

The prognostic value of pre-diagnosis health-related quality of life on survival: a prospective cohort study of older Americans with lung cancer

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Abstract

Purpose Health-related quality of life (HRQOL) after cancer diagnosis is prognostic for overall survival (OS). However, no studies have assessed if HRQOL before diagnosis is predictive for OS. The objective of this study was to determine the association between pre-lung cancer diagnosis HRQOL and OS.

Methods Our prospective cohort study used surveillance, epidemiology, and end results linked to the Medicare Health Outcomes Survey. We included 6290 individuals 65 years or older diagnosed with incident lung cancer from 1998 to 2013. We assessed the prognostic value of (1) short-form 36 summary component and domain-specific scores, (2) activities of daily living (ADL), and (3) two global HRQOL questions. Cox-proportional hazards models were used to examine associations between HRQOL and OS, adjusting for demographics, comorbid conditions, and clinical characteristics.

Results Worse pre-diagnosis HRQOL was significantly associated with greater risk of death across HRQOL measures. An above average physical or mental component summary score was associated with 16 and 24% decreases in

the hazard of death, respectively ($p < 0.0001$). Being unable to perform ADLs, such as bathing oneself, was associated with an 89% increased hazard of death ($p < 0.0001$). Reporting “poor” versus “excellent” health was associated with a 74% increase in the hazard of death ($p < 0.0001$).

Conclusion This population-based study reinforces the importance of self-reported health status as a predictor for OS. Routine HRQOL screening may identify patients who could benefit from early interventions to improve HRQOL. Future studies should explore associations between changes in HRQOL before and after cancer diagnosis and OS.

Keywords Quality of life · Survival · Lung cancer

Background

Lung cancer is the most common cancer in the world and accounts for 18% of cancer-related deaths [1]. Incidence of lung cancer continues to grow, and North America has the highest rates of diagnosis [1]. Mortality rates for this cancer type are high, with 1- and 5-year survival of 42 and 16%, respectively [2]. Lung cancer is associated with higher symptom burden compared to other cancers, and treatment-related symptoms are associated with clinical outcomes, including disease-free and overall survival (OS) and treatment success [3, 4]. Symptoms, such as fatigue, chest pain, and persistent cough frequently exist before diagnosis and may impact health-related quality of life (HRQOL) [3, 4].

HRQOL is a multidimensional construct defined as an individual’s self-reported sense of well-being as it relates to health-related event or illness and includes several domains, such as physical, functional, social, and emotional well-being [5–7]. HRQOL has been shown to be significantly associated with OS and healthcare services use in non-cancer diseases,

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Table 1 Demographic and clinical characteristics for individuals with lung cancer

	Died, <i>N</i> = 5107		Alive at end of study, <i>N</i> = 1183		<i>P</i> value
	<i>N</i>	%	<i>N</i>	%	
Age categories					<0.0001***
65–69	417	8	96	8	
70–74	1390	27	320	27	
75–79	1643	32	422	36	
80–84	1064	21	265	22	
85+	593	12	80	7	
Female	2440	48	693	59	<0.0001***
Race					
White	4087	80	920	78	0.0081**
Black	379	7	92	8	
Hispanic	271	5	61	5	
Asian	230	5	83	7	
Other	140	3	27	2	
Married	2691	53	673	57	0.0091**
Geographic region					0.0733
West	2771	54	597	50	
Midwest	448	9	122	10	
South	953	19	243	21	
Northeast	935	18	221	19	
Level of education					0.004**
Some high school	3373	66	729	62	
Some college	1088	21	302	26	
More than college	525	10	130	11	
Missing	121	2	22	2	
Smoking status					<0.0001***
Never smoked	1416	28	557	47	
Former smoker	1797	35	364	31	
Current smoker	1612	32	234	20	
Missing	282	6	28	2	
Proxy completed survey	506	10	90	8	0.0025**
Completed paper survey	4459	87	1039	88	0.6298
Non-small-cell lung cancer	4341	85	1108	94	<0.0001***
Small-cell lung cancer	766	15	75	6	
Stage of disease at diagnosis					<0.0001***
Local	724	14	508	43	
Regional	1228	24	364	31	
Distant	2864	56	269	23	
Missing stage	291	6	42	4	
Received surgery	695	14	587	50	<0.0001****
Received radiation	1810	35	368	31	0.0015**
Comorbid conditions					
Hypertension	2835	56	708	60	0.0123*
Heart disease	1716	34	359	30	0.0319*
Stroke	450	9	85	7	0.0579
COPD	1247	24	329	28	0.0195*
GI	227	4	55	5	0.7994

Table 1 (continued)

	Died, <i>N</i> =5107		Alive at end of study, <i>N</i> =1183		<i>P</i> value
	<i>N</i>	%	<i>N</i>	%	
Arthritis	2362	46	590	50	0.0245*
Sciatica	1162	23	287	24	0.3191
Diabetes	936	18	218	18	0.9897

* <0.05 , ** <0.01 , *** <0.0001

such as arthritis and HIV [8–10]. A systematic review of the prognostic value of HRQOL for OS in cancer clinical trials found strong associations across 36 of 39 studies evaluated [8]. Twelve of these studies were conducted in lung cancer [8]. The review found that HRQOL was more predictive of OS than a clinician-rated performance status, which is routinely assessed in clinic [8]. Studies specific to lung cancer have confirmed significant relationships between HRQOL measured after cancer diagnosis and OS [11–13]. In lung cancer, the most commonly used instrument to capture HRQOL was the EORTC QLQ-C30, which was associated with statistically significantly 11–12% increases in the hazards of death [14, 15]. Global HRQOL measures, which have a narrower range of scores, were associated with large increases in the hazard of death with significant hazard ratios of 1.62 and 1.76 [16]. However, in all the studies included in the systematic review, HRQOL was measured after cancer diagnosis. Post-diagnosis (and often post-treatment) assessments may be confounded by exposure to diagnosis-related stress and treatment-related morbidities, which have been shown to negatively impact HRQOL [17]. To our knowledge, no study has examined associations between pre-diagnosis HRQOL and OS among individuals with lung cancer.

