

Patterns of comorbidities in hospitalised cancer survivors for palliative care and associated in-hospital mortality risk: A latent class analysis of a statewide all-inclusive inpatient data

Palliative Medicine
2019, Vol. 33(10) 1272–1281
© The Author(s) 2019



Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0269216319860705
journals.sagepub.com/home/pmj



Lan Luo¹, Wei Du¹ , Shanley Chong², Huibo Ji³ and Nicholas Glasgow¹

Abstract

Background: At the end of life, cancer survivors often experience exacerbations of complex comorbidities requiring acute hospital care. Few studies consider comorbidity patterns in cancer survivors receiving palliative care.

Aim: To identify patterns of comorbidities in cancer patients receiving palliative care and factors associated with in-hospital mortality risk.

Design, Setting/Participants: New South Wales Admitted Patient Data Collection data were used for this retrospective cohort study with 47,265 cancer patients receiving palliative care during the period financial year 2001–2013. A latent class analysis was used to identify complex comorbidity patterns. A regression mixture model was used to identify risk factors in relation to in-hospital mortality in different latent classes.

Results: Five comorbidity patterns were identified: ‘multiple comorbidities and symptoms’ (comprising 9.1% of the study population), ‘more symptoms’ (27.1%), ‘few comorbidities’ (39.4%), ‘genitourinary and infection’ (8.7%), and ‘circulatory and endocrine’ (15.6%). In-hospital mortality was the highest for ‘few comorbidities’ group and the lowest for ‘more symptoms’ group. Severe comorbidities were associated with elevated mortality in patients from ‘multiple comorbidities and symptoms’, ‘more symptoms’, and ‘genitourinary and infection’ groups. Intensive care was associated with a 37% increased risk of in-hospital deaths in those presenting with more ‘multiple comorbidities and symptoms’, but with a 22% risk reduction in those presenting with ‘more symptoms’.

Conclusion: Identification of comorbidity patterns and risk factors for in-hospital deaths in cancer patients provides an avenue to further develop appropriate palliative care strategies aimed at improving outcomes in cancer survivors.

Keywords

Complex comorbidity patterns, palliative care, cancer, end of life

What is already known about the topic?

- Palliative care seeks to eliminate or manage distressing symptoms and may support cancer patients at their end lives still receiving care with curative intent.
- Co-existing morbidities may limit the choice of treatment and care in cancer patients, which complicates the overall care and in turn further increases the risk of death.

What this paper adds?

- This study reveals five major patterns of complex comorbidities in palliative cancer patients receiving acute hospital care, that is, ‘multiple comorbidities and symptoms’, ‘more symptoms’, ‘few comorbidities’, ‘genitourinary and infection’, or ‘circulatory and endocrine’ group.

¹Research School of Population Health, Australian National University, Canberra, ACT, Australia

²South Western Sydney Local Health District and University of New South Wales, Sydney, NSW, Australia

³Health Economics and Modelling Branch, Department of Health, Canberra, ACT, Australia

Corresponding author:

Lan Luo, Research School of Population Health, Australian National University, Building 63, Eggleston Road, Acton, Canberra, ACT 2601, Australia.

Email: Lan.CZ.Luo@hotmail.com

- Cancer patients with ‘few comorbidities’ experienced the highest in-hospital mortality rate, and therefore their care was less complicated by comorbidities than other patients, and probably mainly related to cancer itself.
- The association between intensive care unit (ICU) care and in-hospital death varies across the identified five classes, with elevated risk in patients with ‘multiple comorbidities and symptoms’ and reduced risk in patients with ‘more symptoms’.

Implications for practice, theory or policy

- Clinicians should carefully evaluate the benefits and harms of various interventions for palliative cancer patients with different comorbidity profiles to avoid adopting ineffective interventions. Enhanced understanding of comorbidity patterns and how these vary across patient groups has potential for optimising comorbidity care by developing patient-centred policies and resource allocation during episodes of acute hospital care.

Introduction

Cancer is a disease requiring continuing care and treatment.¹ Studies have shown that nearly half of people with cancer experience uncontrollable pain at the end of life and ultimately die in hospital. This phenomenon is particularly evident in high-income countries.^{2,3} Specifically, most advanced cancer patients have exacerbations of symptoms requiring urgent hospitalisation several times in the last year of their lives and many receive aggressive medical interventions, including extensive stays in intensive care units (ICUs),^{3–6} a trend that has increased over time.⁷

Palliative care focuses on whole person care. It is concerned with patients’ quality of life, comfort and support and places emphasis on both individual and family/carer needs. It may support the care of people still receiving care with curative intent.⁸ It seeks to eliminate or manage distressing symptoms¹ and neither attempts to delay nor to accelerate death.^{1,2,9} Palliative care is appropriately delivered to patients far earlier than just the last days of life. According to their unique circumstances, patients may receive palliative care for a few days, weeks, months or even years.^{1,2,9}

Cancer patients often have complex comorbidities.^{10–12} More than half of cancer patients aged over 65 years will have at least one significant co-existing disease.¹⁰ Concurrent diseases are closely related to mortality in cancer patients and frequently contribute as underlying causes of death.^{12–15} The presence of comorbidities may limit the choice of treatment and care, which in turn further increases the risk of death.^{11,16} Delivering optimal whole person palliative care to cancer patients requires careful attention to the management symptoms arising from the cancer and all comorbidities.

