**Missed opportunity? Worsening breathlessness as a harbinger of death. A cohort study.**

David C. Currow1,2

Joanna M. Smith3

Phichai Chansriwong4

Simon I R Noble5

Theodora Nikolaidou2

Diana Ferreira6

Miriam J Johnson 2

Magnus Ekström1,7

1IMPACCT, Faculty of Health, University of Technology Sydney, Ultimo, NSW. Australia. 2007

2Wolfson Palliative Care Research Centre, Hull York Medical School, University of Hull. United Kingdom. HU6 7RX

3 Silver Chain Group, Perth, Western Australia

4Internal Medicine Department, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

5Marie Curie Palliative Care Research Group, Cardiff University, Cardiff, Wales, UK

6 Discipline, Palliative and Supportive Services, Flinders University, Adelaide, South Australia, Australia

7Department of Clinical Sciences, Division of Respiratory Medicine & Allergology, Lund University, Lund, Sweden

**Corresponding author:**

Prof David Currow

Faculty of Health

University of Technology Sydney

P O Box 123 Ultimo

New South Wales, Australia 2007 [david.currow@uts.edu.au](mailto:david.currow@uts.edu.au)

Word count (excluding abstract, references, tables and figures)

Abstract word count: 199

References 43

Tables and Figures 4

Take home message

People with reasonable function and heart/lung diseases are at risk of breathlessness, increasing at the end of life.

**ABSTRACT**

**Introduction:** To explore trajectories of breathlessness intensity by function and life-limiting illness diagnosis in the last 3 weeks of life in palliative care patients.

**Methods:** Prospective, consecutive cohort with point-of-care data of patients of Silver Chain Hospice Care 2011-2014 (n=4,638; 51,494 data points). Breathlessness intensity (0-10 Numerical Rating Scale (NRS)) and physical function (Australia-modified Karnofsky Performance Scale (AKPS)) were measured each visit. Time was anchored at death. Breathlessness trajectory was analysed by physical function and diagnosis using mixed effects regression.

**Results:** Mean age was 71.5 (SD 15.1) years; 55.2% males; most with cancer. The last recorded AKPS was >40 for 26.8%. Breathlessness was worst in people with cardio-respiratory 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).

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

**Introduction**

Chronic breathlessness affects one in eleven 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 and, 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 were 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 three 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, Western Australia providing care for approximately 2,800 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 hours/day, 7 days/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 7,896 patients seen by 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 6,801 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:
  + Demographic characteristics (age, gender, living arrangement, caregiver status, and place of death);
  + Dominant cause of life-limiting illness (cardio-respiratory diseases (primary lung cancer, respiratory disease, cardiac failure) and other); and
* Clinical data recorded at each clinical encounter:
* 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 (SAS) [17]; and
* Clinician-rated performance status using the Australia-modified Karnofsky Performance Scale (AKPS) 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]
* 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 one day. Frequency of visits tend to increase as time of death approaches but depends on the needs of the patients and their families.

Data quality was optimised by routine point-of-care data entry by SCHCH staff into mobile phone data systems for all fields relating to that clinical encounter.

*Statistical analyses*

## The cohort and service characteristics were reported using descriptive statistics and were compared using Chi square analyses for categorical data and analysis of variance for continuous variables for normally distributed data and Kruskal-Wallis test for non-normally 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 cardio-respiratory disease and those with other diseases. The secondary comparators were the trajectories of breathlessness by 10-point AKPS (10, 20, 30 or 40) in the last three weeks of life, further stratified by the presence of cardio-respiratory 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 seven days of data being included into week 1, week 2 including 8 to 14 days and week three including 15 to 21 days from death.

Factors related to change in breathlessness were analysed using mixed effects regression accounting for repeated measurements, adjusted for age, gender, 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 (CI). No missing data were imputed. Statistical significance was defined as a two-sided p<0.05. Data were analysed using Stata version 14.0 statistical analysis software (Stata Corporation, 2015, College Station, TX).