To fill this knowledge gap, we used a unique, population-based data set: the National Cancer Institute's (NCI) Surveillance Epidemiology and End Results (SEER) cancer registry linked with data from the Center for Medicare and Medicaid Service's (CMS) Medicare Health Outcomes Survey (MHOS). SEER provides detailed clinical data, and the MHOS includes HRQOL data for Americans 65 years and older (and disabled individuals under 65) enrolled in the Medicare Advantage Program. Our study's objective was to determine if HRQOL measured before diagnosis could be predictive of OS and how relationships varied by HRQOL domain.

Methods

Data

The SEER consortium collects information on newly diagnosed cancer cases within SEER geographic regions

covering 26% of the US population [18]. The MHOS is a questionnaire administered annually to 1000–1200 randomly selected beneficiaries from each managed care organization in the Medicare Advantage Program [18]. A baseline survey is administered along with a follow-up survey 2 years later [18]. Our study included 14 MHOS cohorts from 1998 to 2013. As Medicare Advantage plans are not represented in all SEER regions, there is an overrepresentation from California, Detroit, and Seattle [18]. We obtained Institutional Review Board permission from the University of North Carolina at Chapel Hill.

Participants

We identified 7421 individuals with small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), whose first SEER-confirmed cancer diagnosis occurred after baseline or follow-up MHOS. We only included individuals, whose lung cancer was the first and only cancer in SEER. Among these, 1131 (15%) were excluded due to lack of diagnostic confirmation of lung cancer. Some individuals completed multiple HRQOL assessments prior to diagnosis, in which case we took their closest assessment before diagnosis. Our sample consisted of 6290 diagnostically confirmed adults with incident lung cancer aged 65 years and older who completed an HRQOL assessment before diagnosis.

Covariates

Self-reported MHOS demographic characteristics collected pre-diagnosis included marital status, highest level of education completed, smoking status, and pre-existing health conditions. Age at diagnosis, sex, and race was also included. We adjusted for whether or not the MHOS was completed by a proxy (e.g., spouse or caregiver), as this may indicate worsened health status as well as if the survey was administered on paper or by telephone. We also controlled for SEER-reported cancer stage at diagnosis (local, regional, or distant), whether the lung cancer was NSCLC or SCLC, and treatments received (surgery and radiation).

Table 2 Adjusted Cox-proportional model hazard ratios for short-form 36 measures

	Total cohort, <i>N</i> =6290		Over 2 years, <i>N</i> =3369		Within 2 years, <i>N</i> =2921		Within 1 year, <i>N</i> =1709	
	HR-5 pt	95% CI	HR-5 pt	95% CI	HR-5 pt	95% CI	HR-5 pt	95% CI
MCS	0.96	(0.95–0.98)**	0.98	(0.96–1.00)	0.95	(0.93–0.97)***	0.96	(0.93–0.99)**
PCS	0.93	(0.92–0.94)***	0.94	(0.93–0.96)***	0.95	(0.93–0.97)***	0.96	(0.93–0.98)**
PF	0.93	(0.91–0.94)***	0.93	(0.91–0.95)***	0.96	(0.94–0.98)**	0.96	(0.94–0.99)**
GH	0.96	(0.94–0.99)*	0.96	(0.94–0.99)**	0.95	(0.93–0.97)***	0.95	(0.92–0.98)**
RP	0.95	(0.93–0.96)***	0.96	(0.94–0.98)***	0.96	(0.94–0.98)***	0.96	(0.94–0.99)**
RE	0.96	(0.95–0.97)***	0.98	(0.96–0.99)*	0.95	(0.93–0.97)***	0.97	(0.94–0.99)*
MH	0.96	(0.94–0.98)**	0.97	(0.95–0.99)*	0.96	(0.94–0.98)**	0.97	(0.95–1.00)
SF	0.95	(0.94–0.96)***	0.98	(0.96–0.99)*	0.95	(0.93–0.97)***	0.97	(0.94–0.99)*
BP	0.96	(0.95–0.98)**	0.98	(0.96–1.00)***	0.95	(0.93–0.97)***	0.95	(0.92–0.98)**
VT	0.94	(0.92–0.95)***	0.95	(0.93–0.97)***	0.94	(0.92–0.96)***	0.94	(0.91–0.96)***

SF-36 scores are normed scores mean 50, SD 10

5-point HR hazard ratio, 95% CI confidence interval, MCS mental component summary, PCS physical component summary, PF physical function, GH general health, RP role physical, RE role emotional, MH mental health, SF social function, BP bodily pain, VT vitality

* <0.05 , ** <0.01 , *** <0.0001

Measures

OS

SEER-MHOS obtains information about death from death certificates. OS was calculated as number of months between MHOS survey and date of death (from SEER). Fifteen participants were diagnosed with lung cancer from their death certificate or via autopsy.

