Missed opportunity? Worsening breathlessness as a harbinger of death: a cohort study

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ABSTRACT The aim of the study was to explore trajectories of breathlessness intensity by function and life-limiting illness diagnosis in the last 3 weeks of life in palliative care patients.

A prospective, consecutive cohort study obtained point-of-care data of patients of Silver Chain Hospice Care Service (Perth, Australia) over the period 2011–2014 (n=6801; 51 494 data-points). Breathlessness intensity (0–10 numerical rating scale) and physical function (Australia-modified Karnofsky Performance Status (AKPS)) were measured at each visit. Time was anchored at death. Breathlessness trajectory was analysed by physical function and diagnosis using mixed effects regression.

Mean±SD age was 71.5±15.1 years and 55.2% were male, most with cancer. The last recorded AKPS was >40 for 26.8%. Breathlessness was worst in people with cardiorespiratory disease and AKPS >40, and breathlessness in the last week of life increased most in this group (adjusted mean 2.92 *versus* all others 1.51; p=0.0001). The only significant interaction was with diagnosis and function in the last week of life (p<0.0001).

Breathlessness is more intense and increases more in people with better function and cardiorespiratory disease immediately before death. Whether there are reversible causes for these people should be explored prospectively. Omitting function from previous population estimates may have overestimated breathlessness intensity for many patients in the days preceding death.

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Introduction

Chronic breathlessness affects one in 11 people in the general population [1]. For most people, this will be attributed to an underlying medical condition such as respiratory disease [2] which may be treatable, but not curable, and which is likely to contribute to suffering near death [3].

Severe breathlessness is one of the most frightening experiences. Unlike other symptoms such as pain, an episode of severe breathlessness is often associated with an ongoing terror of imminent death [4]. It is therefore unsurprising that the mode of dying, in particular a fear of severe breathlessness or suffocation, may be a major anxiety for people with a life-limiting illness [5]. Many people may have vivid memories of a relative dying with serious respiratory distress, and past memories and fears affect central perception and anticipation of breathlessness [6].

In the weeks prior to death in a palliative care population, the prevalence and intensity of breathlessness is reported to increase and functional status most often worsens [7, 8]. This phenomenon has been described in several datasets and includes people with a wide range of recorded causes of death, including frailty, dementia and those perceived to have had a "sudden" death [9–12]. To date, two cohort studies have proposed contradictory effects of performance status on chronic breathlessness at the end of life: one suggested that decreasing performance status is associated with the increasing breathlessness and the other, the opposite [10, 13]. Given that no study has evaluated whether the trajectory of breathlessness differs in relation to the patient's physical functional status and underlying condition(s) in the last weeks before death, and the role of functional status in the two studies that have been done to date was contradictory, this current study was conceived to explore this relationship.

The relationship between breathlessness and functional status at the end of life is important to inform clinical discussions with concerned patients and their relatives, and to guide research in ways of best palliating breathlessness. At least two distinct trajectories of function and their relation to breathlessness need to be understood: 1) progressive functional decline and 2) sudden deterioration in the setting of a known life-limiting illness [9, 12]. Such patterns may also provide important insights into the underlying pathologies leading to different trajectories of dying and the need to pay heed to symptom exacerbations even in the last weeks of life.

The aim of this study was to evaluate patterns of breathlessness by levels of function in the last 3 weeks of life in palliative care. The null hypothesis was that there would be no difference in the trajectories of breathlessness intensity between diagnostic groups categorised by function in the 21 days preceding death.

Methods

Study setting

Silver Chain Hospice Care Service (SCHCS) is the sole community palliative care provider for metropolitan Perth in Australia, providing care for approximately 2800 patients annually in their own homes. The SCHCS comprises an interdisciplinary team that includes general practitioners, registered nurses, care aides, volunteers, counsellors and pastoral care workers. Registered nurses are available 24 h per day, 7 days per week, supported by clinical nurse consultants and other staff. The service is funded by the state government and is free of charge to palliative care patients.

