Dementia Subtypes, Cognitive Decline and Survival Among Older Adults Attending a Memory Clinic in Cape Town, South Africa: A Retrospective Study

By

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DECLARATION

I, Michael Ssonko, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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ABSTRACT

Background: There are no published longitudinal studies from Africa of people with dementia seen in memory clinics. The aim of this study was to determine the proportions of the different dementia subtypes, rates of cognitive decline, and predictors of survival in patients diagnosed with dementia and seen in a memory clinic.

Methods: Data were collected retrospectively from clinic records of patients aged ≥60 seen in the memory clinic at Groote Schuur Hospital, Cape Town, South Africa over a 10-year period. Diagnostic and Statistical Manual of Mental Disorders (DSM–5) criteria were used to identify patients with Major Neurocognitive Disorders (dementia). Additional diagnostic criteria were used to determine the specific subtypes of dementia. Linear regression analysis was used to determine crude rates of cognitive decline, expressed as mini-mental state examination (MMSE) points lost per year. Changes in MMSE scores were derived using mixed effects modelling to curvilinear models of cognitive change, with time as the dependent variable. Multivariable cox survival analysis was used to determine factors at baseline that predicted mortality.

Results: Of the 165 patients who met inclusion criteria, 117(70.9%) had Major Neurocognitive Disorder due to Alzheimer's disease (AD), 24(14.6%) Vascular Neurocognitive Disorder (VND), 6(3.6%) Dementia with Lewy Bodies (DLB), 5(3%) Parkinson disease-associated dementia (PDD), 3(1.8%) fronto-temporal dementia, 4(2.4%) mixed dementia and 6(3.6%) other types of dementia. The average annual decline in MMSE points was 2.2(DLB/PDD), 2.1(AD) and 1.3(VND). Cognitive scores at baseline were significantly lower in patients with 8 compared to 13 years of education and in those with VND compared with AD. Factors associated with shorter survival included age at onset greater than 65 (HR=1.82, 95% C.I. 1.11, 2.99, p=0.017), lower baseline MMSE (HR=1.05, 95% C.I. 1.01, 1.10, p=0.029) , Charlson's comorbidity scores of 3 to 4 (HR=1.88, 95% C.I. 1.14, 3.10, p=0.014), scores of 5 or more (HR=1.97, 95% C.I. 1.16, 3.34, p=0.012) and DLB/PDD (HR=3.07, 95% C.I. 1.50, 6.29,

p=0.002). Being female (HR=0.59, 95% C.I.0.36, 0.95, p=0.029) was associated with longer survival.

Conclusions: Knowledge of dementia subtypes and survival outcomes will help inform decisions about patient selection for potential future therapies and for planning dementia services in resource-poor settings.

Keywords

Cognitive decline, Comorbidity score, Dementia subtype, Memory clinic, Mini-mental state examination, Survival, Time to event

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With a sense of gratitude, I'm unreservedly thankful to the multi-disciplinary team that assessed and reviewed the patients that attended the memory clinics at Groote Schuur Hospital during the study period.

Most importantly, I am grateful and indebted to the patients whose records were used for this research study.

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Abbreviations

AD – Major Neurological Disorder due to Alzheimer's disease

DLB – Dementia with Lewy Body

DSM – Diagnostic and Statistical Manual of Mental Disorders

FTD – Frontotemporal dementia

HIV – Human Immuno-deficiency Virus

MMSE – Mini-Mental State Examination

MoCA – Montreal Cognitive Assessment

PDD – Parkinson disease Dementia

RBANS – Repeatable Battery for the Assessment of Neuropsychological Status

TTE – Time to Event

VND – Major Vascular Neurocognitive Disorder

WHO – World Health Organization

1.0 CHAPTER 1: INTRODUCTION

1.1 Context of the study

The world population aged 65 and over is projected to more than double, reaching over 1.5 billion in 2050 from 524 million persons in 2010 [1]. The older adult population in sub-Saharan Africa is expected to grow from 32 million in 2019 to 101 million in 2050 [1].

Neurocognitive disorders like dementia are on the rise in developing countries due to the increase in the ageing population [2]. In response, memory clinics have been established in some parts of sub-Saharan Africa to identify, investigate, and treat memory disorders such as dementia [3, 4].

Studies on people living with dementia who have been seen in memory clinics or hospital-clinics in Africa are small and have usually had a cross-sectional design [3-5]. The most common dementia subtypes found in these studies were Major Neurocognitive Disorder due to Alzheimer's disease (AD) and Vascular Neurocognitive Disorder (VND) [3, 5]. Other types were Dementia with Lewy bodies (DLB), Parkinson Disease Dementia (PDD), Frontotemporal dementia (FTD), HIV-associated dementia, alcohol related dementia and mixed dementia [3, 5].

Dementia subtypes have been shown to have different rates of cognitive decline [6]. Different forms of pathophysiology could explain the differences in cognitive decline [7, 8]. A European multi-center study assessing cognitive decline using mean annual MMSE score declines found declines of 2.1 points with DLB, 1.6 points for AD and 1.8 points for PDD [9]. No published African study has described cognitive decline among memory clinic patients and possible factors associated with cognitive decline.

There are no longitudinal studies from memory clinics in Africa assessing mortality, and predictors of mortality. A European memory clinic study found predictors of mortality to include low MMSE, male gender, higher number of medications, institutionalization, and age

after dementia diagnosis [10]. Other factors established elsewhere that appear to influence survival outcomes of dementia are the dementia subtype and rates of cognitive decline [11, 12]. Dementia subtypes have distinctive natural histories. Precise diagnosis may lead to a better understanding of prognosis. Data regarding rates of cognitive decline and survival of the different dementia subtypes have also largely been derived from populations in the developed world.

1.1.1 Purpose of the study

Accurate clinical diagnosis is especially important in resource poor settings where expensive investigations are not readily available. With future advent of potential specific drug therapies, an accurate diagnosis as well as a knowledge of probable survival outcomes of dementia subtypes may be useful. A knowledge of the characteristics of patients seen in memory clinics and their longitudinal trajectories can also be used to further develop these clinics and services for older people with dementia.

The objectives of this study are as follows.

1.1.2 Objectives

1. To determine the proportions of dementia subtypes among older adults attending the memory clinic at Groote Schuur Hospital using standard diagnostic criteria.

2. To examine the rates of cognitive decline of the different dementia subtypes among older adults attending the memory clinic at Groote Schuur Hospital.

3. To determine whether correlations exist between dementia sub-types and survival.

1.2 Ethical considerations

Ethics approval was obtained from the Human Research Ethics Committee (HREC) of the Faculty of Health Sciences, University of Cape Town (HREC-REF: 403/2021). This study was conducted by retrospective review of patients' case notes. A waiver for consent was obtained

from the HREC. Permission to conduct the study was obtained from the medical superintendent of Groote Schuur Hospital.

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1.3.16 References for Chapter 1

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2.0 CHAPTER 2: PUBLICATION-READY MANUSCRIPT

Dementia Subtypes, Cognitive Decline and Survival Among Older Adults Attending a Memory Clinic in Cape Town, South Africa: A Retrospective Study

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2.1 Background

Neurodegenerative disorders like dementia are on the rise in sub–Saharan Africa due to an increase in the numbers of older people [13]. In response, memory clinics have been established in some parts of sub-Saharan Africa to identify, investigate, and treat cognitive disorders such as dementia [3, 4]. There are few studies that have described these cohort of patients, and none that we are aware of that have reported out-patient longitudinal data. Memory clinic or hospital-based studies on people living with dementia in Africa have usually been small or have had a cross-sectional design [3-5].

Kalula *et al* described a cohort of patients seen regardless of age in a memory clinic in Cape Town, South Africa. Within a period of five years, 305 people were seen of whom 74% had dementia [3]. Of these 44% had Major Neurocognitive Disorder due to Alzheimer's disease (AD), 28% Major Vascular Neurocognitive Disorder (VND), and 15% mixed Alzheimer's and vascular dementia. Thirteen percent had other forms of dementia, namely Dementia with Lewy bodies (DLB), Parkinson disease-associated dementia (PDD), fronto-temporal dementia (FTD), HIV-associated dementia, alcohol-related dementia, history of previous head injury and undetermined forms [3]. In this study, however, dementia diagnoses were based on clinicians' impressions rather than standardized diagnostic criteria. In 2011 a Nigerian hospital-based study profiled dementia phenotypes of 108 patients who were inpatients over a 10-year period [5]. Of these 57.4% were diagnosed with AD, 16.7% VND, 3.7% mixed dementia, 3.7% FTD, 2.8% DLB, 2.8% alcohol related dementia, 0.9% PDD and undetermined subtypes 12% [5]. None of the memory clinic studies we reviewed that were conducted in Africa reported rates of cognitive decline or mortality data.

Mini-mental state examination (MMSE) scores have been used to determine cognitive decline in studies conducted in Western and Asian memory clinics [9, 14, 15]. A retrospective chart review of a cohort of people seen in two University Alzheimer's Disease centres in the USA

showed an average annual MMSE decline of 3.2 points in AD and 4.7 points in FTD [14]. A mainly European multi-centre study found mean annual MMSE score declines of 2.1 points with DLB, 1.6 points for AD and 1.8 points for PDD [9]. A memory clinic study in the Republic of Korea comparing AD, VND and PDD subtypes showed more rapid decline in patients with AD compared with the others [15]. Factors like age of symptom onset, level of education, and cardiovascular risk factors have also been shown to predict rates of decline [16-18]. Gerritsen et al showed that neuropsychiatric symptoms were associated with higher rates of cognitive decline [19].

Dementia subtypes and rates of cognitive decline appear to influence survival outcomes in dementia [11, 12]. Slower rates of cognitive decline and longer survival have been shown in Alzheimer's dementia compared with DLB and FTD [12, 20]. A Californian study, where type of dementia was confirmed by autopsy, found a survival from time of diagnosis of 4.2 years for FTD compared to 6 years for AD [12]. In this cohort, FTD had a higher cognitive decline of mean annual rate of 6.7 points compared to AD with 2.3 points [12]. A study of people seen in memory clinics in Sweden with a mean follow-up of 2.5 years found that low baseline MMSE, male gender, higher number of medications, institutionalization, and age were associated with increased mortality after dementia diagnosis [10]. A retrospective study carried out in three Italian dementia out-patient clinics found age, gender and functional status to be the main determinants of patient survival [21]. An Australian study with participants from nine memory clinics found that 57.4% of 779 patients with dementia had died within eight years [22]. In this study, greater deterioration in dementia severity and functional impairment over time predicted mortality independent of baseline levels [22]. A study in specialised outpatients' dementia clinics in Spain found AD to have the best survival while subtypes like Parkinson-Plus Syndromes and dementia due to multiple aetiologies sub-types had the worst prognosis [23]. A Dutch study carried out among patients with young onset dementia in specialised

centres found AD to have a worse survival compared with VND subtype [24]. The same study found a trend of decreased survival for the participants with AD compared with FTD [24].

