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Quality of life after treatment with immune checkpoint inhibitors for lung cancer; the impact of age

E. Suazo-Zepeda [a,*], P.C. Vinke [a], M.A. Heuvelmans [a], G. Sidorenkov [a], T.J.N. Hiltermann [b], G. H. de Bock [a]

[a] Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[b] Department of Pulmonology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

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ABSTRACT

Introduction: Immune checkpoint inhibitors (ICIs) have revolutionized lung cancer treatment. However, it remains unclear as to whether changes in Health-Related Quality-of-Life (HRQoL) are associated with the age of lung cancer patients treated using ICIs. This study aimed to evaluate this possible association and to compare ICI-treated patients' HRQoL scores with normative data of an age-matched non-cancer general population.

Methods: Lung cancer patients from the OncoLifeS data-biobank were included if they were treated with ICIs, irrespective of other treatments, at the University Medical Center Groningen between 2015 and 2021 and had completed the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTCQLQ-C30), both at the start of ICI treatment and after six months. Association of age as a continuous variable (per 10 years) and changes in HRQoL scores between baseline and 6 months was assessed using multivariable regression analyses. Clinical relevance of differences in HRQoL scores between OncoLifeS and the general population was classified into trivial, small, medium, and large, for three age groups (<60, 60–69 and ≥ 70 years).

Results: 151 patients were included with a mean age of 65.8 years. An increase in age per 10 years was associated with a larger decrease in the summary HRQoL score(β = -3.28,CI95%-6.42;-0.14), physical(β = -4.8, CI95% −8.71;-0.88), cognitive(β = −4.51,CI95%-8.24;−0.78), role functioning(β = −5.41,CI95%-10.78;−0.05), symptom burden(β = −3.66,CI95%-6.6;-0.73), and smaller negative changes in financial difficulties(β = 6.5 95 % CI 3.16; 9.85). OncoLifeS HRQoL scores were lower than those of the general population and differences were most often classified as large and medium.

Conclusion: Older lung cancer patients experience larger deteriorations in most HRQoL domains after 6 months of ICI treatment. Also, these patients showed significantly lower HRQoL scores compared to the general population.

1. Introduction

Lung cancer is the leading cause of cancer death worldwide [1]. Lately, the introduction of immune checkpoint inhibitors (ICIs) has offered new treatment options for lung cancer patients [2,3]. ICIs have been shown to increase overall survival in lung cancer patients compared to chemotherapy and have good safety profiles [4].

Lung cancer, and treatment thereof, have a large impact on patients' physical and psychological well-being resulting in reduced health related quality of life (HRQoL) [5–7]. When diagnosed with lung cancer, younger patients will see their emotional functioning is particularly affected [8]. After treatment with chemo and/or radiotherapy, physical and cognitive functioning of older patients is expected to deteriorate, whereas in younger patients financial problems and social functioning are expected to worsen [9]. The use of ICIs might impact patients' HRQoL differently when compared to chemo and/or radiotherapy. ICIs have better toxicity profiles, albeit also longer treatment duration [10–12].

With the increasing use of ICIs in lung cancer treatment, it is necessary to understand the role of age in patients' HRQoL after ICIs initiation. Physicians will gain more insight unto which patients will likely be negatively impacted by the use of ICIs, and in turn be able to make shared decisions with patients about the treatment regimen when taking into account possible repercussions. Previous research has shown

* Corresponding author at: Graduate School of Medical Sciences, University of Groningen, Zusterhuis, Hanzeplein 1, Groningen, the Netherlands.
E-mail address: e.suazo.zepeda@umcg.nl (E. Suazo-Zepeda).

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that treatment with ICIs, compared to chemotherapy, can improve quality of life and has positive effects on symptom burden [13,14]. As older people are more vulnerable, age-related differences can be expected. In a previous study combining three clinical trials, after three months follow up, greater impairment in physical functioning was observed in patients aged ≥70 years who were treated with PD-1/PD-L1 inhibitors, whereas patients <70 years showed greater negative changes in role, social and emotional functioning [15]. However, this descriptive study did not test the association between age-changes and HRQoL. Therefore, the aim of our study was to evaluate the association of age with changes in HRQoL in patients with lung cancer treated with ICIs, using real world data, adjusting for factors that may confound this association. Furthermore, to put these results in perspective, we compared ICI-treated patients' HRQoL scores with normative data of an age-matched non-cancer general population.

2. Methods

2.1. Patients

Patients were included if they had given written informed consent to the Oncological Life Study: Living well as a cancer survivor study (OncoLifeS). OncoLifeS is a prospective cohort study started in 2014 at the University Medical Center Groningen (UMCG), recruiting cancer patients referred to this center from the northern provinces of the Netherlands [16]. It gathers data on patients' clinical characteristics, lifestyle information, social conditions and patient reported HRQoL through a questionnaire provided after their first medical visit. HRQoL is assessed at baseline at the start of the ICI treatment, and followed at 6, 12, 18 and 24 months. OncoLifeS is approved by the Medical Ethical Committee of the UMCG.

