SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY THIRUVANANTHAPURAM, KERALA

NEUROPSYCHOLOGICAL AND IMAGING PREDICTORS OF LONGITUDINAL COGNITIVE TRENDS IN MILD COGNITIVE IMPAIRMENT (MCI)

Thesis submitted in partial fulfillment of the rules and regulations for DM Degree Examination of Sree Chitra Tirunal Institute for Medical Sciences and Technology

By

Dr Prashanth Poulose

DM Neurology Resident

Month and Year of Submission: August 2021

DEPARTMENT OF NEUROLOGY

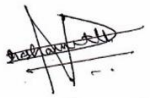
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY

THIRUVANANTHAPURAM

2019-2021

CERTIFICATE

I, **Dr Prashanth Poulose**, hereby declare that this project titled "Neuropsychological and Imaging Predictors of Longitudinal Cognitive Trends in Mild Cognitive Impairment (MCI)" was undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.



Place: Thiruvananthapuram

Date: 30-07-2021

Dr Prashanth Poulose

Resident in Neurology

Forwarded

The candidate, **Dr Prashanth Poulose**, has completed the project titled "Neuropsychological and Imaging Predictors of Longitudinal Cognitive Trends in Mild Cognitive Impairment (MCI)" under my guidance.

Place: Thiruvananthapuram

Date: 30/07/2021

Dr. Ramshekhar N Menon

Additional Professor

Department of Neurology

SCTIMST

Forwarded

The candidate, **Dr. Prashanth Poulose** has carried out the study titled "Neuropsychological and Imaging predictors of Longitudinal cognitive trends in Mild Cognitive Impairment (MCI)" as part of the minimum required project.

Place: Thiruvananthapuram

Date: 30/07/2021

Dr Sanjeev V Thomas

Professor and Head

Department of Neurology, SCTIMST

ACKNOWLEDGEMENT

*I take this opportunity to express my sincere gratitude to **Dr.Ramshekhar N Menon**, Additional Professor of Neurology, SCTIMST, my guide for the study, for his expert guidance, constant review, kind help and keen interest at each and every step of the study*

*I am thankful to **Dr.Sanjeev V Thomas**, Professor and Head, Department of Neurology for his guidance, encouragement and valuable suggestions during the period of the study.*

*I express my sincere thanks to **Dr.Raviprasad Varma**, Professor, Achutha Menon Centre for Health Science Studies for helping me with the statistical analysis of this study.*

*I express my sincere thanks to **Ms Gouthami Nair**, **Ms Sushama**, **Ms Meenu** and **Ms Anjali** for assisting me in the detailed neuropsychology evaluation of the cases.*

*I sincerely thank **Dr Vikas, Ms Sheela** and **Mr Rajesh** for analyzing images and doing the quantitative MRI analysis.*

*I am extremely grateful to **Mrs. Remisha** for editing and organising my thesis.*

Last but not the least, I extend my gratitude to all my patients, their primary caregivers who willingly participated in this study.

Dr Prashanth Poulose

Senior Resident

Department of Neurology

SCTIMST, Trivandrum, Kerala

CONTENTS

NEUROPSYCHOLOGICAL AND IMAGING PREDICTORS OF LONGITUDINAL COGNITIVE TRENDS IN MILD COGNITIVE IMPAIRMENT (MCI)

INTRODUCTION

There is a gradual but significant increase in elderly population across the world. According to the World Population Aging Report, 2020, Globally, there were 727 million persons aged 65 years or over in 2020(1). Over the next three decades, the number of older persons worldwide is projected to more than double, reaching over 1.5 billion in 2050. All regions will see an increase in the size of the older population between 2020 and 2050 Globally, the share of the population aged 65 years or over is expected to increase from 9.3 per cent in 2020 to around 16.0 per cent in 2050(1). With increase in ageing globally, cognitive impairment is becoming a major public health issue. Cognitive decline is becoming the most feared aspect of growing old because cognitive decline herald's dementia and reduces life span.

In India memory problems and changes in instrumental activities of daily living are often seen as a part of senescence rather than early symptoms of a disease. Most often these early symptoms are overlooked by the family as well as the primary physicians at first contact. Therefore, lack of awareness about MCI and dementia both among families and health sector added to the other challenges like lack of resources, poor help seeking, cultural beliefs, poor education, and untreated chronic co-morbidities are barriers to early identification and interventions.

Mild cognitive impairment (MCI) or Mild neurocognitive disorder (MCD) consider as a transitional state between the cognition of normal aging and mild dementia(2,3). Mild cognitive impairment (MCI) occurs along a continuum with normal cognition at one end of the continuum and dementia at the other(2).

Patients with MCI have mildly impaired performance on objective neuropsychological tests but relatively intact global cognition and daily functioning(4).

There is considerable etiological and clinical heterogeneity within MCI; however, there is a unifying increased risk of progression to dementia, hence it

warrants an appropriate stage for intervention to prevent its progression to dementia and therefore, requires early identification for which various diagnostic modalities such as neuroimaging, neuropsychological tests, and biological markers are considered(5).

MCI identifies a spectrum of diseases that includes impairment in both memory (amnestic) and nonmemory cognitive domains (non amnestic). MCI can be divided further into single domain or multiple domains, based on the involvement of the number of cognitive domains affected(2,5).

MCI may not always convert to dementia. Around 20- 40%, cases appear to improve over time on retesting. After diagnosis, the subtype may change on follow-up. MCI may have different outcomes(6,7). Multi-domain amnestic MCI appear to be at the greatest risk of dementia. Amnestic MCI has the highest risk for conversion to Alzheimer's dementia, whereas multi-domain presentation to vascular dementia (8–10). A non-amnestic subtype with multiple domain involvement more likely converts to non-AD, with the single domain dysexecutive subtype at particular risk of progressing to fronto-temporal dementia(11).

Rates of progression from MCI to dementia vary between hospital cohorts 20-30% and community cohorts 5-10% with a few outliers at the lower and higher ends of the spectrum (12,13). Some studies have found that the annualised conversion rate was between 10-15% for hospital cohort and less than 5 % for community cohorts (14) .

Progression of MCI may be determined by the following factors includes, older age, fewer years of education, multidomain amnestic MCI, high fat diet, medical comorbidities(9,15). Medical comorbidities involving metabolic syndrome, chronic inflammatory diseases, vascular disease, thyroid disorders, and elevated homocysteine levels, Excessive alcohol intake, Stressful lifestyle, Untreated depression, Presence of apolipoprotein E (ApoE), E4 allele and Magnetic resonance imaging (MRI), with volumetric measurements of the hippocampus at or below the 25th percentile for matched age and sex(16).

REVIEW OF LITERATURE

EVOLUTION OF MCI

The concept of memory impairment developing with aging has been discussed in the literature for many years. Perhaps the first discussion of this type of problem was introduced by Kral (1962) with the term, "Benign senescent forgetfulness" which referred to memory changes that were likely relatively stable and not indicative of a progressive disorder.

In 1986, the National Institute of Mental Health organized a workgroup to address cognitive changes with age and coined the term, "Age associated memory impairment" (AAMI). The criteria included a subjective memory impairment, normal general cognition, no dementia, and an objective memory impairment 1 SD below that of young adults.

Levy and colleagues with the International Psychogeriatric Association proposed a revision of the AAMI with the notion of "Aging-associated cognitive decline" (AACD). This concept broadened the notion of impairment to domains other than memory. Persons with AACD may have deficits in memory, attention, language, or visuospatial skills, and performance was referenced to age-appropriate norms. The deficits were not believed to be sufficiently severe to impair functional activities. The criteria for AACD referred to a person who is aware of a cognitive decline for at least 6 months and has objective evidence of a cognitive decline in learning, memory, attention, thinking, language, and visuospatial skills of a magnitude of at least 1 SD below age and education norms.

The DSM IV addressed cognitive changes with age in the research nomenclature in the manual and proposed the term, Aging-related cognitive decline. This term was meant to refer to cognitive changes resulting from the aging process, such as a change in memory or other cognitive process not believed to be related to neurologic or psychiatric disorders. However, this concept was somewhat vague and did not address the issue of normal aging and incipient disease.

The International Classification of Disease 10 (ICD 10) proposed the concept of a Mild cognitive disorder, which referred to an impairment of memory or

concentration that was not believed to be due to dementia or other nervous system disorders but, rather, to systemic illnesses. In this sense, the concept is only tangentially related to the notion of MCI.

The Canadian Study of Health and Aging has used the term, 'cognitive impairment no dementia' (CIND), to characterize intermediate cognitive function of insufficient severity to cause dementia(17).

MCI -OVERVIEW

MCI was first introduced in late 1980s by Reisberg ,but it was first fully characterized by Petersen and associates in 1997 .MCI refers to impairment in cognition above that which is seen with normal age-related cognitive decline, but not severe enough to cause significantly impaired daily function(18).MCI validated as qualitatively different from both normal ageing and dementia and has been a matter of debate regarding whether or not it is a risk factor for the development of dementia(2,19).MCI is a syndrome defined as cognitive decline greater than that expected for an individual's age and education level but that does not interfere notably with activities of daily life(20).

Age related cognitive decline can affect 6 main cognitive domains that could potentially be affected (learning and memory, social functioning, language, visuospatial function, complex attention, or executive functioning). The term MCI generally refers to a decline in the ability to learn new information or recall stored information.

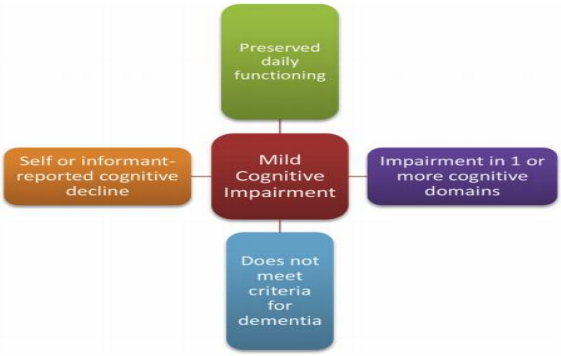


Figure 1: MCI CORE COMPONENTS

DEFINITIONS

In 2004 the International Working Group on MCI published a consensus report in which the following criteria were proposed for MCI: (i) the person is neither normal nor demented; (ii) there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective report of decline by self and/or informant in conjunction with objective cognitive deficits; and (iii) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired(19).

The National Institute on Ageing and Alzheimer's Association (2010) revised the criteria of MCI as: 1) concern regarding change in cognition, 2) impairment in one or more cognitive domains, 3) preservation of independence in functional abilities, and 4) not demented(21).

MCI due to AD-If the subject meets the Core Clinical Criteria for MCI, and in addition has positive biomarkers for both Amyloid β deposition (CSF Aβ42, PET amyloid imaging) and neuronal injury (CSF tau ,hippocampal or medial temporal atrophy by volumetry) this provides the highest level of certainty that over time the individual will progress to AD dementia(21).

Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V) classifies MCI as a "mild neurocognitive disorder," and specifies that there must be both a subjective and objective decline from previous level of functioning in 1 or more of the 6 cognitive domains, not substantially interfering with instrumental activities of daily living, and not occurring in the context of delirium or other psychological disorders(3).

EPIDEMIOLOGY

The prevalence of MCI in those greater than 65 years of age is thought to be around 3% to 22%, depending on the demographics of the population studied(22).

The rates of MCI reported vary from 3 to 17%, it being 3% at 60 years to 15% at the age of 75. In fact, the rate of development of MCI was about 5.3% per year (3.5% in the seventh decade of life and 7.2% in the eighth decade)(23,24).

Petersen et al,in his study revealed that MCI prevalence was 6.7% for ages 60–64, 8.4% for 65–69, 10.1% for 70–74, 14.8% for 75–79, and 25.2% for 80–84. Cumulative dementia incidence was 14.9% in individuals with MCI older than age 65 years followed for 2 years(25).

An Indian study from Calcutta reported 14.89% prevalence of MCI-of which the amnestic type (more seen in men) was 6.04% and the multiple domain types (more seen in men) was 8.85%(26). The study from Cochin also reported the prevalence to be about 14.89%. Satishchandra and group on the other hand reported an incidence in a clinical setting to be as high as 47.1%. Mridula, Alladi *et al*.(n=1190) in their clinic sample reported a rate of 59% with MCI, in their elder population(27).

Conversion rates from MCI to the AD found to be 10- 15% as reported by Petersen in his sample at a specialty clinic, whilst it was 8-10% in the general population(28). Mridula, Alladi *et al*. in their clinic sample, showed 11% conversion rate to AD, during a 13 month follow up(27).

PRESENTATIONS AND SUBTYPES

MCI can be further classified as “amnestic” versus “nonamnestic.” Amnestic MCI refers to impairment purely in one’s ability to recall stored information, whereas non amnestic MCI refers to impairment in one or more of the other cognitive domains, while memory remains relatively intact. MCI also be classified into single and multidomain(2,4).

The concept of different aetiologies causing MCI was also introduced: degenerative, vascular, psychiatric and traumatic(2). A model with MCI subtypes of different aetiologies representing different prodromal dementia disorders was put forward. Amnestic MCI (aMCI) of degenerative aetiology was suggested to represent prodromal AD; amnestic MCI with multiple domains impaired (maMCI) of degenerative aetiology would also represent prodromal AD; maMCI of vascular aetiology would represent vascular dementia (VaD); non- amnestic MCI with multiple domains impaired (mdMCI) of degenerative aetiology dementia was suggested to be prodromal dementia with Lewy bodies (DLB); mdMCI of vascular

aetiology VaD; non-amnestic MCI with single domain impaired would be prodromal frontotemporal dementia (FTD) or DLB(16).

MILD BEHAVIOURAL IMPAIRMENT (MBI)

In the prodromal phase of dementia, another group observed, known as "mild behavioural impairment" (MBI) that presented only with behavioural symptoms and yet progressed toward dementia. Thus, Taragano et al.[11] proposed another classification: 1) MCI with neuropsychiatric symptoms, 2) MCI without neuropsychiatric symptoms, 3) MBI with cognitive symptoms, and 4) MBI without cognitive symptoms(29).

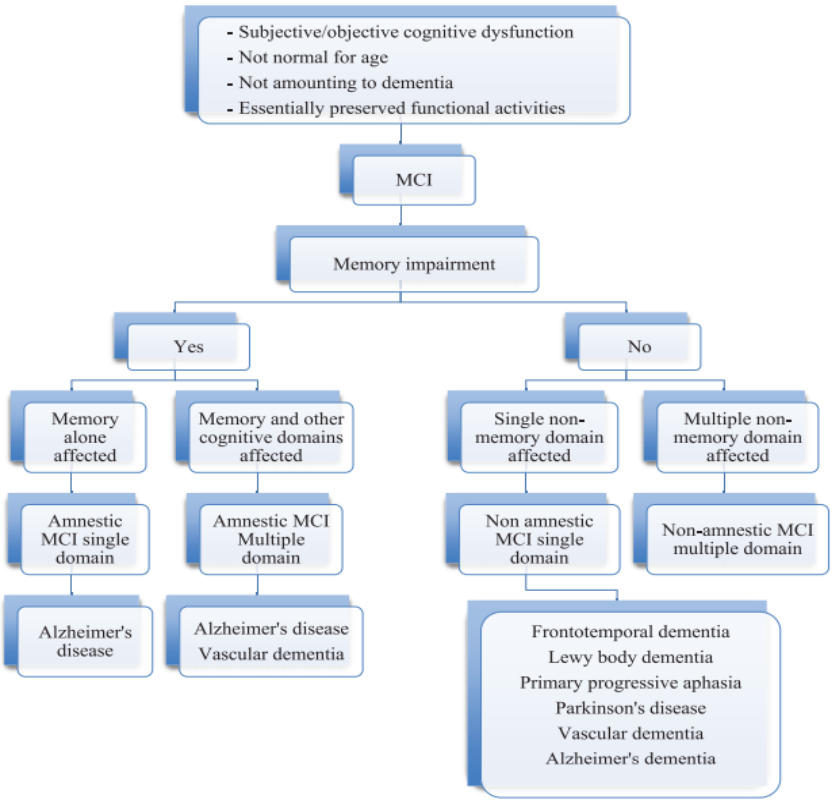


Figure 2: MCI CLASSIFICATION

PREDICTORS OF CONVERSION

GENERAL OVERVIEW

There are several risk factors that increase the risk for developing MCI, with age being the strongest. Other well-established risk factors include male sex, presence of the apolipoprotein E allele, family history of cognitive impairment, and

the presence of vascular risk factors such as hypertension, dyslipidemia, coronary artery disease, and stroke(11,16,30).

One study focusing on multimorbidity and development of MCI found that those participants with 4 or more chronic conditions, particularly 2 of the following—hypertension, dyslipidemia, coronary artery disease, and osteoarthritis—had the highest risk of MCI(31). Other chronic medical conditions, such as chronic obstructive pulmonary disease, depression, and diabetes mellitus, are also known risk factors. Lifestyle plays a role as well, with those who are cognitively and/or physically sedentary at greater risk for developing MCI(32).

About 30% to 50% of those originally diagnosed with MCI reverting back to "normal" cognition at subsequent follow-up. Some factors found to be associated with a greater likelihood of return to normal cognition include single domain impairment, presence of depression, use of anticholinergic medications, absence of the apolipoprotein E ε4 allele, greater hippocampal volume on neuroimaging and higher scores on neuropsychology testing(16,20,32).

Despite the high reversion rate, however, there is a 5% to 10% annual rate of progression to dementia in those with MCI, which is much higher than the 1% to 2% incidence per year among the general population(30,33).

This dichotomy between the annual reversion rate to normal cognition and the conversion rate to dementia indicates that there are modifiable factors that may be contributing to cognitive decline and makes the case for the necessity of early screening and diagnosis.

Since all MCIs do not convert, follow-up studies are needed to know the rate of conversion in the Indian context and to identify any demographic, clinical, biochemical, or neuropsychological profile that would aid in identifying those at higher risk of conversion to dementia so that preventive measures could be initiated at the time of identification of MCI.

CLINICAL PREDICTORS

Table 1: MCI clinical predictors literature review

Study	Title	Method	Conclusion
Claudia Cooper et al 2015(15)	Modifiable Predictors of Dementia in MCI : A Systematic Review and Meta-Analysis	Longitudinal follow up study looked at modifiable risk factors for incident dementia after MCI .76 articles reporting 62 studies were included	Diabetes increased the risk of conversion to dementia. Other factors that predict risk are prediabetes, metabolic syndrome, neuropsychiatric symptoms, depression and low dietary folate.
Atti et al 2019(34)	Metabolic Syndrome(MetS), MCI, and Dementia: A MetaAnalysis of Longitudinal Studies	Nine longitudinal studies were selected for the meta-analysis. A total of 18,313 participants aged older than 40 years with mean MetS prevalence of 22.7% were followed for 9.41 yrs	No significant association was found between MetS and incident dementia and AD. MetS increased the incidence of pure VaD risk of progression from MCI to dementia
Bin Zhou et al 2016(35)	Shanghai Cohort Study on MCI: Study Design and Baseline Characteristics	Prospective cohort study that included 400 subjects with MCI and a follow-up once annually for three years	At baseline age, education and being single influenced MMSE, ADAS-cog13 and most domains of cognition
Forlenza et al	MCI: clinical characteristics and predictors of	Included 1,698 articles, 248 were critically eligible	Cross-sectional diagnosis of MCI has limited prognostic relevance The

2013(36)	dementia	(cross-sectional and longitudinal studies) between 1999-2012	characterization of persistent and/or progressive cognitive deficits over time is a better approach for identification of cases
Pal et al 2018(37)	MCI and progression to dementia in people with diabetes, prediabetes and metabolic syndrome: a systematic review and meta-analysis	Included 15 articles reporting 12 studies (6865 participants).	Diabetes and MetS were both associated with an increased incidence of dementia when co-existing with MCI. -Intensive cardiovascular risk reduction and lifestyle changes for patients presenting with MCI and diabetes, prediabetes or MetS reduces incidence of dementia in high risk population
Mingyue Hu et al 2020(38)	Neuropsychiatric symptoms as prognostic makers for the elderly with MCI: a meta-analysis	Prospective cohort studies were included if they reported on at least one NPS at baseline and had MCI as the outcome. Obtained 13 cohort studies with a total population of 33,066	-Depression was associated with an approximately 1.5-folds increased risk of the progression to MCI in the population with normal cognition. - Other NPSs with underlying predictive value deserve more attention
Natalia et al	Neuropsychiatric profiles and	A total of 2137 MCI patients monitored in	Irritability and Apathy were predictors of conversion to

2021(39)	conversion to dementia in MCI, a latent class analysis	a memory clinic were included in the study	dementia Anxiety/depression class showed no risk effect of conversion when compared to Asymptomatic class.
Palmer et al 2007(40)	Predictors of progression from MCI to Alzheimer disease	185 persons with no cognitive impairment and 47 with MCI (amnestic and multidomain), ages 75 to 95, from the population-based Kungsholmen Project, Stockholm, Sweden, for 3 years.	Predictive validity of MCI for identifying future Alzheimer disease (AD) cases is improved in the presence of anxiety symptoms. -Depression in preclinical AD appeared in persons both with and without MCI
Ramakers et al 2010(41)	Affective symptoms as predictors of Alzheimer's disease in subjects with MCI: a 10-year follow-up study	263 subjects with MCI older than 55 years were selected from a memory clinic and followed up after 2, 5 and 10 years. - Predictors investigated were: symptoms of depression, anxiety, apathy and sleeping problems	-Depression was associated with a decreased risk for AD only in subjects without amnestic MCI, but not in subjects with amnestic MCI.
Visser et al 2008(42)	MCI as predictor for Alzheimer's disease in clinical practice: effect of	-Non-demented subjects older than 40 (n=320) were reassessed 5 years	-The predictive accuracy of MCI for AD is dependent on age and the definition of MCI used.

	age and diagnostic criteria	later for the presence of AD. -Analyses were conducted on the entire sample and on subgroups of subjects aged 40-54, 55-69 and 70-85 years.	-The predictive accuracy is good only for amnestic MCI in subjects 70-85 years.
Solfrezzi et al 2011(43)	Metabolic syndrome, MCI, and progression to dementia. The Italian Longitudinal Study on Aging	Large longitudinal Italian population-based sample with a 3.5-year follow-up. A total of 2097 participants from a sample of 5632, 65–84-year-old subjects from the Italian Longitudinal Study on Aging were evaluated	Among MCI patients the presence of MetS independently predicted an increased risk of progression to dementia over 3.5 years of follow-up.
Tze et al 2016(44)	Metabolic Syndrome and the Risk of MCI and Progression to Dementia Follow-up of the Singapore Longitudinal Ageing Study Cohort	Prospective population based longitudinal study with 1519 cognitively normal adults more than 55 yrs were followed up from2003, through 2009, South East region of Singapore.	The MetS was associated with an increased incidence of MCI and progression to dementia. Identifying individuals with diabetes mellitus or the MetS with or without MCI is a promising approach in early interventions to prevent or slow progression to dementia

NEUROPSYCHOLOGY PARAMETERS OF PREDICTION

Most of these neuropsychological and imaging studies are done in western population. There is a real dearth of Indian data on neuropsychological profile of MCI, its radiological correlates or its conversion rate to AD.

Extensive survey of literature shows that the hospital based conversion rate worldwide is 20-30% and for community based studies annualised conversion rate was between 3-10%.(13,14,33). A meta-analysis revealed that using Mayo defined MCI at baseline and adjusting for sample size, the cumulative proportion of MCI who progressed to dementia, to Alzheimer's disease (AD) and to vascular dementia (VaD) was 39.2%, 33.6% and 6.2%, respectively in specialist settings and 21.9%, 28.9% and 5.2%, respectively in population studies. The adjusted annual conversion rate (ACR) from Mayo defined MCI to dementia, AD and VaD was 9.6%, 8.1% and 1.9%, respectively in specialist clinical settings and 4.9%, 6.8% and 1.6% in community studies.(33) .Thus the annual adjusted conversion rate is approximately 5–10% and most people with MCI will not progress to dementia even after 10 years of follow-up. A study from India by Mukku et al 2019 showed annualised conversion rate of 28.6% with a mean duration of follow up 1.4 yrs

The overall conclusions of all the studies is that poor performance on delayed recall and executive function tests indicate a high risk of progression to dementia, particularly delayed recall, since this measure was a highly accurate predictor of progression to dementia in longitudinal studies of 2–10 years' duration in clinical samples and large epidemiological samples(45–49).

The MCI Multidomain subtype of MCI has shown increased conversion to dementia , 2/3 of multidomain converted whereas only less than half of single domain MCI developed dementia on follow up(8–10,50).

Low baseline CDR and IADL showed faster decline to dementia and are important parameters to assess conversion(8,14,51,52).

The gaps in literature is study of correlation between functional imaging and baseline neuropsychological scores in predicting progression.

HOSPITAL BASED COHORTS

Table 2: MCI HOSPITAL BASED COHORTS LITERATURE REVIEW

Study	Title	Method	Conclusion
Yong S. Shim et al 2016(12)	Clinical Predictors for MCI Progression in a Korean Cohort Multicentric Hospital based prospective cohort study	Korean cohort of 778 that included older adults with MCI who completed at least one follow-up visit (mean duration 1.42±0.72 yr)	27.63% of cohort progressed to dementia The best predictors were age, apolipoprotein ε4 allele Clinical predictors were reliable for the progression from MCI to dementia
Maria Eugenia et al 2016(53)	Searching for Primary Predictors of Conversion from MCI to Alzheimer's Disease: A Multivariate Follow-Up Study	Multivariate follow up study -33 MCI patients followed up for 2-year -MCI were divided into two subgroups according to their outcome: The "stable" MCI group (sMCI, 21 subjects) and the "progressive" MCI group (pMCI, 12 subjects).	-Combination of left hippocampal volume, occipital cortex theta power, and clock drawing copy subtest scores predicted conversion to AD with a 100% of sensitivity and 94.7% of specificity -Anatomical, cognitive, and neurophysiological markers may be considered as "first order" predictors of progression to AD
Mitchell et al 2009(33)	Rate of progression of mild cognitive impairment to dementia – meta-analysis of 41 robust inception cohort studies	Meta-analysis of 41 cohorts of MCI - Hospital and community based cohorts	Adjusted annual conversion rate (ACR) from Mayo defined MCI to dementia, AD and VaD was 9.6%, 8.1% and 1.9%, (Hospital based) and 4.9%, 6.8% and 1.6% in

			community studies
Tabert et al 2006(54)	Neuropsychological Prediction of Conversion to Alzheimer Disease in Patients With MCI	Longitudinal follow up study One hundred forty-eight patients reporting memory problems and 63 group-matched controls	MCI patients with memory plus other cognitive domain deficits, rather than those with pure amnestic MCI, constituted the high-risk group. Deficits in verbal memory and psychomotor speed/executive function abilities strongly predicted conversion to AD.
Farias et al 2009(14)	Progression of MCI to Dementia in Clinic- vs Community -Based Cohorts	Prospective longitudinal study of 111 MCI for average 2.4 yrs -Among the participants, 46% were recruited from a clinical setting and 54% were recruited directly through community outreach	- The clinic sample had an annual conversion rate of 13%, whereas the community sample had an annual conversion rate of 3%. Degree of functional impairment at baseline measured by CDR (and no demographic, cognitive, or neuroimaging variables or MCI subtype) is an important predictor of conversion to dementia
Woong Roh et al 2016(55)	Clinical Conversion or Reversion of MCI in Community versus Hospital Based Studies: GDEMCIS	-The two studies had nearly the same protocol and were performed over a similar period. -We used	- The hospital based cohort had hazards of 2.13 for conversion and HR of 0.34 for time to reversion compared to community based cohort

	(Gwangju Dementia and MCI Study) and CREDOS (Clinical Research Center for Dementia of South Korea)	propensity score matching for baseline comparability. -After that, Cox proportional hazards regression analyses were conducted to estimate the hazard ratios and 95% confidence intervals of clinical conversion or reversion	-Hence even after the matching process and adjustments for baseline covariates, recruitment source greatly affected the course of MCI.
Chen et al 2016(13)	Progression from normal cognition to MCI in a diverse clinic-based and community-based elderly cohort	-Rates and predictors of conversion were assessed in 254 cognitively normal subjects clinic (5%) and community sample (95%) followed up for 7yrs -Prospective longitudinal study at University of California, Davis, Alzheimer's Disease Center from 2000 to 2015	The clinic-based sample showed an annual conversion rate of 30% per person-year, whereas the community-based sample showed a conversion rate of 5% per person-year. -Risk factors for conversion include clinic-based recruitment, being older, lower executive function and worse functional assessment at baseline, and smaller total brain volume

