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The level of distress from fatigue reported in the final two months of life by a palliative care population; An Australian national prospective, consecutive case series

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Abstract

Context: Fatigue is the most commonly reported symptom in life-limiting illnesses, though not much is known about the distress it causes patients as they approach death.

Objectives: To map the trajectory of distress from fatigue reported by an Australian palliative care population in the last 60 days leading up to death.

Methods: A prospective, longitudinal, consecutive cohort study using national data from the Australian Palliative Care Outcomes Collaboration between 1 July 2013 and 31 December 2018. Patients were included if they had at least one measurement of fatigue on a 0-10 numerical rating scale in the 60 days before death. Descriptive statistics were used to analyse patients by diagnostic cohort and functional status.

Results: A total of 116,604 patients from 203 specialist palliative care services were analysed, providing 501,104 data points. Distress from fatigue affected up to 80% of patients referred to palliative care, with the majority experiencing moderate or severe distress. Malignant and non-malignant diagnoses were equally affected, with the neurological cohort showing the greatest variability. The degree of distress correlated with a patient's functional level; it worsened as a patient's function declined until a patient became bedbound when the reporting of distress reduced.

Conclusions: Distress from fatigue is high in this cohort of patients. Interventions to reduce this distress need to be a research priority.

Key Message: This article describes a prospective, longitudinal, consecutive cohort study exploring distress from fatigue in the last two months of life in a palliative care population. Results indicate that the majority of patients experience moderate or severe distress. Interventions to minimise distress need to be prioritised early in the disease trajectory.

Key words: palliative care, fatigue, consecutive cohort study, end of life care, symptom intensity

Running Title: Fatigue in the last two months of life

Introduction

Fatigue is reported as being one of the most prevalent and distressing symptoms encountered by people with life-limiting illnesses. It affects more than 80% of patients, equally affecting those with cancer diagnoses as those with other progressive, life-limiting non-cancer diagnoses, such as multiple sclerosis (MS), chronic renal failure and chronic lung disease[1]. There is no consensus definition, but it is a multi-dimensional issue affecting physical, social, emotional and cognitive functioning. Key factors are that it is subjective, persistent, and may cause significant distress and interference in usual functioning[2]. It is often described as a feeling of tiredness, weakness or lack of energy not relieved by rest, late in the course of a life-limiting illness[1].

Fatigue is frequently under-recognised, and significantly impacts on a patient's quality of life, independence and dignity[1-4]. Even when adequately recognised, late in the course of a life-limiting illness, little can be done to reduce the symptom and its impact on the activities of daily living. It remains a very challenging symptom to manage effectively. Current literature suggests that a multi-modal, multi-disciplinary intervention is most promising[1-2,5]. This type of intervention would include education, an individual exercise program, cognitive behavioural therapy (CBT), and energy conservation and restoration strategies, such as sleep and nutrition counselling[2]. Pharmacological interventions are generally not recommended. A Cochrane systematic review by Mucke et al of 45 studies including both malignant and non-malignant diagnoses concluded that there was insufficient evidence to support the use of medications to treat fatigue in palliative care patients, although there was slightly superior effect of methylphenidate when compared to placebo in cancer-related fatigue[6]. In clinical practice, all interventions are inconsistently implemented and, as a result, distress from fatigue remains high[7]. This high distress level is in part due to a lack of appropriate interventions[7]. There is also limited evidence of efficacy late in a patients' illness; although studies have recruited patients with metastatic disease, they are those with a much higher level of functioning than many palliative care patients.

Little is currently known about the patterns of fatigue experienced by patients at the very end of life, especially with prospectively collected data. It is hoped that by exploring the trajectory in different disease groups, we will more effectively be able to research interventions that may be of benefit and reduce distress from fatigue. Most studies to date have focused on patients primarily receiving chemotherapy or radiotherapy, or the cancer survivor population[8-10].

The aim of this study was to describe the patterns of distress from fatigue in the last 60 days of life in an Australian palliative care population, while comparing underlying diagnoses, with the aim to identify any sub-populations that may be at particular risk of more prevalent or more severe fatigue.

Methods

Study design and population:

The study used prospectively collected data from a consecutive cohort of patients who died in the care of all Australian specialist palliative care services participating in the Palliative Care Outcomes Collaboration (PCOC) between 1 July 2013 and 31 December 2018. The time point of death was used as an anchor and data from the preceding 60 days were analysed. All clinical assessments for the patients were obtained from the information held in the PCOC national longitudinal database by services who saw that patient. Where possible, additional information was added for persons cared for by multiple palliative care services using a statistical linkage key in combination with the person's residential postcode.

