

Abstract

Background : Knowledge on survival in dementia is essential for patients and public health planning. Vascular dementia (VaD) is the second most common cause of dementia after Alzheimer disease.

Objectives: To define the mortality rate of VaD at the Memory Clinic (MC) at Siriraj Hospital and to characterize mortality risk factors of VaD.

Methods: This is a retrospective cross-sectional study of 200 individuals diagnosed as having VaD at the MC at Siriraj Hospital during 2002-2017.

Results: Two hundred cases of VaD were registered at the MC at Siriraj Hospital during 2002-2017. The mean follow up time at our memory clinic was 9.51(sd= 4.48) years. Thirty nine (19.5%) died during the follow up time. Younger age, lower cognitive scores, high serum cholesterol levels, and high blood sugar levels at baseline were significantly associated with death. Regarding medical comorbidity, the mortality risk factors were diabetes mellitus type 2 ($p<0.01$), chronic obstructive pulmonary disease (COPD) ($p <0.01$), having a history of arrhythmia ($p=0.04$), a history of previous cerebrovascular disease (CVD) ($p= 0.02$), a history of thyroid disease ($p <0.01$), and a history of hypnotic drug use ($p<0.01$)

Conclusion: The mortality rate of VaD was 19.5%. Mortality risk factors in our study were younger age, poorer cognition, COPD, Thyroid diseases, use of hypnotics, and other vascular risk factors namely DM, previous CVD, arrhythmia, and dyslipidemia. We did not find gender difference as mortality risk.

Key words: vascular dementia, mortality risk factors, co-morbidity

Factors Predicting Mortality of Vascular Dementia in Thai Cohort at the Memory Clinic at Siriraj Hospital

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Introduction

Dementia is a progressive degenerative disorder of the brain leading to severe cognitive impairment, behavioural disturbances, and loss of functional ability to perform activities of daily living. Cerebrovascular disease is the second leading cause of cognitive impairment in the elderly being second only to Alzheimer's disease (AD). Vascular dementia (VaD) is presumed to account for 20% or more of dementia cases¹.

Many of literatures showed that even mild levels of cognitive impairment gave rise to increased risk of mortality. Some studies found that mortality was similar in AD and VaD, some revealed that VaD had higher mortality than AD or other late onset neurodegenerative dementia^{2,3}.

The purpose of this study was to look at the mortality rate of VaD at the Memory Clinic (MC) at Siriraj Hospital, Thailand, and to evaluate the predictive factors of mortality in vascular dementia individuals.

Material and Methods

This study was a retrospective, cross-sectional study of VaD individuals registered at the Memory Clinic (MC) at Siriraj Hospital from January 2002- January 2017. Dementia was diagnosed by the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*⁴. VaD was defined by the National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria⁵. Subject characteristics recorded in this study included age, gender, baseline body weight, body mass index (BMI), Thai Mental state examination⁶ (TMSE score), Thai

Activity daily living scale⁷ (Thai ADL scale), Clinical dementia rating scale-sum of the boxes⁸ (CDR-sb), Neuropsychiatric inventory⁹ (NPI), Functional assessment questionnaire¹⁰ (FAQ), Fasting blood sugar, HbA1C%, blood sugar levels, blood urea nitrogen levels, lipid profile levels, vitamins B12 level.

Statistical analysis

Variables with normally distribution continuous pattern were express as mean, standard deviation (SD), and differences between groups were assessed with a T-test. Discrete variables were compared with chi-square test. The P value less than 0.05 were considered statistically significant. SPSS version 20.0 was used to analyze data. This study was approved by the committee on human research (Institutional Review Board) at the Faculty of medicine Siriraj Hospital.

Results

Two hundred patients were diagnosed with VaD. Thirty-nine of 200 were death after follow up. The mean follow up time at our memory clinic was 9.51(SD= 4.48) years. The mortality of VaD was 19.5% (95%CI=14.6-22.5), Among the death group, the median age was 75.92 years, 63.16% were men, median body mass index was 21.62 kg/m², mean ADL score was 4.79, mean CDR-sb score was 3.5, mean NPI score was 1.5 and mean FAQ score was 6.50. There was statistical significance between those who were alive and dead in age, TMSE score, blood cholesterol levels, and fasting blood sugar (BS) levels. Lower age, poorer cognition, higher cholesterol levels and higher BS levels were predictors of the mortality in this study. (Table 1)

Table 1: Subject baseline characteristics and blood chemistry results (mean, SD)

