience.** Resilience was defined as maintenance or improvement (decrease) in disability scores from baseline evaluated at the 1-month and 8-month follow-up time points. A 1-point increase in functional status score (increase in disability) was considered a meaningful decline in function, representing a 0.5 SD change on the EQ-5D-5L. This definition is consistent with prior research in other cancer groups.8

**Covariates**

**Treatment, Performance Status, and Comorbidities.** Treatment type was abstracted from the medical record and categorized as follows: chemotherapy, chemotherapy plus immunotherapy, or targeted treatment. ECOG PS score (0–5)30 was assigned by the treating physician. Medical comorbidities were documented by International Classification of Diseases, Tenth Revision, codes corresponding to diagnoses in the Charlson Comorbidity Index scores equal to 0 to 1531,32 that occurred at any time before the stage IV NSCLC diagnosis, excluding the six points due to metastatic cancer.

**Psychological Symptoms. Depression.** The PHQ-919 evaluated depressive symptoms in the past two weeks. The total score ranges from 0 to 27, with higher values indicating more severe depressive symptoms. Symptom level classes are 0 to 7 = none/mild, 8 to 14 = moderate, 15 to 19 = moderate to severe, and 20 to 27 = severe.19

**Anxiety.** The GAD-720 evaluated anxiety symptoms in the past 2 weeks.33 The total score ranges from 0 to 21, with higher values indicating more severe anxiety. Symptom level classes are 0 to 9 = none/mild, 10 to 14 = moderate, and 15 to 21 = moderate to severe/severe.20

**Cancer-Specific Stress and Symptoms.** The IES-Revised22,23 assesses cancer-specific stress (e.g., intrusive thoughts about the disease, avoidant thoughts/behaviors, and hyperarousal) present in the past week. The total score can range from 0 to 64, with higher scores indicating more severe stress.

The QLQ-LC1321 was used to assess lung-specific symptoms. The QLQ-LC13 is a supplementary module to the EORTC-QLQ-C3031 for patients with lung cancer and consists of 13 items, assessing symptoms such as coughing, pain, neuropathy, and dyspnea. In accordance with the EORTC Scoring Manual,34 a linear transformation was used to standardize the raw scores to scores equal to 0 to 100.

**Statistical Analyses**

Analysis was restricted to patients with complete baseline data on the EQ-5D-5L (n = 207 [70.4%] of N = 294; Supplementary Fig. 1). A joint model using group-
based latent class trajectory modeling\textsuperscript{35,36} was used to estimate clinically distinct trajectories of functional disability and attrition probability (death or dropout) in 8 months. This method fits a semiparametric (discrete) mixture model to longitudinal data (9 time points) using maximum-likelihood estimation. On the basis of the distribution of the functional scores (minimum = 0, maximum = 12), we used a censored normal model. The censored normal distribution accounts for floor and ceiling effects when an outcome score has a minimum or maximum allowed value. Bayesian information criterion (BIC) was used to inform the optimal number of trajectories from two to six and to determine the best fit of each trajectory: intercept only, linear, quadratic, or cubic. The participants were classified to a specific trajectory based on the maximum estimated posterior probability of assignment (PPA), and PPA was used to assess model fit. An average PPA greater than or equal to 0.9 was considered an excellent fit, whereas a value less than 0.7 was considered a poor fit.\textsuperscript{37} The final trajectory model was chosen by comparing the BIC and the average PPA for each group and evaluating the distinctiveness and interpretability of the trajectories and group sizes.

The functional trajectory groups were contrasted on baseline sociodemographic and cancer characteristics using chi-square tests for categorical variables and one-way analysis of variance for continuous variables. For baseline characteristics that were found to be associated with group membership ($p < 0.05$), additional subgroup analyses were performed to compare trajectory groups using exact chi-square tests for categorical variables and analysis of variance for continuous variables. These were not adjusted for multiple comparisons because they are exploratory and not inferential. We also evaluated the relationship between the three trajectories and two resilience groups using Fisher’s exact test. As a sensitivity analysis, we repeated the group-based trajectory modeling replacing intermittent missing data (Supplementary Table 1) with the average of the months directly before and after the month with missing functional score. Baseline characteristics of resilient versus nonresilient groups at 8 months of follow-up were compared using similar methods as described previously. Participants who missed the 8-month assessments ($n = 10$) were excluded from the resilience analyses. All analyses were performed with the use of SAS software (version 9.4) or Stata (version 14). A two-sided $p$ value less than 0.05 was considered statistically significant.