Study cohort and design

This was a longitudinal study using all data on breathlessness and level of function, aggregated each day from a consecutive cohort of 7896 patients seen by the SCHCS between January 1, 2011 and December 31, 2014. There were 1095 patients who had no data recorded in the last 21 days of life. These patients were excluded, leaving 6801 patients for analysis with 51 494 data-points [7, 14, 15]. We included all data-points collected in the last 21 days of life for everyone who died, with simultaneously recorded breathlessness intensity and functional scores, categorised into broad diagnostic groups. As the only time-point that is constant in referral-dependent hospice and palliative care is death [16], the longitudinal analysis used time anchored at death in this cohort of people whose expected outcome was death.

Data collection from SCHCS records

All data were collected in the clinical setting contemporaneously with each face-to-face visit by a health professional from the SCHCS. Processes including staff recording of patient rating of symptoms remained constant during the study period. De-identified data included demographic and clinical data recorded once on admission to the service, and clinical data recorded at each clinical encounter. Data quality was optimised by routine point-of-care data entry by SCHCS staff into mobile phone data systems for all fields relating to that clinical encounter.

Demographic and clinical data recorded once on admission to the service

1) Demographic characteristics (age, sex, living arrangement, caregiver status and place of death). 2) Dominant cause of life-limiting illness (cardiorespiratory diseases (primary lung cancer, respiratory disease, cardiac failure) and other).

Clinical data recorded at each clinical encounter

1) Patient-rated intensity of breathlessness on an 11-point numerical rating scale (NRS) between 0 ("no") to 10 ("worst imaginable") using the Symptom Assessment Scale [17]. 2) Clinician-rated performance status using the Australia-modified Karnofsky Performance Status (AKPS) scale ranging from 100 ("functioning normally and without symptoms or assistance") to 0 ("dead") in 10-point decrements. An AKPS of 40 indicates high levels of care for basic activities of daily living and a score of 20 represents almost total dependence on others for care. AKPS has been validated in palliative care populations [18]. 3) Patients were visited in their homes by clinicians as required. This may have been on a weekly basis, every few days, daily or several times in a day. Frequency of visits tend to increase as time of death approaches, but depends on the needs of the patients and their families.

Statistical analyses

The cohort and service characteristics were reported using descriptive statistics, and were compared using Chi-squared analyses for categorical data, ANOVA for continuous variables for normally distributed data and the Kruskal–Wallis test for nonnormally distributed data. Data were tested for normality by graphing them.

For each of the last 21 days of life, the intensity of breathlessness was compared between people with an AKPS ⩽40 on that day and those with higher functional status, and between people with underlying cardiorespiratory disease and those with other diseases. The secondary comparators were the trajectories of

TABLE 1 Characteristics of a consecutive cohort of people referred to a community palliative care service between January 2011 and December 2014 including diagnostic group, and breathlessness and functional scores

	No cardiorespiratory disease	Cardiorespiratory disease	Total
Subjects n	5114	1687	6801
Sex n (%)			
Male	2734 (53.46)	1017 (60.28)	3751 (55.2)
Female	2380 (46.54)	670 (39.72)	3050 (44.8)
Age at death years mean±SD	71.0±16.0	72.7±11.7[#]	71.5±15.1
Diagnosis n (%)			
Cardiorespiratory disease			
Primary lung cancer			1398 (20.6)
Respiratory failure			153 (2.3)
Cardiac failure			136 (2.00)
No documented cardiorespiratory disease			5114 (75.2)
Time from referral to death days median (IQR)	40 (78)	51 (84)[¶]	42 (79)
Observations per patient in the last week of life median (IQR)	7 (6)	6 (5)	7 (6)
Last measurement before death			
AKPS n (%)			
>40	544 (32.2)	1282 (25.1)	1826 (26.8)
⩽40	3831 (74.9)	1143 (67.7)	4974 (73.2)
Days median			
AKPS >40	8	7	1
AKPS ⩽40	0	0	
Breathlessness (0–10 NRS) median (IQR)	0 (4)	3 (4)[+]	1 (4)

IQR: interquartile range; AKPS: Australian-modified Karnofsky Performance Status; NRS: numerical rating scale. [#]: p=0.0001, the subgroup with documented cardiorespiratory disease was older than the subgroup without; [¶]: p=0.0001, the subgroup with documented cardiorespiratory disease had a longer length of time between referral and death; [+]: p=0.0001, the subgroup with documented cardiorespiratory disease experienced greater breathlessness.

breathlessness by 10-point AKPS (10, 20, 30 or 40) in the last 3 weeks of life, further stratified by the presence of cardiorespiratory disease. Lung cancer was included in the cardiorespiratory group.

