Comparing functional decline and distress from symptoms in people with thoracic life-limiting illnesses: lung cancers and non-malignant end-stage respiratory diseases.

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Abstract

Background

Malignant and non-malignant respiratory diseases account for >4.6 million deaths annually worldwide. Despite similar symptom burdens, serious inequities in access to palliative care persists for people with non-malignant respiratory diseases.

Aim

To compare functional decline and symptom distress in advanced malignant and non-malignant lung diseases using consecutive, routinely collected, point-of-care national data.

Setting/participants

The Australian national Palliative Care Outcomes Collaboration collects *functional status* (Australia-modified Karnofsky Performance Status (AKPS)) and *symptom distress* (patient-reported 0-10 numerical rating scale) in inpatient and community settings. Five years of data used Joinpoint and weighted scatterplot smoothing.

Results

In lung cancers (89,904 observations; 18,586 patients) and non-malignant end-stage respiratory diseases (14,827 observations; 4,279 patients), age at death was significantly lower in people with lung cancer (73 years; inter-quartile range (IQR) 65, 81) than non-malignant end-stage respiratory diseases (81 years; IQR 73, 87 years; $p<0.001$). Four months before death, median AKPS was 40 in lung cancers and 30 in non-malignant end-stage respiratory diseases ($p<0.001$). Functional decline was similar in the two groups and accelerated in the last month of life. People with non-malignant diseases accessed palliative care later.

Pain-related distress was greater with cancer and breathing-related distress with non-malignant disease. Breathing-related distress increased towards death in malignant, but decreased in non-malignant disease. Distress from fatigue and poor sleep were similar for both.

Conclusions

In this large dataset unlike previous datasets, the pattern of functional decline was similar as was overall symptom burden. Timely access to palliative care should be based on needs not diagnoses.

Key Messages

What is the key question?

Do the trajectories of functional decline and symptom intensity differ between people with late stage lung cancers and non-malignant end-stage respiratory diseases?

What is the bottom line?

Trajectories of functional decline are very similar between these two groups, but pain is the predominant symptom in people with cancer, while it is breathlessness in people with non-malignant end-stage respiratory diseases.

Why read on?

In this large, consecutive cohort study, understanding these patterns of functional decline and symptom burden will empower clinicians to better predict key needs for patients at the end of life.

Introduction

Lung cancers and non-malignant end-stage respiratory diseases are significant causes of morbidity and mortality worldwide. Lung cancers cause 1.6 million deaths each year and is the most fatal cancer internationally. [1] Of the 200 million people with chronic obstructive pulmonary disease (COPD) globally, 65 million people are living with moderate to severe disease, generating more than three million deaths annually. [2,3]

People with lung cancers and non-malignant end-stage respiratory diseases have been reported to experience a similar symptom burden, [4-8] but survival in lung cancer is generally shorter than people with end-stage lung diseases. [5,8] People with COPD are symptomatic for nearly six times as long as those with lung cancers [4] and have lower levels of function. [6,9,10] Despite similar palliative care needs experienced by those with these two conditions, [4,10,11] supportive and palliative care support for people with non-malignant lung disease is less common than for cancer patients. Further, palliative care access for people with COPD appears to be driven largely by the presence of comorbid lung cancers. [12] Even in people with lung cancer, needs-based access to palliative care is often less than ideal.[13] If people with non-malignant end-stage respiratory diseases do access palliative care services, this often occurs much later than for people with lung cancer.[5,8,9,14-18]