Data collection:

Services participating in PCOC (inpatient (direct care, consultative) and community (home, outpatient clinic, residential aged care facility)) provided data on each patient, including demographic information, underlying disease and setting(s) of care. Each patient was assessed using standardised and validated clinical assessment tools including:

- Australia-modified Karnofsky Performance Status (AKPS); an 11-point ordinal measure of patients' function and ability to perform ordinary tasks (10 = comatose or barely rousable, 100 = normal function)[11].
- Symptom Assessment Scale (SAS); a measure of the severity of distress from each of seven common symptoms over the previous 24 hours (not the severity of each symptom). It uses a numerical rating scale (NRS) of 0 ('absent or no distress') to 10 ('worst possible distress') which is completed by either the patient or by proxy (family member/carer or health care professional)[12].
- Palliative Care Phase (hereafter phase); defines four clinically relevant categories that describe each patient's palliative care stage of illness: stable, unstable, deteriorating, and terminal. A new phase was assigned whenever a clinical change required patient/family reassessment or modification of the care plan[13].

Clinical assessments were reported to PCOC at the beginning of care, at each change in phase and upon discharge from the service (or change in setting of care). Clinical assessments were not reported at the point of death.

Statistical analyses:

The primary outcome was patient-reported distress from fatigue in the 60 days prior to death. All assessments for all patients were included to ensure that no diagnoses were over- or under-reported. Descriptive statistics were reported for patients by diagnostic cohort (cancer, end stage organ failure, neurological conditions and all other conditions) to examine the differences by diagnosis and also for the whole cohort. Data was analysed using average SAS score and percentages of distress categories; no distress (SAS score 0), mild distress (SAS score 1-3), moderate distress (SAS score 4-7), and severe distress (SAS score 8-10). This data was presented graphically. The average SAS score for the last 60 days prior to death for each diagnosis category was analysed visually using Loess smoothing. Distress categories were also compared to the patients' level of functioning using AKPS.

Ethical considerations:
PCOC has been approved by the Human Research Ethics Committee of the University of Wollongong (approval ID: HE2006/045). Data collection was of routine, de-identified, aggregated clinical data and individual consent was not required.

Results

We included 116,604 patients from 203 specialist palliative care services across Australia providing 501,104 data points in the final sixty days of life (Table 1). Of these, 91.7% had valid fatigue scores. The frequency of assessments increased two weeks prior to death, which represents a period when patients require more frequent palliative care involvement generating more frequent assessments (Figure 1).

Females accounted for 46.2% of the population, and 64% were born in Australia with 69.4% being English speaking (Table 2). The average age at death was 74 years, and the majority of patients died in hospital (71.9%), while 19.6% died at home and 6.6% in residential aged care facilities. Compared to other disease cohorts, patients with end-stage liver disease had a smaller proportion of female patients (31.3%, P <0.0001) and younger average age at death (65.8 years, P <0.0001).

Cancer represented the most prevalent diagnosis (n = 85,048, 72.9%) and of these patients, lung (18.2%), colorectal (9.7%) and other gastrointestinal cancers (7.9%) had the greatest number of valid fatigue assessments (Table 3). Neurological disorders were the most prevalent non-malignant condition (n = 8,841, 7.6%).

Distress from fatigue affected up to 80% of all palliative care patients in this cohort to some degree in the last sixty days of life, with the majority reporting moderate or severe distress from fatigue (Figure 2). Patients with cancer, end-stage organ failure and all other diagnoses reported similar levels of distress throughout their disease trajectory, noting a reduction in the frequency of reporting in the last 5 days of life. Distress from fatigue is reported as affecting a lower proportion of the cohort with neurological disorders compared to other diagnoses and shows the greatest variability of reported distress over the disease trajectory. The frequency of reporting decreased earlier in this sub-group at about 14 days before death (Figure 2c).

The average daily SAS scores reported for distress from fatigue were constant for all disease cohorts up until 10 days prior to death, when they reduced. The reported scores were similar across all of the sub-groups: patients with cancer or end-stage cardiac or respiratory disease failure reported the highest SAS scores (3-4) although this was not significantly higher than other sub-groups (scores 2-3). Neurological conditions reported the lowest average daily SAS scores (Figure 3).