The number of days from death was transformed into a three-point categorical variable with the last 7 days of data being included into week 1, week 2 including 8–14 days and week 3 including 15–21 days from death.

Factors related to change in breathlessness were analysed using mixed effects regression accounting for repeated measurements, adjusted for age, sex, carer status, length of stay (from referral to the service until death) and diagnostic group. Interaction terms between week from death and 1) AKPS, 2) cardiorespiratory diagnosis, and 3) both AKPS and cardiorespiratory diagnosis were evaluated by including interaction terms in the fully adjusted model. Mean differences in breathlessness intensity were presented with 95% confidence intervals. No missing data were imputed. Statistical significance was defined as a two-sided $p<0.05$. Data were analysed using Stata version 14.0 (StataCorp, College Station, TX, USA).

Ethical considerations

The study was approved by Silver Chain Human Research Ethics Committee. Given that these were aggregated, de-identified data, individual consent was not required. This paper is reported using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [19].

Results

In total, 6801 people were included in the analysis, generating 51 494 data-points in the last 21 days of life; 55.2% males, mean±SD age at death 71.5±15.1 years and mean±SD time from referral to death 78.4 ±107.1 days (table 1). Most people had cancers as their documented life-limiting illness (5114 out of 6801; 75.2%). Of the people who died, 26.8% (1826 out of 6801) had their last recorded AKPS >40. Similar numbers of assessments were carried out in the last week of life in those with and without cardiorespiratory disease, and the time from the last recorded clinical observation until death for each subpopulation was similar (table 1).

Breathlessness was higher in people with cardiorespiratory disease at all time-points. Breathlessness was also higher in people with better levels of function, and increased in intensity most markedly in people with cardiorespiratory disease and higher levels of function (figure 1). People with a cardiorespiratory life-limiting illness also had higher breathlessness intensity scores (adjusted mean 2.92 on a 0–10 NRS) than people with no documented cardiorespiratory diagnosis on each day (adjusted mean of 1.51; $p=0.0001$). This was seen in both AKPS groups ($p<0.001$ for each). This was seen in the AKPS strata

