從一般族群分析失智症病人的風險及死亡率：10 年健保資料庫分析

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摘 要

失智症是造成病人殘障的高風險疾病，很少研究指出一般族群中失智症的累進風險。本研究希望評估台灣族群中失智症的共病風險以及存活率。我們從全民健康保險研究數據庫(TNHIRD)分析，從1999-2008 收集共 48710 位失智症病人，平均年齡≧18 歲，根據 ICD-9 代碼(290-290.9，294，331-失智症診斷碼)，按照年齡和性別，以 1：1 方式隨機匹配對照組。利用邏輯回歸比較失智症共病比例，及 Cox-Proportional 模型，了解相對風險值(RR=Relative Risks)，並分析病人 10 年累積存活率。結果年齡增加失智症風險亦提高。而具有共病症者失智症更高，包含腦血管疾病、糖尿病、高血壓、冠心病、週邊動脈疾病、充血性心臟疾病、慢性肺阻塞性疾病、胃腸道出血、以及癌症。由回歸模式分析，失智症比起非失智症約有 1.1～1.7 倍的相對風險(RR)；其中腦血管疾病的 6.42 倍最高，具統計意義(個別 P 值 < 0.01)。長期追蹤失智症病人，其累積生存率隨之下降(第 1 年 0.93，第 5 年 0.82，第 9 年 0.77，log-rank test, p<0.0001)。調整及多變數回歸分析，失智症的死亡平均風險，約多了 2.23 倍 (RR2.23，95%信賴區間 CI=2.13-2.34)。10 年分析結果顯示失智症和許多共病有關。而年齡因素更與高死亡率相關。如何於一般族群中尋找具有認知功能障礙者，早期篩選可能共病症加以控制，或許可以改善失智症的不良預後。

關鍵詞：失智症，風險及死亡率，共病症，十年資料分析

The Risks and Mortality of Dementia among General Population: A 10-Year Registration Study in Taiwan

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Abstract

The aim of this study was to assess the risk and mortality of dementia in Taiwan. We analyzed the data collected from Taiwan National Health Insurance Research Database (TNHIRD) 1999-2008, and got a cohort of 48710 subjects aged≧18 yrs old. Dementia was defined based on ICD-9 code (290-290.9, 294,331) with a randomly matched control 1:1 by age and sex. The logistic regression and Cox proportional model were adopted for the baseline demographics and relative risk (RR). The cumulative survival years were estimated between dementia and non-dementia patients in general population. Results showed dementia was increasing with age, and co-morbidities were higher in dementia together with cerebrovascular disease, diabetes, hypertension,

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coronary artery disease, peripheral artery disease, congestive heart disease, chronic pulmonary obstructive disease, gastrointestinal bleeding, or cancer. By conditional regression models, we found that RRs for dementia were 1.1~1.7 times higher than those for non-dementia patients, and that the highest RRs appeared in cerebral vascular disease, reaching 6.42 times, with statistically significance (individual $p<0.01$). The cumulative survival rate decreased with years in dementia than in non-dementia (1-year 0.93, 5-year 0.82, 9-year 0.77, log-rank test, $p<0.0001$). Adjusting confounders with multivariate regression led us to the finding that RRs for dementia was 2.25 times higher (RR 2.23, 95% confidence interval (CI) 2.13–2.34). In brief, the 10-year analysis indicated that dementia were associated with other diseases, and age played a key role. Implications emerge that screening for cognitive impairment in advance might help control dementia and its co-morbid disorders.

Keywords: Dementia, Risk and Mortality, Co-Morbidities, 10-Year Registration

I. Introduction

Dementia is a major disabling disease in elderly people [1]. This disease may induce immense distress among family and care givers, leaving economic and social burden behind [2]. In general population in US, the prevalence is much higher than in Europe and Asia countries [3]. The etiology is still out of our understanding. Genetic factor may play a major role, but vascular-related mechanisms are still the mainstream for causes of dementia in addition to the degenerative process [4-6]. In our previous studies we pointed out that carotid atherosclerosis among hemodialysis (HD) patients are associated with higher rates of cognitive impairment or dementia [7]. We also estimated the risks in uremic patients with hemodialysis and found that the prevalence of dementia was much higher in age-stratified and co-morbid patients compared to the controls [7]. Searching from recent literatures, the worldwide and large-scale studies in the incidence or prevalence of dementia in the general population are lacking. The aim of our study is to evaluate the risk and mortality of dementia in a large national-based registration in Taiwan.

