

Association between palliative care and life-sustaining treatments for patients with dementia: A nationwide 5-year cohort study

Short title: Palliative care and life-sustaining care for dementia

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Abstract

Background: The association between palliative care and life-sustaining treatments for patients with dementia is unclear in Asian countries.

Aim: To analyse the use of palliative care and its association with aggressive treatments based on Taiwanese national data.

Design: A matched cohort study was conducted. The association between intervention and outcome was evaluated using conditional logistic regression analyses.

Setting/participants: The source population comprised 239,633 patients with dementia diagnosed between 2002 and 2013. We selected patients who received palliative care between 2009 and 2013 (the treatment cohort; $N=1996$) and assembled a comparative cohort ($N=3992$) through 1:2 matching for confounding factors.

Results: After 2009, palliative care was provided to 3,928 (1.64%) patients of the dementia population. The odds ratio for undergoing life-sustaining treatments in the treatment cohort versus the comparative cohort was <1 for most treatments (e.g. 0.41 for mechanical ventilation (95% confidence interval [CI] 0.35–0.48)). The odds ratio was >1 for some treatments (e.g. 1.73 for tube feeding (95% CI 1.54–1.95)). Palliative care was more consistently associated with fewer life-sustaining treatments for those with cancer.

Conclusions: Palliative care is related to reduced life-sustaining treatments for patients with dementia. However, except in the case of tube feeding, which tended to be provided

alongside palliative care regardless of cancer status, having cancer possibly had itself a protective effect against the use of life-sustaining treatments. Modifying the eligibility criteria for palliative care in dementia, improving awareness on the terminal nature of dementia, and facilitating advance planning for dementia patients may be priorities for health policies.

Keywords: cross-cultural comparison, dementia, life-support care, national health programs, neoplasms, palliative care

What is already known about the topic?

- Although palliative care for dementia is a culture-specific issue, current data from Asian populations and countries are insufficient.
- Taiwan was one of the earliest Asian countries to provide nationwide single-payer palliative care for dementia and has offered these services since 2009.

What this paper adds

- Palliative care was used by 1.64% of patients with dementia after 2009 in Taiwan. It was associated with reduced utilisation of some life-sustaining treatments, such as haemodialysis, most invasive respiratory therapies, and cardiopulmonary resuscitation, but more consistently so in patients who also had cancer.
- Palliative care for patients with dementia was associated with increased use of tube feeding, enteral tube insertion and non-invasive positive pressure ventilators especially in those without cancer.

Implications for practice, theory, or policy

- Malignancy status may influence clinicians' and relatives' perception of a terminal illness, as well as the paradigm of palliative care practice for patients with dementia.
- The national health care system could prioritize modification of the eligibility criteria to ensure timely introduction of palliative care for patients with dementia and to improve public awareness on the terminal nature of dementia.

Introduction

Dementia is a neurodegenerative disease that has a substantial impact on the healthcare system and presents a large socioeconomic burden.¹ As a life-limiting disease without an effective curative treatment, dementia is currently one of the major causes of death in Western countries and the leading cause in England and Wales.^{2,3} A clear need for palliative care for patients with dementia calls for an increase in studies and actions targeting the delivery of proper health care services including at the end of life.^{4,5} However, there is a large gap in relevant data concerning the policy and service pattern of palliative care and dementia in Asian populations and countries.⁶

Life-sustaining treatments may cause tremendous physiological and psychosocial burdens for patients but may not provide promising benefits on survival outcomes, functional capability, quality of life, or family-reported quality of end-of-life care for older people or critically ill patients with multiple comorbidities.⁷⁻¹⁰ Having dementia was associated with a very low prevalence rate of admission to intensive care units (ICUs) and invasive respiratory therapies in studies in the US and Netherlands and in the Danish nationwide database.^{11,12} Previous surveys in Taiwan, a Chinese culture-based society, found that patients with dementia underwent more life-sustaining interventions during their last year of life than their counterparts in Western countries and that the use of these life-saving or diagnostic procedures at an end-of-life stage differed according to whether patients had dementia,

cancer, or both.^{13,14} Cross-cultural differences might explain a gap in the use of medical intervention for people with dementia between Taiwan and Western countries and trigger the need for further study.