There is limited published research from administrative data sets regarding comorbidity patterns in cancer patients receiving palliative care.^{10,11} Defining common patterns of comorbidity in cancer patients receiving palliative care may assist clinicians to optimise whole-patient care; communicate with patients, their families and/or

carers; and illuminate different progression trajectories for people in different clusters, which could in turn optimise the deployment of medical resources.

Latent class analysis is an effective method for identifying patterns in heterogeneous populations and is thus useful for filling the gap.^{17,18} Instead of generating all possible groupings, it classifies the data to the simplest clusters or classes. Researchers have identified subgroups of cancer patients using different measurements and have then distinguished the demographic and clinical characteristics of these subgroups.^{5,19,20} A retrospective study in Taiwan identified three subgroups among aggressive palliative care patients, with the ‘symptom crisis’ group accounting for more deaths in hospital.⁵ A Swedish retrospective study assessed differences in the causes of death among various subgroups and reported that 37.0% of patients with relieved pain died of comorbid circulatory conditions and 18.8% died of comorbid dementia.¹⁹ Furthermore, a collaborative study between Australia and the United States identified four subgroups of distinct symptoms and reported their differences in relation to quality of life according to demographic and clinical characteristics.²⁰ However, the current literature review indicates a dearth of studies attempting to clarify comprehensive comorbidity patterns in the context of palliative care.

Therefore, using latent class modelling techniques, this study aims to identify patterns of complex comorbidities in cancer patients receiving palliative care, characterise demographic and clinical factors of patients in each identified subgroup and evaluate the association between subgroup characteristics and in-hospital deaths.

Methods

Data source

The New South Wales (NSW) Admitted Patient Data Collection (APDC) maintained by the NSW Health Department is a complete census of inpatient data from NSW hospitals. It covers all NSW public, private and

Table 1. Model fit statistics for latent class model.

Number of classes	Akaike information criterion	Bayesian information criterion	Sample size–adjusted Bayesian information criterion	<i>p</i> Value for Lo–Mendell–Rubin likelihood ratio test	<i>p</i> Value for Bootstrap likelihood ratio test	Entropy
1	498,902.178	498,998.577	498,963.619	–	–	–
2	479,871.445	480,073.006	479,999.912	0.0000	0.0000	0.558
3	478,229.563	478,536.287	478,425.056	0.0000	0.0000	0.503
4	477,056.045	477,467.930	477,318.564	0.0000	0.0000	0.636
5	476,068.077	476,585.125	476,397.623	0.0000	0.0000	0.604
6	475,639.791	476,262.001	476,036.362	0.1216	0.0000	0.527

repatriation hospitals in addition to private outpatient centres. The APDC data sets comprise inpatients' demographic and clinical information. Clinical reasons for hospital care were coded at separation using the Australian Modification of 10th version of International Statistical Classification of Diseases and Related Health Problems (ICD-10 AM).²¹

In accordance with the Data Use Agreement established with the NSW Health Department, we selected cancer patients (ICD10-AM C codes) hospitalised for palliative care (Z51.5). There were multiple updates to the ICD-10 AM during the study period, which did not affect these codes. The study only considered cases for acute care ($n=48,553$) to reduce the impact of multiple counting. Of the study population, approximately 2.7% ($n=1288$) of study subjects were excluded on account of unknown age, gender, marital status, or postal residential address. Ethical approval was granted by the Australian National University Science & Medical Delegated Ethics Review Committee (#2016/030).

Measures

Latent indicator variables were comorbid disease groups (based on ICD-10 AM diagnosis codes). To ensure the presence within each latent class of sufficient numbers of patients with each disease group and make the comorbidity characteristics of patients in each subgroup more prominent, it was necessary to reject those comorbidities within the data set with a prevalence rate <10% (e.g. skin disorders and sensory impairment) or >85% (e.g. the commonly observed osteoporosis among the study population). Finally, 11 concurrent disease groups were considered for latent class analysis. These were infectious diseases, blood immune diseases, endocrine diseases, mental and behavioural disorders, nervous diseases, circulatory diseases, respiratory diseases, digestive diseases, genitourinary diseases, injury and poisoning and symptoms and signs. The presence of each comorbidity group was categorised as 'yes' or 'no'.

Distal outcome variable was in-hospital deaths, categorised as alive or death at separation. Patients' demographic

and clinical characteristics were considered for latent mixture modelling, that is, sex as male or female; age group as under 65, 65–84, or 85+ years; marital status as partnered or single; rurality of residence as urban or rural; private insurance as yes or no; ICU use as yes or no; and severity of comorbidities as minor (Charlson Index score=0), moderate (Charlson Index score=1 or 2), or severe (Charlson Index score ≥ 3) using the modified Charlson Index.²² Financial year was treated as a continuous variable.