	Being alive (n=162)	Death (n=38)	T test: p value
Age	78.49 (7.22)	75.92 (5.81)	0.04
Gender	Men=94 (79.66%)	Men=24(20.34%)	0.78
	Women=68(82.93%)	Women=14(17.07%)	
Body weight (kgms)	56.97(7.72)	59.47(6.84)	0.05
Body mass index	22.53(2.86)	21.63(2.25)	0.07
TMSE	20(5.84)	17.47(5.69)	0.02
Thai ADL scale scores	5.33(4.47)	4.79(3.06)	0.48
CDR-sb	3.13(2.98)	3.50(0.71)	0.86
NPI (Yes)	1.29(1.88)	1.50(0.71)	0.88
FAQ	6.45(7.0)	6.50(0.71)	0.99
Serum cholesterol (mg/dL)	194.82(50.67)	218.47(44.57)	0.01
Serum triglycerides (mg/dL)	137.61(82.94)	141.76(35.99)	0.64
Blood urea nitrogen (mg/dL)	17.47(22.24)	15.13(5.16)	0.52
Vitamin B12 (ng/mL)	787.39(985.67)	638.25(206.71)	0.76
Hemoglobin A _{1c} (%)	6.82(1.38)	6.85(0.89)	0.89
Fasting blood sugar (mg/dL)	111.91(28.29)	134.03(19.50)	<0.0001

TMSE= Thai Mental State Examination,

Thai ADL= Thai Activity of Daily Livings,

CDR-sb= Clinical Dementia Rating- sum of the boxes,

NPI= Neuropsychiatric Inventory (yes items),

FAQ= Functional Assessment Questionnaires

We found that certain medical comorbidities were statistically related to mortality in VaD. They were diabetes mellitus (DM) type 2 ($p<0.01$, LR=8.79), chronic obstructive pulmonary disease(COPD) ($p<0.01$, LR=9.62), a history of arrhythmia ($p=0.04$, LR=3.72), a history of previous cerebrovascular disease (CVA) ($p=0.02$, LR=5.79), a history of thyroid disease ($p<0.01$, LR=22.85),

and a history of hypnotic drug use($p<0.01$, LR=8.43). (Table 2.) Survival analysis of DM type 2 in persons with VaD revealed that mean survival time of VaD with DM type 2 was 9.34(95%CI= 7.79, 10.89) years while mean survival time of VaD without DM type2 was 11.41(95%CI=10.09, 12.72) years (Chi square test $p=0.006$) (Figure1.).

Table 2 Medical comorbidity and death in individuals with vascular dementia

Having histories of medical comorbidities	Death N=38	Being alive N=162	Chi-square test
Hypertension	Y= 86.8% N = 13.2%	Y= 82.1% N= 17.9%	0.48
Diabetes mellitus type 2	Y= 63.2% N = 36.8%	Y= 36.6% N= 63.4%	<0.01 LR=8.79
COPD	Y = 21.1% N = 78.9%	Y = 4.4% N = 95.6%	<0.01 LR=9.62
History of arrhythmia	Y = 18.4% N = 81.6%	Y = 7.4% N = 92.6%	0.04 LR=3.72
History of coronary artery disease	Y =2.6% N = 97.4%	Y = 2.5% N = 97.5%	0.954
History of valvular heart disease	Y = 0.0% N = 100%	Y = 1.9% N = 98.1%	0.398
History of congestive heart failure	Y = 2.6% N=97.4%	Y = 3.1% N = 96.9 %	0.882
History of osteoarthritis knees	Y = 13.2% N= 86.8%	Y = 10.5% N = 89.5 %	0.253
History of rheumatoid arthritis	Y = 0% N = 100%	Y = 0.6% N = 99.4 %	0.62
History of cerebrovascular disease	Y = 57.9% N = 42.1%	Y = 36.4% N = 63.6%	0.02 LR=5.79
History of thyroid disease	Y =28.9% N = 71.1%	Y = 5.6% N=94.4%	<0.01 LR=22.85
Use of hypnotic drugs	Y = 32.4% N = 67.6%	Y =11.7% N = 87.3%	<0.01 LR=8.43
Use of antidepressants	Y = 10.5% N = 89.5%	Y = 11.1% N 88.9%	0.917