Previous studies have shown that palliative care was associated with reduced hospital and ICU admissions for cancer patients and decreased use of artificial nutrition and hydration and referrals to the emergency department (ED) for patients with dementia.¹⁵⁻¹⁸ A randomised control trial in the US of palliative care for patients with advanced dementia who were admitted to the hospital demonstrated that the palliative care intervention did not affect the use of feeding tubes or mechanical ventilation or decisions to forgo cardiopulmonary resuscitation (CPR).¹⁹ However, there have been very few other studies to support the evidence base regarding the effect of palliative care on life-sustaining treatments for patients with dementia.⁵ It is also important to examine the benefit of palliative care for dementia in Taiwan, and to provide base-line figures, because of the increasing burden of aggressive interventions in the national healthcare system and the risk of medically futile treatments for suffering patients.²⁰

The National Health Insurance (NHI) in Taiwan provides a single-payer health service scheme and covers 99.9% of Taiwan's legal residents.²¹ The NHI has reimbursed the costs of all palliative care services for patients with cancer or amyotrophic lateral sclerosis, including (i) community palliative care since 1996, (ii) inpatient care in palliative care units (PCUs) in

acute hospitals since 2000, and (iii) hospital liaison palliative care since 2011.²² Additionally, Taiwan was one of the earliest Asian countries to extend NHI-paid palliative care services to patients with non-cancerous diseases and has been offering these services since 2009²³ (The eligibility criteria for people with dementia are shown in Table 1). Patients who receive palliative care are not restricted to use only comfort-oriented treatments but can obtain any medical service in the NHI scheme, making an investigation of the linkage between palliative care and life-sustaining treatments possible.

Palliative care has been gradually accepted as a standard for cancer treatment by clinicians and patients during the past three decades in Taiwan.²⁴ The rate of CPR dropped by 54.3% between 1997 and 2004 for cancer patients at the same time as the expansion of palliative care services and the implementation of the Hospice Palliative Care Act 2000 in Taiwan.²⁵ Our population-based study in Taiwan aimed to investigate the utilisation of palliative care and its association with the following aggressive interventions for patients with dementia and to analyse whether the association differed between those with and without cancer during the initial years of extending the national palliative care services from cancer-based practice to non-cancerous diseases.

Methods

Study design and data source

We conducted a nationwide cohort study with matched controls using Taiwan's National Health Insurance Research Database (NHIRD), which includes inpatient and ambulatory care claims data between 2000 and 2013. The information contained in this database included the date of hospitalisation; disease diagnoses based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes; medical expenditures; and prescriptions. Because patient identifiers were removed and all patient information was analysed anonymously, ethics approval regarding the need for informed patient consent was waived by the institutional review board of Chi-Mei Medical Center, Taiwan.

Cohort definition

The study population included patients aged 18 years and older who had been newly diagnosed with dementia from 2002 to 2013. Dementia was defined by ICD-9-CM codes 290.1x-209.4x, 291.2, 292.82, 294.1x, 294.8, 331.0, 331.1x, 331.2, or 331.82; at least one inpatient record of an ICD-9-CM dementia code; or at least three outpatient records within 1 year after the first dementia code. As the palliative care payment scheme was extended to non-cancer patients in 2009,²³ patients with dementia with any palliative care claim before 2009 were excluded. Those with missing information such as date of birth or gender were also excluded (Figure 1).

Next, patients with dementia who obtained palliative care between 2009 and September 2013 were selected. Palliative care was identified by the claims and ambulatory care orders in

PCUs, liaison palliative care, and community palliative care. The upper limit of reimbursement was once per week for liaison palliative care and two times per week for community care. For each patient who had palliative care, to reduce the potential for confounding, two comparative samples were assembled from the patients without palliative care by matching for age, gender, cancer status (ICD-9-CM: 140–208), Charlson Comorbidity Index, the same year of dementia diagnosis, and index date. The index date was defined as the first date of obtaining palliative care for the treatment cohort and the date of hospital admission for the comparative cohort. Malignancy status was considered in the matching procedure because the paradigm for providing palliative care in conventional clinical practice in Taiwan was cancer-based.^{14,21}

Baseline comorbidities and Charlson Comorbidity Index were defined based on information from at least one inpatient record or three outpatient records from within 1 year before the index date. Other comorbidities were classified using ICD-9-CM codes: diabetes mellitus, coronary artery disease, cerebrovascular disease, and chronic obstructive pulmonary disease. Death from 2009 to 2013 was determined if a patient was coded as ‘in-hospital death’ or had withdrawn from the NHI programme within 30 days after the last hospital discharge without any other health care visits.