There are four functional patterns in the dying derived from activities of daily living (ADL) data: sudden death; terminal illness (decline in the last three months after a plateau period); organ failure (chronic remitting and relapsing diseases) and frailty.[19] Developments in disease-modifying therapies allow people to live longer with disease, potentially changing these proposed trajectories.[20] Although two contemporary patterns in trajectory of functional decline have been identified in the last 4 months of life in people who do not have lung cancers or non-malignant end-stage respiratory diseases,[20] there are few data, illustrating current patterns of disease trajectory dying from these conditions. Despite this, these less predictable trajectories have been suggested as a reason why people with non-malignant disease have less access to palliative care. Studies of symptom burden by diagnosis show that populations with cancer have symptoms which often worsen rapidly over the weeks prior to death.[4,10,21,22] A small longitudinal study comparing people with lung cancer or COPD showed rapidly increasing symptoms due to lung cancer close to death, but that in people with COPD, symptoms gradually increased over a longer period of time.[4] Individual trajectories of breathlessness varied in people with both diagnoses,[4,10] although these patterns may not be representative of larger populations.

The aim of this study was to describe and compare changes in function and symptom-related distress in people with lung cancers or non-malignant end-stage respiratory diseases, in a large national dataset of patient-reported, point-of-care clinical measures, in the last four months of life.

Methods

Study setting

The Australian national Palliative Care Outcomes Collaboration (PCOC) is a voluntary program. Participating services represent more than 85% of all people referred for palliative care each year equating to patient outcome measures for about 25% of all predictable deaths in Australia annually. Currently, the data from PCOC represent 37.1% of all lung cancer deaths over that period and 6.7% of all deaths from respiratory diseases. Data were collected at point-of-care in inpatient and community settings at admission and discharge and at every change in phase of care (‘stable’, ‘unstable’, ‘deteriorating’, and ‘terminal’).[23] Palliative care phase is a reliable measure that can be used to plan responsive clinical care.[24,25] PCOC patient/proxy reported outcomes data are used at the time that they are collected to aid clinical decision making and, when aggregated, routine benchmarking of outcomes between services.

Study Design
This was a repeated, cross-sectional consecutive cohort study using prospectively collected clinical data from the Australian national PCOC database with a similar methodology to previously described trajectories in other life-limiting illnesses.[20,25] Analysis and reporting of anonymised data collected as part of the PCOC programme were approved by the Human Research Ethics Committee of the University of Wollongong (approval ID: HE2006/045). Routine PCOC clinical data are de-identified and aggregated, and separate patient consent was not required. Using death as the anchor time point, data from the preceding four months were examined.

Participants and variables
This analysis included all patients with at least one recorded Australia-modified Karnofsky Performance Status (AKPS) score [26] who died in the care of participating palliative care services between 1st January 2013 – 31st December 2018. Data were integrated using a statistical linkage key in combination with the patient’s residential postcode. Diagnostic group was allocated based on the principal life-limiting illness that resulted in a palliative care referral. Patients were grouped into three diagnostic cohorts: lung cancers; chronic respiratory disease and all others (where the latter has been reported previously).[20]

The Australia-modified Karnofsky Performance Status (AKPS) scale is an ordinal tool that reports functional status (100 –independent, no evidence of disease with ten point decrements to 0 – dead).[26] A person with an AKPS score of 40 is in bed more than 50% of the time.

Symptom distress data were collected from patients at each clinical encounter and, if the patient was unable to respond, from their caregiver/proxy. The Symptom Assessment Scale is a numerical 0-10 patient self-rating scale (NRS) [8] used to capture symptom distress. Symptom distress analysed in this study were pain, breathlessness, fatigue and sleep problems.

Statistical methods
Cohort characteristics were reported using descriptive statistics (counts and percentages). All longitudinal analyses of the trajectory of patient function were undertaken using number of days before death, which was the anchor point.[20] Joinpoint regression was used to identify time points prior to death associated with significant changes in the slope of functional decline at the group level in the lung cancers and non-malignant end-stage respiratory diseases cohorts over time. (Joinpoint Regression Program, Version 4.3.1.0 - April 2016; Statistical Methodology and Applications Branch, Surveillance Research Program, National Cancer Institute) Locally weighted scatterplot smoothing (lowess) was used to investigate trends in patient function (AKPS) and symptom distress. Lowess smoothing was undertaken using R 3.4.4 (R Core Team 2018, Vienna, Austria).