Further, patients were included if they were; ≥18 years old, diagnosed with de novo or recurrent lung cancer and treated with immune checkpoint inhibitors (ICI's) between January 2015 and November 2021, had completed a HRQoL questionnaire at baseline and 6 months follow-up and started treatment with any ICI as monotherapy or in combination with other ICI, chemotherapy, radiotherapy, or surgery in the period between 10 weeks before the date of filling in the baseline questionnaire and 6 weeks after. This selection was made irrespectively of previous treatments history. ICI treatment included the following monoclonal antibodies: Nivolumab, Pembrolizumab, Atezolizumab, Avelumab, Durvalumab, Ipilimumab, Tremelimumab.

Power analysis for a multiple linear regression was conducted to obtain a power of at least 0.8 (alpha = 0.05, effect size $f^2 = 0.16$ [17]); a sample size of 51 was identified as sufficient. Accordingly, HRQoL data from 12-, 18- and 24-months follow-up was not considered in this study as this population size could not be reached.

2.2. Data collection

Baseline data on participants'; age, sex, education, smoking status, and HRQOL, and at 6 months follow-up HRQOL, were used. Performance status, comorbidities, presence of concomitant cancer, clinical stage of the tumor, ICI combination with chemotherapy, other treatments (previous chemotherapy, surgery, and use of radiotherapy) and severe immune-related adverse events (irAEs) were derived from electronic medical records. Variable descriptions are presented in the Table A1.

2.3. Normative data from the general population

HRQoL data from OncoLifeS participants was compared to normative data from the general population, as provided by Patient Reported Outcomes Following Initial treatment and Long-term Survivorship (PROFILES). This data was collected through online questionnaires by the CentERdata research institute, University of Tilburg, the Netherlands. This repository complies 2000 randomly selected Dutch households. Participants are asked to fill in HRQoL questionnaires online, providing normative data from the Dutch general population [18,19]. For the purpose of the here presented comparison, participants from the PROFILES cohort were selected to match the age range of the OncoLifeS cohort (37 to 87 years of age), and participants with previous diagnosis of cancer were excluded.

2.4. Quality of life assessment

Quality of life of patients was evaluated by means of the European Organization for Research and Treatment of Cancer Quality of Life questionnaire C 30 (EORTC QLQ-C30). This questionnaire consists of five functional scales (physical, role, cognitive, emotional, and social functioning), a global health scale, and nine symptom scales (fatigue, nausea and vomiting, pain, appetite loss, diarrhea, dyspnea, constipation, insomnia, financial difficulties). Scores are represented on a scale from 0 to 100. For the functional and global HRQoL scales, a high score reflects a better HRQoL, whilst higher scores on the symptom scales represent a worse quality of life.

A summary score was calculated as the mean of thirteen EORTC QLQ-30 subscales. The global health and financial impact scores were excluded since the first is a general self-perception score and the last is not clinical. To calculate a sum score, symptom scales were inverted; a higher score represented a better HRQoL (100-value of the symptomatic scale). A symptom burden summary score was calculated from the mean of all symptom burden scales, not including financial difficulties. Financial difficulties score was evaluated separately and also inverted. A higher number on this sum score represented a better overall quality of life [20].

HRQoL score differences between OncoLifeS and PROFILES cohorts were classified into trivial, small, medium, and large using previously published guidelines (Table 4 from Cocks et al.) [21]. Moreover, OncoLifeS cohort's intra-group changes in HRQoL from baseline to 6 months were classified into trivial, small, medium, and large according to their corresponding guidelines (Table 4 from Cocks et al.) [22]. These guidelines were developed combining expert opinions and *meta*-analysis data from studies reporting HRQoL data using the EORTC QLQ-C30. Large, medium, and small differences were defined as those with unequivocal, probable, and subtle clinical relevance, respectively, while trivial differences were defined as those likely to lack clinical relevance.

2.5. Statistical analysis

Patients were categorized in three age groups using tertiles. The cut-off points were rounded to the closest multiple of 10 for ease of interpretation, resulting into three age groups, namely <60, and 60–69 and ≥70 years of age. Patient characteristics were compared between the three age groups using chi-square test. Analysis of variance (ANOVA) was used to assess differences in HRQoL summary scores and functional scales between the three age groups.