Outcome measurements

The life-sustaining treatments consisted of enteral tube insertion, tube feeding, blood

transfusions, haemodialysis, respiratory therapies including non-invasive positive pressure ventilators, and cardiopulmonary life-sustaining treatments. Use of these interventions was defined as a dichotomous variable.

Statistical analysis

Data are presented as frequencies and percentages for categorical variables and as means and standard deviations or median and interquartile ranges for continuous variables. To compare differences between patients with dementia who had and did not have palliative care, a Pearson's χ^2 test and Student's *t*-test or Wilcoxon rank-sum test were used for categorical and continuous variables, respectively.

A conditional logistic regression model was used to evaluate the association between the use of palliative care and life-sustaining treatments in the study cohorts and a subgroup analysis of patients with dementia with or without cancer and to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) after adjusting for other comorbidities. Statistical significance was set at a *p* of <0.05 (two-tailed). SAS 9.4 for Windows (SAS Institute, Inc., Cary, North Carolina, USA) was used to conduct all statistical analyses.

Results

Table 2 presents the distribution of the baseline characteristics of the patients with dementia in the source population (*N*=239,633) and the samples after matching (*n*=5988). Palliative

care was provided to 457 patients before 2009 and 3,928 patients after 2009. The overall percentage of receiving palliative care among whole dementia population is 1.83% (1.64% after 2009). In the source population, patients who had palliative care were older, and there were higher proportions of patients with a cancer diagnosis than those without palliative care (37.93% and 11.53%, respectively).

The matched samples comprised 1996 patients who had palliative care (treatment cohort) and 3992 matched subjects who did not have palliative care (comparative cohort; Table 2, right columns). The treatment cohort had a significantly higher percentage of ED visits before the index date and a higher mortality during the study period, as well as a shorter survival time after registration.

The length of stay and frequency for three categories of palliative care services for patients with dementia are illustrated in Table 3. As for those without cancer, the percentage of liaison palliative care use was higher, and the rate of community palliative care use was lower (54.88% and 20.12%, respectively) than the corresponding rates in the overall group of cases. More than 30% of patients had two or more types of palliative care (Supplementary Figure 1).

The association between palliative care and life-sustaining treatments for the matched cohorts is presented in Table 4 while the total utilisation of life-sustaining treatments in the source population is shown in Supplementary Table 1. Patients receiving palliative care had lower

odds of undergoing haemodialysis, mechanical ventilation, endotracheal intubation, tracheostomy, defibrillation, temporary pacemakers, and CPR than a comparative cohort. Conversely, the treatment cohort had a higher utilisation rate and odds of enteral tube insertion, tube feeding, and non-invasive ventilator use.

In a subgroup analysis of those with and without cancer, except for enteral tube insertion and tube feeding, palliative care was more consistently associated with fewer life-sustaining treatments for those with cancer (Figure 2). Moreover, of the interventions among those without cancer, palliative care was only associated with a significantly reduced risk of CPR.

Discussion

Based on data from the first 5-year period when the pioneer national palliative care scheme was extended to non-cancerous diseases in Asia, we found that the rate of palliative care use for patients with dementia was 1.64% and that the services remained limited to an end-of-life stage (median survival time after service: 36 days). Patients with dementia who received palliative care had a decreased risk of undergoing treatments such as invasive respiratory therapies and CPR, but had increased odds of enteral tube insertion, tube feeding, and non-invasive ventilator use. However, as for palliative care services for patients with dementia, malignancy status was also associated with reduced life-sustaining treatments. This phenomenon in Taiwan implies that practitioners and families do not sufficiently consider

advanced dementia a terminal illness such as cancer and that patients without cancer are less well recognised in the traditional paradigm of palliative care in a Chinese culture-based society, resulting in a lower probability of withholding or withdrawing life-sustaining treatments.²⁶ The challenges faced in Taiwan may inform policy in countries that are initiating a national palliative care scheme for dementia or for Chinese culture-based areas.