SF-36

The SF-36 was included in the MHOS from 1998 to 2005 [19]. The SF-36 has eight subscales: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Mental Health, Role Emotional, and Social Functioning [19]. The instrument also includes two summary scores: the Physical Component Summary (PCS) and Mental Component Summary (MCS). The eight subscales and PCS and MCS are normed scores with mean of 50 and standard deviation (SD) of 10 in the US general population with higher scores indicating better HRQOL [19].

MHOS cohorts from 2006 to 2013 used the Veterans Rand-12 (VR-12) instrument, which includes 12 items reflecting the eight SF-36 subscales and PCS and MCS [20]. We used an NCI algorithm to create comparable subscale and summary scores to combine data for those who completed the SF-36 in 1998–2005 with those who completed the VR-12 in 2006–2013 [21]. Subscales, MCs and PCS were normed with mean of 50 and SD of 10 in the US general population with higher scores representing better HRQOL.

Although there is no widely accepted standard minimally important difference (MID) for the SF-36 among individuals with cancer, we defined that an MID is a difference in group scores considered clinically relevant for patients or providers [22]. A review of the literature found SF-36 MID ranges from 0.2 to 0.5 SDs [23–25]. For our study, we used Cohen's medium effect size of 0.5 of the SD [26]. Therefore, for the ten SF-36 normed scores, we used an MID of 5 point. We reported adjusted hazard ratios (HRs) associated with MID of 5 points. To convert our estimates, we took beta-coefficients for 1-unit increases, multiplied by 5 (the MID for these measures) and exponentiated the value. This allows us to present and interpret hazard ratios for MID in the SF-36 measures, which may be more clinically relevant than 1-point increases. Previous studies assessing associations between HRQOL and OS categorized PCS and MCS as below or above the mean of 50 [13, 27, 28]. We also dichotomized PCS and MCS scores to compare HRs to what was previously published.

General HRQOL

Our study included two single-item global questions. The first item asked, "In general, would you say your health is: excellent, very good, good, fair, or poor?" The second was, "In general, compared to other people your age, would you say that your health is: excellent, very good, good, fair or poor?" Excellent was used as our reference category.

ADLs

We examined responses to Katz's basic ADLs (e.g., eating, bathing, dressing, getting in or out of chairs, walking,

Table 3 Adjusted Cox-proportional model hazard ratios for short-form 36 measure stratified by non-small-cell and small-cell lung cancers

	Total cohort, <i>N</i> =6290		NSCLC, <i>N</i> =5449		SCLC, <i>N</i> =841	
	HR-5 pt	95% CI	HR-5 pt	95% CI	HR-5 pt	95% CI
MCS	0.96	(0.95–0.98)**	0.96	(0.95–0.98)***	0.96	(0.93–1.00)
PCS	0.93	(0.92–0.94)***	0.93	(0.92–0.95)***	0.92	(0.88–0.95)***
PF	0.93	(0.91–0.94)***	0.93	(0.91–0.94)***	0.92	(0.89–0.96)***
GH	0.96	(0.94–0.99)*	0.95	(0.94–0.97)***	0.90	(0.87–0.94)***
RP	0.95	(0.93–0.96)***	0.94	(0.93–0.96)**	0.95	(0.92–0.99)*
RE	0.96	(0.95–0.97)***	0.95	(0.94–0.97)***	0.98	(0.94–1.00)
MH	0.96	(0.94–0.98)**	0.97	(0.95–0.98)***	0.95	(0.92–0.99)*
SF	0.95	(0.94–0.96)***	0.96	(0.94–0.97)***	0.94	(0.90–0.97)**
BP	0.96	(0.95–0.98)**	0.97	(0.95–0.98)***	0.94	(0.90–0.98)**
VT	0.94	(0.92–0.95)***	0.94	(0.92–0.96)***	0.91	(0.88–0.95)***

SF-36 scores are normed scores mean 50, SD 10

5-point HR hazard ratios, 95% confidence intervals are presented. MCS mental component summary, PCS physical component summary, PF physical function, GH general health, RP role physical, RE role emotional, MH mental health, SF social function, BP bodily pain, VT vitality

* <0.05 , ** <0.01 , *** <0.0001

and using the toilet) [29]. Each item was phrased, “Because of a health or physical problem, do you have any difficulty doing the following activities without special equipment or health from another person?” Response options included, “No, I do not have difficulty”, “Yes, I have difficulty”, and “I am unable to do this activity”. Each ADL was assessed in a separate model, adjusting for demographic, comorbid, clinical, and treatment characteristics. “No difficulty” was the reference category.

Statistical analysis

Unadjusted comparisons of demographic, comorbid, clinical, and treatment characteristics between individuals who died and those alive at the end of follow-up were done using *t* tests and Chi-square tests. Model covariates were consistent with the previous SEER-MHOS studies [17, 22, 30, and 31]. Cox-proportional hazards models were used to examine associations between pre-diagnosis HRQOL and OS. Characteristics in Table 1 were adjusted for in all models. Although age at diagnosis is presented categorically in Table 1, it was treated as a continuous variable in analyses. We also adjusted for time from baseline HRQOL assessment to diagnosis as a continuous variable in our models. Our sample included 5107 deaths. Given the standard of ten or more events per covariate in a Cox-Proportional Hazards model, our models with 19 covariates were appropriate [32]. We computed adjusted HRs and 95% confidence intervals (CI) for each estimate. There were 3999 individuals who completed their MHOS more than 2 years before diagnosis. As these assessments may be less representative of HRQOL near diagnosis, we performed stratified analyses by those who completed assessments less or more than

2 years before diagnosis. We conducted additional sensitivity analyses restricting models to those with an assessment within 1 year of diagnosis. As there are distinct clinical differences between individuals with SCLC and NSCLC, we performed stratified analyses between the two groups. We also performed additional sensitivity analyses removing the 15 individuals who were diagnosed by autopsy or death certificate, but our estimates remained unchanged. Finally, we performed a sensitivity analysis removing HRQOL assessments that were completed by proxy respondents (9% of the sample), but the statistical significance and magnitude of the hazard ratios did not change. As such, as included an indicator for whether or not the HRQOL assessment was completed by a proxy in all models, but did not exclude these assessments from our models. Analyses were performed in SAS Version 9.3 with 2-sided statistical tests and a significance level of 5%.

