Protocol: Trends in survival following dementia diagnosis, 2000-2018: a multinational cohort study

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1. Introduction

Dementia is a highly disabling syndrome that is often devastating for persons who have it and for their families. At present, it is estimated that 47 million people globally have dementia, and the prevalence is expected to reach more than 131 million by 2050. The prevalence of dementia (like any other condition) is driven by both the incidence of dementia and the average duration of the disease episode, i.e., survival.[1] Although survival estimates from clinical service are confounded by time of diagnosis, studies on survival from the point of clinical diagnosis of dementia may offer an important estimate of the extent of the workload generated by this population. However, very few studies have been conducted to track mortality among people with dementia. Large scale studies using electronic health records are even more scarce. A cohort study from the UK used data from The Health Improvement Network (THIN), a primary database, to estimate survival after a diagnosis of dementia in primary care, compared with people without dementia.[2] The median survival for people with dementia diagnosis was estimated at 6.7 years at age 60-69 and only 1.9 years at age 90 or over. More recently, a Taiwan study used data from the 2001 to 2010 National Health Insurance Research Database (NHIRD) and concluded a median survival time of 3.38 years.[3]

2. Aims

By using data retrieved from electronic health record from eight databases, this study aims to:
1) To estimate median survival from the point of recorded diagnosis of dementia of any kind for different countries.
2) To estimate relative mortality risk of people diagnosed with dementia over time and compared with the general population, by specific, gender, age, and types of dementia.

3. Methods

3. 1 Description of data source

The data source will vary by country/region; however, all sites will contribute data that is derived from electronic health data about dementia diagnosis and vital status in a defined population (e.g. entire country or defined region within a country). The study period of interest will be the longest period available for each site (e.g., Hong Kong: 1st January 2002 to 31st December 2018). An individual site may not be able to contribute to all parts of each objective. However, estimates of median survival time after the first record of dementia and standardized mortality ratio (SMR) are the highest priority.

Data sources from different countries/regions include:

1. UK: The Health Improvement Network (THIN)
2. Germany: German statutory health insurance, Allgemeine Ortskrankenkasse (AOK)
3. Finland: The Finnish MEDALZ (Medication use and Alzheimer's disease) cohort
4. Ontario, Canada: The administrative-data derived dementia cohort held at ICES (formerly known as the Institute for Clinical Evaluative Science)
5. New Zealand: Data from the National Minimum Dataset (NMDS), National Non-Admitted Patient Collection (NNPAC), and the Mortality Collection (MORT)
6. South Korea: National Health Insurance Service (NHIS) data
7. Taiwan National Health Insurance Research Database (NHIRD)
8. Hong Kong Clinical Data Analysis and Reporting System (CDARS)

3.2 Participants

Diagnosis: Dementia diagnosis will be measured by the presence of ICD-9-CM codes for dementias (290), dementia in conditions classified elsewhere (294.1), unspecified dementia (294.2), Alzheimer's disease (331.0), frontotemporal dementia (331.1), and dementia with Lewy bodies (331.82). Corresponding ICD-10 codes are listed in Table 1.

Table 1. ICD-9 and ICD-10 codes for dementia

	Germany	**Finland**	**Canada**	**New Zealand**	**South Korea**	**Taiwan**	**Hong Kong**
Classification system	ICD-10-GM (German modification)	ICD-10	ICD-9 (2000-2001) and ICD-10-CA (2002+)	ICD-10-AM/ACHI/ACS	ICD-10-CM	ICD-10-CM T	ICD-9-CM
Dementia	F00-03 F05.1 G30, G31.0 G31.1 G31.82 G31.9	-	Using ICD-9: 290 294.1 294.2 331.0 331.1 Using ICD-10-CA: F00-03 G30 G31.8	F00-03 G30 G31.1 G31.83	F00-03 G30 G31.1 G31.83	F00-03 G30 G31.1 G31.83	290 294.1 294.2 331.0 331.1 331.82
Alzheimer's Disease	F00, G30	F00, G30	Using ICD-9: 331.0 Using ICD-10-CA: F00, G30	F00, G30	F00, G30	F00, G30	331.0
Vascular dementia	F01	-	Using ICD-9: 290.4 Using ICD-10-CA:	F01	F01	F01	290.4

			F01				
Lewy body dementia	F02.8 G31.82	-	Using ICD-10-CA: F02.8 G31.8		G31.83		331.82

Our primary interest is dementia of any kind. As a secondary objective, we will also explore the feasibility of estimating survivals by subtypes of dementia: Alzheimer's disease (331.0), vascular dementia (290.4), and Lewy body dementia (331.82).