Jang et al 2017(10)	Prediction Model of Conversion to Dementia Risk in Subjects with Amnestic MCI: A Longitudinal, Multi-Center Clinic-Based Study	-A total of 338 aMCI patients from two hospital-based cohorts were followed up and conversion to dementia was the primary outcome - All patients were classified into 1) verbal, visual, or both, 2) early or late, and 3) single or multiple-domain aMCI	-In logistic regression models, both modalities compared with visual only , late compared to early, and multiple compared to single domain aMCI were significantly associated with dementia conversion within 3 years.
Xie et al 2011(56)	Predictors of Future Cognitive Decline in Persons with MCI	187 MCI patients were evaluated serially with the MMSE for up to 3.5 years.	Patient age and performance on delayed recall, constructional praxis, attention, and orientation to time and floor predicted future cognitive decline
Edith et al 2018(57)	Longitudinal Follow-Up of a Population with MCI: Predictive Value of the MIS Test with Delayed Recall for Progression to Dementia	Memory Impairment Screen with delayed recall (MIS-DR) was used to predict conversion to dementia in patients with MCI. -In retrospective study 502 patients	- There were no significant differences in terms of gender, education level or vascular risk factors among patients who converted and those who did not convert to dementia -MIS-DR is a useful and valid test to detect

		over 60 years old, evaluated -During follow up, 28.6%converted and the average time of progression to dementia were 23 months.	episodic memory impairment and to identify patients at risk of progression to dementia
Marcos et al 2006(58)	Neuropsychological Markers of Progression from MCI to Alzheimer's Disease	Neuropsychological tests were performed on 82 MCI subjects	Three cognitive variables (CAMCOG, Memory, and Perception) were able to predict the risk of progression from MCI to AD with high sensitivity
Julayanont et al 2014(59)	Montreal Cognitive Assessment Memory Index Score (MoCA-MIS) as a Predictor of Conversion from MCI to Alzheimer's Disease	One hundred fourteen participants progressed to AD (MCI-AD), and 51 did not (nonconverters; MCI-NC)	Individuals with MCI with a low MoCA-TS and a low newly devised memory index score (MoCA-MIS) are at greater risk of short-term conversion to AD.
Hye-Geum Kim et al 2020(60)	Neuropsychological predictors of cognitive deterioration in non-demented individuals	106 participants with subjective cognitive complaints (SCCs) classified as non-demented (90 MCI and 16 SCD) Correlation analysis showed a	They concluded that SCD and MCI individuals with significantly poor initial executive function and memory abilities should be closely monitored for future cognitive decline

		significant correlation between the deterioration of the CDR scores and baseline language, memory, and frontal lobe function scores.	
Seok Ho Yun et al 2020(61)	Characteristics of Individuals Who Converted to Dementia during a 5-Year Follow-Up	107 participants were evaluated periodically for 5 years. Assessment items included demographic information, including age, sex, and education; 5 cognitive domains of a comprehensive neuropsychological test including memory, language, attention, visuospatial functions, and frontal (executive) function; Barthel's IADL the mini-mental state examination findings; and CDR	Concluded that individuals with prominent memory decline or problems with social activities should be carefully observed for dementia conversion

Tian et al 2003(62)	Neuropsychological prediction of conversion to dementia from questionable dementia: statistically significant but not yet clinically useful	195 patients with QD seen in a National Health Service hospital outpatient clinic 135 seen for a mean follow up of 24.5 months Conversion rate to dementia was 27.4% (37 of 135).	Use of cognitive indicators combined with neuroradiological, neuropathological, and genetic factors for predicting conversion to dementia might prove more reliable
Chapman et al 2010(63)	Predicting conversion from MCI to Alzheimer's disease using neuropsychological tests and multivariate methods	Longitudinally studied 43 patients of MCI, baseline evaluation were first reduced to underlying components (principal component analysis, PCA), and then the component scores were used in discriminant analysis to classify MCI individuals as likely to convert or not.	When empirically weighted and combined, episodic memory, speeded executive functioning, recognition memory, visuospatial memory processing speed, and visuospatial episodic memory were together strong predictors of conversion to AD
Chasles et al 2019(64)	An Examination of Semantic Impairment in Amnestic MCI and	Ninety-six participants divided into three equal groups (N = 32:	These results indicate a semantic memory impairment in aMCI revealed by a simple,

	AD: What Can We Learn From Verbal Fluency?	AD, aMCI and Controls) were included in this study - Compared verbal fluency performance of aMCI patients to those of AD and elderly controls matched one-to one for age and education.	commonly-used neuropsychological test
Nesset et al 2014(65)	Brief Tests such as the Clock Drawing Test or Cognistat Can Be Useful Predictors of Conversion from MCI to Dementia in the Clinical Assessment of Outpatients	Retrospective, longitudinal study of 90 patients of MCI at a psychogeriatric clinic in Norway was conducted. - Baseline scores on the Mini-Mental State Examination (MMSE), Clock Drawing Test (CDT), and Neurobehavioral Cognitive Status Examination (Cognistat) were used during 46 months	ACDT and Cognistat significantly predicted the conversion from MCI to dementia and are therefore considered appropriate tests in clinical practice

Tierney et al 1996(66)	Prediction of probable Alzheimer's disease in memory-impaired patients: A prospective longitudinal study	123 MCI patients were followed longitudinally for 2 years with a research battery of neuropsychological tests	Two tests contributed significantly to this model: the delayed recall from the Rey Auditory Verbal Learning Test and the Mental Control subtest of the Wechsler Memory Scale
Serrano et al 2013(9)	MCI: Risk of Dementia according to Subtypes	-A total of 127 patients diagnosed with MCI average age 70.21yrs were evaluated with a neuropsychological battery. -They were classified into 3 groups: amnestic MCI (n=20), multiple-domain MCI (n=98), non-amnestic MCI (n=9). -Seventeen normal subjects with average age 74.59 yrs were included	-27.1% of cohort converted and average conversion time was 11.12 months -Thirty-five percent of amnestic MCI converted to AD It was found that 31.6% of multiple domain MCI converted to AD 15.3% 6 months and 16.3% at 12 months -Age and retirement being the variables that increased the likelihood of conversion to Dementia

COMMUNITY BASED COHORTS

Table 3: LITERATURE REVIEW OF COMMUNITY BASED MCI COHORTS

Study	Title	Methods	Conclusion
Belleville et al 2017(67)	Neuropsychological Measures that Predict Progression from MCI to Alzheimer's type dementia in Older Adults: a Systematic Review and Meta-Analysis	Twenty-eight longitudinal studies met the eligibility criteria (2365 participants) and reported predictive values from 61 neuropsychological tests with a 31-month mean follow-up	Cognitive tests (esp verbal memory and language tests) are excellent at predicting MCI individuals who will progress to dementia and should be a critical component of any toolkit intended to identify AD at the predementia stage.
Sara Garcia et al 2016(48)	Neuropsychological predictors of conversion to probable Alzheimer disease in elderly with MCI	Predictive value of the cognitive tests included in a neuropsychological battery for conversion to AD among MCI participants -A total of 105 participants were assessed with a neuropsychological battery at baseline and during a 3-year follow-up period.	The results reveal the relevance of the NPT tests of episodic verbal memory tests and tests that assess visuospatial and executive components at baseline predicted risk for conversion -The logistic regression analysis determined that the long delay cued

			recall and the performance time of the Rey figure test were the best predictive tests of conversion to dementia after an MCI diagnosis.
Joubert et al 2020(68)	A Meta-Analysis of Semantic Memory in MCI	22 studies (476 healthy participants, 476 MCI patients, mean MMSE of the MCI patients: 27.05 ± 0.58) were included in the meta-analysis	Semantic deficits are a key feature of MCI. Semantic tests should be incorporated in routine clinical assessments
Rindge et al 2017(51)	Neuropsychological and Psychological Predictors of Conversion from MCI to Alzheimer's Dementia	210 subjects with MCI and aimed to determine to what extent neuropsychological measures, depression, and ratings of everyday functional status predict conversion from MCI	CDR was the only significant predictor of conversion from MCI to AD, with 17 times more likely to convert to AD for each one-unit increase on the CDR.
Helen Amieva et al 2004(69)	Annual Rate and Predictors of Conversion to Dementia in Subjects Presenting MCI Criteria Defined according to a Population-	- Ninety elderly volunteers with memory complaint diagnosed with MCI on the basis of their functional and neuropsychological performances were followed up within 2 years. Neuropsychological	-Within the 2 years, 29 subjects (32.2%) presented a conversion to dementia Logistic regression showed Letter Cancellation Test

	Based Study	measures used were (Mac Nair Scale, Mini-Mental State Examination, Benton Visual Retention Test, Isaacs Set Test, Digit Symbol Substitution Task, Letter Cancellation Task, digit span tasks and finger-tapping test)	was shown to be an independent predictor for conversion to dementia
Larrieu et al 2002(6)	Incidence and outcome of MCI in a population-based prospective cohort	A community-based cohort of nondemented elderly people (Personnes Agées QUID [PAQUID]) was followed longitudinally for 5 years.	MCI was a good predictor of AD with an annual conversion rate of 8.3% and a good specificity, but it was very unstable over time: Within 2 to 3 years, only 6% of the subjects continued to have MCI, whereas 40% reverted to normal
Thomas et al 2018(49)	Word-list Intrusion Errors Predict Progression to MCI	Cognitively normal participants (n=525) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were followed for up to five years and classified as either "stable normal" (n=305) or "progressed-to-MCI" (n=220)	Baseline RAVLT intrusion errors predicted progression to MCI

Boyle et al 2006(70)	MCI Risk of Alzheimer disease and rate of cognitive decline	786 community-based persons (221 with MCI and 565 without cognitive impairment) from the Rush Memory and Aging Project, a longitudinal clinical-pathologic study of common chronic conditions of old age. All participants underwent detailed annual clinical and neuropsychological evaluations.	MCI is associated with a greatly increased risk of incident Alzheimer disease,6.7 times higher risk and a more rapid rate of decline in cognitive function
Daly et al 2000(52)	MCI is associated with a greatly increased risk of incident Alzheimer disease and a more rapid rate of decline in cognitive function	165 subjects of which 123 had CDR of 0.5 and 42 with CDR of zero were followed up annually for three years	After 3 yr follow up 18.6% (CDR-0.5)subjects were diagnosed with AD
Fleisher et al 2007(71)	Clinical predictors of progression to Alzheimer disease in amnestic MCI	539 participants with aMCI from the Alzheimer's Disease Cooperative Study clinical drug trial of donepezil, vitamin E, or placebo. During the study period of 36 months, 212 aMCI participants progressed to AD.	Progression from amnestic MCI to Alzheimer disease in this cohort was best determined by combining four cognitive measures Symbol Digit Modalities Test, Delayed 10-Word List Recall, New

			York University Paragraph Recall Test (Delayed), and the ADAS-cog total score
Ganguli et al 2004(22)	MCI, amnestic type An epidemiologic study	The subjects were drawn from voter registration lists, composing a cohort of 1,248 individuals with mean age of 74.6 (5.3) years, who were nondemented at entry and who were assessed biennially over 10 years of follow-up.	MCI showed overall increased Odds for conversion 27% developed dementia,21.2% remained stable and 55.6% reverted to normal over the next 10 years
Di Carlo et al 2007(8)	CIND and MCI in the Italian elderly Frequency, vascular risk factors, progression to dementia	Evaluated CIND and MCI in the Italian Longitudinal Study on Aging. The neuropsychological battery assessed global cognitive function, memory and attention. Two thousand eight hundred thirty participants were examined at baseline and after a mean follow-up of 3.9 0.7 years	-Incidence of dementia was higher in CIND and MCI. Among MCI multidomain subtype had higher risk of progression -Among baseline variables, only previous stroke and impairment IADL significantly increased the risk of dementia at follow-up
Katie et al	MCI in the general population:	Occurrence per 100 nondemented persons of	Two-thirds of MCI-multi domains, but

2008(50)	occurrence and progression to Alzheimer disease Population-based Swedish study	MCI-amnestic, MCI-multi domain, and MCI-single-nonmemory was 2.1%, 1.8%, and 7.2%, respectively.	only half of MCI-amnestic progress to AD. -MCI-multidomain showed the highest progression to AD
Ding ding et al 2016(72)	Progression and predictors of MCI in Chinese elderly: A prospective follow-up in the Shanghai Aging Study	362 individuals with MCI diagnosed at baseline through a clinical and neuropsychological interview.	Approximately 6% of elderly with MCI progress and 7.8% revert to normal annually. Amnestic MCI multiple domains was the most risky type for dementia (conversion rate: 14.2 per 100 person-years) Older age ,ApoE4 and low MMSE were predictors
Qi Gao et al 2018(7)	MCI reversion and Progression: Rates and Predictors in Community-Living Older Persons in the Singapore Longitudinal Ageing Studies Cohort	Determined MCI reversion and progression among 473 community-living adults aged ≥55 yrs with an average of 6 years of follow-up and estimated association with baseline variables	44% reverted to normal 4% progressed to dementia -Higher rates of MCI reversion and lower rates of MCI progression were predicted by the positive effects of Leisure time

			activity and a higher MMSE score

NEUROIMAGING

With advancements in Magnetic Resonance Imaging (MRI) brain volumetric techniques, increasing number of longitudinal studies have been focusing on structural (volumetric or morphometric) predictors of MCI conversion.

Available research has largely implied hippocampus, temporal lobe, and entorhinal cortex as areas most commonly affected in patients with AD. The decreased size of the hippocampus on volumetric measures is suggestive of MCI and correlated with the likelihood of progression to Alzheimer's dementia(73,74).

The FAZEKA score showed correlation with baseline neuropsychology parameters especially in word-list learning-recall and WMS verbal delayed recall in predicting conversion to dementia especially non Alzheimer's dementia(75–77).

Table 4: IMAGING PREDICTORS OF PROGRESSION IN MCI

Study	Title	Methods	Conclusion
Salka et al 2009(75)	Progression of MCI to Dementia and Contribution of Cerebrovascular Disease Compared With Medial Temporal Lobe Atrophy	152 consecutive patients with MCI who underwent baseline MRI to identify presence of medial temporal lobe atrophy and vascular disease (presence of lacunes, microbleeds, and infarcts was determined, and	Deep WMHs and periventricular hyperintensities predicted progression to non-Alzheimer dementia. Converters were older and had lower MMSE at baseline Baseline medial temporal lobe atrophy predicted progression to AD

		WMHs were rated on a semiquantitative scale) , mean follow 2±1yrs	
Holz et al 2017(76)	Cognitive performance in patients with MCI and Alzheimer's disease with white matter hyperintensities	40 participants (18MCI, 22AD patients) aged ≥ 65 years. Spearman's correlation was performed among cognitive performance (memory, language, visuospatial ability, and executive function) and WMH evaluated by the Fazekas and ARWMC scales	Fazekas score exhibited significant correlation with all cognitive domains evaluated. Fazekas score was better predicted by episodic visual memory and age
Karas et al 2008(78)	Amnestic MCI : Structural MR Imaging Findings Predictive of Conversion to Alzheimer Disease	Twenty-four amnestic patients with MCI were included. After 3 years, 46% had progressed to AD, for 13 patients remained as MCI	Converters versus nonconverters, atrophy beyond the medial temporal lobe to be characteristic of MCI progressors. Atrophy of structures such as the left lateral temporal lobe and left parietal cortex may independently predict conversion
Henneman	Hippocampal	Included 64	They concluded,

et al 2009(79)	atrophy rates in Alzheimer disease Added value over whole brain volume measure	patients with AD, 44 patients with MCI (21/23), and 34 controls (16/18).	hippocampal measures, especially hippocampal atrophy rate, best discriminate MCI from controls. Whole brain atrophy rate discriminates AD from MCI
Devanand et al 2007(80)	Hippocampal and entorhinal atrophy in MCI Prediction of Alzheimer disease	Performed MRI in 139 patients with MCI broadly defined, and 63 healthy controls followed for an average of 5 years (range 1 to 9 years). Hippocampal and entorhinal cortex volumes were each largest in controls, intermediate in MCI non converters, and smallest in MCI converters to AD	Smaller hippocampal and entorhinal cortex volumes each contribute to the prediction of conversion to Alzheimer disease
Fleisher et al 2008(81)	Volumetric MRI vs clinical predictors of Alzheimer disease in MCI	Baseline MRI scans from 129 subjects with amnestic MCI were obtained from participants in ADCS Measures of whole brain, ventricular,	Use of MRI measures did not improve predictive accuracy beyond that obtained by cognitive measures alone. APOE status, MRI, or demographic variables were not necessary for the

		hippocampal, and entorhinal cortex volumes were acquired. Of the four MRI measures evaluated, only ventricular volumes and hippocampal volumes were predictive of progression to AD.	optimal predictive model
Korolev et al 2016(82)	Predicting Progression from MCI to Alzheimer's Dementia Using Clinical, MRI, and Plasma Biomarkers via Probabilistic Pattern Classification	Baseline data from 259 MCI patients -139 developed AD-type dementia during three-year follow-up period	Predictors of progression included scores on the Alzheimer's Disease Assessment Scale, Rey Auditory Verbal Learning Test, and Functional Activities Questionnaire, as well as volume/cortical thickness of three brain regions (left hippocampus, middle temporal gyrus, and inferior parietal cortex

MOLECULAR IMAGING

Functional imaging techniques, such as 18F-fluorodeoxyglucose positron-emission tomography (18FDG-PET), which provide an index of synaptic integrity, have also been evaluated as predictors of progression to dementia. Studies indicate that patients with a pattern of hypometabolism in the temporal and parietal regions of the brain on 18FDG-PET, which is suggestive of Alzheimer’s disease, may be at

increased risk for rapid progression from MCI to Alzheimer's disease as compared with patients without this pattern. A multicenter longitudinal study, showed that for subjects with MCI who had this pattern of hypometabolism on 18FDG-PET, the risk of progression to Alzheimer's disease during the next 2 years was 11 times the risk among subjects who did not have this pattern(16,83–85).

The use of molecular imaging, particularly of amyloid plaques in the brain , has also been studied as a possible approach to risk stratification. In several studies, subjects with MCI in whom amyloid was detected on positron-emission tomography (PET) with the use of the amyloid-binding carbon 11–labelled Pittsburgh compound B had more rapid progression to Alzheimer's disease than did subjects in whom amyloid was not detected. Assessment with 18-FDG Pittsburgh Compound B (PiB) PET was found sensitive in differentiating amnestic and nonamnestic MCI. It shows a good correlation with cognitive measures in patients with MCI, with a sensitivity of 92% and specificity of 89% to predict conversion to AD(86).

CEREBROSPINAL FLUID BIOMARKERS

Analysis of markers in the cerebrospinal fluid has also been proposed as a means of assessing the risk of progression to Alzheimer's disease. A Swedish study showed that subjects with MCI who had low levels of β-amyloid peptide 42 (Aβ42) and elevated levels of tau protein in cerebrospinal fluid were significantly more likely to undergo progression to Alzheimer's disease than subjects without this profile(87–89).

GENETIC MARKERS

The presence of mutations in A4 precursor protein (APP) and PS1 and PS2 genes are likely predictors of the conversion of MCI to early Alzheimer's dementia. In addition, there is increased risk for the development of dementia in an individual with MCI, in the presence of apolipoprotein (Apo) E4 allele. On the other hand, E2 allele is associated with decreased risk(90).

NEUROPATHOLOGY

Most patients with amnestic MCI demonstrate the deposition of tau proteins in neurofibrillary tangles in the medial temporal lobe and neuronal plaques due to

deposition of beta amyloid(5,11). There is down-regulation of trkA RNA in persons with MCI and those with AD had a significant loss in the number of trkA-containing neurons, (46% decrease for MCI, and 56% for an AD)(91).

In individuals with MCI and mild AD, ChAT activity was unchanged in the inferior parietal, superior temporal and anterior cingulate cortices. On the contrary, ChAT activity in the superior frontal cortex was significantly elevated above normal controls in MCI subjects, whereas the mild AD group was not different. ChAT activity in the hippocampus was significantly higher in MCI subjects. The up-regulation in frontal cortex and hippocampal ChAT activity could be an important factor in preventing the transition of MCI subjects to AD(92).

Table 5: INDIAN DATA ON MCI

Study	Title	Methods	Conclusion
Mukku et al 2019(93)	MCI – A hospital-based prospective study	21 patients with MCI with repeat NPT above 50 years from NIMHANS between 2012 and 2014 ,mean duration of follow up 1.43 yrs - Hindi Mental Status Examination (HMSE), Everyday Abilities Scale for India (EASI), NIMHANS neuropsychological battery for Indian elderly, and Clinical Dementia Rating (CDR) scale instruments were used	28.6% progressed to AD and rest retained MCI status -Executive function learning and memory like total word list learning , design construction copy, total figures cancelled in figure cancellation test , and total omissions on figure cancellation test were the domains predominantly affected in the converters compared to nonconverters

		for assessment	
SK Das et al 2007(26)	An epidemiologic study of MCI in Kolkata, India Community based study	960 subjects(745 underwent full NPT) from Kolkata India older than 50 yrs.	An overall prevalence of MCI detected based on NPSY testing was 14.89%. -Prevalence of the amnestic type was 6.04% and that of the multiple domain type was 8.85% . - Hypertension and diabetes mellitus were the major risk factors for both types of MCI
Srikala et al 2017(94)	Clinical and neuropsychological profile of persons with MCI, a hospital based study from a lower and middle income country Community based study	-7469 persons aged 60 yrs, between 2012-2014, NIMHANS OPD & community services were screened for early cognitive deficits. Underwent detailed clinical and neuropsychological assessments. Neuropsychiatric symptoms were prevalent in 55% of MCI group	Persons with MCI perform worse not only on memory tasks but also on some of the attention and executive functions tasks. -Amnestic multiple-domain MCI was the most common type of MCI and performed worse on episodic memory, logical memory, attention and executive functions

			-Indigenous assessment tools were of significant value in distinguishing MCI from normal ageing
Alladi et al 2014(95)	MCI : clinical and imaging profile in a memory clinic setting in India Community based study	1,190 patients were evaluated for MCI were included and underwent clinical and neuropsychological examination as well as standard brain imaging.	12% of the cohort was classified by imaging biomarkers as having MCI with intermediate likelihood of AD
Sheelakumari et al 2018(96)	Structural correlates of MCI: A clinic volumetric study Hospital based case control study	24 patients classified as having "non-progressor" MCI, 13 as having an early AD, and 25 controls, and assessed using neuropsychological evaluation, multimodal MRI were included in the study Both voxel-based morphometry and automated regional volumetry to assess the topographical patterns of volume loss	Identification of the pattern of volumetric abnormalities in patients with amnestic MCI in addition to atrophy of the medial temporal lobes necessitates a close follow up to continuously assess these patients for their progression to early AD
Sheelakumari	Multimodality	-33 participants with	The combined

et al 2018(97)	Neuroimaging in MCI: A Cross-sectional Comparison Study Hospital based study	cognitively stable amnestic MCI; 15 MCI converters to early Alzheimer's disease (AD; diseased controls) and 20 healthy controls underwent high-resolution T1-weighted volumetry, MRI DTI and MR spectroscopy	method of grey matter atrophy, white matter tract changes, and metabolite variation achieved a better performance at classifying MCI compared to the application of individual MRI biomarkers
B Thomas et al 2019(98)	Regional Cerebral Blood Flow in the Posterior Cingulate and Precuneus and the Entorhinal Cortical Atrophy Score Differentiate MCI and Dementia Due to Alzheimer Disease	-Analyzed MR imaging from a prospective data base of 3 age-matched groups: 21 cognitively healthy controls, 20 patients with MCI, and 19 patients with early Alzheimer disease. -The highest entorhinal cortical atrophy score (ERICA) and an atlas-based measurement of CBF in the posterior cingulate and precuneus were estimated in these groups.	Combining entorhinal cortical atrophy(ERICA) and regional CBF could be a potential imaging biomarker in distinguishing mild cognitive impairment and Alzheimer disease
Divya et al	Post-stroke	Logistic regression	Significant

2016(77)	cognitive impairment - A cross-sectional comparison study between MCI of vascular and non-vascular etiology	analysis adjusted for age and sex comparing VaMCI [N=50] with controls [N=27]	differences were noted in word-list learning-recall and WMS verbal delayed recall between VaMCI with mild versus moderate to severe deep white matter hyperintensities on neuroimaging

GAP AREAS IN CURRENT KNOWLEDGE

1. There is a paucity of large scale hospital based studies on conversion rates of MCI in India. It is not certain whether the annual conversion rates in hospital based cohorts are higher than community based cohorts in India.
2. It is uncertain about which neuropsychological measures at baseline predict conversion or progression in MCI . It is also not clear whether these measures are more relevant than baseline clinical variables such as vascular risk factors and after correction for age which variables provide the best predictive estimates.
3. The absence of prediction scores with regard to risk of progression or conversion in MCI
4. Relevance of baseline structural MRI and volumetric variables in MCI to predict conversion is not certain .
5. Relevance of subtypes of MCI in India with regard to longitudinal outcomes in terms of conversion or progression is not certain.

HYPOTHESIS

1. Majority of patients with single domain MCI exhibit stability over time as opposed to multi-domain
2. Vascular risk factors are important predictors of progression in MCI as in dementia
3. Learning and recall measures at baseline are the most important neuropsychological predictive variables.
4. Progressors /Converters have distinctive imaging signatures at baseline as opposed to stable MCI

AIMS AND OBJECTIVES

1. To determine the longitudinal cognitive trends in an MCI cohort with single and multi-domain cognitive impairment
2. To ascertain the clinical, neuropsychological and imaging predictors of cognitive decline in MCI
3. To correlate neuropsychological trends with imaging biomarkers in MCI
4. To estimate logistic regression based stratification of MCI based on progression and conversion risk

DEFINITIONS

1. Petersen's MCI definition (Appendices 1)
2. DSM-IV criterion (Appendices 2)
3. Alzheimer's dementia criterion (Appendices 3)
4. **MCI types definition** (99,100)

    1) Single domain MCI – Subjective memory impairment with objective evidence of memory decline in any two neuropsychology tests of memory (ACE registration, ACE recall, RAVLT, WMS) **or** any two test of executive functioning (Trail A time, Trail B time, errors, WCST-categories passed, errors) which is less than Mean -1.5 SD for appropriate age and education status

    2) Multidomain MCI - Subjective memory impairment with objective evidence of memory decline in any two tests of neuropsychology tests of memory (ACE registration, ACE recall, RAVLT, WMS) **and** any two tests of executive functioning (Trail A time, B time, errors, WCST categories passed, errors) which is less than Mean -1.5 SD for appropriate age and education status

    3) Amnestic MCI - Subjective memory impairment with objective evidence of memory decline in any two neuropsychology tests of memory (ACE registration, ACE recall, RAVLT, WMS) which is less than Mean -1.5 SD from cognitively normal subjects for appropriate age and education status

    4) Dysexecutive MCI - Subjective memory impairment with objective evidence of memory decline in any two neuropsychology tests of test of executive functioning (Trail A time, B time, errors, WCST- categories passed, errors) which is less than Mean -1.5 SD from cognitively normal subjects for appropriate age and education status

    5) Converter – MCI patients who had shown clinical and or neuropsychological decline on follow up and had fulfilled the DSM-IV criterion for dementia with worsening in outcome measures IADL and CDR (>1).

6) **Non converter –** MCI subjects who's cognitive status had remained stable on clinical and neuropsychological tests on follow up or has progressed but still remains independent for ADLs and has not fulfilled the DSM-IV criterion for dementia or the outcome measures IADL and CDR (<1).
7) **Stable MCI –** MCI patients remaining static clinically and or on neuropsychological tests as single /multidomain MCI on follow up
8) **Progressors –** MCI patients who has shown decline in cognition on clinical and neuropsychology parameters from single domain MCI to multidomain or from single /multidomain MCI have converted to dementia on follow up

METHODOLOGY

1) STUDY TYPE

The study is a hospital based retrospective and prospective consecutive study to assess the clinical, neuropsychology and MRI predictors of conversion of MCI.

2) INCLUSION CRITERION

1. MCI diagnosed as per modified Petersen's criteria
2. Age 55-80 years at time of recruitment
3. At least one neuropsychological assessment at baseline and clinical follow up of 2 yrs should be available at time of inclusion
4. These subjects should have baseline MRI Brain structural scans and preferably T1 volumetric sequences
5. Clinical Dementia rating -CDR (sum of boxes) <1 at time of inclusion into cohort
6. Domain specific test scores on atleast 2 neuropsychological tests < mean-1.5SD for age and education based cut-off
7. Conversion to AD based on Mckhann et al criteria, 2011
8. Patients who are on follow up for evaluation of the treatment from the date of IEC approval -June 2019 till Jun 2021

3) EXCLUSION CRITERION

1. Dementia diagnosis at baseline as per DSM IV

2. Clinically significant anxiety depression
3. Major cardiovascular or medical comorbidity (uncontrolled DM, HT, CAD)
4. Past stroke, Traumatic Brain Injury, psychosis
5. CDR >1 at the time of inclusion into cohort
6. Lack of clinical follow up beyond two years from baseline
7. MRI Brain showing changes of early AD as per NIAA criteria

4) STUDY DESIGN AND FOLLOW UP

A cohort study was designed based on the registry of patients who has a diagnosis of MCI recruited between 2010-2018 with at least one formal neuropsychological assessment at baseline and clinical follow up of a minimum of 2 yrs with MRI Brain at baseline. The prospective study was completed based on clinical evaluation at last follow up ,information provided by bystander and where available longitudinal neuropsychological tests on follow up after obtaining proper informed consent. All these patients were literate and spoke, read and wrote in primarily in Malayalam language (L1) and were under regular follow up with Cognitive and Neuro behaviour section, Department of Neurology, SCTIMST, Trivandrum. The recruitment of subjects for the study was done by the principal investigator from the date of institutional ethics committee approval after obtaining informed consent.

Subjects who were lost to follow up or in whom clinical follow up was not available between 2020-21 due to COVID-19 pandemic were contacted over phone. The last available clinical status was documented based on DSM IV criteria for dementia, IADL and CDR status. A cognitive neurologist with more than 10 years experience verified the clinical diagnosis at baseline and last follow up as well as the categorization into MCI and dementia subtypes.

CLASSIFICATION OF MCI

The MCI subjects were classified into three groups for analysis a) Non Converters vs Converters b) Stable MCI Vs Progressors c) Single domain MCI Vs Multidomain MCI.

The MCI converters were further classified into MCI due to Alzheimers dementia (Mc KHANN et al 2011) (101), MCI due to Vascular dementia - Hachinski Ischemic Score (HIS)(102), MCI due to FTD (FTD Consortium criterion)(103), MCI due to Lewy Body dementia (DLB consortium criterion-fourth consensus)(104).