\section*{Results}

\subsection*{Descriptive}

Among 207 participants with aNSCLC, the mean age was 63.5 years (range: 34–92), 58.9\% male, 6.8\% African American/black, 73.3\% former smokers, and 35\% resided in a rural area (Table 1). Most had adenocarcinoma histology (74.9\%), an ECOG PS score less than or equal to 1 (85\%), and received either chemotherapy alone or a combination of chemotherapy and immunotherapy as first-line treatment (46.9\%) versus immunotherapy alone (21.7\%) or targeted treatments (18.8\%). Less than half of the participants had brain metastases (40.3\%) or bone metastases (46.1\%) at the time of diagnosis. The average PHQ-9 score was 6.4 (SD = 5.1), indicating mild depressive symptoms; GAD-7 score was 5.2 (SD = 5.3), indicating mild anxiety symptoms; and IES score was 16.2 (SD = 15), indicating mild to moderate levels of cancer-specific stress. Most participants had impairment in usual activities, self-care, and mobility but no impairment with self-care. Cumulative attrition at 8 months due to withdrawal or death was 91 participants. Participant status, survey completion, and functional scores by domain can be found in Supplementary Tables 1 and 2, respectively.

Overall, 42\% of the participants completed the baseline assessment before receiving treatment, 45.4\% completed it within 30 days of treatment start, and 12.6\% of participants did not receive any treatment.

\subsection*{Trajectory Groups}

Two, three, and four group models yielded BIC values of $-2449.79, -2407.59$, and $-2407.93$, respectively. The three-group model had a BIC of $-2408$, average PPA greater than or equal to 0.9 for all the three groups (none/mild disability = 0.95, moderate = 0.90, and severe = 0.92), and distinct trajectories, and it was chosen as the final model. Among 207 participants, the three groups were none/mild disability ($n = 79, 38.2\%$), moderate disability ($n = 99, 47.8\%$), and severe disability ($n = 29, 14.0\%$; Fig. 1). Monthly attrition probabilities were highest for the severe disability group (Fig. 2). Impairment in usual activities, self-care, and mobility differed across the three trajectory groups (Table 2, $p < 0.001$ for each functional domain). Sensitivity analyses yielded comparable trajectories and PPA values (Supplementary Fig. 2A and B). The sensitivity analyses resulted in only two participants moving to another trajectory (one participant moved from the none/mild disability to the moderate disability group and one participant moved from the moderate to the severe disability group).

The none/mild disability group started with an average score of 1.0 at baseline and slowly improved in the 8 months with a reduction to a mean of 0.2. This group had the lowest attrition from death or dropout with a rate of 20\%. The moderate disability group started with an average score of 2.6 and remained...
Table 1. Participant Characteristics for the Total Sample (N = 207) of Patients With Stage IV NSCLC

