Outcomes of Dementia Among Dialysis Patients: A Nationwide Population-Based Study in Taiwan

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Abstract: *Background*: High prevalence of cognitive impairment or dementia is associated with end-stage renal disease (ESRD). The risk for dementia and its prognostic significance remain unclear. This study aimed to determine the prevalence, correlations and outcomes of dementia in chronic ESRD dialysis patients. *Methods*: Using Taiwan National Health Insurance Research Database (NHIRD), we analyzed ESRD patients who received dialysis between 1999 and 2005 to determine the associations between baseline dementia and subsequent outcomes after dialysis. The cumulative survival rate after dialysis was calculated using the Kaplan-Meier method. Cox proportional hazards model was used to identify the risk factors for all-cause mortality. *Results*: A total 51,238 incident dialysis patients were examined in this study, including 867 patients with dementia. The prevalence of dementia was increasing with age. The proportional rate of dementia in elderly (≧75) patients was 10 times higher than that in aged 18~44 years old of baseline. The co-morbidity with cerebrovascular disease was independently associated with dementia in dialysis population. The 1-, 5-, and 9- year cumulative survival rate were 82.1, 32.7, and 16.5% in ESRD patients with dementia, and 93.5, 62.8, and 41.6% in those without dementia (log-rank: p <0.001). ESRD patients with dementia were associated with 53% higher death risk than those without dementia (HR 1.53, 95% CI: 1.40-1.68). *Conclusions*: Dementia was associated with poor outcome and co-morbidities among ESRD dialysis patients.

Keywords: Dialysis, elderly, end-stage renal disease, dementia, outcome.

INTRODUCTION

Dementia is characterized by progressive deterioration in cognitive ability and capacity for independent living beyond the expectations from normal aging subjects [1, 2]. The increasing dementia population is emerging as a global disease recently [3]. Patients with dementia have higher mortality than those subjects without cognitive impairments [4, 5]. 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%) [6]. 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 [7-9].

The global prevalence and incidence of end-stage renal disease (ESRD) have been increasing annually especially in the elderly population [10, 11]. The prevalence of dementia is higher in ESRD dialysis patients than that in general population [12-16], and dialysis patients with dementia have higher mortality rate than those without dementia. Extant research suggests that the survival rate was 24% and 66% for patients with and without dementia at two-year follow ups respectively after starting to dialysis [17].

The increasing number of dementia superimposed on chronic dialysis patients often have more complex multisystem problems, which will result in changing demands on health care and changing healthcare arrangement. The incidence and prevalence rates of patients with ESRD on dialysis are high in Taiwan. However, the existing research on the association with dementia and its prognostic significance in ESRD is scarce. This study aimed to evaluate the epidemiology and long-term mortality rate of dementia in ESRD dialysis patients. We used a large data set from the Taiwan National Health Insurance Research Database (NHIRD) to design this cohort.

Database

For this study, we retrieved ambulatory care claims, all inpatient claims, and the updated registry for all ESRD patients receiving dialysis from 1999 to 2008. Data was collected from Taiwan's NHIRD provided by Taiwan's National Health Insurance (NHI), a compulsory universal health insurance program which

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has covered the healthcare costs of all of Taiwan's residents except prison inmates since 1995. The program required all medical institutions to use standard computerized claim documents for reimbursement of medical expenses. Patients with end-stage renal disease (ESRD) were eligible for every type of renal replacement therapy without any charge, and all their expenses were covered by NHI. The NHIRD contained nearly all (99%) inpatient and outpatient medical benefit claims for the 24 million residents of Taiwan, and had been used extensively in various studies. This database provided a great deal of information, including gender, birth date, dates of admission and discharge, the medical institutions providing the services, the ICD-9-CM (International Classification of Diseases, 9th Revision, Clinical Modification) diagnostic and procedure codes (up to five each), and encrypted outcomes. NHIRD was released with de-identified secondary data for public research purposes. All personal identification information on files connected with the present study was scrambled using surrogate identification numbers to ensure patient confidentiality. The Bureau of National Health Insurance approved this application (NHRI-NHIRD-99182).

Patient Selection and Definition

We designed a longitudinal cohort study and selected adult ESRD patients (≥18 years old) on maintenance dialysis beginning between January 1, 1999 and 2005. ESRD patients on maintenance dialysis were defined as having undergone dialysis for more than 90 days. Patients who had undergone renal transplantation before beginning dialysis were excluded. Patients were followed from the first reported date of dialysis to the date of death, end of dialysis, or December 31, 2008. The data of 51,238 incident dialysis patients were enrolled and analyzed.