5) SAMPLE SIZE ESTIMATION

Total number - 95

Assuming 10% of patients to have single domain non-amnestic MCI, and conversion rates to AD of 11.1% for non-amnestic MCI and 31.6% for multi-domain MCI. The sample size required to meet all statistical requirements for such a study (computed using Open Epi version 3.1) would be 396. This number may be feasible only with multi-centric or registry based studies or studies with extensive community screening and recruitment and is beyond the feasibility of the current exercise. However we anticipate a number of 95 patients who fulfil the inclusion and exclusion criteria. This number will suffice to capture predictors that have a risk ratio of approximately 6 or above and are sufficiently common in the studied population. Predictors that are less strongly associated with conversion or are rare may not be found significant in this study. But the descriptive data will help identify patterns and anticipate sampling and methodological aspects for future studies

6) STATISTICAL ANALYSIS

A) UNIVARIATE ANALYSIS AND DEMOGRAPHIC PROFILES

- Quantitative variables were summarized as means and standard deviations
- Qualitative (Categorical variables) were summarised as proportions

B) BIVARIATE ANALYSIS

- Means were compared using Unpaired T test /ANOVA or Mann Whitney U test as appropriate
- Proportions were compared using Chi Square test /Fisher's exact test

- Correlations were explored using Spearman's Rank correlation test

C) MULTIVARIATE ANALYSIS

- Variables significant on bivariate analysis were taken for multivariate analysis using the Binary logistic regression (Forward Conditional Method)
- Age was forced into the model even if it was not significant in the forward conditioning model and predictors were derived for Convertors and Progressors
- An equation was generated based on the logistic model for converters and a new score was created.
- The validity of the derived score in classifying converters from non converters was tested using ROC analysis
- Youden's J was computed for each of the cut off values and the J Max was reported

D) REPEATED ANOVA MEASURES

- Age adjusted repeated measure ANOVA was done for CDR and IADL among Non Converters /Converters and Non Progressors /Progressors between baseline and final follow up and also between all follow ups with the aim to explore trends over time

E) SURVIVAL ANALYSIS

- Kaplan Meier survival analysis was done to compare survival across baseline MCI groups (single Vs multidomain), CDR and based on the generated new prediction score for conversion.
- The log rank test was used to check statistical significance

Throughout the statistical analysis a p value of <0.05 was considered statistically significant

SPSS version 25.0 was used for this study

MRI METHODOLOGY

All the MRI Brain sequences were obtained on 3T Siemens MRI scanner. The volumetric structural data were processed using voxel-based morphometry (VBM 8) toolbox in SPM8 (statistical parametric mapping software, Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm). First, the images were registered into the MNI space using high-dimensional DARTEL normalization algorithm. Then, the images were segmented into three different tissues: grey matter (GM), white matter (WM), and CSF. After segmentation, the GM images were smoothed with a Gaussian kernel of 8 mm full width half maximum. The smoothed images were then multiplied with the binary masks of 11 region of interests (ROIs) bilaterally (including temporal neocortex, precuneus, and posterior cingulate) chosen priori from automated anatomic labelling atlas. We computed the volume of each of the ROI region using MATLAB scripting.

FAZEKA SCORE (105,106)

- The periventricular and deep white matter hyperintensities were graded according to the Fazekas grading as given below: Total Score Minimum, 0; Maximum, 6
- Periventricular and deep WMCs are rated separately. A total score is obtainable by summing the 2 partial scores.

Periventricular Hyperintensities

- Periventricular Hyperintensities Scores are as follows: 0-absence, 1-“caps” or pencil-thin lining, 2-smooth “halo,” and 3- irregular periventricular hyperintensities extending into the deep white matter.

Deep White Matter Hyperintensities

- Deep White Matter Hyperintense Signals Scores are as follows: 0-absence, 1-punctuate foci, 2-beginning confluence of foci, and 3-large confluent areas.

ERICA SCORE (98,107)

The medial temporal lobe atrophy was graded as per the ERICAs score.

ERICA scores were defined as 0 for normal volume of the entorhinal cortex and para hippocampal gyrus, 1 for mild atrophy with widening of the collateral

sulcus, 2 for moderate atrophy with detachment of the entorhinal cortex from the cerebellar tentorium (which we termed the “tentorial cleft sign”), and 3 for pronounced atrophy of the para hippocampal gyrus and a wide cleft between entorhinal cortex and the cerebellar tentorium

CEREBRAL MICROBLEEDS(108)

The presence of Cerebral Micro bleeds (CMB) was noted and the number and location were noted.

These MRI characteristics-FAZEKA, ERICAs score and cerebral microbleed index were correlated with neuropsychology test domains.

7) TOOLS AND OUTCOME MEASURES

A) CLINICAL (Appendices 4)

B) NEUROPSYCHOLOGICAL TESTS (Appendices 5)

1) **MMSE and ACE**- ACE Malayalam III and domain specific scores(100)

2) MEMORY

a) Working memory -Digit span test, ACE orientation

b) Short term memory -

1) Rey Auditory Verbal Learning Test (RAVLT)(109)

- New learning total score, 20 minutes delayed recall and recognition scores, Omission errors and commission errors

d) Weschler Memory Scale (WMS)(110)

- Verbal, visual subsets
- Assess working and short term memory in the verbal and visual domains

3) EXECUTIVE

a) Trail A - Psychomotor speed, sustained attention

b) Trail B – Psychomotor speed, attention, executive function, set shifting, omission and commission errors

c) Wisconsin card sorting -Categories passed, omission errors, commission /perseverative errors (111)

d) Categorical and lexical fluency on ACE

4) LANGUAGE - Fluency, semantic battery and ACE language subsets

5) VISUOSPATIAL

- WMS visual subsets (immediate, ACE visuospatial subsets (cube, construction, clock drawing)

6) DEPRESSION AND ANXIETY SCALES(112)

a) Hospital Anxiety Depression Scale (HADS-A)

b) Hospital Anxiety Depression Scale (HADS-D)

7) OUTCOME MEASURES

a) Instrumental Activities of Daily Living (ADL) score(113)

b) Clinical Dementia Rating scale (CDR)(114)

C) APO- E4 AT BASELINE (in subjects who underwent estimation)

D) IMAGING PARAMETERS

1) QUALITATIVE (Subset analysis in patients who had structural MRI 3T scans)

a) ERICAS SCORE-Regional or diffuse atrophy

b) FAZEKAS GRADING for small vessel disease

c) Cerebral microbleed index

2) QUANTITATIVE (Subset analysis in patients in whom volumetric 3T MRI measures were available)

Voxel based morphometry (whole brain) and volumetry

RESULTS

1) BASELINE DEMOGRAPHICS (Table No-1)

Ninety five patients with MCI with mean age 68.4 ±6.4 at baseline were followed up for a mean duration of 6.4 ±3.15 yrs .The duration from symptom onset was 8.7±3.5 yrs.

68.4% (n=65) were males and 31.6% (n=30) of the cohort were females.

The mean years of education was 12.8±3.8 yrs and majority of the subjects had atleast or more than 12 yrs of education (94.8%).

A positive family history of dementia was present in 11.6% and Apo E allele was positive in 41.6% (10/24).

Major Comorbidities

The major comorbidities were Hypertension (49.5%), diabetes 41.1%, Obstructive sleep apnoea 35.8%, Dyslipidemia 23.2%, CAD 17.9%, Thyroid illness 14.8% and seizures 11.6%.

33.7% had psychiatric illness at baseline and majority of patients had depression 53%.

41.1% showed evidence of small vessel disease on MRI Brain on FAZEKA grading.

TABLE 1 – BASELINE DEMOGRAPHIC, CLINICAL, MCI PROFILE AND MRI FINDINGS

Variable	RESULTS N (%)
Age	68.14 ±6.76 (45-84yrs)
Male Female	65 (68.4) 30 (31.6)
Duration of symptoms Duration of follow up	8.7±3.5 yrs (2-23 yrs) 6.4 ±3.15 yrs (1-18yrs)
Years of education Primary	12.8±3.8 yrs (3-24yrs) 2 (2.1)

Middle school High school Diploma Graduate Professional	3 (3.2) 34 (35.8) 13 (13.7) 26 (27.4) 17 (17.9)
Family history of dementia First degree relative with dementia	11 (11.6) 8/11 (8.42)
APOE (Estimated in N=24) E2/E3 E3/E3 E3/E4 E4/E4	10 (41.6) 1 (4.16) 10 (41.6) 9 (37.5) 4 (16.6)
COMMORBIDITIES	
Diabetes	39 (41.1)
Hypertension	47 (49.5)
Dyslipidemia	22 (23.2)
CAD	17 (17.9)
Stroke	8 (8.4)
POVD	3 (3.2)
Head injury	3 (3.2)
OSACS	34 (35.8)
Thyroid illness Hypothyroidism Hyperthyroidism	14 (14.8) 13 (13.7) 1 (1.1)
COPD/Asthma	3 (3.15)
Chronic Kidney disease (CKD)	2 (2.1)
Psychiatric illness Depression	32 (33.7) 17 (17.9)

Anxiety Psychosis	14 (14.7) 1 (1.1)
History of seizures	11 (11.6)
Baseline Executive dysfunction on history apart from memory complaints	23 (24.2)
Follow up Executive function on history apart from memory complaints	37 (38.9)
Mood and behaviour changes	18 (18.9)
Visuospatial impairment	2 (2.1)
MCI status at baseline Single domain Multidomain	 56 (58.9) 39 (41.1)
MCI subgroups Amnestic MCI Dysexecutive MCI Multidomain MCI	 32 (33.6) 27 (28.4) 36 (37.9)
MCI status on follow up Non convertor Convertor	 74 (77.9) 21 (22.1)
MCI Progression status Stable Progressor	 69 (72.6) 26 (27.4)
MRI characteristics FAZEKA Mild Moderate Severe	 39 (41.1) 14 (14.7) 9 (9.5) 6 (6.3)
Microbleed Superficial	15 (15.8) 8 (8.4)

Deep	3 (3.2)
Mixed	4 (4.1)
ERICA score	51 (53.7)
Mild	30 (31.6)
Moderate	10 (10.5)
Severe	1 (1.1)

CORE OUTCOMES

The core outcomes were the cumulative conversion rate was 22.2% (21/95) and the annualised conversion rate (ACR) was 3.3 % per year of follow up . The majority of subjects who had converted had multidomain MCI (66%).

Neuropsychological tests at baseline for memory (ACE recall, RAVLT, WMS) and executive function (Trail A, B errors and WCST) are definitely reliable than clinical or MRI parameters in predicting progression.

The MCI converters had more decline in the baseline outcome measures CDR and IADL, both of which are good predictors of conversion

Only FAZEKA changes on MRI brain had shown correlation with baseline neuropsychology tests of memory such as ACE recall, RAVLT delayed recall.

MCI status at baseline and final follow up

MCI status at baseline showed 58.9 % with single domain and 41.1% had multidomain MCI.

Among the patients with single domain MCI 33.6% had amnestic MCI and 28.4% had dysexecutive MCI at baseline.

On follow up 22.1% of MCI had converted to dementia and 27.4% were progressors.

7 patients had expired during the follow up period of which five MCI converters expired due to advanced dementia, one MCI converter due to head injury and one non converter due to sudden cardiac arrest.

MCI EVOLUTION AMONG CONVERTERS ON FOLLOW UP (Table-2)

Majority of the converters evolved into Early AD (72%) followed by moderate and advanced AD (27.7%). Few patients in the cohort evolved into DLB and FTD

TABLE 2 - DEMENTIA SUBTYPES ON LAST AVAILABLE FOLLOW UP

Dementia type	N (%)
Early AD Moderate AD Advanced AD	13 (72) 2 (11.1) 3 (16.6)
MCI due to DLB	2 (9.5)
MCI due to FTD	1 (4.7)

2) NEUROPSYCHOLOGY SCORES- BASELINE AND FOLLOW UP (Table 3)

A baseline full neuropsychology battery was done for all patients of the cohort, however 68 and 37 patients only had full second and third follow up neuropsychology tests respectively.

The outcome measures CDR and IADL were available for all subjects of cohort (n=95) at baseline and final follow up

TABLE 3 – BASLINE AND FOLLOW UP NEUROPSYCHOLOGY SCORES

NEUROPSYCHOLOGY PARAMETERS	VISIT-1 (N=95)	VISIT -II (N=68)	VISIT-III (N=37)
MMSE	28.09± 1.82	28.01± 1.95	27.75± 3.13
ACE total	84.42±7.5	83.82±9.52	84.46±10.21
ACE recall	4.99±2.56	5.06±2.69	6.24±2.84
ACE registration	18.91±3.8	19.04±4.02	19.49±4.68
ACE orientation	9.67±0.936	9.66±0.96	9.44±1.44
ACE visuospatial	4.22 ±1.18	4.19 ±1.07	4.22 ±1.04

ACE language	26.95 ±1.646	26.98 ±1.89	26.83±1.9
P fluency	8.90 ±3.51	8.51 ±3.59	8.44 ±3.13
Animal fluency	10.05±3.51	9.34±3.36	9.50±3.35
RAVLT total	35.47±9.07	35.38±9.83	36.08±12.33
RAVLT Immediate	4.36 ±2.91	6.5±3.95	7.00±3.40
RAVLT delayed recall (20min)	5.52±3.67	5.41±3.86	6.08±4.03
RAVLT Recognition	10.91±3.49	12.12±3.23	13.06±2.91
Omission error	3.78±3.13	2.63±2.87	2.08±2.93
Commission error	5.22±4.89	5.14±6.04	5.76±5.96
WMS visual immediate	21.78±9.13	21.05±10.73	22.57±9.17
WMS visual delayed	12.19±10.09	15.19±11.93	15.38±11.01
WMS digit forward	6.14±1.86	5.73±1.82	5.78±1.84
WMS digit backward	4.91±1.88	4.92±1.54	4.89±1.31
WMS logical memory immediate	13.35±8.38	16.16±7.61	16.82±9.33
WMS logical memory delayed	8.78±7.37	10.52±7.47	12.03±8.03
Trail A	4.56±17.96	5.08±15.24	10.64±27.43
Error A	0.27±1.025	0.23±0.98	0.28±1.25
Trail B	11.17±43.32	15.63±45.41	21.86±72.63
Error B	2.60±5.3	3.77±7.54	7.5±10.08
Faces	18.89±3.503	46.9±124.09	21.11±2.84
WCST Category	4.54±1.96	4.42±2.06	4.42±1.96
WCST error	5.9±6.14	4.94±3.86	1.94±2.36
WCST -P errors	1.19±1.24	1.35±1.67	2.78±3.79
WCST letters	7.11±6.82	6.19±3.87	4.75±4.83

PD	17.74±4.36	17.67±5.44	19.57±0.78
CA	7.05±3.61	8.54±2.22	9±1.91
IADL	1.88±2.1	2.11±2.83	1.15±1.60
HADS-A	4.06±3.874	3.15±3.33	2.94±2.58
HADS-D	2.86±3.27	2.67±2.72	2.61±2.51
CDR	0.445±0.157	0.587±0.354	0.500±0.193

3) CDR AND IADL SCORES -BASELINE AND FOLLOW UP (Table 4)

There were significant decline in the CDR and IADL scores at baseline and final follow up

TABLE -4 -CDR and IADL baseline and follow up

Variable	Baseline (n=95)	Final follow up (n=95)
CDR-4	0.445±0.157	0.64±0.56
IADL-4	1.88±2.1	3.10±5.29

4) BRAIN MRI PARAMETERS (Table 5)

The MRI parameters could be retrieved for 61 subjects. All of the patients had undergone imaging with 3 T MRI.

The mean GM score at baseline were 551.87±48.53 ,WM scores 452.46±58.4 and CSF volumetry was 500.87±115.4

The mean Left hippocampal , Right hippocampal scores were 2.9±0.76 and 3.12±0.64 respectively

The mean cerebral microbleed number was 2.67±3.06

TABLE 5- VOLUMETRIC IMAGING PARAMETERS

IMAGING PARAMETERS	RESULTS (in mm^3)
GM	551.87±48.53
WM	452.46±58.4
CSF	500.87±115.4
TIV	1505.86±154.27
Left Hippocampus	2.9±0.76
Right Hippocampus	3.12±0.64
Left Amygdala	0.89±0.31
Right Amygdala	0.90±0.35
Cerebral microbleed number	2.67±3.06

B) BIVARIATE ANALYSIS

NON CONVERTER Vs CONVERTER

1) CATEGORICAL VARIABLES AMONG CONVERTERS AND NON CONVERTERS (Table 6)

66.6% of the dementia converters had multidomain MCI ($p<0.05$)

There were 36.1% Multidomain MCI, 12.9% amnestic and 11.1% dysexecutive MCI among converters at baseline which was statistically significant ($p <0.05$)

The FAZEKAS score at baseline showed significance among converters ($p<0.05$).

TABLE 6 – QUALITATIVE VARIABLES- NON CONVERTERS AND CONVERTERS

VARIABLE	**Non converter (n=74) N(%)**	**Converter(n=21) N(%)**	**P value** (Fisher's exact test)
Sex			
Male	51 (78.5)	14 (21.5)	0.845
Female	23 (76.7)	7 (23.3)	
Family history			
Absent	67 (79.8)	17 (20.2)	0.253
Present	7 (63.6)	4 (36.4)	
MCI baseline status			
Single domain	49 (87.5)	7 (12.5)	
Multi domain	29 (64.1)	14 (35.9)	**0.007**
Amnestic MCI	27 (87.1)	4 (12.9)	
Dysexecutive MCI	24 (88.9)	3 (11.1)	**0.01**
Multidomain MCI	23 (63.9)	13 (36.1)	
FAZEKA grade			
Absent	32 (82.1)	7 (17.9)	
Mild	12 (85.7)	2 (14.3)	
Moderate	5 (55.6)	4 (44.4)	**0.026**
Severe	2 (33.3)	4 (66.7)	
Microbleed			
Absent	36 (76.6)	11 (23.4)	1.00
Present	11 (73.3)	4 (26.7)	
ERICA score			
Normal	10 (100)	0	
Mild	21 (70)	9 (30)	0.08
Moderate	7 (70)	3 (30)	
Severe	0	1(100)	

2) NON CONVERTERS (N=74) AND CONVERTERS (N=21)- NEUROPSYCHOLOGY PARAMETERS (Table 7)

The mean age was high among converters .The mean duration of diagnosis and years of education were similar across groups

The neuropsychology scores at baseline which were significant for predicting conversion were ACE orientation, tests for memory and learning - ACE recall, RAVLT recognition, WMS visual immediate, WMS visual delayed, WMS digit forward, WMS logical memory immediate and tests of executive function Trail A errors, Trail B errors, WCST perseverative errors.

The rest of the quantified variables including measured brain volumes were not significant.

TABLE-7 – STATISTICALY SIGNIFICANT/CLINICALY PERTINENT NEUROPSYCHOLOGY VARIABLES BETWEEN NON CONVERTERS AND CONVERTERS

Variable	Group	Mean ±SD First visit	Mean ±SD Second visit	Mean ±SD Third visit	P Value (ANOVA/ Mann Whitney's U test) First visit
Age	Non converter Converter	67.51±7.09 70.33±4.99			0.092
Duration of diagnosis	Non converter Converter	8.28± 3.43 8.24± 3.93			0.959
Years of education	Non converter Converter	12.72±3.43 13.48 ±3.93			0.39
MMSE	Non converter Converter	28.27 ±1.73 27.37 ±2.01	28.58±1.05 26.07±2.94	28.94±1.28 23.67±4.15	**0.05**
ACE total	Non converter Converter	85.09 ±7.27 82.05 ±7.99	86.54±7.39 75±10.54	87.34±7.58 74±12.13	0.10

ACE orientation	Non converter Converter	9.81 ±0.79 9.11 ±1.23	9.92±0.27 8.80±1.69	10±0.0 7.14±2.12	**0.004**
ACE recall	Non converter Converter	5.26 ±2.43 4.05 ±2.85	5.83±2.31 2.56±2.33	6.79±2.32 4.25±3.77	**0.05**
Phonemic fluency	Non converter Converter	9.12±3.74 8.11±2.42	8.87±3.673 7.38±3.160	8.97±3.134 6.29±2.215	0.26
Categorical fluency	Non converter Converter	10.32±3.54 9.00±3.25	9.81±3.296 7.73±3.173	9.72±3.673 8.57± 1.27	0.15
RAVLT Total	Non converter Converter	36.4 ±8.78 32.24 ±9.53	37.67±9.34 27.86±7.55	39.48±10.73 23.75±9.93	0.06
RAVLT delayed recall	Non converter Converter	5.75±3.23 4.71±4.91	6.57±3.55 1.87±2.35	7.14±3.78 2.25±2.25	0.255
RAVLT Recognition	Non converter Converter	11.52 ±2.93 8.65 ± 4.47	12.40±3.05 11.29±3.73	13.68±1.61 10.88±5.05	**0.002**
WMS visual immediate	Non converter Converter	23.09 ±9.02 17.06 ±8.06	23.33±10.28 14.20±9.26	24.76±8.547 14.63±6.989	**0.01**
WMS visual delayed	Non converter Converter	13.59 ±10.27 7.28 ±7.80	18.36±11.76 5.87±6.32	17.55±10.408 7.50±9.986	**0.02**
WMS digit forward	Non converter Converter	6.38 ±1.68 5.38 ±2.21	5.76±1.84 5.67±1.79	6.03±1.700 4.88±2.167	**0.03**
WMS logical memory immediate	Non converter Converter	14.49 ±8.07 9.33 ±8.43	18.27±6.87 10.15±6.49	20.00±7.568 5.00±4.397	**0.02**
Trail A	Non converter Converter	2.59 ±9.05 10.07±33.93	5.78±17.46 2.87±1.56	12.67±30.78 3.30±1.85	0.110
Trail error A	Non converter Converter	0.11 ±0.43 0.88 ±2.02	0.26±1.08 0.14±0.53	0.34±1.396 0.00	**0.005**

Trail B	Non converter Converter	7.73 ±28.11 22.60 ±78.04	14.89±47 17.95±41.58	25.75±81.57 7.26±3.04	0.169
Trial error B	Non converter Converter	2.73±4.49 4.06±7.41	2.65±5.98 7.46±10.77	4.38±8.415 20.43±4.577	**0.05**
WCST P	Non converter Converter	1.05 ±1.20 1.69 ±1.30	1.24±1.74 1.69±1.43	2.24±3.951 4.71±2.563	0.071
HADS-A	Non converter Converter	4.26 ±3.97 3.27 ±3.41	3.48±3.48 2.08±2.59	3.17±2.647 2.00±2.23	0.377
HADS-D	Non converter Converter	2.87 ±3.21 2.80 ±3.59	2.45±2.63 3.38±3.01	2.69±2.634 2.29±2.05	0.94
CDR	Non converter Converter	0.43 ±0.17 0.50 ±0.00	0.54±0.32 0.71±0.40	0.468±0.179 0.600±0.210	0.08
IADL	Non converter Converter	1.81 ±1.94 2.18 ±2.63	1.86±2.75 2.83±3.04	0.65±1.018 3.00±2.082	0.595

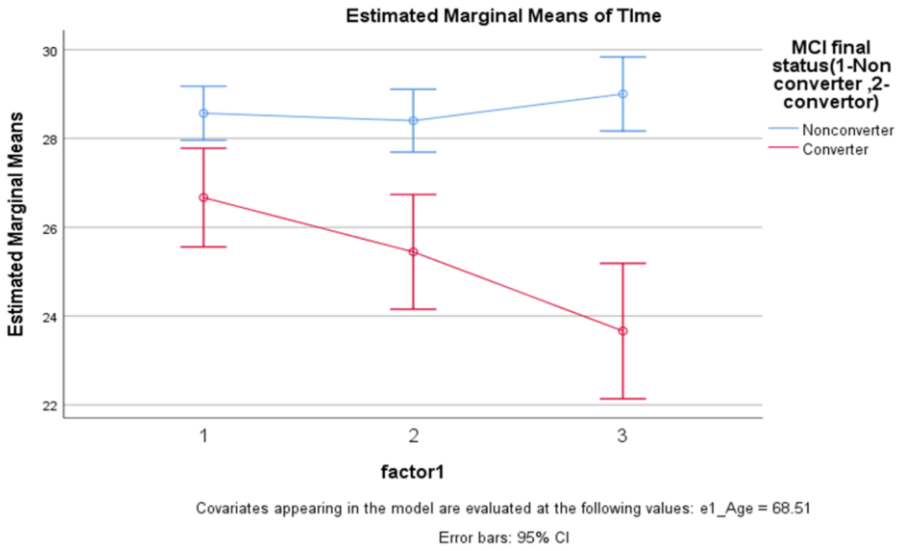
3) NEUROPSYCHOLOGY PARAMETERS- TRENDS (Among patients who underwent serial neuropsychological tests)

A) MMSE

The baseline MMSE scores in converters were 27.37 ±2.01 (p 0.053) and showed further decline on last follow up were 23.67±4.15 ($p<0.01$)

In Non converters the baseline MMSE scores were 28.27 ±1.73 and the final follow up scores were 28.94±1.28

Figure -1 – Trends in MMSE between Non Converters and Converters

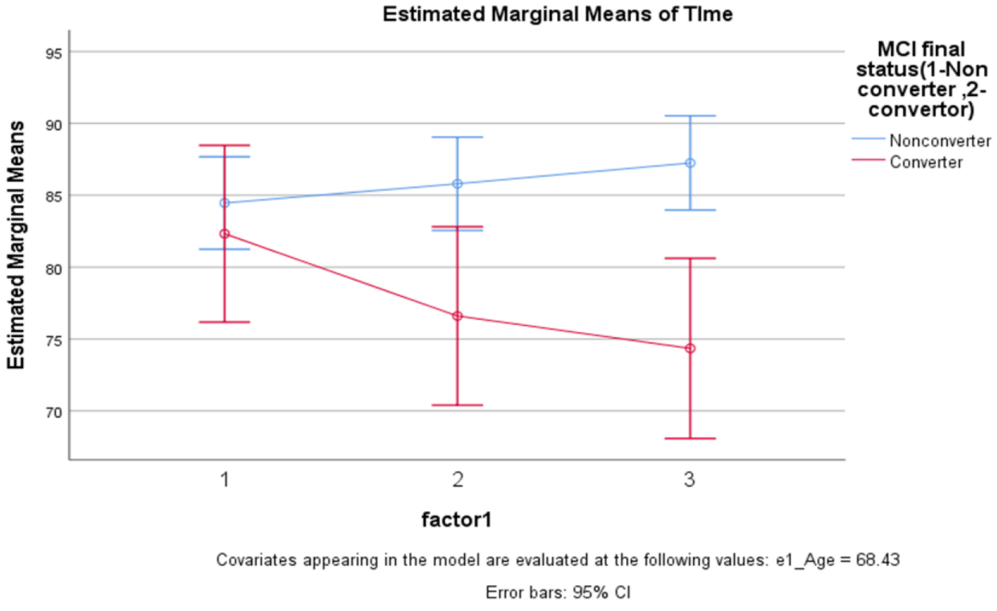


B) ACE TOTAL

The baseline ACE scores in converters were 82.05 ±7.99 (p 0.101) and during last follow up was 74±12.13 (p <0.01)

Non converter group the baseline total ACE scores were 85.09 ±7.27 and the final follow up scores were 87.34±7.58

Figure -2 Trends in ACE TOTAL scores between Non Converters and Converters

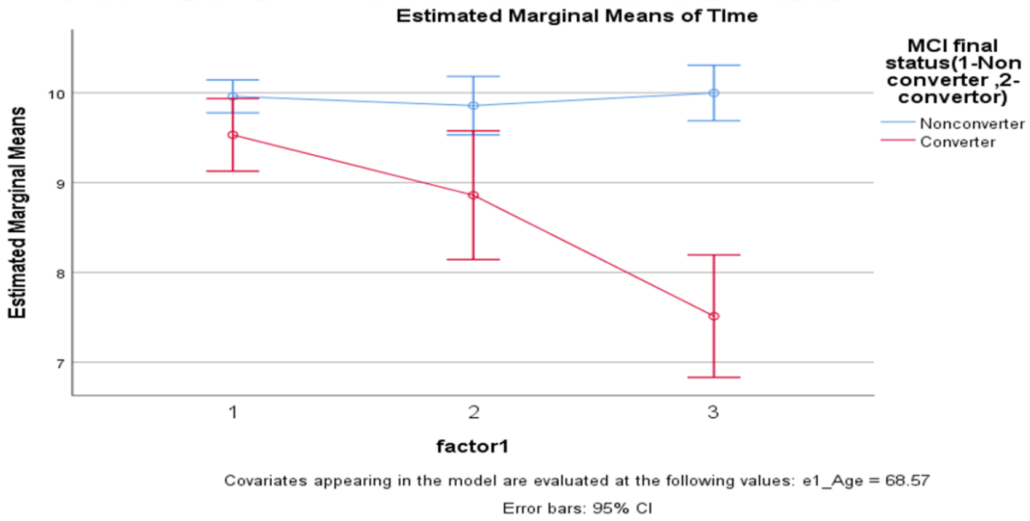


C) ACE ORIENTATION

The baseline ACE orientation scores in converters were 9.11 ±1.23 (p - 0.004) and on last follow up declined to 7.14±2.12 (p value - <0.01)

In non converters the baseline ACE orientation scores were 9.81 ±0.79 and the final follow up scores were 10±0.0

Figure -3 -Trends in ACE ORIENTATION between Non Converters and Converters

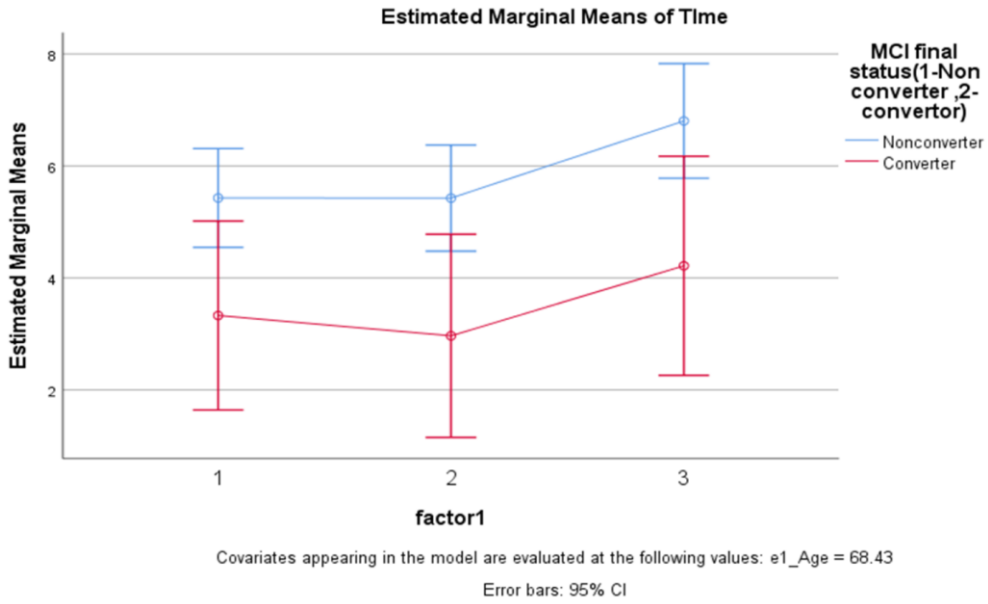


D) ACE RECALL

The baseline ACE recall scores in converters were 4.05 ±2.85 (p 0.05) and on last follow up was 4.25±3.77 (p value 0.02)

Among the non converters the baseline and final follow up scores were 5.26 ±2.43 and 6.79±2.32 respectively

Figure -4 -Trends in ACE RECALL between Non Converters and Converters

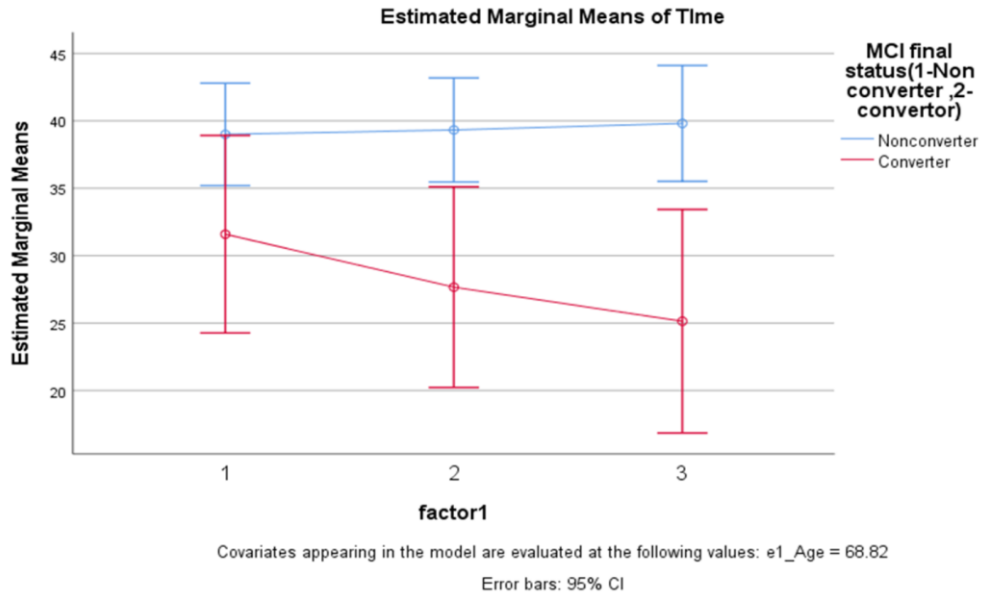


E) RAVLT-TOTAL

The baseline RAVLT total scores in converters were 32.24 ±9.53 (p 0.06) and it declined to 23.75±9.93 (0.001) on final follow up.