Sensitivity analysis
There are no agreed national or international criteria for referral to specialist palliative care. As such, late referrals have the potential to influence the modelled trajectories. To investigate

this, a sensitivity analysis was performed by re-running the regression model algorithm, with patients referred to palliative care during the last 14 days of life removed from the data set.

Reporting quality framework
The study is reported in accordance with the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) checklist.[27]

Results

A total of 89,904 observations were made from 18,586 patients with lung cancer and 14,827 observations in 4,279 patients with non-malignant end-stage respiratory diseases. The majority of observations were made in the last ten days of life. (Figure 1)

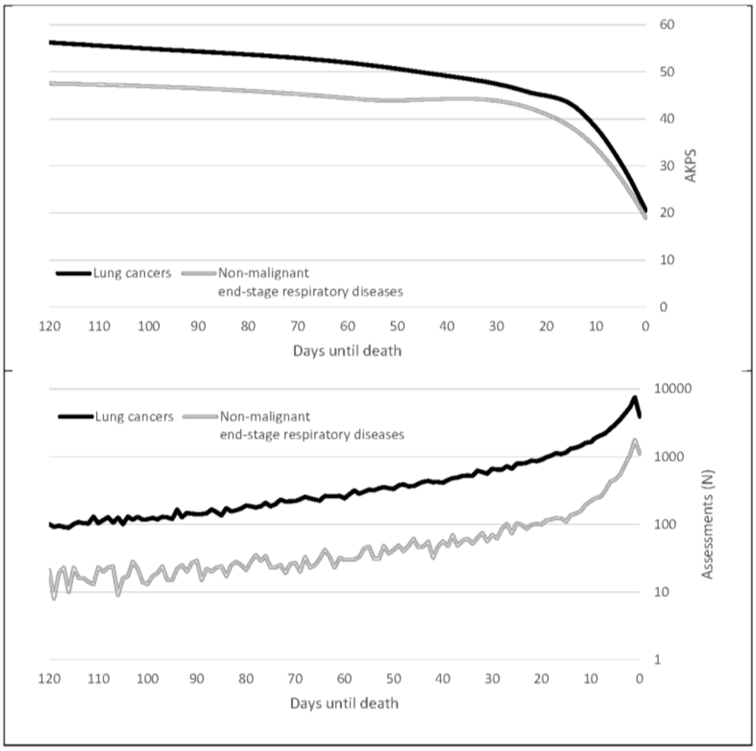

Figure 1. Graph of mean Australia-modified Karnofsky Performance Scale (AKPS) trajectories in lung cancers (89,904 observations; 18,586 patients) and non-malignant end-stage respiratory diseases (14,827 observations; 4,279 patients) in the 120 days leading to death, including the incidence of observations in the study period.

Demographic data (Table 1) show similar characteristics between the groups, with an exception of median age at death, being significantly lower in people with lung cancer (73 years (inter-quartile range (IQR) 65, 81 years) than people with non-malignant end-stage respiratory diseases (81 years IQR 73, 87 years). Both groups contain fewer women than men, with the majority being born in Australia and almost all speaking English. Time from referral to death was longer in people with lung cancers (median of 22 days (IQR 6, 72 days) compared to 6 days (IQR 2, 40 days) for people with non-malignant end-stage respiratory diseases.

Table 1. Characteristics of the two diagnostic cohorts of thoracic life-limiting illnesses in prospectively collected national data from the participating palliative care services for the last 120 days of life.