Patients' reported distress from fatigue was cross-tabulated with the clinician-rated level of function (Figure 4). Patients with an AKPS of 100 (normal function) reported significantly less distress from fatigue than patients with lower AKPS scores. As a person's level of function declined, their distress from fatigue increased. The highest proportion of patients reporting any level of distress had an AKPS of 70 ('cares for self, unable to carry on normal activity or do active work') – the level below which requires additional support for the activities of daily living from other people; over 80% reported some level of distress. Patients with AKPS 30-50 had the highest levels of moderate or severe distress from fatigue, with those with an AKPS of 30 ('almost completely bedfast)' having the highest proportion of severe distress. When a patient became completely bedfast however (AKPS 10-20) reports of fatigue considerably reduce to approximately 40% for AKPS 20 and 10% for AKPS 10.

Discussion

Main findings:

This is the largest study that has focussed specifically on fatigue at the end of life with prospectively collected data in the palliative population, including those with non-malignant diagnoses which are less frequently reported. Although it is accepted that fatigue is a significant issue, the results confirm that fatigue equally affects patients with malignant and non-malignant diagnoses, the majority experiencing moderate or severe distress from this symptom at the end of life. This finding is important, as patients with end-stage cardiac, respiratory or renal diseases are less frequently included in the research of fatigue or interventions to try to address this symptom than patients with cancer [14-15]. It emphasises the need to screen all palliative care patients for fatigue regardless of diagnosis and ensure that all cohorts have equal access to multi-disciplinary interventions.

Reported distress from fatigue reduces in the last days before death. This decrease can be seen when correlated to the patients AKPS; when bedbound, distress from fatigue is reported significantly less (approximately 10% reporting compared to the 80% reporting when AKPS >30). It is important to acknowledge that patients' distress from fatigue is being considered, not the severity of fatigue, and that fatigue will have different meanings to different individuals across their disease trajectory. A patient's experience of fatigue has strong correlations with mood disturbance, psychological distress and quality of life, and it is recommended that the recording of fatigue levels occurs concurrently with the measurement of psychological symptoms[16-17]. Symptom distress scales are not clearly differentiated from, or validated against symptom severity or intensity scales, but there is evidence to support a correlation between fatigue severity and psychological distress[18] and in some scenarios symptom distress scales are often defined as measures of symptom severity[19]. The selection of the fatigue distress scales was a pragmatic decision based on the established measures within PCOC (the SAS score). However, the results of this study and understanding the personal meaning of fatigue and the influencing psychological factors are important considerations in clinical practice and future studies.

Acknowledging that all palliative care patients experience some level of distress from fatigue is not a new phenomenon and it is well recognised in current literature[1-2] and is supported by this study. What is less well understood is how it changes as death approaches. Patients' responses to fatigue changes at the end of life as they not only adapt their priorities, but as their physical abilities change. When fatigue becomes all consuming, patient goals are redefined as they adapt to their physical decline. Complex activities cease first, and over time assistance is needed with all activities, inducing constant feelings of frustration and guilt[20]. Lundh Haglein *et al* reported that all dimensions of fatigue worsen towards death, reaching statistical significance at two weeks pre-death compared to four months, but that the association between fatigue and quality of life/emotional functioning decreases. They hypothesised that this 'response shift' or change in internal values and priorities, was adaption to the situation to serve as protection from suffering[16]. An expert working group for the European Association for Palliative Care (EAPC) agrees that fatigue in the terminal phase is considered acceptable as it offers shielding and protection from patient suffering. They recommend ceasing fatigue interventions at this stage, allowing weakness and sedation, to minimise patient distress[1]. Our results are congruent with these hypotheses of a 'protective mechanism', as reported distress from fatigue increases as a patient's function worsens, with a peak as they become bedbound, before reducing in all cohorts at about 5-10 days pre-death.

Of patients with non-malignant diagnoses, neurological conditions have the greatest variability in reports of distress from fatigue. The cause of this is uncertain but it is hypothesised that due to the underlying nature of their condition, patients' perception of fatigue and/or their ability to recollect/report distress may be affected (such as patients with cognitive impairment or those with aphasia after a stroke). Certain conditions that we know are significantly affected by fatigue, are also likely to have been underrepresented in this study population, such as MS and Parkinsons disease, as they are less frequently referred to palliative care services due to the perception that they are chronic conditions[21].

It should be noted that the daily average SAS score for distress from fatigue (Figure 3) is reported as 4 or less. The remaining data confirms however, that distress from fatigue affects up to 80% of this large palliative care population, and up to 10% have severe distress from fatigue. The overall daily mean therefore likely has a wide distribution. We hypothesise that a patient's current function causes the greatest impact on this difference, as when patients are stratified by functional level, their distress increases to nearly 20% at AKPS 30.