Dementia is characterized by progressive deterioration in cognitive ability and capacity for independent living beyond the expectations from normal aging subjects [8]. The increasing dementia population is emerging as a global disease recently [9]. Patients with dementia have higher mortality than those subjects without cognitive impairments [10, 11]. According to the World Health Organization’s global burden disease report in 2003, dementia contributed to 11.2% of disability among those people aged 60 years and older. It has been demonstrated that this disability caused by dementia is generally higher than that entailed by other co-morbidities, such as stroke (9.5%), cardiovascular disease (5.0%), and all kinds of cancer (2.4%) [12]. Moreover, individuals with dementia are more likely to be hospitalized for bacterial pneumonia, congestive heart failure, dehydration, duodenal ulcer, and urinary tract infections than aged-matched controls [13, 14].

In addition to the personal suffering of patients beyond economic and social burden, many elderly people feared to become dementia even they are in good activities at present that will leave the preventive strategy away from these population [15]. Another issues that most studies on the occurrence of dementia in the general population were cross-sectional, or small sample size in community or hospitals [16, 17], leading to the incidence under-estimated [18]. The incidence rates reflect the probability of getting dementia conditional on being alive. These rates are based on the experience of a population. Of more interest on the individual level is a person's absolute risk of developing dementia in the next few years or during the rest of his or her life [19]. To calculate these absolute risks, one should take into account the competing risk of dying. Therefore, we performed a large-scaled retrospective study on the incidence of dementia in the general population in Taiwan, which enabled us to calculate period and lifetime risks of developing dementia.

II. Database

The National Health Insurance (NHI) program has provided compulsory universal health insurance in Taiwan since 1995 [7, 20]. With the exception of prison inmates, all citizens are enrolled in the program. All contracted medical institutions must submit standard computerized claim documents for medical expenses. Patients with dementia are easily recognized and registered by physicians without difficulty using proper diagnosis criteria.

Data were obtained from the National Health Insurance Research Database (NHIRD), released for research by the Taiwan National Health Research Institute (NHRI). The NHIRD covers nearly all (99%) inpatient and outpatient medical benefit claims for Taiwan's 23 million residents, is one of the largest and most comprehensive databases in the world, and has been used extensively in various studies. Patient identification numbers, gender, birthday, dates of admission and discharge, medical institutions providing the services, the ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) diagnostic (up to five) and procedure codes (up to five), and outcomes are encrypted. We used the NHIRD for ambulatory care claims, all inpatient claims, and the updated registry for beneficiaries from 1999 to 2008 for this study. All datasets can be interlinked through each individual's unique personal identification number.

1. Patient selection and definition

We designed a longitudinal retrospective cohort study and selected all adult patients (≥18 years old) who was registered in databank between January 1, 1999, and December 31, 2008 (n =48710) as dementia in general population. Dementia was defined based on ICD-9 code (290-290.9, 294,331) with randomly matched control 1:1 by age and sex. The logistic regression was used to determine the baseline correlates to dementia, and Cox proportional hazards models to determine the relative risk (RR). The cumulative survival years were estimated between dementia and non-dementia patients in our databases.

2. Demographics and variable co-morbidities

We linked to the diagnostic codes through the inpatient and outpatient claims databases of the NHI. Our research included the demographics, gender, age of registered dementia at onset, and co-morbidities. Baseline co-morbid diseases such as diabetes (DM), hypertension (HTN), congestive heart failure (CHF), coronary artery disease (CAD), cerebrovascular accident (CVA), peripheral vascular disease (PVD), other cardiac disease, dysrhythmia, chroninc obstructive pulmonary disease(COPD), gastrointestinal bleeding(GI bleeding), liver disease and cancers were assessed since the beginning in dementia and non-dementia control group. The ICD-9-CM codes used to define each condition are shown in Appendix 1. Selected co-morbidities were determined based on diagnostic codes in ambulatory visits at least 3 times within a year or hospitalization database at least 1 time in past year before to make the diagnosis of dementia.