We linked study subjects to their claim data to identify underline co-morbidity with dementia (ICD-9-CM 290-290.9, 294, 331). Selected co-morbidities were determined based on diagnostic codes in ambulatory visits at least 3 times in the first year before the start of dialysis or hospitalization databases. A total of 867 patients were diagnosed with dementia during the follow-up period.

Ascertaining the Demographic and Co-Morbid Variables

We linked to the diagnostic codes through the inpatient and outpatient claims databases of the NHI. Our research included not only survival status, but also date of death, patient demographics, and baseline co-morbidities. Important factors affecting the survival of ESRD dialysis patients were assessed at the start of dialysis. Baseline co-morbidities, such as dementia, diabetes (DM), hypertension (HTN), congestive heart failure (CHF), coronary artery disease (CAD), cerebrovascular accident (CVA), peripheral vascular disease (PVD), other cardiac disorder, dysrhythmia, chronic obstructive pulmonary disease (COPD), gastrointestinal bleeding (GI bleeding), chronic liver disease and cancers, were all estimated.

Statistical Analyses

The data were analyzed using the Statistical Package for Social Sciences for Windows 17.0 (SPSS Inc; Chicago, IL, USA). Parametric Pearson's chi square test was used to compare each variable in the groups of patients with and without dementia. Age was entered as a categorical variables (18 - 44, 45 - 59, 60-74 and 75 years or older). Significance with $p < 0.05$ was set up with two-side analysis. We estimated the prevalence of dementia in the overall population and within the subgroups by age stratification. The cumulative proportion of survival after starting of dialysis was calculated using the Kaplan-Meier method. The log rank test was used to analyze the significance, and Cox proportional hazards models were utilized to identify the risk factors of mortality with Hazard ratios (HRs) and 95% confidence intervals (CIs). To adjust for potential confounding between co-morbidities and the risk of mortality, univariate and multivariate analyses were used to analyze the all-cause mortality.

RESULTS

Demographics and Clinical Characteristics

This cohort comprised 51,238 subjects; among these, a total of 867 (M/F=0.81) patients were identified as having dementia (Table **1**). The overall prevalence of dementia was 1.7 %, and the elderly had much more higher incidence (Figure **1**). The occurrence of dementia was non-linearly associations with age when patients were younger than 60 years old. Only 0.5% of the patients by 18-44 years old, 0.6% by 45-59 years, 2.0% by 60-74 years, and 4.6% by ≥75 years of stratifications had dementia (chi square test, $p < 0.001$). ESRD patients who received hemodialysis (HD) seemed to have a higher rate of dementia than those who received peritoneal dialysis (PD) with statistical significance ($p < 0.001$). Additionally, ESRD with

dementia had more co-morbidities, such as DM, HTN, CHF, CAD, CVA, PVD, dysrhythmia, COPD and GI bleeding, than those subjects without dementia (individual $p < 0.05$).

Table 1: Patients Characteristics and Association with and without Dementia on End Stage Renal Disease (ESRD) Dialysis

	Without Dementia		With Dementia		*p*-value
	n	(%)	n	(%)	
Gender					0.076
Female	26242	(98.2)	478	(1.8)	
Male	24129	(98.4)	389	(1.6)	
Age at onset of hemodialysis (years)					<0.001
18-44	7646	(99.5)	35	(0.5)	
45-59	15743	(99.4)	89	(0.6)	
60-74	19718	(98.0)	394	(2.0)	
≥ 75	7264	(95.4)	349	(4.6)	
Initial dialysis modality					<0.001
Hemodialysis	46927	(98.3)	835	(1.7)	
Peritoneal dialysis	3444	(99.1)	32	(0.9)	
Baseline co-morbidity					
Diabetes Mellitus					<0.001
No	25886	(98.5)	383	(1.5)	
Yes	24491	(98.1)	484	(1.9)	
Hypertension					<0.001
No	10633	(98.7)	140	(1.3)	
Yes	39738	(98.2)	727	(1.8)	
Congestive Heart Failure					0.001
No	38090	(98.4)	614	(1.6)	
Yes	12281	(98.0)	253	(2.0)	
Coronary Artery Disease					0.007
No	39133	(98.4)	640	(1.6)	
Yes	11238	(98.0)	227	(2.0)	
Cerebrovascular Disease					<0.001
No	44646	(99.0)	461	(1.0)	
Yes	5725	(93.4)	406	(6.6)	
Peripheral Vascular Disease					0.005
No	48282	(98.3)	814	(1.7)	
Yes	2089	(97.5)	53	(2.5)	
Other Cardiac disorder					0.769
No	45907	(98.3)	788	(1.7)	
Yes	4464	(98.3)	79	(1.7)	