Results

Participant characteristics

Patient characteristics are presented in Table 1. Given our large sample size, some small differences between those who died and were alive at the end of follow-up were statistically significant, but, overall, we felt that age, race, SEER geographic region, education, marital status, and comorbid conditions were similarly distributed. Smoking status varied, as 47% of individuals alive at the end of follow-up identified as “never smokers” compared to 28% ($p<0.0001$) among individuals who died. Fifteen percent of individuals who died had SCLC compared to 6% among

Table 4 Adjusted Cox-proportional model hazard ratios for activities of daily living measures

	Total cohort		Over 2 years		Within 2 years	
	HR	95% CI	HR	95% CI	HR	95% CI
Difficulty bathing (ref: no problem)						
Unable to do	1.89	(1.47–2.44)***	1.86	(1.23–2.80)**	1.61	(1.15–2.24)**
Some difficulty	1.27	(1.15–1.41)***	1.15	(0.98–1.34)	1.18	(1.03–1.37)*
Difficulty dressing (ref: no problem)						
Unable to do	1.88	(1.36–2.59)***	1.55	(0.91–2.64)	1.89	(1.26–2.86)**
Some difficulty	1.28	(1.14–1.43)***	1.09	(0.92–1.29)	1.22	(1.05–1.42)*
Difficulty eating (ref: no problem)						
Unable to do	1.72	(1.20–2.48)**	1.56	(0.90–2.72)	2.05	(1.26–3.34)**
Some difficulty	1.39	(1.17–1.65)**	1.31	(0.99–1.70)	1.18	(0.94–1.49)
Difficulty chair (ref: no problem)						
Unable to do	1.57	(1.13–2.17)**	1.29	(0.77–2.17)	2.23	(1.44–3.44)**
Some difficulty	1.17	(1.08–1.27)**	1.15	(1.03–1.29)*	1.12	(0.99–1.26)
Difficulty walking (ref: no problem)						
Unable to do	1.67	(1.35–2.07)***	1.54	(1.11–2.14)*	1.54	(1.16–2.05)**
Some difficulty	1.22	(1.14–1.31)***	1.26	(1.14–1.39)***	1.11	(1.01–1.23)*
Difficulty toilet (ref: no problem)						
Unable to do	1.57	(1.13–2.18)**	1.64	(1.02–2.63)*	2.05	(1.27–3.30)**
Some difficulty	1.14	(0.99–1.31)	1.08	(0.88–1.33)	1.03	(0.86–1.25)

HR hazard ratio, 95% CI confidence interval

* <0.05 , ** <0.01 , *** <0.0001

those alive ($p < 0.0001$). Over 50% of those who died presented with metastatic disease, and 14% had surgery (50% had surgery in the alive group). Median time from HRQOL assessment to diagnosis was 28 months (interquartile range of 12–65 months).

SF-36 HRQOL

Mean PCS and MCS scores were 39.0 (SD 11.9) and 51.1 (SD 10.7), respectively. Adjusted HRs and p values for 5-point increments of PCS, MCS, and eight SF-36 subscales are shown in Tables 2 and 3. We present results for the overall cohort, those with an HRQOL assessment more than 2 years before diagnosis and for those with an HRQOL assessment within 2 years and 1 year of diagnosis (Table 2). We also present results stratified by NSCLC and SCLC (Table 3). As higher scores on SF-36 measures indicate better HRQOL, HRs in Tables 2 and 3 are below 1.0. That is, increases in HRQOL were associated with decreases in the hazard of death.

Adjusting for demographic, comorbidities, clinical and treatment characteristics, a 5-point increase in PCS or MCS was associated with a 7 and 4% decrease in the hazard of death, respectively, in the overall cohort. Among individuals with an HRQOL assessment within 2 years of diagnosis, a 5-point increase in PCS or MCS was associated with a 5% decrease in the hazard of death. A 5-point increase in PCS was significantly associated with a 6% decrease in

the hazards of death among those whose HRQOL assessment occurred more than 2 years before diagnosis. Results were similar when we restricted analyses to those with an HRQOL assessment within 1-year before diagnosis (Table 2). Having a PCS or MCS score above 50 was associated with 16 and 24% decreased hazards of death, respectively, and these results were similar when we subset analyses to individuals with an HRQOL assessment within 2 years of diagnosis. Five-point increases in SF-36 subscales were associated with 3–4% decreased hazards for the overall cohort, 5% among those with an HRQOL assessment within 2 years, 4% among those with an HRQOL assessment within 1 year, and 2–6% in those with an assessment more than 2 years before diagnosis. Compared to NSCLC, individuals with SCLC had larger HRs for PCS, Physical Function, Mental Health, Social Function, General Health, Bodily Pain, and Vitality domains (Table 3).