		Diagnostic group				
		Lung cancers		Non-malignant end-stage respiratory diseases		
		Patients	18,586	Patients	4,279	
		Assessments	*89,904*	*Assessments*	*14,287*	
Cohort characteristics	Female	7,379	39.7%	1,921	44.9%	p<0.001
	Born in Australia	11,672	62.8%	2,730	63.8%	p=0.173
	English speaking	16,839	90.6%	3.911	91.4%	p=0.130
	Age at death					p<0.001
	median	73		81		
	range (IQR)	0-103	(65-81)	0-103	(73-87)	
	Australia-modified Karnofsky Performance Scale (AKPS)					p<0.001
	median	40		30		
	range (IQR)	10-100	(20-50)	10-100	(30-50)	
	Time from referral until death (days)					p<0.001
	median	22		6		
	range (IQR)	0-2710	(6-72)	0-1852	(2-40)	

IQR – interquartile range

Four months from the end of life, the median AKPS was 40 in people with lung cancer and 30 in people with non-malignant end-stage respiratory diseases. (Figure 1). For changes in functional status over time, the scatterplot showing the mean daily AKPS and the fitted model superimposed are shown in Figure 2 and tabulated in Table 2. In the lung cancer cohort, the segmented regression algorithm found that a four break point model best described the trajectory of functional decline at the group level. At 120 days prior to death, the modelled average AKPS was 55.4. Function declined over the entire period, with significant changes occurring at 56, 20, 8 and 3 days prior to death. The most rapid decline in function occurs during the last three days of life, with a mean daily decrease in AKPS of 4.2 points. The model for people with non-malignant end-stage respiratory diseases showed a similar model with three break points at 26, 8 and 2 days before death. (Table 2, Figure 2)

Table 2 Summary of Joinpoint predicted AKPS from 120 days before death, at each break point and last recorded AKPS before death.

	Break point #	Days until death	Predicted AKPS	Daily percentage change
Lung cancers				
	-	120	55.4	0.2%
	4	56	51.6	0.4%
	3	20	44.6	1.3%
	2	8	38.0	4.2%

1	3	29.7	14.8%
-	0	16.4	-
Non-malignant end-stage respiratory diseases			
-	120	49.6	0.2%
3	26	40.9	0.7%
2	8	35.0	5.4%
1	2	23.9	17.2%
-	0	15.7	-

AKPS – Australia-modified Karnofsky Performance Status scale

The sensitivity analysis removed data from people only referred in the last 14 days of life (Table 3). For both cohorts, removing referrals during the last 14-days of life had little impact on the fitted model.

