BMJ Oncology

Exploring the value of routinely collected data on EQ-5D-5L and other electronic patient-reported outcome measures as prognostic factors in adults with advanced non-small cell lung cancer receiving immunotherapy

Kuan Liao [1], David C Wong,[2] Fabio Gomes,[3] Corinne Faivre-Finn,[4,5] Laura Moliner,[3] Matthew Sperrin,[1] Janelle Yorke,[6,7] Sabine N van der Veer[1]

For numbered affiliations see end of article.

Correspondence to
Dr Kuan Liao;
kuan.liao@manchester.ac.uk

ABSTRACT

Objective Investigate whether routinely collected electronic patient-reported outcome measures (ePROMs) add prognostic value to clinical and tumour characteristics for adults with advanced non-small cell lung cancer (NSCLC) receiving immunotherapy.

Methods and analysis We retrospectively analysed data from adults with advanced NSCLC commencing immunotherapy between April 2019 and June 2022. Prognostic factors were ePROMs on quality of life (EuroQoL five-dimension five-level (EQ-5D-5L); EuroQoL Visual Analogue Scale (EQ-VAS)) and symptoms (patient-reported version of the Common Terminology Criteria for Adverse Events v5.0) completed at baseline and the first follow-up. We performed Cox proportional hazard regression for overall survival and time-to-progression as outcomes, and logistic regression for the onset of severe treatment toxicities (grade ≥3).

Results We included 379 patients; 161 (42.5%) completed ePROMs at baseline. Median overall survival and time-to-progression were 13.5 months (95% CI 11.3 to 16.7) and 10.5 months (95% CI 8.8 to 13.7), respectively. 36 (9.5%) experienced severe treatment toxicities during follow-up. Patients with lower EQ-5D-5L utility scores (HR per 0.1 unit increase 0.84, 95% CI 0.74 to 0.95) and higher symptom burden (HR 1.11; 95% CI 1.04 to 1.19) had poorer overall survival. This was also true for those with decreased EQ-VAS and increased symptom burden between baseline and the first follow-up. Lastly, only decreased EQ-5D-5L utility scores between baseline and the first follow-up were associated with shorter time-to-progression.

Conclusion ePROMs may add prognostic value to clinical and tumour characteristics for overall survival in adults with advanced NSCLC receiving immunotherapy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Decision-making for adults with advanced non-small cell lung cancer (NSCLC) receiving immunotherapy requires prognostic information derived from both clinical and tumour characteristics and electronic patient-reported outcome measures (ePROMs).

⇒ The ePROMs remain underused in the context of immunotherapy for advanced NSCLC.

WHAT THIS STUDY ADDS

⇒ Baseline measurements of EuroQoL five-dimension five-level (EQ-5D-5L) utility score and symptom burden score derived from a patient-reported version of the Common Terminology Criteria for Adverse Events v5.0 were prognostic factors for overall survival.

⇒ Changes in EuroQoL Visual Analogue Scale and symptom burden score at the first follow-up also have prognostic value for overall survival.

⇒ Change in EQ-5D-5L utility score at the first follow-up is a prognostic factor for time-to-progression.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND POLICY

⇒ ePROMs may provide prognostic information independently and in addition to clinical and tumour prognostic factors. Researchers should consider how to use ePROMs to predict survival outcomes accurately and further inform the decision-making in people with advanced NSCLC receiving immunotherapy.

INTRODUCTION

Lung cancer is the most common cause of cancer death in the UK in males and females.[1] For many years, treatment options for people diagnosed with advanced non-small cell lung cancer (NSCLC) were limited to chemotherapy, which increased median survival time by 1.5 months compared with best supportive care.[2] In the last decade, immunotherapy has revolutionised the treatment for advanced NSCLC[3] with the availability of immune checkpoint inhibitors,

such as atezolizumab (an anti-programmed death-ligand 1, anti-PD-L1 inhibitor) and pembrolizumab (an anti-programmed death 1, anti-PD-1 inhibitor). Randomised controlled trials showed that immunotherapy alone or in combination with chemotherapy compared with chemotherapy alone significantly improved clinical outcomes, such as response, survival and incidence of toxicities, in people with advanced NSCLC.[4–6] However, guideline bodies have highlighted that immune checkpoint inhibitors for treatment of advanced NSCLC is an expensive treatment and that not all people respond to it.[7] Furthermore, people with advanced NSCLC receiving immunotherapy may develop severe or even life-threatening treatment toxicities.[8]

In current clinical practice, guidelines for prescribing immunotherapy treatments are based on evidence from randomised trials.[9] However, trials participants are often younger and healthier compared with patients that oncologists routinely see in their clinic. For example, the majority of clinical trials in people with advanced NSCLC receiving immunotherapy excluded those with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or higher,[10] while this group makes up approximately 30% of patients with lung cancer in clinical practice. The difference of baseline clinical and tumour characteristics between trial cohorts and people attending oncology clinics may affect treatment response and tolerability.[11–13] This means that clinical trial data only support decisions for prescribing immunotherapy in a selected group of people with advanced NSCLC.

