ORIGINAL ARTICLE

Functional Trajectories and Resilience Among Adults With Advanced Lung Cancer

Carolyn J. Presley, MD, MHS,[a,*] Nicole A. Arrato, MA,[b] Peter G. Shields, MD,[a] David P. Carbone, MD, PhD,[a] Melisa L. Wong, MD, MAS,[c,d] Jason Benedict, MS,[e] Sarah A. Reisinger, PhD, MPH,[a] Ling Han, MD, PhD,[e] Thomas M. Gill, MD,[f] Heather Allore, PhD,[f] Barbara L. Andersen, PhD,[b] Sarah Janse, PhD[e]

[a]*Division of Medical Oncology, Department of Internal Medicine, The Ohio State University, Columbus, Ohio*
[b]*Department of Psychology, The Ohio State University, Columbus, Ohio*
[c]*Division of Hematology/Oncology, Department of Medicine, University of California, San Francisco, San Francisco, California*
[d]*Division of Geriatrics, Department of Medicine, University of California, San Francisco, San Francisco, California*
[e]*Department of Biomedical Informatics, The Ohio State University, Columbus, Ohio*
[f]*Section of Geriatric Medicine, Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut*

Received 16 December 2021; revised 11 April 2022; accepted 30 April 2022
Available online - 17 May 2022

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.

***Corresponding author.**

Drs. Andersen and Janse contributed equally as having co-senior authorship.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Carolyn J. Presley, MD, MHS, The Ohio State University Comprehensive Cancer Center/The James Cancer Hospital & Solove Research Institute, 13th Floor Lincoln Tower, 1300 Cannon Drive, Columbus, OH 43210. E-mail: carolyn.presley@osumc.edu

Cite this article as: Presley CJ, Arrato NA, Shields PG, et al. Functional trajectories and resilience among adults with advanced lung cancer. *JTO Clin Res Rep*. 2022;3:100334.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2022.100334

Keywords: Functional status; Disability; Lung cancer; Immunotherapy; Targeted kinase inhibitors

Introduction

Many older adults with cancer consider the maintenance of functional status as equally or more important than overall survival.[1] Functional status is a person's ability to perform basic activities of daily living[2,3] (ADLs, e.g., bathing), instrumental ADLs[4,5] (e.g., managing medication), and mobility.[6] Few cancer studies have incorporated repeated measures of functional status as defined by ADLs, instrumental ADLs, and mobility.[7] 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.[8,9] 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.[10] 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,[11] 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.[2,7,12–16] 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.[11,16] 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).[12] 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[17] and the presence of depressive symptoms.[12]

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.[18]

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 depressive symptoms (Patient Health Questionnaire—9 [PHQ-9][19]), anxiety symptoms (Generalized Anxiety Disorder—7 Scale [GAD-7][20]), 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]—Revised[22,23]), 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 of 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 Codes[26] 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 15[31,32] that occurred at any time before the stage IV NSCLC diagnosis, excluding the six points due to metastatic cancer.

Psychological Symptoms. *Depression.* The PHQ-9[19] 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-7[20] 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-Revised[22,23] 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-LC13[21] was used to assess lung-specific symptoms. The QLQ-LC13 is a supplementary module to the EORTC-QLQ-C30[31] 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[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.[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.

Results

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 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.

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. 2*A* 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) (min, max)	63.5 (11.0) (34, 92)
Sex, n (%)	Male	122 (58.9)
Race/ethnicity,[a] n (%)	Latinx/Hispanic ancestry	2 (1.0)
	White	196 (94.7)
	African American/Black	14 (6.8)
	American Indian/Alaskan Native	18 (8.7)
	Other	3 (1.5)
Marital status, n (%)	Currently married	122 (59.2)
	Single, never married	24 (11.7)
	Separated or divorced	39 (18.8)
	Widowed	22 (10.7)
Modified CCI	Mean (SD) (min, max)	1.7 (2.0) (0, 15)
Education, n (%)	Less than high school	27 (13.1)
	High school	73 (35.4)
	More than high school	107 (51.7)
Employment, n (%)	Currently employed	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)
	IO only	45 (21.7)
	Targeted	39 (18.8)
	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) (min, max)	6.4 (5.1) (0, 24)
GAD-7	Mean (SD) (min, max)	5.2 (5.3) (0, 21)
IES-R[b]	Mean (SD) (min, max)	16.2 (15.0) (0, 80)
Symptoms (QLQ-LC13)[c]		
Dyspnea[d]	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)

[a]Options were select all that apply so totals may add to more than 100%.
[b]n = 20 missing.
[c]Due to the nature of the scoring of the QLQ-LC13, the range for all symptoms is (0, 100).
[d]n = 19 missing.
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