There are, to our knowledge, no published longitudinal studies of patients with dementia from memory clinics in sub-Saharan Africa that have characterized the subtypes, cognitive decline, survival outcomes and predictors of survival. Dementia subtypes have distinctive natural histories. A precise diagnosis may lead to a better understanding of prognosis. Data regarding rates of cognitive decline and survival of the different dementia subtypes have also largely been derived from populations in the developed world. Accurate clinical diagnosis is especially important in resource poor settings where expensive investigations are not readily available. With the future advent of potential specific drug therapies, an accurate diagnosis as well as a knowledge of probable survival outcomes of dementia subtypes may be useful. A knowledge of the characteristics of patients seen in memory clinics and their longitudinal trajectories can also be used to further develop these clinics and services of older people with dementia. The aim of this study, using data collected on older adults who attended the memory clinic at Groote Schuur Hospital in Cape Town, was to determine the proportions of the different dementia subtypes, the rates of cognitive decline, trajectories of decline of the different dementia subtypes, and to determine whether their correlations exist between dementia subtypes and survival rates.

2.2 Methods

2.2.1 Study Design and Procedure

Data were obtained from patients' memory clinic case records using a standardized data collection form for patients aged 60 and above seen during a 10-year study period from 1st January 2010 to 31st December 2019.

The memory clinic is a sub-specialist outpatient clinic of Groote Schuur Hospital in Cape Town, South Africa. The clinic is held weekly, and its clinical staff consists of a team of

geriatric medicine physicians, neuropsychiatrists, a neurologist, neuropsychologists, and sub-specialty trainees. Patients are referred from general practitioners, family physicians, medical officers from community health clinics and state or private specialists in the Western Cape region. The clinical staff triage the referrals into those who would be seen in the memory or geriatric clinics. In general, patients with higher MMSE scores (≥15) are more likely to be testable using the full neuropsychology battery and are therefore seen in the memory clinic. Those with lower MMSE scores are seen in a geriatric clinic, where a less detailed and more focused cognitive assessment is performed. Patients are usually accompanied by a family member/caregiver who assists with collateral history. Patients undergo a full medical examination. Baseline cognitive assessments were generally administered in English by the neuropsychology team. If a patient didn't speak English, the tests were informally translated by a relative or by the tester who could speak the patient's first language. The tests include assessing general cognitive functioning using MMSE and Montreal Cognitive Assessment (MoCA) scores. Specific cognitive abilities are assessed as follows: Learning and memory by Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) list learning with delayed recall, RBANS Story Memory with delayed recall and RBANS Figure Recall. Language is assessed by verbal fluency that includes both semantic and phonemic assessments, Boston Naming test (short form), and an assessment for speech quality (i.e., clarity, difficulty in making oneself understood, and difficulty in understanding). Attention and/or working memory is assessed by digit span forward and backwards and months of the year backwards. Frontal lobe or executive functioning by trails A, MoCA Trail, trails B, CLOX 1 and 2, Luria recursive figures and hand sequence. Visuo-perceptual or spatial ability is assessed by the RBANS figure copy, and CLOX test.

Laboratory investigations to exclude reversible causes of cognitive impairment are conducted. These include tests of renal, liver, and thyroid function, serum calcium levels, serum levels of

vitamin B-12, HIV, and syphilis serology tests. Patients undergo neuroimaging - usually computed tomography (CT) of the brain - but other neuroimaging modalities such as Magnetic Resonance Imaging (MRI), Single Photon Emission Computed Tomography (SPECT), and 18-fluoro deoxy glucose Positron Emission Tomography (18-FDG-PET) are occasionally done if indicated.

The multi-disciplinary team meets at the end of each clinic to discuss the patients' likely diagnoses and plan of action. Cognitive assessments using MMSE and/or MoCA are usually carried out by the attending clinician at six-monthly intervals corresponding with the patient's follow-up clinic visits. Once a treatment plan is agreed upon, patients are discharged back to the care of the referring centre.

For this study, a consensus diagnosis of dementia and dementia sub-type was determined by a retrospective review of hospital records by the Neurologist (MC) and the trainee sub-specialist in geriatric medicine (MS). The Diagnostic and Statistical Manual of Mental Disorders (DSM–5) criteria for Major Neurocognitive Disorder were used to determine if the patients had dementia. To determine dementia subtypes the following criteria were used: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association for AD [25], National Institute of Neurological Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (for cerebral vascular disease description) for VND [26], Work Group on fronto-temporal dementia and Pick's disease for FTD [27], and consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies [28]. We also used a validated set of diagnostic criteria for PDD [29, 30].

A participant was classified as having the subtype of dementia if he/she met the probable or the possible criteria. It was possible for participants to meet criteria for two different subtypes

of dementia. If a participant met two different probable or two different possible dementia diagnoses according to criteria, they were classified as having mixed dementia. If participants met the criteria for probable dementia of one type and possible dementia of another type, they were categorized as only having the probable dementia subtype (e.g., if they met criteria for probable AD and possible VND, they were categorized as AD). Table 1 shows details of how this was done using AD and VND as examples.

Table 1: Approach to determining a participant's dementia subtype if the participant met two dementia subtype criteria (using AD and VND as an example)

First Dementia Subtype criteria	Second dementia subtype criteria	Dementia subtype Category for Study
Probable AD	Probable VND	Mixed Dementia
Possible AD	Possible VND	Mixed Dementia
Probable AD	Possible VND	AD
Possible AD	Probable VND	VND

The baseline visit was identified as the date the patient was first seen during the study period and met the study criteria. The education level was the highest level attained at baseline. Duration of symptoms prior to diagnosis was estimated from the earliest symptom of dementia as obtained from the patient and/or caregiver. Comorbidity scores were derived from the Charlson's Weighted Index of Comorbidity [31]. Baseline laboratory investigations were carried out within three months before or after dementia diagnosis. Blood pressure measurements and MMSEs were carried out at baseline and subsequent clinic visits, usually with intervals of six months. Cholinesterase inhibitors were prescribed for patients who could afford to purchase them from private pharmacies since they were not available in state services. We checked for dates of death at the state registry managed by the South African Medical Research Council (MRC) for all enrolled participants on 30th November 2021.

Participants with advanced dementia (unable to complete at least 50% of neuropsychology battery tests and dependent on three or more basic activities of daily living), were excluded from the study.

Ethics approval was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town (HREC-REF: 403/2021). Permission to conduct the study was obtained from the medical superintendent of Groote Schuur Hospital.

2.2.2 Statistical Analysis

Characteristics

Analyses were performed using Stata version 17.0 [32]. Proportions of participants diagnosed with different sub-types of dementia were expressed as percentages of the total number of participants in the study. Frequency tables and cross tabulations of sociodemographic and clinical variables were undertaken. Normally distributed data were expressed as means and standard deviations and compared using one way analysis of variance (one-way anova). Tukey or Scheffe tests were used for post-hoc comparisons to assess which group pairs differed significantly. Non-normally distributed data were expressed as median and interquartile ranges and compared using Kruskal-Wallis tests. Comparisons of categorical variables were performed using chi-square tests of independence.

Cognitive decline

Periods of 12-month intervals of mean MMSE scores, for participants who had more than one annual score, were used for the analysis of cognitive decline. Linear regression was used to determine the crude rates of cognitive decline, expressed as MMSE points lost per year. We used MMSE scores with mixed effects modelling to curvilinear models of cognitive change with time as the dependent variable. Different models using time to event (TTE) i.e., from onset of symptoms to death or end of study period, age at onset of dementia symptoms and age at diagnosis of dementia, were used to determine whether independent variables like gender,

years of education, comorbidity score and dementia subtypes predicted cognitive decline. There was no serious deviation from assumptions of normality and constant variance.