| Variables                        | Category/Score | Total   |
|---------------------------------|----------------|---------|
| Demographics                    |                |         |
| Age (y)                          | Mean (SD)      | 63.5 (11.0) |
|                                 | (min, max)     | (34, 92) |
| Sex, n (%)                       | Male           | 122 (58.9) |
| Race/ethnicity, n (%)            | Latinx/Hispanic ancestry | 2 (1.0) |
|                                 | White          | 196 (94.7) |
|                                 | African American/Black | 14 (6.8) |
|                                 | American Indian/Alaskan | 18 (8.7) |
|                                 | Other          | 3 (1.5) |
| Marital status, n (%)            | Currently married | 122 (59.2) |
| Smoking status, n (%)            | Current        | 51 (24.8) |
|                                 | Disabled or unemployed | 51 (24.8) |
|                                 | Retired        | 105 (50.7) |
| Income, n (%)                    | $<25,000        | 44 (21.3) |
|                                 | $25,000 – $100,000 | 111 (53.9) |
|                                 | >$100,000      | 35 (17.0) |
|                                 | Do not know or refused | 17 (8.3) |
| Smoking status, n (%)            | Current        | 36 (17.4) |
|                                 | Former         | 151 (73.3) |
|                                 | Never          | 20 (9.7) |
| Living setting                   | Rural          | 72 (35.0) |
| Cancer characteristics           |                |         |
| Lung cancer type, n (%)          | Adenocarcinoma | 155 (74.9) |
| Treatment type, n (%)            | Chemo/chemo + IO | 97 (46.9) |
|                                 | Targeted       | 45 (21.7) |
|                                 | IO only        | 45 (21.7) |
|                                 | No systemic treatment | 26 (12.6) |
| Treatment timing, n (%)          | Baseline completed before receiving treatment | 87 (42.0) |
|                                 | Baseline completed within 40 d of treatment start | 94 (45.4) |
|                                 | No treatment received | 26 (12.6) |
| Brain metastases, n (%)          | Yes            | 83 (40.3) |
| Bone metastases, n (%)           | Yes            | 95 (46.1) |
| ECOG PS, n (%)                   | Score 1        | 176 (85.0) |
| Psychological symptoms           |                |         |
| PHQ-9                            | Mean (SD)      | 6.4 (5.1) |
|                                 | (min, max)     | (0, 24) |
| GAD-7                            | Mean (SD)      | 5.2 (5.3) |
|                                 | (min, max)     | (0, 21) |
| IES-R                           | Mean (SD)      | 16.2 (15.0) |
|                                 | (min, max)     | (0, 80) |

Table 1. Continued

| Variables                        | Category/Score | Total   |
|---------------------------------|----------------|---------|
| Symptoms (QLQ-LC13)             |                |         |
| Dyspnea                         | Mean (SD)      | 71.3 (25.7) |
| Coughing                        | Mean (SD)      | 41.9 (30.1) |
| Hemoptysis                      | Mean (SD)      | 5.0 (15.5) |
| Sore mouth                      | Mean (SD)      | 6.0 (15.8) |
| Dysphagia                       | Mean (SD)      | 8.9 (19.8) |
| Peripheral neuropathy           | Mean (SD)      | 13.7 (25.0) |
| Alopecia                        | Mean (SD)      | 7.6 (20.6) |
| Pain in chest                   | Mean (SD)      | 16.4 (24.3) |
| Pain in arm or shoulder         | Mean (SD)      | 18.7 (28.9) |
| Pain in other parts of body     | Mean (SD)      | 27.1 (27.2) |

Options were select all that apply so totals may add to more than 100%.

Due to the nature of the scoring of the QLQ-LC13, the range for all symptoms is (0, 100).

CCI, Charlson Comorbidity Index; Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; GAD-7, Generalized Anxiety Disorder—7-item scale; IES-R, Impact of Events Scale—Revised; IO, immunotherapy; max, maximum; min, minimum; PHQ-9, Patient Health Questionnaire—9-item scale; QLQ-LC13, Quality of Life Questionnaire Lung Cancer—13-item scale.

consistent in the 8 months with an average score of 2.8 at the 8-month time point. The moderate disability group had an attrition rate of 55%. The severe disability group started with an average score of 5.4 and had increasing disability scores that peaked at a score of 6.9 at month 4. Approximately 59% of this group had dropped out or died by 4 months. The remaining participants had a decrease in disability through the 8-month time point, ending with an average score of 3.3 for the 28% participants assessed at month 8. The severe disability group had the highest attrition (72%).

Table 2 displays the bivariate baseline characteristics across the disability groups. Differences were found in race (p = 0.05), employment status (p = 0.04), ECOG PS (p = 0.01), PHQ-9 score (p < 0.001), GAD-7 score (p < 0.001), IES score (p = 0.02), and lung cancer symptoms (dyspnea, p = 0.001). For example, participants in the severe disability group had significantly higher PHQ-9 scores (p < 0.001). Symptoms of dyspnea, sore mouth, dysphagia, and pain were significantly worse in the severe disability group as compared with the none/mild disability group.