The RAVLT total scores in the Non converter group at baseline and final follow up were 36.4 ±8.78 and 39.48±10.73

Figure -5 -Trends in RAVLT TOTAL between Non Converters and Converters

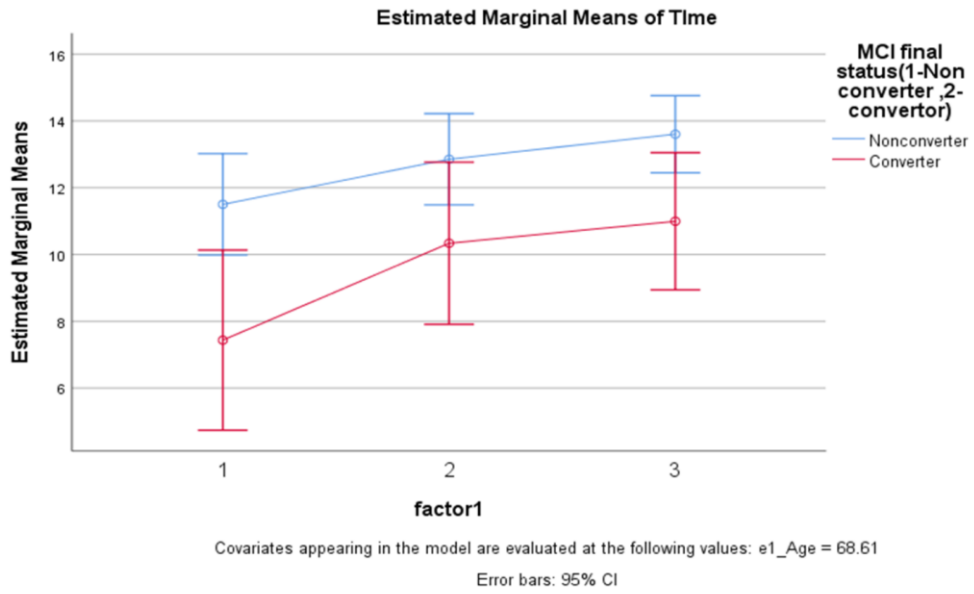


F) RAVLT-RECOGNITION

The RAVLT recognition score at baseline in converters were 8.65 ± 4.47 (p value 0.002) and mean scores on final follow were 10.88±5.055 (p-0.01).

The RAVLT recognition scores in Non converters at baseline and final follow up were 11.52 ±2.93 and 13.68±1.611 respectively.

Figure -6 -Trends in RAVLT RECOGNITION between Non Converters and Converters

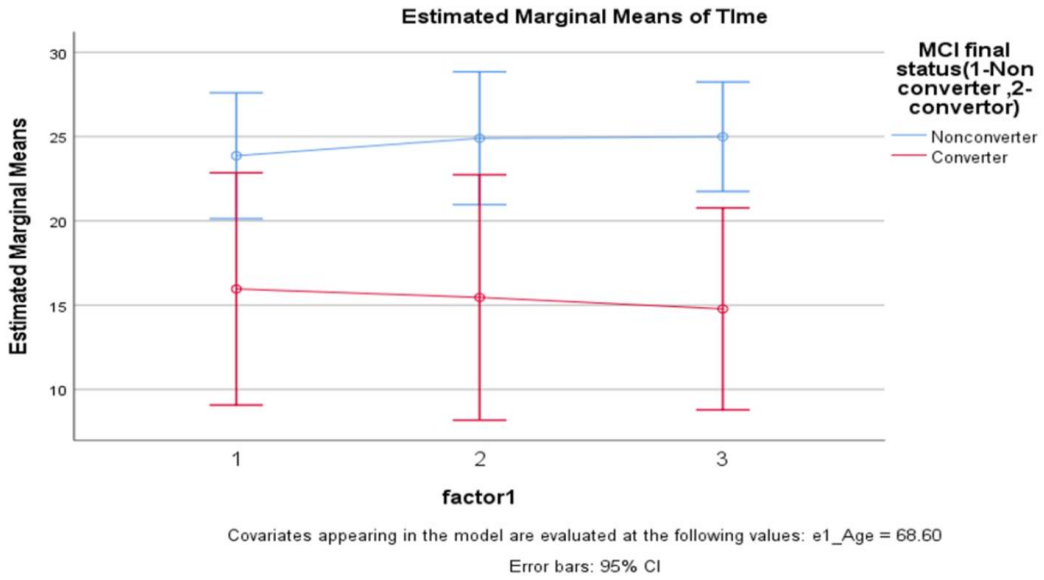


G) WMS -VISUAL IMMEDIATE

The mean WMS visual immediate score at baseline in converters were 17.06 ±8.06 (p -0.012) and on final follow up was 14.63±6.989 (p value 0.004)

Among Non converters the scores were 23.09 ±9.02 at baseline and 24.76±8.547 on final follow up

Figure -7 – Trends in WMS VISUAL IMMEDIATE between Non Converters and Converters

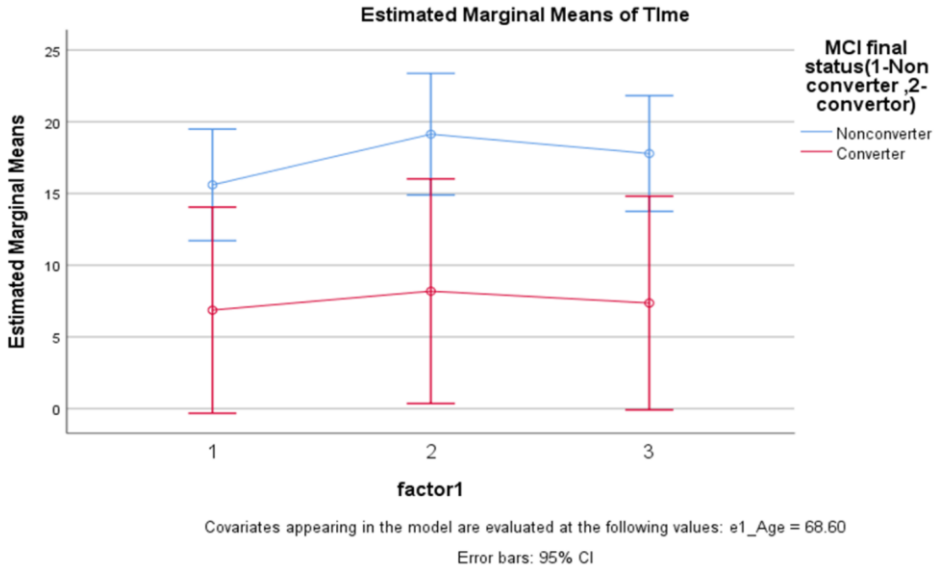


H) WMS -VISUAL DELAYED

The mean WMS visual delayed scores at baseline in converters were 7.28 ±7.80 (p-0.01) and on final follow up were 7.50±9.986 (p -0.02)

Among Non converters the scores were 13.59 ±10.27 at baseline and 17.55±10.408 on final follow up

Figure 8- Trends in WMS VISUAL DELAYED between Non Converters and Converters

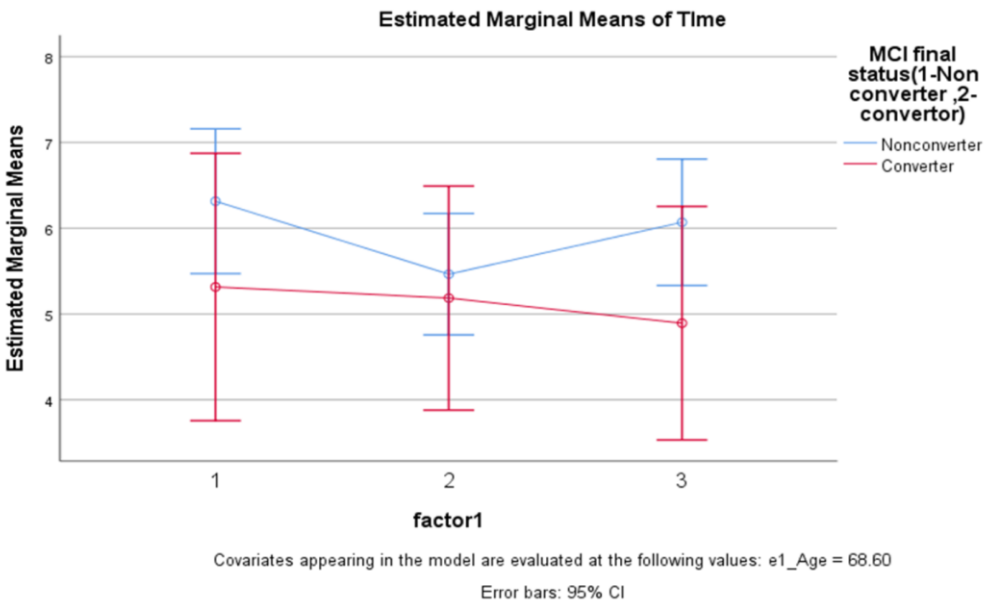


I) WMS -DIGIT FORWARD

The WMS digit forward mean scores at baseline in converters were 5.38 ±2.21 (p 0.02) and on follow up were 4.88±2.167 (p 0.1)

Among Non converters the mean scores were 6.38 ±1.68 at baseline and 6.03±1.700 on last follow up

Figure 9- Trends in WMS DIGIT FORWARD between Non Converters and Converters

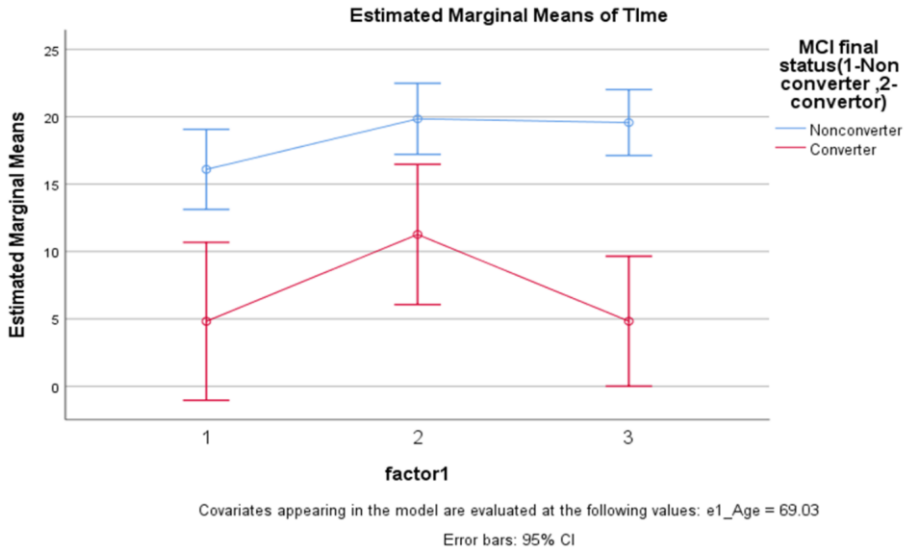


J) WMS -LOGICAL MEMORY IMMEDIATE

The WMS logical memory immediate scores at baseline in converters were 9.33 ±8.43 (p 0.02) and on final follow were 5.00±4.397 (p<0.01)

Among the Non converters the mean scores were 14.49 ±8.07 at baseline and 20.00±7.568 during final follow up

Figure 10- Trends in WMS LOGICAL MEMORY IMMEDIATE between Non Converters and Converters

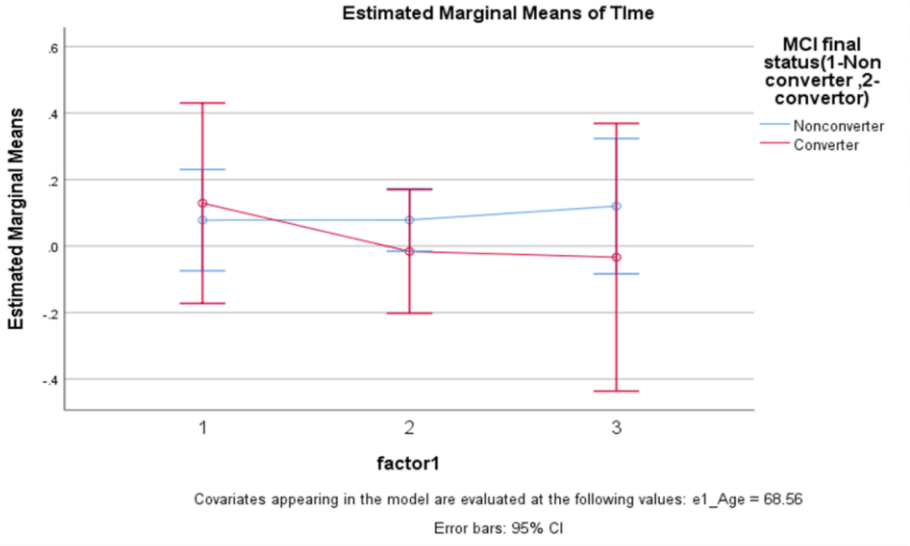


K) TRAIL A -ERROR

Among converters the baseline mean Trail A error were 0.88 ±2.02 (0.005) and on follow up were 0

In Non converters the baseline scores were 0.11 ±0.43 and the final follow up scores were 0.34±1.396

Figure 11- Trends in TRAIL A ERRORS between Non Converters and Converters

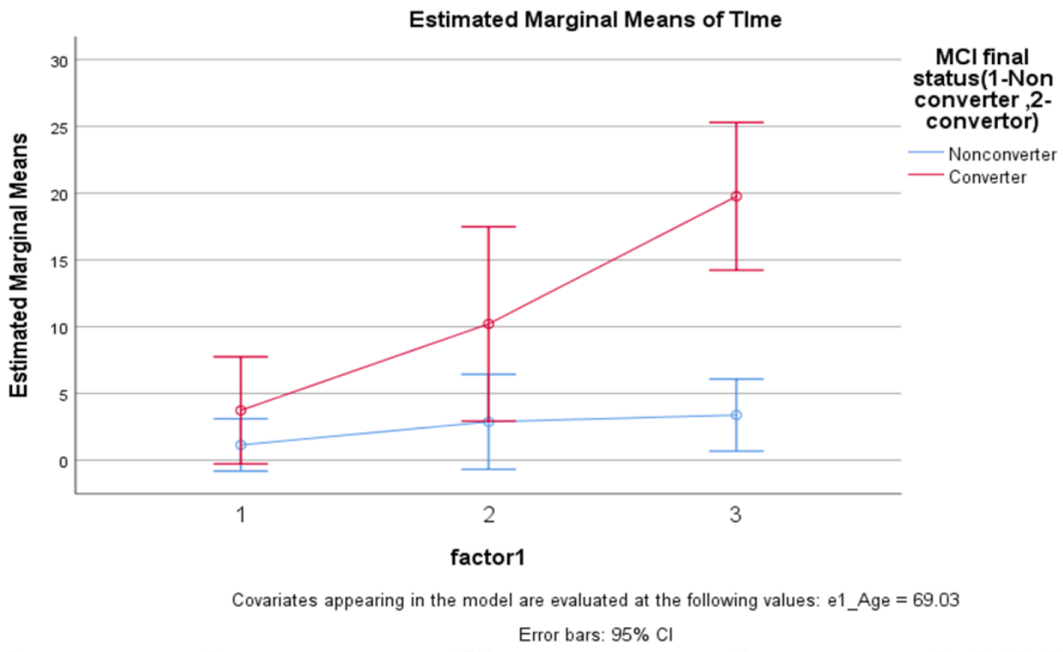


L) TRAIL B- ERROR

Among converters the baseline Trail B error scores were 4.06±7.41 (p 0.05) and on last follow up were 20.43±4.577 (p <0.01)

In Non converters the baseline mean scores were 2.73±4.49 and on final follow up were 4.38±8.415

Figure 12- Trends in TRAIL B ERROR between Non Converters and Converters

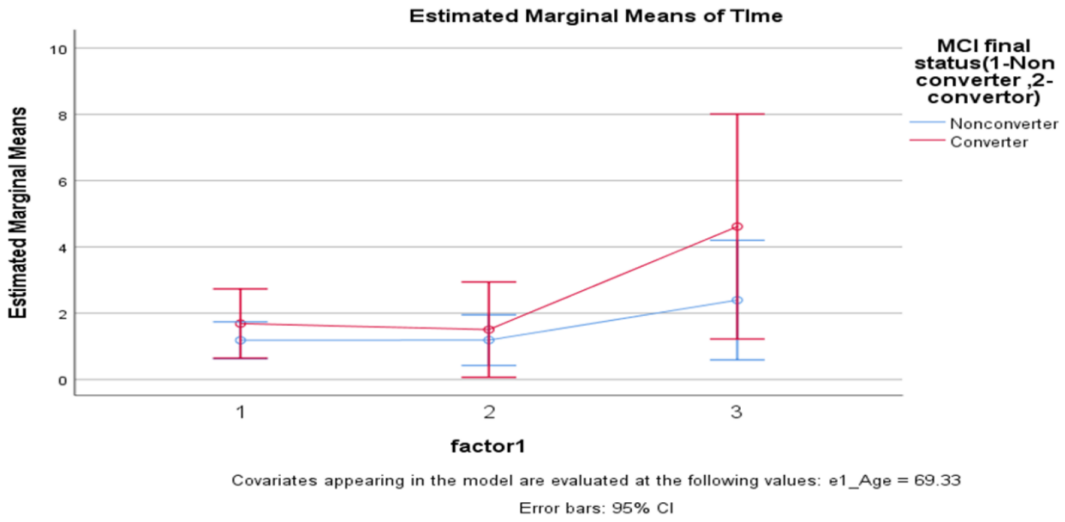


M) WCST-Perseverative errors (WCST-P)

The WCST -P scores in converters at baseline were 1.69 ±1.30 (p 0.07) and on last follow up were 4.71±2.563 (p 0.13)

Among Non converters the baseline mean scores were 1.05 ±1.20 and on final follow up were 2.24±3.951

Figure 13- Trends in WCST -P ERRORS between Non Converters and Converters

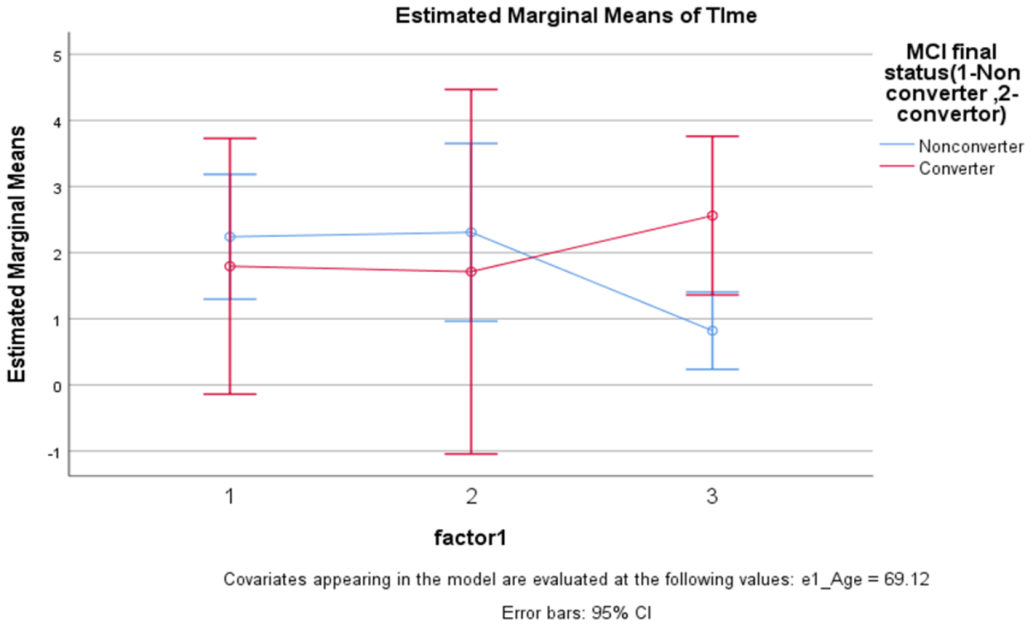


N) IADL

The mean IADL scores at baseline among converters were 2.18 ±2.63 (p 0.59) and on last follow up were 3.00±2.082 (<0.01)

In Non converter group the baseline mean scores were 1.81 ±1.94 and on final follow up were 0.65±1.018

Figure 14- Trends in IADL between Non Converters and Converters

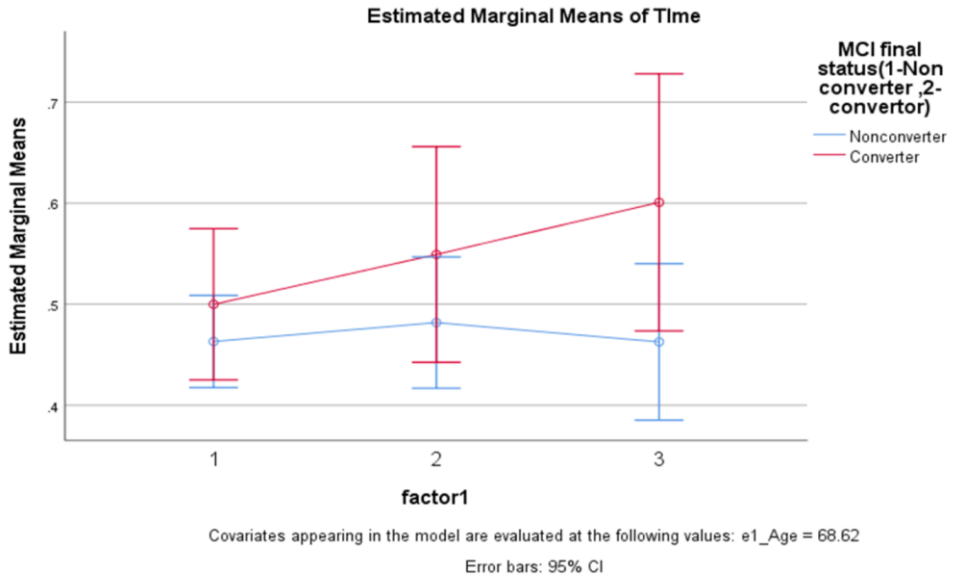


O) CLINICAL DEMENTIA RATING (CDR)

The mean CDR scores at baseline among converters were 0.50 ±0.00 (p 0.07) and on final follow up were 0.600±0.210 (p value 0.05)

In Non Converters the baseline scores of CDR were 0.43 ±0.17 and the final follow up scores were 0.468±0.179

Figure 15- Trends in CDR between Non Converters and Converters



STABLE VS PROGRESSOR

4) CATEGORICAL VARIABLES AMONG STABLE AND PROGRESSORS (Table 8)

Multidomain MCI showed 46.2 % progression in MCI status and 14.3% of the progressors were single domain MCI at baseline ($p<0.01$).

There were 47.2% multidomain MCI, 16.1% amnestic MCI and 11.1% dysexecutive MCI among converters ($p<0.05$).

The FAZEKAS score also showed significance among progressors -14.3% mild, 44.4%had moderate and 83.3% of progressors had grade 3 FAZEKA ($p<0.05$).

TABLE 8 – QUALITATIVE VARIABLES STABLE MCI AND PROGRESSORS

VARIABLE	Stable n=69 N(%)	Progressor n=26 N(%)	P value (Fisher's exact test)
Sex			
Male	47 (72.3)	18 (27.7)	0.91
Female	22 (73.3)	8 (26.7)	
Family history			
Absent	63 (75)	21 (25)	0.16
Present	6 (54.4)	5 (45.5)	
OSACS			
Mild	11 (100)	0	
Moderate	5 (100)	0	**0.02**
Severe	3 (50)	3(50)	
MCI baseline status			
Single domain	48 (85.7)	8 (14.3)	
Multi domain	21 (53.8)	18 (46.2)	**0.001**
Amnestic MCI	26 (83.9)	5 (16.1)	
Dysexecutive MCI	24 (88.9)	3 (11.1)	**0.002**
Multidomain MCI	19 (52.8)	17 (47.2)	
FAZEKA			
Absent	29 (74.4)	10 (25.6)	
Mild	12 (85.7)	2 (14.3)	
Moderate	5 (55.6)	4 (44.4)	**0.01**
Severe	1 (16.7)	5 (83.3)	
Microbleed			
Absent	34 (72.3)	13 (27.7)	0.75
Present	10 (66.7)	5 (33.3)	
ERICA score			
Normal	10 (100)	0	
Mild	19 (63.3)	11 (36.7)	0.06
Moderate	7 (70)	3 (30)	
Severe	0	1 (100)	

5) NEUROPSYCHOLOGICAL VARIABLES BETWEEN STABLE(N=69) AND PROGRESSORS (N=26) [Table 9]

The MCI progressors were significantly older and the mean duration of diagnosis and years of education were similar among both groups

The Neuropsychology scores at baseline which were significant among MCI progressors from baseline were MMSE, ACE orientation, tests for memory and learning - ACE recall, RAVLT recognition, Omission error, WMS visual immediate, WMS visual delayed, WMS digit forward, WMS logical memory immediate and tests for executive function – Trail A errors, and CDR.

The rest of the quantified variables including measured brain volumes were not significant.