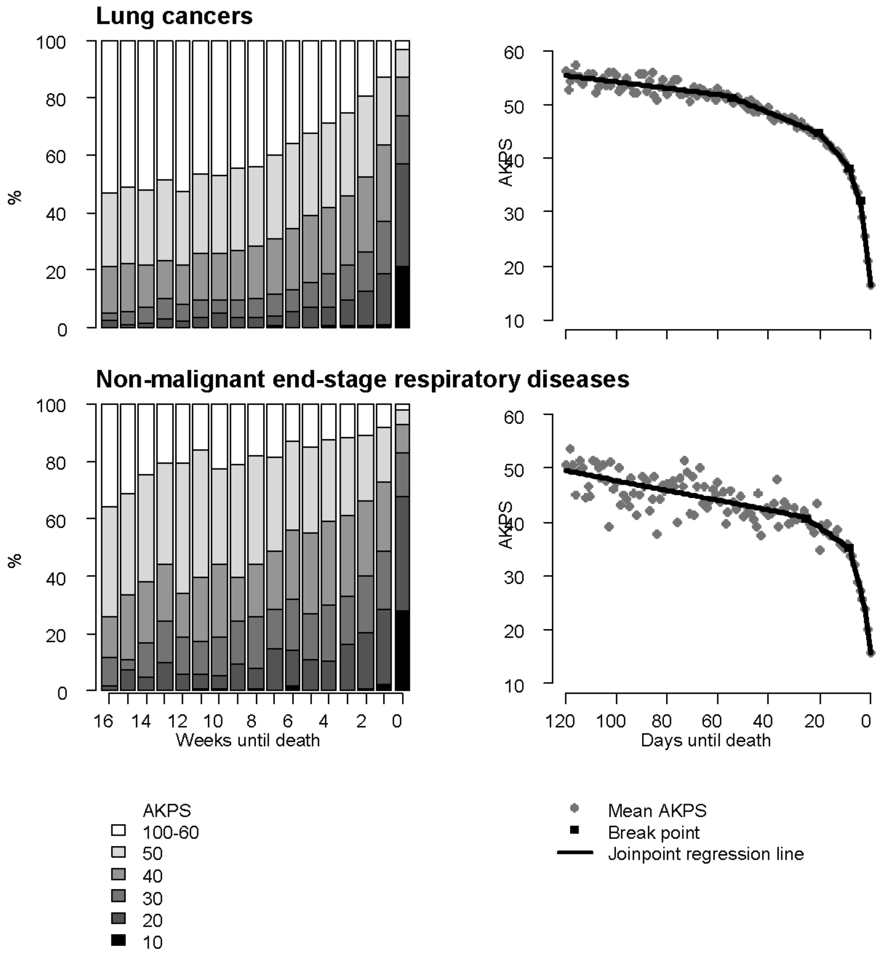

Figure 2. Matrix plot displaying the distribution of Australia-modified Karnofsky Performance Status scale (AKPS) from 16 weeks prior to death in the left hand panel, and mean daily AKPS and superimposed Joinpoint regression models in the 120 days before death in the right hand panel

Table 3 Results of Joinpoint regression models and sensitivity analyses for lung cancers and non-malignant end-stage respiratory diseases cohorts

	Lung cancers	**Non-malignant end-stage respiratory diseases**
Full model		
Model Coefficients	**Estimate (95% confidence interval)**	
Break point (days before death)[a]		
4 (further from death)	56 (45-68)	-
3	20 (16-25)	26 (12-44)
2	8 (6-10)	8 (5-11)
1 (closer to death)	3 (2-4)	2 (2-3)
Rate of functional decline (slope)[b]	**Estimate (standard error)**	
5 (further from death)	0.1 (0.008)	-
4	0.2 (0.011)	0.1 (0.010)
3	0.6 (0.038)	0.3 (0.066)
2	1.6 (0.121)	1.9 (0.211)
1 (closer to death)	4.4 (0.115)	4.1 (0.408)
Mean AKPS at death (Intercept)[c]	16.4 (0.134)	15.7 (0.293)
Sensitivity analysis[d]		
Model Coefficients	**Estimate (95% confidence interval)**	
Break point (days)[a]		
4 (further from death)	56 (46-67)	-
3	20 (17-23)	26 (13-40)
2	8 (6-9)	7 (5-14)
1 (closer to death)	3 (2-4)	2 (2-5)
Rate of functional decline (slope)[b]	**Estimate (standard error)**	
5 (further from death)	0.1 (0.007)	-
4	0.2 (0.010)	0.1 (0.010)
3	0.6 (0.040)	0.3 (0.068)
2	1.7 (0.154)	1.9 (0.457)
1 (closer to death)	4.2 (0.151)	4.4 (0.792)
		H
Mean AKPS at death (Intercept)[c]	16.1 (0.175)	16.5 (0.602)

AKPS – Australia-modified Karnofsky Performance Scale

[a] The break points describe the number of days prior to death where there is a significant change in the rate of functional decline.

[b] The model slope is rate of functional decline (i.e. the decrease in average AKPS for each day closer to death). Slope 1 indicates the rate of rate of functional decline in the period just prior to death.

[c] The model intercept is the average AKPS on the day that the patient died.

[d] The sensitivity analysis describes the results obtained after re-running the algorithm with late referrals (last 14 days) removed from the analysis.