Survival

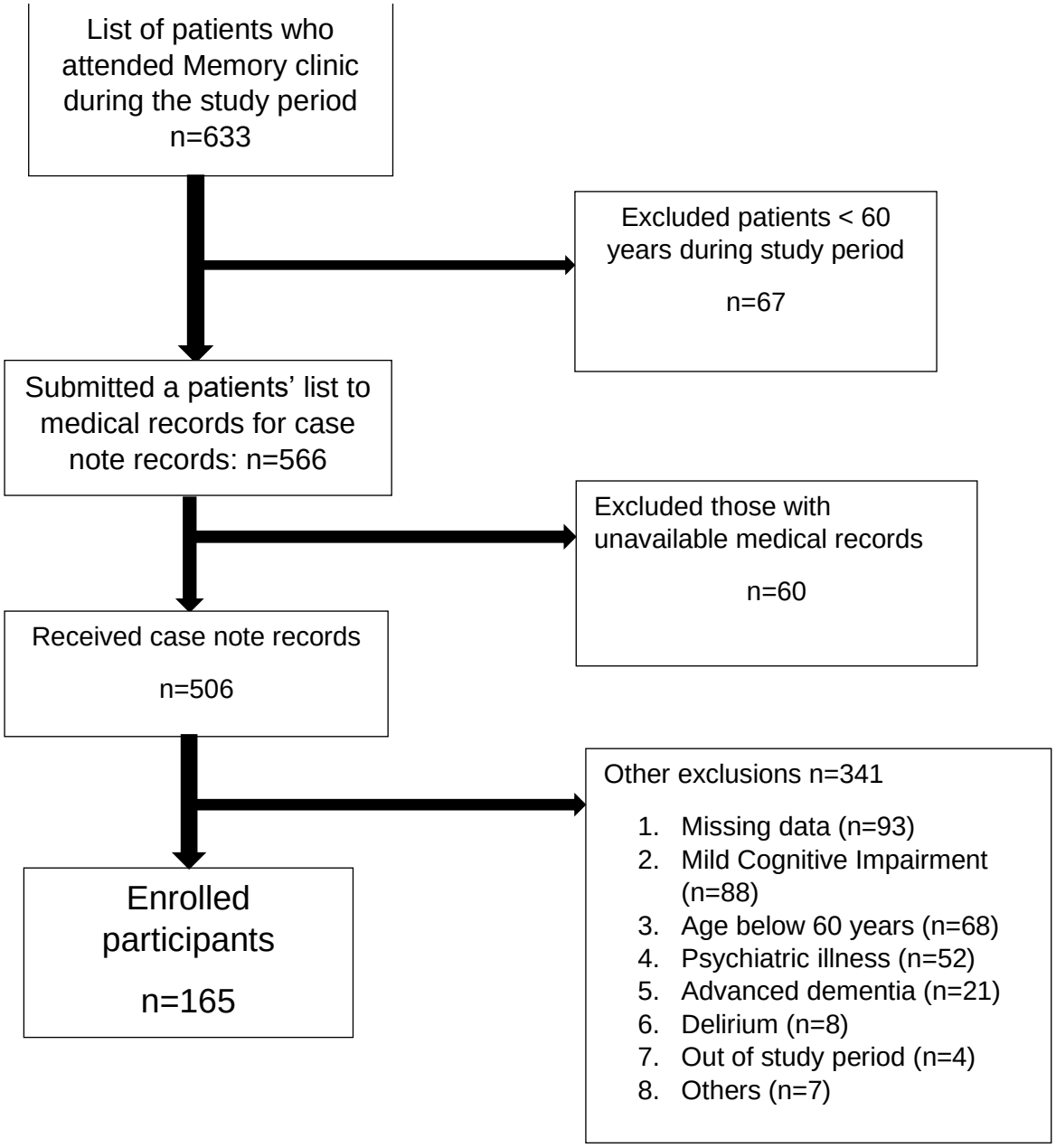
Survival time was defined as time from symptom onset of dementia until the date of death. The Kaplan–Meier method was used to estimate the mean and median survival times among the different dementia sub-types. A comparison of survival rates was done by the log rank test. We used Kruskal-Wallis test to assess survival outcomes between the dementia subtype groups because of the non-normally distributed data. Post hoc comparison tests were used to assess which group pairs differed, and significant results were based on a Bonferroni adjusted level alpha of 0.005. Cox models were used to determine factors associated with survival. Potential risk factors for reduced survival and those with p-values of <0.2 in univariate analysis, were entered into multivariate modelling. Variables were also included in the multivariate model of Cox regression with the Breslow method for ties to determine which factors at baseline predicted reduced survival. The model was found to have reasonable predictive power (using Harrell's C concordance statistic) and there were no serious violations of the assumptions of proportionality (based on Schoenfeld residuals). The significance level was set at $p < 0.05$.

2.3 Results

A total of 633 patients attended the memory clinic over the 10-year study period. Of those, 67 who were aged less than 60 years, were excluded. A list of 566 patients was submitted to the medical records department for retrieval of their case records. Of these we received 506 (89.4%). A total of 341 patients were excluded as they did not meet the study criteria, resulting in a final study cohort of 165 participants as shown in Figure 1. The main reasons for exclusion after reviewing the case notes on the 506 included missing data (n=93), a diagnosis of mild cognitive impairment (n=88), age below 60 years (n=68), psychiatric illness (n=52), advanced dementia (n=21), delirium (n=8), out of study period (n=4), and other reasons (n=3 seen in the

Geriatric clinic, n=1 no cognitive impairment, n=1 metastases to the brain, n=1 tuberculous meningitis and n=1 intellectual disability).

Figure 1: Flow chart of study participants cohort with dementia



2.3.1 Dementia Subtypes

Table 2 shows the categorization of the study cohort by dementia subtypes. We classified 117 (70.9%) as having AD, 24 (14.6%) with VND, 6 (3.6%) with DLB, 5 (3%) with PDD, 3 (1.8%) with FTD, 4 (2.4%) with mixed dementia and 6 (3.6%) with other types of dementia.

Table 2: Frequencies of the types of dementia

Dementia sub-type	n (%)
AD	117 (70.9)
VND	24 (14.6)
DLB	6 (3.6)
PDD	5 (3.0)
FTD	3 (1.8)
Mixed Dementia	**4 (2.4)**
AD + VND	3 (1.8)
AD + DLB	1 (0.6)
Others	**6 (3.6)**
Alcohol Related	2 (1.2)
Huntington's	1 (0.6)
Brain Tumour	1 (0.6)
HSV Encephalitis	1 (0.6)
Craniopharyngioma	1 (0.6)

Abbreviations: n, number; AD, Major Neurocognitive Disorder due to Alzheimer's disease; VND, Major Vascular Neurocognitive Disorder; DLB, Dementia with Lewy bodies; PDD, Parkinson's disease dementia; FTD, Fronto-temporal dementia; HSV, Herpes Simplex Virus.

2.3.2 Demographic and clinical characteristics

Table 3 shows the socio-demographic and clinical characteristics of the study cohort. There were more females 101 (61.2%) than males. The majority 104 (63.4%) had duration of symptoms for two or more years prior to dementia diagnosis. Most participants had a comorbidity score of 1 to 2 (40%) followed by a score of 3 to 4 (33.3%). At baseline, 39 (23.6%) had MMSE scores of 25 to 30, 89 (53.9%) MMSE scores 19 to 24 and 35 (21.2%) MMSE scores of 10 to 18. Two individuals with low MMSEs of <10 had a diagnosis of Primary Progressive Aphasia and another with Alcohol Related Dementia. Both had fair functionality though with communication challenges and able to complete 50% of the applied test batteries.

Table 3: Socio-demographic and clinical characteristics of participants

Characteristics	*n (%)*
Age at Diagnosis	
60 - 65	30 (18.2)
66 - 70	39 (23.6)
71 - 75	40 (24.2)
76 - 80	35 (21.2)
81 - 85	16 (9.7)
> 85	5 (3.0)
Gender	
Male	64 (38.8)
Female	101 (61.2)
Marital Status	
Married	91 (55.2)
Divorced	20 (12.1)
Widowed	47 (28.5)
Single	7 (4.2)
Years of Education	
0 to 7	39 (23.8)
8 to 12	105 (64.0)
> 12	20 (12.2)
Duration of symptoms (months)	
< 6	3 (1.8)
6 to 11	11 (6.7)
12 to 23	46 (28.0)
>23	104 (63.4)
Charlson's Weighted Comorbidity score	
1 to 2	66 (40.0)
3 to 4	55 (33.3)
≥5	44 (26.7)
Baseline MMSE	
25 - 30	39 (23.6)
19 - 24	89 (53.9)
10 to 18	35 (21.2)
<10	2 (1.2)
Vitamin B12 (pmol/L)	
>150	128 (77.6)
≤150	14 (8.5)
Not Done	23 (13.9)
Syphilis	
Non - Reactive	133 (80.6)
Not Done	32 (19.4)
TSH (mlU/L)	
0.38 to 5.33	132 (80.0)
< 0.38	6 (3.6)
> 5.33	12 (7.3)
Not Done	15 (9.1)
HIV	
Negative	68 (41.2)
Not Done	97 (58.8)

Abbreviations: n, number; MMSE, Mini-Mental State Examination; TSH, Thyroid Stimulating Hormone; HIV, Human Immunodeficiency Virus. TSH, Thyroid Stimulating Hormone – Normal range = 0.38 to 5.33 mIU/L; Vitamin B12 – Normal range = 145 to 569 pmol/L(<150pmol/L is WHO cut off for vitamin B12

defficiency);WHO, World Health Organisation; Footnote table 3: the number with missing results are as follows: years of education (n=1), duration of symptoms (n=1),

Table 4 shows the demographic and clinical characteristics of the study cohort by dementia subtype. The mean age at diagnosis of dementia was 72.4 years and was highest for the AD group (73.6 years, SD=7.2). There was a statistically significant difference in age at diagnosis for the dementia subtypes F (4, 154) = 3.88, p=0.005. Using the Scheffe test, the mean age at diagnosis was only significantly different between AD and VND (mean difference=5.09, p=0.029). Participants with DLB or PDD had the highest age at onset of 70.9 years, SD=6.2, F (4, 153) = 3.17, p=0.016. The Tukey test indicated that the mean age at onset was only different between AD and VND (mean difference=4.32, p=0.046). The overall time since symptom onset and diagnosis was 30.6 months (SD=23.1) and highest for FTD with 60 months, SD=24, F (4, 153) = 2.43, p=0.05. The Tukey test showed that participants with FTD tended to differ from VND (mean difference=37.13, p=0.066). The overall mean follow-up time since symptom onset was 7.2 years (SD=3.3) and least for DLB/PDD group with 4.96 years, SD=2.5. There was a statistically significant difference in mean follow-up time for the dementia subtypes $\chi^2(4)$ =15.39, p=0.04.

Table 4: Demographic and clinical characteristics of participants according to dementia subtype

Characteristics	All (n = 165)	AD (n = 117)	VND (n = 24)	DLB or PDD (n = 11)	FTD (n = 3)	Mixed (n = 4)	F-test	p-value
Age at Diagnosis (years)								
Mean (SD)	72.4 (7.0)	73.6 (7.2)	68.5 (5.5)	73.1 (5.7)	69 (7.2)	66.3 (5.1)	3.88	0.005
[#]Age at onset (years)	**(n = 164)**	**(n=116)**						
Mean (SD)	69.7 (7.1)	70.74 (7.2)	66.4 (5.4)	70.9 (6.2)	64 (8.7)	64.5 (4.8)	3.17	0.016
[#] Time since symptom onset and diagnosis (months)	**(n = 164)**	**(n=116)**						
Mean (SD)	30.6 (23.1)	32.3 (22.4)	22.9 (27.4)	26.2 (16.8)	60 (24)	19.5 (13.3)	2.43	0.05
Mean Follow-up time: Years (SD)	7.2 (3.3)	7.8 (3.4)	5.8 (2.6)	4.96 (2.5)	7.7 (1.9)	6.3 (4.4)	15.39^	0.004
Gender: n (%)								
Male	64 (38.8)	34 (29.1)	19 (79.2)	6 (54.6)	2 (66.7)	1 (25.0)	23.55*	p < 0.001
Female	101 (61.2)	83 (70.9)	5 (20.8)	5 (45.5)	1 (33.3)	3 (75.0)	0.39*	p < 0.001
Marital Status: n (%)								
Married	91 (55.2)	59 (50.4)	18 (75.0)	2 (100.0)	2 (66.7)	3 (75.0)	18.45*	0.103
Divorced	20 (12.1)	12 (10.3)	4 (16.7)	0	1 (33.3)	1 (25.0)	0.20*	0.051
Single	7 (4.2)	5 (4.3)	0	0	0	0		
Widowed	47 (28.5)	41 (35.0)	2 (8.3)	0	0	0		
Years of Education: n (%)								
0 to 7	39 (23.8)	33 (28.5)	3 (12.5)	1 (9.1)	1 (33.3)	1 (25.0)	14.24*	0.076
8 to 12	105 (64.0)	69 (59.5)	18 (75.0)	9 (81.8)	0	3 (75.0)	0.21*	0.108
> 12	20 (12.2)	14 (12.1)	3 (12.5)	1 (9.1)	2 (66.7)	0		
Baseline MMSE								
Median (IQR)	21 (5)	21 (5)	23 (8)	23 (11)	19 (23)	19.5 (10.5)	3.74^	0.442
Charlson's Weighted Comorbidity score								
1 to 2	66 (40.0)	49 (41.9)	7 (29.2)	4 (36.4)	1 (33.3)	1 (25.0)	12.33*	0.137