Table 1 continue …

	Without Dementia		With Dementia		*p*-value
	n	(%)	n	(%)	
Dysrhythmia					0.001
No	47229	(98.4)	789	(1.6)	
Yes	3142	(97.6)	78	(2.4)	
Chronic Obstructive Pulmonary Disease					<0.001
No	45663	(98.4)	738	(1.6)	
Yes	4708	(97.3)	129	(2.7)	
Gastrointestinal Bleeding					<0.001
No	39290	(98.6)	578	(1.4)	
Yes	11081	(97.5)	289	(2.5)	
Chronic Liver Disease					0.815
No	45957	(98.3)	789	(1.7)	
Yes	4414	(98.3)	78	(1.7)	
Cancers					0.47
No	47412	(98.3)	811	(1.7)	
Yes	2959	(98.1)	56	(1.9)	

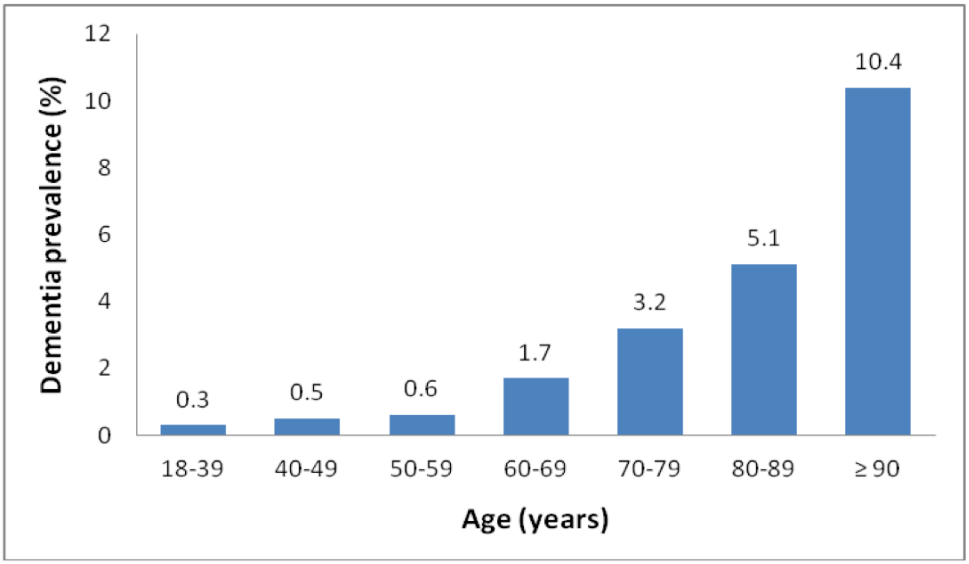


Figure 1: Prevalence of dementia by different age groups among ESRD dialysis patients.

By multivariate analysis, there was no significant difference between sex and dialysis modality (Table **2**). The significant associations among age stratifications and co-morbidities were defined. ESRD dialysis patients aged ≥ 75 years old were associated with 7~10 times greater of dementia than those with 18-44 years baseline (adjusted OR 7.40, 95% CI: 5.18-10.58). In addition, ESRD patients with CVA were also associated with a higher rate of dementia (adjusted OR 5.64, 95% CI: 4.88-6.49).

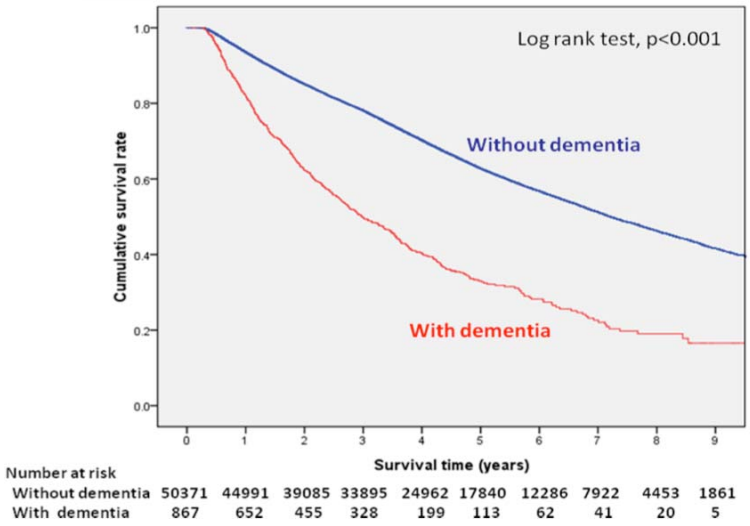
Cumulative Survival Rate and Risk for All-Cause Mortality