TABLE 9 - STATISTICALY SIGNIFICANT/CLINICALY PERTINENT NEUROPSYCHOLOGY VARIABLES ACROSS STABLE MCI VS PROGRESSORS

Variable	Group	Mean ±SD First visit	Mean ±SD Second visit	Mean ±SD Third visit	P Value First visit (ANOVA/ Mann Whitney's U test)
Age	Stable Progressor	67.23±7.191 70.54±4.810			0.033
Duration of diagnosis	Stable Progressor	8.35± 3.267 8.08± 4.223			0.74
Years of education	Stable Progressor	12.58±3.376 13.69±3.957			0.175
MMSE	Stable Progressor	28.32±1.766 27.42±1.840	28.60±1.067 26.53±2.776	28.97±1.299 24.10±4.15	**0.03**
ACE total	Stable Progressor	85.29±7.422 82.12±7.361	86.94±7.462 76.35±9.954	87.32±7.722 75.56±12.269	0.06
ACE	Stable	9.80 ±0.808	9.91±0.285	10.00±0.0	**0.01**

orientation	Progressor	9.24 ±1.179	9.00±1.609	7.50±2.204	
ACE recall	Stable Progressor	5.36±2.407 3.96± 2.761	5.85±2.388 3.15±2.455	6.89±2.299 4.22±3.528	**0.02**
Phonemic fluency	Stable Progressor	9.13±3.632 8.26±3.122	8.77±3.760 7.90± 3.161	8.86±3.135 7.00± 2.878	0.314
Categorical fluency	Stable Progressor	10.28±3.530 9.36±3.430	9.67±3.335 8.53± 3.373	9.61±3.685 9.13± 1.959	0.293
RAVLT Total	Stable Progressor	36.40±9.046 33.04 ±8.852	38.67±8.990 27.72±7.193	40.04±10.507 23.78±9.298	0.11
RAVLT delayed recall	Stable Progressor	5.87±3.246 4.62± 4.544	7.07±3.256 1.74± 2.232	7.29±3.76 2.33± 2.12	0.14
RAVLT Recognition	Stable Progressor	11.66±3.0 8.95± 3.994	12.74±2.682 10.78±3.949	13.74±1.607 11.00±4.743	**0.002**
OE	Stable Progressor	3.36±2.972 4.86±3.342	2.00±2.335 4.06±3.506	1.46±1.795 4.00±4.743	**0.05**
WMS visual immediate	Stable Progressor	23.02±9.166 18.57±8.387	24.51±9.709 13.58±9.057	25.04±8.570 14.89±6.585	**0.05**
WMS visual delayed	Stable Progressor	14.10±10.365 7.35±7.596	19.25±11.849 6.63±6.370	17.75±10.543 8.00±9.460	**0.006**
WMS digit forward	Stable Progressor	6.47±1.709 5.30±2.010	5.83±1.883 5.53±1.712	6.11±1.685 4.78±2.048	**0.01**
WMS logical memory immediate	Stable Progressor	14.84±7.86 9.57±8.638	18.49±7.010 10.73±6.204	20.44±7.377 5.50±4.309	**0.001**
Trail A	Stable Progressor	3.03±9.38 8.53±30.53	6.10±18.25 2.77±1.52	13.07±31.27 3.09±1.83	0.186
Trail error A	Stable Progressor	0.11±0.451 0.68±1.810	0.26±1.127 0.17±0.514	0.36±1.420 0.00	**0.03**
Trail B	Stable Progressor	7.83±26.06 19.52±70.124	15.69±49.27 15.5±36.68	26.49±82.918 6.96±2.98	0.246
Trail error B	Stable	2.20±4.642	2.28±5.740	3.93±8.205	0.267

	Progressor	3.68±6.785	7.18±9.983	20.00±4.408	
WCST P	Stable	1.08 ±1.238	1.15±1.778	2.00±3.845	0.195
	Progressor	1.50± 1.235	1.76±1.393	5.13±2.642	
HADS-A	Stable	4.18± 3.978	3.55±3.5	3.14±2.690	0.67
	Progressor	3.75±3.640	2.24±2.71	2.25±2.188	
HADS-D	Stable	2.86 ±3.287	2.45±2.638	2.61±2.644	0.99
	Progressor	2.85±3.297	3.18±2.942	2.63±2.134	
CDR	Stable	0.43 ±0.179	0.500±0.2440	0.467±0.18	**0.04**
	Progressor	0.500 ±0.0	0.775±0.47	0.59±0.20	
IADL	Stable	1.84±1.965	2.03±2.823	0.56±0.92	0.81
	Progressor	2.00 ±2.483	2.27±2.939	3.00±1.92	

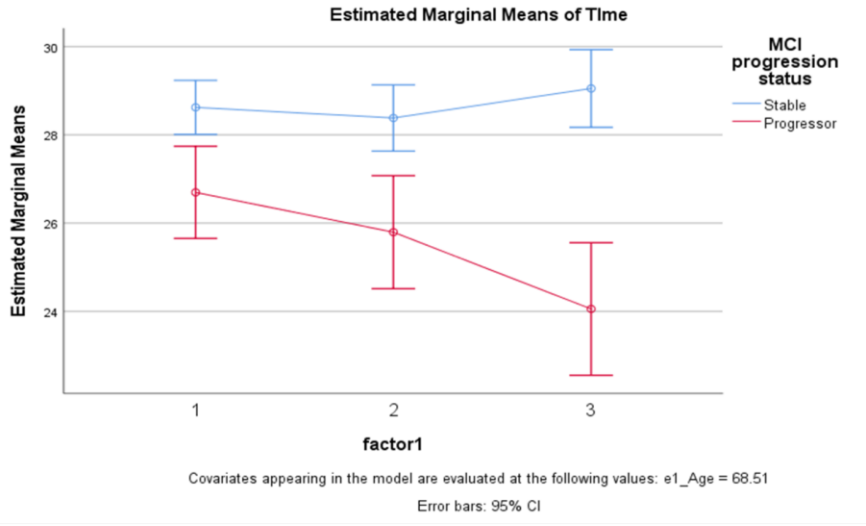
6) NEUROPSYCHOLOGY TRENDS -STABLE Vs PROGRESSORS

a) MMSE

The baseline MMSE scores in progressors were 27.42±1.840 (p 0.035) and it showed further decline on last follow up 24.10±4.15 (<0.001).

In stable MCI the baseline MMSE scores were 28.32±1.766 and the final follow up scores were 28.97±1.299.

Figure 16- Trends in MMSE between Stable and Progressors

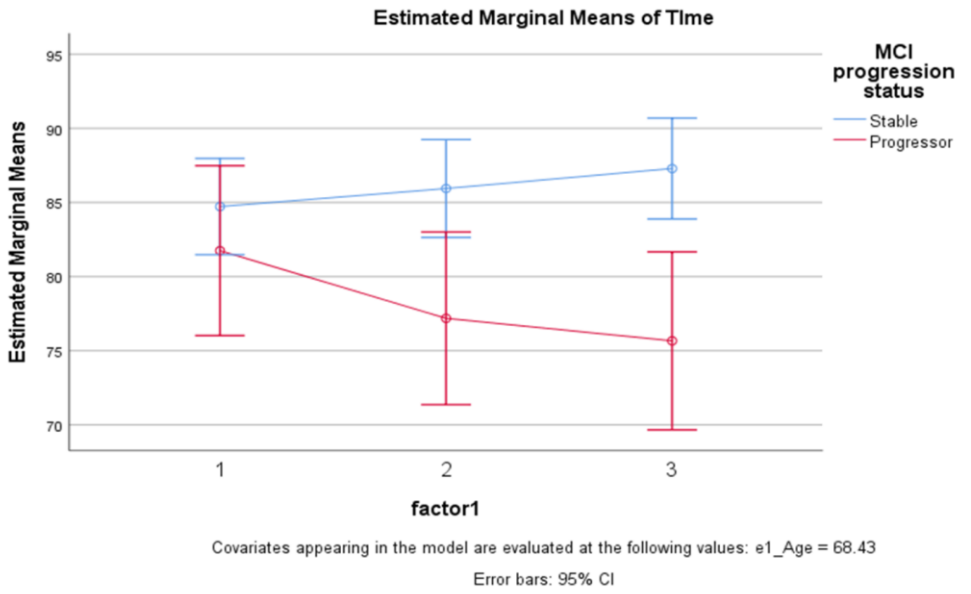


b) ACE TOTAL

The baseline ACE scores in progressors were 82.12±7.361 (p- 0.066) and during last follow up was 75.56±12.269 (p-0.001).

Among the stable MCI group the baseline total ACE scores were 85.29±7.42and the final follow up scores were 87.32±7.722.

Figure 17- Trends in ACE TOTAL between Stable and Progressors

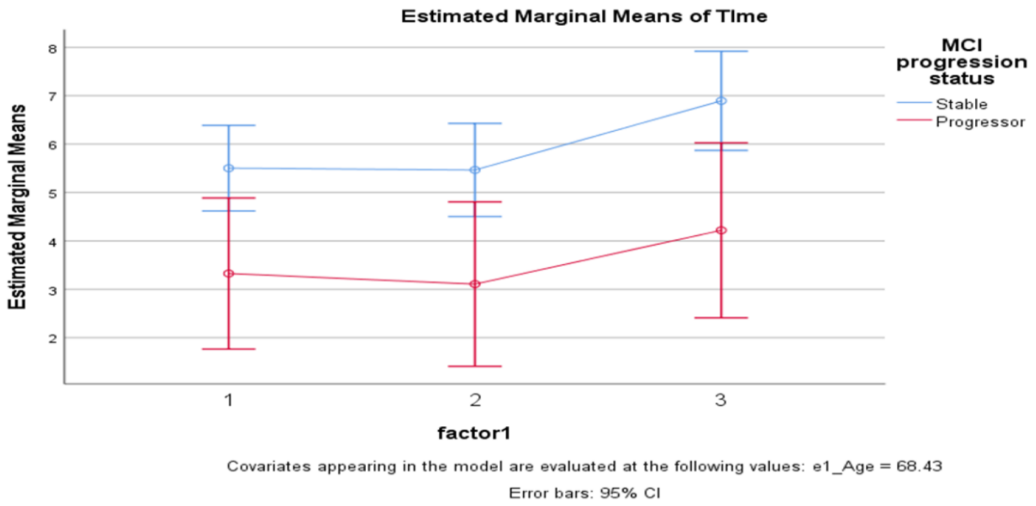


c) ACE Recall

The baseline ACE recall scores in progressors were 3.96± 2.76 (p 0.018) and on last follow up was 3.15±2.455 (p value-0.01).

Among the stable MCI the baseline and final follow up scores were 5.36±2.407and 6.89±2.29 respectively.

Figure 18 - Trends in ACE RECALL between Stable and Progressors

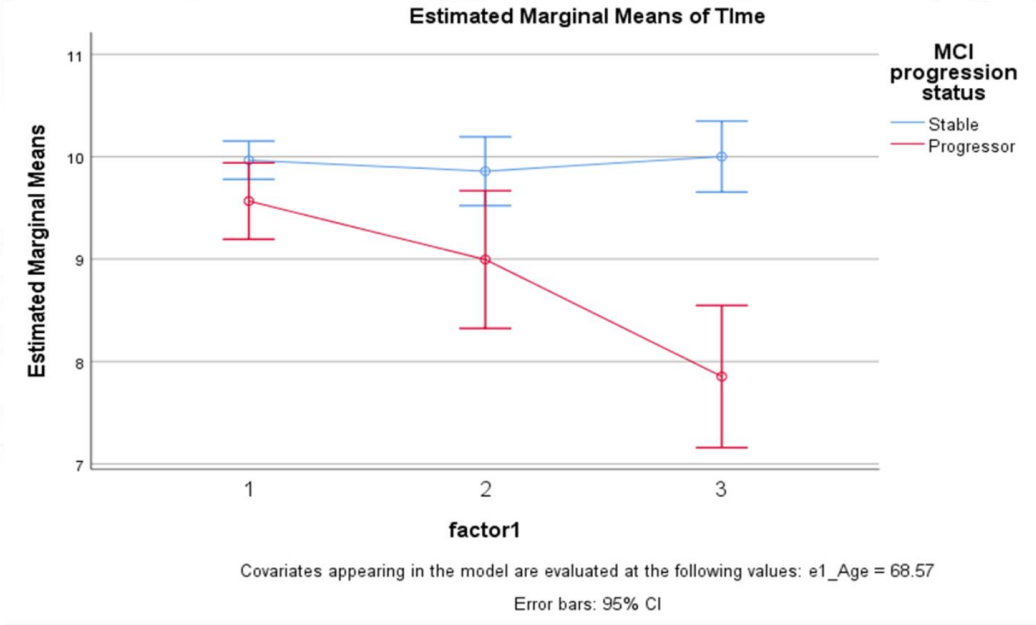


d) ACE ORIENTATION

The baseline ACE orientation scores in progressors were 9.24 ±1.179 (p - 0.015) and on last follow up declined to 7.50±2.20 (<0.001)

In stable MCI the baseline ACE orientation scores were 9.80 ±0.81 and the final follow up scores were 10.00±0.0

Figure 19 - Trends in ACE ORIENTATION between Stable and Progressors

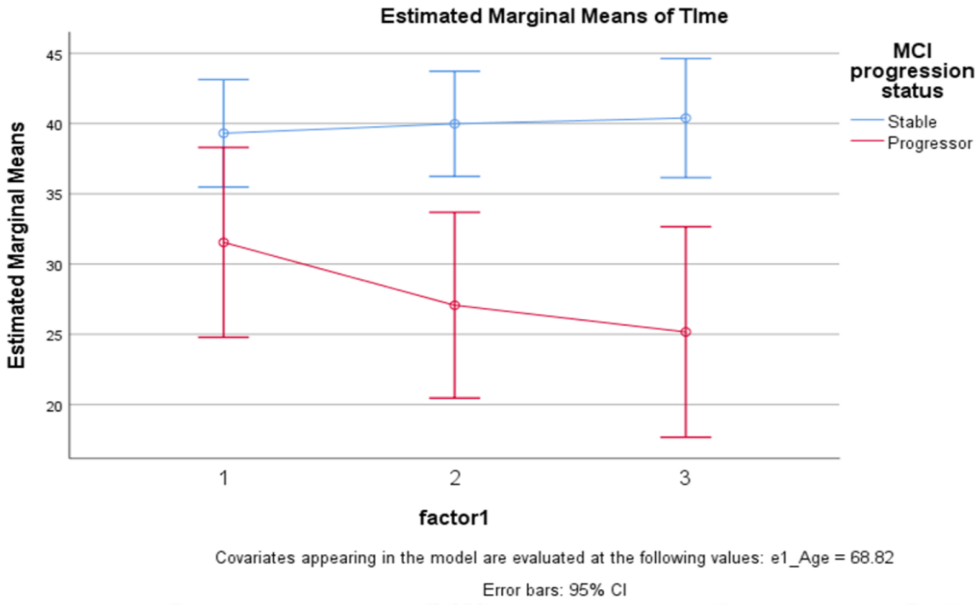


e) RAVLT TOTAL

The baseline RAVLT total scores in progressors were 33.04 ±8.852 (p-0.109) and it declined to 23.78±9.298 (p-<0.01) on final follow up.

The RAVLT total scores in the stable MCI group at baseline and final follow up were 36.40±9.046 and 40.04±10.507.

Figure 20 - Trends in RAVLT TOTAL between Stable and Progressors

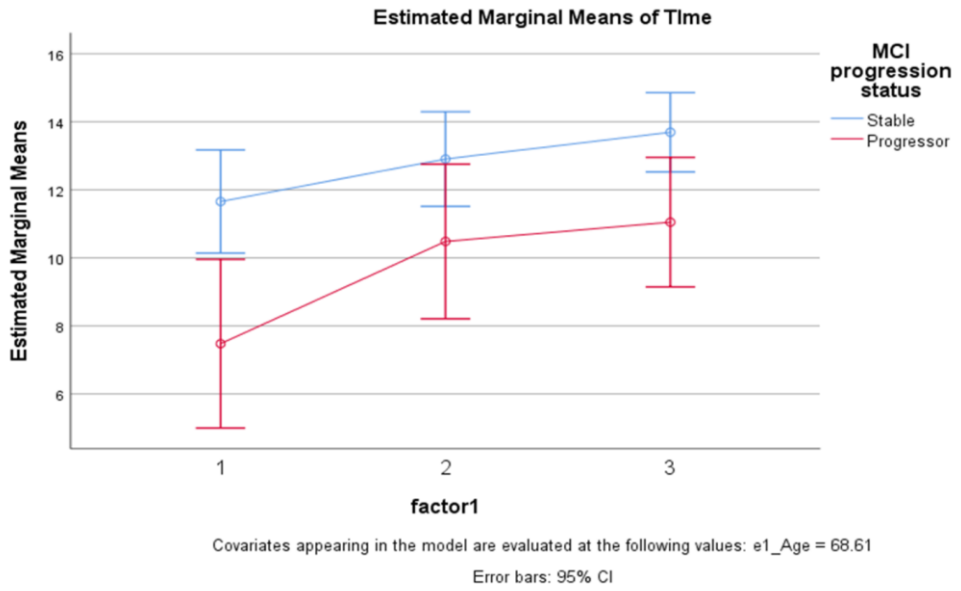


f) RAVLT RECOGNITION

The RAVLT recognition score at baseline in progressors were 8.95± 3.994 (p value-0.002) and mean scores on final follow were 11.00±4.743 (p-0.01).

The RAVLT recognition scores in stable MCI at baseline and final follow up were 11.66±3.0 and 13.74±1.607 respectively.

Figure 21- Trends in RAVLT RECOGNITION between Stable and Progressors

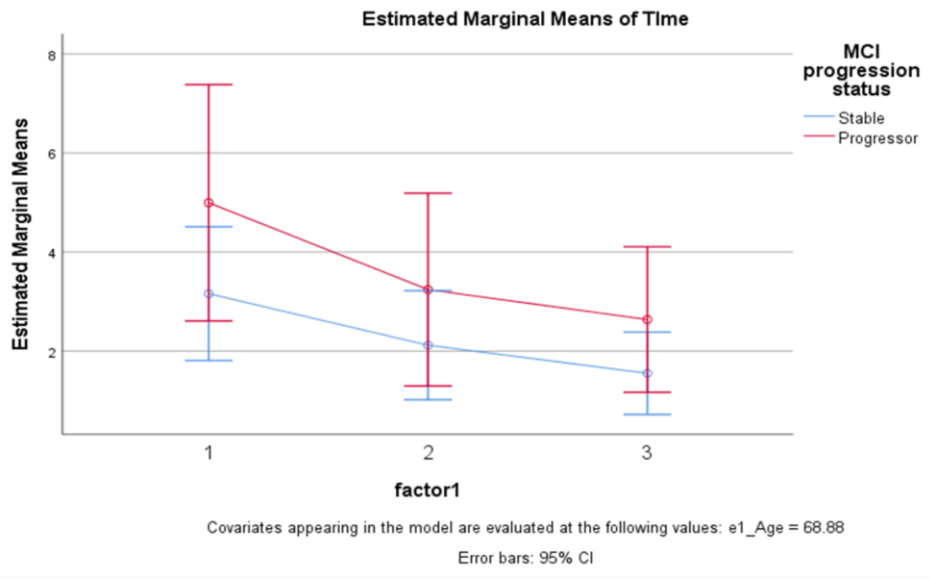


g)OMISSION ERROR (OE)

The OE score at baseline in progressors were 4.86±3.342 (p value-0.05) and mean scores on final follow were 4.00±4.743 (p-0.02)

The OE scores in stable MCI at baseline and final follow up were 3.36±2.972 and 1.46±1.795 respectively

Figure 22 - Trends in OMISSION ERROR (OE) between Stable and Progressors

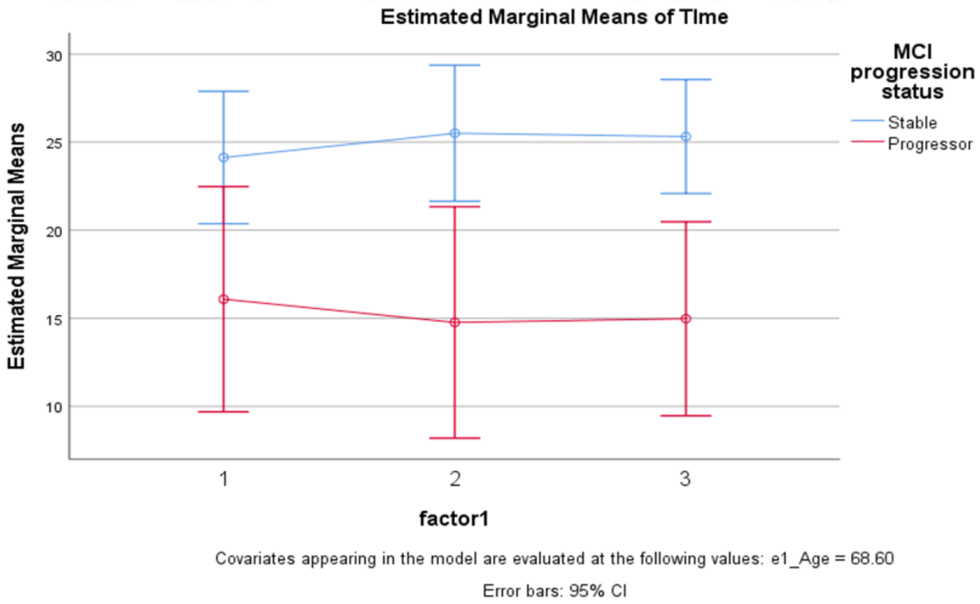


h) WMS VISUAL IMMEDIATE

The mean WMS visual immediate score at baseline in progressors were 18.57±8.387 (p -0.046) and on final follow up was 14.89±6.585 (p value-<0.01).

Among stable MCI the scores were at baseline and on final follow up were 23.02±9.166 and 25.04±8.570 respectively.

Figure 23 - Trends in WMS VISUAL IMMEDIATE between Stable and Progressors

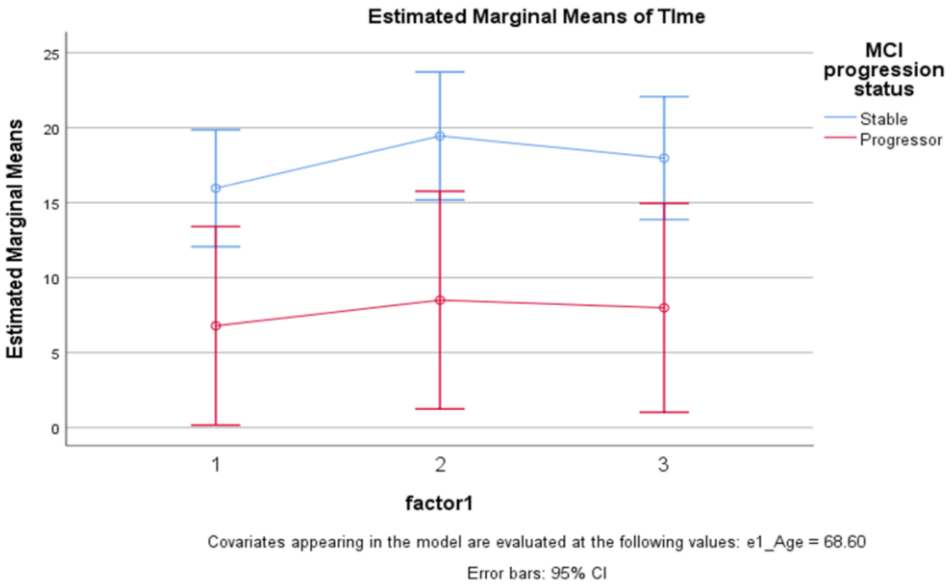


i) WMS VISUAL DELAYED

The mean WMS visual delayed scores at baseline in progressors were 7.35±7.596 (p-0.006) and on final follow up were 8.00±9.460 (p -0.01).

Among stable MCI the scores were 14.10±10.36 at baseline and on final follow up were 17.75±10.54.

Figure 24 - Trends in WMS VISUAL DELAYED between Stable and Progressors

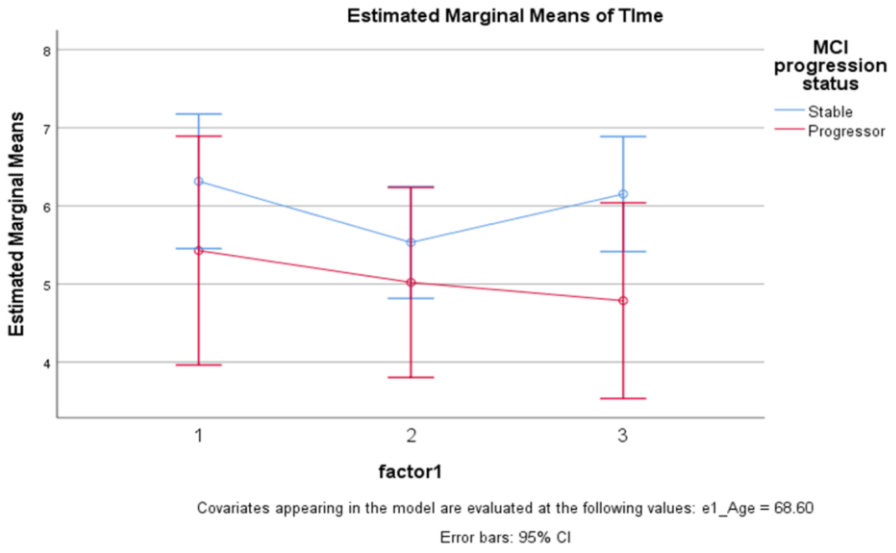


j) WMS DIGIT FORWARD

The WMS digit forward mean scores at baseline in progressors were 5.30±2.010 (p -0.011) and on follow up were 4.78±2.048 (p -0.05).

Among stable MCI the mean scores at baseline were 6.47±1.709 and on last follow up showed 6.11±1.68.

Figure 25 - Trends in WMS DIGIT FORWARD between Stable and Progressors

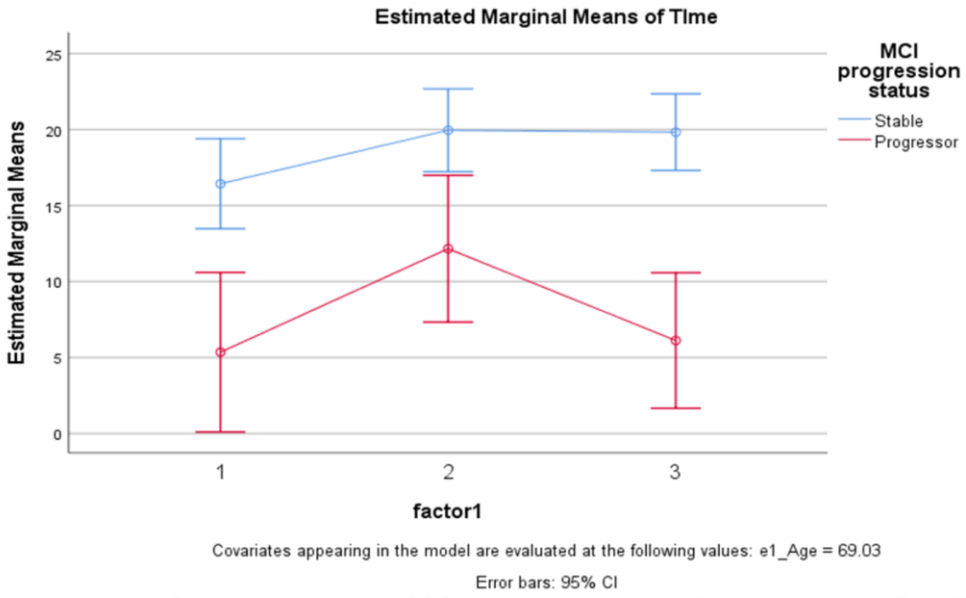


k) WMS LOGICAL MEMORY IMMEDIATE

The WMS logical memory immediate scores at baseline in progressors were 9.57±8.638 (p-0.001) and on final follow were 5.50±4.309 (p<0.01).

Among the stable MCI the mean scores were 14.84±7.86 at baseline and during final follow up were 20.44±7.37.

Figure 26 - Trends in WMS LOGICAL MEMORY IMMEDIATE between Stable and Progressors

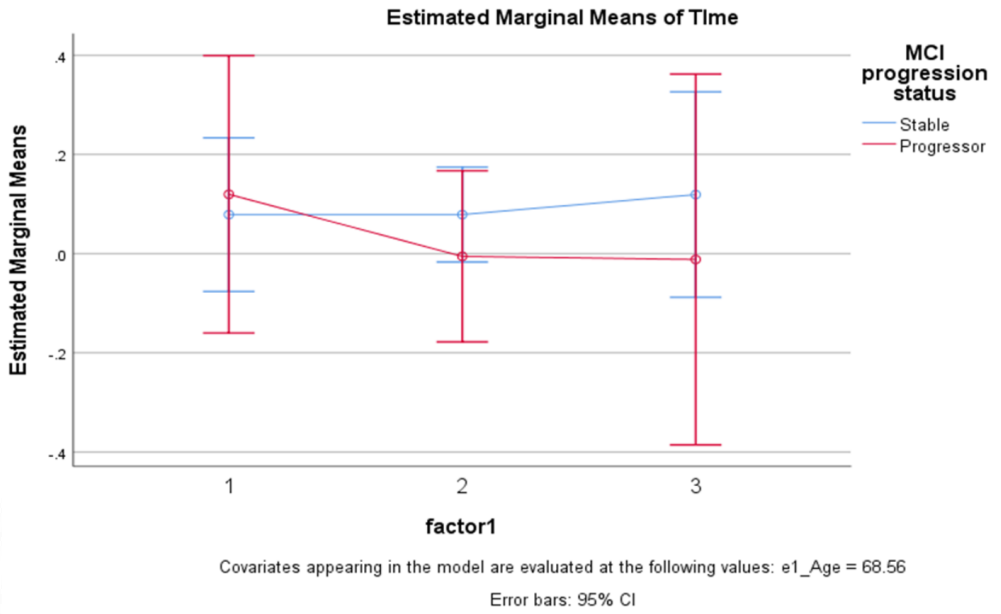


l) TRAIL A -ERROR

Among progressors the baseline mean Trail A error were 0.68±1.810 (p-0.02) and on follow up was zero.

In stable MCI the baseline scores were 0.11±0.451 and the final follow up scores were 0.36±1.420.

Figure 27 - Trends in TRAIL A ERROR between Stable and Progressors

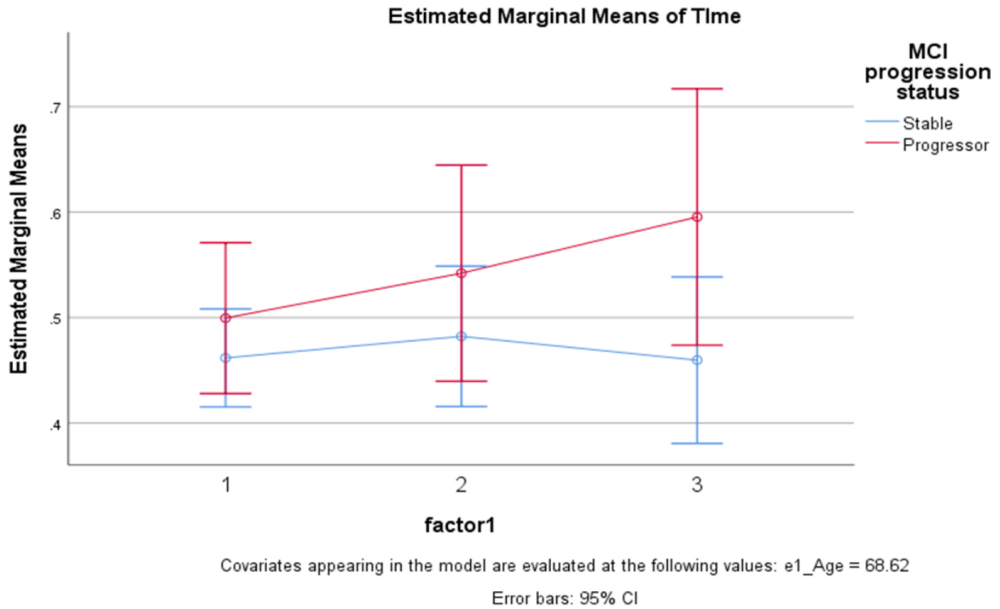


m) CLINICAL DEMENTIA RATING (CDR)

The mean CDR scores at baseline among progressors were 0.500 ±0.0 (p-0.004) and on final follow up were 0.59±0.20 (p value-0.06).