The main outcome was defined as changes in EORTC QLQ-30 scores from baseline to 6 months follow-up, and its association with age was evaluated using univariate and multivariable regression models. Age was considered a continuous variable (per 10 years). We built four multivariable models for summary score, physical, role, emotional, cognitive, and social functioning, as well as a symptom burden, financial difficulties, and global health status scores, taking into account factors that could confound the association between the age of the patient and the changes in HRQoL scores. Model 1 was adjusted for corresponding HRQoL subscale baseline score (or baseline summary score in its case). Model 2 was composed of model 1 and adjusted for sex and education. Model 3 included model 2 plus performance status, the presence of comorbidities, lung cancer stage (stage IV vs stage II/III lung cancer) and the appearance of severe irAEs. Finally, model 4 included model 3 plus past treatments (previous chemotherapy, surgery, radiotherapy) and the

use of combination therapy (Chemotherapy + ICI). A sensitivity analysis was performed with age as a categorical variable (<60, and 60–69 and ≥70) to test the association between age and changes on each of HRQoL domains using univariate and multivariable models previously described.

Descriptive statistics were used to present PROFILES' normative data on sex, education, and comorbidities for the three age groups. An independent *t*-test was used to compare means of EORTC QLQ-C30 summary score and the functional and symptom scales from the PROFILES cohort with those of the OncoLifeS cohort at baseline and 6 months follow-up. All Data analyses were performed using SPSS software version 25.

3. Results

Of the 1133 OncoLifeS patients diagnosed with lung cancer; 151 (13.3 %) patients were included in this study (Fig. 1). The mean age was 65.8 (SD = 9.25, min 37, max. 87) years. Ninety-nine (65.6 %) were men. One (0.7 %) patient had a stage II tumor, 26 (17.2 %) had a stage III and 124 (82.1 %) had a stage IV tumor. Fourteen patients (9.3 %) had a major surgery within one year prior to the start or during the immunotherapy treatment. Twenty-seven patients were treated with a combination of immunotherapy and chemotherapy (21.8 %) (Table 1). When comparing the three age groups, we found a higher proportion of men and more comorbidities in both older age groups ($p = 0.005$ and 0.001, respectively, Table 1).

3.1. Changes in HRQoL scales: Descriptive

Statistically significant differences in mean scores of financial difficulties were observed between the three age groups, both at baseline and 6 months follow-up.

When looking at the change in HRQoL scores between baseline and 6 months follow-up, the ≥70 years group showed the biggest decline in the cognitive function (88.7(SD = 18.2) at baseline to 79.7(SD = 26.8) at 6 months follow-up), this change was classified as medium. Mean emotional functioning score showed the largest improvements in the <60 years group (from 69.3(SD = 24.21) to 78.3(SD = 18.74)), and in the 60–69 group (from 72.2(SD = 23.78) to 78.5(SD = 18.43)); these improvements were classified as small. Physical functioning on the other hand, declined in all age groups. The biggest decline occurred in the 60–69 and ≥70 groups (from 76.1(SD = 20.99) to 69.7(SD = 21.04) and from 73.6(SD = 20.26) to 66.2(SD = 26.78) respectively), albeit both were classified as small changes. Social functioning score declined after 6 months in the oldest age group (78.2(SD = 23.37) to 71.8(SD = 30.18)), this change was classified as small. All other changes were classified as trivial (Table 2) (Fig. 2).

3.2. Normative data from the general population

A total of 1665 patients belonging to the PROFILES cohort were selected to be compared with the OncoLifeS cohort. PROFILES' data on sex, education, and comorbidities for the three age groups are presented in Table A2.