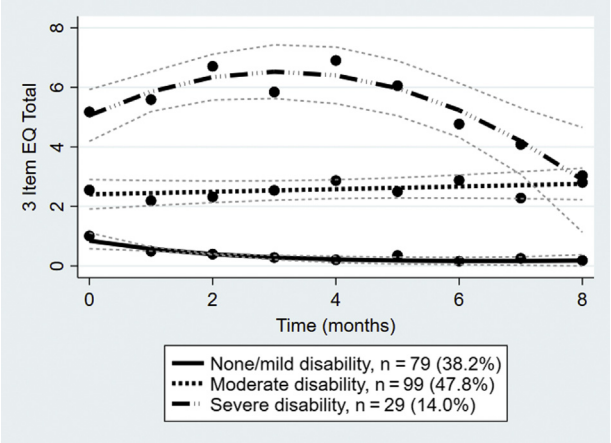

Figure 1. Functional trajectories in 8 months jointly modeled with attrition.

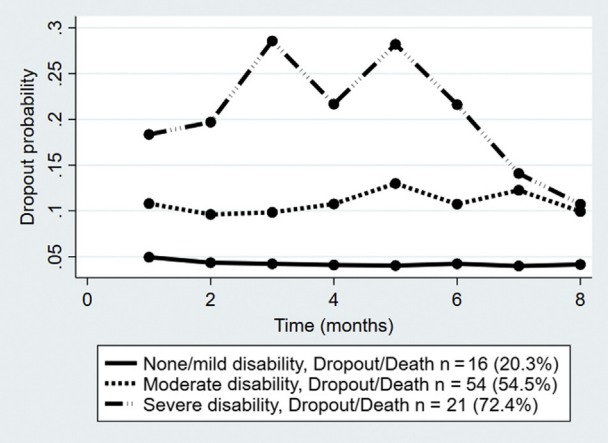

Figure 2. Probability of dropout over time by functional trajectory group for patients with NSCLC (N = 207). Trajectories of functional disability in 8 months jointly modeled with attrition. (1) Trajectories of functional disability measures by the 3-item EQ total. Higher scores indicate increased functional disability. The black lines represent the unadjusted observed monthly least square means of total disability within each trajectory, and the gray dashed lines are the predicted mean disability counts (95% CIs) based on the latent class trajectory model. (2) Monthly attrition probabilities. Attrition was jointly modeled with the functional disability trajectories. Legend: n and percentage of dropout. CI, confidence interval.

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.[38,39]

Psychological symptoms differed at baseline between disability groups. There were higher levels of depressive and anxiety symptoms within the moderate

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* Value[a]
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) (0, 12)	2 (2.2) (0, 15)	1.7 (1.6) (0, 5)	0.12
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,e,f] mean (SD) (min, max)	4.3 (3.4) (0, 16)	6.8 (5.0) (0, 21)	10.7 (6.4) (1, 24)	<0.001
GAD-7,[c,f] mean (SD) (min, max)	4.1 (4.3) (0, 20)	5.2 (5.2) (0, 21)	8.6 (6.3) (1, 21)	<0.001
IES-R,[c,g] mean (SD) (min, max)	12.7 (12.6) (0, 52)	17.2 (14.6) (0, 61)	22.7 (20.1) (1, 80)	0.02
Physical symptoms (QLQ-LC13)				
Dyspnea,[c,e,h] mean (SD)	78.5 (22.7)	68.6 (24.5)	58.0 (32.3)	0.001

(continued)

Table 2. Continued

Variables	None/Mild Disability (n = 79)	Moderate Disability (n = 99)	Severe Disability (n = 29)	*p* Value[a]
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,[c,f] mean (SD)	2.5 (10.4)	6.4 (15.6)	13.8 (24.4)	0.004
Dysphagia,[c,e] 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,[i] 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,[c,f] mean (SD)	14.8 (27.1)	17.2 (27.5)	34.5 (33.9)	0.006
Pain in other parts of body,[c,f] mean (SD)	22.4 (25.4)	26.3 (25.3)	42.5 (33.2)	0.003

Note: Denotes column percentages.
[a]*p* values from exact chi-square or ANOVA for categorical or continuous variables. respectively, between trajectory groups.
[b]Options were select all that apply so totals may add to more than 100%.
[c]Groups 1 and 3 are statistically different ($p < 0.05$) by means of subgroup analysis.
[d]n = 1 missing from trajectory groups 1 (mild) and 2 (moderate).
[e]Groups 1 and 2 are statistically different ($p < 0.05$) by means of subgroup analysis.
[f]Groups 2 and 3 are statistically different ($p < 0.05$) by means of subgroup analysis.
[g]n = 6, n = 10, and n = 4 missing from trajectory groups 1, 2, and 3 (severe), respectively.
[h]n = 4, n = 9, and n = 6 missing from trajectory groups 1, 2, and 3, respectively.
[i]n = 2 missing from trajectory group 3.
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.