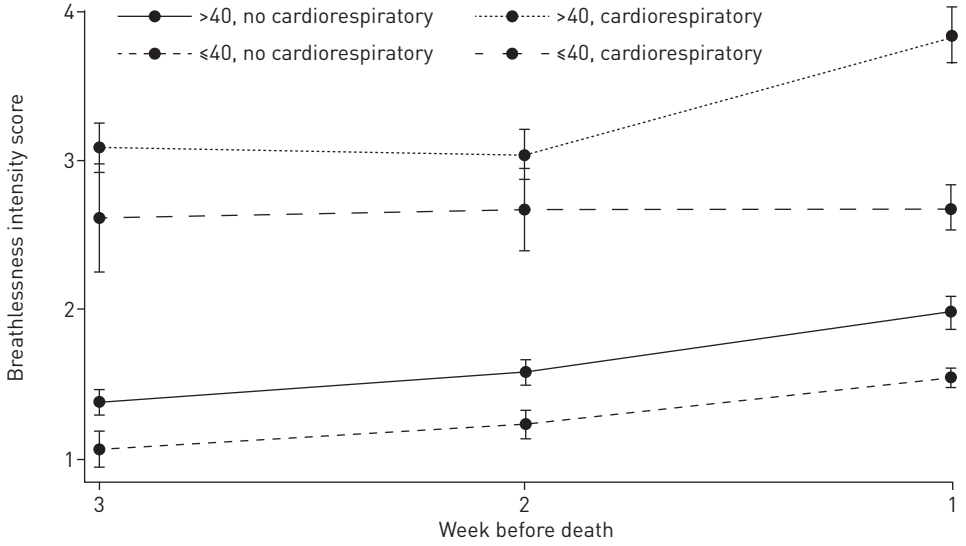

FIGURE 1 Adjusted mean breathlessness intensity scores on a 0–10 numerical rating scale in the 3 weeks before death by diagnosis (cardiorespiratory life-limiting illness or not) and functional status (≤40 or >40 using the Australia-modified Karnofsky Performance Status (AKPS) scale) having adjusted for age, sex and length of stay. 6768 clients with 48 385 observations. People with a cardiorespiratory life-limiting illness had higher breathlessness intensity scores (adjusted mean 2.92) than people with no documented cardiorespiratory diagnosis on each day (adjusted mean 1.51; $p=0.0001$). This was seen in both AKPS groups ($p<0.001$ for each).

dichotomised between 40 and 50 by diagnostic group (p<0.001 for each) (figure 1). These differences were clinically significant [20] (table 2). When split by cardiorespiratory status and AKPS 10, 20, 30 and ⩾40, similar patterns were seen (supplementary figure S1).

In the adjusted mixed effects regression model accounting for repeated measures and adjusting for the available factors, independent predictors of worsening breathlessness were proximity to death (0.6, 95% CI 0.49–0.72), cardiorespiratory disease (breathlessness was 1.72 points worse, 95% CI 1.53–1.90 points worse), while factors reducing the likelihood of breathlessness included poorer performance status (0.31, 95% CI 0.17–0.45) and being female (0.28, 95% CI 0.18–0.37). The relationship between breathlessness and a person's level of function remained significant in the mixed effects regression model when interaction terms (week×diagnosis; week×function; week×diagnosis×function) were added, with the only significant interaction term being diagnosis and function in the last week of life (p<0.0001), suggesting that in the last week, there is a real difference in trajectories between groups.

Discussion

This is the first study to stratify trajectories of breathlessness by functional status near death and whether the person has a cardiorespiratory life-limiting illness, extending previous analyses of breathlessness in the final weeks of life [7, 13]. The increase in breathlessness in the last 21 days of life is seen least in the numerically largest of four subgroups in the data, *i.e.* those with poorer levels of function and no documented cardiorespiratory disease. This group did not experience the same crescendo in breathlessness seen in the subgroup with better function and cardiorespiratory disease. Numerically, the smallest subgroup (*i.e.* those with better function and cardiorespiratory life-limiting illness) had the highest levels of breathlessness intensity across the last 21 days of life and experienced the largest absolute increase in breathlessness across that time.

Previous studies have reported that breathlessness increases as death approaches (along with fatigue), whereas other symptoms tend to decrease [7, 10, 13]. Importantly, in contrast to this new analysis, none of these studies adjusted for functional status. These three previous analyses adjusted for underlying life-limiting illnesses and defined higher levels of breathlessness in people with chronic respiratory disease. Bringing both factors into the current analysis sees the increase in breathlessness as death approaches disappear for the majority of patients, suggesting that the results of previous reports were being driven by increases seen in the breathlessness scores before their sudden death from this one subgroup, *i.e.* the

TABLE 2 Multivariate model of breathlessness in relation to time before death, diagnosis and function adjusted for confounders

	Coefficient (95% CI)	p-value >|z|
Breathlessness		
Week 3		
Week 2	0.203 (0.115–0.291)	<0.001
Week 1	0.607 (0.491–0.724)	<0.001
Age	0.001 (−0.002–0.005)	0.401
Length of stay	0.000 (−0.000–0.001)	0.240
Diagnosis		
No cardiorespiratory		
Cardiorespiratory	1.716 (1.529–1.904)	<0.001
AKPS		
>40		
⩽40	−0.314 (−0.453–−0.175)	<0.001
Sex		
Male		
Female	−0.275 (−0.371–−0.179)	<0.001
Interaction between week, functional status and cardiorespiratory diagnoses		
Week 3, ⩽40, cardiorespiratory	−0.147 (−0.547–0.252)	0.470
Week 2, ⩽40, cardiorespiratory	−0.015 (−0.329–0.299)	0.926
Week 1, ⩽40, cardiorespiratory	−0.711 (−0.956–−0.466)	<0.001