At 1-month of follow-up relative to baseline, most participants (74.4%) did not experience functional decline but were able to maintain their functional status, that is, having resilience. Nevertheless, 11.1% experienced functional decline, 8.7% missed their survey, 1.0% had withdrawn from the study, and 4.8% had died. At
month 8 relative to baseline, 45.9% of the participants were classified as resilient but 11 (5.3%) experienced functional decline, 10 (4.8%) missed their survey, 22 (10.6%) had withdrawn, and 69 (33.3%) had died. Table 3 illustrates a significant association between the trajectory groups and resilient versus nonresilient classification at month 8 (Fisher’s exact test, \( p < 0.0001 \)). Most of the resilient participants (76.0%) were in the none/mild disability group versus those not resilient (77.8%) which were in the severe disability group. The remaining 33.7% of the resilient participants were in the moderate disability group.

Discussion

Among more than 200 patients with newly diagnosed aNSCLC, we identified the following three distinct functional trajectories from baseline to 8-month follow-up: none/mild disability (38.2% of participants), moderate disability (47.8%), and severe disability (14.0%). Our results found that attrition rates roughly followed the shape of the functional trajectories, with greater disability leading to higher attrition rates. Participants on the trajectory with no or mild disability over time experienced a low, stable level of attrition. Participants on the moderate disability trajectory had a moderate, stable level of attrition. Participants on the severe disability trajectory had the highest level of attrition over the entire study period but had similar estimates to the moderate disability trajectory group at the end of 8 months. Most participants had functional resiliency at month 1 (74.4%). Nevertheless, this decreased to 45.9% of the participants having resiliency at month 8. Unfortunately, 33% of the participants died by month 8, even with the newest lung cancer treatments. At baseline, demographic characteristics were similar across the disability groups. Brain metastases at baseline and treatment types used were similar across the trajectory groups. Though not statistically significant at a \( p \) value of less than 0.05, most participants who were currently employed, never smokers, and received targeted treatment were in the none/mild disability group (\( p < 0.1 \)). Most participants in the severe disability trajectory group were current or former smokers, living in a rural area, and with a lower income (\( p < 0.1 \)). These factors warrant future study. The severe disability group had a higher percentage of bone metastases at baseline as compared with the other disability groups, and 20% did not receive any systemic treatment. The severe disability group also had the highest impairment in self-care at baseline (31.0%) and subsequently experienced most deaths and dropout throughout the study period (72.4%). This finding reveals that self-care may be an important prognostic indicator associated with survival within the first year of cancer treatment, regardless of treatment type or ECOG PS. Thus, frequent assessment of patients’ ability to perform self-care activities may be beneficial. In addition, patients with bone metastases at diagnosis may benefit from early intervention programs, such as those using physical and/or occupational therapy.

Psychological symptoms differed at baseline between disability groups. There were higher levels of depressive and anxiety symptoms within the moderate disability group. Table 3 illustrates a significant association between the trajectory groups and resilient versus nonresilient classification at month 8 (Fisher’s exact test, \( p < 0.0001 \)). Most of the resilient participants (76.0%) were in the none/mild disability group versus those not resilient (77.8%) which were in the severe disability group. The remaining 33.7% of the resilient participants were in the moderate disability group.
## Table 2. Baseline Characteristics of Patients With NSCLC (N = 207) Categorized by Disability Group