In stable MCI the baseline scores of CDR were 0.43 ±0.179 and the final follow up scores were 0.467±0.18.

Figure 28- Trends in CDR between Stable and Progressors

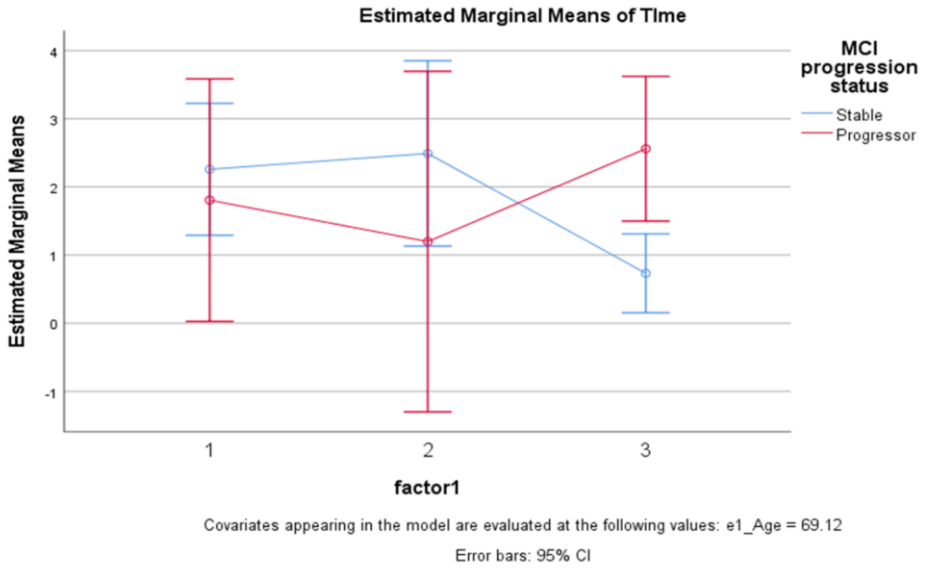


n) IADL

The mean IADL scores at baseline among progressors were 2.00 ±2.483 (p-0.8) and on last follow up were 3.00±1.92 (p- <0.01).

In stable MCI group the baseline mean scores were 1.84±1.96 and on final follow up were 0.56±0.92.

Figure 29 - Trends in IADL between Stable and Progressors



SINGLE VS MULTIDOMAIN

7) Categorical measures between single and multidomain MCI (Table 10)

A positive family history of dementia and higher FAZEKA score was found among Multidomain MCI, but it was not statistically significant. Proportion of subjects with moderate atrophy on ERICA score was found to be higher among multidomain MCI in comparison to single domain MCI and those with no atrophy on ERICA score were more prevalent among single-domain MCI

TABLE 10 – QUALITATIVE VARIABLES SINGLE DOMAIN AND MULTIDOMAIN MCI

VARIABLE	Single domain n=56 N(%)	Multidomain n=39 N(%)	P value (Fisher's exact test)

Sex			
Male	39 (60)	26 (40)	0.759
Female	17 (56.7)	13 (43.3)	
Total	56 (58.9)	39 (41.1)	
Family history			
Absent	51 (60.7)	33 (39.3)	0.35
Present	5 (45.5)	6 (54.5)	
Total	56 (58.8)	39 (41.1)	
FAZEKA score			
Absent	23 (59)	16 (41)	
Mild	9 (64.3)	5 (35.7)	0.77
Moderate	4 (44.4)	5 (55.6)	
Severe	4 (66.7)	2 (33.3)	
Cerebral Microbleed			
Absent	27 (57.4)	20 (42.6)	
Present	9 (60)	6 (40)	0.86
ERICA score			
Normal	9 (90)	1 (10)	
Mild	15 (50)	15 (50)	**0.03**
Moderate	3 (30)	7 (70)	
Severe	1 (100)	0	

The mean age was high among multidomain MCI (p-0.16)

8) SINGLE (N=56) VS MULTIDOMAIN(N=39) -NEUROPSYCHOLOGY PARAMETERS (Table 11)

The Neuropsychology scores which were significant across the Single and Multidomain MCI groups at baseline were MMSE, ACE total, ACE orientation S, ACE language, tests for memory- ACE recall RAVLT total , RAVLT delayed recall, WMS visual immediate, WMS visual delayed, WMS logical memory immediate and test for executive function Trail A errors.

TABLE 11 - STATISTICALY SIGNIFICANT/CLINICALY PERTINENT NEUROPSYCHOLOGY VARIABLES ACROSS SINGLE DOMAIN MCI VS MULTIDOMAIN MCI

Variable	Group	Mean ±SD First visit	Mean ±SD Second visit	Mean ±SD Third visit	P Value (ANOVA/ Mann Whitney's) First visit
Age	Single domain Multi domain	67.32±7.259 69.31±5.877			0.16
Duration of diagnosis	Single domain Multi domain	8.61±3.696 7.79±3.270			0.27
Years of education	Single domain Multi domain	12.98±3.651 12.74±3.462			0.75
MMSE	Single domain Multi domain	28.43±1.597 27.61±2.021	28.56±1.343 27.15±2.428	28.88±1.509 25.87±4.155	**0.03**
ACE total	Single domain Multi domain	86.27±6.754 81.77±7.808	87.12±8.520 78.50±8.746	87.75±8.023 78.38±11.318	**0.004**
ACE orientation	Single domain Multi domain	9.89 ±0.320 9.32±1.387	9.79±0.522 9.44±1.387	9.83±0.834 8.77±2.006	**0.005**
ACE recall	Single domain Multi domain	5.79±2.294 3.82± 2.524	6.05±2.459 3.46±2.284	6.96±2.053 4.92±3.639	**<0.001**
ACE visuospatial	Single domain Multi domain	4.40±0.884 3.94± 1.51	4.49±0.756 3.71± 1.33	4.39±0.941 3.92± 1.18	0.08
ACE language	Single domain Multi domain	27.32±1.123 26.40±2.117	27.36±1.646 26.40± 2.121	27.13±1.792 26.31± 2.057	**0.009**
Phonemic fluency	Single domain Multi domain	8.80±3.382 9.03±3.722	8.55±3.210 8.46±4.207	8.48±3.073 8.38±3.380	0.771
Categorical fluency	Single domain Multi domain	10.14±3.534 9.92±3.516	9.22±3.410 9.54±3.337	9.39±3.858 9.69±2.359	0.77
RAVLT Total	Single domain Multi domain	38.35±9.44 31.41±6.76	39.06±9.58 29.88±7.45	39.25±11.37 30.23±12.28	**<0.001**
RAVLT Delayed	Single domain Multi domain	6.67±3.61 3.90±3.11	7.25±3.01 2.76±3.43	7.13±4.06 4.15±3.28	**<0.001**

recall					
WMS visual immediate	Single domain Multi domain	24.26±8.642 18.70±8.88	25.58±9.373 14.25±9.028	25.33±8.18 17.46±8.97	**0.005**
WMS visual delayed	Single domain Multi domain	16.31±9.48 7.03±8.389	21.26±10.87 6.33±6.812	17.88±10.56 10.77±10.68	**<0.001**
WMS logical memory immediate	Single domain Multi domain	16.52±7.45 9.17±7.75	18.29±7.03 12.68±7.39	20.05±8.40 10.36±7.86	**<0.001**
Trail A time	Single domain Multi domain	3.03±10.42 6.68±24.93	6.36±19.63 3.18±2.44	12.78±32.64 6.70±13.79	0.34
Trail error A	Single domain Multi domain	0.07±0.327 0.51±1.465	0.03±0.167 0.54±1.503	0.30±1.460 0.23±0.832	**0.04**
Trail B time	Single domain Multi domain	7.86±28.65 15.99±58.68	16.58±51.16 13.94±34.08	30.28±88.95 5.68±3.070	0.38
Trial error B	Single domain Multi domain	1.70 ±4.447 3.80±6.120	2.97±7.006 5.10±8.372	3.96±6.912 13.77±11.938	0.08
WCST P	Single domain Multi domain	1.00±1.342 1.44±1.076	0.84±1.186 2.15±2.007	2.50±4.395 3.25±2.633	0.14
HADS-A	Single domain Multi domain	3.66± 3.698 4.61±4.092	3.31±3.667 2.91±2.859	2.83±2.605 3.15±2.641	0.29
HADS-D	Single domain Multi domain	2.61±3.157 3.18±3.432	2.44±2.828 3.00±2.611	2.26±2.359 3.23±2.743	0.45
CDR	Single domain Multi domain	0.43±0.169 0.45±0.138	0.54±0.356 0.66±0.345	0.48±0.17 0.533±0.229	0.47
IADL	Single domain Multi domain	1.69±1.895 2.18±2.343	2.14±3.015 2.05±2.614	0.60±1.046 2.00±1.958	0.39
CSF volumes	Single domain Multi domain	469.56±94.6 535.5±127.5			**0.03**

9) CDR and IADL Final follow up (Table 12)

The CDR and IADL scores showed significant decline across Non converter Vs Converter, Stable Vs Progressor, Single domain Vs Multidomain MCI.

The CDR and IADL showed no statistically significant decline among amnestic, dysexecutive and multidomain MCI.

TABLE 12 - CDR AND IADL ACROSS THREE GROUPS FINAL VISIT

Variable	CDR 4	P value	IADL 4	P value
Non Converter(NC) Converter(C)	0.44±0.17 1.33±0.87	**0.000**	0.77±1.27 11.28±5.94	**0.000**
Stable (S) Progressor(P)	0.43±0.16 1.19±0.83	**0.000**	0.76±1.25 9.31± 6.77	**0.000**
Single domain (SD) Multidomain (MD)	0.61±0.57 0.67±0.56	0.595	2.23±4.81 4.35±5.75	**0.05**
Amnestic Dysexecutive Multidomain	2.0± 1.68 1.24 ±2.07 2.29±2.34	0.28	2.45±5.20 2.22 ±5.06 4.15 ±5.46	0.27

AMNESTIC Vs DYSEXECUTIVE Vs MULTIDOMAIN MCI

10)FAZEKA grade among MCI subgroup (Table 13)

The FAZEKA grade across MCI subgroups (amnestic, dysexecutive and multidomain) showed no statistical significance

Table 13 – MCI subgroups and FAZEKA grading

Baseline MCI status	FAZEKA grade				
	Absent	Mild	Moderate	Severe	P value
Amnestic	45.8 (11)	20.8 (5)	20.8 (5)	12.5 (3)	0.17
Dysexecutive	68.4 (13)	21.1 (4)	0	10.5 (2)	
Dysexecutive	68.4 (13)	21.4 (4)	0	10.5 (2)	0.267
Multidomain	58.3 (14)	20.8 (5)	16.7 (4)	4.2 (1)	
Amnestic	45.8 (11)	20.8 (5)	20.8 (5)	12.5 (3)	0.68
Multidomain	58.3 (14)	20.8 (5)	16.7 (4)	4.2 (1)	

11)Comparison of baseline MCI subgroups and final outcomes (Non converter/Converter) (Table 14, 15 and 16)

On comparison between amnestic vs multidomain MCI and dysexecutive vs multidomain MCI, there was significant association of multidomain MCI at baseline and converter status at follow up.

Table 14 - Amnestic and Dysexecutive MCI at baseline and final status (Non converter / Converter)

Baseline MCI status		MCI final status	
		Nonconverter	Converter
Amnestic	N (%)	27 (87.1)	4 (12.9)
Dysexecutive	N (%)	24 (88.9)	3 (11.1)

p=0.99 (Fisher exact)

Table 15- Dysexecutive and Multidomain MCI at baseline and final status (Non converter /Converter)

Baseline MCI status		MCI final status	
		Nonconverter	Converter
Dysexecutive	N(%)	24 (88.9)	3 (11.1)
Multidomain	N(%)	23 (63.9)	13 (36.1)

p=0.024 (Fisher exact)

Table 16 - Amnestic and Multidomain MCI at baseline and final status (Non converter /Converter)

Baseline MCI status		MCI final status	
		Nonconverter	Converter
Amnestic	N(%)	27 (87.1)	4 (12.9)
Multidomain	N(%)	23 (63.9)	13 (36.1)

p=0.030 (Fisher exact)

12)Comparison of baseline MCI subgroups and final outcomes (Stable Vs Progressor) (Table 17, 18 and 19)

The multidomain MCI at baseline had shown significant progression on follow up on comparing Dysexecutive vs Multidomain MCI and Amnestic Vs Multidomain MCI

Table 17- Amnestic and Dysexecutive MCI at baseline and final status (Stable / Progressor)

Baseline MCI status		MCI progression status	
		Stable	Progressor
Amnestic	N(%)	26 (83.9)	5 (16.1)
Dysexecutive	N(%)	24 (88.9)	3 (11.1)

p=0.712 (Fisher exact)

Table 18 - Dysexecutive and Multidomain MCI at baseline and final status (Stable /Progressor)

Baseline MCI status		MCI progression status	
		Stable	Progressor
Dysexecutive	N(%)	24(88.9)	3(11.1)
Multidomain	N(%)	19(52.8)	17(47.2)

p=0.002 (Fisher exact)

Table 19 - Amnestic and Multidomain MCI at baseline and final status (Stable /Progressor)

Baseline MCI status		MCI progression status	
		Stable	Progressor
Amnestic	N(%)	26 (83.9)	5 (16.1)
Multidomain	N(%)	19 (52.8)	17 (47.2)

p=0.007 (Fisher exact)

13) OUTCOME MEASURES AMONG MCI SUBGROUPS (Table 20, 21)

The outcome measures (CDR and IADL) showed decline between baseline and final visit across amnestic /dysexecutive/multidomain MCI but was not statistically significant (ANOVA and Post hoc Bonferroni analysis).

Table 20 – Comparison between MCI baseline subgroups and CDR and IADL at baseline and follow up

MCI status at baseline	CDR baseline	CDR final follow up	IADL baseline	IADL final follow up
Amnestic	0.43±0.17	2.0±1.68	0.64±0.59	2.45±5.2
Dysexecutive	0.44±0.16	1.24±2.07	0.611±0.59	2.222±5.06
Multidomain	0.45±0.14	2.29±2.34	0.65±0.54	4.15±5.46
P value (ANOVA)	0.827	0.288	0.957	0.271

Table 21- Baseline MCI subgroups and outcome measures at baseline and final follow up Post hoc tests (Bonferroni) test

Outcome measure	Baseline	Baseline	Sig. (p value)
CDR baseline	Amnestic	Dysexecutive	1.000
		Multidomain	1.000
	Dysexecutive	Amnestic	1.000
		Multidomain	1.000
	Multidomain	Amnestic	1.000
		Dysexecutive	1.000
CDR final follow up	Amnestic	Dysexecutive	1.000
		Multidomain	1.000
	Dysexecutive	Amnestic	1.000
		Multidomain	1.000
	Multidomain	Amnestic	1.000
		Dysexecutive	1.000
IADL baseline	Amnestic	Dysexecutive	0.796
		Multidomain	1.000
	Dysexecutive	Amnestic	0.796
		Multidomain	0.371
	Multidomain	Amnestic	1.000
		Dysexecutive	0.371
IADL final follow up	Amnestic	Dysexecutive	1.000
		Multidomain	0.572
	Dysexecutive	Amnestic	1.000
		Multidomain	0.460
	Multidomain	Amnestic	0.572
		Dysexecutive	0.460

C) CORRELATION -FAZEKA AND NEUROPSYCHOLOGY SCORES

On correlation analysis between FAZEKA changes on MRI and Neuropsychology variables ACE orientation, ACE recall and RAVLT delayed recall showed significant negative correlation at baseline (p value <0.05).

TABLE 22– CORRELATION -FAZEKA & NEUROPSYCHOLOGY TESTS

Neuropsychology variable	Spearman's	First visit	Second visit	Third visit	Fourth visit
MMSE	Correlation Coeff	-0.126	-0.197	-0.053	
	Sig (Two tailed)	0.313	0.195	0.783	
ACE	Correlation Coeff	-0.090	-0.125	0.055	
	Sig (Two tailed)	0.465	0.408	0.784	
ACE orientation	Correlation Coeff	-.291*	-0.091	0.344	
	Sig (Two tailed)	0.021	0.556	0.086	
ACE registration	Correlation Coeff	0.034	0.065	0.063	
	Sig (Two tailed)	0.783	0.668	0.754	
ACE recall	Correlation Coeff	-.247*	-.327*	-0.316	
	Sig (Two tailed)	0.044	0.026	0.109	
ACE visuospatial	Correlation Coeff	-0.086	-.369*	0.080	
	Sig (Two tailed)	0.499	0.015	0.696	
ACE language	Correlation Coeff	-0.036	0.019	0.000	
	Sig (Two tailed)	0.777	0.905	0.998	
P fluency	Correlation Coeff	-0.161	-0.270	-0.055	
	Sig (Two tailed)	0.211	0.069	0.790	
Animal fluency	Correlation Coeff	-0.183	-0.207	-0.113	
	Sig (Two tailed)	0.158	0.173	0.582	
RAVLT total	Correlation Coeff	-0.198	-0.263	-0.226	

	Sig (Two tailed)	0.108	0.088	0.256	
RAVLT immediate recall	Correlation Coeff Sig (Two tailed)	-0.442 0.173	-.785** 0.007	-0.617 0.192	
RAVLT delayed recall	Correlation Coeff Sig (Two tailed)	-.376** **0.002**	-.323* 0.035	-0.315 0.109	
RAVLT Recognition	Correlation Coeff Sig (Two tailed)	-0.186 0.162	-0.066 0.686	-0.343 0.079	
Commission error	Correlation Coeff Sig (Two tailed)	0.172 0.189	.453** 0.003	0.278 0.160	
WMS Logical memory immediate	Correlation Coeff Sig (Two tailed)	-0.053 0.692	-0.323 0.051	-0.214 0.315	
Position discrimination	Correlation Coeff Sig (Two tailed)	.458* 0.048	-0.120 0.742	-0.280 0.543	
IADL	Correlation Coeff Sig (Two tailed)	0.272 0.082	0.331 0.055	.474* 0.017	0.164 0.180
CDR	Correlation Coeff Sig (Two tailed)	0.101 0.417	0.194 0.212	-0.229 0.215	.321** 0.008

D) MULTIVARIATE ANALYSIS – CONVERTORS (TABLE 23)

In the multivariate analysis, the age corrected models across converters showed age (p-0.3, Odds 1.05, 95% CI 0.933-1.203), RAVLT recognition (p-0.006, Odds -0.73, 95% CI -0.589-0.916), WMS logical memory immediate (p-0.033, Odds-0.885, 95% CI -0.790-0.990), WCST perseverative (p-0.004, Odds-3.116, 95% CI-1.425-6.817) could predict conversion of MCI.

It implies that lower RAVLT recognition score, WMS logical memory immediate scores and higher WCST perseverative error scores at baseline were independent predictors of MCI conversion on binary logistic regression.

1) AGE CORRECTED MODEL

TABLE 23 - SIGNIFICANT PARAMETERS ON MULTIVARIATE ANALYSIS AMONG NON CONVERTERS AND CONVERTERS

	B	**Sig (p value)**	**Exp B (Adjusted Odds ratio)**	**95% Confidence Interval (Lower-Upper)**
Age	0.058	0.371	1.059	0.933-1.203
RAVLT Recognition	-0.308	**0.006**	0.735	0.589-0.916
WMS Logical memory immediate	-0.123	**0.03**	0.885	0.790-0.990
WCST Perseverative error	1.137	**0.004**	3.116	1.425-6.817
Constant	-2.703	0.560	0.067	

2) CONVERSION SCORE

An equation was generated based on the logistic model for converter and a new score was created which could predict conversion from MCI during the mean duration of follow up 6.49 years

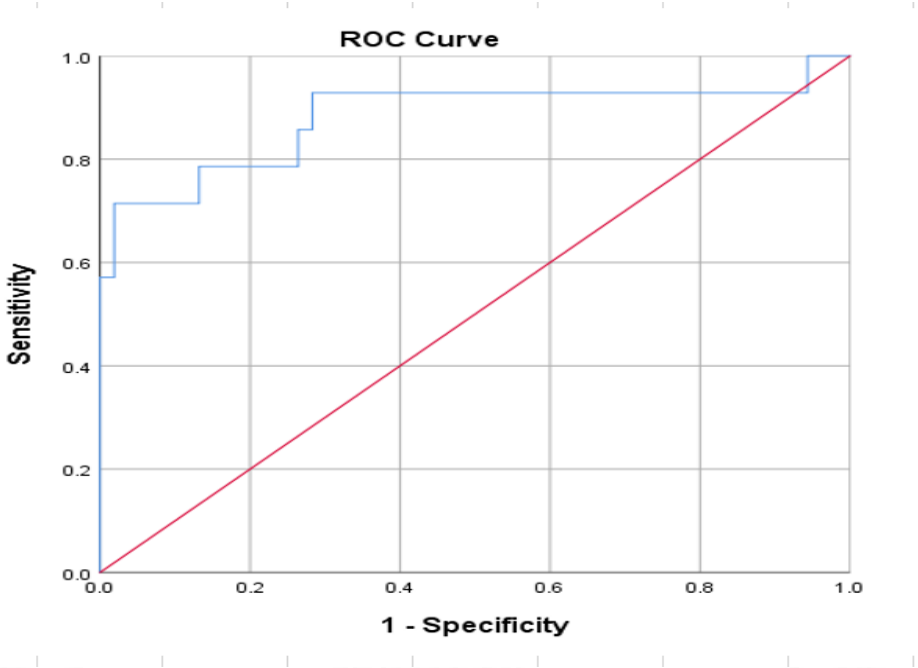
CONVERSION SCORE=-0.308 (RECOG) - 0.123(WMS L1) +1.137 (WCST P) +0.058*AGE

3) ROC CURVE

The variables derived were from Beta logarithmic form and they were converted to linear regression model. Hence the validity of the derived score was tested using the ROC Analysis and the conversion score was found to be valid with AROC 0.881 ($p < 0.001$)

The new score was able to classify converters from Non converters.

FIGURE 30 - ROC ANALYSIS



AROC – 0.881 (p <0.001)

Predicted cut off score

The Youden's J was computed for each cut off values and the J Max was reported

A conversion score greater than or equal to 2.6105, could predict with sensitivity of 71.4 % and specificity of 98.1%, Youden's J max 0.695 for the risk of conversion over a period of 6.4 yrs .

Sensitivity and Specificity of Conversion score (Youden's J max) - Appendices 6.

4) MULTIVARIATE ANALYSIS -STABLE Vs PROGRESSORS (TABLE 24)

The logistic regression model for stable Vs Progressors showed significance of the baseline MCI status (single or multidomain) with p-0.012, Adjusted Odds 4.591 and 95% Confidence Interval 1.395-15.116.

TABLE 24 - FORCED MODEL WITH MCI BASELINE GROUP (STABLE VS PROGRESSORS)

Parameter	Sig (P value)	Exp B -Adjusted Odds	95% Confidence Interval (LL-UL)
Age	0.141	1.070	0.978-1.170
WMS Logical memory immediate	0.222	0.955	0.887-1.028
MCI baseline (Single / Multidomain)	**0.01**	4.591	1.395-15.116
Constant	0.073	0.003	

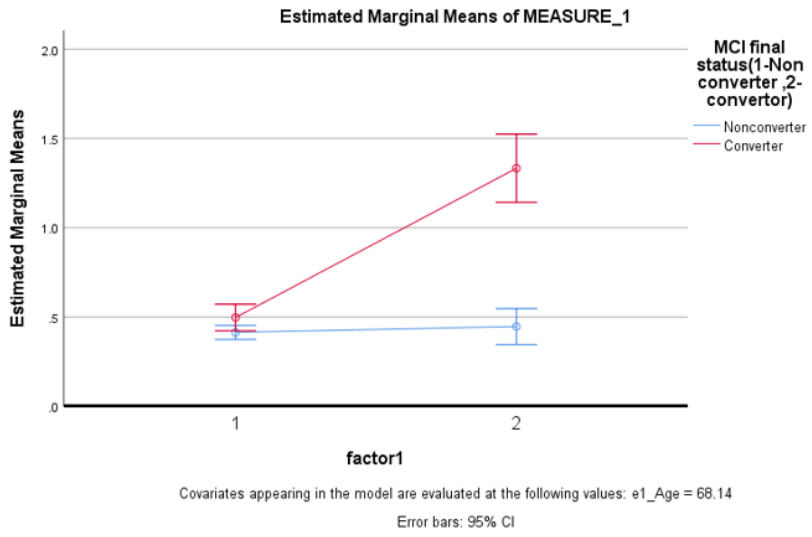
E) REPEATED MEASURE ANOVA

1) CDR-NON CONVERTER VS CONVERTER

a) CDR repeated measures - (Baseline and final follow up)

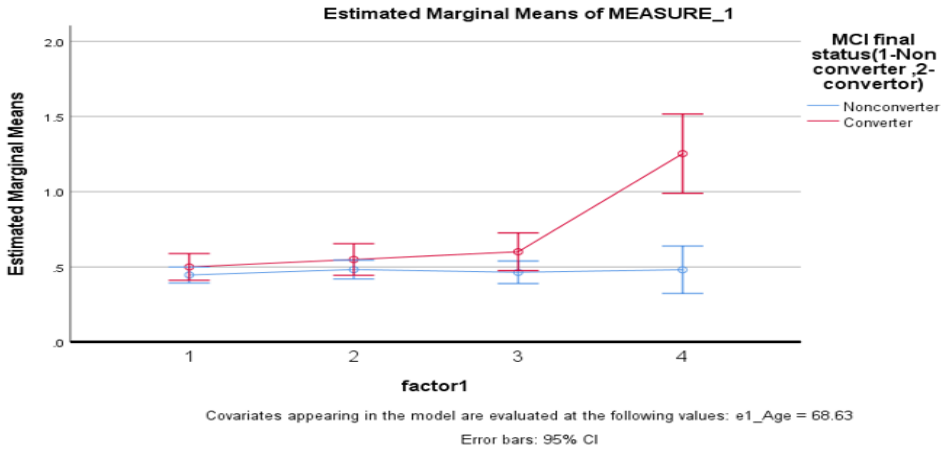
The CDR repeated measure ANOVA among Converters and Non converters showed decline between and also within each groups from baseline and final follow up

FIGURE 31 - CDR REPEATED MEASURE ANOVA - BASELINE AND FINAL VISIT NON CONVERTER VS CONVERTER



b) CDR all four visits

FIGURE 32 - CDR REPEATED MEASURE ANOVA -ALL FOUR VISITS NON CONVERTER VS CONVERTER

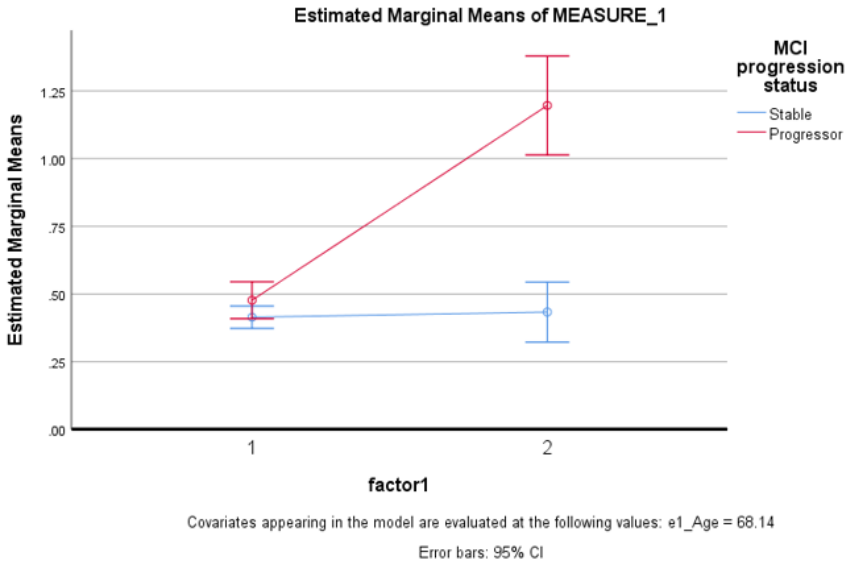


2) CDR-STABLE VS PROGRESSOR

a) CDR repeated measured (Between baseline and Final follow up)