3 to 4	55 (33.3)	43 (37.5)	5 (20.8)	3 (27.3)	1 (33.3)	3 (75.0)	0.20*	0.121
≥5	44 (26.7)	25 (21.4)	12 (50.0)	4 (36.4)	1 (33.3)	0		
MAP	**(n=93)**	**(n=66)**	**(n=15)**	**(n=6)**	**(n=1)**	**(n=2)**		
Median (IQR)	101.7 (16.7)	100 (16.7)	104.7 (15)	107.5 (17.3)		116 (21.3)	2.28^	0.684
Vitamin B12 (pmol/L)	**(n = 138)**	**(n = 104)**	**(n = 20)**	**(n=7)**	**(n=3)**	**(n=4)**		
Median (IQR)	293 (174)	295.5 (179)	309.5 (226)	252 (67)	309 (141)	211.5 (248.5)	0.89^	0.927
TSH mlU/L	**(n=150)**	**(n=107)**	**(n=21)**	**(n=10)**	**(n=3)**	**(n=4)**		
Median (IQR)	1.52 (1.4)	1.44 (1.4)	1.9 (1.9)	1.1 (0.8)	1.5 (0.9)	1.6 (0.8)	4.98^	0.29

* chi-square value for the chi-square test of independence to compare two categorical variables

^ *Kruskal-Wallis tests: non-normally distributed data*

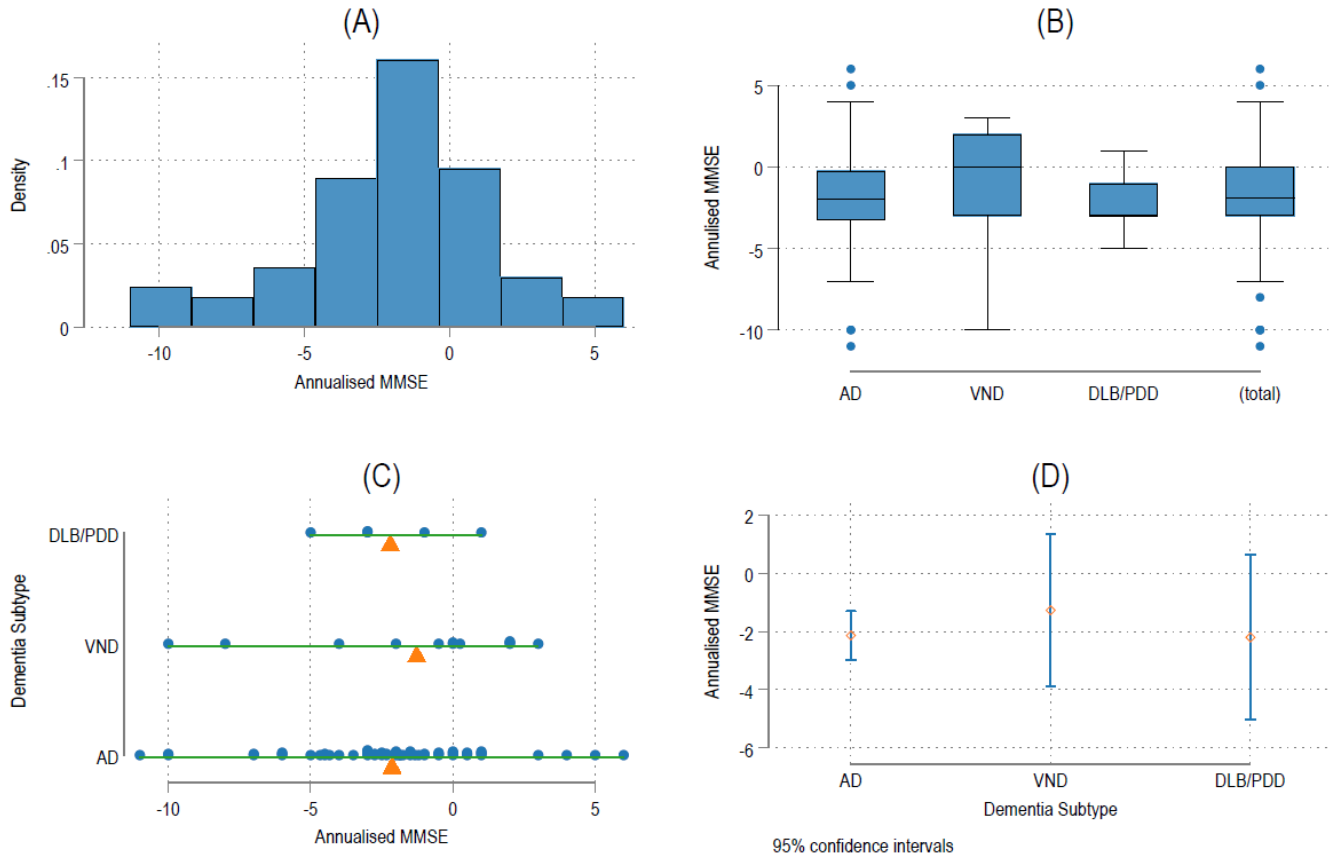
 # Missing data for duration of symptoms prior to diagnosis in a participant with AD

Abbreviations: n, number; SD, Standard Deviation; IQR, Inter Quartile Range; MMSE, Mini-Mental State Examination; MAP, Mean Arterial Pressure; TSH, Thyroid Stimulating Hormone – Normal range = 0.38 to 5.33 mIU/L; Vitamin B12 – Normal range = 145 to 569 pmol/L; AD, Major Neurocognitive Disorder due to Alzheimer's disease; VND, Major Vascular Neurocognitive Disorder; DLB, Dementia with Lewy bodies; PDD, Parkinson's disease dementia; FTD, Fronto-temporal dementia.

2.3.3 Cognitive Decline

Figure 2 shows assessments for annualised cognitive decline among the dementia subtypes. The histogram (A) shows that there were no serious deviations from normality. We were therefore able to use the mean MMSE to reflect the drop in annual MMSE points. The beam (C) and confidence interval (D) plots show annual drop in MMSE points of 2.2, 2.1 and 1.3 of participants with DLB/PDD, AD, and VND respectively. These results should be interpreted with caution since 26 participants had one baseline MMSE score and were not analysed for cognitive decline.

Figure 2: Annualised cognitive decline among the dementia subtypes



Abbreviations: MMSE, Mini-Mental State Examination; AD, Major Neurocognitive Disorder due to Alzheimer's disease; VND, Major Vascular Neurocognitive Disorder; DLB, Dementia with Lewy bodies; PDD, Parkinson's disease dementia; FTD, Fronto-temporal dementia

Table 5 shows mixed effects modelling for MMSE cognitive scores. Cognitive scores differed significantly for those with 13 years and above of education. They had higher MMSE scores compared to participants with less than 8 years of education in the three different mixed effects modeling which included either TTE (4.07; 95% C.I. 1.90, 6.25; p <0.0001), age at symptom onset (4.15; 95% C.I. 2.00, 6.31; p <0.0001) or age at dementia diagnosis (4.27; 95% C.I. 2.11, 6.43; p <0.0001). Cognitive scores also differed significantly for VND compared with AD. The VND group had higher MMSEs on all three mixed effects models: TTE (2.37; 95% C.I. 0.43, 4.31; p=0.017), age at symptom onset (2.81; 95% C.I. 0.88, 4.74; p=0.004) and age at dementia diagnosis (2.82; 95% C.I. 0.87, 4.77; p=0.005).

Table 5: Mixed effects modelling of factors associated with mini-mental state examination scores

Model 1 with TTE				Model 2 with Age at Onset				Model 3 with Age at Diagnosis			
	Coeff	**95% CI**	**p-value**		**Coeff**	**95% CI**	**p-value**		**Coeff**	**95% CI**	**p-value**
TTE	-0.37	-1.19 - 0.45	0.375	**Age at Onset**	0.80	-0.62 - 2.22	0.270	**Age at Diagnosis**	0.91	-0.67 - 2.49	0.260
TTE^2	0.02	-0.03 - 0.06	0.482	**Age at Onset^2**	-0.005	-0.01 - 0.05	0.339	**Age at diagnosis^2**	-0.01	-0.02 - 0.05	0.299
Sex				**Sex**				**Sex**			
Male	-0.48	-1.87 - 0.91	0.500	***Male***	-0.15	-1.52 - 1.22	0.826	***Male***	-0.19	-1.55 - 1.81	0.789
Years of Education				**Years of Education**				**Years of Education**			
8 to 12 years	1.38	-0.14 - 2.90	0.075	**8 to 12 years**	1.34	-0.15 - 2.84	0.078	**8 to 12 years**	1.45	-0.04 - 2.95	0.057
≥ 13 years	4.07	1.90 - 6.25	**< 0.0001**	**≥ 13 years**	4.15	2.00 - 6.31	**<0.0001**	**≥ 13 years**	4.27	2.11 - 6.43	**<0.0001**
Comorbidity Score				**Comorbidity Score**				**Comorbidity Score**			
3 to 4	0.95	-0.51 - 2.41	0.201	**3 to 4**	0.83	-0.62 - 2.28	0.259	**3 to 4**	0.95	-0.50 - 2.39	0.200
≥ 5	1.63	-0.04 - 3.31	0.056	**≥ 5**	1.44	-0.23 - 3.10	0.091	**≥ 5**	1.50	-0.13 - 3.14	0.072
Dementia Subtype				**Dementia Subtype**				**Dementia Subtype**			
VND	2.37	0.43 - 4.31	**0.017**	**VND**	2.81	0.88 - 4.74	**0.004**	**VND**	2.82	0.87 - 4.77	**0.005**
DLB/PDD	-0.16	-2.64 - 2.32	0.901	**DLB/PDD**	0.05	-2.34 - 2.44	0.968	**DLB/PDD**	0.07	-2.34 - 2.49	0.951
FTD	0.25	-4.80 - 5.30	0.923	**FTD**	0.93	-4.08 - 5.94	0.716	**FTD**	0.39	-4.63 - 5.42	0.878

Abbreviations: TTE, Time to Event =from onset of symptoms to death or end of study period; Coeff, Coefficient; CI, confidence interval; Age at Onset = Age at onset of symptoms of dementia; Age at Diagnosis = Age when diagnosis of dementia was established; TTE^2 = TTE-squared variables; Age at Onset^2= age at onset-squared variables; Age at diagnosis^2= age at diagnosis-squared variables; VND, Major Vascular Neurocognitive Disorder; DLB, Dementia with Lewy bodies; PDD, Parkinson's disease dementia; FTD, Fronto-temporal dementia.