Statistical analysis

We used Stata 15.1 to calculate frequencies and proportions. We used Mplus 7.4 to run a series of latent class models to examine clusters of complex comorbidities in the study population. *Stage 1 – latent class analysis*: the five-class model was selected through a sequential comparison of k -class and $(k-1)$ -class model parameters (k starts from 2) (Table 1), with number of groups chosen based on interpretability, smaller value of the Akaike information criterion (AIC), the Bayesian information criterion (BIC), and the sample size–adjusted Bayesian information criterion (SABIC), as well as no significant improvement as assessed by the Lo–Mendell–Rubin (LMR) likelihood ratio test, and a relatively higher entropy score.^{23–25} These model-based criteria primarily utilising the log-likelihood value, penalising model complexity and considering sample size, are the most recommended to select the number of classes. We compared all models using the BIC difference between k - and $(k-1)$ -class models and observed a substantial decrease in BIC difference from 18,925.6 (between the two-class and one-class models) to 323.1 (between the six-class and five-class models). Although the six-class model had the smallest BIC, the BIC difference in comparison with the five-class model was relative small. Given a non-statistically significant result of LMR likelihood ratio test when comparing the six- and five-class models, we further plotted conditional probability for each latent indicator in the specific class, visualised the difference of class profile between models, and observed little material change in terms of class interpretation. Based on a non-statistically significant difference in

Table 2. Study population demographic and clinical characteristics during July 2001 to June 2014 ($n=47,265$).

	Total		Class 1: Multiple comorbidities and symptoms		Class 2: More symptoms		Class 3: Few comorbidities		Class 4: Genitourinary and infection		Class 5: Circulatory and endocrine	
	N	%	N	%	N	%	N	%	N	%	N	%
Gender												
Male	26,552	56.2	2460	56.9	7379	57.6	10,457	56.2	2052	49.8	4204	57.0
Female	20,713	43.8	1862	43.1	5440	42.4	8164	43.8	2072	50.2	3175	43.0
Age group (years)												
<65	15,217	32.2	1127	26.1	4597	35.9	6719	36.1	1120	27.2	1654	22.4
65–84	26,683	56.4	2622	60.7	6921	54.0	10,054	54.0	2352	57.0	4734	64.2
85+	5365	11.4	573	13.2	1301	10.1	1848	9.9	652	15.8	991	13.4
Marital status												
Partnered	28,198	59.7	2483	57.4	7605	59.3	11,558	62.1	2364	57.3	4188	56.8
Single	19,067	40.3	1839	42.6	5214	40.7	7063	37.9	1760	42.7	3191	43.2
Private insurance												
Yes	12,731	26.9	1113	25.8	3549	27.7	5176	27.8	1144	27.7	1749	23.7
No	34,534	73.1	3209	74.2	9270	72.3	13,445	72.2	2980	72.3	5630	76.3
Rurality of residence												
Rural	4031	8.5	129	3.0	747	5.8	2409	12.9	231	5.6	515	7.0
Urban	43,234	91.5	4193	97.0	12,072	94.2	16,212	87.1	3893	94.4	6864	93.0
Severity of comorbidities												
Minor	8765	18.5	499	11.5	2384	18.6	4315	23.2	673	16.3	894	12.1
Moderate	6741	14.3	664	15.4	2053	16.0	2147	11.5	644	15.6	1233	16.7
Severe	31,759	67.2	3159	73.1	8382	65.4	12,159	65.3	2807	68.1	5252	71.2
Intensive care												
Yes	706	1.5	307	7.1	170	1.3	50	0.3	59	1.4	120	1.6
No	46,559	98.5	4015	92.9	12,649	98.7	18,571	99.7	4065	98.6	7259	98.4

the LMR likelihood ratio test comparing the five- and six-class models, as well as interpretable classes and maximum membership probability to make a final class assignment,¹⁸ the parsimonious five-class model was selected as the final model. To encapsulate the profile of each class, the conditional response probabilities of each latent indicator were plotted for each latent class. *Stage 2 – latent class with the distal outcome*: the identified latent class membership in relation to the distal outcome (in-hospital death) was further quantified in terms of odds ratio (OR) and 95% confidence interval (CI), with statistical significance set as a p value < 0.05 .^{23,26,27} Considering underestimation error,^{18,23,26} we used the 3-STEP approach in all subsequent regression analyses to correct the estimation error.²⁶ *Stage 3 – regression mixture modelling*: the identified latent class membership acting as a moderator was added to the regression model of independent variables (demographic and clinical characteristics) and the dependent variable (death outcome).²⁶

Results

Of the study population (47,265 cancer patients receiving palliative care), there were more males (56.2%), more aged 65–84 years (56.5%), more with partners (59.7%),

more living in urban areas (91.5%), and more without private health insurance (73.1%) (Table 2). Approximately 43.5% ($n=20,573$) patients died in hospitals.