Study participants. We include only people with incident diagnosis of dementia during the study period. If there is no measure of whether a diagnosis is an incident diagnosis (commonplace in electronic medical records and claims data), a one-year lookback period will be needed to ascertain whether a diagnosis is the first diagnosis of dementia. Take Hong Kong data as an example, although data is available between 2001 and 2018, year 2001 will be treated as the lookback year and the study period will be defined as 2002-2018. Individuals with a diagnosis record during the lookback period will be excluded. We include only adults aged 60 years or over at the date of the first diagnosis of dementia.

3.3 Other information required

a) Individual level information

- Gender
- Date of birth
- Admission date of the first diagnosis of dementia
- Vital status (1=death, 0=alive)
- Date of death
- Censor: if patients were transferred out of the practice, had not consulted in three years, or were alive at the end of the study period.
- Comorbidities: history of diabetes, cardiovascular disease, hypertension, cerebrovascular disease, and high cholesterol. Information on commodities are optional.

The individual level data should in general have the following form

Patient ID	Date of birth	Age	Gender	Diagnosis	Start date	End date	Vital Status
285	15/04/1924	77	0	331.0	01/01/2001	08/12/2005	1
368	05/08/1930	78	1	290.4	16/07/2008	31/12/2010	0

Note that each patient should contribute to only one line in the dataset. All records before the onset of dementia should be removed. The "Start date" is the date of the first diagnosis.

b) Aggregated population level data

Mortality data from an official government census are needed to calculate the Standardized Mortality Ratio (SMR) during the study period. Relevant data include population size and number of deaths for a given year by gender and age group.

3.4 Analysis

SAS will be used to perform statistical analysis. We will use Kaplan-Meier estimator to estimate the survival function for the dementia cohort. We categorize age at diagnosis into five-year age bands and estimate the survival function separately. The survival function for Alzheimer's disease, vascular dementia, and Lewy body dementia will also be compared, if possible. Cox proportional hazards models will be used to determine the effect of covariate on overall survival, including age, gender, calendar year of the first diagnosis. The impact of the diagnosis will be estimated using the SMR. SMR is quantified as the ratio of observed number of deaths in the study group to expected number of deaths in the general population. The expected number of deaths will be calculated as the total number of person-years at risk in each sex-, age group- and calendar year band, multiplied by the corresponding age- (5-year age groups or other, depending on the population data available), sex- and calendar-year specific (e.g., HK: 2001–2010) death rate in the general population.

4. Results (with preliminary results from Hong Kong as an example)

Note that the data are only preliminary result obtained from an example data that are for illustration purpose only.

4.1 Basic descriptive statistics

Table 2. Sample characteristics

	Hong Kong, N(%)	UK	Taiwan	Korea	Finland
Total *N*	25873				
Alzheimer's Disease	5967 (23.1)				
Vascular dementia	7959 (30.8)				
Lewy body dementia	-				
Other dementia	11947 (46.2)				
Female	15886 (61.4)				
Age at diagnosis, M(sd)	82.6 (7.9)				
Number of deaths	14765 (57.1)				

Table 3. Annual number of dementia diagnosis by age and gender in Hong Kong

	Total	Age band (years)						Gender	
		60-64	65-69	70-74	75-79	80-84	85+	Male	Female
2001	5119	77	229	499	877	1182	2255	3309	1810
2002	3926	52	178	401	662	928	1705	2465	1461
2003	1410	45	90	181	151	364	468	826	584
2004	1415	36	86	177	291	325	500	806	609
2005	1512	24	106	153	292	401	536	908	604
2006	1653	35	73	191	319	413	622	1011	642
2007	1621	30	57	170	321	417	626	925	696
2008	2398	39	90	212	457	575	1025	1450	948
2009	4217	63	123	376	703	1049	1903	2555	1662
2010	2602	30	68	221	413	660	1210	1631	971

4.2 Survival estimates

Table 4. Median survival time by age, gender, and types of dementia (in days)

	Hong Kong	UK	Taiwan	Korea	Finland
Total *N*	1145 (1117,1182)				
Types of dementia					
Alzheimer's Disease	1470 (1390, 1597)				
Vascular Dementia	1255 (1197, 1322)				
Lewy body dementia	-				
Gender					
Female	1317 (1274, 1364)				
Male	956 (917, 991)				
Age at diagnosis					
60-64	2863 (2370, -)				
65-69	2188 (1913, 2437)				
70-74	1882 (1703, 1995)				
75-79	1529 (1462, 1623)				
80-84	1291 (1226, 1350)				
85+	778 (753, 808)				