To better understand who may benefit from immunotherapy and who may not, previous studies identified the predictive biomarker PD-L1 expression, and prognostic factors to support treatment decision-making, such as ECOG PS and neutrophil-to-lymphocyte ratio (NLR),[14–16] or developed prognostic models incorporating clinical and blood biomarkers.[17–19] However, patients with poor prognoses based on these factors or models may still benefit from immunotherapy.[15 20] At the same time, severe treatment toxicities could result in discontinuation of immunotherapy and even death.[21 22] This indicates a need for identifying further factors to provide prognostic information for guiding decisions on treating people with advanced NSCLC with immunotherapy.

Patient-reported outcome measures (PROMs) help to gain insight into symptom status, physical function, mental health and health-related quality of life (QoL) from the patient's perspective.[23] With the transition to more patient-centred care, routine collection of electronic PROMs (ePROMs) is now becoming more common in oncology practice.[24 25] Although studies have reported PROM data in patients with advanced NSCLC receiving immune checkpoint inhibitors, most of these studies have focused on PROMs collected as part of a clinical trial.[26–28] Only a few studies were conducted in routine care settings.[29–31] Moreover, McLouth *et al*[29] indicated that PROM values collected in clinical practice might differ from those in clinical trials.[29] A systematic review by Efficace *et al*[32] concluded that PROMs may have prognostic value for overall survival across cancer populations, including those with lung cancers.[32] A subsequent scoping review of evidence on the prognostic value of PROMs in patients with NSCLC found that several studies reported the prognostic value of PROMs to predict other clinical outcomes.[33] However, only a few of these used routinely collected PROM data sets, and even fewer investigated outcomes other than overall survival; none had been conducted using routinely collected PROMs in the context of immunotherapy.

Therefore, this study aimed to explore the prognostic value of routinely collected ePROMs in people with advanced NSCLC receiving immunotherapy, both at baseline and the first follow-up, for predicting survival and treatment toxicity to inform decisions among those patients on immunotherapy.

METHODS
We designed and conducted a prognostic factor study following the recommendations of the Prognosis Research Strategy (PROGRESS) 2: Prognostic Factor Research[34] framework and reported this in accordance with REporting recommendations for tumour MARKer prognostic studies (REMARK) guideline.[35]

Study context and data collection procedures
The context of this single-centre observational study was a large tertiary cancer hospital in England (UK). The hospital started integrating ePROM questionnaires into care pathways for patients with lung cancers in January 2019,[36] implying that the ePROM data for the current analyses were collected as part of routine care rather than in the context of a research study. Patients were automatically enrolled in the ePROM service but could actively opt-out if they wished or could decide not to complete the ePROM survey at any time point. ePROM questionnaires included disease-specific symptom questions adapted using plain English from the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 and the EuroQoL five-dimension five-level questionnaire (EQ-5D-5L); we describe these instruments in more detail below. Enrolled patients received a text message with a web link to the ePROM questionnaires either at 17:00 on the day of a new patient appointment or 3 days before a scheduled follow-up appointment. They received immediate automated feedback on their responses on completion.[36]

Study sample
The study retrospectively included consecutive people with advanced NSCLC who started immunotherapy between 19 April 2019 and 1 June 2022. People were included if they were (1) aged ≥18 years or older with advanced (or stage IV) NSCLC based on pathological confirmation; (2) commencing immunotherapy drugs (atezolizumab or pembrolizumab) alone or chemoimmunotherapy using

atezolizumab or pembrolizumab as an immunotherapy regimen as any line of treatment. Eligible patients were all included in the study, regardless of whether they completed ePROMs or not.