Stage 1

Figure 1 illustrates the conditional probabilities for comorbidity groups in relation to five latent classes, based on multiple model selection criteria. The univariate entropy ranged from 0.12 to 0.28 for these comorbidity groups (Table 3), reflecting a less clear separation of the classes based on their respective contribution alone, but a more realistic complex palliative care setting. Nevertheless, as indicated by the overall larger entropy (0.604), some of the classes have been very clearly distinguished. Class 1 consisted of 9.1% of the patients with a consistently high presence of all comorbidities, comprising a ‘typical’ patient with diabetes, hypertension, chronic kidney disease, functional intestinal disorders, urinary incontinence, nausea, vomiting, and cognitive impairment, referred to here as the ‘multiple comorbidities and symptoms’ group (Table 3). Approximately 27.1% of the patients were allocated membership of Class 2, referred to here as the ‘more symptoms’ group, comprising a ‘typical’ patient with functional intestinal disorders and volume depletion

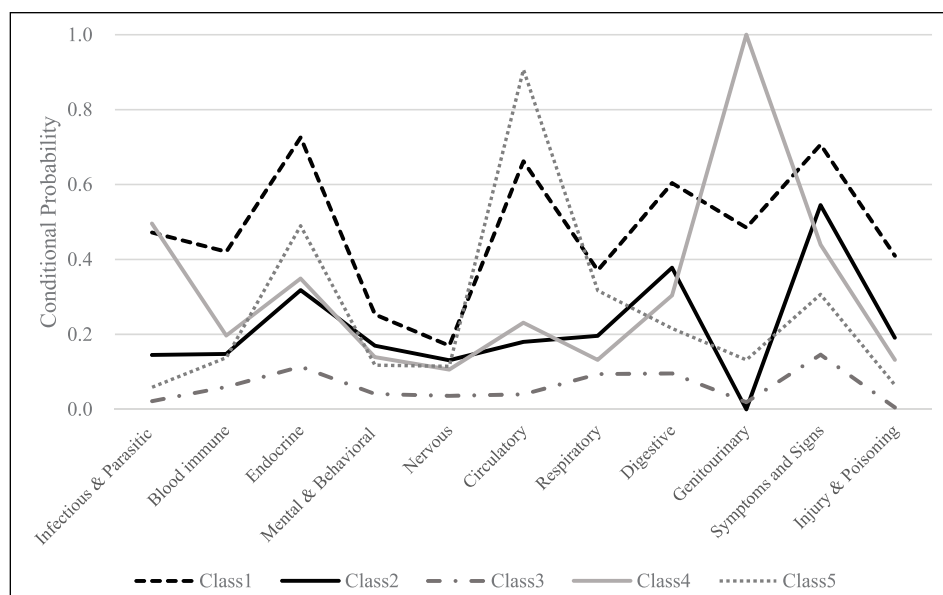


Figure 1. Conditional probability for each comorbidity group indicator by class.

Table 3. Five-class model: prevalence of latent classes and conditional probabilities.^a

	Univariate entropy	Total (%)	Class 1	Class 2	Class 3	Class 4	Class 5
			9.14%	27.12%	39.40%	8.73%	15.61%
			N = 4322	N = 12,819	N = 18,621	N = 4124	N = 7379
			Multiple comorbidities and symptoms	More symptoms	Few comorbidities	Genitourinary and infection	Circulatory and endocrine
Infectious and parasitic	0.171	15.2	0.472	0.145	0.022	0.496	0.059
Blood immune	0.134	14.8	0.421	0.148	0.060	0.197	0.138
Endocrine	0.166	31.1	0.726	0.318	0.114	0.349	0.490
Mental and behavioural	0.126	12.2	0.253	0.170	0.041	0.139	0.118
Nervous	0.119	10.0	0.170	0.131	0.036	0.106	0.115
Circulatory	0.251	27.5	0.662	0.180	0.040	0.231	0.907
Respiratory	0.128	18.7	0.371	0.196	0.094	0.132	0.317
Digestive	0.155	27.2	0.604	0.378	0.096	0.304	0.216
Genitourinary	0.279	15.5	0.485	0.000	0.019	1.000	0.132
Symptoms and signs	0.168	37.6	0.707	0.545	0.146	0.440	0.307
Injury and poisoning	0.158	12.5	0.410	0.191	0.005	0.132	0.065

^aConditional probability value greater than and approximating 0.5 are given in bold.

symptoms. While more than half Class 2 patients (54.5%) had clinical symptoms and signs such as nausea, vomiting, cognitive impairment, dysphagia, and oedema, there were no diagnoses of genitourinary diseases. Class 3 represented the largest latent subgroup (39.4%) and was classified as the 'few comorbidities' group, comprising a 'typical' patient with very few comorbid conditions, particularly in contrast to Class 1 patients with apparent presence of multiple comorbidities. The smallest group was Class 4 (8.7%), referred to here as the 'genitourinary and

infection' group comprising a 'typical' patient with urinary disorders, acute kidney failure, and bacterial infections. Class 5 (15.6% of the study population) represented the 'circulatory and endocrine' group comprising a 'typical' patient with hypertension, chronic ischaemic heart disease, and diabetes. Cancer patients with chronic obstructive pulmonary disease (COPD) were also observed in the Class 5 group.