Those patients with an AKPS 30-50 have the highest distress scores from fatigue, but given their frailty, any intervention should be initiated prior to this, before their distress levels escalate and whilst they are well enough to engage. Current guidelines suggest that patients with high fatigue levels have a multi-disciplinary review including a full medical assessment to screen for potential reversible contributors, before initiating fatigue specific interventions such as education, an individualised exercise program, CBT, nutrition counselling and energy conservation strategies[5,22]. The patients' current stage of illness and treatment goals will influence how intensively these guidelines are followed.

The need to intervene at a meaningful time point before death, before distress from fatigue is severe and when the patient is physically and cognitively capable of participating in interventions, is also supported by other literature. Later interventions may not be feasible, nor make a comparatively meaningful difference to patient outcomes. A study by Stukenborg *et al* showed that patients with higher patient-reported fatigue scores (in the cancer population) have a clinically meaningful absolute difference in the probability of poor survival at 6 and 12 months, compared to those with lower scores[23]. It is also recognised that a patient's AKPS worsens as death approaches and in the cancer population, Morgan *et al* identified that there is a significant change from 43 days before death (when the AKPS reduces from 50). This pattern can also be seen in patients with organ failure, the exception being those with neurological conditions and dementia, where functional decline is over a longer time period[24]. This finding emphasises the need to anticipate significant fatigue and intervene before patients report high distress scores, and before their AKPS falls below 50. After this time point, their prognosis may be sufficiently poor and their function so low that intervention is considered clinically inappropriate[1]. Our data supports that clinically significant fatigue should be anticipated in all disease groups, and so therefore be managed universally in the palliative care population.

Strengths and limitations:
The strengths of this study include that these are prospectively collected data in a large, national, multi-centre cohort at multiple time points for each patient using validated tools[11-13]. Limitations include confounding factors or secondary causes of fatigue that might have influenced reporting, such as concurrent treatments or medications, mood disturbances or other symptoms on which data was not collected. PCOC data also has limitations, including proxy reporting (without being able to codify when proxy reporting occurs). Fatigue is a symptom where proxy report is likely to significantly understate the impact that patients themselves perceive[25-27]. By definition, this data only includes patients receiving specialist palliative care; you might expect that their scores would be different/worse without this input. SAS scores use distress from fatigue and not all patients may have understood or been aware of this and so may in some circumstances reported severity of fatigue and not distress.

Implications for research and clinical practice:
The outcomes support the need to optimise fatigue assessment in all palliative care patients, including patients with diagnoses other than cancer, as it causes a high level of distress in a significant proportion. It is important that we consider the implications to the individual across the disease trajectory, including examining what fatigue means to patients as they get closer to death to better understand why distress levels decrease at this time. Fatigue interventions ideally need to be considered early (i.e. prior to a change in patients normal functioning) to prevent it becoming such a distressing symptom (or at least slow the rate of change) before it is an irreversible issue prior to imminent death. If this is not possible, we also need to consider interventions that could be applied later in the disease trajectory. Given the paucity of evidence on the best interventions for fatigue management for patients with palliative care needs, future research needs to target this.

Conclusions

This study revealed that in the last 60 days of life most palliative patients will experience moderate to severe distress related to their fatigue. Patients with both malignant and non-malignant diagnoses are equally affected by distress from fatigue, however the neurological sub-group reported the most variability in levels of distress. As a patient's function declines, distress from fatigue increases until the time point when they are totally bedfast when the reporting of distress from fatigue decreases. The study highlights the importance of assessing fatigue early and developing fatigue interventions that could be offered earlier in the disease trajectory to reduce distress later on; evaluating the efficacy of these interventions in future controlled studies needs to be prioritised.

Competing interests: The authors declare no competing interests

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Figure 1 Number of assessments by day as death approaches