The cumulative survival rate for patients without dementia was 93.5% at one-year, 62.8% at five-year, and 41.6% at nine-year, compared to those with

Table 2: Analysis of Covariates with Dementia Among ESRD Dialysis Patients

Covariate	Univariate analysis	Multivariate analysis
	OR (95% CI)	OR (95% CI)
Sex (Male v Female)	0.89 (0.77-1.01)	-
Age at initiation of dialysis		
18-44 (Reference)	1	1
45-59	1.24 (0.83-1.83)	1.01 (0.68-1.50)
60-74	4.37 (3.09-6.17)*	3.13 (2.19-4.46)*
≥ 75	10.50 (7.40-14.88)*	7.40 (5.18-10.58)*
Diabetic Mellitus (yes v no)	1.34 (1.17-1.53)*	1.06 (0.91-1.22)
Hypertension (yes v no)	1.39 (1.16-1.67)*	0.95 (0.78-1.15)
Congestive Heart Failure (yes v no)	1.28 (1.10-1.48)*	-
Coronary Artery Disease (yes v no)	1.24 (1.06-1.44)*	0.81 (0.68-1.05)
Cerebrovascular Disease (yes v no)	6.87 (5.99-7.87)*	5.64 (4.88-6.49)*
Peripheral Vascular Disease (yes v no)	1.51 (1.14-1.99)*	1.09 (0.82-1.46)
Other Cardiac (yes v no)	1.03 (0.86-1.30)	-
Dysrhythmia (yes v no)	1.49 (1.17-1.88)*	0.94 (0.74-1.21)
Chronic Obstructive Pulmonary Disease (yes v no)	1.70 (1.40-2.05)*	1.09 (0.90-1.33)
Chronic Liver Disease (yes v no)	1.03 (0.81-1.30)	-
Cancers (yes v no)	1.11 (0.84-1.45)	-

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



Cumulative survival rate:

	1-year	3-year	5-year	7-year	9-year
without dementia	93.5%	78.1%	62.8%	51.2%	41.6%
with dementia	82.1%	49.7%	32.7%	22.1%	16.5%

Figure 2. Crude overall survival curves for incident ESRD patients stratified by with and without dementia at the onset of dialysis.

dementia was 92.1% at one-year, 32.7% at five-year, and 16.5% at nine-year respectively. The log-rank test showed a significant difference in survival rates between these two groups (log-rank p <0.001) (Figure **2**). A multivariate Cox proportional hazards analysis of baseline data showed that male gender, older age,

Table 3: Risk Factors for All-Cause Mortality Among Dialysis Patients

Covariate	Univariate analysis	Multivariate analysis
	HR (95% CI)	HR (95% CI)
Sex (Male v Female)	1.18 (1.15-1.22)*	1.18 (1.15-1.22)*
Age at initiation of dialysis		
18-44 (Reference)	1	1
45-59	2.30 (2.16-2.45)*	1.83 (1.72-1.96)*
60-74	4.43 (4.17-4.71)*	3.25 (3.05-3.46)*
≥ 75	8.20 (7.68-8.75)*	6.12 (5.72-6.55)*
Dementia (yes v no)	2.53 (2.31-2.76)*	1.53 (1.40-1.68)*
Diabetic Mellitus (yes v no)	2.16 (2.10-2.22)*	1.85 (1.79-1.91)*
Hypertension (yes v no)	1.33 (1.29-1.38)*	0.89 (0.86-0.93)*
Congestive Heart Failure (yes v no)	1.87 (1.82-1.93)*	1.32 (1.28-1.36)*
Coronary Artery Disease (yes v no)	1.82 (1.77-1.88)*	1.13 (1.09-1.17)*
Cerebrovascular Disease (yes v no)	1.92 (1.85-1.99)*	1.34 (1.29-1.39)*
Peripheral Vascular Disease (yes v no)	1.39 (1.31-1.48)*	1.11 (1.04-1.18)*
Other Cardiac disorder (yes v no)	1.32 (1.26-1.38)*	1.07 (1.02-1.12)*
Dysrhythmia (yes v no)	1.86 (1.71-1.89)*	1.18 (1.12-1.24)*
Chronic Obstructive Pulmonary Disease (yes v no)	1.77 (1.70-1.85)*	1.18 (1.13-1.23)*
Gastrointestinal Bleeding (yes v no)	1.44 (1.39-1.48)*	1.19 (1.15-1.23)*
Chronic Liver Disease (yes v no)	1.40 (1.34-1.46)*	1.36 (1.29-1.42)*
Cancers (yes v no)	1.74 (1.65-1.83)*	1.52 (1.44-1.60)*