2.3.4 Survival

Table 6 shows survival characteristics of participants according to dementia subtype. Of the 165 participants, 112 (67.9%) died during the study period. The mean age at death of all participants with dementia was 77.3 years (SD=7.3) and was highest for AD (78.9 years,

SD=7.4). Using the Kruskal-Wallis test, there was a significant difference between the dementia subtype groups for mean age at death ($\chi^2(4)$ =13.51, p=0.009). The Mann-Whitney test showed that the mean age at death was only significantly different between AD and VND (p=0.001). The mean survival time of all deceased participants with dementia was 6.7 years (SD=3.4), being highest for AD (7.3 years, SD=3.5) and least with mixed dementia (4.1 years, SD=0.2) followed by DLB/PDD (4.8 years, SD=2.6). There was a statistically significant difference among the dementia subtype groups ($\chi^2(4)$ =11.15, p=0.025). The Mann-Whitney test showed a significant difference of the mean survival time only between AD and DLB/PDD (p=0.004).

Table 6: Survival characteristics of participants according to dementia subtype

Characteristics	**All(n= 165)**	**AD (n = 117)**	**VND (n= 24)**	**DLB/PDD (n = 11)**	**FTD (n = 3)**	**Mixed (n = 4)**	**F-test**	**p-value**
Number of deaths	112	79	16	10	3	2	4.69*	0.321
(%)	67.9	67.5	66.7	90.9	100	50	0.17*	0.334
Mean Age at Death	**(n=112)**	**(n=79)**	**(n=16)**	**(n=10)**	**(n=3)**	**(n=2)**		
(SD)	77.3 (7.3)	78.9 (7.4)	73.5 (5.7)	76.1 (5.6)	72 (7.2)	73 (0)	13.51^	0.009
Mean Follow-up time Years (SD)	7.2 (3.3)	7.8 (3.4)	5.8 (2.6)	4.96 (2.5)	7.7 (1.9)	6.3 (4.4)	15.39^	0.004
Mean survival time (Deceased)	**(n=111)**	**(n=78)**	**(n=16)**	**(n=10)**	**(n=3)**	**(n=2)**		
Years (SD)	6.7 (3.4)	7.3 (3.5)	5.5 (2.9)	4.8 (2.6)	7.7 (1.9)	4.1 (0.2)	11.15^	0.025

* chi-square value for the chi-square test of independence to compare two categorical variables

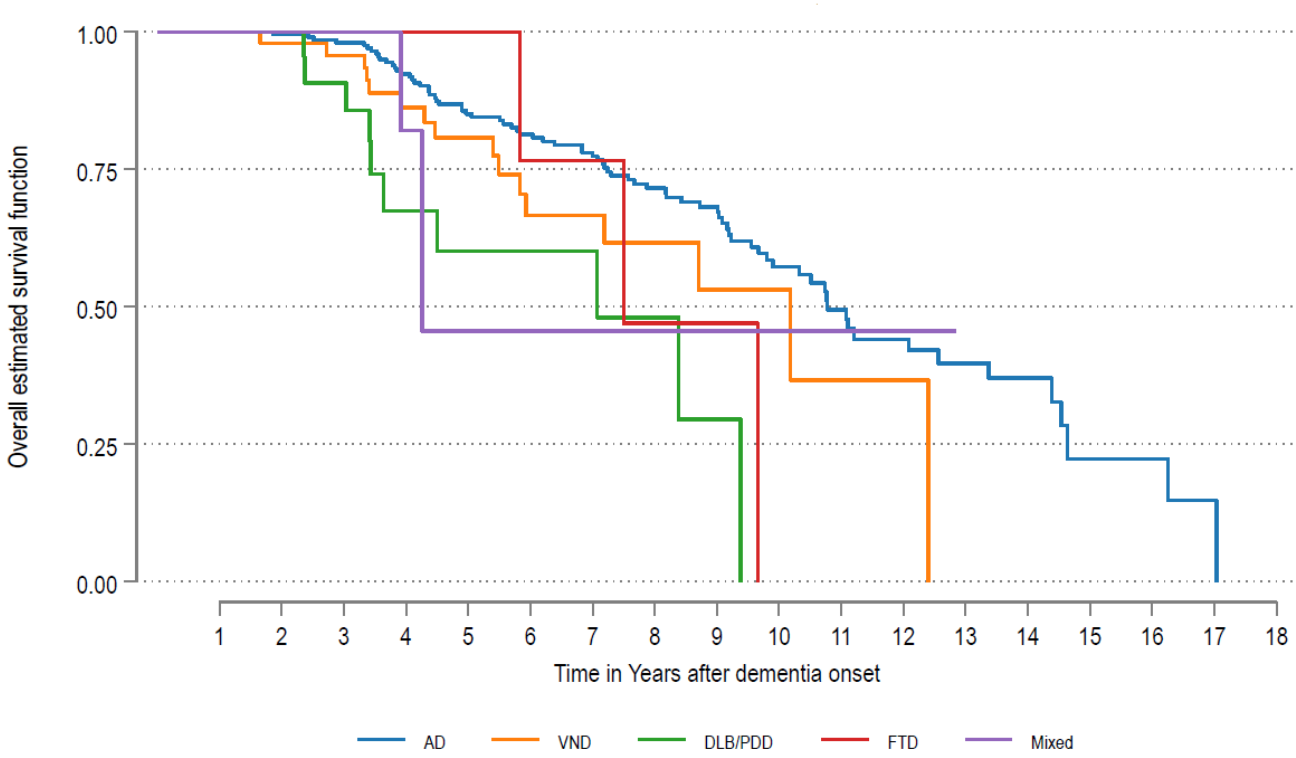
^ *Kruskal-Wallis tests: non-normally distributed data*

Abbreviations: n, number; SD, Standard Deviation; AD, Major Neurocognitive Disorder due to Alzheimer's disease; VND, Major Vascular Neurocognitive Disorder; DLB, Dementia with Lewy bodies; PDD, Parkinson's disease dementia; FTD, Fronto-temporal dementia.

Figure 3 shows the survival curves for the different groups of dementia subtypes. A log rank test showed significantly different survival among the different dementia subtypes ($\chi^2(4)$ =18.03) with a p-value=0.0001. Survival was only significantly different between AD and

DLB/PDD participants, log rank test (χ^2 (1) =15.31) and p-value=0.0001 with AD having a longer survival.

Figure 3: Age and sex adjusted survival rates of dementia subtypes



Abbreviations: AD, Major Neurocognitive Disorder due to Alzheimer's disease; VND, Major Vascular Neurocognitive Disorder; DLB, Dementia with Lewy bodies; PDD, Parkinson's disease dementia; FTD, Fronto-temporal dementia, Mixed = Mixed dementia

Table 7 shows the results of univariate survival analysis. Women had a longer survival compared to the men (HR=0.59, 95% C.I. 0.40, 0.86, p=0.006). Participants with Charlson's Weighted Comorbidity scores of 5 and above had a shorter survival than those with scores between 1 to 2 (HR=1.81, 95% C.I. 1.13, 2.89, p=0.013). VND group had a shorter survival than AD (HR=1.83, 95% C.I. 1.06, 3.18, p=0.03). Participants with DLB/PDD also had a significantly shorter survival compared to AD (HR= 3.55, 95% C.I. 1.82, 6.97, p < 0.001).

Table 7: Univariate analysis of baseline characteristics and survival

Characteristics	Alive	Dead	HR (95% CI)	p value
Age at onset (years)				
< 65 years	17 (32.1)	29 (26.1)	1	
> 65 years	36 (67.9)	82 (73.9)	1.41 (0.92 - 2.16)	0.117
Gender: n (%)				
Male	18 (34.0)	46 (41.1)	1	
Female	35 (66.0)	66 (58.9)	0.59 (0.40 - 0.86)	**0.006**
Marital Status: n (%)				
Divorced	4 (7.6)	16 (14.3)	1	
Married	35 (66.0)	56 (50.0)	0.86 (0.49 - 1.50)	0.596
Single	0	7 (6.3)	2.05 (0.84 - 5.02)	0.115
Widowed	14 (26.4)	33 (29.5)	0.72 (0.39 - 1.32)	0.291
Years of Education: n (%)				
0 to 7	13 (25.0)	26 (23.2)	1	
8 to 12	31 (59.6)	74 (66.1)	1.37 (0.86 - 2.17)	0.181
> 12	8 (15.4)	12 (10.7)	1.16 (0.58 - 2.34)	0.671
Charlson's Weighted Comorbidity score				
1 to 2	27 (50.9)	39 (34.8)	1	
3 to 4	16 (30.2)	39 (34.8)	1.43 (0.91 - 2.24)	0.117
≥5	10 (18.9)	34 (30.4)	1.81 (1.13 - 2.89)	**0.013**
Baseline MMSE				
Median (IQR)	22 (5)	21 (6)	0.97 (0.94 - 1.01)	0.201
MAP				
Median (IQR)	99.3 (18.3)	101.7 (16.7)	1.01 (0.99 - 1.03)	0.512
Mean (SD)	101.0 (14.0)	103.5 (14.5)		
Dementia subtype				
AD	38 (77.6)	79 (71.8)	1	
VND	8 (16.3)	16 (14.6)	1.83 (1.06 - 3.18)	**0.030**
DLB/PDD	1 (2.0)	10 (9.1)	3.55 (1.82 - 6.97)	< **0.001**
FTD	0	2 (2.7)	1.77 (0.56 - 6.65)	0.334
Mixed	2 (4.1)	2 (1.8)	1.01 (0.25 - 4.15)	0.986

Abbreviations: n, number; SD, Standard Deviation; IQR, Inter Quartile Range; MMSE, Mini-Mental State Examination; MAP, Mean Arterial Pressure; HR, Hazard Ratio; CI, confidence interval; AD, Major Neurocognitive Disorder due to Alzheimer's disease; VND, Major Vascular Neurocognitive Disorder; DLB, Dementia with Lewy bodies; PDD, Parkinson's disease dementia; FTD, Fronto-temporal dementia.