The high burden imposed by aggressive interventions for patients with dementia in Taiwan may be attributed to cultural, legal, and health care policy-related factors. The majority of older Taiwanese adults feel that discussing death-related topics is taboo, and this presents a barrier to advance care planning (ACP).²⁷ Clinical decision-making often relies solely on surrogate decisions made by relatives who lack knowledge of the benefits and burdens of life-sustaining treatments.²⁸ Even for dementia patients who have declared their preferences in advance, the implementation of ACP could be a challenge; for example, the rate of discrepancy between Taiwanese patients and their family caregivers regarding treatment-related preferences was found to be 48.3% for tube feeding, 48.5% for CPR, and 60.3% for mechanical ventilation.²⁶ The prevailing value of life preservation in Chinese cultures,²⁹ as well as a lack of a practical mechanism in the Taiwanese legal system that protects incompetent patients' advance choices or best interest, may also result in the frequent overriding of their preferences or medical professionals' suggestions by families to use aggressive procedures rather than comfort-only care.³⁰

The low coverage and late availability of palliative care in Taiwan might also have resulted from insufficient background knowledge on the norms and standards of palliative care practice for dementia among clinical practitioners and the general population. Moreover, the NHI eligibility criteria for palliative care for dementia in Taiwan, which were developed according to the symptoms burden and care needs for cancer population, might not be applicable for patients with dementia.^{23,31} Another controversy of current eligibility criteria is employing stage 5 on the Clinical Dementia Rating scale,³² which is uncommon in literature reviews and we feel it may not convince many neurologists and psychiatrists to refer patients to palliative care. The profoundly diminished physical condition of these patients who were enrolled based on the criteria for palliative care may explain the high prevalence of long-term use of artificial nutrition.

Cancer, renal failure, respiratory failure, and mechanical ventilation have been found to be strong predictors of hospice referral in hospitalised patients with dementia.³³ Taiwanese patients with dementia were often considered for hospital-based palliative care if they had initially undergone a series of life-sustaining treatments to reverse an acute illness or critical condition and then encountered the dilemma of withdrawing or withholding the interventions because of a poor prognosis.^{34,35} For the selected life-sustaining treatments in this study, families, as well some medical professionals, in Taiwan often consider enteral feeding, blood transfusions, non-invasive ventilators, and haemodialysis as less uncomfortable than other

invasive respiratory therapies and CPR.^{23,34} Therefore, even after obtaining palliative care, withdrawing or withholding the aforementioned interventions may be more emotionally challenging and commonly postponed until death was imminent, especially for those without cancer who were less likely to be considered terminally ill. Those patients who tended to have a prolonged trial of aggressive treatments were mainly admitted to ICUs or other wards rather than PCUs. Most of the patients, however, had a lower likelihood of being discharged alive, resulting in a high proportion of liaison palliative care services at the end of life but in a low utilisation of home care as observed in our data.

European and North American studies have reported that a varied but consistently lower proportion of patients with dementia received tube feeding at an end-of-life stage (less than 2% to 25%),³⁶⁻³⁸ but, in Asia, the data indicated that more than one-half of patients with dementia had ever been enterally fed in Hong Kong,²⁹ Israel,³⁹ and this Taiwanese study. Many family caregivers in Taiwan are deeply influenced by traditional Chinese customs and believe that artificial nutrition is essential to basic care and that dying patients become 'hungry ghosts' if they are not provided adequate nutrition;⁴⁰ these caregivers are thus usually reluctant to prevent the aggressive intubation of patients with dementia.⁶

Kiely et al. reported that more than one-half of the residents with advanced dementia in long-term care facilities who were referred to hospice had an eating problem.⁴¹ Enteral tube insertion and feeding are predominantly performed during acute hospital referral for not only

dysphagia but also acute infection and dehydration.⁴² The more frequent ED visits in the treatment cohort might have contributed to the insertion of enteral tubes, as it is common in Taiwan to continue tube feeding without swallow training once the tube has been inserted because of a misunderstanding of its advantages for preventing patients with dementia from choking and aspiration pneumonia.⁴³

In the 2015 Quality of Death Index report, the quality of end-of-life care in Taiwan was ranked high in relation to the care provided in other countries worldwide.²⁴ However, the system of palliative care for patients with non-cancerous diseases in Taiwan needs urgent improvement; the current paradigm for initiating palliative care services should be shifted from considering survival prediction towards the maximisation of comfort throughout the entire disease course and that ACP should be initiated earlier with patients and families.^{1,4} In response to this objective, the first government-sponsored guidebook for clinical practice and public education on palliative care for dementia in Taiwan was edited by a domestic scientific committee and published in October 2016.⁴⁴ At the end of 2015, Taiwan legalised the Patient Autonomy Act, which acknowledges the statutory role of ACP and will facilitate more advance decisions for patients with dementia.