3. Statistical analyses

The data were analyzed using the Statistical Package for Social Sciences for Windows 17.0 (SPSS Inc; Chicago, IL, USA). Baseline characteristics of patients with and without dementia were compared using Pearson $\chi 2$ tests. Significance was set at $P < 0.05$. We estimated the prevalence of dementia in the overall population and within the subgroups by age. Logistic regression [expressed as odds ratios (OR) with 95% confidence intervals (95% CIs)] was done to determine the association among a variety of patients characteristics and dementia. Overall patient survival was described using the Kaplan-Meier method based on with and without dementia. Hazard ratios (HRs) and 95% CIs were derived from Cox proportional hazards models. The assumption of

proportionality of risks met in their Cox models. To adjust for potential confounding in the relationship between co-morbidities and the risk of mortality, multivariate analyses were used to model to all-cause mortality.

III. Results

1. Clinical demographic characteristics

This cohort comprised totally 48710 subjects with matched control by 1:1 were identified having dementia (Table 1). Male to female was 1:0.9. Dementia was increasing with age. The co-morbid disease such as DM, HTN, CHF, CAD, CVA, PVD, dysrhythmia, COPD, GI bleeding, and cancers are all statistically significant(individual P < 0.05) between dementia and non-dementia groups in this cohort. During all significant co-morbid variables, CVA is a major portion of dementia, with 6~8 times higher than non-dementia subjects (adjusted OR 6.42, 95% CI: 6.00-6.87, P <0.05). It was considered the vascular dementia was more likely in our data (Table 2).The prevalence of dementia in general population was increasing with age, and aged ≧75 yrs was 7~10 times higher than aged-control from 18~44 years old after adjusting covariates(adjusted OR 7.37, 95% CI: 6.46-8.42).This non-linearly association was similarly to age-stratification group as in literature reports. The overall mortality in dementia group was 2.23 times higher than control by regression analysis, with all co-morbidity are all independent risks (individual P <0.05) (Table 3).

Table 1 Patients characteristics and association with and without dementia

	with Dementia N=24355		without Dementia N=24355		*p*-value
	n	(%)	n	(%)	
Gender					1.0000
Female	11699	(50.00)	11699	(50.00)	
Male	12656	(50.00)	12656	(50.00)	
Age at onset (years)					0.9187
18-44	2790	(50.00)	2790	(50.00)	
45-59	2923	(49.99)	2924	(50.01)	
60-74	7775	(49.79)	7842	(50.21)	
≥ 75	10867	(50.16)	10799	(49.84)	
Baseline co-morbidity					
Diabetes Mellitus					<0.0001
No	19303	(46.78)	21958	(53.22)	
Yes	5052	(67.87)	2397	(32.18)	
Hypertension					<0.0001
No	13143	(42.12)	18061	(57.88)	
Yes	11212	(64.05)	6294	(35.95)	
Congestive Heart Failure					<0.0001
No	22530	(48.88)	23565	(51.12)	
Yes	1825	(69.79)	790	(30.21)	
Coronary Artery Disease					<0.0001
No	20381	(47.81)	22246	(52.19)	
Yes	3974	(65.33)	2109	(34.67)	

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Cerebrovascular Disease					<0.0001
No	17220	(42.63)	23172	(57.37)	
Yes	7135	(85.78)	1183	(14.22)	
Peripheral Vascular Disease					<0.0001
No	23564	(49.53)	24013	(50.47)	
Yes	791	(68.81)	342	(30.19)	
Other Cardiac disorder					<0.0001
No	22962	(49.13)	23778	(50.87)	
Yes	1393	(70.71)	577	(29.29)	
Dysrhythmia					<0.0001
No	22385	(48.78)	23504	(51.22)	
Yes	1970	(68.83)	851	(30.17)	
Chronic Obstructive Pulmonary Disease					<0.0001
No	20783	(47.86)	22640	(52.14)	
Yes	3572	(67.56)	1715	(32.44)	
Gastrointestinal Bleeding					<0.0001
No	20524	(47.59)	22607	(52.41)	
Yes	3831	(68.67)	1748	(31.33)	
Chronic Liver Disease					<0.0001
No	22675	(49.04)	23560	(50.96)	
Yes	1680	(67.88)	795	(32.12)	
Cancers					<0.0001
No	23023	(49.37)	23611	(50.63)	
Yes	1332	(65.16)	744	(35.84)	