*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 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [19].

**RESULTS**

In total, 6,801 people were included in the analysis generating 51,494 data points in the last 21 days of life; 55.2% males, mean age at death 71.5 (SD 15.1) years, and mean time from referral to death 78.4 (SD 107.1) days (Table 1). Most people had cancers as their documented life-limiting illness (5,114/6801; 75.2%). Of the people who died, 26.8% (1826/6801) had their last recorded AKPS >40. Similar numbers of assessments were carried out in the last week of life in those with and without cardio-respiratory disease and the last recorded clinical observation for each sub-population in the same order of magnitude. (Table 1)

Breathlessness was higher in people with cardio-respiratory 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 cardio-respiratory disease and *higher* levels of function. (Figure 1) People with a cardio-respiratory life-limiting illness also had higher breathlessness intensity scores (adjusted mean 2.92 on a 0-10 NRS) than people with no documented cardio-respiratory 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 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 cardio-respiratory status and AKPS 10, 20, 30 and ≥40, similar patterns are seen. (Web appendix 1)

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% confidence interval (CI) 0.49,0.72), cardiorespiratory disease (breathlessness was 1.72 points worse; 95% CI 1.53, 1.90), while factors reducing the likelihood of breathlessness include 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 x diagnosis; week x function; week x diagnosis x 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 cardio-respiratory 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 sub-groups in the data: those with poorer levels of function and no documented cardio-respiratory disease. This group did not experience the same crescendo in breathlessness seen in the sub-group with better function and cardio-respiratory disease. Numerically, the smallest sub-group (better function, cardio-respiratory life-limiting illness) has 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 sub-group: the people with higher levels of function and documented cardio-respiratory 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 sub-group.

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 to sudden arrhythmic death. [22] This means that the predicted mode of death (sudden vs. non-sudden) 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 (NYHA) 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 hours, but over the previous 4 weeks. [26] For this reason, information on events immediately surrounding the death and in the weeks leading up to death will help in the future to understand better 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 (PE), 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 that hospice inpatients with a higher risk of venous thrombo-embolism (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, PE 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 cardio-respiratory 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 inter-current 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 cardio-respiratory disease and higher levels of function. By contrast, in the sub-group of people with better levels of function and no documented cardio-respiratory 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 under-estimated as people with conditions causing increasing breathlessness (acute coronary syndrome, arrhythmias, pulmonary embolism, acute lower respiratory tract infections) may be more likely to be admitted. Further, 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 under-estimate the intensity of breathlessness, although some studies have found family and specialist palliative care staff proxy assessments are reasonable 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 data 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 cardio-respiratory 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 well-being. [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 and, 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 cardio-respiratory 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 under-estimation 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, PE, or pericardial effusions, any of which may cause relatively acute worsening of breathlessness intensity in people with pre-existing cardio-respiratory 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.

**Acknowledgements**

Funding: This study drew on discretionary funding held by the researchers and staff positions. No external, competitive funding contributed to this study.

**References**

1. Currow DC, Plummer J, Crockett A, Abernethy AP. A community population survey of prevalence and severity of dyspnoea in adults*. J Pain Symptom Manage* 2009; 38(4): 533-545.

2. Johnson M, Bowden J, Abernethy AP, Currow DC. To what causes do people attribute their chronic breathlessness? A population survey. *J Palliat Med* 2012; 15(7): 744-750.

3. Currow DC, Clark K, Kamal A, Collier A, Agar MR, Lovell MR, Phillips JL, Ritchie C. The population burden of chronic symptoms that substantially predate the diagnosis of a life-limiting illness. *J Palliat Med* 2015; 18(6); 480-485.

4. Bailey PH. Death stories: acute exacerbations of chronic obstructive pulmonary disease. *Qual Health Res* 2001 May; 11(3): 322-338.