For symptom distress, more people with lung cancer experienced distress from pain compared to people with non-malignant end-stage respiratory diseases over the whole 120 days prior to death (Figure 3). Distress from breathing was greater in people with non-malignant end-stage respiratory diseases for the entire study period, although distress reduced in the 20 days prior to death. (Figure 3) However, in people with lung cancer, distress from breathlessness worsened from about three weeks before death. Distress from fatigue and poor sleep were similar in both groups. (Figure 3)

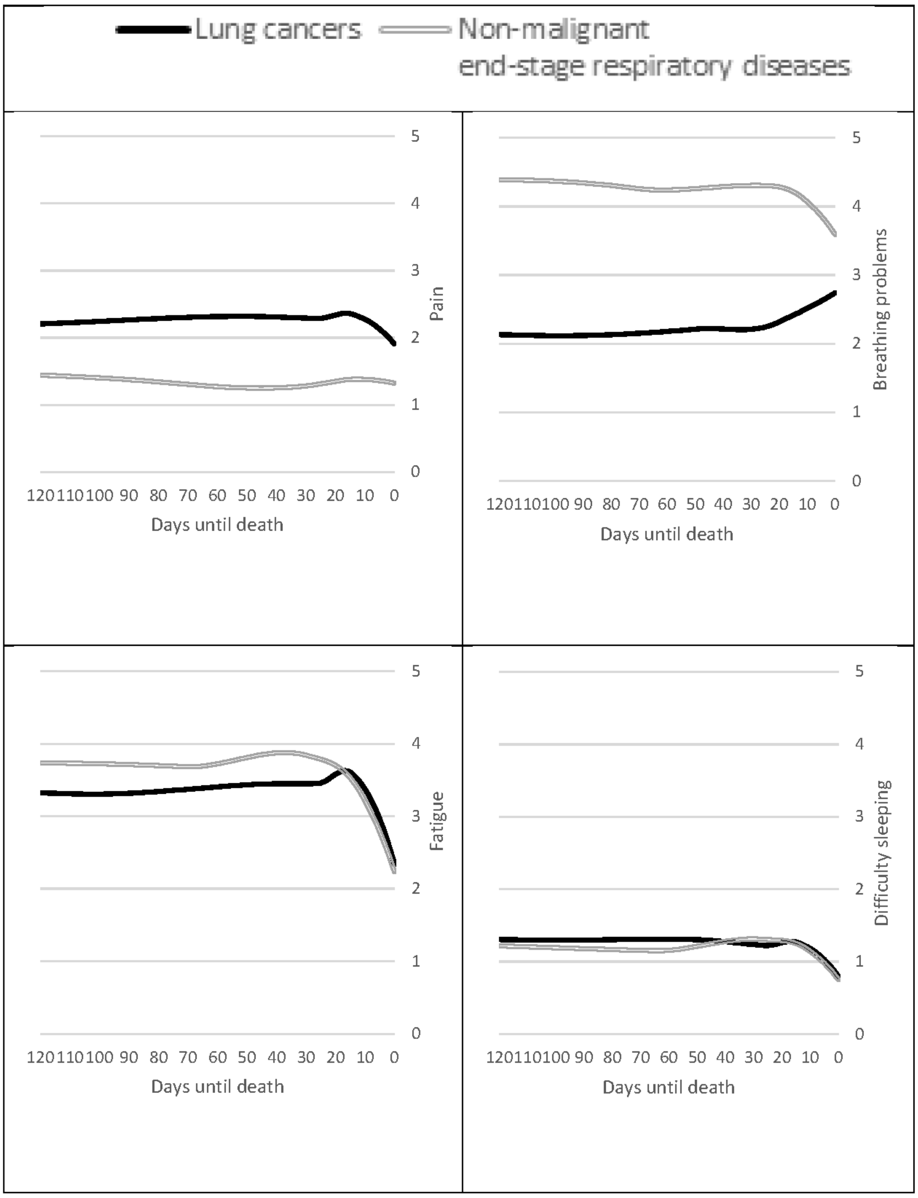

Figure 3. Graphs of mean symptom distress (pain, breathlessness, fatigue & sleep) measured on a 0-10 numerical rating scale plotted against the 120 days before death in prospectively collected national data in people with lung cancers (89,904 observations; 18,586 patients) and non-malignant end-stage respiratory diseases (14,827 observations; 4,279 patients)