Table 2 Risk factor Analysis of covariates with dementia (conditional logistical regression)

Covariate	Univariate analysis	Multivariate analysis
	OR (95% CI)	OR (95% CI)
Diabetic Mellitus (yes v no)	2.46 (2.33-2.59)*	1.61 (1.52-1.71)*
Hypertension (yes v no)	2.65 (2.54-2.76)*	1.47 (1.41-1.54)*
Congestive Heart Failure (yes v no)	2.45 (2.25-2.67)*	1.17 (1.06-1.29)*
Coronary Artery Disease (yes v no)	2.09 (1.98-2.22)*	1.18 (1.11-1.26)*
Cerebrovascular Disease (yes v no)	8.44 (7.91-9.01)*	6.42 (6.00-6.87)*
Peripheral Vascular Disease (yes v no)	2.36 (2.08-2.69)*	1.44 (1.25-1.66)*
Other Cardiac (yes v no)	2.51 (2.28-2.77)*	1.63 (1.46-1.81)*
Dysrhythmia (yes v no)	2.46 (2.26-2.67)*	1.38 (1.26-1.52)*
Chronic Obstructive Pulmonary Disease (yes v no)	2.33 (2.19-2.48)*	1.60 (1.50-1.72)*
Gastrointestinal Bleeding (yes v no)	2.43 (2.29-2.58)*	1.69 (1.58-1.80)*
Chronic Liver Disease (yes v no)	2.21 (2.02-2.41)*	1.60 (1.45-1.75)*
Cancers (yes v no)	1.84 (1.68-2.02)*	1.60 (1.45-1.76)*

OR: Odds ratios; CI: Confidence interval; * significant $p < 0.05$.

Table 3 Risk factors for all-cause mortality

Covariate	Univariate analysis	Multivariate analysis
	HR (95% CI)	HR (95% CI)
Sex (Male v Female)	1.24 (1.20-1.29)*	1.32 (1.27-1.38)*
Age stratification		
18-44 (Reference)	1	1
45-59	2.25 (1.92-2.62)*	1.98 (1.70-2.31)*
60-74	5.53 (4.84-6.31)*	4.23 (3.70-4.84)*
≥ 75	9.53 (8.36-10.85)*	7.37 (6.46-8.42)*
Dementia (yes v no)	2.81 (2.70-2.93)*	2.23 (2.13-2.34)*
Diabetic Mellitus (yes v no)	2.19 (2.09-2.29)*	1.44 (1.37-1.50)*
Hypertension (yes v no)	2.24 (2.16-2.33)*	1.17 (1.12-1.22)*
Congestive Heart Failure (yes v no)	2.95 (2.77-3.13)*	1.50 (1.41-1.60)*
Coronary Artery Disease (yes v no)	2.01 (1.92-2.11)*	1.02 (0.97-1.07)*
Cerebrovascular Disease (yes v no)	2.55 (2.45-2.66)*	1.35 (1.29-1.41)*
Peripheral Vascular Disease (yes v no)	2.07 (1.88-2.28)*	1.18 (1.07-1.30)*
Other Cardiac disorder (yes v no)	1.87 (1.73-2.02)*	1.06 (0.98-1.15)*
Dysrhythmia (yes v no)	2.17 (2.04-2.31)*	1.11 (1.04-1.19)*
Chronic Obstructive Pulmonary Disease (yes v no)	2.46 (2.34-2.58)*	1.35 (1.28-1.42)*
Gastrointestinal Bleeding (yes v no)	1.93 (1.84-1.93)*	1.16 (1.10-1.22)*
Chronic Liver Disease (yes v no)	1.81 (1.69-1.94)*	1.39 (1.29-1.49)*
Cancers (yes v no)	2.67 (2.49-2.86)*	1.84 (1.72-1.98)*

HR: Hazard ratio; CI: Confidence interval; *$P < 0.05$.