The strengths of our study include its national population-based approach, large number of cases, and comparative analysis matched for multiple factors. One limitation is that despite adjusting for the Charlson Comorbidity Index, the absence of information on disease severity

and functional status in the database may have confounded the analysis. Second, the exact initiation date of liaison palliative care during hospitalisation could not be determined from the database, and thus, the day on which the hospital admission occurred was substituted as the index date. This method may have overestimated the time from the index date to death and might also have limited our ability to distinguish the sequence of care between liaison palliative care services and life-sustaining treatment. However, this bias might have been adjusted for after matching because the same criteria were applied to the index date for the comparative group. Finally, the potential for under-reporting of symptoms because of patients' poor communication capacity and limitations regarding the number of diagnoses coded in the dataset could have contributed to an underestimation of comorbidities for the patients with dementia.

Conclusion

Palliative care for patients with dementia in Taiwan is rarely used but is associated with reduced life-sustaining treatments except for tube feeding and non-invasive ventilators. Malignancy status may influence clinicians' and relatives' perception of terminal illness and the paradigm of healthcare practice. Objectives should include: modifying the indications to enable the timely introduction of palliative care to patients with dementia and their relatives; increasing public awareness of the terminal nature of dementia; and facilitating ACP and shared decision-making between healthcare practitioners, patients, and their families. Further

studies with a pre-post or randomised trial design are recommended to evaluate the effectiveness of palliative care on reducing life-sustaining treatments for patients with dementia.

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Declaration of conflicts of interest

The authors have no conflicts of interests to declare.

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Figure legend

Figure 1. Flowchart of study subject selection. NHIRD = National Health Insurance

Research Database.