Outcomes of interest

Outcomes of interest included overall survival, time-to-progression and treatment toxicities. We defined *overall survival* as the length of time from initiating immunotherapy to the time of death from any cause or censored at the last day of follow-up. *Time-to-progression* was defined as the time from initiating immunotherapy to the time of documented disease progression and censored at the last clinical visit or the time of death from any cause. In the absence of response evaluation criteria in solid tumours data for most patients in our sample, we used a clinician-anchored approach to define the time of documented disease progression as the date of the first CT scan report mentioning progressive disease in the radiologist's conclusion, or the date of the first clinical note stating progressive disease, when the CT scan report was not documented in the electronic patient record.[37] Lastly, we defined *severe treatment toxicities* as the onset of any severe adverse events using the clinician-reported CTCAE v5.0.[38] The CTCAE v5.0 lists relevant toxicities for people with lung cancer on systemic therapies as being absent or present; toxicities are graded based on their severity and frequency on a scale from 1 (mild) to 5 (death related to adverse events). We considered treatment toxicity severe if they had been graded 3 or higher.

Demographic and clinical covariates at baseline

Online supplemental appendix 1 shows our selection of eight covariates reflecting baseline demographic and clinical characteristics. We selected these based on prognostic and prediction models from published studies[39 40] and the expertise of the clinical members of our research team (CF-F, FG and JY). Data on covariates were extracted from the electronic patient record, considering a time window from 90 days before until 14 days after the start of immunotherapy treatment.

ePROMs as prognostic factors of interest

As prognostic factors of interest, we considered four ePROMs measuring QoL and symptom burden, which we describe in more detail in online supplemental appendix 2. For ePROM scores at baseline, we considered data collected in the 6 weeks before starting immunotherapy treatment. For our early change in ePROM analyses, a change in ePROM was computed as the difference between the ePROM value at baseline and the corresponding value at the first follow-up visit during immunotherapy with the ePROM completed.

The *EQ-5D-5L* is a validated questionnaire to capture health-related QoL.[41 42] It consists of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, rating each dimension at five levels ranging from 1 (no/problems) to 5 (extreme/problems).

To use the EQ-5D-5L as a prognostic factor, we calculated the utility score as per the standard value set for England, of which the values range from −0.285 (extreme/problems on all dimensions) to 1 (full health).[43] The EuroQoL Visual Analogue Scale (*EQ-VAS*) asks people to indicate their overall health on a 0–100 hash-marked, vertical visual analogue scale, with 0 indicating the worst and 100 the best imaginable health.[41]

For symptom burden as a prognostic factor, we used an adapted, patient-reported version of the CTCAE v5.0 asking people in plain English to rate the presence and severity of 14 disease-specific symptoms including pain, swallowing, shortness of breath, cough, coughing up blood, tiredness, appetite loss, feeling sick, vomiting, diarrhoea, constipation, numbness, pins and needles or tingling in arms/legs/hands or feet, weakness in arms/legs/hands or feet and skin rash (see online supplemental appendix 3 for the full questionnaire). Severity grades were defined as: (1) it does not stop me from doing daily activities (coded as mild); (2) it stops me from doing daily activities (moderate); (3) as a result, I struggle to care for myself (severe). A grade of 0 was coded as 'symptom absent'. The symptom items from the questionnaire were matched with items from the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire along with its lung cancer specific module (EORTC QLQ-C30/LC13) and validated in clinical practice.[44] The questionnaire used to measure the presence and severity of the 14 disease-specific symptoms is presented in online supplemental appendix 3. We summed up the scores to compute the *symptom burden score* ranging between 0 and 42, with higher scores indicating higher symptom burden. As a sensitivity analysis, we used the *number of moderate to severe symptoms*, defined as the count of symptoms with a grade ≥2, reported by patients in the patient-reported version of the CTCAE v5.0. The value for this factor ranged from 0 to 14, with higher score indicating more moderate to severe symptoms.

Missing data

Missing values in routinely collected data for the purpose of prognostic factor analysis can be handled in different ways, as missingness itself may provide information.[45] Therefore, we performed three different methods to handle missing data for the analyses both at baseline and first follow-up: multiple imputation (in our main analyses), as well as complete case analysis and multiple imputation plus a 'missing' indicator for the prognostic factors of interest.

In the complete case analyses of baseline data, we only included patients with complete information at baseline; for the first follow-up analysis, we included those with complete information at baseline and first follow-up. Given the fraction of the missing values in the variables of interest was around 50%, we performed multivariate imputation by chained equations (MICE) using the information of both baseline characteristics and outcomes to iteratively impute 40 datasets.[46–48] MICE assumes that

the data are missing at random, which is a less restrictive assumption than complete case analysis, which requires missing completely at random. In addition, to account for potential informative missingness, we also explored the information of missing ePROMs at baseline and the first follow-up by incorporating a missing indicator with MICE.

Descriptive analyses

We summarised baseline characteristics and both baseline and the first follow-up ePROMs as means with SDs for continuous variables with non-skewed distribution, as medians with IQR for skewed-distributed continuous variables, and as numbers with percentages for binary and categorical variables. We used Kaplan-Meier curves to describe the overall survival and time-to-progression. We compared characteristics and outcomes between baseline ePROM completers and non-completers to assess the risk of non-response bias.