In contrast to the 'few comorbidity' group, rural residency was under-represented in the other groups, in

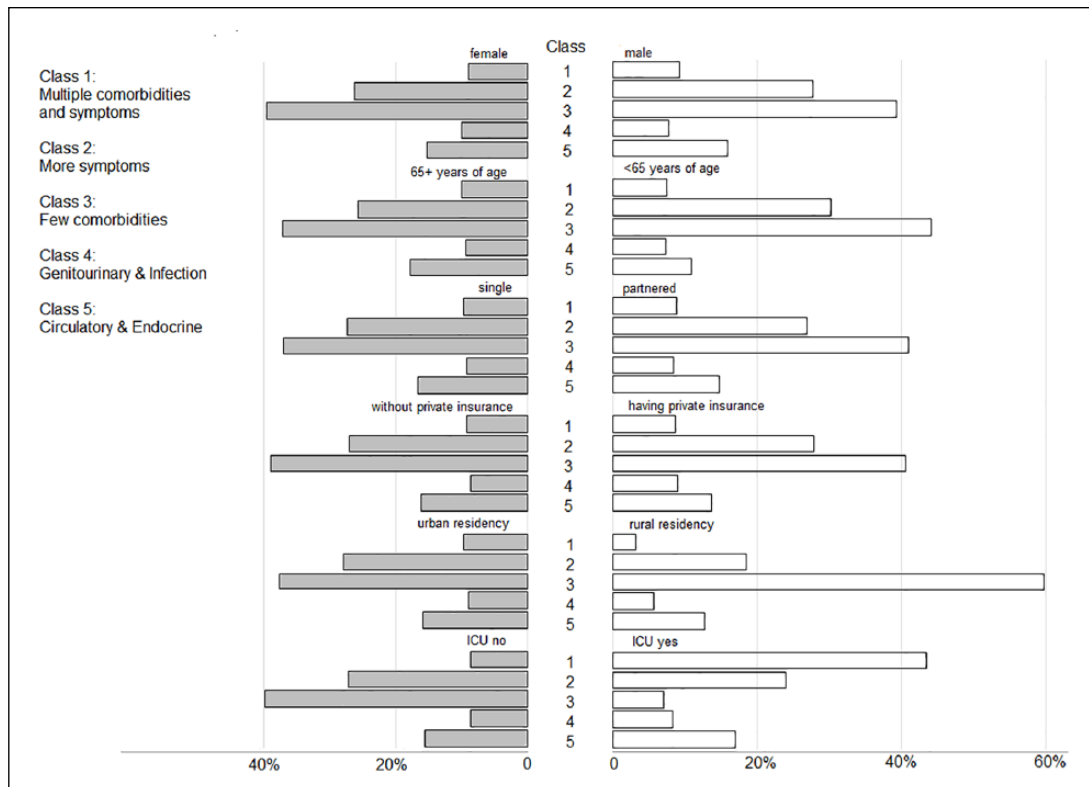


Figure 2. Selected characteristics, proportion by class.

particular, the ‘multiple comorbidities and symptoms’ group (Figure 2). Relative to those patients aged 65 years and above, younger patients appeared to be over-represented with ‘more symptoms’ and ‘few comorbidities’. Patients in the ‘multi-comorbidities and symptoms’, ‘more symptoms’ or ‘circulatory and endocrine’ groups accounted for the majority of ICU care, and female patients were over-represented in the ‘genitourinary and infection’ group.

Stage 2

In-hospital mortality is the highest for the ‘few comorbidities’ group (modelled probability: 0.55), followed by ‘circulatory and endocrine’ group (0.47), ‘multiple comorbidities and symptoms’ group (0.41), ‘genitourinary and infection’ group (0.40) and ‘more symptoms’ group (0.32). In comparison with those in the ‘few comorbidities’ group, patients in the ‘circulatory and endocrine’, ‘multiple comorbidities and symptoms’, ‘genitourinary and infection’ and ‘more symptoms’ groups were 29% (95% CI: 16%–40%), 44% (36%–50%), 46% (39%–52%) and 63% (59%–66%), respectively, less likely to die in hospitals.

Stage 3

Female patients with any complex comorbidity patterns were less likely to die in hospital (Table 4). While older age

seemed protective in the ‘multiple comorbidities and symptoms’ group, it was associated with elevated risk of in-hospital deaths in other groups. Having private health insurance were associated with elevated mortality in patients from the ‘multiple comorbidities and symptoms’, ‘more symptoms’ and ‘few comorbidities’ groups. ICU care was associated with a reduced risk of in-hospital deaths for those presenting with more symptoms (Class 2) or few comorbidities (Class 3). The likelihood of in-hospital death increased over years in the ‘more symptoms’, ‘few comorbidities’, ‘genitourinary and infection’ and ‘circulatory and endocrine’ groups.

Discussion

This population-based study focusing on palliative cancer care in hospitals describes clusters of comorbidity burden variation in patients and suggests there may be challenges in the allocation of limited medical resources to these patients in the Australian acute hospital care setting. Although palliative cancer care is a high-priority research area in Australia and internationally, there is limited understanding of comorbidity patterns and how these vary across patient groups. To the best of our knowledge, this research constitutes the first latent class analysis of complex comorbidities in cancer patients for palliative care. The results indicate that multiple comorbidities

Table 4. Regression mixture model for death outcome.