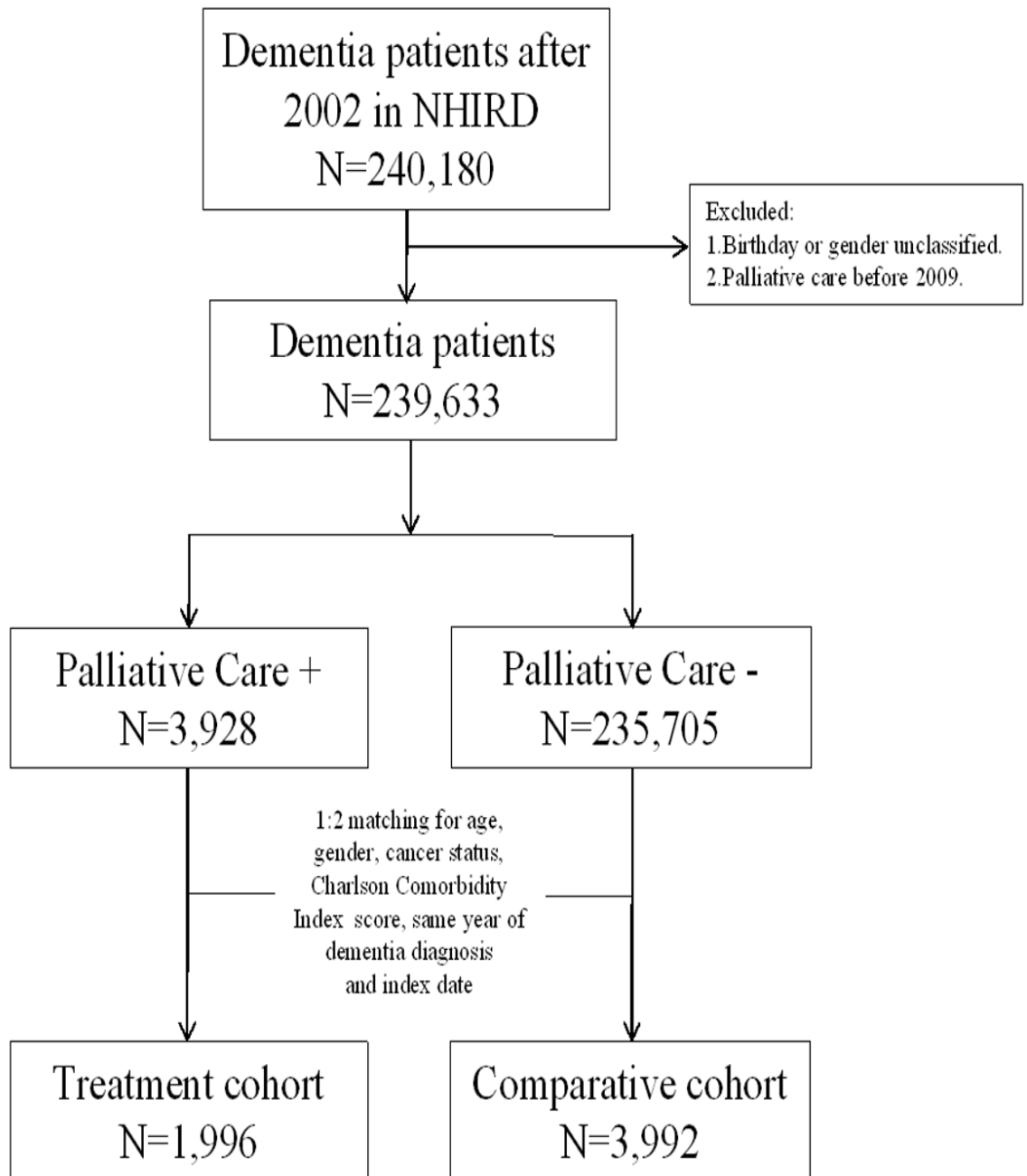


Figure 2. Forest plot of the risk of life-sustaining treatments associated with palliative care for dementia patients with and without cancer. CI = confidence interval. HFOV = high frequency oscillatory ventilation.