5. Gysels MH, Higginson IJ. The lived experience of breathlessness and its implications for care: a qualitative comparison in cancer, COPD, heart failure and MND. *BMC Palliat Care* 2011 Oct 17; 10(1): 15.

6. Herigstad M, Hayen A, Wiech K, Pattinson KT. [Dyspnoea and the brain.](https://www.ncbi.nlm.nih.gov/pubmed/21295457) *Respir Med* 2011; 105(6): 809-817.

7. Currow DC, Smith J, Davidson PM, Newton PJ, Agar MR, Abernethy AP. Do the trajectories of dyspnoea differ in prevalence and intensity by diagnosis at the end of life? A consecutive cohort study. *J Pain Symptom Manage* 2010; 39(4): 680-690.

8. Johnson MJ, Bland JM, Gahbauer E Gahbauer E, Ekström M, Sinnarajah A, Gill TM, Currow DC. Breathlessness in elderly adults during the last year of life sufficient to restrict activity. Prevalence, pattern, and associated factors. *J Am Geriatr Soc* 2016; 64(1): 73-80.

9. Ekström M, Vergo MT, Ahmadi Z, Currow DC. Prevalence of sudden death in palliative care: data from the Australian Palliative Care Outcomes Collaborative. *J Pain Symptom Manage* 2016; 52(2): 221-227.

10. Ekström M, Johnson MJ, Kaasa S, Jensen M, Schiöler L, Currow DC. Who experiences higher and increasing breathlessness in advanced cancer? The longitudinal EPCCS Study. *Support Care Cancer* 2016; 24(9): 3803-3811.

11. Seow H, Barbera L, Sutradhar R, Howell D, Dudgeon D, Atzema C, Liu Y, Husain A, Sussman J, Earle C. Trajectory of performance status and symptom scores for patients with cancer during the last six months of life. *J Clin Oncol* 2011; 29:1151–1158

12. Currow DC, Vergo ML, Ekstrom M. Sudden death in palliative care. *J Pain Symptom Manage* 2015; 50(3): e1-e2

13. Ekström PM, Allingham S, Eagar K, Yates P, Johnson C, Currow DC. Breathlessness during the last week of life in palliative care: an Australian prospective, longitudinal study. *J Pain Symptom Manage* 2016; 51(5): 816-823.

14. Currow DC, Agar M, Smith J, Abernethy AP. Does palliative home oxygen improve dyspnoea? A consecutive cohort study. *Palliat Med* 2009; 23(4): 309-316.

15. Currow DC, Christou T, Smith J, Carmody S, Lewin G, Aoun S, Abernethy AP. Do terminally ill people who live alone miss out on home oxygen treatment? An hypothesis generating study? *J Pall Med* 2008;11(7):1015-1022.

16. Currow DC, Abernethy AP, Fazekas BS. Specialist palliative care needs of whole populations. A feasibility study using a novel approach. *Palliat Med* 2004; 18(3): 239-247.

17. Kristjanson L, Pickstock S, Yuen K, Davis S, Blight J, Cummings A, Oldham L, Cousins K, Webster J, Dean A: Development and testing of the revised Symptom Assessment Scale (Final Report). Perth: Edith Cowan University, 1999.

18. Abernethy AP, Shelby-James T, Fazekas BS, Woods D, Currow DC. The Australia-modified Karnofsky Performance Status (AKPS) scale: a revised scale for contemporary palliative care clinical practice [ISRCTN81117481]. *BMC Palliat Care* 2005 Nov 12;4:7.

19. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative . The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Prev Med*. 2007; 45(4): 247-51.

20. Johnson MJ, Bland JM, Oxberry SG, Abernethy AP, Currow DC. Clinically important differences in the intensity of chronic refractory breathlessness. *J Pain Symptom Manage* 2013; 46(6): 957-963.