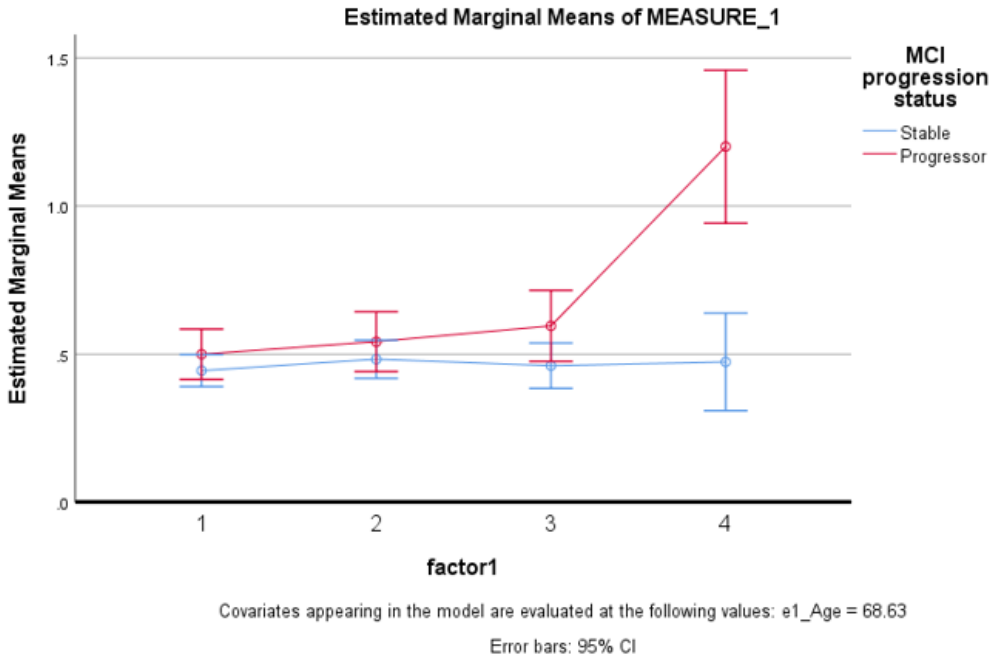
The CDR repeated measure ANOVA across stable Vs progressors showed decline between and within each groups from baseline and final follow up

FIGURE 33 - CDR REPEATED MEASURE ANOVA -BASELINE AND FINAL VISIT STABLE AND PROGRESSOR



b) CDR repeated measures – all four readings

FIGURE 34- CDR REPEATED MEASURE ANOVA ACROSS ALL FOUR VISIT IN STABLE VS PROGRESSORS

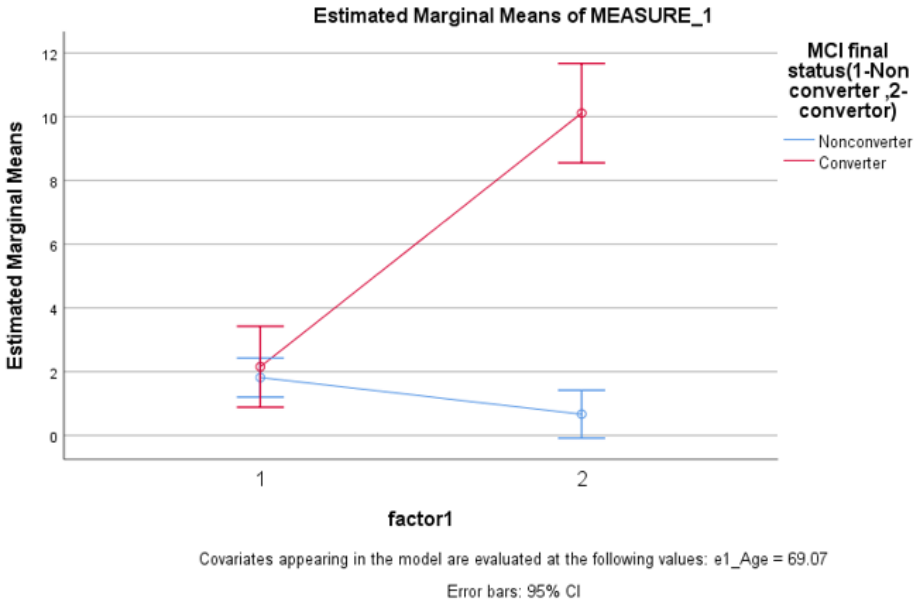


3) IADL REPEATED MEASURES -NON CONVERTOR VS CONVERTER

a) IADL repeated measures– baseline and final

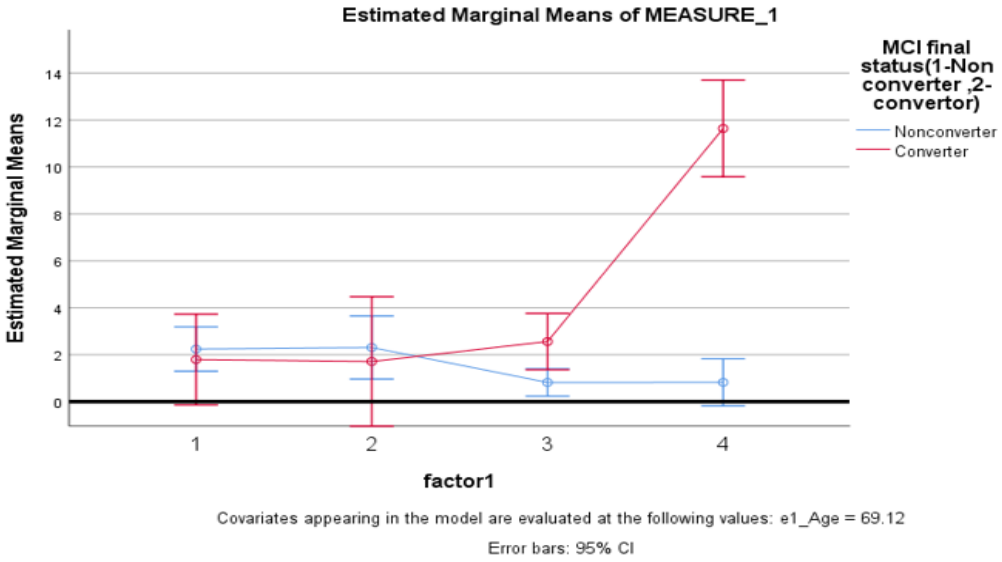
The IADL repeated measure ANOVA among Converters and Non converters showed decline between and also within each groups from baseline and final follow up

FIGURE 35 - IADL REPEATED MEASURE ANOVA -BASELINE AND FINAL FOLLOW UP IN NON CONVERTERS VS CONVERTERS



b) IADL repeated measures -All four visits

FIGURE 36 - IADL REPEATED MEASURE ANOVA -ALL FOUR VISITS IN NON CONVERTERS VS CONVERTERS

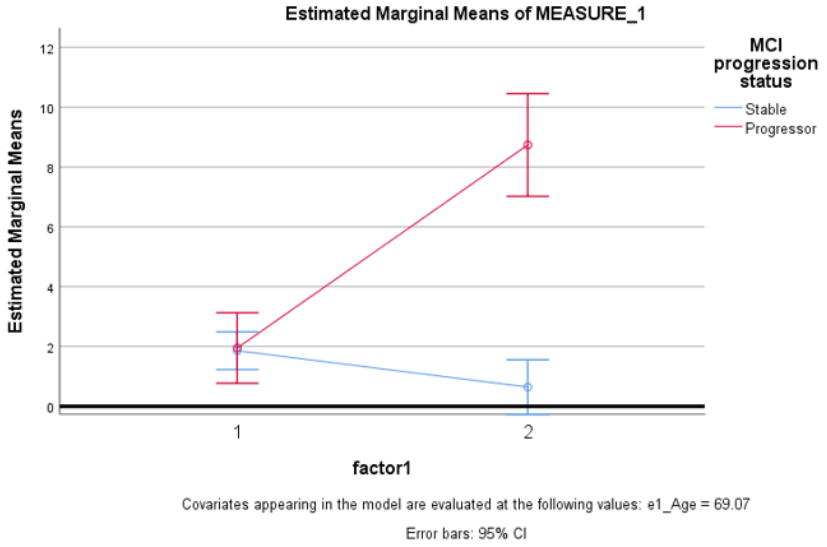


4) IADL Repeated measure STABLE VS PROGRESSOR

a) IADL repeated measures baseline and final follow up

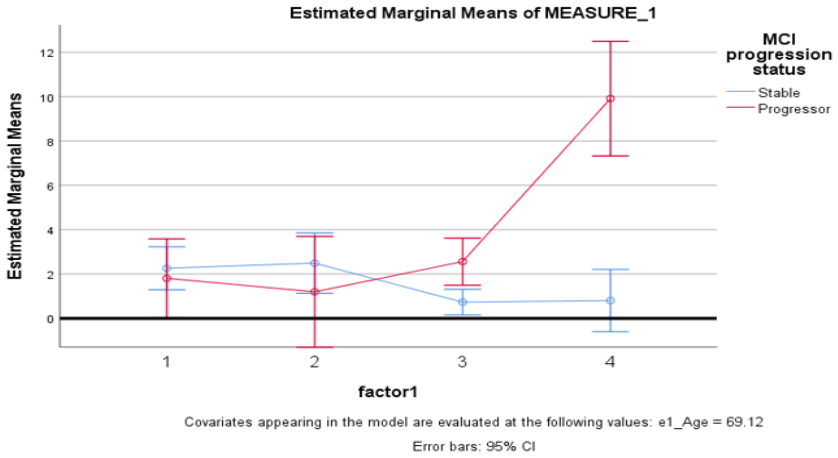
The IADL repeated measure ANOVA across Stable and Progressors showed decline between and also within each groups from baseline and final follow up

FIGURE 37- IADL REPEATED MEASURE ANOVA – BASELINE AND FINAL FOLLOW UP IN STABLE VS PROGRESSORS



b) IADL repeated measures - All four readings

FIGURE 38 - IADL REPEATED MEASURE ANOVA – ALL FOUR VISITS IN STABLE VS PROGRESSORS



F) KAPLAN MEIER SURVIVAL CURVE

1) SINGLE DOMAIN Vs MULTIDOMAIN MCI-SURVIVAL ANALYSIS (TABLE 25)

The Kaplan Meier survival analysis showed Multidomain MCI would convert to dementia over a mean duration of 10.46 yrs (95% CI 8.261-12.666) when compared to single domain MCI 12.45 yrs (95% CI 11.230-13.687) and the log rank test showed significant p values (p-0.003).

FIGURE 39- KAPLAN MEIER SURVIVAL ANALYSIS SINGLE DOMAIN VS MULTIDOMAIN MCI

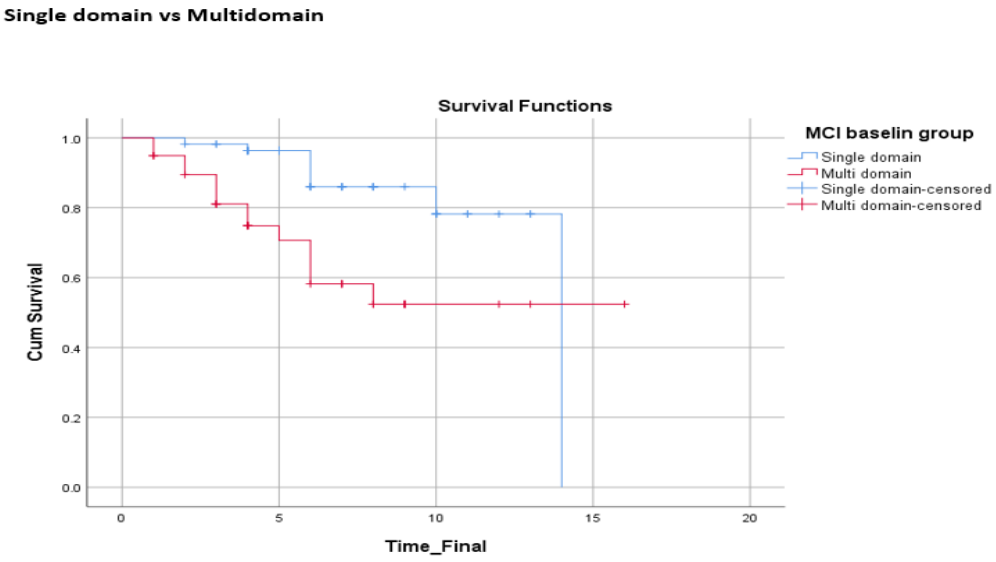


TABLE 25 – CONVERSION ESTIMATES BETWEEN SINGLE AND MULTIDOMAIN

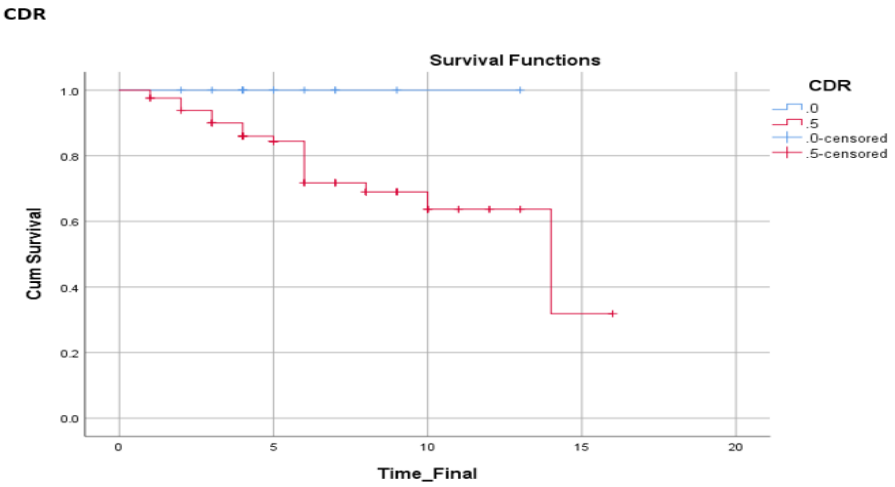
MCI Baseline group	Estimate	95% Confidence Interval (Lower Bound-Upper Bound)
Single Domain	12.458	11.230-13.687
Multidomain	10.463	8.261-12.666
Overall	11.879	10.365-13.393

Log Rank test p=0.003

2) SURVIVAL ANALYSIS -CDR

Subjects with higher CDR scores at baseline had more decline and would convert earlier to dementia than subjects with low CDR.

FIGURE 40 - SURVIVAL ANALYSIS – BASELINE CDR AND HAZARDS FOR PROGRESSION



3) NEW SCORE BASED CUT OFF (above 2.615) [TABLE 26]

The Kaplan Meier survival curve for the conversion score with cut off above 2.615 showed conversion to dementia over 4.576 yrs (95% CI 2.909 -6.243, log rank test p <0.001) when compared to score below 2.615 which would convert over 14.805 (95% CI 13.671-15.939).

Means and Medians for Survival Time

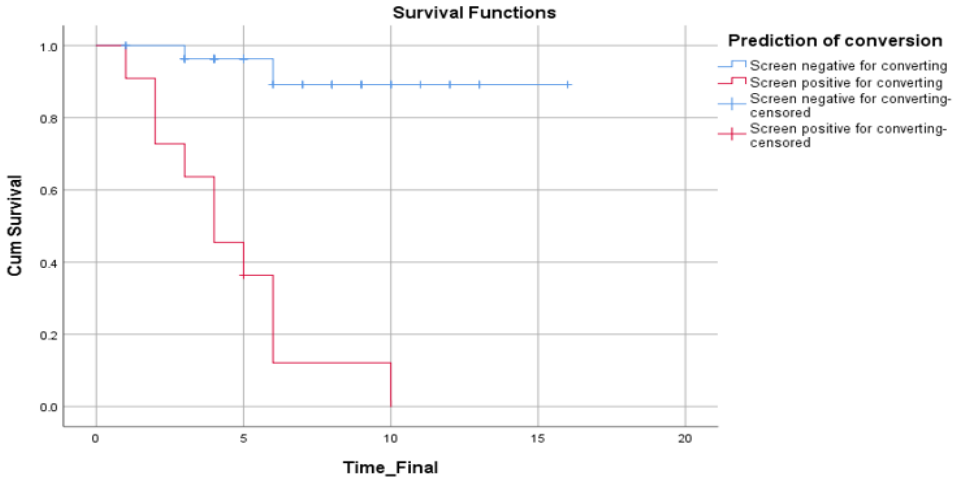
TABLE-26- CONVERSION ESTIMATES BASED ON NEW SCORE (ABOVE 2.615)

Prediction of Conversion	Estimate	95%Confidence Interval (Lower bound-Upper bound)
Screen negative for converting	14.805	13.671-15.939
Screen positive for converting	4.576	2.909-6.243

Overall	12.570	10.988-14.153

Log rank test p <0.001

FIGURE 41- KAPLAN MEIER SURVIVAL ANALYSIS FOR CONVERSION SCORE CUT OFF ABOVE 2.615



G) ANNUALIZED CONVERSION RATE

Cumulative conversion rate at mean (SD) period of follow up= 21/95 **(22.2%)**

Total Person time of follow up in years = 636

Total events = 21

Annualized conversion computes to be 3.30 per 100 person years

Hundred persons followed up for one year – Three persons will convert

Hence over a period of follow up for 6.4 yrs in our cohort , around 19.2 patients out of hundred converted to dementia

DISCUSSION

The was a real gap in knowledge was the dearth in indigenous literature as there were no similar Hospital based studies which identified MCI predictors and also looked at the longitudinal trends of evolution in MCI from the Indian subcontinent.

A community based cohort from Kolkata by Das et al showed the prevalence of MCI was around 14.89% however the estimate of conversion to dementia is uncertain(26).

DEMOGRAPHIC PROFILE

Ninety five patients with MCI 68.4% males 31.6% females, with age 68.4 ±6.4 , at baseline were followed up for a mean duration of 6.4 yrs and the mean duration from symptom onset was 8.7yrs.

AGE

The mean age was higher among converters 70.33yrs, progressors 70.54 yrs and multidomain MCI 69.31yrs. The predictive accuracy for conversion of MCI is dependant on age and age is an independent factor for MCI conversion as has been found in other studies (12,13,35,42).

Even though in our analysis we could not find significance, anticipating a potential confounding effect, it was forced into the logistic regression model and the conversion score .Hence we relied on a logistic regression based estimation to look at the independent effect of neuropsychological variables at baseline on risk of conversion.

EDUCATION STATUS

Our study population were from Kerala and it consisted of a highly literate population and 94.8% of cohort had more than 12 yrs of education. At 96.2 per cent, Kerala emerged as the most literate state in India once again. In Kerala, the female literacy rate has been pegged at 95.2 per cent in contrast to the male literacy rate at 97.4 per cent (The report on 'Household Social Consumption: Education in India as part of the 75th round of National Sample Survey).The mean years of education did not differ significantly across the three groups .

The education status has a definite influence on most of domains of cognition and is protective against MCI conversion(9,14,35). This can also potentially explain our lower ACR which is similar to that of community based cohorts (6,70,72) but significantly lower than other hospital-based cohorts. This could indicate a higher proportion of 'worried well' persons who are keen not to disregard their cognitive issues as simple aging associated memory impairment and preference for early diagnosis and intervention is sought better among persons with higher education.

11.6% patients had positive family history of dementia and Apo E4/E4 allele was positive in 41.6% (10/24) in our subset analysis. However positive family history or Apo E4 homozygosity did not significantly differ among non convertors and convertors as has been shown in other studies (115)

MAJOR COMORBIDITIES

Most of the studies have shown significant association between vascular risk factors, metabolic syndrome, hypothyroidism with cognitive decline and dementia conversion on follow up(15,36,37,43,44).

The major comorbidities were Hypertension (49.5%), diabetes 41.1%, Obstructive sleep apnoea 35.8%, dyslipidemia 23.2%, CAD 17.9%, Thyroid illness 14.8% and seizures 11.6%. Kerala is a state with a higher burden of these disorders compared to the rest of the country (116,117) ,which made it particularly relevant to determine the relevance of these factors on conversion risk.

None of the comorbidities had a significant bearing on dementia conversion in our cohort as opposed to the findings of other hospital community based cohorts (15,37,43,44). This may be because of the higher health seeking behaviour and early identification and further control and follow up of patients with these comorbidities with medications and other interventions. Similar findings on the non significance of clinical variables as opposed to neuropsychology variables on the risk of conversion has been demonstrated in studies such as by Edith et al(57).

NEUROPSYCHIATRIC ILLNESS AND MCI

Neuropsychiatric symptoms as prognostic markers for MCI conversion were looked at by various studies and the common conclusions were depression was associated with increased risk of progression(15,38,40,41). Some studies have found association with irritability and apathy as conversion predictors(39).

A large community based data by Srikala et al from India showed that the prevalence of neuropsychiatric symptoms were 55%(94).

33.7% had psychiatric illness at baseline and 17.9% had depression and 14.7% had anxiety at baseline. The lack of significant association in our study may be because we excluded patients with clinically significant anxiety, depression, psychosis and bipolar disorders. Also we did not find the HADS scores to differ in convertors or progressors. Another aspect could be of the early treatment and targeted treatment including psychiatric referral which were reflected in follow up as improvement of HADS score.

MCI CONVERSION

The cumulative conversion rate was 22.1% on follow up .This was almost comparable to the multiple hospital based cohorts worldwide(13,14,55).

An Indian study by Mukku et al which had only 21 MCI cohorts with median follow up 1.4 yrs found 28.6% conversion and rest of the MCI retained the status without any reversion(93). Our study demonstrated the relevance of memory variables, particularly learning and encoding measures as determined by recognition score and executive function as determined by errors on set shifting to be particularly relevant. This is similar to the results of other studies (13,54,56–58,63,66) and ours is the first study from Indian to demonstrate the superior relevance of neuropsychological tests after correction for age in comparison to baseline comorbidities to be a factor that estimates conversion. Conversion rate as shown in the review of literature is multifactorial and baseline measures of memory, executive function and profile of MCI at baseline are likely to determine this. It is well known that baseline neuropsychological measures even among persons with subjective memory deficits and minimal cognitive impairment ascertain cognitive

reserve and are likely to determine the future clinical course (14,54,56,63,66). Development of neuropsychological changes are known to post-date pathological changes in pre-clinical AD (118) and thus baseline performance of memory and executive function will prove to be robust clinical biomarkers of MCI due to a neurodegenerative cause with a definite risk of progression. We have explored the combination of tests which are relevant robustly in our multivariate analysis as will be discussed further.

SINGLE AND MULTIDOMAIN MCI

58.9% had single domain MCI and 41.1% multidomain MCI at baseline and on follow up 66.6% of the multidomain MCI converted to dementia 33.6% had amnestic MCI and 28.4% had dysexecutive MCI at baseline.

Amnestic MCI was significantly associated with dementia conversion especially AD(9,10) and multidomain MCI at baseline had significant conversion (more than half to two thirds) in various studies(8,9,50,72). Conversion to AD was noted in a significant proportion of our cohort with rare patients converting to DLBD and FTD as has been noted in other studies (119–123). This also suggests that AD is more likely to have a prolonged prodromal phase as MCI (124,125) as opposed to DLBD and FTD which are syndromes which can present to the geriatric psychiatrist as mild behavioural impairment (MBI) and will be evaluated neurologically only once overt neurological decline is apparent to the extent of affliction of activities of daily living (eg delirium, resistant hallucinations or mood disorders with dysexecutive syndrome which do not respond to conventional psychiatry treatment). Our results do not seem to indicate a large proportion of MBI who met the neuropsychological criteria of MCI probably due to the exclusion criteria for our study.

A study from NIMHANS have found that multidomain MCI was the most common type of MCI and had performed worse on episodic memory ,logical memory ,attention and executive functions in the cross sectional data , however the follow up evolutions were not looked into(94).

AMNESTIC Vs DYSEXECUTIVE Vs MULTIDOMAIN MCI

In our subgroups multidomain MCI at baseline was significant among converters and amnestic, dysexecutive MCI at baseline found no significance in predicting conversion or progression to dementia. We did not find significant association between FAZEKA grade and outcome measures (CDR and IADL) across these groups between baseline and follow up.

The risk of dementia conversion were more among amnestic and multidomain MCI based on multiple prior studies (9,10,72) . However we did not observe a higher rate of progression in isolated amnestic MCI indicating that presence of subtle executive deficits on cognitive testing needs to be ascertained and the focus should not be restricted to the memory domain alone. Attention, executive and visuospatial deficits are known to be harbingers of cognitive decline in prodromal AD(126,127)

NEUROPSYCHOLOGY TESTS IN MCI

Literature survey shows that intra-individual change in neuropsychological test scores over time can diagnose trends in MCI and also conversion to dementia much earlier than other clinical , MRI Brain or functional imaging parameters(81). The results of our study were in concurrence with the same. The baseline neuropsychology evaluation has showed significant impairment on tests of memory and executive functions in MCI converters and progressors and also in multidomain MCI subjects and these subjects have a more rapid decline in the cognitive functions when compared to Non converters / stable MCI and single domain MCI.

Tabert et al found that deficits in verbal memory and psychomotor speed /executive function abilities strongly predicted conversion to AD(54).

COMPARISON OF NEUROPSYCHOLOGICAL PARAMETERS ACROSS GROUPS

The poor performance in test of memory especially delayed recall and executive functions at baseline predicted MCI conversion to dementia in multiple hospital based cohort(13,56,58,60,63,66). The community based cohorts have also found similar associations(48,49,67,68,71).

Our MCI cohort also revealed similar findings concordant with multiple hospital and community based cohorts. There was significant decline in the tests for memory and learning (RAVLT total, RAVLT recognition, WMS visual immediate, delayed, digit forward, WMS logical memory immediate) and tests for executive function (Trail A errors, Trial B errors, WCST P) from baseline among converters and progressors.

OUTCOME MEASURES

Higher Clinical dementia rating score (CDR) and IADL at baseline has been associated with a greater risk of MCI conversion(14,51,52,61,82). Our cohort also exhibited similar results.

MRI PARAMETERS AND MCI

Hippocampal volume loss is directly corroborated pathologically to neuronal loss and clinically to memory deficits. The measure of hippocampal volume has been used for predicting MCI and further conversion to AD. In several longitudinal studies, total hippocampal volume was reported as reduced in the following order: control> MCI >AD(79,80,82).

Hence we had analysed the MRI parameters across three groups of MCI in a subset analysis ,but none of the MRI Brain parameters except FAZEKA grading were found to be significant to predict progression /conversion in our study. Crucially a study by Fleisher et al also found that MRI measures did not improve predictive accuracy beyond that obtained by cognitive measures(81). After correction for age on our bivariate analysis no volumetric variable was found to be significantly correlated with conversion however multidomain MCI demonstrated an increase CSF volume in comparison to single-domain which may be a compensatory change or an indirect marker of global cerebral atrophy and is likely to be more pronounced in the former. This has been demonstrated in other studies (128).

Imaging differences between single-domain and multidomain MCI were apparent on ERICA score with moderate atrophy more frequent in the latter subgroup . Thus a qualitative score may be of utility in determining the imaging

phenotype of MCI. However this was not proven to be a factor deterministic for conversion or progression.

FAZEKA GRADE AND NEUROPSYCHOLOGICAL PARAMETERS CORRELATION

The progression of MCI to dementia was studied by Salka et al and found that higher FAZEKA score correlated with progression to non Alzheimer's dementia and medial temporal lobe atrophy predicted progression to AD(75). Holz et al found that FAZEKA score exhibited significant correlation with all cognitive domains but especially with episodic visual memory(76).

In our study 41.1% showed evidence of small vessel disease on MRI Brain on FAZEKA grading

On correlation analysis between FAZEKA changes on MRI and Neuropsychology variables like ACE orientation, ACE recall and RAVLT delayed recall showed significant correlation at baseline in converters and progressors . This raises the significance of white matter integrity as a measure of dementia risk among persons with MCI. Prior studies have also demonstrated this correlation between memory measures and Fazeka's grading in Va MCI (77) and tensor imaging has also been found to be a robust measure on multimodality imaging .(97)As has been shown in longitudinal community cohorts (Framingham study(129)), the importance of baseline white matter ischemia or disordered tensor metrics could suggest in utility as an imaging biomarker in MCI at risk of progression. However this measure was not found to be significant on multivariate analysis indicating that age in itself could determine the Fazeka's grading in combination with vascular risk factors such as diabetes and hypertension which were found in a significant proportion of patients in our study. This aspect has also been demonstrated in other studies (129,130). In the absence of longitudinal community based cohort data or case-control comparisons we are unable to determine the role of higher prevalence of risk factors such as DM, hypertension, smoking, alcohol use or sleep apnoea with regard to conversion risk in our MCI cohort.

MULTIVARIATE ANALYSIS -LOGISTIC REGRESSION

The multivariate logistic regression has found low RAVLT recognition, WMS immediate logical memory scores and high WCST -perseverative errors as predictors of progression and none of the clinical and MRI parameters could reliably predict conversion in bivariate or multivariate analysis. Prior studies which have attempted to provide similar logistic regression based estimates have combined neuropsychology test of memory and executive functions and found significance in delayed recall on logical memory and trail making test (sensitivity 86%,specificity 83%)(63), RAVLT(49), semantic deficits(68), clock drawing test (sensitivity of 100% and specificity of 94.7%)(53), semantic fluency (sensitivity 84%, specificity 64%)(67), delayed recall(131). Garcia et all found that long delay cued recall (sensitivity 85.7, specificity 98.3) and the performance time of the Rey figure test (sensitivity 70%, specificity 62%)(48) were the best predictive tests of conversion to dementia after an MCI diagnosis

CONVERSION SCORE

A conversion score was derived based on data from the logistic regression which if was higher than 2.615 could predict risk of conversion with sensitivity of 72% and specificity of 98% over a period of 6.4 yrs follow up ,suggesting the utility of our equation which combined age, learning and encoding score with executive errors to predict conversion in MCI.

ROC CURVE

The validity of the derived score was tested using the ROC Analysis and the conversion score was found to be valid with AROC 0.881 ($p < 0.001$).

SURVIVAL ANALYSIS AND HAZARDS CURVE

The Kaplan Meier survival analysis showed that the hazards of conversion of multidomain MCI to dementia would take around 10.46 yrs when compared to 12.45 yrs in single domain MCI.

The survival analysis curve for the cut off score 2.615 showed conversion to dementia over 4.5 yrs when compared to score below 2.615 which would convert over 14.8 yrs

CDR AND IADL REPEATED MEASURE ANOVA ANALYSIS

The CDR and IADL repeated measure ANOVA across Non converters Vs converters and stable Vs progressors showed decline between and within each groups from baseline and final follow up. This was supportive of evidence from multiple studies that CDR and IADL are reliable predictors of MCI progression(14,51,52,61,82).