Global HRQOL

For the single-item measure, “In general, would you say your health is: excellent, very good, good, fair, or poor?” reporting poor (versus excellent) health was associated with a 74% increase in hazards of death ($p < 0.0001$) for the overall cohort. Reporting fair or good health was associated with 47 and 30% increases, respectively ($p < 0.01$). Smaller effects were observed for the second single-item question comparing one’s health to others. Reporting poor (versus

excellent) health was associated with a 40% increase in the hazard of death. Reporting fair or good health was associated with 28 and 17% increases, respectively ($p < 0.001$). As worse HRQOL was associated with increased hazard of death, both global HRQOL questions had HRs above 1.0. We saw similar HRs in analyses restricted to individuals with HRQOL assessments within 2 years and 1 year of diagnosis (results not shown). HRs were similar between individuals with NSCLC and SCLC.

ADLs

Self-reporting that one was unable to complete any ADL compared to having no difficulty was significantly associated with the largest increases in hazard of death. In the overall cohort, being unable to bathe or dress oneself was associated with adjusted HRs of 1.89 (95% CI 1.47–2.44) and 1.88 (95% CI 1.36–2.59), respectively (Table 4). Magnitudes of HRs increased once we restricted models to individuals with HRQOL assessments within 2 years of diagnosis, but conclusions remained consistent (Table 4). When we assessed individuals with assessments more than 2 years before diagnosis, HR magnitudes generally decreased and some became insignificant. Being unable to bathe oneself, walk or use the toilet remained highly predictive of OS with adjusted HRs of 1.86, 1.54 and 1.64, respectively (Table 4).

Discussion

Our findings indicate that HRQOL collected before lung cancer diagnosis is a significant predictor for OS. Associations between poor HRQOL and increased mortality were seen across ten SF-36 measures, two single-item HRQOL measures, and six ADLs. Associations remained consistent when we restricted analyses to individuals with an HRQOL assessment within 1 and 2 years of diagnosis. Magnitude of adjusted HRs varied by HRQOL measures and domains. Differences in HR magnitudes between SF-36 domains and ADLs are mostly due to the fact that the SF-36 ranges from 0 to 100, whereas ADLs have three levels. One-unit increases in ADLs were associated with larger increases in the hazard of death compared to one-unit increases in SF-36 domains. We addressed this by interpreting MIDOs for PCS, MCS, and eight subscales of the SF-36 instrument. ADLs also capture the basic physical functioning; thus, limitations or incapacity to complete activities signal poor health and are indicative of poor survival. Within the SF-36, physical health domains were more strongly associated with mortality risk than mental health domains.

Psychosocial SF-36 domains were also significantly associated with increased risk of death. The magnitude

of the HRs for mental health domains and OS became larger when we restricted the cohort to individuals with an HRQOL assessment within 1 or 2 years of diagnosis, whereas they became a bit smaller for the physical health domains. This observation supports the value of routine screening for psychosocial HRQOL in clinical practice, as individuals with worse Role Emotional, Social Functioning, Mental Health, and Vitality were at increased risk of mortality. Furthermore, this association was consistent between NSCLC and SCLC patients, suggesting that psychosocial HRQOL may not be as related to specific disease characteristics as physical HRQOL.

A strength of our study is that we compared the prognostic value of single- and multi-item HRQOL measures on OS. Using single-item measures, we assessed overall perspectives of HRQOL, and since these are quick to measure and easy to report, they are clinically useful [11]. However, global measures do not allow for insights on granular, domain-specific HRQOL decrements identified with multi-item instruments [11]. Including results from both types of measures allowed for a comprehensive understanding of associations among different HRQOL domains and OS.

Our study findings are consistent with the previous work in lung cancer that examined associations between post-diagnosis HRQOL and OS. Ediebah et al. assessed associations between clinically meaningful 10-point increases in the EORTC QLQ-C30 and OS. They found increases/decreases in adjusted HRs ranging from 7% for physical functioning, 8% for pain, and 9% for social functioning [4]. Maione et al. found single-item global HRs ranging from 1.62 to 1.76, which are similar to our results (1.74 and 1.40) [16]. Another lung cancer study did not find ADLs to be predictive of OS, but found that Lawton's Instrumental ADLs were associated with OS [16, 33].

Limitations

Our study only included adults with lung cancer 65 years and older, which limits generalizability to younger ages and other cancers. Individuals were in managed care plans, which may not generalize to Medicare fee-for-service beneficiaries. Evidence on whether or not managed care beneficiaries have better or worse health compared to Medicare fee-for-service beneficiaries is mixed [17, 34–36]. There are also limitations in the reliability of SEER treatment variables, such as radiation and surgery [37]. As receipt of chemotherapy is not included in SEER, we did not adjust for this in analyses. In addition, comorbid conditions are self-reported and do not have clinical confirmation. Approximately 9% of the MHOS were completed by proxies, and although we adjust for this in our analyses, it is a limitation.

The SF-36 was used between 1998 and 2005 and the VR-12 in 2006–2013. Although we used an NCI algorithm to combine scores, we recognize inherent limitations in using different instruments. In addition, we used the most recent MHOS for HRQOL assessments, but 50% had assessments more than 2 years before diagnosis. As such, stratified analyses between individuals with HRQOL assessments more and less than 2 years before diagnosis were conducted. Given associations between HRQOL and OS remained consistent regardless of when HRQOL was assessed, we find our findings striking, as patients may be aware of poor health well before diagnosis.