2. Cumulative survival rate and risk of all-cause mortality

The cumulative survival rate for patients without dementia was 98.1% at one- year, 94.7% at three-tear, 91.5% at five-year, 88.3% at sever-year, 85.5% at nine-year, compared to those with dementia was 91.2% at one-year, 82.0% at three-year, 75% at five-year, 70% at sever-year, and 65.7% at nine-year respectively (Table 4). The overall survival rate showed a significantly different between these two groups (log-rank p <0.001) that dementia group had predictive survival decline by 20% in 10-year follow ups (Figure 1). A multivariate Cox proportional hazards analysis showed that male gender, older age, dementia, co-morbid with DM, CHF, CAD, CVA, PVD, chronic lung disease, chronic liver disease, and cancers were all significantly associated with a higher mortality rate.

Table 4 The survival rate in each independent year with/without dementia

	1-year	3-year	5-year	7-year	9-year
without dementia	98.1%	94.7%	91.5%	88.3%	85.5%
with dementia	91.2%	82.0%	75.0%	70.0%	65.7%

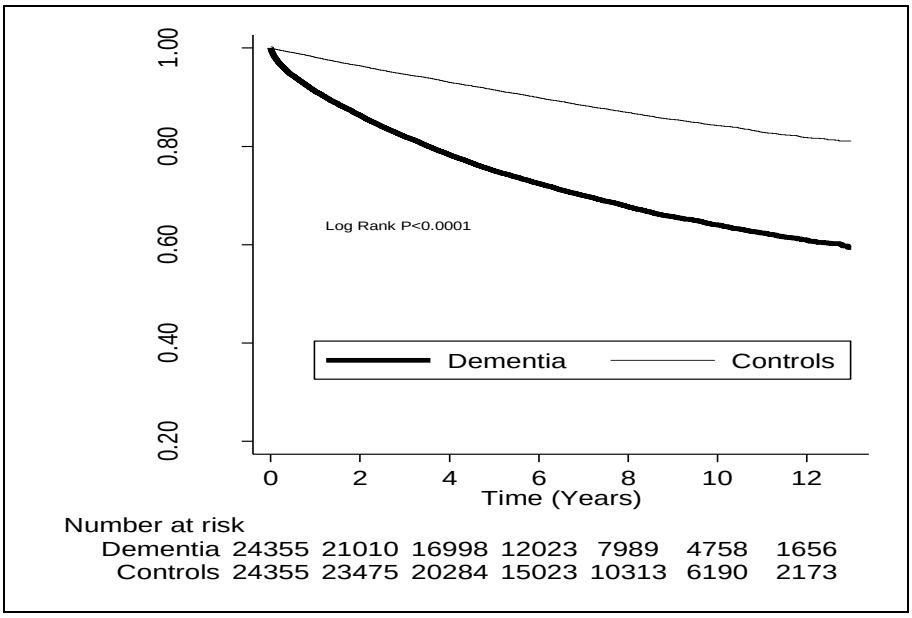

Fig. 1 Using Kaplan-Meier survival statistics, it showed crude overall survival curves by with and without dementia (log-rank P<0.0001)

IV. Discussion

This study used a national representative database, the NHIRD, to investigate the epidemiology of dementia and mortality in general population in Taiwan. The results showed that older age and all co-morbid disorders were independently associated with dementia in this population surveillance, and CVA-related group had much higher odd ratio to have dementia. All these independent variables are relevant to mortality about 1~2 times than non-dementia subjects without risks.