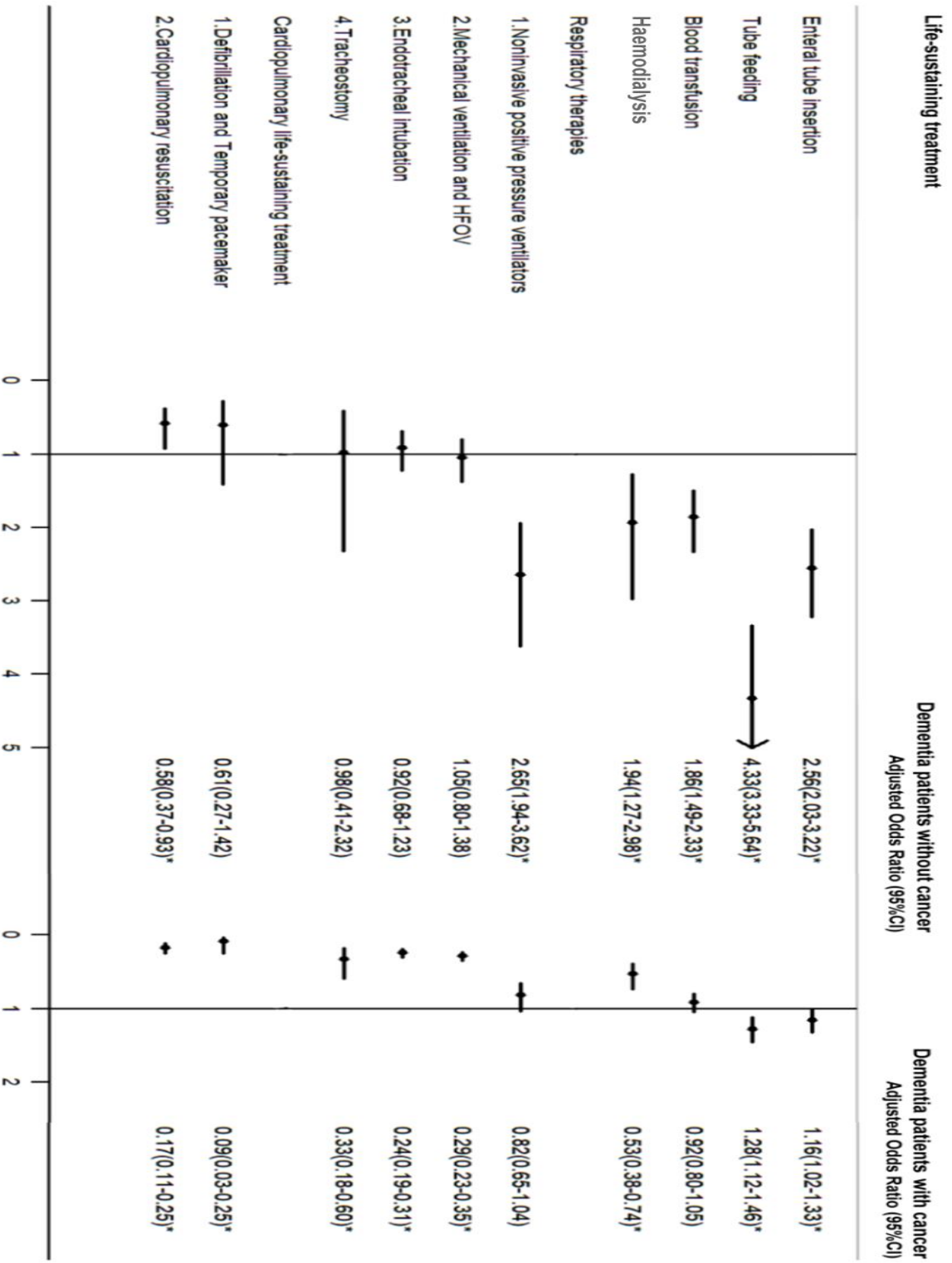


Table 1. Eligibility criteria for palliative care in dementia in Taiwan.

I. Essential criteria: Clinical Dementia Rating³² (CDR) = 5

Patients with dementia have deteriorated in terms of complete inability to communicate, dysphagia, total dependence on feeding (oral or tube), incontinence, bed-bound, and joint contracture

II. Associated clinical conditions^a:

Patients experience acute deterioration of one or multiple following conditions during their disease course

1. Electrolyte imbalance
 2. Pain
 3. Severe dyspnoea
 4. Malignant bowel obstruction
 5. Severe vomiting
 6. Fever, suspect infection
 7. Seizure
 8. Delirium
 9. Pre-dying state
-

^aThese conditions are exactly the same as the eligibility criteria for the palliative care of cancer patients.

Table 2. Baseline characteristics of the source population ($N = 239,633$) and study participants ($n = 5,988$).

	Source population			Matched cohorts	
	Dementia with palliative care $N = 3928$	Dementia without palliative care $N = 235705$	p -value ^a	Dementia with palliative care $N = 1996$	Dementia without palliative care $N = 3992$
Characteristics used for matching					
Age, mean \pm SD	77.81 \pm 10.02	74.73 \pm 13.78	<0.0001	80.02 \pm 7.16	80.02 \pm 7.16
Gender, n (%)					
Male	2053 (52.27)	117288 (49.76)	0.0018	1086 (54.41)	2172 (54.41)
Charlson Comorbidity Index			<0.0001		
<3	906 (23.07)	82208 (34.88)		18 (3.52)	36 (3.52)
3–5	1284 (32.69)	91878 (38.98)		219 (42.77)	438 (42.77)
≥ 6	1738 (44.25)	61619 (26.14)		275 (53.71)	550 (53.71)
Comorbidities, n (%)					
Malignant neoplasm	1491 (37.93)	27177 (11.53)	<0.0001	1484 (74.35)	2968 (74.35)
Other Characteristics					
Other comorbidities, n (%)					

Diabetes	1470 (37.42)	83799 (35.55)	0.0151	937 (46.94)	2166 (54.26)
Coronary artery disease	1658 (42.21)	98976 (41.99)	0.7834	1078 (54.01)	2467 (61.80)
Cerebrovascular disease	2087 (53.13)	120690 (51.20)	0.0165	1378 (69.04)	2986 (74.80)
Chronic obstructive pulmonary disease	1488 (37.88)	81128 (34.42)	<0.0001	1054 (52.81)	2386 (59.77)
ED (1 year before registration), <i>n</i> (%)	2841 (72.33)	N/A ^b		416 (81.25)	686 (66.99)
<3 times	1431 (50.37)	N/A ^b		300 (58.59)	779 (76.07)
≥3 times	1410 (49.63)	N/A ^b		212 (41.41)	245 (23.93)
Death, <i>n</i> (%)	3372 (85.85)	N/A ^b		1746 (87.47)	1848 (46.29)
Time from index date to death, days					
Median (Q1–Q3)	36 (16–88)	N/A ^b		33 (15–76)	38 (10–181)
≤7 days, <i>n</i> (%)	404 (11.98)	N/A ^b		213 (12.20)	367 (19.86)
8–180 days, <i>n</i> (%)	2578 (76.45)	N/A ^b		1379 (78.98)	1019 (55.14)
>180 days, <i>n</i> (%)	390 (11.57)	N/A ^b		154 (8.82)	462 (25.00)

ED: emergency department; N/A: not applicable; Q1: first quartile; Q3: first quartile; SD: standard deviation.