21. Goodlin SJ, Hauptman PJ, Arnold R, Grady K, Hershberger RE, Kutner J,  [Masoudi F](https://www.ncbi.nlm.nih.gov/pubmed/?term=Masoudi%20F%5BAuthor%5D&cauthor=true&cauthor_uid=15190529), [Spertus J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Spertus%20J%5BAuthor%5D&cauthor=true&cauthor_uid=15190529), [Dracup K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Dracup%20K%5BAuthor%5D&cauthor=true&cauthor_uid=15190529), [Cleary JF](https://www.ncbi.nlm.nih.gov/pubmed/?term=Cleary%20JF%5BAuthor%5D&cauthor=true&cauthor_uid=15190529), [Medak R](https://www.ncbi.nlm.nih.gov/pubmed/?term=Medak%20R%5BAuthor%5D&cauthor=true&cauthor_uid=15190529), [Crispell K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Crispell%20K%5BAuthor%5D&cauthor=true&cauthor_uid=15190529), [Piña I](https://www.ncbi.nlm.nih.gov/pubmed/?term=Pi%C3%B1a%20I%5BAuthor%5D&cauthor=true&cauthor_uid=15190529), [Stuart B](https://www.ncbi.nlm.nih.gov/pubmed/?term=Stuart%20B%5BAuthor%5D&cauthor=true&cauthor_uid=15190529), [Whitney C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Whitney%20C%5BAuthor%5D&cauthor=true&cauthor_uid=15190529), [Rector T](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rector%20T%5BAuthor%5D&cauthor=true&cauthor_uid=15190529), [Teno J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Teno%20J%5BAuthor%5D&cauthor=true&cauthor_uid=15190529), [Renlund DG](https://www.ncbi.nlm.nih.gov/pubmed/?term=Renlund%20DG%5BAuthor%5D&cauthor=true&cauthor_uid=15190529). Consensus statement: palliative and supportive care in advanced heart failure. *J Card Fail* 2004; 10(3): 200-209.

22. No authors listed - Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999 Jun 12; 353(9169): 2001-2007.

23. Implantable cardioverter defibrillators and cardiac resynchronisation therapy for arrhythmias and heart failure <https://www.nice.org.uk/guidance/ta314/chapter/1-guidance> [accessed 16 November 2017]

24. Pratt CM, Greenway PS, Schoenfeld MH, Hibben ML, Reiffel JA. Exploration of the precision of classifying sudden cardiac death. Implications for the interpretation of clinical trials. *Circulation* 1996; 93: 519 - 24

25. Kinch Westerdahl A, Sjöblom J, Mattiasson AC, Rosenqvist M, Frykman V. Implantable cardioverter-defibrillator therapy before death: high risk for painful shocks at end of life. *Circulation* 2014; 129(4): 422-429.

26. [Marijon E](https://www.ncbi.nlm.nih.gov/pubmed/?term=Marijon%20E%5BAuthor%5D&cauthor=true&cauthor_uid=26720493), [Uy-Evanado A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Uy-Evanado%20A%5BAuthor%5D&cauthor=true&cauthor_uid=26720493), [Dumas F](https://www.ncbi.nlm.nih.gov/pubmed/?term=Dumas%20F%5BAuthor%5D&cauthor=true&cauthor_uid=26720493), [Karam N](https://www.ncbi.nlm.nih.gov/pubmed/?term=Karam%20N%5BAuthor%5D&cauthor=true&cauthor_uid=26720493), [Reinier K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Reinier%20K%5BAuthor%5D&cauthor=true&cauthor_uid=26720493), [Teodorescu C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Teodorescu%20C%5BAuthor%5D&cauthor=true&cauthor_uid=26720493), [Narayanan K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Narayanan%20K%5BAuthor%5D&cauthor=true&cauthor_uid=26720493), [Gunson K](https://www.ncbi.nlm.nih.gov/pubmed/?term=Gunson%20K%5BAuthor%5D&cauthor=true&cauthor_uid=26720493), [Jui J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Jui%20J%5BAuthor%5D&cauthor=true&cauthor_uid=26720493), [Jouven X](https://www.ncbi.nlm.nih.gov/pubmed/?term=Jouven%20X%5BAuthor%5D&cauthor=true&cauthor_uid=26720493), [Chugh SS](https://www.ncbi.nlm.nih.gov/pubmed/?term=Chugh%20SS%5BAuthor%5D&cauthor=true&cauthor_uid=26720493). Warning Symptoms Are Associated With Survival From Sudden Cardiac Arrest. [*Ann Intern Med*.](https://www.ncbi.nlm.nih.gov/pubmed/26720493) 2016 Jan 5; 164(1): 23-29.