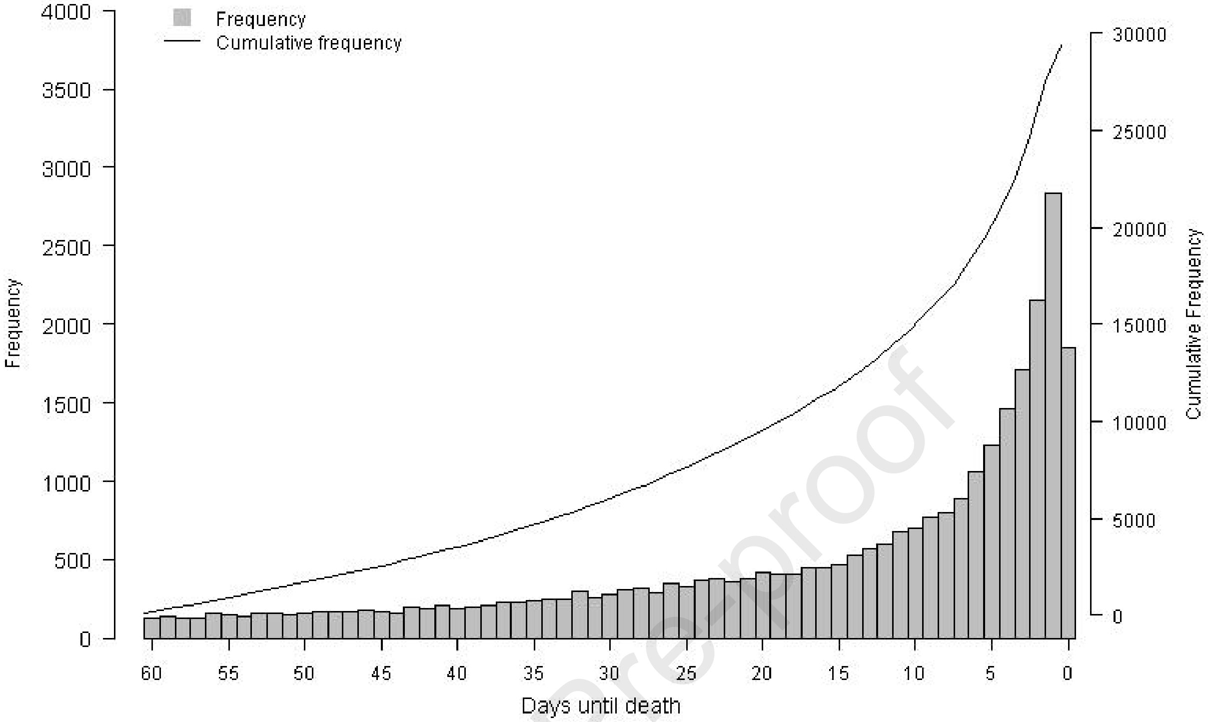
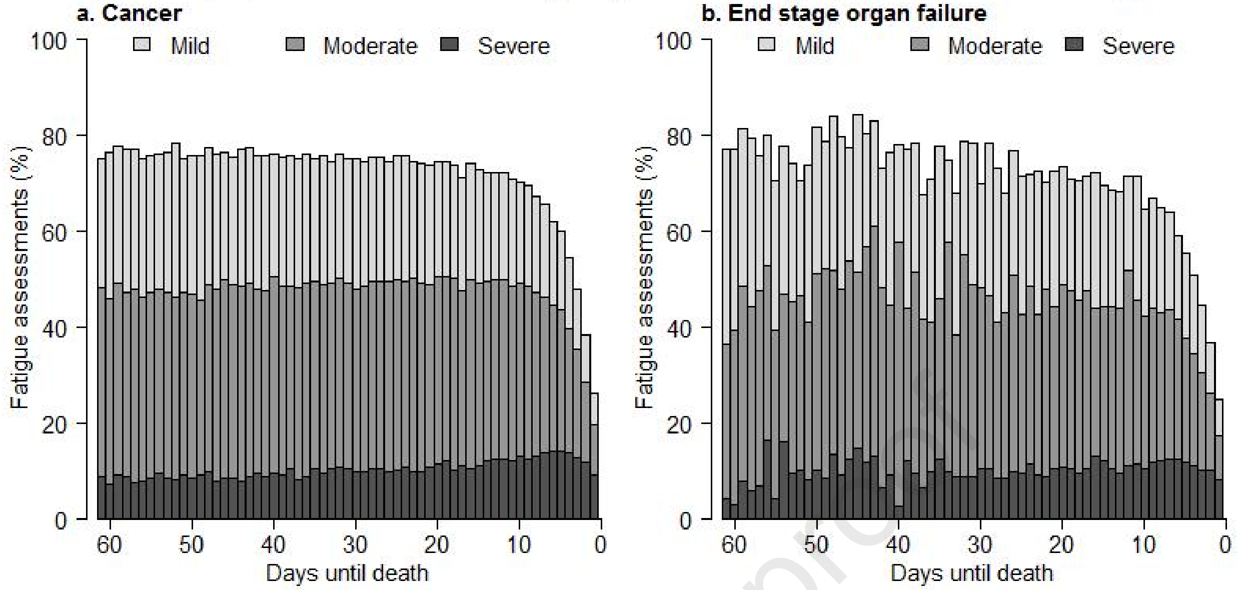