AKPS: Australia-modified Karnofsky Performance Status. Mixed effects linear regression model, accounting for repeated measurements and clustering over individuals; 48385 observations in 6768 patients with complete data on the model variables. Three interaction terms are included.

people with higher levels of function and documented cardiorespiratory disease. Previous data may therefore have been skewed across the population in the weeks leading up to death by the data from this new identifiable subgroup.

Chronic heart failure has a trajectory of acute exacerbations interspersed with periods of stability [21]. Recognition of worsening symptoms may allow intense support and recovery nearly to previous levels of function. In heart failure, as the disease severity worsens, death from progressive circulatory failure becomes relatively more common compared with sudden arrhythmic death [22]. This means that the predicted mode of death (sudden *versus* nonsudden) may change with advancing symptoms and signs of disease, and this helps better target interventions. For example, cardiac defibrillators are not recommended for patients with New York Heart Association class IV disease [23]. During these acute exacerbations or as a result of arrhythmias or infarction, a group of people with reasonable function died very rapidly.

Apparent "sudden" cardiac death may have premonitory symptoms, most commonly chest pain or breathlessness, even in younger, apparently fit people, or may be secondary to another terminal event [24, 25]. A cohort study of middle-aged people suffering out-of-hospital sudden cardiac arrest found that some had had symptoms not just in the preceding 24 h, but over the previous 4 weeks [26]. For this reason, information on events immediately surrounding death and in the weeks leading up to death will help in the future to better understand the disease trajectory and identify any opportunities to modify clinical care.

The worsening levels of breathlessness may represent events which could be treatable or, in the case of pulmonary emboli, preventable. Pulmonary emboli are reported in 50% of autopsies in patients with cancer yet it is unclear whether these represent the sole cause of death, a contributory pathology within the agonal process [27, 28] or a clinically incidental finding. Since 50% of hospice inpatients have evidence of asymptomatic deep vein thrombosis when sought [29], and hospice inpatients with a higher risk of venous thromboembolism (VTE) are more likely to have symptoms known to be related to VTE [30], it is reasonable to consider VTE as a potential contributory factor to worsening breathlessness in those who die from inanition and those with a higher AKPS who experience a "sudden death". Indeed, it has been demonstrated that fatal, apparently sudden, pulmonary emboli are rarely asymptomatic, and are dominated by tachycardia and breathlessness often with symptoms preceding death by days or weeks having been either ignored or misattributed [31]. People with incidentally diagnosed cancer-related VTE are often found on closer questioning to have had symptoms for some time [32, 33].

Mechanisms

The present findings confirm an increase in breathlessness intensity as death approaches, but the increase is more marked in people with cardiorespiratory disease and, then, those with better function. In this latter group, it is not apparent whether breathlessness intensity is a result of continued mobility, acute intercurrent pathology, faster progression of the person's primary condition or a mixture of all three. Acute pathology manifesting itself over several weeks is a likely contributor for many people given the magnitude of increase seen.

People with lung cancer form a substantial proportion of the group with cardiorespiratory disease and higher levels of function. By contrast, in the subgroup of people with better levels of function and no documented cardiorespiratory disease (composed almost entirely of people with cancer), the pattern of markedly worsening breathlessness is not seen in the week before death, raising the possibility that VTE with a prodrome of breathlessness is less likely to be a contributing factor to sudden death. Such hypotheses can only be tested in a bespoke, prospective, longitudinal study.

Strengths and limitations

This was a large, prospectively collected dataset used in clinical care, with low levels of missing data and an emphasis on patient-reported measures during clinical encounters. It has a large number of observations for each patient admitted to the service. The numbers of observations increase each week as death approaches.