Modelling procedures

We performed Cox proportional hazard regression to predict overall survival and time-to-progression, and logistic regression to predict severe treatment toxicity using ePROM data at baseline and at the first follow-up visit during immunotherapy with completed ePROMs. We conducted separate analyses for each ePROM score in online supplemental appendix 2, so there were eight analyses in total (ie, four using the start of immunotherapy and four using the first follow-up as time zero). For each ePROM analysis, we fitted three models, adding up to a total of 24 models: (1) ePROM-only model, using only the ePROM score as a prognostic factor, (2) partially adjusted model, additionally adjusted for ECOG PS and PD-L1 score and (3) fully adjusted model, adjusted for the ePROM score and all nine prognostic factors (note that smoker vs non-smoker and ex-smoker vs non-smoker were considered as two separate prognostic factors) listed in online supplemental appendix 1.

To account for regression to the mean in the longitudinal multivariable cox regression analyses, we incorporated the baseline ePROM score, as well as an interaction term between change in ePROM score and months since baseline ePROM completion at the time of first ePROM completion during follow-up.

We conducted a sensitivity analysis in patients receiving first-line immunotherapy, as patients receiving first-line immunotherapy may have a different prognosis than those receiving non-first-line immunotherapy.[49]

We used R (V.4.2.0) for all analyses. All p values were two-sided, with a significance level of <0.05. All estimated statistics were reported with their 95% CIs.

Sample size calculations

To estimate the minimum required sample size for our analyses, we used the 'pmsampsize' package in R, which follows the sample size criteria for developing multivariable prediction model recommended by Riley *et al*.[50]

Online supplemental appendix 4 shows the minimum required sample sizes for fully observed cases in all planned analyses. For the fully adjusted model of the survival outcomes, the minimum sample size required is 166 and 199 for the analyses at baseline and the first follow-up, respectively. The minimum sample size for the fully adjusted model of severe treatment toxicities is 1858 and 2229 for the analyses at baseline and the first follow-up, respectively. We considered findings for analyses hypothesis-generating if they had actual sample sizes smaller than those required.

Patient and public involvement

Patients and members of public were not involved in this study.

RESULTS

Description of baseline characteristics and ePROM scores, change in ePROM scores at the first follow-up and outcomes

Baseline characteristics and ePROMs

Table 1 summarises the baseline characteristics and ePROM scores of our study sample. We identified 379 patients treated between 19 April 2019 and 1 June 2022. The mean age was 66.3±10.3 years. The majority of patients (81.8%) had non-squamous cell carcinoma as their histological subtype, an ECOG PS of 0–1 (92.9%), and received immunotherapy as part of their first-line treatment (84.5%).

Of the 379 patients, 161 (42.5%) patients completed the ePROM questionnaire before the start of the immunotherapy. These completers were significantly younger and had a significantly lower proportion of missing NLR, compared with the non-completers (table 1).

Change in ePROMs scores at the first follow-up

Among the 161 completers of a baseline ePROM, 134 patients completed a follow-up ePROM at least once during immunotherapy. Table 2 shows that the median time between baseline and first ePROM response during immunotherapy was 0.82 months (IQR 0.67–1.37 months) and that apart from the EQ-5D-5L utility score, ePROM scores changed significantly between baseline and follow-up, all reflecting a deterioration of patients' health status.

Outcomes

With the median follow-up (censoring) time of 24.5 months (95% CI 19.7 to 30.2) and 142 (37.5%) patients censored, 237 of 379 patients (62.5%) had died, 208 (54.9%) had disease progression, and 36 (9.5%) had experienced severe treatment toxicities. The median overall survival was 13.5 months (95% CI 11.3 to 16.7) and the median time-to-progression was 10.5 months (95% CI 8.8 to 13.7) (figure 1).