Table 8 shows the results of the multivariate Cox regression survival analysis. Age at symptom onset greater than 65 compared to age at symptom onset 65 or younger was associated with shorter survival (HR=1.82, 95% C.I. 1.11, 2.99, p=0.017). Female gender was associated with increased survival compared to males (HR=0.59, 95% C.I. 0.36, 0.95, p=0.029). Comorbidity

scores of 3 to 4 (HR=1.88, 95% C.I. 1.14, 3.10, p=0.014) and scores of 5 or more (HR=1.97, 95% C.I. 1.16, 3.34, p=0.012) were associated with shorter survival compared to scores of 1 to 2. Lower baseline MMSE was associated with shorter survival (HR=1.05, 95% C.I. 1.01, 1.10, p=0.029). Survival decreased by 5% for every one unit decrease in MMSE. The group with DLB/PDD had shorter survival compared to those with AD (HR=3.07, 95% C.I. 1.50, 6.29, p=0.002). Harrell's C concordance statistic was 0.681.

Table 8: Predictors of survival among patients with dementia - Multivariate cox regression analysis

	Std err	z	HR	95% CI	p-value
Age at onset					
> 65 years	0.46	2.38	1.82	1.11 - 2.99	**0.017**
Gender					
Female	0.14	-2.18	0.59	0.36 - 0.95	**0.029**
Marital Status					
Married	0.26	-0.44	0.86	0.48 - 1.58	0.660
Single	0.99	1.44	2.02	0.78 - 5.26	0.149
Widowed	0.23	-1.16	0.67	0.34 - 1.32	0.246
Years of Education					
8 to 12	0.40	1.65	1.54	0.92 - 2.57	0.098
≥ 13	0.42	0.24	1.10	0.51 - 2.33	0.813
Charlson's Weighted Comorbidity score					
3 to 4	0.48	2.46	1.88	1.14 - 3.10	**0.014**
≥5	0.53	2.52	1.97	1.16 - 3.34	**0.012**
Baseline MMSE					
Median (IQR)	0.02	2.18	1.05	1.01 - 1.10	**0.029**
Dementia subtype					
VND	0.44	0.91	1.34	0.71 - 2.55	0.365
DLB/PDD	1.12	3.07	3.07	1.50 - 6.29	**0.002**
FTD	1.06	0.74	1.63	0.45 - 5.87	0.458
Mixed	1.28	0.74	1.73	0.41 - 7.36	0.457

Abbreviations: *n, number; IQR, Inter Quartile Range; MMSE, Mini-Mental State Examination; HR, Hazard Ratio; CI, confidence interval; VND, Major Vascular Neurocognitive Disorder; DLB, Dementia with Lewy bodies; PDD, Parkinson's disease dementia; FTD, Fronto-temporal dementia*

2.4 Discussion

In our study, the commonest dementia subtype was AD followed by VND. The overall duration from symptom onset until diagnosis (date of first clinic visit) was 2.5 years. The combined

DLB/PDD subtype group had the highest age of symptom onset while AD had the highest age at diagnosis. Cognitive scores were significantly higher for VND compared to AD subtypes and higher for participants with longer duration of education. Cognitive decline was faster in the DLB/PDD subtype and in the AD group compared with VND. Survival in the DLB/PDD group was lower compared to the AD group. Other factors significantly associated with reduced survival were older age of dementia onset, lower baseline cognition, and higher comorbidity scores. Female gender was associated with increased survival.

We found AD to be the commonest dementia subtype (70.9%), followed by VND (14.6%). Our results are not consistent with other studies as our AD frequency was higher [5, 33, 34]. In memory clinic or hospital-based studies from different parts of the world, the prevalence of AD ranged between 38% and 67% and 5% to 26% for VND [5, 33-36]. Our findings of a higher proportion of AD could relate to how we categorized AD subtype. For example, participants with combinations of AD plus cerebrovascular disease (CVD) or participants with probable AD plus possible DLB were all classified primarily as AD. Differences in proportions of our dementia subtypes could be influenced by variations in criteria to categorize dementia and differences in the interpretation of these criteria. Findings of the Lewy Body-containing dementias of DLB (3.6%) and PDD (3%) as the third commonest dementia subtype have been shown in previous memory clinic studies [33, 36]. Our finding of a prevalence of FTD of 1.8% is similar to a cohort from a memory clinic in Hong Kong of a comparable mean age at diagnosis as our study of 76.1 years [33]. Findings from a large memory clinic cohort in France with a mean age of 56 years found a higher prevalence of FTD of 9.7% [37]. The low frequency of FTD in our study could therefore be due to the higher inclusion criterion age cut-off of 60 years.

The highest age of symptom onset of 70.9 years in our study was in the DLB/PDD group. Amoo et al in study of a Nigerian hospital cohort found the AD group to have the highest mean

age of symptom onset of 72.8 years compared to DLB patients with a mean age of symptom onset of 65 years [5]. It is unclear from the publication whether the cohort comprised outpatients, in-patients, or both. Our age of symptom onset for DLB/PDD dementias is, however, similar to the findings of a recent Chinese study which reported a mean age of symptom onset of 68.6 years [38].

Our study found an overall duration of illness of 30.6 months, from symptom onset to diagnosis. This is comparable to memory clinic study findings in India and Hong Kong [33, 34]. A lower duration of 13.8 months was found in an Italian study [39]. In the developed world, organizational challenges of memory clinics coupled with long waiting lists are thought to explain the longer duration from symptom onset to diagnosis [40]. Our challenges of long waiting lists due to fewer qualified personnel in the memory clinic are similar to findings elsewhere [41]. Also in our context, significant functional impairment is often the trigger for caregivers to seek medical help, and this usually occurs late [39, 42]. In our cohort, duration from symptom onset to diagnosis could have been shortest in VND (22.9 months) followed by those with DLB/PDD (26.2 months) because of the earlier motor or other non-cognitive symptoms that lead to patients or caregivers recognising the illness sooner. In our setting, early symptoms of AD are more likely to be seen as "old age" until patients become very functionally impaired and present late to the clinic.

The dementia subtype with the highest age at diagnosis of 73.6 years was AD. Our inclusion criterion of age 60 years and above and the triage of some people to the geriatric clinic could have contributed to an exclusion bias of people with young onset dementia and older frail people with dementia [43].

The mean annual rate of cognitive decline of MMSE points per dementia subtype in our study was 2.2 for the group with DLB/PDD, 2.1 for AD and 1.3 for VND. The decline in cognition

between DLB and PDD is similar to that shown by a Swedish study [44]. We considered DLB and PDD as one group in the analyses due to the small numbers in each of these groups. DLB and PDD may, in any case, be considered on the same spectrum of pathological disorders [45]. In our study, cognitive decline of DLB/PDD and AD were similar, a finding different to a multi-centre cohort study [9]. The similar annual rates of decline between DLB/PDD and AD in our study could be due to the combination of AD+DLB pathologies which we could have classified as AD. Studies have shown that dual AD+DLB pathology has a faster cognitive decline than either individual dementia subtypes [20, 46-48].

We found significantly higher MMSE scores for VND compared to AD, findings similar to those of a Canadian study [49]. In our study, we used the MMSE, an inferior tool for detecting subcortical dysexecutive cognitive related impairment, hence the higher VND scores [50]. The Montreal Cognitive Assessment (MoCA) was not universally used until the later years of the study period.

Thirteen or more years compared to less than eight years of education was also associated with significantly higher MMSE scores in our study. Education levels have been shown to affect performance of cognitive tests like MMSE [51]. Higher levels of education have been associated with higher MMSE scores in both developed and developing countries [51-53]. Majority of our participants could have had high MMSE scores due to the literacy and the MMSE score criteria in the triage of who would be seen in the memory or geriatric clinics.

The finding of the DLB/PDD group having a higher mortality compared to AD is consistent with previous studies [54, 55]. We did not explore possible causes of death, but a previous study has shown that fall-related injuries and pneumonias contributed to mortality [54]. Shorter survival due to onset of dementia symptoms ≥ 65 years has also been shown in studies elsewhere [22, 56]. We found a proportion of our cohort died (67.9%) during the follow-up

period with a mean survival time of 6.7 years. This is comparable to other studies [10, 22]. Females were associated with increased survival compared to males, a finding again consistent with other studies [10, 22]. In our study, survival decreased by 5% for every one unit decrease in MMSE score. This is consistent with the findings from similar published studies showing shorter survival with a lower MMSE scores [10, 57, 58]. Higher comorbidity as characterized by Charlson's comorbidity index scores of 3 to 4 and 5 and above in our study, was associated with higher mortality among dementia patients. Previous studies have assessed comorbidity differently [58-60]. Our study relied on the documented comorbidities limited to Charlson's index tool [31]. We therefore did not consider geriatric syndromes and other conditions not in the Charlson's comorbidity index that could also influence survival.

To our knowledge, this is the first published longitudinal study carried out in a memory clinic in Africa, describing dementia subtypes, cognitive decline, and survival over a 10-year period. The strengths of the study include the categorization of dementia using validated diagnostic criteria as well as obtaining complete survival data with a mean follow up period of 7.2 years. The study cohort was, however, a specific group of people referred to a memory clinic and so the results are not generalizable to all people with dementia in the community.