COPD= Chronic obstructive pulmonary disease

LR= Likelihood Ratio

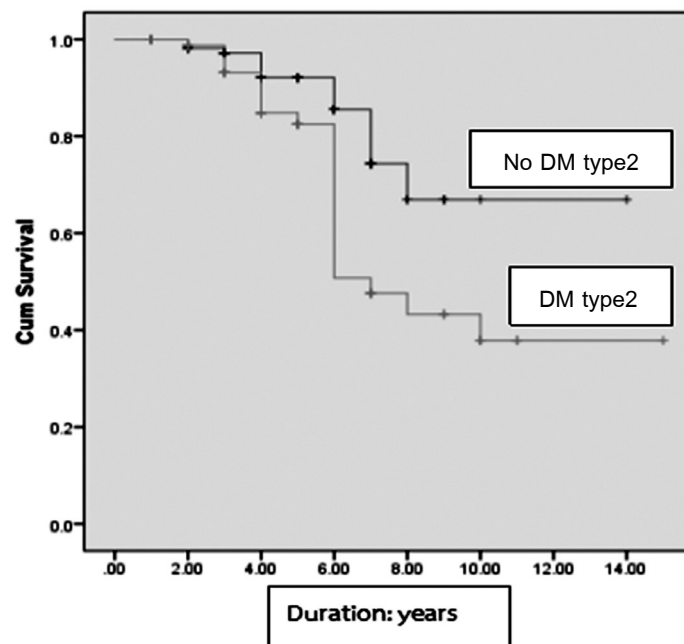


Figure 1. Survival analysis of having diabetes mellitus type 2 (DM type2) in individuals with vascular dementia

Mean survival time of VaD with DM type 2 =9.34 (95%CI= 7.79, 10.89) years

Mean survival time of VaD without DM type2 = 11.41(95%CI=10.09, 12.72) years

Chi square test $p=0.006$

Discussion

We demonstrated that VaD mortality rate in our study was 19.5% (95%CI=14.6-22.5). Predictors of mortality of VaD were older age, poorer cognition, higher cholesterol levels and higher BS levels. Certain vascular comorbidities were also predictors of mortality in VaD.

We did not find gender as a predictor of mortality in this study. Some other studies showed that men had higher mortality risk than women³. Recent review showed that in both, men and women, older age were associated with shorter survival time¹¹.

Our study indicated that cardiovascular diseases and cardiovascular risk factors such as arrhythmia and DM were predicting the mortality in VaD. Previous Australian community study¹² showed that among 25,006 community dwelling individuals with 17.3% diabetes, dementia onset and death

occurred an average 2.2 years and 2.6 years earlier, respectively, in diabetic compared with non-diabetic patients. Age-specific mortality rates were also increased in patients with diabetes. Italian community study¹³ revealed the study of 37,025 patients, 10,161 (27%) developed atrial fibrillation (AF) and 1,535 (4.1%) developed dementia, and AF was independently significantly associated with senile, vascular, and AD dementia^{14,15}.

The Rochester Epidemiology Project¹⁶ during 1985-1989 identified 483 dementia subjects matched to 479 reference population, where 420 referent subjects were individuals from the same Rochester population. They found that VaD with temporally related to a stroke had a worse related mortality (RR=4.5; 95%CI 2.7-7.4) than those with only imaging evidence of bilateral infarctions of grey matter (RR=2.4, 95%CI 1.5-3.8). They also demonstrated that patients with VaD had a higher RR of

death (RR=2.7; 95%CI 1.9-3.9) than patients with dementia overall (RR=1.8; 95%CI 1.6-2.1) and those with AD (RR=1.4; 95%CI 1.2-1.7). We did not identify the temporal relationship to stroke in our study. While, the survival study of dementia in England and Wales in 2005¹⁷ revealed that significant factors that predicted mortality in the presence of dementia during the follow-up included sex, age of onset, and disability. Our study did not find that disability from Thai ADL scale was a predictor of mortality in our cohort.

Other studies showed that vascular risk factors and cerebrovascular disease were association with both VaD and AD, as well as the fact that they reduced life expectancy, with an average survival time of between 4.2 and 10 years after diagnosis¹⁸⁻²⁰. Hypnotic drugs are widely used by elderly, and their impact on mortality is well established²¹. Our study showed the association between the use of hypnotics and mortality in vascular dementia patients. The past study identified that Chronic obstructive pulmonary disease could be a possibly risk factor for the development of mild cognitive impairment and later dementia²². Our study showed that it increased mortality risk patients with VaD.

The main limitations of this study are retrospective design which some information wasn't recorded in database and small sample size. Further study is required for longitudinal population base study with door to door recruitment with biological biomarkers if possible.

The study also has some major strength. Firstly, the possibility to follow all individuals with major comorbidities until they died with causes of death recorded in the death certificates, therefore there was no loss to follow up. Secondly, the follow-up period was relatively long and allowed com-

parisons with most previous reports. Finally, vascular dementia increases significantly the risk for mortality, independently from physical disability. Determining the factors associated with mortality in vascular dementia patients helps detect persons likely to be in terminal phase, making it possible to provide them with the right type of care according to their health and improving the quality of life they have left.

Acknowledgement

We thanked Dr Saowalak Hunnangkul from Department of Research and Development, Faculty of Medicine Siriraj Hospital for her assistance with statistical analysis.

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