	Class 1: Multiple comorbidities and symptoms	Class 2: More symptoms	Class 3: Few comorbidities	Class 4: Genitourinary and infection	Class 5: Circulatory and endocrine
	Odds ratio	Odds ratio	Odds ratio	Odds ratio	Odds ratio
Female	0.87 ^a	0.92 ^a	0.92 ^a	0.76 ^a	0.91 ^b
Age					
65–84	0.95	1.22 ^a	1.34 ^a	1.11	1.14 ^a
85+	0.83 ^a	1.23 ^a	1.34 ^a	1.16	1.18 ^b
Single	1.00	0.88 ^a	0.89 ^a	0.99	0.87 ^a
Private insurance	1.20 ^a	1.17 ^a	1.14 ^a	1.11	1.02
Financial year	1.00	1.02 ^a	1.06 ^a	1.02 ^b	1.02 ^a
Rural residence	1.16	1.46 ^a	1.21 ^a	1.33 ^b	1.49 ^a
Severity of comorbidities					
Moderate	0.97	0.75 ^a	0.57 ^a	0.84	0.86 ^b
Severe	1.20 ^a	1.15 ^a	1.06	1.23 ^b	1.05
ICU	1.37 ^a	0.78 ^a	0.34 ^a	0.79	0.98

ICU: intensive care unit.

^a*p* value < 0.01.

^b*p* value < 0.05.

cluster in unique ways. It was noted that females were less likely to die in hospital than males across all groups, which is consistent with previous research.²⁸ Similarly, all rural patients experienced a higher probability of death in hospitals, perhaps implying a general lack of acute medical resources in rural areas. Other than these, the probability of in-hospital deaths and associated risk factor profiles varies across these clusters. These findings point to the potential for optimising appropriate comorbidity care by focusing on these different patterns, which could assist hospital professionals to improve palliative care for cancer patients as well as to develop countermeasures and reduce in-hospital deaths.

The ‘few comorbidities’ group accounted for 40% of the study population and demonstrated the highest in-hospital mortality. There are two possible explanations of the observed high hospital mortality in this group. First, while in general ICU use may reduce risks of in-hospital deaths, in these patients ICU admission may not be consistent with the goals of care and this could explain the lowest ICU admission rates observed in this group, and, in turn, explain the higher observed mortality rates. Second, most patients had partners and families and possessed private health insurance. Both factors might positively correlate with the adoption of more aggressive medical care in an attempt to extend life without full comprehension of the patients’ prognosis. However, both propositions are speculative and require further research to confirm their validity.

The in-hospital mortality among patients in the ‘circulatory and endocrine’ group was the second highest. No evidence was found that high use of ICU in this group significantly reduced the in-hospital deaths of these patients.

Furthermore, patients with partners were associated with elevated risk of in-hospital deaths. One possible explanation would be again related to excessive use of more aggressive care. It is worth noting, therefore, that the association between family involvement in clinical decisions and the extensive use of aggressive palliative care is an area warranting further investigation. For cancer patients presenting with ‘circulatory and endocrine’ comorbidities, clinical decisions should involve proper selection of appropriate care pathways to avoid excessive and ineffective aggressive end-of-life care.

Patients in the ‘multiple comorbidities and symptoms’ group had the third highest probability of in-hospital deaths. Because the comorbidity pattern of this group demonstrated the most complex profile, comprehensive care plans for this group would become more complex. ICU care in this group was commonplace, which somehow demonstrated a risk proxy for in-hospital death. This finding raises a question as to whether patients in this group have had their end-of-life care preferences explored and documented, including whether admission to an ICU is necessary, given that previous studies have reported aggressive ICU care in similar patients did not enhance lifespan.²⁹ In addition, holding private health insurance may make adoption of aggressive care more affordable in this group and, in turn, affect patients’ survival. When patients access palliative care with complex comorbidity profiles, there is a need for clinicians to carefully discuss with them the potential benefits and harms of different interventions, including admission to ICU, and document these to mitigate the risk of adopting ineffective interventions during their hospital stay.

The in-hospital mortality rate for the 'genitourinary and infection' group was lower than the previous three groups, possibly because the majority of these patients were females in whom the infections might be diagnosed then treated at an early stage. Considering infection was one of the leading causes of death in cancer patients,¹⁶ the synergistic effect of infection and other comorbid conditions may affect a patient's chance of survival. For cancer patients with a 'genitourinary and infection' comorbidity pattern, palliative care would focus on the provision of appropriate management and control of infections.

The 'more symptoms' group had the lowest hospital mortality rate. These patients were the youngest of all the groups, which may contribute to the relatively low mortality rate for the entire group on average. ICU care reduced the risk of in-hospital death in these patients, which indicates that these patients were in a relatively ICU appropriate condition. Treatment focused on symptom relief would potentially meet their acute care needs.^{30–32} Therefore, palliative care delivery for them may primarily involve multiple symptom relief treatment plans and consider the use of ICU care to alleviate symptoms and improve survival.