Discussion

In this mortality follow-back analysis of a large prospectively collected data set, the pattern of functional decline in the last 120 days of life occurred in parallel, unlike previous descriptions. Although overall symptom burden was similar, the pattern differed between the two disease groups; pain was mainly a feature of lung cancer, and breathlessness of non-malignant lung disease. Despite this, people with non-malignant disease accessed palliative care later. Breathlessness increased nearer death in people with malignant disease, and decreased in people with non-malignant, lung diseases.

These data potentially challenge some previous models based on smaller data sources with derived measures,[19] from qualitative interviews and expert opinion showing different patterns of functional decline. However, other findings were consistent with previous reports. Functional decline accelerated for both groups closer to death confirming other studies that excluded people with thoracic diseases,[20] including other mortality follow-back studies.[28] People with non-malignant end-stage respiratory diseases had a lower baseline functional status,[9-11,19] perhaps due to previously noted older age at the end of life.[4,5,8] However, the difference in functional status between the group was less marked in our study; clinically marginal at most. Despite the similarities in trajectories, people with non-malignant disease were referred to palliative care later than people with lung cancer, consistent with other population studies. [5,8,9,14-18]

Like others, we found a similar overall symptom burden is experienced by people with lung cancers and non-malignant end-stage respiratory diseases, but lung cancer is associated with worse pain-related distress [5,7,29] and non-malignant end-stage respiratory diseases experience clinically important greater distress from breathlessness.[4,22,30] People with lung cancer experienced greater breathlessness-related distress as death approaches,[11,31] and those with non-malignant disease experienced increasing pain-related distress prior to death.

Prevalence of sleeping difficulties has been reported at 35% [31] comparable to the baseline values in this study. However, we found no difference by disease group unlike a previous review [8] where those with lung cancer were three times more likely to experience insomnia (30% vs 10%). Findings related to fatigue were consistent with previous reports.[8,31,32]

Strengths and Limitations

The Australian national Palliative Care Outcomes Collaboration (PCOC) collects data predominantly from services providing specialist palliative care, which may overstate population prevalence of symptoms as only a proportion of people with life-limiting illness access specialist services. Potentially, the people with greater symptom burden may be more likely to be referred to palliative care services.

There are no universal criteria for referral to specialist palliative care and only about half of people dying are referred.[15,16] Therefore, these trajectories may not be representative of all people dying with lung cancers or people with non-malignant end-stage respiratory diseases. PCOC data are collected when patients interact with healthcare services. Therefore, one also needs to consider the impact of other factors on referral and uptake of specialist palliative care services such as income, geographical and environmental factors, and patient preference.[15,16]

This is the largest trajectory study undertaken [20,22,33] with two distinct cohorts with thoracic diseases: lung cancers or non-malignant end-stage respiratory diseases. This is a consecutive case-series, which lessens selection bias. Standardised assessment tools including AKPS were used for both diagnostic groups collected at point-of-care allowing comparisons between the disease trajectories.[26] Many studies look at non-small cell lung cancer (NSCLC) and COPD, rather than all lung cancers and all non-malignant end-stage respiratory diseases. Therefore, any differences between previous studies and these results may be explained by the current study including more diagnoses.