The study was retrospective. We depended on the data collected at the time and the clinicians' notes. Clearly a prospective study with a data collection protocol set up in advance would have considerably reduced the number of exclusions (93 in total) we had to make for missing data. We excluded patients with advanced dementia. These exclusions would have affected dementia sub-type proportions and survival outcomes. However, determining dementia sub-type in advanced disease would be difficult anyway.

Another important limitation was not having clinical diagnoses validated by autopsy which is the ultimate reference standard for dementia diagnosis. However, we used diagnostic criteria that have been validated in some post-mortem brain studies [61].

2.5 Conclusion

In conclusion, we have reported comparable proportions of dementia subtypes and their characteristics from this 10-year longitudinal memory clinic cohort in South Africa. We describe cognitive decline of some dementia subtypes and factors affecting cognitive scores such as dementia subtype and education level. There was a high death rate in this cohort, comparable to other similar populations. The factors associated with shorter survival included DLB/PDD group, older age of symptom onset, lower baseline cognition, and higher comorbidity scores. Females were associated with increased survival.

Future longitudinal studies in Africa could explore dementia subtype proportions for younger onset dementia subtypes and cognitive decline of specific dementia subtypes like FTD, which we were unable to analyze due to a smaller number of participants. There is a further need to assess other known predictors of mortality like neuropsychiatric symptoms, polypharmacy, and functional impairment including how activity of daily living scores or carer burden change over time in larger longitudinal memory clinic studies in Africa. An early reliable dementia subtype diagnosis and knowledge of survival outcomes is important where complex investigations may be lacking but where potential disease-modifying therapies may become available in the future.

2.6 List of Abbreviations

AD – Major Neurocognitive Disorder due to Alzheimer's disease

DLB – Dementia with Lewy Body

DSM – Diagnostic and Statistical Manual of Mental Disorders

FTD – Fronto-temporal dementia

HIV – Human Immuno-deficiency Virus

MMSE – Mini-Mental State Examination

MoCA – Montreal Cognitive Assessment

PDD – Parkinson disease dementia

RBANS – Repeatable Battery for the Assessment of Neuropsychological Status

TTE – Time to Event

VND – Major Vascular Neurocognitive Disorder

WHO – World Health Organization

2.7 Declarations

2.7.1 Ethics approval and consent to participate

The study was approved by the the Human Research Ethics Committee of the Faculty of Health Sciences, University of Cape Town (HREC-REF: 403/2021). Permission to conduct the study was obtained from the medical superintendent of Groote Schuur Hospital. A waiver of consent to participate was obtained in view of the retrospective study design and the anonymization of the individual participant data.

2.7.2 Consent for publication

Not Applicable

2.7.3 Availability of data and materials

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

2.7.4 Competing interests

The authors declare that they have no competing interests.

2.7.5 Funding

Not applicable

2.7.6 Authors' contributions

MS was involved in study concept and design, review of patient records, analyses, and interpretation of data.

AH was involved in the analysis and interpretation of data.

VN was involved in interpretation of data.

SK was involved in design, analyses and interpretation of data.

MC was involved in study concept and design, review of patient records, analyses, and interpretation of data.

All five authors were involved in the preparation and approval of the final manuscript version. They agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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2.9 Appendix

2.9.1 Diagnostic Criteria

Date:

ID Number:

Study Number:

DSM-5 Major Neurocognitive Disorder		
Criteria	**Present/Yes**	**Absent/No**
A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:		
1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and		
2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.		
B. The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).		
C. The cognitive deficits do not occur exclusively in the context of a delirium.		
D. The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).		
Diagnosis: All the above		

Date:
ID Number:
Study Number:

DSM-5 criteria for major neurocognitive disorder due to Alzheimer disease

Criteria	Present	Absent	Diagnosis
A. Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains*:			
			At least 1out of 6
a) Learning and memory.			
b) Language.			
c) Executive function.			
d) Complex attention.			
e) Perceptual-motor.			
f) Social cognition.			
B. The cognitive deficits interfere with independence in everyday activities. At a minimum, assistance should be required with complex instrumental activities of daily living, such as paying bills or managing medications.			B + C + D+ E
C. The cognitive deficits do not occur exclusively in the context of a delirium.			
D. The cognitive deficits are not better explained by another mental disorder (eg, major depressive disorder, schizophrenia).			
E. There is insidious onset and gradual progression of impairment in at least two cognitive domains.			
F. Either of the following:			
a) Evidence of a causative Alzheimer disease genetic mutation from family history or genetic testing.			(a) **OR** (b)1,2,3
b) All three of the following are present:			
1. Clear evidence of decline in memory and learning and at least one other cognitive domain.	x		

2. Steadily progressive, gradual decline in cognition, without extended plateaus.		x	
3. No evidence of mixed etiology (ie, absence of other neurodegenerative disorders or cerebrovascular disease, or another neurological, mental, or systemic disease or condition likely contributing to cognitive decline).		x	
* Evidence of decline is based on: Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and a substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.			
Diagnosis: Not AD			

Date:
ID Number:
Study Number:

NINCDS / ADRDA (Alzheimer's Disease)			
Criteria	**Present**	**Absent**	**Diagnosis**
0. Negative			
1. Possible			
i)Presence of a dementia syndrome, in absence of other neurological, psychiatric or systemic disorders capable of causing dementia, but with atypical features, such as variations in the onset, presentation or clinical course of the illness.			(i) OR (ii) OR (iii)
ii)Presence of a second systemic disease or brain disorder sufficient to produce dementia, but not considered to be the cause of the dementia.			
iii)Single, gradually progressive, severe cognitive deficit (eg. worsening amnestic syndrome), in the absence of another identifiable cause.			
2. Probable			
i)Dementia, established by history & clinical examination, and documented with, or confirmed by, cognitive or neuropsychological tests e.g. MMSE (<23), CAMCOG (<80).			(i) to (vi)

ii) Deficits in 2 or more areas of cognition.			
iii) Progressive worsening of memory and other cognitive functions.			
iv) No disturbance of consciousness.			
v) Age of onset > 40; usually > 65.			
vi) Absence of systemic disorders or other brain diseases [or psychiatric disorders] that could in themselves account for the progressive deficits in memory & cognition.			
3. Definite			
i) Probable AD on clinical criteria.			(i) and (ii)
ii) Histopathological evidence (biopsy, autopsy).			
A) Supportive evidence for the diagnosis of Probable AD:			
i) Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);			Any of (i) to (iii)
ii) impaired activities of daily living and altered patterns of behaviour;			
iii) family history of similar disorders, particularly if confirmed neuropathologically; and			
iv) laboratory results of:			
a) normal lumbar puncture as evaluated by standard techniques;			(a) or (b) or (c)
b) normal pattern or non-specific change in EEG, such as increased slow wave activity, and			
c) evidence of cerebral atrophy on CT with progression documented by serial observation.			
B) Clinical features consistent with the diagnosis of Probable AD:			
i) Plateaus in the course of progression of the illness;			Any of (i) to (v)
ii) Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional or physical outbursts, sexual disorders and weight loss;			

iii) Other neurological abnormalities in some patients, especially those with more advanced disease, including motor signs such as increased motor tone, myoclonus or a gait disorder;			
iv) Seizures in advanced disease;			
v) CT normal for age.			
C) Features that make the diagnosis of Probable AD uncertain or unlikely include:			
i) Sudden apoplectic onset;			
ii) Focal neurological signs such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness;			Any of (i), (ii), (iii)
iii) Seizures or gait disturbances at the onset or very early in the course of the illness.			
Diagnosis:			

Date:
ID Number:
Study Number:

Fronto-Temporal Dementia
McKhann GM, et al. Arch Neurol 2001; 58: 1803-1809

	Present	Absent
1.The development of behavioural or cognitive deficits manifested by either:		
a) early and progressive change in personality, characterised by difficulty in modulating behaviour, often resulting in inappropriate responses or activities, or		
b) early and progressive change in language, characterised by problems with expression of language or severe naming difficulty and problems with word meaning.		
2. The deficits outlined in 1a) or 1b) cause significant impairment in social or occupational functioning and represent a significant decline from a previous level of functioning.		
3. The course is characterised by a gradual onset and continuing decline in function.		
4. The deficits outlined in 1a) or 1b) are not due to other nervous system conditions (eg cerebrovascular disease), systemic conditions (eg hypothyroidism), or substance-induced condition.		
5. The deficits do not occur exclusively during a delirium.		
6. The disturbance is not better accounted for by a psychiatric diagnosis (eg depression).		

Diagnostic criteria for primary progressive aphasia	**Present**	**Absent**
Inclusion: criteria 1-3 must be answered positively		

1. Most prominent clinical feature is difficulty with language		
2. These deficits are the principal cause of impaired daily living activities		
3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease		
Exclusion: criteria 1-4 must be answered negatively		
1. Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders		
2. Cognitive disturbance is better accounted for by a psychiatric diagnosis		
3. Prominent initial episodic memory, visual memory, and visuoperceptual impairments		
4. Prominent, initial behavioural disturbance		
PPA: primary progressive aphasia.		
Gorno-Tempini ML, Hillis AE, Weintraub S, et al. Classification of primary progressive aphasia and its variants. Neurology 2011; 76:1006. DOI: 10.1212/WNL.0b013e31821103e6. Copyright © 2011 American Academy of Neurology.		
Diagnostic criteria for nonfluent/agrammatic variant PPA		
I. Clinical diagnosis of nonfluent/agrammatic variant PPA		
At least one of the following core features must be present:		
1. Agrammatism in language production		
2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)		
At least 2 of 3 of the following other features must be present:		
1. Impaired comprehension of syntactically complex sentences		
2. Spared single-word comprehension		
3. Spared object knowledge		

II. Imaging-supported nonfluent/agrammatic variant diagnosis		
Both of the following criteria must be present:		
1. Clinical diagnosis of nonfluent/agrammatic variant PPA		
2. Imaging must show one or more of the following results:		
a. Predominant left posterior fronto-insular atrophy on MRI		
b. Predominant left posterior fronto-insular hypoperfusion or hypometabolism on SPECT or PET		
III. Nonfluent/agrammatic variant PPA with definite pathology		
Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:		
1. Clinical diagnosis of nonfluent/agrammatic variant PPA		
2. Histopathologic evidence of a specific neurodegenerative pathology (eg, FTLD-tau, FTLD- TDP, AD, other)		
3. Presence of a known pathogenic mutation		

AD: Alzheimer disease; FTLD: frontotemporal lobar degeneration; PPA: primary progressive aphasia.