When comparing mean scores from the OncoLifeS cohort with the

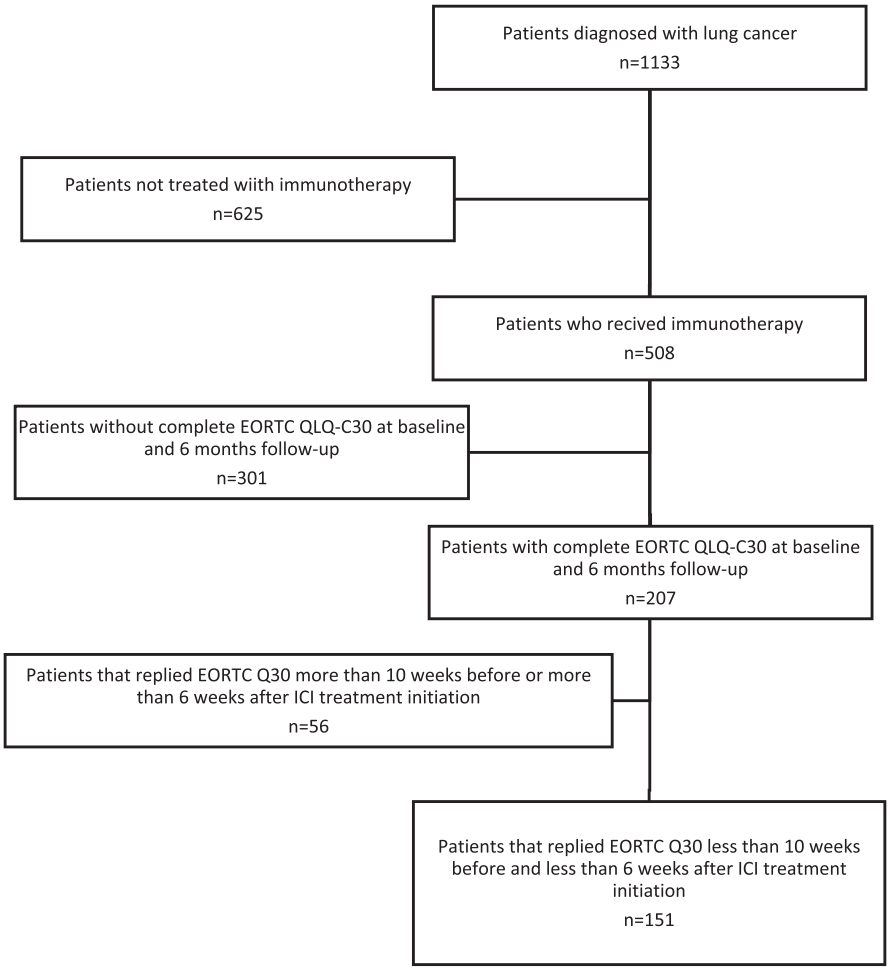


Fig. 1. Flowchart of patients' selection.

Table 1
Patients characteristics for each age group.

		Age						
		>60		60–69		≥70		
		N = 38	%	N = 48	%	N = 65	%	*p* value
Sex	Man	18	(47.4)	30	(62.5)	51	(78.5)	0.005§
	Woman	20	(52.6)	18	(37.5)	14	(21.5)	
Education	Low	16	(43.2)	31	(67.4)	36	(63.2)	0.148
	Medium	12	(32.4)	9	(19.6)	9	(15.8)	
	High	9	(24.3)	6	(13)	12	(21.1)	
Smoking status	Current smoker	7	(18.4)	5	(10.4)	13	(20.3)	0.57
	Previous smoker	27	(71.1)	40	(83.3)	47	(73.4)	
	Never smoker	4	(10.5)	3	(6.3)	4	(6.3)	
Performance status	0–1	24	(64.9)	26	(54.2)	31	(47.7)	0.379
	2	13	(35.1)	20	(41.7)	30	(46.2)	
	>=3	0	(0)	2	(4.2)	4	(6.2)	
Comorbidities [a]	Yes	17	(44.7)	41	(85.4)	54	(83.1)	<0.001§
	No	21	(55.3)	7	(14.6)	11	(16.9)	
Lung cancer stage [b]	IV	31	(81.6)	40	(83.3)	53	(81.5)	0.903
	II/III*	7	(18.4)	8	(16.7)	12	(18.5)	
Concomitant cancer [c]	Yes	0	(0)	0	(0)	4	(6.2)	0.066
	No	38	(100)	48	(100)	61	(93.8)	
Combination therapy [d]	Yes	8	(21.1)	5	(10.4)	14	(21.5)	0.263
	No	30	(78.9)	43	(89.6)	51	(78.5)	
Chemotherapy [e]	Yes	22	(57.9)	28	(58.3)	34	(52.3)	0.774
	No	16	(42.1)	20	(41.7)	31	(47.7)	
Surgery [f]	Yes	4	(10.5)	4	(8.3)	6	(9.2)	0.941
	No	34	(89.5)	44	(91.7)	59	(90.8)	
Radiotherapy [g]	Yes	9	(23.7)	5	(10.4)	11	(16.9)	0.257
	No	29	(76.3)	43	(89.6)	54	(83.1)	
Severe irAEs [h]	Yes	6	(15.8)	6	(12.5)	8	(12.3)	0.866
	No	32	(84.2)	42	(87.5)	57	(87.7)	

a. Previous diagnosis of cardiovascular disease, diabetes, hypertension, dementia, or chronic obstructive pulmonary disease.
b. At the time of the start of immunotherapy.
c. Within one year prior to the start of immunotherapy.
d. Use of immunotherapy combined with chemotherapy.
e. Up to one year before the start of immunotherapy.
f. Any type of major surgeries from one year before or during the immunotherapy treatment.
g. Use of radiotherapy in any target organ within the immunotherapy period.
h. Immune-related adverse events grade 3 or higher according to the CTCAE v.5.0.
*1 patient with stage II.
§ Statistically significant ($p < 0.05$).

general population at baseline and 6 months follow-up, the summary, physical, role, and social functioning scores, and symptom burden were significantly lower in the OncoLifeS cohort than the non-cancer general population for all three age groups. In the <60 age group, differences were classified as large for physical and social functioning at 6 months. Also, large differences were observed in social functioning when comparing baseline and 6 months follow-up scores for the 60–69 and ≥70 age groups. Large differences were also observed in the self-perceived global health status at baseline in the ≥70 age group (Table 2) (Fig. 2).