As this study does not include people admitted to hospital for their terminal care, the overall levels of breathlessness intensity may be underestimated as people with conditions causing increasing breathlessness (*e.g.* acute coronary syndrome, arrhythmias, pulmonary embolism and acute lower respiratory tract infections) may be more likely to be admitted. Furthermore, breathlessness as a reason for admission to hospital was not available either from this dataset.

There are no data distinguishing between patient-reported measures and proxy measures. The latter are more likely to be needed in people with very poor levels of AKPS (10 or 20) and may underestimate the intensity of breathlessness, although some studies have found family and specialist palliative care staff proxy assessments are reasonably valid for breathlessness [34–37]. Whether breathlessness was occurring

at rest, on minimal exertion or, in the case of people with better functional status, on even greater levels of exertion cannot be derived from the available data.

Data on cause of death were not available and a clinical review of several thousand cases was beyond the scope of this current project. Likewise, given the documented inaccuracy of death certificates, these were not sought for this study [38].

A priori, the clinical categories were defined. Given the high correlation between prolonged exposure to tobacco, chronic obstructive pulmonary disease and lung cancer, it was decided to include primary (but not secondary) lung cancer in the group of patients with cardiorespiratory diseases.

Implications for clinical practice

In people with metastatic cancer, the cut-point of AKPS used in this study has prognostic significance. In one consecutive cohort, median survival in people with AKPS ⩽40 was 29 days compared with 146 days for those with AKPS >40 and poor physical wellbeing [39]. The sudden deaths described in this current analysis may therefore be a clinically important decrement in life expectancy, especially if potentially reversible causes can be identified. This may be of great importance to many patients.

There appears to be a warning of increasing breathlessness 7–9 days before death; for some patients, this is likely to allow for potentially reversible causes to be investigated and treated, if that were the patient's wish, or to support the patient and family in their preferred place of death. This study suggests that worsening breathlessness should alert clinicians to an increased likelihood of death in people with reasonable function in the setting of documented cardiorespiratory disease. For people with better functional status, this raises the question of whether there are reversible causes for both the symptom and for what may be a premature death in these circumstances. There appears to be a window for a clinical response to define potentially reversible factors.

In addition, this study is a reminder that some causes of sudden death may be preventable. The incidence of VTE increases with cancer progression and it remains the second most common cause of death associated with malignancy [27, 28, 40]. Despite national policies to implement VTE risk assessment and thromboprophylaxis of all people admitted to hospital, this has very low take-up in palliative care units [41]. Here, people with AKPS >40 may well be admitted for symptom management rather than end-of-life care, yet risk assessment for and thromboprophylaxis of VTE is not standard practice [41, 42]. Hospice and palliative care services should review their approach to risk assessment for VTE and thromboprophylaxis for those at higher risk.

Implications for future research

Future research should focus on whether any increase in breathlessness in people with a progressive, life-limiting disease has an underlying and potentially modifiable cause such as VTE, cardiac ischaemia, arrhythmia or infection. For example, previous work has suggested systematic underestimation of deep vein thromboses in this patient population [43].

The two trajectories that are identified in this study need to be documented with more clinical detail in a large, prospective, consecutive cohort study designed specifically to analyse these current findings. The first trajectory hypothesised is for people with an AKPS ⩽40 who appear to have an inexorable decline associated with lower levels of breathlessness and are more likely to be experiencing progressive cachexia. The second trajectory hypothesised may represent the relatively unexpected death of patients with better functional status preceding death and much higher levels of breathlessness. Acute events including infections, cardiac ischaemia, arrhythmias, pulmonary emboli or pericardial effusions, any of which may cause relatively acute worsening of breathlessness intensity in people with pre-existing cardiorespiratory disease, could help to explain the findings in this current study. If breathlessness in people with relatively good function and documented cardiorespiratory disease is a harbinger of impending death, this has significant clinical implications.

There will also need to be a larger cohort that includes inpatients and people who have presented to the emergency department to have a fuller picture of changes in breathlessness intensity by level of function at the end of life.

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