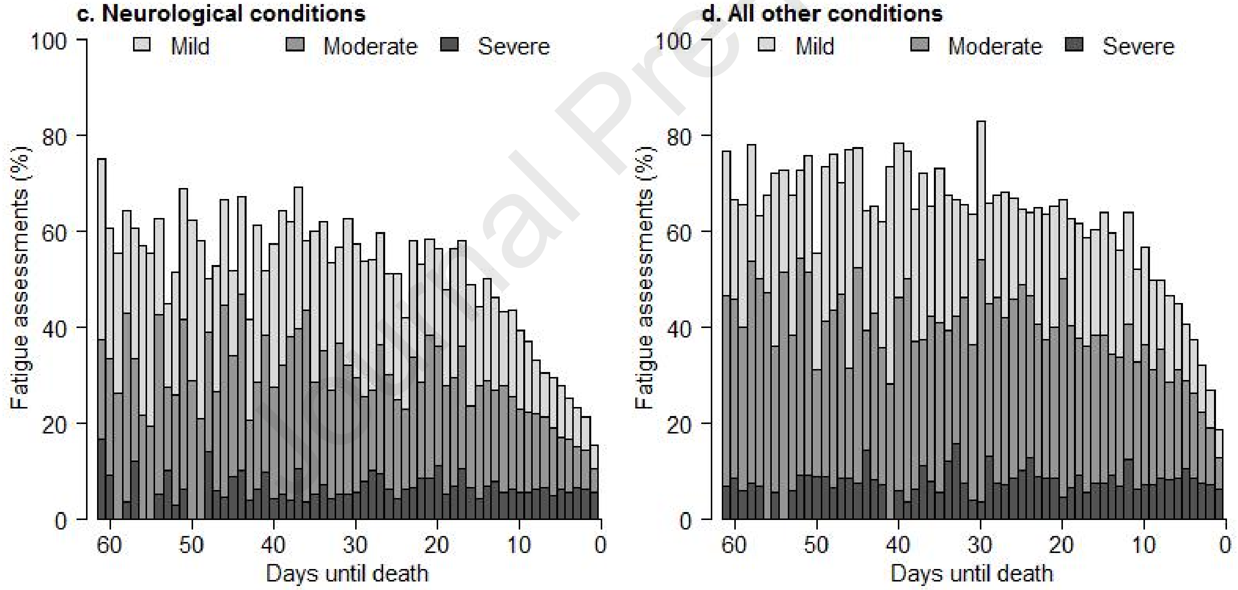