There was no difference between ePROM completers and non-completers for overall survival but that may be not true for time-to-progression, although the difference

Table 1 Baseline demographics and ePROM values for the whole study sample, as well as compared between ePROM completers* and non-completers

Characteristic	Total (N=379)	Completers (n=161)	Non-completers (n=218)	P value†
Demographics				
Age (years), mean (SD)	66.3 (10.3)	64.6 (10.6)	67.5 (9.9)	0.006
Sex, n (%)				0.91
Female	179 (47.2)	75 (46.6)	104 (47.7)	
Male	200 (52.8)	86 (53.4)	114 (52.3)	
ECOG PS, n (%)‡				0.41
0	117 (30.9)	55 (34.2)	62 (28.4)	
1	235 (62.0)	93 (57.8)	142 (65.1)	
2	23 (6.0)	12 (7.5)	11 (5.0)	
3	4 (1.1)	1 (0.6)	3 (1.4)	
Smoking status, n (%)				0.07
Current smoker	96 (25.3)	32 (19.9)	64 (29.4)	
Ex-smoker	252 (66.5)	113 (70.2)	139 (63.8)	
Life-long never	30 (7.9)	16 (9.9)	14 (6.4)	
Missing	1 (0.3)	0	1 (0.5)	
PD-L1 score group, n (%)				0.14
<1%	118 (31.1)	57 (35.4)	61 (28.0)	
≥1%, <50%	79 (20.8)	35 (21.7)	44 (20.2)	
≥50%	158 (41.7)	58 (36.0)	100 (45.9)	
Missing	24 (6.3)	11 (6.8)	13 (6.0)	
NLR, mean (SD)	6.9 (5.5)	6.9 (5.8)	6.9 (5.2)	0.98
Missing NLR, n (%)	22 (5.8)	2 (1.2)	20 (9.2)	0.002
Histology				0.83
Non-squamous cell carcinoma	310 (81.8)	133 (82.6)	177 (81.2)	
Squamous cell carcinoma	69 (18.2)	28 (17.4)	41 (18.8)	
Line of immunotherapy				0.32
First-line	320 (84.4)	132 (82.0)	188 (86.2)	
Not first-line	59 (15.6)	29 (18.0)	30 (13.8)	
Treatment				0.16
Immunotherapy	196 (51.7)	76 (47.2)	120 (55.0)	
Immuno-chemotherapy	183 (48.3)	85 (52.8)	98 (45.0)	
ePROM scores§				
EQ-5D-5L utility score, median (IQR)		0.81 (0.72–0.92)		
EQ-VAS score, median (IQR)		70 (50–80)		
Symptom burden score, median (IQR)		3 (2–5)		

*ePROMs completers were people who completed ePROMs within 6 weeks before starting immunotherapy.
†Hypothesis testing for the difference between ePROMs completers and non-completers. χ^2 tests for sex, smoking history, PD-L1 score group, missing NLR, histology and line of immunotherapy. Two sample t-test for age and NLR. Wilcoxon rank sum test for ECOG PS.
‡The distribution of ECOG PS scores in our study population was similar to that of other studies.[60 61]
§No comparison available because ePROM non-completers did not have ePROM scores at baseline.
ECOG PS, Eastern Cooperative Oncology Group performance status; ePROM, electronic patient-reported outcome measure; EQ-5D-5L, EuroQoL five-dimension five-level; EQ-VAS, EuroQoL Visual Analogue Scale; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed death-ligand 1.

Table 2   Absolute change of ePROMs between baseline and the first follow-up* (n=134)

ePROM	Mean difference in score (95% CI)	P value†
EQ-5D utility score	−0.02 (-0.05 to 0.01)	0.26
EQ-VAS	−5.81 (−10.54 to 1.09)	0.02
Symptom burden score	1.31 (0.70 to 1.93)	<0.001

*Median months between baseline and the first ePROM response during follow-up was 0.82 (IQR 0.67–1.37).
†T-test of the mean difference in score between baseline and the first follow-up.
ePROM, electronic patient-reported outcome measure; EQ-5D, EuroQoL five dimension; EQ-VAS, EuroQoL Visual Analogue Scale.

was not statistically significant. Online supplemental appendix 5 shows that completers had a median overall survival of 13.5 months (95% CI 10.3 to 19.8 months) versus 14.1 months (95% CI 10.3 to 19.8 months) in non-completers (p=0.89), while the completers had a shorter median time-to-progression of 8.7 months (95% CI 6.5 to 12.2 months) versus 11.9 months for non-completers (95% CI 9.8 to 19.6 months, p=0.21). There was also no difference between completers and non-completers for severe treatment toxicities (9.9% vs 9.2%, χ^2=0.005, p=0.94).