Conclusion

Our results have important clinical implications, as we observed a consistent pattern between pre-diagnosis HRQOL and OS as has been previously established with post-diagnosis HRQOL and OS. The current study does not address if HRQOL assessment timing (before or after diagnosis) is better. However, our results raise important consideration if routine monitoring of self-reported health status may have positive downstream effects. Routine HRQOL data collection in clinical practice has been shown to be feasible and acceptable to both patients and clinicians [38, 39]. Evidence also indicates that HRQOL monitoring enhances patient-physician communication and improves quality of care [39–42]. HRQOL may be used to identify individuals who are at a greater risk of death and who might benefit from targeted supportive HRQOL services [11]. Our study evaluated the prognostic value of various types of HRQOL assessments from domain-specific measures, questions about activities of daily living, and global HRQOL measures.

Allowing clinicians to intervene earlier when individuals report limited functioning or increased symptom burden may enable opportunities to mitigate effects of the underlying disease and perhaps, with earlier detection of cancer, potentially improve OS. However, this will need to be determined in a future study. Poor HRQOL ratings can be used for clinical follow-up for underlying physical and psychological causes [4, 11]. Consistent with the previous work, we recommend that HRQOL be routinely monitored throughout an individual's interaction with the health care system [39]. Future studies should consider assessing associations between HRQOL changes (before and after cancer diagnosis) and OS to determine whether or not the same pattern is observed.

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Compliance with ethical standards

Conflict of interest All other authors (Dr. Pinheiro, Dr. Zagar, and Dr. Reeve) declare that they have no conflicts of interest to disclose.

Informed consent Informed consent from study subjects was not needed as the University of North Carolina at Chapel Hill IRB granted this research exemption from review.

References

1. Ferlay, J., Shin, H. R., Bray, F., Forman, D., Mathers, C., & Parkin, D. M. (2010). Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International Journal of Cancer Journal International du Cancer*, 127(12), 2893–2917. doi:10.1002/ijc.25516.
2. Claassens, L., van Meerbeeck, J., Coens, C., Quinten, C., Ghislain, I., Sloan, E. K., Wang, X. S., Velikova, G., & Bottomley, A. (2011). Health-related quality of life in non-small-cell lung cancer: an update of a systematic review on methodologic issues in randomized controlled trials. *Journal of Clinical Oncology*, 29(15), 2104–2120. doi:10.1200/jco.2010.32.3683.
3. Akin, S., Can, G., Aydiner, A., Ozdilli, K., & Durna, Z. (2010). Quality of life, symptom experience and distress of lung cancer patients undergoing chemotherapy. *European Journal of Oncology Nursing*, 14(5), 400–409. doi:10.1016/j.ejon.2010.01.003.
4. Ediebah, D. E., Coens, C., Zikos, E., Quinten, C., Ringash, J., King, M. T., Schmucker von Koch, J., Gotay, C., Greimel, E., Flechtner, H., Weis, J., Reeve, B. B., Smit, E. F., Taphoorn, M. J., & Bottomley, A. (2014). Does change in health-related quality of life score predict survival? Analysis of EORTC 08975 lung cancer trial. *British Journal of Cancer*, 110(10), 2427–2433. doi:10.1038/bjc.2014.208.
5. Hennessy CH, Moriarty DG, Zack MM, Scherr PA, Brackbill R (1994) Measuring health-related quality of life for public health surveillance. *Public health reports (Washington, DC, 1974)* 109(5):665–672.
6. Lopez-Class, M., Perret-Gentil, M., Kreling, B., Caicedo, L., Mandelblatt, J., & Graves, K. D. (2011). Quality of life among immigrant Latina breast cancer survivors: realities of culture and enhancing cancer care. *Journal of Cancer Education*, 26(4), 724–733. doi:10.1007/s13187-011-0249-4.
7. Donovan, K., Sanson-Fisher, R. W., & Redman, S. (1989). Measuring quality of life in cancer patients. *Journal of Clinical Oncology*, 7(7), 959–968. doi:10.1200/jco.1989.7.7.959.
8. Gotay, C. C., Kawamoto, C. T., Bottomley, A., & Efficace, F. (2008). The prognostic significance of patient-reported outcomes in cancer clinical trials. *Journal of Clinical Oncology*, 26(8), 1355–1363. doi:10.1200/jco.2007.13.3439.
9. Singh, J. A., Nelson, D. B., Fink, H. A., & Nichol, K. L. (2005). Health-related quality of life predicts future health care utilization and mortality in veterans with self-reported physician-diagnosed arthritis: the veterans arthritis quality of life study. *Seminars in Arthritis and Rheumatism*, 34(5), 755–765. doi:10.1016/j.semarthrit.2004.08.001.
10. Cunningham, W. E., Crystal, S., Bozzette, S., & Hays, R. D. (2005). The association of health-related quality of life with survival among persons with HIV infection in the United States. *Journal of General Internal Medicine*, 20(1), 21–27. doi:10.1111/j.1525-1497.2005.30402.x.