Figure 1. Kaplan-Meier survival curves

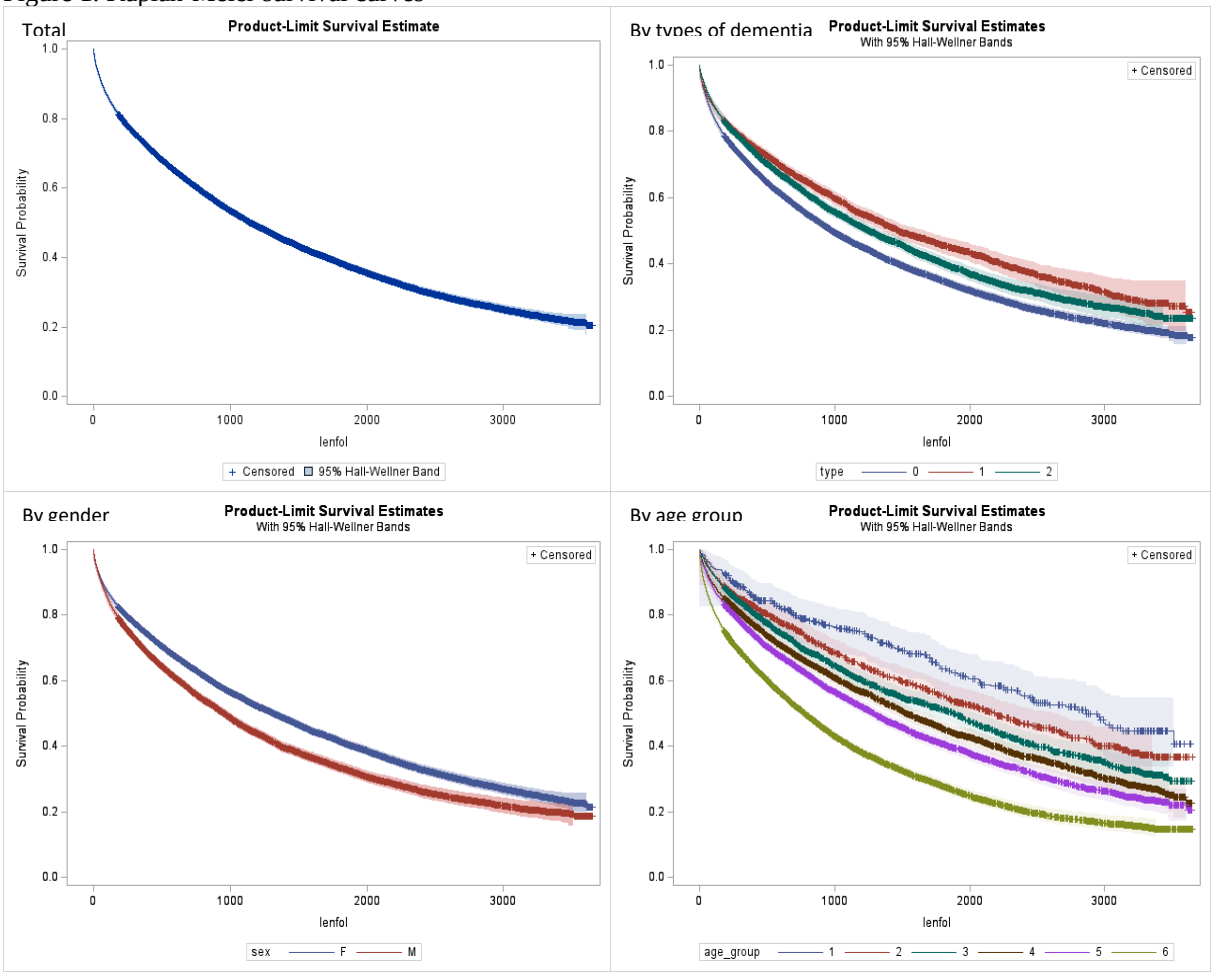

Table 5. Estimates of hazard ratios from Cox proportional hazard regression

	Hong Kong	UK	Taiwan	Korea	Finland
Types of dementia (ref: other dementia)					
Alzheimer's Disease	0.780***				
Vascular dementia	0.894***				
Lewy body	-				
Gender (ref: male)					
Female	0.711***				
Age at diagnosis (ref: 60-64)					
65-69	1.300**				
70-74	1.525***				
75-79	1.800***				
80-84	2.089***				
85+	3.089***				
Comorbidities					

Table 6. All-cause standardized mortality ratio (SMR) by calendar year

	Hong Kong		UK		Finland	
Year	SMR	SMR 95% CI	SMR	SMR 95% CI	SMR	SMR 95% CI
2001	2.65	(2.52-2.77)				
2002	2.94	(2.82-3.07)				
2003	2.41	(2.28-2.54)				
2004	2.36	(2.23-2.49)				
2005	2.15	(2.02-2.27)				
2006	2.44	(2.31-2.58)				
2007	2.43	(2.30-2.56)				
2008	2.24	(2.13-2.35)				
2009	2.45	(2.35-2.55)				
2010	3.58	(2.31-3.84)				

Reference

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3. Lee K-C, Hsu W-H, Chou P-H, et al. Estimating the survival of elderly patients diagnosed with dementia in Taiwan: A longitudinal study. *PloS one* 2018; 13: e0178997.