Future directions and implications

Palliative care often occurs in acute hospital care settings and palliative patients may not receive appropriate end-of-life care in hospitals. Using an all-inclusive inpatient data collection, this study shows how comorbidity burden varies and clusters in cancer patients during acute hospital care. Variation among the five groups identified in the study suggests person-centred care should include comorbidity care that is informed by these patterns. This study further demonstrates apparent heterogeneity of in-hospital mortality in cancer patients with various comorbidity burdens. Combining the comorbidity patterns with the demographic and clinical characteristics of cancer patients may assist clinicians optimise care and plan resource allocation. Training in comorbidity pattern identification and person-centred adverse outcome evaluation for clinicians is recommended in different palliative care contexts.

Given the globally recognised right to high-quality care for all at the end of life,³³ it is important to tailor personalised palliative care programmes for all cancer patients that target the most relevant comorbidity patterns. Currently, there are multiple programmes aiming to improve the quality and safety of palliative care.^{34–36} This study adds to the supportive evidence related to these programmes and emphasises the importance of identification of comorbidity patterns to improve care outcomes, which in turn facilitates the establishment of appropriate palliative care programmes, thereby not only avoiding deaths in hospital but also improving patient quality of life as a global achievement.

Limitations

Although model selection criteria based on model-derived statistics are recommended to determine the number of latent classes, trade-offs exist whether these statistical criteria act in concert or not. Clinical knowledge of the subject area is also important and required to guide model selection. In this study, we carried out a careful model comparison strategy considering the plausibility, interpretability, and parsimony, in addition to the statistical approach, and therefore our results are somewhat robust explaining the likely patterns of comorbidities in cancer patients receiving palliative care in NSW hospitals. Nonetheless, appropriate care should be given to interpret the identified number of classes when comparing results from other study settings. There are several limitations in this study. First, it is a descriptive study of observed patterns in an administrative data set and does not explain the underlying reasons for those observed patterns. It is possible that some cancer patients received appropriate palliative care and opted to die in hospitals as their preferred place of death.^{37,38} Second, the use of administrative APDC data limited the ability to comprehensively consider palliative care scenarios for risk adjustment. Based on a limited range of predefined data fields, the regression analysis was unable to differentiate effects from unmeasured factors or by chance alone. It would be prudent to be cautious extrapolating beyond the current study setting. Third, the entropy value (0.604) of the five-class model indicated errors in patient group assignment, and therefore association results should be interpreted with caution. Nonetheless, the identified patterns of comorbidities seem clinically relevant and thus an informative guide for those seeking to improve palliative care for cancer patients.

Conclusion

This study confirmed the heterogeneity and complexity of comorbidity profiles as well as their relationship to in-hospital deaths in cancer patients during their palliative care. Recognition of various patterns of comorbidities and identification of risk factors for in-hospital deaths provide an avenue to develop appropriate palliative care strategies with attention to improve care these patients deserve at the end of their lives, passing on in peace and dignity instead of uneasiness and fear.

Author contributions

W.D. made substantial contributions to study conception, design, and analysis. N.G. made a substantial contribution to data acquisition and interpretation. L.L. was a major contributor in the study design, data analysis, result interpretation, and the first draft. W.D., S.C., H.J. and N.G. contributed to design, analysis, and interpretation of data

and revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Wei Du  <https://orcid.org/0000-0003-3622-2265>