Figure 2 Symptom Assessment Scale (SAS) distress category for fatigue as death approaches



a. Cancer

b. End stage organ failure



c. Neurological conditions

d. All other conditions

Figure 3 Mean Symptom Assessment Scale (SAS) score for fatigue as death approaches

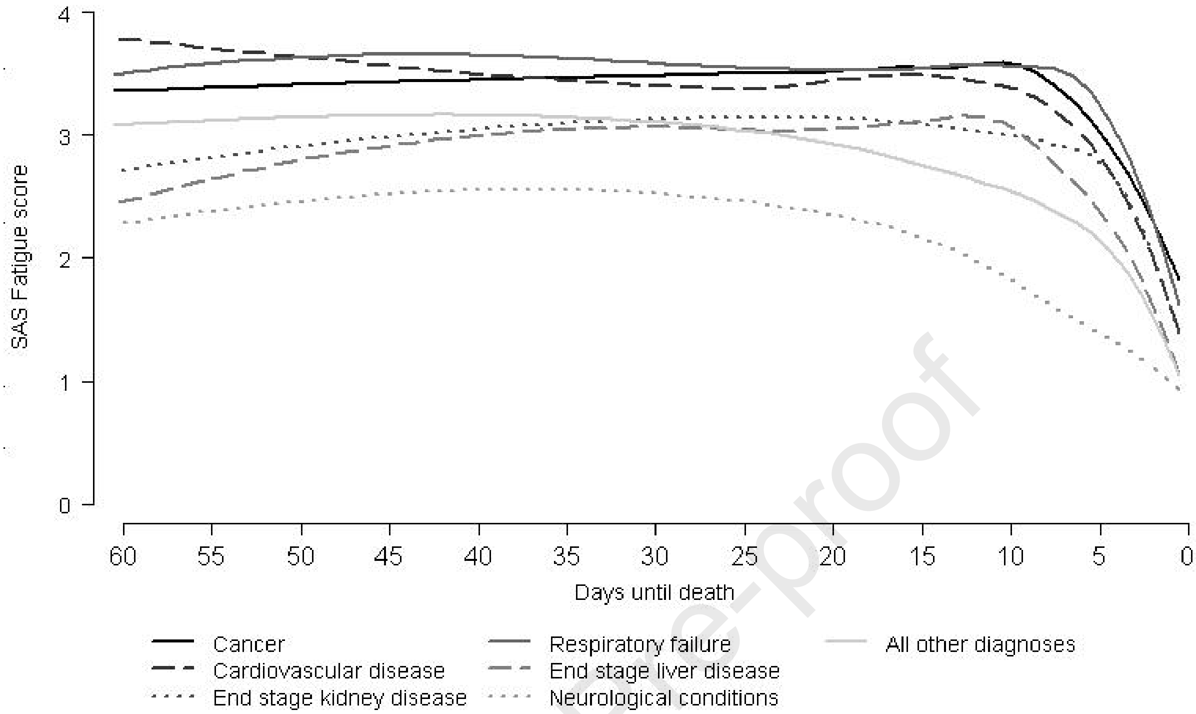


Figure 4 Distress category for fatigue by level of function

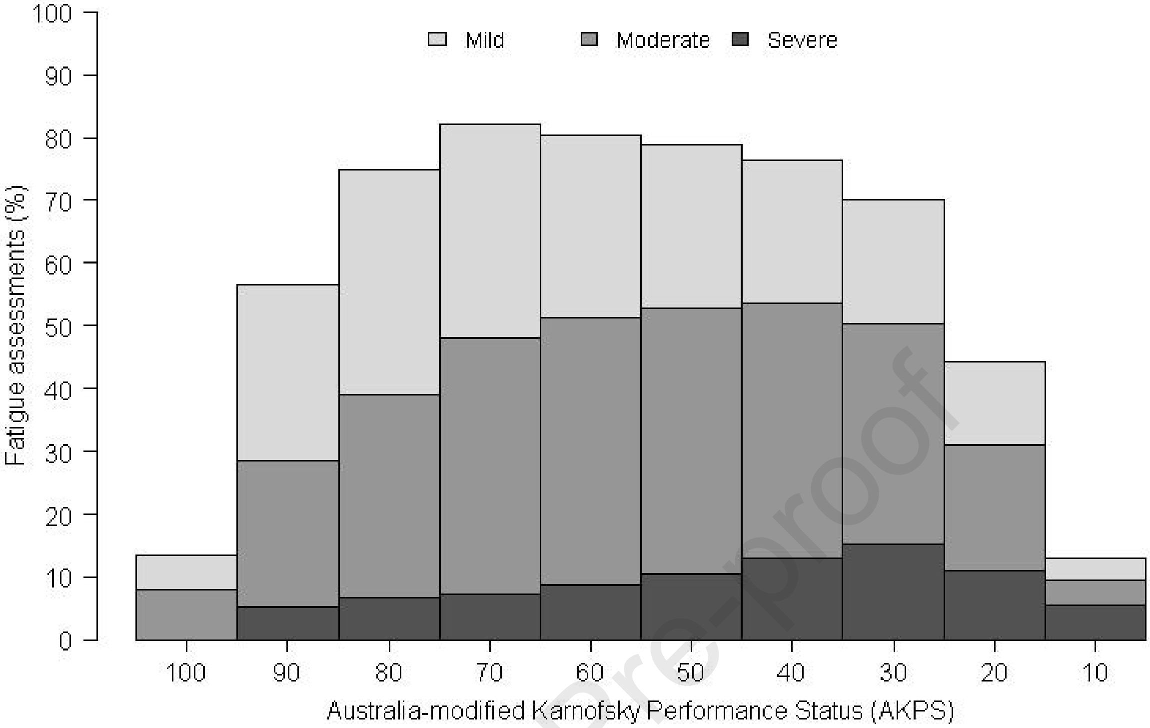


Table 1 Number of records included in the dataset, by type

	N
Patients	116,604
Episodes	179,204
Phases	447,907
Assessments[1]	501,104

[1] Phase start and discharge scores split into two in order to make modelling against Days until death simpler

Table 1 shows the number of patients, episode, phases and assessments which formed the analysis dataset for this research.