| Variables                                | None/Mild Disability (n = 79) | Moderate Disability (n = 99) | Severe Disability (n = 29) | p Valuea |
|------------------------------------------|-------------------------------|-----------------------------|---------------------------|----------|
| **Demographics**                         |                               |                             |                           |          |
| Age (y)                                  | 61.9 (11.6)                   | 64.6 (10.5)                 | 64.2 (11.0)               | 0.25     |
| Mean (SD) (min, max) (34, 84)            | (37, 92)                      | (42, 81)                    |                           |          |
| Male, n (%)                              | 45 (57)                       | 58 (58.6)                   | 19 (65.5)                 | 0.73     |
| **Race/ethnicity,b n (%)**               |                               |                             |                           |          |
| Latinx/Hispanic ancestry                 | 2 (2.5)                       | 0 (0)                       | 0 (0)                     | 0.41     |
| Caucasian/white                          | 71 (89.9)                     | 96 (97)                     | 29 (100)                  | 0.05     |
| African American/black                   | 8 (10.1)                      | 5 (5.1)                     | 1 (3.4)                   | 0.40     |
| American Indian/Alaskan Native           | 4 (5.1)                       | 9 (9.1)                     | 5 (17.2)                  | 0.14     |
| Other                                    | 1 (1.3)                       | 2 (2)                       | 0 (0)                     | 1.00     |
| **Marital status, n (%)**                |                               |                             |                           | 0.44     |
| Currently married                        | 51 (64.6)                     | 55 (55.6)                   | 16 (55.2)                 |          |
| Other                                    | 28 (35.4)                     | 44 (44.4)                   | 13 (44.8)                 |          |
| **Modified CCI, mean (SD) (min, max)**   | 1.4 (1.9)                     | 2 (2.2)                     | 1.7 (1.6)                 | 0.12     |
| (0, 12)                                  | (0, 15)                       | (0, 5)                      |                           |          |
| **Children under 18 y living at home, n (%)** | 11 (13.9)            | 15 (15.2)                   | 3 (10.3)                  | 0.89     |
| **Education, n (%)**                     |                               |                             |                           | 0.81     |
| Less than high school                    | 10 (12.7)                     | 12 (12.1)                   | 5 (17.2)                  |          |
| High school                              | 25 (31.6)                     | 37 (37.4)                   | 11 (37.9)                 |          |
| More than high school                    | 44 (55.7)                     | 50 (50.5)                   | 13 (44.8)                 |          |
| **Employment, c n (%)**                  |                               |                             |                           | 0.04     |
| Currently employed                       | 28 (35.4)                     | 20 (20.2)                   | 3 (10.3)                  |          |
| Disabled or unemployed                   | 16 (20.3)                     | 28 (28.3)                   | 7 (24.1)                  |          |
| Retired                                  | 35 (44.3)                     | 51 (51.5)                   | 19 (65.5)                 |          |
| **Income, n (%)**                        |                               |                             |                           | 0.10     |
| <$25,000                                 | 14 (17.7)                     | 23 (23.2)                   | 7 (24.1)                  |          |
| $25,000–$100,000                         | 37 (46.8)                     | 56 (56.6)                   | 18 (62.1)                 |          |
| >$100,000                                | 20 (25.3)                     | 14 (14.1)                   | 1 (3.4)                   |          |
| Do not know or refused                   | 8 (10.1)                      | 6 (6.1)                     | 3 (10.3)                  |          |
| **Smoking status, n (%)**                |                               |                             |                           | 0.09     |
| Current                                  | 14 (17.7)                     | 15 (15.2)                   | 7 (24.1)                  |          |
| Former                                   | 52 (65.8)                     | 78 (78.8)                   | 21 (72.4)                 |          |
| Never                                    | 13 (16.5)                     | 6 (6.1)                     | 1 (3.4)                   |          |
| **Rural living setting, n (%)**          | 26 (32.9)                     | 35 (35.4)                   | 11 (37.9)                 | 0.85     |
| **Cancer characteristics**              |                               |                             |                           |          |
| Adenocarcinoma cancer type, n (%)        | 63 (79.7)                     | 73 (73.7)                   | 19 (65.5)                 | 0.30     |
| **Treatment type, n (%)**                |                               |                             |                           | 0.10     |
| Chemo + IO                               | 29 (36.7)                     | 54 (54.5)                   | 14 (48.3)                 |          |
| IO Only                                   | 19 (24.1)                     | 20 (20.2)                   | 6 (20.7)                  |          |
| Targeted                                 | 22 (27.8)                     | 14 (14.1)                   | 3 (10.3)                  |          |
| No systemic treatment                    | 9 (11.4)                      | 11 (11.1)                   | 6 (20.7)                  |          |
| **Treatment timing, n (%)**              |                               |                             |                           | 0.70     |
| Baseline completed before receiving treatment | 33 (41.8)                | 42 (42.4)                   | 12 (41.4)                 |          |
| Baseline completed within 30 d of treatment start | 37 (46.8)                | 46 (46.5)                   | 11 (37.9)                 |          |
| No treatment received                    | 9 (11.4)                      | 11 (11.1)                   | 6 (20.7)                  |          |
| **Brain metastases, n (%)**              | 29 (36.7)                     | 42 (42.4)                   | 12 (41.4)                 | 0.80     |
| **Bone metastases, n (%)**               | 33 (41.8)                     | 43 (43.4)                   | 19 (65.5)                 | 0.08     |
| ECOG PS ≤ 1,c,d,n (%)                    | 72 (91.1)                     | 84 (84.8)                   | 20 (69.0)                 | 0.01     |
| **Psychological symptoms and stress**    |                               |                             |                           |          |
| PHQ-9, c,d,e,f mean (SD) (min, max)      | 4.3 (3.4)                     | 6.8 (5.0)                   | 10.7 (6.4)                | <0.001   |
| (0, 16)                                  | (0, 21)                       | (1, 24)                     |                           |          |
| GAD-7, c,d,e,f mean (SD) (min, max)      | 4.1 (4.3)                     | 5.2 (5.2)                   | 8.6 (6.3)                 | <0.001   |
| (0, 20)                                  | (0, 21)                       | (1, 21)                     |                           |          |
| IES-R, c,d,e,f mean (SD) (min, max)      | 12.7 (12.6)                   | 17.2 (14.6)                 | 22.7 (20.1)               | 0.02     |
| (0, 52)                                  | (0, 61)                       | (1, 80)                     |                           |          |
| **Physical symptoms (QLQ-LC13)**         |                               |                             |                           |          |
| Dyspnea, c,d,e,f mean (SD)               | 78.5 (22.7)                   | 68.6 (24.5)                 | 58.0 (32.3)               | 0.001    |
| (continued)
and severe disability groups, as compared with the none/mild disability group. Nevertheless, our data did not allow us to determine the direction of this relationship; we do not know whether the depressive/anxious symptoms at baseline are resulting in disability or whether the disability is causing the depression/anxiety. Previous research has revealed that psychological symptoms are associated with worse overall survival among patients with advanced lung cancer, providing further rationale for interventions to reduce depressive/anxiety symptoms. Future directions will investigate the directionality of longitudinal psychological symptoms and disability.