27. Sproul EE. Carcinoma and venous thrombosis: the frequency of association of carcinoma in the body or tail of the pancreas with multiple venous thrombosis. *Am J Cancer* 1938; 34: 566–85.

28. Ambrus JL, Ambrus CM, Mink IB, Pickren JW. Causes of death in cancer patients. *J Med* 1975; 6: 61–64.

29. Johnson MJ, Sproule MW, Paul J. The prevalence and associated variables of deep venous thrombosis in patients with advanced cancer? – prevalence and associated variables. *Clin Oncol* 1999; 11(2): 105–110.

30. Johnson MJ, B McMillan, C Fairhurst, R Gabe, J Ward, J Wiseman, B Pollington, S Noble. Primary Thromboprophylaxis in Hospices: The association between risk of venous thromboembolism and development of symptoms. *J Pain Symptom Manage* 2014; 48(1); 56-64

31. Havig O. Deep vein thrombosis and pulmonary embolism. An autopsy study with multiple regression analysis of possible risk factors. *Acta Chir Scand* Suppl. 1977; 478: 1-120.

32. Cronin CG, Lohan DG, Keane M,  [Roche C](https://www.ncbi.nlm.nih.gov/pubmed/?term=Roche%20C%5BAuthor%5D&cauthor=true&cauthor_uid=17579167), [Murphy JM](https://www.ncbi.nlm.nih.gov/pubmed/?term=Murphy%20JM%5BAuthor%5D&cauthor=true&cauthor_uid=17579167). Prevalence and significance of asymptomatic venous thromboembolic disease found on oncologic staging CT. *AJR Am J Roentgenol* 2007; 189: 162-170.

33. van Es N, Bleker SM, Di Nisio M. Cancer-associated unsuspected pulmonary embolism. *Thromb Res* 2014; 133 Suppl 2: S172-178.

34. Higginson I, Priest P, McCarthy M. Are bereaved family members a valid proxy for a patient's assessment of dying? *Soc Sci Med* 1994; 38(4): 553-557.

35. Quinn C, Dunbar SB, Higgins M. Heart failure symptom assessment and management: can caregivers serve as proxy? *J Cardiovasc Nurs* 2010; 25(2): 142-148.

36. Moody JE, McMillan S. Dyspnea and quality of life indicators in hospice patients and their caregivers. *Health Qual Life Outcomes* 2003, 1:9

37. Simon ST, Altfelder N, Alt-epping B, Bausewein C, Weingärtner V. Is breathlessness what the professional says it is? Analysis of patient and professionals’ assessments from a German nationwide register. *Support Care Cancer* 2014; 22.7:1825-1832.

38. Johansson LA, Westerling R. certificates: implications for mortality statistics. *Int J Epidemiol* 2000; 29(3): 495-502.

39. Hwang SS, Scott CB, Chang VT, Cogswell J, Srinivas S, Kasimis B. Prediction of survival for advanced cancer patients by recursive partitioning analysis: role of Karnofsky performance status, quality of life, and symptom distress. *Cancer Invest* 2004; 22(5): 678-687.

40. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA* 2005; 293: 715-722.

41. ISTH Steering Committee for World Thrombosis Day. Venous thromboembolism: A Call for risk assessment in all hospitalised patients. *Thromb Haemost* 2016; 116(5): 777-779.