References

- Rome RB, Luminais HH, Bourgeois DA, et al. The role of palliative care at the end of life. *Ochsner J* 2011; 11(4): 348–352.
- Chan R and Webster J. End-of-life care pathways for improving outcomes in caring for the dying. *Cochrane Database Syst Rev* 2010; 1: CD008006.
- Cotogni P, Saini A and De Luca A. In-hospital palliative care: should we need to reconsider what role hospitals should have in patients with end-stage disease or advanced cancer? *J Clin Med* 2018; 7(2): 18.
- Henson LA, Gomes B, Koffman J, et al. Factors associated with aggressive end of life cancer care. *Support Care Cancer* 2016; 24(3): 1079–1089.
- Chen ML, Chen YY and Tang ST. Latent class analysis identifies three subtypes of aggressive end-of-life care: a population-based study in Taiwan. *Eur J Cancer* 2013; 49(15): 3284–3291.
- Cooke CR, Feemster LC, Wiener RS, et al. Aggressiveness of intensive care use among patients with lung cancer in the surveillance, epidemiology, and end results-Medicare registry. *Chest* 2014; 146(4): 916–923.
- Ho TH, Barbera L, Saskin R, et al. Trends in the aggressiveness of end-of-life cancer care in the universal health care system of Ontario, Canada. *J Clin Oncol* 2011; 29(12): 1587–1591.
- World Health Organization. Definition of palliative care. <http://www.who.int/cancer/palliative/definition/en/> (accessed 5 March 2019).
- Kaasa S, Loge JH, Aapro M, et al. Integration of oncology and palliative care: a Lancet Oncology Commission. *Lancet Oncol* 2018; 19(11): e588–e653.
- Ritchie CS, Kvale E and Fisch MJ. Multimorbidity: an issue of growing importance for oncologists. *J Oncol Pract* 2011; 7(6): 371–374.
- Sarfati D, Koczwara B and Jackson C. The impact of comorbidity on cancer and its treatment. *CA Cancer J Clin* 2016; 66: 337–350.
- Sogaard SM, Thomsen RW, Bossen KS, et al. The impact of comorbidity on cancer survival: a review. *Clin Epidemiol* 2013; 5(Suppl. 1): 3–29.
- Albertsen PC, Moore DF, Shih W, et al. Impact of comorbidity on survival among men with localized prostate cancer. *J Clin Oncol* 2011; 29(10): 1335.
- Edwards BK, Noone AM, Mariotto AB, et al. Annual report to the nation on the status of cancer, 1975–2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. *Cancer* 2014; 120(9): 1290–1314.
- Iversen LH, Nørgaard M, Jacobsen J, et al. The impact of comorbidity on survival of Danish colorectal cancer patients from 1995 to 2006 – a population-based cohort study. *Dis Colon Rectum* 2009; 52(1): 71–78.
- Nagy-Agren S and Haley H. Management of infections in palliative care patients with advanced cancer. *J Pain Symptom Manage* 2002; 24(1): 64–70.
- Lanza ST and Rhoades BL. Latent class analysis: an alternative perspective on subgroup analysis in prevention and treatment. *Prev Sci* 2013; 14(2): 157–168.
- Ohlen J, Russell L, Hakanson C, et al. Variations in care quality outcomes of dying people: latent class analysis of an adult national register population. *J Pain Symptom Manage* 2017; 53(1): 13–24.
- Miaskowski C, Dunn L, Ritchie C, et al. Latent class analysis reveals distinct subgroups of patients based on symptom occurrence and demographic and clinical characteristics. *J Pain Symptom Manage* 2015; 50(1): 28–37.
- Collins LM and Lanza ST. *Latent class and latent transition analysis: with applications in the social, behavioral, and health sciences*. Hoboken, NJ: John Wiley & Sons, 2010.
- National Centre for Classification in Health. *International statistical classification of diseases and related health problems, 10th revision, Australian modification (ICD-10-AM)*. 7th ed. Sydney, NSW, Australia: NCCH, 2010.
- Quan H, Li B, Couris C, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011; 173(6): 676–682.
- VanHorn ML, Jaki T, Masyn K, et al. Assessing differential effects: applying regression mixture models to identify variations in the influence of family resources on academic achievement. *Dev Psychol* 2009; 45(5): 1298.
- Nylund KL, Asparouhov T and Muthén BO. Deciding on the number of classes in latent class analysis and growth mixture modeling: a Monte Carlo simulation study. *Struct Equ Modeling* 2007; 14(4): 535–569.
- Jung T and Wickrama K. An introduction to latent class growth analysis and growth mixture modeling. *Soc Person Psychol Compass* 2008; 2(1): 302–317.
- Bakk Z, Tekle FB and Vermunt JK. Estimating the association between latent class membership and external variables using bias-adjusted three-step approaches. *Sociol Methodol* 2013; 43(1): 272–311.
- Asparouhov T and Muthén B. Auxiliary variables in mixture modeling: three-step approaches using Mplus. *Struct Equ Modeling* 2014; 21(3): 329–341.
- Houttekier D, Cohen J, Peppersack T, et al. Dying in hospital: a study of incidence and factors related to hospital death using death certificate data. *Eur J Public Health* 2013; 24(5): 751–756.

29. Wright AA, Zhang B, Ray A, et al. Associations between end-of-life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. *JAMA* 2008; 300(14): 1665–1673.
30. Scarborough BM and Smith CB. Optimal pain management for patients with cancer in the modern era. *CA Cancer J Clin* 2018; 68: 182–196.
31. Baltenberger EP, Schmitt G and Thomas CJ. Treatment of depressive symptoms in patients with cancer. *Ment Health Clin* 2014; 4(3): 114–117.
32. Wilkinson S, Lockhart K, Gambles M, et al. Reflexology for symptom relief in patients with cancer. *Cancer Nurs* 2008; 31(5): 354–360, quiz 361.
33. Junger S, Payne S, Brearley S, et al. Consensus building in palliative care: a Europe-wide Delphi study on common understandings and conceptual differences. *J Pain Symptom Manage* 2012; 44(2): 192–205.
34. Department of Health. *National palliative care projects*. Canberra, ACT, Australia: Australia Government Department of Health, 2018.
35. Clinical Excellence Commission. *End of life program*. Sydney, NSW, Australia: NSW Clinical Excellence Commission, 2018.
36. Agency for Clinical Innovation. *NSW ambulance authorised palliative care plans*. Sydney, NSW, Australia: NSW Agency for Clinical Innovation, 2015.
37. Choi J, Miyashita M, Hirai K, et al. Preference of place for end-of-life cancer care and death among bereaved Japanese families who experienced home hospice care and death of a loved one. *Support Care Cancer* 2010; 18(11): 1445–1453.
38. Virdun C, Lockett T, Davidson PM, et al. Dying in the hospital setting: a systematic review of quantitative studies identifying the elements of end-of-life care that patients and their families rank as being most important. *Palliat Med* 2015; 29(9): 774–796.