PD: Peritoneal dialysis; HD: Hemodialysis; HR: Hazard ratio; CI: Confidence interval; *$P < 0.05$.

dementia, co-morbid with DM, CHF, CAD, CVA, PVD, chronic lung disease, chronic liver disease, and cancers were all associated with a significantly higher mortality rate (Table **3**). Overall, ESRD patients with underline dementia were associated with an increasing rate in mortality by 53% (HR 1.53, 95% CI: 1.40-1.68).

DISCUSSION

This study used a national representative database, the NHIRD, to investigate the epidemiology of dementia and mortality in ESRD dialysis patients in Taiwan. The results showed that older age and CVA were independently associated with dementia in ESRD dialysis population. ESRD patients with underline dementia had higher mortality after dialysis than those without dementia.

Dementia is a common disease but is frequently underestimated in dialysis patients. Varied cognitive disorders have been recognized as a complication of ESRD. However, its treatment, the guidelines for the detection, prevention, and management of these disorders are lacking. Our study found the prevalence of dementia was 1.7 %, which was lower than the report of 4% by Kurella and colleagues [16]. The discrepancy might result from the lack of clinical awareness of diagnosis and useful assessment tools for dementia. Murray *et al.* reported that up to 40% of ESRD dialysis patients have various severities of dementia by different cognitive tests; yet, only 2.9 % of ESRD dialysis patients had the diagnosis on their medical records [13]. Sehgal *et al.* found that 30% of ESRD dialysis patients had a varied degree of cognitive impairment [14].

The prevalence of dementia increased with age [16]. It ranged from 0.3 to 0.6% in patients aged < 60 years old. As previous studies indicated, the incidence of dementia became more obvious in patients aged ≥ 60 years old, and evidence showed that age, race, CVA, DM, HTN, hyperlipidemia and smoking are all the

risk factors for dementia [18]. Since age is either a modifier or a driving force of confounder behind dementia, it will affect the accumulative prognosis. In our study, we found that the elderly people and co-morbid with CVA had higher independently risk for dementia in ESRD population. It was considered that atherosclerotic change with epithelium dysfunction played a most important role in the mechanism of cognitive impairment [19]. Simply from this point of view, the modification and correction of vascular-related risks may be a strategy for preventive deterioration in ESRD patients with dementia. It still needs further study in the future.

Dementia is associated with a higher risk of multiple adverse outcomes [20]. In our study, ESRD patients with dementia had a lower survival rate than those without. It is reasonable to predict that the incidental events will happen more frequently in dementia subjects. The ESRD with dementia were associated with higher risks of dialysis withdrawal, hospitalization [10], disability, and mortality [16, 21] especially in delirium status. The ESRD dialysis patients with severe cognitive impairment have approximately 2-fold increased risk of death and dialysis withdrawal [16, 17, 22]. There was substantial practice variation surrounding this issue, leading to a recommendation of renal palliative care. A suggestion from the Renal Physician's Association (RPA) in 2001 pointed out that it was appropriate to withdraw dialysis from patients with advanced dementia due to the lack of decision-making capacity, profound neurological impairment, purposeful behavior, and awareness of self and environment. There should be considered for palliative management in such a kind of ESRD with advanced dementia to determine the ongoing procedures with patients or their families [23].

One of the advantages in our study is that the national-based retrospective cohort was conducted. The samples size was big enough to analyze the accumulative outcomes in ESRD patients 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 ESRD dialysis patients in long-term follow-ups. However, there were some limitations, including the 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 prevalence underestimation in this cohort study.

In summary, the study showed that dementia was associated with adverse outcomes and many co-morbidities among ESRD patients received dialysis. The associated dementia was much higher proportional to all-cause mortality in 9-year follow ups. Therefore, the routine screening for cognitive impairment among dialysis patients in order to identify those at risk for associated adverse outcomes is warranted.

DISCLOSURE

There are no conflict interests in this manuscript.

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