In the case of emotional functioning, significant lower scores were seen in the OncoLifeS cohort compared to the general population at baseline for all age groups, but this was not the case for 6 months follow-up in the <60 age group. Conversely, cognitive functioning was not significantly different in the ≥70 group at baseline. Nevertheless, at 6 months follow-up the score decreased and became significantly lower than in the general population. Finally, financial difficulties in the <60 OncoLifeS cohort age group were significantly higher at baseline and at 6 months follow-up, showing the biggest difference with the general population among all scales (Table 2).

3.3. Univariate and multivariable regression models

When testing the association between age and changes in summary and subscales of the HRQoL score, significant associations were found across the four models. Older age (per 10-year increment) was negatively associated with change in HRQoL for the summary score (β = −3.28; CI 95 % −6.42, −0.14), physical (β = −4.8; CI 95 % −8.71, −0.88) and cognitive functioning (β = −4.51; CI 95 % −8.24, −0.78), as well as symptom burden (β = −3.66; CI 95 % −6.6, −0.73). Similarly, a negative relationship between higher age and change in role functioning was observed in model 3 (β = −5.7; CI 95 % −11.22, −0.18) and model 4 (β = −5.41; CI 95 % −10.78, −0.05). On the other hand, increased age showed a positive association with changes in financial difficulties in all four multivariable models (β = 6.5; CI 95 % 3.16, 9.85) (Table 3) (Table A3).

In the sensitivity analysis, when age was considered as categorical variable, associations were less visible. Symptom burden worsened after 6 months of treatment with ICIs when comparing the ≥70 with the <60 years group (β = −7.74; CI 95 % −14.70, −0.78). In contrast, a higher age was associated with less severe changes in financial difficulties when comparing ≥70 vs <60 (β = 13.68; CI 95 % 5.76, 21.61) and 60–69vs <60 (β = 11.93; CI 95 % 3.88, 19.98) (Table A4).