^a*p*-value was based on a Pearson's chi-square test for categorical variables and Student's *t*-test or Wilcoxon rank-sum test for continuous variables.

^bNot applicable because there was no defined index date for the registration of dementia patients who did not have palliative care for the source population.

Table 3. Categories of palliative care services for patients with dementia.

	<i>N</i> (%)	Mean ± SD	Median (Q1–Q3)
Dementia patients who received palliative care (total, <i>N</i> = 1996; multiple categories possible)			
Category A ^a , per person, days	1150 (57.62)	17.14 ± 24.74	10 (4–21)
Category B ^b , per person, times	888 (44.49)	1.67 ± 1.22	1 (1–2)
Category C ^c , per person, times	679 (34.02)	13.19 ± 20.59	6 (3–15)
Dementia patients with cancer who received palliative care (<i>N</i> = 1484; multiple categories possible)			
Category A ^a , per person, days	881 (59.37)	18.34±26.95	10 (5-23)
Category B ^b , per person, times	607 (40.90)	1.77±1.33	1 (1-2)
Category C ^c , per person, times	576 (38.81)	12.37±19.15	6 (3-13)
Dementia patients without cancer who received palliative care (<i>N</i> = 512; multiple categories possible)			
Category A ^a , per person, days	269 (52.54)	13.22 ± 14.77	8 (3–18)
Category B ^b , per person, times	281 (54.88)	1.46 ± 0.89	1 (1–2)
Category C ^c , per person, times	103 (20.12)	17.78 ± 26.92	10 (4–22)

Q1: first quartile; Q3: first quartile; SD: standard deviation.

^aCategory A: Palliative care unit/hospice ward.

^bCategory B: Hospital liaison palliative care/hospice shared care, with the upper limit of service reimbursement: once per week.

^cCategory C: Community palliative care/hospice home care, with the upper limit of service reimbursement: twice per week.

Table 4. Association between palliative care and life-sustaining interventions for matched cohorts of patients with dementia.

	Dementia with palliative care <i>N</i> = 1996	Dementia without palliative care <i>N</i> = 3992	Adjusted odds ratio ^a (95% CI)
Enteral tube insertion^b, <i>n</i> (%)	1151 (57.67)	1994 (49.95)	1.42 (1.27–1.59)
Tube feeding, <i>n</i> (%)	1305 (65.38)	2156 (54.01)	1.73 (1.54–1.95)
Blood transfusion^c, <i>n</i> (%)	855 (42.84)	1641 (41.11)	1.07 (0.95–1.20)
Haemodialysis, <i>n</i> (%)	106 (5.31)	283 (7.09)	0.74 (0.56–0.96)
Respiratory therapies			
Non-invasive positive pressure ventilators ^d , <i>n</i> (%)	217 (10.87)	386 (9.67)	1.22 (1.01–1.46)
Mechanical ventilation and HFOV, <i>n</i> (%)	240 (12.02)	1006 (25.20)	0.41 (0.35–0.48)
Endotracheal intubation, <i>n</i> (%)	171 (8.57)	827 (20.72)	0.37 (0.31–0.44)
Tracheostomy, <i>n</i> (%)	22 (1.10)	99 (2.48)	0.44 (0.27–0.71)
Cardiopulmonary life-sustaining treatment			
Defibrillation and temporary pacemaker, <i>n</i> (%)	13 (0.65)	98 (2.45)	0.23 (0.12–0.43)
Cardiopulmonary resuscitation, <i>n</i> (%)	55 (2.76)	401 (10.05)	0.25 (0.18–0.33)

CI: confidence interval. HFOV: high frequency oscillatory ventilation.

^aAdjusted for confounding covariates including comorbidities.

^bIncluded nasogastric tube insertions, gastrostomy, and jejunostomy.

^cWhole blood or packed red blood cell transfusion.

^dIncluded Nasal PAP (positive airway pressure), CPAP (continuous positive airway pressure), and Bi-PAP (bi-level positive airway pressure).