Measures of multi-morbidity were not available in this study, although a simultaneous diagnosis of non-malignant end-stage respiratory diseases and lung cancers is possible, especially given shared risk factors. Studies have shown 14.5-43.0% of people with lung cancer are reported to also have COPD.[11,34] However, including people with both non-malignant end-stage respiratory diseases and lung cancers simultaneously represents a more genuine clinical picture as these patients with comorbidity are seen in practice although people with lung cancer are much more likely to be referred to palliative care.[12]

A key challenge in assessing trajectories of functional decline is that measures such as AKPS is an ordinal variable. To analyse with tools such as Joinpoint requires the assumption that the scales are close to a continuous variable where each step on the scale is close to equal to all other steps. There is no simple way to establish this property but, importantly, in this study the two groups had data collected contemporaneously by the same clinicians, and the analyses were identical for both groups in order to allow a direct comparison.

Our study analysed aggregate data which we recognise as poorly representative of individual trajectories of those dying with non-malignant disease; previously reported as variable and even “chaotic”.[35] It is interesting to note, however, that in studies of individual trajectories only a minority of those studies followed the previously described theoretical trajectories of dying.

Implications for Clinical Practice

Use of palliative care services improves quality of life in people with lung cancer [36] and, with early access, is associated with patient outcomes and reduced costs of end-of-life care.[11] This, alongside the comparable symptom burden, similar functional decline and significant global burden of chronic respiratory diseases, highlights the need for more proactive and patient-centred policies regarding active referral to palliative care for people with non-malignant end-stage respiratory diseases. A focus on current needs and concerns would mitigate against the challenges of prognostication in both malignant and non-malignant disease.

Given these findings, distress from breathing should be specifically identified and assessed. Given similar trajectories of functional decline, ensuring adequate pre-planning for deteriorating physical function and increasing needs for assistance with activities of daily living is essential. Occupational therapists and physiotherapists in particular employ a range of strategies that aim to optimise patient function through the non-pharmacological management of breathlessness.[37] The ability to remain as active as possible for as long as possible is a priority for those with non-malignant end-stage respiratory diseases.[38] Defining needs generated by functional decline is the responsibility of every health professional who has contact with people who have end-stage disease so that appropriate allied health practitioners can be engaged to help optimise function before functional decline accelerates.[39]

Implications for future research
This study combined all non-malignant end-stage respiratory diseases. It is possible that there are different trajectories and symptom burden profiles for differing causes of malignant (non-small cell lung cancer, small cell lung cancer) and non-malignant end-stage respiratory diseases. Future research will need to have data on sufficient numbers of patients for each respiratory condition that leads to end-stage disease in order to define any differences between causes of non-malignant end-stage respiratory diseases.

This study provides robust evidence for what had previously been assumed as the case in functional decline and symptom distress at the end-of-life. The data on sleep need further prospective investigation, especially distinguishing between those who do and do not have long term sleep problems such as obstructive sleep apnoea.

Generalisability
The PCOC data are collected from a high-income country with universal health insurance and well-established specialist palliative care services, and therefore findings can only be compared to similar countries. Further, PCOC data will not be captured for people who have not been referred to a participating service.

Conclusions

This large mortality follow-back study showed a similar pattern of functional decline in people dying of lung cancers or non-malignant lung diseases. Overall, both groups had an equivalent symptom burden but referral for palliative care services was later for those with non-malignant disease. Timely access to palliative care for both groups should be both possible and actioned. These data speak strongly to the need for proactive, need-based identification immediately as the final, inexorable decline commences so that the appropriate supports and resources are in place for patients and their caregivers.

Declarations:

Authorship:
MB, SA, DM, DF, MJ, KE, DCC made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data;
MB, SA, DM, DF, MJ, KE, DCC drafted the article or revised it critically for important intellectual content;
MB, SA, DM, DF, MJ, KE, DCC approved the version to be published;
MB, SA, DM, DF, MJ, KE, DCC have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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Declaration of conflicts of interests:

The authors declare no competing interests.

Data management and sharing:

All data are available to bona fide researchers through the Australian national Palliative Care Outcomes Collaboration through their standard operating procedure.

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