42. Noble S, Finlay IG. Have Palliative Care Teams’ attitudes to venous thromboembolism changed? A survey of thromboprophylaxis practice across British Specialist Palliative Care Units in the years 2000 and 2005. *J Pain Symptom Manage* 2006 Jul; 32(1): 38-43.

43. Noble S, Nelson A, Finlay IG. Factors influencing hospice thromboprophylaxis policy: a qualitative study. *Palliat Med* 2008; 22(7): 808-813.

**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. (n=6801)**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | | |  | | | **Population** | | | |
|  | | |  | | **Non-cardio-respiratory disease**  **n = 5,114** | | **Cardio-respiratory disease**  **n = 1,687** | **Total**  **n = 6,801** |
| **Factor** | Sex | | Male | n (%) | 2,734 (53.46) | | 1,017 (60.28) | 3,751 (55.2) |
| Female | 2,380 (46.54) | | 670 (39.72) | 3,050 (44.8) |
| Age at death (years) | | Mean (SD) | | 71.0 (16.0) | | \*72.7 (11.7) | 71.5 (15.1) |
| Diagnosis n (%) | | Cardio-respiratory disease | | Primary lung cancer | | | 1,398 (20.6) |
| Respiratory failure | | | 153 (2.3) |
| Cardiac failure | | | 136 (2.00) |
| No documented cardio-respiratory disease | | | | | 5,114 (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 | Days | Median | >40 | (8 | | 7 | 1 |
| ≤40 | 0 | | 0 |
| Breathlessness (0-10 NRS) | Median (IQR) | | 0 (4) | | \*\*3 (4) | 1 (4) |
| AKPS (n%) | >40 | | 544 (32.2) | | 1,282 (25.1) | 1,826 (26.8) |
| ≤40 | | 3,831 (74.9) | | 1,143 (67.7) | 4,974 (73.2) |

\*p=0.0001 – the sub-group with documented cardio-respiratory disease were older than those without.

\*\*p=0.0001 – the sub-group with documented cardio-respiratory disease have a longer length of time between referral and death

\*\*p=0.0001 the sub-group with documented cardio-respiratory disease experience greater breathlessness

**AKPS** Australian-modified Karnofsky performance status; **SD** standard deviation; **NRS** numerical rating scale; **IQR** inter-quartile range

**Table 2: Multivariable model of breathlessness in relation to time before death, diagnosis and function adjusted for confounders.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Breathlessness | Coefficient | p >|z| | 95% Confidence Interval | |
| Week 3 |  | | | |
| Week 2 | 0.203027 | <0.001 | 0.11492 | 0.291135 |
| Week 1 | 0.607341 | <0.001 | 0.490567 | 0.724115 |
|  |  |  |  |  |
| Age | 0.001382 | 0.401 | -0.00184 | 0.004608 |
| Length of Stay | 0.000298 | 0.240 | -0.0002 | 0.000796 |
|  |  |  |  |  |
| Non-Cardiorespiratory Diagnosis |  | | | |
| Cardiorespiratory | 1.716373 | <0.001 | 1.528672 | 1.904075 |
|  |  |  |  |  |
| Karnofsky >40 |  | | | |
| <=40 | -0.31377 | <0.001 | -0.45288 | -0.17466 |
|  |  |  |  |  |
| Male |  | | | |
| Female | -0.27498 | <0.001 | -0.37145 | -0.17852 |
|  |  |  |  |  |
| Interaction between week, functional status and cardiorespiratory diagnoses |  | | | |
| Week 3#<=40#Cardiorespiratory | -0.14737 | 0.470 | -0.54713 | 0.252387 |
| Week 2#<=40#Cardiorespiratory | -0.01479 | 0.926 | -0.32852 | 0.298939 |
| Week 1#<=40#Cardiorespiratory | -0.71082 | <0.001 | -0.956 | -0.46564 |

Mixed effects linear regression model, accounting for repeated measurements and clustering over individuals; 48,385 observations in 6,768 patients with complete data on the model variables. Three interaction terms are included.