11. Sloan, J. A., Zhao, X., Novotny, P. J., Wampfler, J., Garces, Y., Clark, M. M., & Yang, P. (2012). Relationship between deficits in overall quality of life and non-small-cell lung cancer survival. *Journal of Clinical Oncology*, *30*(13), 1498–1504. doi:10.1200/jco.2010.33.4631.
12. Cooley, M. E. (2000). Symptoms in adults with lung cancer. A systematic research review. *Journal of Pain and Symptom Management*, *19*(2), 137–153.
13. Ganz, P. A., Lee, J. J., & Siau, J. (1991). Quality of life assessment. An independent prognostic variable for survival in lung cancer. *Cancer*, *67*(12), 3131–3135.
14. Eton, D. T., Fairclough, D. L., Cella, D., Yount, S. E., Bonomi, P., & Johnson, D. H. (2003). Early change in patient-reported health during lung cancer chemotherapy predicts clinical outcomes beyond those predicted by baseline report: results from Eastern Cooperative Oncology Group Study 5592. *Journal of Clinical Oncology*, *21*(8), 1536–1543. doi:10.1200/jco.2003.07.128.
15. Efficace, F., Bottomley, A., Smit, E. F., Lianes, P., Legrand, C., Debruyne, C., Schramel, F., Smit, H. J., Gaafar, R., Biesma, B., Manegold, C., Coens, C., Giaccone, G., & Van Meerbeeck, J. (2006). Is a patient's self-reported health-related quality of life a prognostic factor for survival in non-small-cell lung cancer patients? A multivariate analysis of prognostic factors of EORTC study 08975. *Annals of Oncology*, *17*(11), 1698–1704. doi:10.1093/annonc/mdl183.
16. Maione, P., Perrone, F., Gallo, C., Manzione, L., Piantedosi, F., Barbera, S., Cigolari, S., Rosetti, F., Piazza, E., Robbiati, S. F., Bertetto, O., Novello, S., Migliorino, M. R., Favaretto, A., Spatafora, M., Ferrau, F., Frontini, L., Bearz, A., Repetto, L., Gridelli, C., Barletta, E., Barzelloni, M. L., Iaffaioli, R. V., De Maio, E., Di Maio, M., De Feo, G., Sigoriello, G., Chiodini, P., Cioffi, A., Guardasole, V., Angelini, V., Rossi, A., Bilancia, D., Germano, D., Lamberti, A., Pontillo, V., Brancaccio, L., Renda, F., Romano, F., Esani, G., Gambaro, A., Vinante, O., Azzarello, G., Clerici, M., Bollina, R., Belloni, P., Sannicola, M., Ciuffreda, L., Parello, G., Cabiddu, M., Sacco, C., Sibau, A., Porcile, G., Castiglione, F., Ostellino, O., Monfardini, S., Stefani, M., Scagliotti, G., Selvaggi, G., De Marinis, F., Martelli, O., Gasparini, G., Morabito, A., Gattuso, D., Colucci, G., Galetta, D., Giotta, F., Gebbia, V., Borsellino, N., Testa, A., Malaponte, E., Capuano, M. A., Angiolillo, M., Sollitto, F., Tirelli, U., Spazzapan, S., Adamo, V., Altavilla, G., Scimone, A., Hopps, M. R., Tartamella, F., Ianniello, G. P., Tinessa, V., Failla, G., Bordonaro, R., Gebbia, N., Valerio, M. R., D'Aprile, M., Veltri, E., Tonato, M., Darwish, S., Romito, S., Carrozza, F., Barni, S., Ardizzoia, A., Corradini, G. M., Pavia, G., Belli, M., Colantuoni, G., Galligioni, E., Caffo, O., Labianca, R., Quadri, A., Cortesi, E., D'Auria, G., Fava, S., Calcagno, A., Luporini, G., Locatelli, M. C., Di Costanzo, F., Gasperoni, S., Isa, L., Candido, P., Gaion, F., Palazzolo, G., Netti, G., Annamaria, A., Rinaldi, M., Lopez, M., Felletti, R., Di Negro, G. B., Rossi, N., Calandriello, A., Maiorino, L., Mattioli, R., Celano, A., Schiavon, S., Illiano, A., Raucci, C. A., Caruso, M., Foa, P., Tonini, G., Curcio, C., & Cazzaniga, M. (2005). Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: a prognostic analysis of the multicenter Italian lung cancer in the elderly study. *Journal of Clinical Oncology*, *23*(28), 6865–6872. doi:10.1200/jco.2005.02.527.
17. Reeve, B. B., Potosky, A. L., Smith, A. W., Han, P. K., Hays, R. D., Davis, W. W., Arora, N. K., Haffer, S. C., & Clauser, S. B. (2009). Impact of cancer on health-related quality of life of older Americans. *Journal of the National Cancer Institute*, *101*(12), 860–868. doi:10.1093/jnci/djp123.
18. Ambs, A., Warren, J. L., Bellizzi, K. M., Topor, M., Haffer, S. C., & Clauser, S. B. (2008). Overview of the SEER–Medicare Health Outcomes Survey linked dataset. *Health Care Financing Review*, *29*(4), 5–21.
19. Ware, J. E. Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care*, *30*(6), 473–483.
20. Fleishman, J. A., Selim, A. J., & Kazis, L. E. (2010). Deriving SF-12v2 physical and mental health summary scores: a comparison of different scoring algorithms. *Quality of Life Research*, *19*(2), 231–241. doi:10.1007/s11136-009-9582-z.
21. Selim AR, W; Qian, S; Rothendler, JA; Kent, EE; Kazis, LE. (2016) A new algorithm to build bridges between two patient-reported health outcome instruments: the MOS SF-36® and the VR-12 health survey. National Cancer Institute.
22. Pinheiro, L. C., Wheeler, S. B., Chen, R. C., Mayer, D. K., Lyons, J. C., & Reeve, B. B. (2015). The effects of cancer and racial disparities in health-related quality of life among older Americans: a case-control, population-based study. *Cancer*, *121*(8), 1312–1320. doi:10.1002/cncr.29205.
23. Angst, F., Aeschlimann, A., & Stucki, G. (2001). Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. *Arthritis and Rheumatism*, *45*(4), 384–391. doi:10.1002/1529-0131(200108)45:4<384::aid-art352>3.0.co;2-0.
24. Swigris, J. J., Brown, K. K., Behr, J., du Bois, R. M., King, T. E., Raghu, G., & Wamboldt, F. S. (2010). The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. *Respiratory Medicine*, *104*(2), 296–304. doi:10.1016/j.rmed.2009.09.006.
25. Bjorner, J. B., Wallenstein, G. V., Martin, M. C., Lin, P., Blaisdell-Gross, B., Tak Piech, C., & Mody, S. H. (2007). Interpreting score differences in the SF-36 Vitality scale: using clinical conditions and functional outcomes to define the minimally important difference. *Current Medical Research and Opinion*, *23*(4), 731–739. doi:10.1185/030079907x178757.
26. Cohen, J. (1965). Some statistical issues in psychological research. In *Handbook of clinical psychology* (pp. 95–121). New York: McGraw-Hill.
27. Pompili, C., Salati, M., Refai, M., Berardi, R., Onofri, A., Mazzanti, P., & Brunelli, A. (2013). Preoperative quality of life predicts survival following pulmonary resection in stage I non-small-cell lung cancer. *European Journal of Cardio-thoracic Surgery*, *43*(5), 905–910. doi:10.1093/ejcts/ezs532.
28. Moller, A., & Sartipy, U. (2012). Quality of life six months after lung cancer surgery is associated with long-term survival. *Acta Oncologica (Stockholm, Sweden)*, *51*(8), 1029–1035. doi:10.3109/0284186x.2012.689112.
29. Katz, S. (1983). Assessing self-maintenance: activities of daily living, mobility, and instrumental activities of daily living. *Journal of the American Geriatrics Society*, *31*(12), 721–727.
30. Reeve, B. B., Stover, A. M., Jensen, R. E., Chen, R. C., Taylor, K. L., Clauser, S. B., Collins, S. P., & Potosky, A. L. (2012). Impact of diagnosis and treatment of clinically localized prostate cancer on health-related quality of life for older Americans: a population-based study. *Cancer*, *118*(22), 5679–5687. doi:10.1002/cncr.27578.
31. Stover, A. M., Mayer, D. K., Muss, H., Wheeler, S. B., Lyons, J. C., & Reeve, B. B. (2014). Quality of life changes during the pre- to postdiagnosis period and treatment-related recovery time in older women with breast cancer. *Cancer*, *120*(12), 1881–1889. doi:10.1002/cncr.28649.
32. Concato, J., Peduzzi, P., Holford, T. R., & Feinstein, A. R. (1995). Importance of events per independent variable in