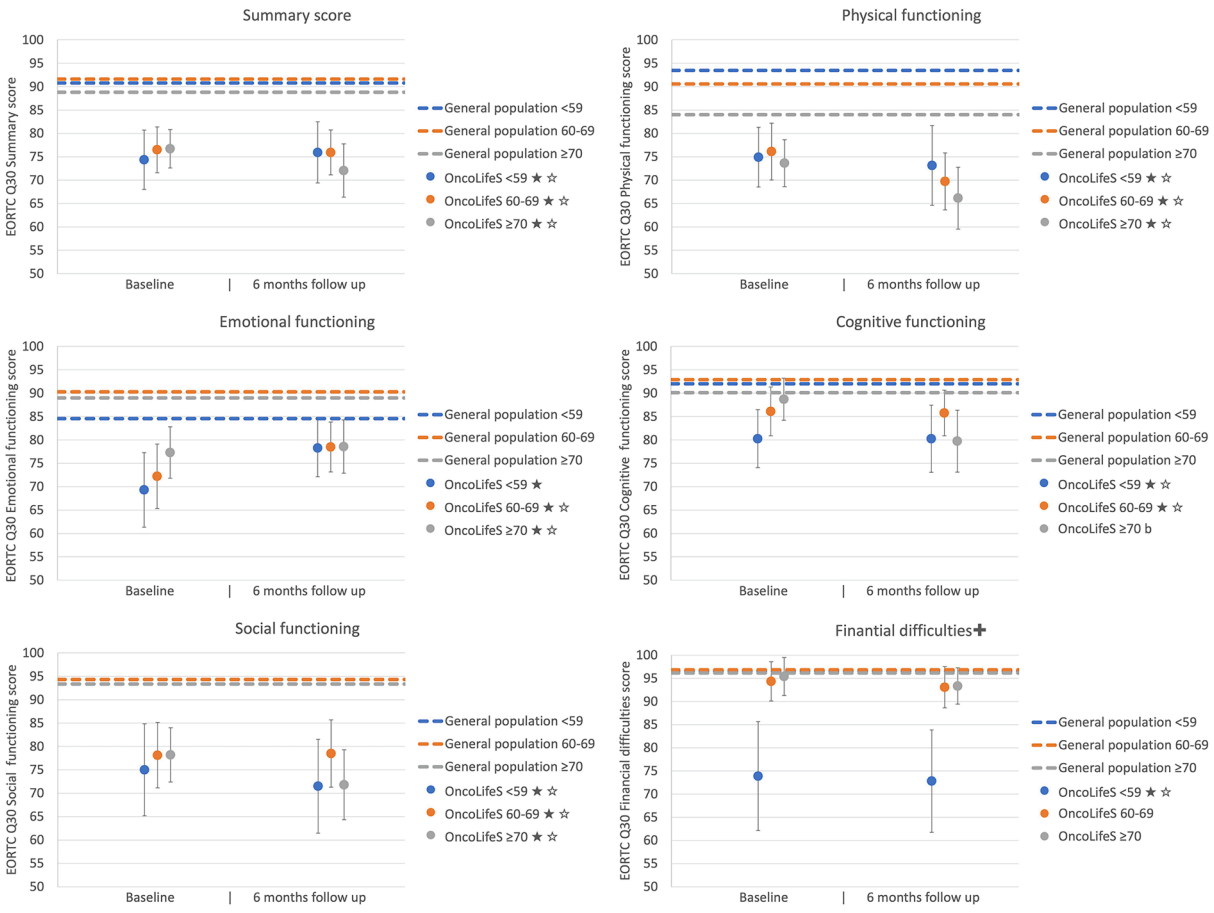
4. Discussion

This longitudinal cohort study analyzed the association of age with changes in HRQoL in lung cancer patients treated with ICIs in a tertiary cancer hospital in the Netherlands. Our study showed that, at 6 months after treatment initiation, an older age is associated with larger negative changes in the overall HRQoL, physical, role and cognitive functioning, as well as a bigger symptom burden, but smaller negative changes in financial difficulties. Additionally, compared with participants from a non-cancer general population, all our participants had significantly

Table 2
Mean scores Comparison between OncoLifeS cohort vs non-cancer normative population by age group for summary score, physical, role, emotional, cognitive, and social functioning, as well as symptom burden with baseline and at 6 months follow-up.

	<59				60–69				≥70			
	Normative population	OncoLifeS			Normative population	OncoLifeS			Normative population	OncoLifeS		
	N = 833	N = 38			N = 465	N = 48			N = 367	N = 65		
		Baseline	6 months follow-up	Change from baseline		Baseline	6 months follow-up	Change from baseline		Baseline	6 months follow-up	Change from baseline
Summary score	90.80	74.37§	75.94§	1.21	91.64	76.50§	75.94§	−0.56	88.83	76.72§	72.06§	−4.66
Physical functioning	93.47	74.92c§	69.73d§	−1.76★	90.57	76.11c§	69.73c§	−6.38☆◆	84.03	73.64b§	66.15c§	−7.49☆
Role functioning	90.66	66.66c§	62.51c§	1.32★	90.11	63.89c§	62.51c§	−1.38★	85.56	62.05c§	59.23c§	−2.82★
Emotional functioning	84.54	69.30§	78.48	8.99☆	90.27	72.22§	78.48§	6.26☆	88.99	77.31§	78.59§	1.28★
Cognitive functioning	92.02	80.27c§	85.76b§	−0.01★	92.90	86.11b§	85.76b§	−0.35★	90.10	88.71a	79.74c§	−8.97●
Social functioning	93.34	75.00d§	78.48c§	−3.51★	94.30	78.12d§	78.48d§	0.36★	93.37	78.20d§	71.79d§	−6.41☆
Symptom burden*	90.79	80.12§	80.87§	2.44	91.72	82.16§	80.87§	−1.29	90.93	80.35§	76.85§	−3.50
Financial problems‡+	96.16	75.68c§	73.69c§	−1.07★	96.56	94.21a	92.91b	−1.27★	96.82	95.39a	93.34b	−2.05★
Global Health Status	75.51	63.82c§	68.41b§	2.84★	78.66	66.15a§	65.07c§	−1.91★	77.38	61.46d§	64.20c§	2.21★

*A higher score represents a lower symptom burden.
+A higher score represents fewer financial problems.
‡Statistically different between age groups, both at baseline and 6 months follow-up based on ANOVA ($p < 0.05$).
§Statistically different from the normative population ($p < 0.05$).
a. Trivial difference compared to the normative population.
b. Small difference compared to the normative population.
c. Medium difference compared to the normative population.
d. Large difference compared to the normative population.
★. Trivial change from baseline.
☆. Small change from baseline.
●. Medium change from baseline.