Diagnostic criteria for semantic variant PPA		
I. Clinical diagnosis of semantic variant PPA		
Both of the following core features must be present:		
1. Impaired confrontation naming		
2. Impaired single-word comprehension		
At least 3 of the following other diagnostic features must be present:		
1. Impaired object knowledge, particularly for low-frequency or low-familiarity items		
2. Surface dyslexia or dysgraphia		
3. Spared repetition		

4. Spared speech production (grammar and motor speech)		
II. Imaging-supported semantic variant PPA diagnosis		
Both of the following criteria must be present:		
1. Clinical diagnosis of semantic variant PPA		
2. Imaging must show one or more of the following results:		
a) Predominant anterior temporal lobe atrophy		
b) Predominant anterior temporal hypoperfusion or hypometabolism on SPECT or PET		
III. Semantic variant PPA with definite pathology		
Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:		
1. Clinical diagnosis of semantic variant PPA		
2. Histopathologic evidence of a specific neurodegenerative pathology (eg, FTLD-tau, FTLD- TDP, AD, other)		
3. Presence of a known pathogenic mutation		
Diagnostic criteria for logopenic variant PPA		
I. Clinical diagnosis of logopenic variant PPA		
Both of the following core features must be present:		
1. Impaired single-word retrieval in spontaneous speech and naming		
2. Impaired repetition of sentences and phrases		
At least 3 of the following other features must be present:		
1. Speech (phonologic) errors in spontaneous speech and naming		
2. Spared single-word comprehension and object knowledge		
3. Spared motor speech		
4. Absence of frank agrammatism		
II. Imaging-supported diagnosis of logopenic variant PPA		
Both criteria must be present:		

1. Clinical diagnosis of logopenic variant PPA		
2. Imaging must show at least one of the following results:		
a) Predominant left posterior perisylvian or parietal atrophy on MRI		
b) Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET		
III. Logopenic variant PPA with definite pathology		
Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:		
1. Clinical diagnosis of logopenic variant PPA		
2. Histopathologic evidence of a specific neurodegenerative pathology (eg, AD, FTLD-tau, FTLD-TDP, other)		
3. Presence of a known pathogenic mutation		

Date:
ID Number:
Study Number:

Revised criteria for the clinical diagnosis of dementia with Lewy bodies (DLB)			
Criteria	**Present**	**Absent**	**Diagnosis**
Probable DLB			
a) Two or more core clinical features of DLB are present, with or without indicative biomarkers; OR			
b) Only one core clinical feature is present, but with one or more indicative biomarkers			(a) OR (b)
c) Probable DLB should not be diagnosed on the basis of biomarkers alone			
Possible DLB			
a) Only one core clinical feature of DLB is present, with no indicative biomarker evidence; OR			
			(a) OR (b)
b) One or more indicative biomarkers are present, but there are no core clinical features			
DLB is less likely			
a) In the presence of any other physical illness or brain disorder including cerebrovascular disease, sufficient to account in part or in total for the clinical picture*			
			(a) OR (b)
b) If parkinsonian features are the only core clinical feature and appear for the first time at a stage of severe dementia¶			
Essential features of Dementia Δ			
Core clinical features (the first three typically occur early and may persist throughout the course)			
1) Fluctuating cognition with pronounced variations in attention and alertness			
2) Recurrent visual hallucinations that are typically well formed and detailed			
3) REM sleep behavior disorder, which may precede cognitive decline			
4) One or more spontaneous cardinal features of parkinsonism (bradykinesia, rest tremor, rigidity)			

Supportive clinical features			
· Severe sensitivity to antipsychotic agents			
· Postural instability			
· Repeated falls			
· Syncope or other transient episodes of unresponsiveness			
· Severe autonomic dysfunction (eg, constipation, orthostatic hypotension, urinary incontinence)			
· Hypersomnia			
· Hyposmia			
· Hallucinations in other modalities			
· Systematized delusions			
· Apathy, anxiety, and depression			
Indicative biomarkers			
· Reduced dopamine transporter uptake in basal ganglia by SPECT or PET			
· Abnormal (low-uptake) 123iodine-MIBG myocardial scintigraphy			
· Polysomnographic confirmation of REM sleep without atonia			
Supportive biomarkers			
· Relative preservation of medial temporal lobe structures on CT/MRI scan			
· Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± cingulate island sign on FDG-PET imaging			
· Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range			

DLB: dementia with Lewy bodies; REM: rapid eye movement; SPECT: single-photon emission computed tomography; PET: positron emission tomography; MIBG: metaiodobenzylguanidine; CT: computed tomography; MRI: magnetic resonance imaging; FDG: fluorodeoxyglucose; EEG: electroencephalography.
* These do not exclude a DLB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation.
¶ DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism. The term "Parkinson disease dementia" (PDD) should be used to describe dementia that occurs in the context of well-established Parkinson disease.
Δ Dementia is defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur early in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.
Diagnosis:

Date:
ID Number:
Study Number:

Major or Mild Vascular Neurocognitive Disorder			
DSM-5 Diagnostic Criteria	**Present**	**Absent**	**Diagnosis**
A. The criteria are met for major or mild neurocognitive disorder			
B. The clinical features are consistent with a vascular etiology, as suggested by either of the following:			
1. Onset of the cognitive deficits is temporally related to one or more cerebrovascular events. i.e. aphasia (language disturbance), apraxia (impaired ability to carry out motor activities despite intact motor function), agnosia (failure to recognize or identify objects despite intact sensory function), disturbance in executive functioning (i.e. planning, organizing, sequencing, abstracting)			1 OR 2
2. Evidence for decline is prominent in complex attention (including processing speed) and fronto-executive function.			
C. There is evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits.			

D. The symptoms are not better explained by another brain disease or systemic disorder.			
Probable vascular neurocognitive disorder is diagnosed if one of the following is present; otherwise possible vascular neurocognitive disorder should be diagnosed:			
1. Clinical criteria are supported by neuroimaging evidence of significant parenchymal injury attributed to cerebrovascular disease (neuroimaging-supported).			Any of 1,2,3
2. The neurocognitive syndrome is temporally related to one or more documented cerebrovascular events.			
3. Both clinical and genetic (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) evidence of cerebrovascular disease is present.			
Possible vascular neurocognitive disorder is diagnosed if the clinical criteria are met but neuroimaging is not available and the temporal relationship of the neurocognitive syndrome with one or more cerebrovascular events is not established.			
Diagnosis:			

2.9.2 Data Collecting Sheet

Participant ID:

DATA COLLECTION SHEET

INCLUSION CRITERIA

1. Age ≥ 60 years YES ☐ NO ☐

2. Attended Clinics from January 2010 to December 2019 YES ☐ NO ☐

3. Dementia diagnosis before December 2019 YES ☐ NO ☐

STOP IF ANSWER NO TO ABOVE CRITERIA

EXCLUSION CRITERIA

1. Unable to 50% of testing and dependent in ≥3 Basic ADL YES ☐ NO ☐

STOP IF ANSWER YES TO ABOVE CRITERIA

SOCIO-DEMOGRAPHICS

1. Date of birth: .....

2. Sex: Male ☐ Female ☐

3. Marital Status: Single ☐ Married ☐ Divorced ☐ Widow/Widower ☐

4. Household: Own ☐ Rented ☐ Other .....

6. Education: Grade ☐ Diploma ☐ University degree ☐

CLINICAL HISTORY

1. Dementia subtype: _____
2. Date of diagnosis: _____
3. Duration of symptoms prior to diagnosis: _____
4. Date of discharge from the clinic: _____
5. Date of death: _____
6. Baseline Laboratory Results

Investigations	**Vitamin B12**	**Syphilis serology**	**TSH**	**Total Cholesterol**	**HbA1C**
Results					

<u>Variables captured at 6-month intervals</u>

Variable	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**	**Visit 10**
MMSE										
Blood Pressure										

CHARLSON'S WEIGHTED INDEX OF COMORBIDITY

Assigned weights for diseases	Conditions	Patient's Score
1	Myocardial infarct	
	Congestive heart failure	
	Peripheral vascular disease	
	Cerebrovascular disease	
	Dementia	
	Chronic pulmonary disease	
	Connective tissue disease	
	Peptic Ulcer disease	
	Mild liver disease	
	Diabetes (without end organ damage)	
2	Hemiplegia	
	Moderate or severe renal disease	
	Diabetes with end organ damage	
	Any malignant solid tumour (non-metastatic)	
	Leukaemia	
	Lymphoma	
3	Moderate or severe liver disease	
6	Metastatic solid tumour AIDS	
		Total score:

Assigned weights for each condition that a patient has

The total equals the score.

Eg: chronic pulmonary (1) and leukaemia (2) = total score (3)

Charlson's Co-morbidity Score: ……

Source: Charlson ME, Pompei P, Ales KL, MacKenzie CR. *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* **J Chronic Dis 1987; 40**(5): 373-83

2.9.3 Ethics Approval letters

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

06 July 2021

HREC REF: 403/2021

Prof M Combrinck
Division of Geriatric Medicine
Ward E7, NGSH
Email: marc.combrinck@uct.ac.za
Student: mikssonko@gmail.com

Dear Prof Combrinck

PROJECT TITLE: DEMENTIA SUBTYPES, COGNITIVE DECLINE AND SURVIVAL AMONG OLDER ADULTS ATTENDING GERIATRIC SPECIALIST CLINICS IN CAPE TOWN, SOUTH AFRICA- MPHIL CANDIDATE-DR MICHAEL SSONKO

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 July 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Michael Ssonko will also be involved in this study.

Please quote the HREC REF 403/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL
Enquiries: Dr Bernadette Eick
e-mail: GSHReserach.Request@westerncape.gov.za

PROFESSOR MARC COMBRINCK
GERIATRIC MEDICINE

E-mail: marc.combrick@uct.ac.za/ mikssonko@gmail.com

Dear Professor Combrinck

RESEARCH PROJECT: Dementia Subtypes, Cognitive Decline and Survival Among Older Adults Attending Geriatric Specialist Clinics in Cape Town, South Africa (MPhil candidate: Dr Michael Ssonko)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 July 2022.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) Confidentiality must always be maintained.
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
m) Kindly submit a copy of the publication or report to this office on completion of the research.
n) At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.
o) Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.

I would like to wish you every success with the project.

Yours sincerely

Signed by candidate

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 13 August 2021

C.C. Mr. L Naidoo, Mr. A Mohamed, Prof. N Ntusi