Among adults with lung cancer, functional impairment and psychological symptoms, such as depression and anxiety, are common and represent potentially modifiable risk factors to achieve resilience and minimize disability during the disease course. This study highlights additional potential risk factors that may be associated with moderate/severe disability, such as employment, treatment type, dyspnea, and pain. These findings are similar to characteristics associated with disability versus resilience in other care settings.

An improved understanding of functional trajectories could improve both overtreatment and undertreatment of patients with aNSCLC. For example, a patient with severe disability may decide to forgo cancer treatment if they are informed that they are likely to experience prolonged disability and/or death during their disease course. Alternatively, if a person has minimal to no disability but is of older age, a clinician may be more empowered to treat them rather than withholding treatment. Evaluating baseline disability may also promote early intervention for palliative care and/or advanced care planning. Though most participants with moderate and severe disability were classified as not resilient, a few were able to maintain or improve their functional status. Characteristics associated with these groups could inform which patients may experience functional decline without improvement versus which experience functional decline but then improve (resilience).

Findings of the study are considered in the context of the cohort study and study of individuals with advanced disease. Because of the high symptomatology of the patients, many were likely too ill to complete some surveys and many died during the study period. This contributed to known missing data; however, our sensitivity analysis provided support for our results. The study population was recruited from an academic medical center, which may decrease its generalizability; however, we did have many died during the study period. This contributed to known missing data; however, our sensitivity analysis provided support for our results. The study population was recruited from an academic medical center, which may decrease its generalizability; however, we did have many died during the study period. This contributed to known missing data; however, our sensitivity analysis provided support for our results. The study population was recruited from an academic medical center, which may decrease its generalizability; however, we did have many died during the study period. This contributed to known missing data; however, our sensitivity analysis provided support for our results. The study population was recruited from an academic medical center, which may decrease its generalizability; however, we did have many died during the study period. This contributed to known missing data; however, our sensitivity analysis provided support for our results. The study population was recruited from an academic medical center, which may decrease its generalizability; however, we did have many died during the study period. This contributed to known missing data; however, our sensitivity analysis provided support for our results. The study population was recruited from an academic medical center, which may decrease its generalizability; however, we did have