Table 2 Patient characteristics by diagnostic cohort

	Cancer (N = 85,048)	Cardiovascular disease (N = 5,141)	End stage kidney disease (N = 3,038)	Respiratory failure (N = 4,279)	End stage liver disease (N = 1,369)	Neurological conditions (N = 8,841)	All other diagnoses (N = 8,167)	Entire cohort (N =116,604)
Female (%)	44.8	47.5	44.6	44.9	31.3	55.6	53.0	46.2
Born in Australia (%)	64.4	61.9	60.4	64.0	65.2	62.2	63.4	64.0
English speaking (%)	68.4	72.1	65.2	74.8	63.8	73.7	72.9	69.4
Age at death								
Mean	71.8	83.4	79.3	79.2	65.8	80.5	80.9	74.0
SD	13.4	11.0	11.4	11.0	13.0	13.2	14.8	13.9
Median	73	86	82	81	66	84	84	76.0
Range	0-109	0-105	24-110	0-103	0-99	0-107	0-112	0-112
Place of death (%)								
Hospital	73.7	68.9	73.0	70.6	82.7	60.0	67.6	71.9
Home	20.3	17.8	17.9	19.5	12.9	15.2	20.2	19.6
Residential aged care	4.1	11.6	8.1	7.3	3.5	23.3	11.0	6.6
Community, not specified	1.9	1.7	1.0	2.6	0.9	1.5	1.3	1.8

Table 2 provides information on the patients included in this study. Demographics and information on the place of death are included.

Table 3 Number of assessments by diagnosis - entire dataset and assessments with a valid SAS Fatigue score

		In entire cohort		With valid SAS Fatigue score		
Group	**Diagnosis**	**N**	**% of cohort**	**N**	**% of cohort**	**% of diagnosis**
Cancer	Malignant – not further defined	4,831	1.0	4,426	1.0	91.6
	Bone and soft tissue cancer	6,232	1.2	5,772	1.3	92.6
	Breast cancer	30,048	6.0	27,535	6.0	91.6
	Central nervous system cancers	9,718	1.9	8,941	2.0	92.0
	Colorectal cancer	48,189	9.7	44,524	9.7	92.4
	Other gastrointestinal cancers	39,270	7.9	36,135	7.9	92.0
	Haematological cancer	21,634	4.3	19,386	4.2	89.6
	Head and neck cancer	21,348	4.3	19,875	4.3	93.1
	Lung cancer	89,904	18.0	82,957	18.1	92.3
	Pancreatic cancer	31,051	6.2	28,700	6.3	92.4
	Prostate cancer	27,696	5.6	25,514	5.6	92.1
	Other urological cancers	18,077	3.6	16,665	3.6	92.2

	Gynaecological cancer	22,115	4.4	20,203	4.4	91.4
	Skin cancer	15,610	3.1	14,593	3.2	93.5
	Unknown Primary	10,207	2.0	9,384	2.1	91.9
	Other primary malignancy	16,396	3.3	15,112	3.3	92.2
End stage cardiac	Cardiovascular disease	14,785	3.0	13,333	2.9	90.2
End stage respiratory	Respiratory failure	14,827	3.0	13,082	2.9	88.2
End stage kidney	End stage kidney disease	9,349	1.9	8,404	1.8	89.9
End stage liver	End stage liver disease	4,338	0.9	3,886	0.9	89.6
Neurological	Stroke	4,480	0.9	3,903	0.9	87.1
	Motor Neurone Disease	4,658	0.9	4,289	0.9	92.1
	Alzheimer’s dementia	2,597	0.5	2,403	0.5	92.5
	Other dementia	4,392	0.9	4,091	0.9	93.1

	Other neurological disease	5,772	1.2	5,054	1.1	87.6
All others	Non Malignant – not further defined	2,402	0.5	2,207	0.5	91.9
	HIV/AIDS	169	0.0	155	0.0	91.7
	Diabetes and its complications	493	0.1	448	0.1	90.9
	Sepsis	2,516	0.5	2,148	0.5	85.4
	Multiple organ failure	1,874	0.4	1,638	0.4	87.4
	Other non-malignancy	13,739	2.8	12,332	2.7	89.8
	Total	**498,717**	**100.0**	**457,095**	**100.0**	**91.7**
	Missing[1]	**2,387**	**-**	**2,216**		**-**

Table 3 shows the number of assessments by diagnostic category for the entire cohort as well as for assessments with a valid SAS Fatigue score. Overall, 91.7% of the assessments had valid SAS Fatigue score