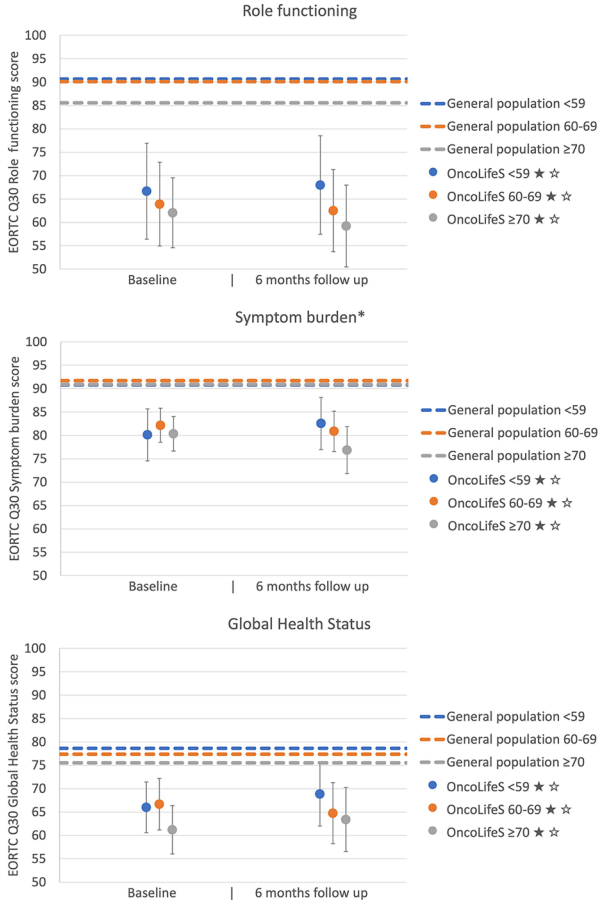


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Fig. 2. Mean EORTC QLQ-30 summary, physical, role, emotional, cognitive, social and symptom burden scores for the general population and OncoLifeS cohort at baseline and for OncoLifeS cohort at 6 months follow-up by age group (<60, 60–79 &≥70 years of age) *A higher score represents a lower symptom burden[+]A higher score represents fewer financial problems.

worse scores in the overall HRQoL summary score and most of its individual domains irrespectively of age. Furthermore, the <60 years age group's emotional functioning scores improved significantly from baseline to 6 months after treatment initiation; whilst the oldest age groups baseline values had declined at 6 months: they showed significantly lower emotional functioning scores compared to the general population.

With increasing age, patients become more vulnerable to changes in different realms of their lives. Older cancer patients are more prone to experience negative changes in their already deteriorated health state by aggressive anti-cancer treatments (chemo and radiotherapy) [9,23–25]. First, this study showed negative associations between age and changes in physical, cognitive and role functioning in lung cancer patients treated with ICIs. This can be explained by the detrimental effect on these domains of the combination of the natural aging process [26] and the pro-inflammatory and hypermetabolic state induced by both cancer and immunotherapy [27–30]. Furthermore, we find important to point out that, despite the reduction in physical functioning with an older age, the <60 years age group OncoLifeS age group show a large difference when compared to their non-cancer counterparts; this shows the great impact of lung cancer and cancer treatments in this age group. Second, association between an older age and a larger symptom burden could result from a higher rate and intensity of symptoms in older lung cancer patients, such as dyspnea and fatigue [31]. Third, we found older age is associated with smaller negative changes in financial difficulties. Older patients are more likely to be retired, with a stable income from government and/or private pensions, whilst in the Netherlands, younger working-age patients on prolonged sick leave will suffer a major income reduction after two years [32,33]. Finally, although non-significant, it is important to note the large recovery from baseline to 6 months in emotional functioning in the <60 age group of the OncoLifeS cohort. Younger patients could suffer a larger emotional impact due to diagnosis and previous failed treatments [8], and possess fewer coping mechanisms to deal with adversity compared to their older counterparts [34]. However, a sense of hope and treatment success can improve these feelings in the short term.

The results of this study correspond, in general, with previous research assessing age differences in diverse cancer populations and more traditional forms of treatment (chemo and radiotherapy). According to Hung et al, higher age is a predictor for worse overall HRQoL in lung cancer patients undergoing chemotherapy, and is significantly associated with reduced physical functioning [23]. A study carried out in lung cancer patients treated with radiotherapy identified age as a predictor of the development of more therapy-related symptoms and interference with daily-life activities [24]. A further study conducted in lung cancer patients from randomized clinical trials treated with chemotherapy and radiotherapy showed that an older age was associated with negative EORTC QLQ-C30 scores in physical functioning, fewer financial difficulties, and higher social functioning scores. However, only baseline scores were evaluated and no previous treatments were taken into account in the multivariable analysis [9]. King-Kallimanisa et al. assessed age differences in changes in HRQoL in lung cancer patients treated with ICIs, however only reported descriptive statistics at 3-months post ICI treatment initiation. They found that patients ≥70 years showed lower scores in physical functioning, and higher role, social and emotional functioning scores at baseline compared to their <70 counterparts; however, only a small decline in social functioning was found in the older age group after 3 months [15]. With a longer follow-up period of 6 months, our study also identified small changes in social functioning in the oldest age group. However, we additionally identified medium changes in cognitive functioning and small changes in physical functioning in the oldest patients (≥70 years), as well as small improvements in emotional functioning in the <60 and 60–70 age groups.