Prognostic value of baseline ePROMs scores
Table 3 presents the pooled HRs or ORs obtained from fully adjusted models using multiple imputation for both baseline ePROMs and change in ePROMs to predict overall survival, time-to-progression and severe treatment toxicities. All ePROMs were associated with overall survival in the fully adjusted ePROM analyses except for EQ-VAS with a borderline insignificant association (HR per 10 unit increase 0.92; 95% CI 0.85 to 1.00). Patients with a lower EQ-5D-5L utility score (HR per 0.1 unit

increase 0.84, 95% CI 0.75 to 0.94) or higher symptom burden score (HR 1.13; 95% CI 1.04 to 1.22) had poorer overall survival. Forest plots of the fully adjusted models for predicting overall survival, including the HRs for the baseline ePROM and the clinical parameters, are shown in online supplemental appendix 6. The complete case analyses and those using multiple imputation with a missing indicator produced similar findings (online supplemental appendix 7). None of the baseline ePROMs were significantly associated with time-to-progression and severe treatment toxicities, regardless of how we addressed the missing data (online supplemental appendices 8 and 9).

Prognostic value of early change in ePROM scores
In table 3, a decrease in EQ-VAS (HR per 10 unit increase 0.89; 95% CI 0.81 to 0.97), an increase in symptom burden score (HR 1.09; 95% CI 1.03 to 1.15) and an increase in number of moderate to severe symptoms (HR 1.16; 95% CI 1.01 to 1.35) were associated with poorer overall survival in the fully adjusted analyses, regardless of how we handled missing data (online supplemental appendix 7). Forest plots of the fully adjusted models for change in
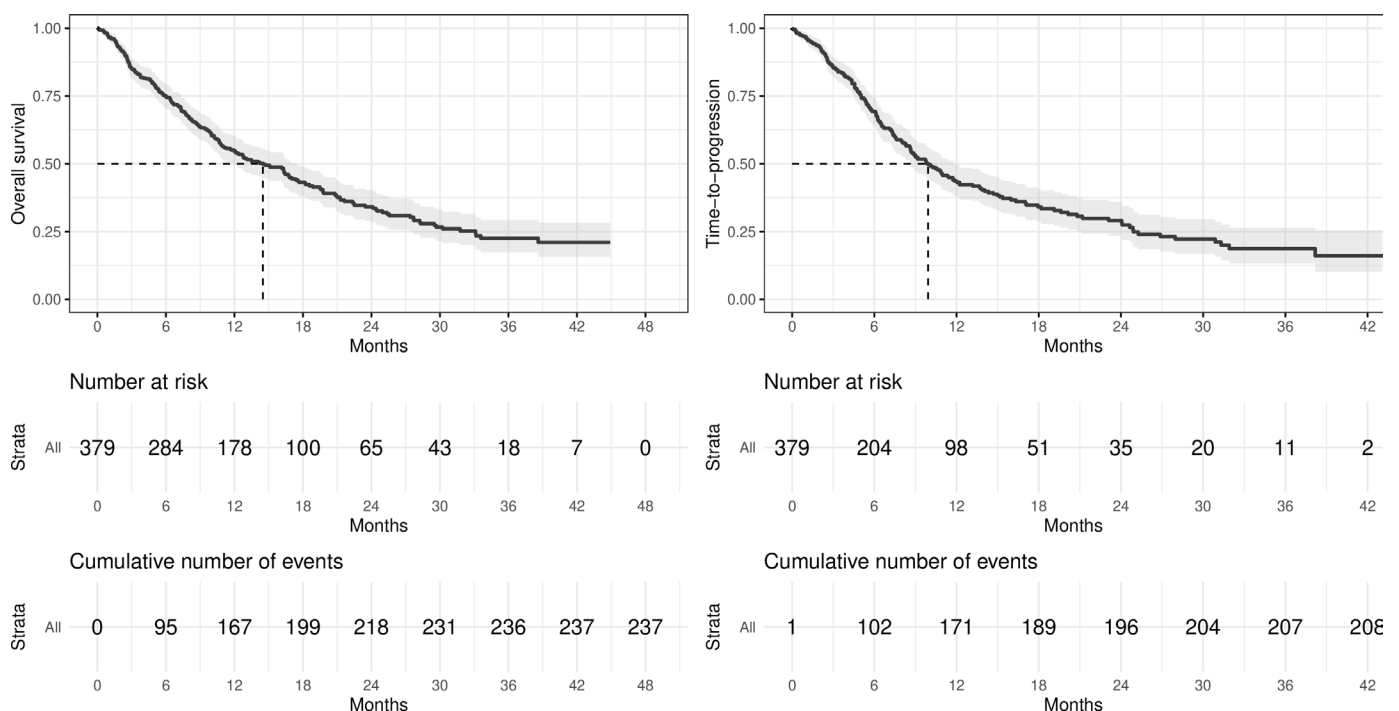

Number at risk									
All	379	284	178	100	65	43	18	7	0
	0	6	12	18	24	30	36	42	48

Cumulative number of events									
All	0	95	167	199	218	231	236	237	237
	0	6	12	18	24	30	36	42	48

Number at risk								
All	379	204	98	51	35	20	11	2
	0	6	12	18	24	30	36	42

Cumulative number of events								
All	1	102	171	189	196	204	207	208
	0	6	12	18	24	30	36	42

Figure 1   Overall survival (left panel) and time-to-progression (right panel) in people with advanced non-small cell lung cancer receiving immunotherapy.