| Variables | None/Mild Disability (n = 79) | Moderate Disability (n = 99) | Severe Disability (n = 29) | p Value |
|-----------|-------------------------------|-----------------------------|---------------------------|----------|
| Coughing, mean (SD) | 41.8 (30.4) | 41.8 (29.1) | 42.5 (33.2) | 0.99 |
| Hemoptysis, mean (SD) | 3.8 (13.1) | 5.7 (15.8) | 5.7 (20.1) | 0.69 |
| Sore mouth, mean (SD) | 2.5 (10.4) | 6.4 (15.6) | 13.8 (24.4) | 0.004 |
| Dysphagia, mean (SD) | 3.0 (9.5) | 11.4 (21.4) | 16.1 (29.0) | 0.002 |
| Peripheral neuropathy, mean (SD) | 8.9 (17.5) | 17.2 (27.9) | 14.9 (30.3) | 0.08 |
| Alopecia, mean (SD) | 5.9 (17.5) | 7.1 (19.2) | 14.8 (31.1) | 0.14 |
| Pain in chest, mean (SD) | 12.2 (20.1) | 17.5 (24.4) | 24.1 (32.0) | 0.06 |
| Pain in arm or shoulder, mean (SD) | 14.8 (27.1) | 17.2 (27.5) | 34.5 (33.9) | 0.006 |
| Pain in other parts of body, mean (SD) | 22.4 (25.4) | 26.3 (25.3) | 42.5 (33.2) | 0.003 |

Note: Denotes column percentages.

*p values from exact chi-square or ANOVA for categorical or continuous variables, respectively, between trajectory groups.

Options were select all that apply so totals may add to more than 100%.

Groups 1 and 3 are statistically different (p < 0.05) by means of subgroup analysis.

*n = 6, n = 10, and n = 4 missing from trajectory groups 1 (mild) and 2 (moderate).

Groups 1 and 2 are statistically different (p < 0.05) by means of subgroup analysis.

Groups 2 and 3 are statistically different (p < 0.05) by means of subgroup analysis.

Groups 1, 2, and 3 are statistically different (p < 0.05) by means of subgroup analysis.

Groups 1, 2, and 3 are statistically different (p < 0.05) by means of subgroup analysis.

Groups 1, 2, and 3 are statistically different (p < 0.05) by means of subgroup analysis.

ANOVA, analysis of variance; CCI, Charlson Comorbidity Index; Chemo, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; GAD-7, Generalized Anxiety Disorder—7-item scale; IES-R, Impact of Events Scale—Revised; IO, immunotherapy; max, maximum; min, minimum; PHQ-9, Patient Health Questionnaire—9-item scale; QLQ-LC13, Quality of Life Questionnaire Lung Cancer—13-item scale.
measurements of physical resiliency and multivariable modeling based on the bivariate screening this study provides.

Conclusions
Patients with aNSCLC may fall into one of the following three distinct functional trajectories: mild, moderate, and severe disability during the course of cancer treatment. Participants with severe disability in self-care had the highest percentage of dropout and death. Psychological symptoms, dyspnea, and pain were also significantly worse among participants in the severe disability group. Interventions that focus on these specific areas which could help patients enhance resilience and prevent functional decline and death during lung cancer treatment are urgently needed.

CRediT Authorship Contribution Statement
Carolyn J. Presley, Sarah Janse, Barbara Andersen: Conceptualization.
Sarah Janse, Nicole Arrato: Data curation.
Sarah Janse, Heather Allore, Ling Han, Jason Benedict: Formal analysis.
Carolyn J. Presley, Peter Shields, David Carbone: Funding acquisition.
Carolyn J. Presley, David Carbone, Peters Shields, Barbara Andersen: Investigation.
Sarah Janse, Heather Allore, Ling Han: Methodology.
Carolyn J. Presley: Project administration.
Carolyn J. Presley, Peter Shields, Sarah Reisinger: Resources.
Peter Shields, Sarah Reisinger: Software.
Barbara Andersen, David Carbone, Sarah Reisinger: Supervision.
Sarah Janse, Jason Benedict: Validation, Visualization.
Carolyn J. Presley, Sarah Janse, Barbara Andersen: Roles/Writeing—original draft.
Carolyn J. Presley, Nicole A. Arrato, Peter G. Shields, David P. Carbone, Melissa L. Wong, Jason Benedict, Sarah A. Reisinger, Ling Han, Thomas M. Gill, Heather Allore, Barbara L. Andersen, Sarah Janse: Writing—review and editing.

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Supplementary Data
Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at [https://doi.org/10.1016/j.jtocrr.2022.100334](https://doi.org/10.1016/j.jtocrr.2022.100334).

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