We analyzed real-world data from a large-size study and patients' trajectory was followed through their clinical records, meaning we were able to adjust for possible confounders. Moreover, we evaluated HRQoL and its domains using the EORTC QLQ-C30, which is widely used in cancer research. This allowed us to compare our results with similar studies. However, EORTC QLQ-30 was designed when immunotherapy was not considered a feasible treatment for lung cancer patients and fails to include symptoms that might appear as consequence of immune-related adverse events (e.g., rash, or arthritis). Consequently, HRQoL scores could have been overestimated. Another advantage is that we conducted a complete-case analysis, including only patients who completed both the baseline and 6 months HRQoL questionnaires. This meant there were no missing data, although it could introduce bias and lead to an overestimation of the HRQoL scores due to the drop off or decease of patients in poor health conditions. Also, longer follow-up periods were not included in the analysis due to too few patients who fully completed the 12-, 18- or 24-months questionnaires. Additionally, given the use of age as a continuous variable, we decided not to classify HRQoL score changes product of our multivariable model according to their clinical relevance, since the size of the association will depend on

Table 3
Univariate and multivariable model 4 regression analysis for the association of age (10 years) with changes of quality of life at 6 months follow-up.

Age (10 years)						
	Univariate			Model 4		
	β	CI 95 %	*p* value	β	CI 95 %	*p* value
Summary score	−3.72	(−6.70; −0.74)	0.014[§]	−3.28	(−6.42; −0.14)	0.041[§]
Physical functioning	−3.94	(−7.70; −0.17)	0.041[§]	−4.80	(−8.71; −0.88)	0.016[§]
Role functioning	−4.38	(−10.09; 1.33)	0.133	−5.41	(−10.78; −0.05)	0.048[§]
Emotional functioning	−3.09	(−6.58; 0.40)	0.082	−0.55	(−3.75; 2.65)	0.737
Cognitive functioning	−4.84	(−8.48; −1.20)	0.009[§]	−4.51	(−8.24; −0.78)	0.018[§]
Social functioning	−3.38	(−8.21; 1.44)	0.169	−0.88	(−5.52; 3.77)	0.711
Symptom burden*	−2.83	(−5.62; −0.04)	0.047[§]	−3.66	(−6.60; −0.73)	0.014[§]
Financial problems[+]	0.19	(−3.16; 3.54)	0.910	6.50	(3.16; 9.85)	<0.001[§]
Global Health Status	−1.32	(−5.50; 2.85)	0.534	−2.54	(−6.79; 1.71)	0.242

Model 4 = Adjusted by corresponding baseline HRQoL score + sex + education + performance status + comorbidities + tumor stage + appearance of severe irAEs + other cancer treatments (previous chemotherapy, surgery, radiotherapy) + use of combination therapy (Chemotherapy + ICI).
*A higher score represents a lower symptom burden.
[+]A higher score represents fewer financial difficulties.
[§] Statistically significant ($p < 0.05$).

the age of the patient being evaluated. Moreover, we included patients with a wide range of age for this type of cancer, from 37 to 87 years. However, this characteristic can introduce heterogeneity in the <60 age group HRQoL scores. Furthermore, the majority of OncoLifeS participants were recruited between 2016 and 2018, when ICI treatments were mostly prescribed as second or further-line monotherapies, changing to first-line combination therapies in recent years. Therefore, the effect of age in HRQoL of current ICI-treated lung cancer populations can differ from the results presented here. Moreover, no data on tumor resectability was available; however, to overcome this limitation we included tumor stage and surgical interventions in the multivariable regression model. Finally, even though treatment response may be an important predictor for HRQoL, due to a lack of correlation with age [35,36], it was not considered to be a confounder and therefore not discussed in the current paper. Future studies should include contemporary patient populations and longer study periods so that age differences and trajectories of HRQoL in the short, medium, and long term can be observed. Moreover, HRQoL measurement instruments should be developed and implemented in lung cancer research which consider adverse events induced by new therapies, such as immunotherapy.

5. Conclusion

We show age of lung cancer patients is significantly associated with changes in HRQoL after immunotherapy initiation. Although this association varies depending on the HRQoL domain being considered, changes are generally less favorable for older patients. HRQoL should not be overlooked in the context of providing ICI treatment to older patients, since negative effects experienced can be substantial. Furthermore, previous studies show older patients prioritize quality of life over longer survival [37,38]. The interdisciplinary health teams of lung cancer patients undergoing ICI treatment should pay special attention to older patients' psycho-social support networks to avoid large HRQoL deteriorations, as well as making joint treatment decisions considering patients' preferences.

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CRediT authorship contribution statement

E. Suazo-Zepeda: Conceptualization, Data curation, Formal analysis, Investigation, Visualization, Writing – original draft. **P.C. Vinke:** Conceptualization, Data curation, Methodology, Supervision, Validation, Writing – review & editing. **M.A. Heuvelmans:** Conceptualization, Data curation, Methodology, Supervision, Validation, Writing – review & editing. **G. Sidorenkov:** Conceptualization, Methodology, Supervision, Validation, Writing – review & editing. **T.J.N. Hiltermann:** Conceptualization, Methodology, Supervision, Writing – review & editing. **G.H. de Bock:** Conceptualization, Methodology, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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This paper draws on data of the Profiles Registry (Patient Reported Outcomes Following Initial treatment and Long-term Survivorship).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2022.12.017.

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