Table 3 Prognostic value of baseline ePROMs and change in ePROM between baseline and first completion at the first follow-up in the fully adjusted models for overall and time-to-progression

Prognostic factor of interest	Overall survival		Time-to-progression	
	HR (95% CI)	P value	HR (95% CI)	P value
Baseline ePROM				
EQ-5D-5L utility score (per 0.1 unit increase)	0.84 (0.74 to 0.95)	0.009	1.06 (0.91 to 1.23)	0.48
EQ-VAS (per 10 unit increase)	0.92 (0.85 to 1.00)	0.06	0.98 (0.90 to 1.06)	0.59
Symptom burden score	1.13 (1.04 to 1.22)	0.004	0.92 (0.77 to 1.10)	0.37
Change in ePROM				
EQ-5D-5L utility score (per 0.1 unit increase)	0.89 (0.76 to 1.05)	0.17	0.84 (0.73 to 0.97)	0.02
EQ-VAS (per 10 unit increase)	0.89 (0.81 to 0.97)	0.01	0.96 (0.88 to 1.06)	0.43
Symptom burden score	1.09 (1.03 to 1.15)	0.008	1.07 (1.00 to 1.14)	0.04

HRs were obtained from the pooled estimates after multiple imputation.
The REporting recommendations for tumour MARKer prognostic studies checklist is presented in online supplemental appendix 13.
ePROM, patient-reported outcome measure; EQ-5D-5L, EuroQoL five-dimension five-level; EQ-VAS, EuroQoL Visual Analogue Scale.

ePROMs for predicting overall survival are presented in online supplemental appendix 10.

An increase in EQ-5D utility score (HR per 0.1 unit increase, 0.84; 95% CI 0.73 to 0.97) was associated with longer time-to-progression in the fully adjusted analysis (table 3). This association became borderline statistically significant in the fully adjusted analysis for a decrease in the symptom burden score (HR, 1.07; 95% CI 1.00 to 1.14), with similar but borderline insignificant result in the (sufficiently powered) partially adjusted analysis (HR 1.05; 95% CI 0.996 to 1.11) (online supplemental appendix 8). Findings were similar for the complete case analyses and those using multiple imputation with a missing indicator (online supplemental appendix 8). Forest plots of the fully adjusted models of change in ePROMs for predicting time-to-progression are presented in online supplemental appendix 11. None of the change in ePROM scores was associated with the severe treatment toxicities, no matter how the missing data were handled (online supplemental appendix 9).

Similar results were found if we summarised the symptom burden ePROM as the number of moderate to severe symptoms (online supplemental appendices 7–9). The sensitivity analysis where we included only patients who received first-line immunotherapy (n=320, table 1) showed largely similar results (online supplemental appendix 12).

DISCUSSION

This study provided insights into the potential prognostic value of routinely collected ePROMs in addition to clinical and tumour characteristics in adults with advanced NSCLC receiving immunotherapy. We found that the baseline measurements of EQ-5D-5L utility score and symptom burden ePROMs were prognostic factors for overall survival, with change in EQ-VAS and symptom burden score at the first follow-up also having prognostic value for this outcome. Apart from the change in

EQ-5D-5L utility score being a prognostic factor for time-to-progression, none of the other baseline or change in ePROM scores showed a significant association with time-to-progression or severe treatment toxicities.

Previous reviews demonstrated the potential of PROMs as prognostic factors for overall survival for people with NSCLC receiving radiotherapy, chemotherapy or targeted therapy.[32 33 51] In addition, Hopkins *et al*[52] concluded that ePROMs may have prognostic value for predicting overall survival and time-to-progression in patients receiving immunotherapy in a clinical trial setting and could therefore serve as a prognostic factor for stratifying trial participants.[52] Our study confirmed these findings in routine practice settings for people with NSCLC receiving immunotherapy, thereby adding insights into the value of ePROMs to guide real-world treatment decisions in the current era of new systemic anticancer therapy. Future model development studies should therefore consider including ePROMs in multivariable clinical prediction models for overall survival in this population and evaluate whether ePROMs enhance the models' predictive performance.