Dementia is a common disease but frequently under-recognized in general population [9, 19, 21]. Varied cognitive disorders have been defined as a complication of stroke and all co-morbidities in this large-scale national-based population [22]. Our cohort researches found the dementia patients had more incidence of co-morbid diseases, which were demonstrated as independent risks. Among all, CVA was the highest risk to develop dementia in following years. It was considered that atherosclerotic change and epithelium dysfunction played an important role in the mechanism of cognitive impairment [23-25]. Since the vascular-related dementia is the secondary leading etiology in clinical practice. Simply from this point of view, the modification and correction of vascular-related risks may be a strategy for preventive cognitive deterioration in general population [24]. The other co-morbid diseases played another role in dementia and all these co-morbidity took different percentage of relevant dementia in study [22, 26-28]. From recent publication from Mainland China that the prevalence was varied even in Chinese population such as in China, Hong-Kong and Taiwan [29]. The authors stated the insufficient or incomplete data might make such differences. However, our data from national dataset have adequate sample sizes in registration, and this information may provide more accurate references in future research. The hazard ratio in our age-stratification was different from cross-sectional study, and it might result from the lack of clinical diagnosis or assessment but just for registration. Murray et al. reported that up to 40% of elderly in general population had various severities of dementia by different cognitive tests, yet, only 2.9 % of registration had the diagnosis on their medical records [30]. In our dataset, the dementia group over 60 years old with estimating up to 76.5%. This discrepancy explained the big-gap from registry and clinical practice [31]. It needs further clarification with uniform method in future works.

The prevalence of dementia increased with age. It ranged from 0.3 to 0.6% in patients aged < 60 years old

in our analysis. As previous studies indicated that the incidence of dementia became more obvious in patients aged ≥ 60 years old. From literature reported that age, race, CVA, DM, HTN, hyperlipidemia and smoking are all risk factors for dementia [22, 27, 28]. Since age is either a modifier or a driving force of confounder behind dementia, it will affect the accumulative prognosis predominantly. Dementia is associated with a higher risk of multiple adverse outcomes [31]. In our study, subjects with dementia had a lower cumulative survival rate and high co-morbidity than those without. It is reasonable to predict that the adverse events will more happen in dementia population. The hazard ratio in dementia group is around 2~3 times of risks than non-dementia subjects. It is similar to the studies with cohort design in literatture [32].

One of the advantages in our study was that the national-based retrospective cohort was conducted. The samples size was big enough to analyze the accumulative outcomes in population with and without dementia. The uniformly national registration excluded the dirty data after adjustment of confounders without missing available information as listing co-morbidities could affect the statistical outcomes in long-term follow ups. However, there were some limitations including lack of actual measurement of cognitive tests with neuropsychological battery or mini-mental status examination, and a possible miscoding or missing code of dementia, which will make the hazard ratio under-estimated in our cohort study.

V.Conclusion

In summary, the study showed that dementia group was associated with adverse outcomes and co-morbidities among large databank registry in general population. The associated dementia was much higher proportional to all-cause mortality and lower cumulative survival rate in 10-year following ups. Therefore, the routine screening for cognitive impairment among population in order to identify those at risk for associated co-morbidities or adverse outcomes are warranted for future ongoing study.

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***Appendix 1*. ICD-9-CM codes used to identify clinical conditions**

Conditions	***ICD-9-CM***
Dementia	290-290.9, 294, 331
Diabetes mellitus	250; 357.2; 362.0X; 366.41
Congestive heart Failure	362.11, 401-405, 437.2
Congestive heart Failure	398.91; 422; 425; 428; 402.X1; 404.X1; 404.X3
Coronary artery disease	410- 414
Cerebrovascular accident/TIA	430-438
Peripheral vascular disease	440-444; 447; 451-453; 557
Other cardiac	420-421; 423-424; 429; 785.0-785.3
Chronic obstructive pulmonary disease	491-494; 496; 510
Gastrointestinal bleeding	456.0-456.2; 530.7; 531-534; 569.84; 569.85; 578
Liver disease	570; 571; 572.1; 572.4; 573.1-573.3
Dysrhythmia	426-427
Cancer	140-172; 174-208; 230-231; 233-234

ICD-9-CM, *International Classification of Diseases, Ninth Revision, Clinical Modification*;
TIA, transient ischemic attack