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.[40] 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[18] 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.[41]

An improved understanding of functional trajectories could improve both overtreatment and undertreatment of patients with aNSCLC.[42] 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 a diverse sample regarding education level, employment status, income, and rural versus urban residence. The analyses were limited to 8 months due to a high level of attrition. Future research will specifically compare overall survival between the disability and resiliency groups and evaluate risk factors for early mortality. The data collection did not capture an objective measurement of physical capability, such as the Short Physical Performance Battery[17,43] or gait speed, and did not evaluate disability due to treatment toxicity. Future prospective studies will incorporate objective

Table 3. Functional Trajectory Group and Resiliency Status at 8 Months

	Trajectory Group[a]		
Sample	None/Mild Disability	Moderate Disability	Severe Disability
Total, N = 197[b]	n = 75	n = 95	n = 27
Resilient, n (%) (n = 95)	57 (76.0)	32 (33.7)	6 (22.2)
Not resilient, n (%) (n = 102)	18 (24.0)	63 (66.3)	21 (77.8)

[a]There is an association between functional trajectory group and resiliency status at 8 months by means of Fisher's exact test ($p < 0.0001$). Cumulative attrition at 8 months = 91 participants.
[b]There are n = 4, n = 4, and n = 2 missing from the three trajectory groups, respectively, as they missed their 8-month assessment.

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 Resisinger: 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/Writing—original draft.

Carolyn J. Presley, Nicole A. Arrato, Peter G. Shields, David P. Carbone, Melisa L. Wong, Jason Benedict, Sarah A. Reisinger, Ling Han, Thomas M. Gill, Heather Allore, Barbara L. Andersen, Sarah Janse: Writing—review and editing.

Acknowledgments

This work was supported by an Ohio State University Comprehensive Cancer Center Pelotonia Grant (P. Shields, principal investigator), The National Institute of Aging (Dr. Presley, 1K76AG074923-01;R03AG064374; Dr. Wong, K76AG064431, P30AG044281), The Ohio State University, United States K12 Training Grant for Clinical Faculty Investigators (Dr. Presley, K12CA133250), and the Claude D. Pepper Older Americans Independence Center at Yale School of Medicine (P30AG021342) from the National Institute on Aging. We thank the patients for their participation in The Ohio State University Beating Lung Cancer in Ohio study. Research reported in this publication was supported by The Ohio State University Comprehensive Cancer Center and the National Institutes of Health, United States (P30 CA016058) and Pelotonia, United States. Data were provided by The Beating Lung Cancer In Ohio Collaboration. We thank the Recruitment, Intervention and Survey Shared Resource at The Ohio State University Comprehensive Cancer Center for data management. The authors are also grateful to the following people who helped support clinical efforts related to the trial: Abdelhalim Belkheyar, Rachel Smith, John Myers, Patricia Thompson, Barbara Schley, Madison Grogan, Benjamin Veneman, Alek Erdel, Guy Brock, and Joseph McElroy.

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 at https://doi.org/10.1016/j.jtocrr.2022.100334.

References

1. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. *N Engl J Med*. 2002;346:1061–1066.
2. Hoppe S, Rainfray M, Fonck M, et al. Functional decline in older patients with cancer receiving first-line chemotherapy. *J Clin Oncol*. 2013;31:3877–3882.

3. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist*. 1970;10:20–30.
4. Bubis LD, Davis L, Mahar A, et al. Symptom burden in the first year after cancer diagnosis: an analysis of patient-reported outcomes. *J Clin Oncol*. 2018;36:1103–1111.
5. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9:179–186.
6. Medysky ME, Dieckmann NF, Winters-Stone KM, Sullivan DR, Lyons KS. Trajectories of self-reported physical functioning and symptoms in lung cancer survivors. *Cancer Nurs*. 2021;44:E83–E89.
7. Loh KP, Lam V, Webber K, et al. Characteristics associated with functional changes during systemic cancer treatments: a systematic review focused on older adults. *J Natl Compr Canc Netw*. 2021;19:1055–1062.
8. Hurria A, Soto-Perez-de-Celis E, Allred JB, et al. Functional decline and resilience in older women receiving adjuvant chemotherapy for breast cancer. *J Am Geriatr Soc*. 2019;67:920–927.
9. Varadhan R, Walston JD, Bandeen-Roche K. Can a link be found between physical resilience and frailty in older adults by studying dynamical systems? *J Am Geriatr Soc*. 2018;66:1455–1458.
10. Denckla CA, Cicchetti D, Kubzansky LD, et al. Psychological resilience: an update on definitions, a critical appraisal, and research recommendations. *Eur J Psychotraumatol*. 2020;11:1822064.
11. Petrick JL, Reeve BB, Kucharska-Newton AM, et al. Functional status declines among cancer survivors: trajectory and contributing factors. *J Geriatr Oncol*. 2014;5:359–367.
12. Presley CJ, Han L, Leo-Summers L, et al. Functional trajectories before and after a new cancer diagnosis among community-dwelling older adults. *J Geriatr Oncol*. 2019;10:60–67.
13. Jones JM, Olson K, Catton P, et al. Cancer-related fatigue and associated disability in post-treatment cancer survivors. *J Cancer Surviv*. 2016;10:51–61.
14. Hirpara DH, Gupta V, Davis LE, et al. Severe symptoms persist for up to one year after diagnosis of stage I-III lung cancer: an analysis of province-wide patient reported outcomes. *Lung Cancer*. 2020;142:80–89.
15. Zucca AC, Boyes AW, Linden W, Girgis A. All's well that ends well? Quality of life and physical symptom clusters in long-term cancer survivors across cancer types. *J Pain Symptom Manag*. 2012;43:720–731.
16. Rosow I, Breslau N. A Guttman health scale for the aged. *J Gerontol*. 1966;21:556–559.
17. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. *N Engl J Med*. 1995;332:556–561.
18. Presley CJ, Arrato NA, Janse S, et al. Functional disability among older versus younger adults with advanced non-small-cell lung cancer. *JCO Oncol Pract*. 2021;17:e848–e858.
19. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606–613.
20. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166:1092–1097.
21. Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. *Eur J Cancer*. 1994;30A:635–642.
22. Horowitz M, Wilner N, Alvarez W. Impact of event scale: a measure of subjective stress. *Psychosom Med*. 1979;41:209–218.
23. Weiss DS, Marmar CR. The impact of event scale—revised. In: Wilson JP, Keane TM, eds. *Assessing Psychological Trauma and PTSD*. New York, NY: The Guilford Press; 1997:399–411.
24. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20:1727–1736.
25. Sage R, Ward B, Myers A, Ravesloot C. Transitory and enduring disability among urban and rural people. *J Rural Health*. 2019;35:460–470.
26. U.S. Department of Agriculture. Rural-urban continuum codes. https://www.ers.usda.gov/data-products/rural-urban-continuum-codes.aspx. Accessed June 2021.
27. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365–376.
28. Khan I, Morris S, Pashayan N, Matata B, Bashir Z, Maguirre J. Comparing the mapping between EQ-5D-5L, EQ-5D-3L, and the EORTC-QLQ-C30 in non-small cell lung cancer patients. *Health Qual Life Outcomes*. 2016;14:60.
29. Gill TM. Disentangling the disabling process: insights from the precipitating events project. *Gerontologist*. 2014;54:533–549.
30. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5:649–655.
31. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
32. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10 version of the Charlson comorbidity index predicted in-hospital mortality. *J Clin Epidemiol*. 2004;57:1288–1294.
33. Andersen BL, DeRubeis RJ, Berman BS, et al. Screening, assessment, and care of anxiety and depressive symptoms in adults with cancer: an American Society of Clinical Oncology guideline adaptation. *J Clin Oncol*. 2014;32:1605–1619.
34. Fayers P, Aaronson NK, Bjordal K, et al. *EORTC QLQ-C30 Scoring Manual*. European Organization for Research and Treatment of Cancer; 1995. https://qol.eortc.org/manuals/. Accessed June 2021.
35. Jones BL, Nagin DS, Roeder K. A SAS procedure based on mixture models for estimating developmental trajectories. *Sociol Methods Res*. 2001;29:374–393.

36. Haviland AM, Jones BL, Nagin DS. Group-based trajectory modeling extended to account for nonrandom participant attrition. *Sociol Methods Res*. 2011;40:367–390.
37. Nagin DS. *Group-Based Modeling of Development*. Cambridge, United Kingdom: Harvard University Press; 2005.
38. Cormie P, Galvão DA, Spry N, Joseph D, Taaffe DR, Newton RU. Functional benefits are sustained after a program of supervised resistance exercise in cancer patients with bone metastases: longitudinal results of a pilot study. *Support Care Cancer*. 2014;22:1537–1548.
39. McDonnell ME, Shea BD. The role of physical therapy in patients with metastatic disease to bone. *J Back Musculoskelet Rehabil*. 1993;3:78–84.
40. Andersen BL, McElroy JP, Carbone DP, et al. Psychological symptom trajectories and non-small cell lung cancer survival: a joint model analysis. *Psychosom Med*. 2022;84:215–223.
41. Colón-Emeric C, Whitson HE, Pieper CF, et al. Resiliency groups following hip fracture in older adults. *J Am Geriatr Soc*. 2019;67:2519–2527.
42. DuMontier C, Loh KP, Bain PA, et al. Defining undertreatment and overtreatment in older adults with cancer: a scoping literature review. *J Clin Oncol*. 2020;38:2558–2569.
43. Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower-extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;49:M85–M94.