- proportional hazards analysis. I. Background, goals, and general strategy. *Journal of Clinical Epidemiology*, 48(12), 1495–1501.
33. Lawton, M. P., & Brody, E. M. (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. *The Gerontologist*, 9(3), 179–186.
 34. Jensen, G. A., & Morrisey, M. A. (2004). Are healthier older adults choosing managed care? *The Gerontologist*, 44(1), 85–94.
 35. Morgan, R. O., Virnig, B. A., DeVito, C. A., & Persily, N. A. (1997). The Medicare-HMO revolving door—the healthy go in and the sick go out. *The New England Journal of Medicine*, 337(3), 169–175. doi:10.1056/nejm199707173370306.
 36. Pourat, N., Kagawa-Singer, M., & Wallace, S. P. (2006). Are managed care Medicare beneficiaries with chronic conditions satisfied with their care? *Journal of Aging and Health*, 18(1), 70–90.
 37. Jagsi, R., Abrahamse, P., Hawley, S. T., Graff, J. J., Hamilton, A. S., & Katz, S. J. (2012). Underascertainment of radiotherapy receipt in surveillance, epidemiology, and end results registry data. *Cancer*, 118(2), 333–341. doi:10.1002/cncr.26295.
 38. Santana, M. J., & Feeny, D. H. (2009). Using the health utilities index in routine clinical care: process, feasibility, and acceptability: a randomized controlled trial. *The patient*, 2(3), 159–167. doi:10.2165/11313620-000000000-00000.
 39. Detmar, S. B., Muller, M. J., Schornagel, J. H., Wever, L. D., & Aaronson, N. K. (2002). Health-related quality-of-life assessments and patient-physician communication: a randomized controlled trial. *JAMA*, 288(23), 3027–3034.
 40. Taenzer, P., Bultz, B. D., Carlson, L. E., Specca, M., DeGagne, T., Olson, K., Doll, R., & Rosberger, Z. (2000). Impact of computerized quality of life screening on physician behaviour and patient satisfaction in lung cancer outpatients. *Psycho-oncology*, 9(3), 203–213.
 41. Velikova, G., Wright, E. P., Smith, A. B., Cull, A., Gould, A., Forman, D., Perren, T., Stead, M., Brown, J., & Selby, P. J. (1999). Automated collection of quality-of-life data: a comparison of paper and computer touch-screen questionnaires. *Journal of Clinical Oncology*, 17(3), 998–1007.
 42. Wagner, A. K., Ehrenberg, B. L., Tran, T. A., Bungay, K. M., Cynn, D. J., & Rogers, W. H. (1997). Patient-based health status measurement in clinical practice: a study of its impact on epilepsy patients' care. *Quality of Life Research*, 6(4), 329–341.