Different to most other studies included in the 2022 scoping review by Liao *et al*,[33] we also explored the prognostic value of ePROMs for predicting onset of severe treatment toxicities in this population but found no associations. In contrast, Iivanainen *et al*[53] developed a machine-learning model that did suggest ePROMs may be associated with this outcome in people with NSCLC treated with immunotherapy.[53] However, they did not adjust for clinical and tumour characteristics and did not account for the fact that severe treatment toxicities are a rare (and therefore imbalanced) outcome, making the predictive performance measures of their model potentially misleading.[54] Yet, ePROMs may help to identify presence of treatment toxicities by facilitating timely capturing of worsening side effects in people while on immunotherapy.[55] The potential diagnostic value of

ePROMs for severe treatment toxicities may therefore warrant further studies.

In contrast to a previous study reporting an improvement in symptom burden and QoL after 6 weeks of starting immunotherapy and other palliative lung cancer therapies,[56] we found a deterioration in these patient-reported aspects after 3–4 weeks. Future analyses may therefore explore if and how timing of ePROM follow-up influences the prognostic value of a longitudinal change in ePROM scores.

Our study has several limitations. First, our sample size for the fully adjusted analyses for overall survival and time-to-progression did not meet the requirements, and the findings from these should thus be considered as hypothesis generating. Yet, for overall survival and time-to-progression, we had sufficient statistical power in the partially adjusted analyses, where we observed similar results. Moreover, our sample size was close to the minimum sample size criteria, especially in the baseline analyses. Although we had initial interest in severe treatment toxicities, the small sample size and number of events did not allow us to draw any robust conclusion or generate any hypotheses for that outcome. Alternative outcomes such as time to next treatment and time to treatment discontinuation could be considered in future research.[57 58] The limited sample size did not allow us to explore the prognostic value of individual patient-reported symptoms listed in our symptom burden ePROM or adjust for more potential prognostic factors in the analysis, such as comorbidity or whether patients had advanced NSCLC as a primary diagnosis (vs a relapse or secondary cancer). Second, we defined time-to-progression based on imaging results available in the hospital's electronic health record system. Consequently, patients discharged to other healthcare providers and for whom we did not have access to all imaging data, were right censored at the date of the last clinical visit. Although we assumed the right censoring was independent of disease progression, we acknowledge that the right censoring could also have been informative. In addition, for the overall survival outcome, a proportion of patients who were lost to follow-up or alive at the end of the data collection were also censored. This means we may have underestimated the number of disease progression cases and reduced statistical power, but this is unlikely to have affected our overall findings because the Cox proportional hazard regression accounts for the right censoring by the maximum partial likelihood estimation, which compares hazard rates while considering censored observations. Third, a large proportion of patients in our sample had missing ePROM data, which reduced the accuracy of our estimates of the prognostic value of ePROMs. However, since our findings were similar regardless of how we handled missing data, this provided some reassurance that having a more complete data set would not change our overall conclusions. Fourth, this study retrospectively analysed routinely collected data from a single centre in England, UK, limiting the generalisability of our findings.

Future research should, therefore, externally validate our results by replicating our analyses in prospective populations treated in different (types of) centres and healthcare systems. Lastly, we used an adapted ePROM to measure symptom burden that is not widely used in other cancer centres, limiting the generalisability of our findings to contexts that use different symptom ePROMs.[59]

CONCLUSION

This study demonstrated that routinely collected ePROMs (based on EQ-5D-5L and symptom burden) before therapy and changes in ePROMs on therapy (based on EQ-VAS and symptom burden) have added prognostic value in adults with advanced NSCLC receiving immunotherapy. This warrants future development and evaluation of clinical prediction models incorporating routinely collected ePROMs as prognostic factors to help identify people with advanced NSCLC who are likely to have good overall survival with immunotherapy. Future studies with larger sample sizes should assess the prognostic value of routinely collected ePROMs for predicting time-to-progression and severe treatment toxicities in this population.

Author affiliations

[1]Centre for Health Informatics, Division of Informatics, Imaging and Data Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, The University of Manchester, Manchester, UK

[2]Department of Computer Science, The University of Manchester, Manchester, UK

[3]Medical Oncology Department, The Christie NHS Foundation Trust, Manchester, UK

[4]Division of Cancer Science, The University of Manchester, Manchester, UK

[5]The Christie NHS Foundation Trust, Manchester, UK

[6]Division of Nursing, Midwifery and Social Work, The University of Manchester, Manchester, UK

[7]Patient-Centred Research Centre, The Christie NHS Foundation Trust, Manchester, UK

X Kuan Liao @KuanLiao2

ORCID iD
Kuan Liao http://orcid.org/0000-0002-8840-0599

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