ANNUALIZED CONVERSION RATE

A cumulative conversion rate of 22.1% over mean period of follow up of 6.4 yrs and over a mean duration of symptoms 8.7 yrs, which is similar to that identified other hospital based cohorts (ranging between 20-30%). The annualized conversion in our study was however 3.3 per hundred person years which means that three patients will convert each year for 100 persons with MCI followed up , hence as the mean duration of follow up in our study was 6.4 yrs, a total of 19.2 patients will convert over that period to dementia from MCI. This conversion rate was much lower than the reviewed data from hospital based cohorts and is similar to other community based cohorts (3-10%) for dementia and its subtypes (13,14,33). This might be due to fact ,the early health seeking behaviour of our patients who were predominantly from urban/semi urban regions of Kerala with high literacy and education levels and where the healthcare systems are well developed(132,133) and the subjects would have an early diagnosis of MCI .Such subjects would be under constant medical care and follow up with constant monitoring and follow up of vascular risk factors and also early identification and treatment of associated neuropsychiatric illness along with other comorbidities which were treated with targeted interventions or pharmacotherapy. It is possible that the MCI non convertors in our subgroup could harbour other etiologies such as VCI (although only a small subset had a past history of stroke) and a longer period of followup could be more relevant given the fact that progressors were older in comparison to non-progressors in our study. This observations reinforces the fact that all MCI

etiologies are not degenerative dementias and early identification of subjects with close follow up might definitely help in preventing progression to dementia as well as improve the quality of life . The recent Lancet 2020 reports indicates a >40% risk reduction with early, mid and late –life interventions to delay the onset of dementia.(134) Our results while not entirely representative of the community could suggest a significant intervention window in MCI and the necessity to have a high specificity for diagnosis of MCI due to AD or other etiologies. It is thus pertinent to determine the etiology of MCI at baseline itself so as to mitigate risk factors for conversion and thus enabling a good intervention time window in MCI. Another possibility for the low conversion rates might be most of our patients might fall in the "worried well" category and they have a tendency of health seeking behaviour and reassurance is also the key, especially if test performances are borderline with regard to the cut off score for that particular age and education status. It is still controversial as to whether one should rely on 2 tests in a cognitive domain with a performance of mean-1 SD to diagnose impairment or impairment on any one test for a given domain with a score of below mean-1.5SD is required. While we relied on the latter performance on 2 tests to diagnose impairment the possibility of over diagnosis remains. Although employing domain specific measures alone may have a role in predicting conversion to dementia, its use in a heterogeneous entity such as MCI irrespective of conversion risk may lead to under-diagnosis. It is also recognized that the best validity for MCI diagnosis is seen when two tests in each domain are employed in composite. Recent evidence from the Framingham cohort demonstrated that only the two-tests approach, i.e. Jak/Bondi criteria (two tests impaired/domain, >1 SD below normal) remained significantly associated with incident dementia on a combined statistical hazard model(135–137).

REFERRAL, MEASUREMENT AND ASSESSMENT BIAS

Our hospital is a quaternary care centre in South India hence there is a possibility that the poor and illiterate persons have delayed access to our centre for memory problems which would result in potential referral bias, but this situation is less likely in Kerala as the literacy rate is very high and healthcare seeking behaviour is high, hence the chance for selection bias is less likely. Many subjects

tend to defer evaluation by simplifying symptoms as ‘aging associated memory impairment’. Only a longitudinal community study can address this limitation.

The neuropsychology measurements were consistent and the same battery of tests were used but different neuropsychologist at various time points have done the assessments, hence minor variations may have crept in which may lead on to a measurement bias / interobserver bias, but the distortion of final results is less likely.

Ascertainment bias also happens when data for a study or an analysis are collected such that some members of the target population are less likely to be included in the final results than others (eg Patients with MCI who did not have complete neuropsychological assessments or did not follow up beyond 1 year were excluded). The resulting study sample becomes biased, as it is systematically different from the target population. Ascertainment bias in our study could be related to sampling bias, selection bias, detection bias, and observer bias. Ascertainment bias can happen when there is more intense surveillance or screening for outcomes among exposed individuals than among unexposed individuals, or differential recording of outcomes.

FUTURE IMPLICATIONS AND DIRECTIONS

These observations tells us that MCI is a window of opportunity for intervention but this needs to be substantiated by future studies which would identify sensitive and specific early longitudinal predictors in MCI and also more robust multicentric data on various subgroups and subtypes of MCI including post mortem pathology studies. Longitudinal case-control hospital-based studies will throw further light on the relevance of clinical factors interlinked to neuropsychological measures and after correction for age. Incorporation of multimodality imaging techniques in conjunction with MRI volumetry such as diffusion tensor imaging, resting state fMRI connectivity, MR spectroscopy arterial spin-labelling based perfusion techniques and when available amyloid-PET imaging may also throw light in to what baseline features can predict conversion or progression in various subtypes of MCI.

CONCLUSION

1. Cumulative conversion rate of 22.2% was noted in our hospital based cohort (of patients with well characterized MCI who were diagnosed based on standard clinical and neuropsychological criteria) similar to as in other studies, however a lower estimate of annualized adjusted conversion rate to dementia of 3.3 per hundred person years was noted (as in community based cohorts).
2. Higher risk of conversion and progression is associated with multidomain MCI at baseline highlighting the importance of subclassifying MCI at baseline .
3. Intra individual change in neuropsychological test scores over time can diagnose dementia better than clinical or imaging parameters.
4. Neuropsychological tests for memory and learning such as Rey Auditory Verbal Learning Test, Wechsler Memory Scale and tests for executive functions as WCST are more specific in predicting conversion to early dementia and are the earliest to show changes.
5. CDR and IADL at baseline can potentially predict risk of progression both within and between the groups , however may not differ between MCI subtypes of amnestic ,dysexecutive and multidomain .
6. FAZEKA changes at baseline correlates with decline in memory tests such as RAVLT, ACE orientation and Recall.
7. Logistic regression based estimations of dementia risk in MCI have a high specificity especially if it takes into consideration age, memory and executive domain test scores.
8. Clinical variables such as vascular risk factors among others, education status and MRI volumetric measures did not differ between convertors to dementia and non-convertors among our cohort of MCI. However the significance of white matter integrity measures which is directly linked to vascular risk factors such as hypertension, diabetes and age needs to be studied in more detail using quantified DTI as Fazeka's score was higher among both convertors and progressors. The significance of atrophy measures such as ERICA is confined to imaging differences between single and multi-domain MCI. However the

qualitative ERICA score at baseline does not seem to be a predictive factor for conversion in MCI

STRENGTHS OF STUDY

The strengths of our study are its prospective follow up limb including a Hospital based cohort of MCI patients, the comprehensive and timely neuropsychological evaluation and the use of imaging predictors in surveying longitudinal cognitive trends in MCI, including a diagnostic workup and a long follow-up. Our results suggest the importance of specific baseline neuropsychological measures of memory (learning, recall, recognition) and executive function measures (especially performance errors on set shifting) to predict MCI at risk of conversion using specific age and neuropsychological test sub scores in a logistic regression based model. The model derived by us can be useful for not only prediction of progression in MCI but also risk of conversion independent of other clinical variables after controlling for the independent effect of age. Other strengths include subsets which have longitudinal neuropsychology, baseline volumetry and qualitative MRI estimates in subsets of patients (especially white matter disease burden) as well as inclusion of different subtypes of MCI (single-domain, multiple domain). We were also able to highlight the neuropsychological differences between convertors and non convertors, progressors and non progressors, amnestic, dysexecutive and multidomain subtypes. The relevance of CDR and IADL measurements at baseline and follow up were also ascertained indicating the necessity to not only measure domain specific test scores but also real-world performance measures in MCI.

Ours is the largest study from India with a cohort of MCI patients and long duration of follow up using a combination of age and neuropsychology predictors.

LIMITATIONS OF STUDY

Our results should be interpreted in light of several limitations-

1. First, this study was carried out in a single centre, thus further large cohort studies are needed to confirm the generalizability of our findings
2. Possible biases related to diagnostic ascertainment and lack of self- referral to memory clinic cannot be excluded. It is possible that a proportion of patients did not seek medical attention for mild memory issues
3. Functional imaging like PET, CSF biomarkers were not done in this study and APO E status could be done only in one fourth of subjects
4. This was a single centre hospital based study hence the sample size was adequate but considering the overall small sample size some statistical assumptions were violated
5. Selection bias and referral bias to hospital based registry. It is possible patients with subjective memory complaints who did not undergo formal neuropsychology assessment a baseline may have been excluded.
6. The neuropsychological tests at various time points were done by different neuropsychologists hence mild interobserver variations may have crept in resulting in measurement bias
7. Although clinical and ADL outcome variables could be evaluated, baseline neuropsychological measures alone were relied upon as the entire cohort did not have identical time points of longitudinal neuropsychological assessment. Referral for neuropsychology is largely clinically driven hence an ascertainment bias is also likely. However DSM IV criteria was relied upon with regard to conversion of the MCI patients all of whom had complete neuropsychological measures available at the baseline visit.

REFERENCES

1. United Nations, Department of Economic and Social Affairs, Population Division. World population ageing 2020 Highlights: living arrangements of older persons. 2020.

2. Petersen RC. MCI as a diagnostic entity. J Intern Med. 2004 Sep;256(3):183–94.

3. Regier DA, Kuhl EA, Kupfer DJ. The DSM-5: Classification and criteria changes. World Psychiatry Off J World Psychiatr Assoc WPA. 2013 Jun;12(2):92–8.

4. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. MCI: clinical characterization and outcome. Arch Neurol. 1999 Mar;56(3):303–8.

5. Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, et al. MCI: Ten Years Later. Arch Neurol [Internet]. 2009 Dec 1 [cited 2021 Jul 10];66(12).

6. Larrieu S, Letenneur L, Orgogozo JM, Fabrigoule C, Amieva H, Le Carret N, et al. Incidence and outcome of MCI in a population-based prospective cohort. Neurology. 2002 Nov 26;59(10):1594–9.

7. Gao Q, Gwee X, Feng L, Nyunt MSZ, Feng L, Collinson SL, et al. MCI Reversion and Progression: Rates and Predictors in Community-Living Older Persons in the Singapore Longitudinal Ageing Studies Cohort. Dement Geriatr Cogn Disord Extra. 2018;8:226–37.

8. Di Carlo A, Lamassa M, Baldereschi M, Inzitari M, Scafato E, Farchi G, et al. CIND and MCI in the Italian elderly: frequency, vascular risk factors, progression to dementia. Neurology. 2007 May 29;68(22):1909–16.

9. Serrano CM, Dillon C, Leis A, Taragano FE, Allegri RF. MCI: risk of dementia according to subtypes. Actas Esp Psiquiatr. 2013 Dec;41(6):330–9.

10. Jang H, Ye BS, Woo S, Kim SW, Chin J, Choi SH, et al. Prediction Model of Conversion to Dementia Risk in Subjects with Amnestic MCI: A Longitudinal, Multi-Center Clinic-Based Study. J Alzheimers Dis JAD. 2017;60(4):1579–87.

11. Roberts RO, Petersen RC. Predictors of early-onset cognitive impairment. Brain. 2014 May;137(5):1280–1.

12. Shim YS, Yang DW, Yoon B, Lee Y, Hong CH, Seo SW, et al. Clinical Predictors for MCI Progression in a Korean Cohort. Dement Neurocognitive Disord. 2016 Sep;15(3):68–74.

13. Chen Y, Denny KG, Harvey D, Farias ST, Mungas D, DeCarli C, et al. Progression from normal cognition to MCI in a diverse clinic-based and community-based elderly cohort. Alzheimers Dement J Alzheimers Assoc. 2017 Apr;13(4):399–405.

14. Farias ST, Mungas D, Reed BR, Harvey D, DeCarli C. Progression of MCI to dementia in clinic- vs community-based cohorts. Arch Neurol. 2009 Sep;66(9):1151–7.

15. Cooper C, Sommerlad A, Lyketsos CG, Livingston G. Modifiable Predictors of Dementia in MCI: A Systematic Review and Meta-Analysis. Am J Psychiatry. 2015 Apr 1;172(4):323–34.

16. Petersen RC. MCI. N Engl J Med. 2011 Jun 9;364(23):2227–34.

17. Graham JE, Rockwood K, Beattie BL, Eastwood R, Gauthier S, Tuokko H, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. Lancet Lond Engl. 1997 Jun 21;349(9068):1793–6.

18. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Kokmen E, Tangelos EG. Aging, memory, and MCI. Int Psychogeriatr. 1997;9 Suppl 1:65–9.

19. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund L-O, et al. MCI--beyond controversies, towards a consensus: report of the International Working Group on MCI. J Intern Med. 2004 Sep;256(3):240–6.

20. Gauthier S, Reisberg B, Zaudig M, Petersen RC, Ritchie K, Broich K, et al. MCI. Lancet Lond Engl. 2006 Apr 15;367(9518):1262–70.

21. Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of MCI due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement J Alzheimers Assoc. 2011 May;7(3):270–9.

22. Ganguli M, Dodge HH, Shen C, DeKosky ST. MCI, amnestic type: an epidemiologic study. Neurology. 2004 Jul 13;63(1):115–21.

23. DeCarli C. MCI: prevalence, prognosis, aetiology, and treatment. Lancet Neurol. 2003 Jan;2(1):15–21.

24. Unexpectedly High Rates of MCI Could Overwhelm Future Health Resources [Internet]. [cited 2021 Jul 11]. Available from: https://www.medscape.com/viewarticle/578715

25. Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, et al. Practice guideline update summary: MCI: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018 Jan 16;90(3):126–35.

26. Das SK, Bose P, Biswas A, Dutt A, Banerjee TK, Hazra AM, et al. An epidemiologic study of MCI in Kolkata, India. Neurology. 2007 Jun 5;68(23):2019–26.

27. Pinto C, Subramanyam AA. MCI: The dilemma. Indian J Psychiatry. 2009 Jan;51(Suppl1):S44–51.

28. Petersen RC, Negash S. MCI : an overview. CNS Spectr. 2008 Jan;13(1):45–53.

29. Taragano F, Allegri R, Lyketsos C. Mild behavioral impairment: A prodromal stage of dementia. Dement Neuropsychol. 2008 Dec 1;2:256–60.

30. Roberts RO, Knopman DS, Mielke MM, Cha RH, Pankratz VS, Christianson TJH, et al. Higher risk of progression to dementia in MCI cases who revert to normal. Neurology. 2014 Jan 28;82(4):317–25.

31. Vassilaki M, Aakre JA, Cha RH, Kremers WK, St Sauver JL, Mielke MM, et al. Multimorbidity and Risk of MCI. J Am Geriatr Soc. 2015 Sep;63(9):1783–90.

32. Sanford AM. Mild cognitive impairment . Clin Geriatr Med. 2017 Aug;33(3):325–37.

33. Mitchell AJ, Shiri-Feshki M. Rate of progression of MCI to dementia--meta-analysis of 41 robust inception cohort studies. Acta Psychiatr Scand. 2009 Apr;119(4):252–65.

34. Forlenza OV, Diniz BS, Stella F, Teixeira AL, Gattaz WF. MCI. Part 1: clinical characteristics and predictors of dementia. Rev Bras Psiquiatr Sao Paulo Braz 1999. 2013 Jun;35(2):178–85.

35. Zhou B, Zhao Q. Shanghai Cohort Study on MCI: Study Desig n and Baseline Characteristics. J Alzheimers Dis Park [Internet]. 2016 [cited 2021 Jun 27];06(02).

36. Atti AR, Valente S, Iodice A, Caramella I, Ferrari B, Albert U, et al. Metabolic Syndrome, MCI, and Dementia: A Meta-Analysis of Longitudinal Studies. Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry. 2019 Jun;27(6):625–37.

37. Pal K, Mukadam N, Petersen I, Cooper C. MCI and progression to dementia in people with diabetes, prediabetes and metabolic syndrome: a systematic review and meta-analysis. Soc Psychiatry Psychiatr Epidemiol. 2018 Nov;53(11):1149–60.

38. Hu M, Shu X, Wu X, Chen F, Hu H, Zhang J, et al. Neuropsychiatric symptoms as prognostic makers for the elderly with MCI : a meta-analysis. J Affect Disord. 2020 Jun 15;271:185–92.

39. Roberto N, Portella MJ, Marquié M, Alegret M, Hernández I, Mauleón A, et al. Neuropsychiatric profiles and conversion to dementia in MCI , a latent class analysis. Sci Rep. 2021 Mar 19;11(1):6448.

40. Palmer K, Berger AK, Monastero R, Winblad B, Bäckman L, Fratiglioni L. Predictors of progression from MCI to Alzheimer disease. Neurology. 2007 May 8;68(19):1596–602.

41. Ramakers IHGB, Visser PJ, Aalten P, Kester A, Jolles J, Verhey FRJ. Affective symptoms as predictors of Alzheimer's disease in subjects with MCI : a 10-year follow-up study. Psychol Med. 2010 Jul;40(7):1193–201.

42. Visser PJ, Verhey FRJ. MCI as predictor for Alzheimer's disease in clinical practice: effect of age and diagnostic criteria. Psychol Med. 2008 Jan;38(1):113–22.

43. Solfrizzi V, Scafato E, Capurso C, D'Introno A, Colacicco AM, Frisardi V, et al. Metabolic syndrome, MCI , and progression to dementia. The Italian Longitudinal Study on Aging. Neurobiol Aging. 2011 Nov;32(11):1932–41.

44. Ng TP, Feng L, Nyunt MSZ, Feng L, Gao Q, Lim ML, et al. Metabolic Syndrome and the Risk of MCI and Progression to Dementia: Follow-up of the Singapore Longitudinal Ageing Study Cohort. JAMA Neurol. 2016 Apr;73(4):456–63.

45. Chen P, Ratcliff G, Belle SH, Cauley JA, DeKosky ST, Ganguli M. Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented. Neurology. 2000 Dec 26;55(12):1847–53.

46. Ritchie K, Artero S, Touchon J. Classification criteria for MCI: a population-based validation study. Neurology. 2001 Jan 9;56(1):37–42.

47. Bäckman L, Small BJ, Fratiglioni L. Stability of the preclinical episodic memory deficit in Alzheimer's disease. Brain J Neurol. 2001 Jan;124(Pt 1):96–102.

48. García-Herranz S, Díaz-Mardomingo MC, Peraita H. Neuropsychological predictors of conversion to probable Alzheimer disease in elderly with MCI . J Neuropsychol. 2016 Sep;10(2):239–55.

49. Thomas KR, Eppig J, Edmonds EC, Jacobs DM, Libon DJ, Au R, et al. Word-list intrusion errors predict progression to MCI. Neuropsychology. 2018 Feb;32(2):235–45.

50. Palmer K, Bäckman L, Winblad B, Fratiglioni L. MCI in the general population: occurrence and progression to Alzheimer disease. Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry. 2008 Jul;16(7):603–11.

51. Rindge M, Moncrief G, Daniel M. A-19Neuropsychological and Psychological Predictors of Conversion from MCI to Alzheimer's Dementia. Arch Clin Neuropsychol. 2017 Sep 1;32(6):667–765.

52. Daly E, Zaitchik D, Copeland M, Schmahmann J, Gunther J, Albert M. Predicting conversion to Alzheimer disease using standardized clinical information. Arch Neurol. 2000 May;57(5):675–80.

53. Lopez ME, Turrero A, Cuesta P, Lopez-Sanz D, Bruna R, Marcos A, et al. Searching for Primary Predictors of Conversion from MCI to Alzheimer's Disease: A Multivariate Follow-Up Study. :11.

54. Tabert MH, Manly JJ, Liu X, Pelton GH, Rosenblum S, Jacobs M, et al. Neuropsychological prediction of conversion to Alzheimer disease in patients with MCI . Arch Gen Psychiatry. 2006 Aug;63(8):916–24.

55. Clinical Conversion or Reversion of MCI in Community versus Hospital Based Studies: GDEMCIS (Gwangju Dementia and MCI Study) and CREDOS (Clinical Research Center for Dementia of South Korea)

56. Xie H, Mayo N, Koski L. Predictors of future cognitive decline in persons with MCI. Dement Geriatr Cogn Disord. 2011;32(5):308–17.

57. Edith L, Marina C, Luis C, Bruno B, Marcelo S. Longitudinal Follow-Up of a Population with MCI: Predictive Value of the MIS Test with Delayed Recall for Progression to Dementia. Adv Alzheimers Dis. 2018 Nov 15;7(4):183–96.

58. Marcos A, Gil P, Barabash A, Rodriguez R, Encinas M, Fernández C, et al. Neuropsychological markers of progression from MCI to Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2006 Jul;21(3):189–96.

59. Julayanont P, Brousseau M, Chertkow H, Phillips N, Nasreddine ZS. Montreal Cognitive Assessment Memory Index Score (MoCA-MIS) as a predictor of conversion from MCI to Alzheimer's disease. J Am Geriatr Soc. 2014 Apr;62(4):679–84.

60. Kim H-G, Jung H-S, Koo B-H, Cheon E-J. Neuropsychological predictors of cognitive deterioration in non-demented individuals. Cognit Neuropsychiatry. 2020 Mar;25(2):99–112.

61. Yun S-H, Jo S-H, Jung H-S, Koo B-H, Kim H-G. Characteristics of Individuals Who Converted to Dementia during a 5-Year Follow-Up. Dement Geriatr Cogn Disord. 2020;49(5):503–10.

62. Tian J, Bucks RS, Haworth J, Wilcock G. Neuropsychological prediction of conversion to dementia from questionable dementia: statistically significant but not yet clinically useful. J Neurol Neurosurg Psychiatry. 2003 Apr;74(4):433–8.

63. Chapman RM, Mapstone M, McCrary JW, Gardner MN, Porsteinsson A, Sandoval TC, et al. Predicting conversion from MCI to Alzheimer's disease using neuropsychological tests and multivariate methods. J Clin Exp Neuropsychol. 2011 Feb;33(2):187–99.

64. Chasles M-J, Tremblay A, Escudier F, Lajeunesse A, Benoit S, Langlois R, et al. An Examination of Semantic Impairment in Amnestic MCI and AD: What Can We Learn From Verbal Fluency? Arch Clin Neuropsychol Off J Natl Acad Neuropsychol. 2019 Jan 24;35(1):22–30.

65. Nesset M, Kersten H, Ulstein ID. Brief Tests such as the Clock Drawing Test or Cognistat Can Be Useful Predictors of Conversion from MCI to Dementia in the Clinical Assessment of Outpatients. Dement Geriatr Cogn Disord Extra. 2014 May;4(2):263–70.

66. Tierney MC, Szalai JP, Snow WG, Fisher RH, Nores A, Nadon G, et al. Prediction of probable Alzheimer's disease in memory-impaired patients: A prospective longitudinal study. Neurology. 1996 Mar;46(3):661–5.

67. Belleville S, Fouquet C, Hudon C, Zomahoun HTV, Croteau J, Consortium for the Early Identification of Alzheimer's disease-Quebec. Neuropsychological Measures that Predict Progression from MCI to Alzheimer's type dementia in Older Adults: a Systematic Review and Meta-Analysis. Neuropsychol Rev. 2017 Dec;27(4):328–53.

68. Joubert S, Gardy L, Didic M, Rouleau I, Barbeau EJ. A Meta-Analysis of Semantic Memory in MCI . Neuropsychol Rev. 2021 Jun;31(2):221–32.

69. Amieva H, Letenneur L, Dartigues J-F, Rouch-Leroyer I, Sourgen C, D'Alchée-Birée F, et al. Annual Rate and Predictors of Conversion to Dementia in Subjects Presenting MCI Criteria Defined according to a Population-Based Study. Dement Geriatr Cogn Disord. 2004;18(1):87–93.

70. Boyle PA, Wilson RS, Aggarwal NT, Tang Y, Bennett DA. MCI : risk of Alzheimer disease and rate of cognitive decline. Neurology. 2006 Aug 8;67(3):441–5.

71. Fleisher AS, Sowell BB, Taylor C, Gamst AC, Petersen RC, Thal LJ, et al. Clinical predictors of progression to Alzheimer disease in amnestic MCI . Neurology. 2007 May 8;68(19):1588–95.

72. Ding D, Zhao Q, Guo Q, Liang X, Luo J, Yu L, et al. Progression and predictors of MCI in Chinese elderly: A prospective follow-up in the Shanghai Aging Study. Alzheimers Dement Amst Neth. 2016;4:28–36.

73. Jack CR, Barkhof F, Bernstein MA, Cantillon M, Cole PE, Decarli C, et al. Steps to standardization and validation of hippocampal volumetry as a biomarker in clinical trials and diagnostic criterion for Alzheimer's disease. Alzheimers Dement J Alzheimers Assoc. 2011 Jul;7(4):474-485.e4.

74. Jack CR, Lowe VJ, Weigand SD, Wiste HJ, Senjem ML, Knopman DS, et al. Serial PIB and MRI in normal, MCI and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. Brain J Neurol. 2009 May;132(Pt 5):1355–65.

75. Staekenborg SS, Koedam ELGE, Henneman WJP, Stokman P, Barkhof F, Scheltens P, et al. Progression of MCI to Dementia. Stroke. 2009 Apr 1;40(4):1269–74.

76. Holz MR, Kochhann R, Ferreira P, Tarrasconi M, Chaves MLF, Fonseca RP. Cognitive performance in patients with MCI and Alzheimer's disease with white matter hyperintensities: An exploratory analysis. Dement Neuropsychol. 2017;11(4):426–33.

77. Divya KP, Menon RN, Varma RP, Sylaja PN, Thomas B, Kesavadas C, et al. Post-stroke cognitive impairment - A cross-sectional comparison study between MCI of vascular and non-vascular etiology. J Neurol Sci. 2017 Jan 15;372:356–62.

78. Karas G, Sluimer J, Goekoop R, van der Flier W, Rombouts S a. RB, Vrenken H, et al. Amnestic MCI : structural MR imaging findings predictive of conversion to Alzheimer disease. AJNR Am J Neuroradiol. 2008 May;29(5):944–9.

79. Henneman WJP, Sluimer JD, Barnes J, van der Flier WM, Sluimer IC, Fox NC, et al. Hippocampal atrophy rates in Alzheimer disease: added value over whole brain volume measures. Neurology. 2009 Mar 17;72(11):999–1007.

80. Devanand DP, Pradhaban G, Liu X, Khandji A, De Santi S, Segal S, et al. Hippocampal and entorhinal atrophy in MCI: prediction of Alzheimer disease. Neurology. 2007 Mar 13;68(11):828–36.

81. Fleisher AS, Sun S, Taylor C, Ward CP, Gamst AC, Petersen RC, et al. Volumetric MRI vs clinical predictors of Alzheimer disease in MCI. Neurology. 2008 Jan 15;70(3):191–9.

82. Korolev IO, Symonds LL, Bozoki AC, Alzheimer's Disease Neuroimaging Initiative. Predicting Progression from MCI to Alzheimer's Dementia Using Clinical, MRI, and Plasma Biomarkers via Probabilistic Pattern Classification. PloS One. 2016;11(2):e0138866.

83. Landau SM, Harvey D, Madison CM, Reiman EM, Foster NL, Aisen PS, et al. Comparing predictors of conversion and decline in MCI . Neurology. 2010 Jul 20;75(3):230–8.

84. Chételat G, Desgranges B, de la Sayette V, Viader F, Eustache F, Baron J-C. MCI : Can FDG-PET predict who is to rapidly convert to Alzheimer's disease? Neurology. 2003 Apr 22;60(8):1374–7.

85. Drzezga A, Grimmer T, Riemenschneider M, Lautenschlager N, Siebner H, Alexopoulus P, et al. Prediction of individual clinical outcome in MCI by means of genetic assessment and (18)F-FDG PET. J Nucl Med Off Publ Soc Nucl Med. 2005 Oct;46(10):1625–32.

86. Wolk DA, Price JC, Saxton JA, Snitz BE, James JA, Lopez OL, et al. Amyloid imaging in MCI subtypes. Ann Neurol. 2009 May;65(5):557–68.

87. De Meyer G, Shapiro F, Vanderstichele H, Vanmechelen E, Engelborghs S, De Deyn PP, et al. Diagnosis-independent Alzheimer disease biomarker signature in cognitively normal elderly people. Arch Neurol. 2010 Aug;67(8):949–56.

88. Mattsson N, Zetterberg H, Hansson O, Andreasen N, Parnetti L, Jonsson M, et al. CSF biomarkers and incipient Alzheimer disease in patients with MCI. JAMA. 2009 Jul 22;302(4):385–93.

89. Hansson O, Zetterberg H, Buchhave P, Londos E, Blennow K, Minthon L. Association between CSF biomarkers and incipient Alzheimer's disease in patients with MCI : a follow-up study. Lancet Neurol. 2006 Mar;5(3):228–34.

90. Ryan NS, Rossor MN. Correlating familial Alzheimer's disease gene mutations with clinical phenotype. Biomark Med. 2010 Feb;4(1):99–112.

91. Chu Y, Cochran EJ, Bennett DA, Mufson EJ, Kordower JH. Down-regulation of trkA mRNA within nucleus basalis neurons in individuals with MCI and Alzheimer's disease. J Comp Neurol. 2001 Aug 27;437(3):296–307.

92. DeKosky ST, Ikonomovic MD, Styren SD, Beckett L, Wisniewski S, Bennett DA, et al. Upregulation of choline acetyltransferase activity in hippocampus and frontal cortex of elderly subjects with MCI . Ann Neurol. 2002 Feb;51(2):145–55.

93. MCI – A hospital-based prospective study Reddy Mukku SS, Varghese M, Bharath S, Kumar KJ - J Geriatr Ment Health [Internet]. [cited 2021 Jul 25].

94. Bharath S, Sadanand S, Kumar KJ, Balachandar R, Joshi H, Varghese M. Clinical and neuropsychological profile of persons with MCI, a hospital based study from a lower and middle income country. Asian J Psychiatry. 2017 Dec;30:185–9.

95. Alladi S, Shailaja M, Mridula KR, Haritha CA, Kavitha N, Khan SA, et al. MCI: clinical and imaging profile in a memory clinic setting in India. Dement Geriatr Cogn Disord. 2014;37(1–2):113–24.

96. Sheelakumari R, Kesavadas C, Lekha VS, Justus S, Sarma PS, Menon R. Structural correlates of MCI: A clinicovolumetric study. Neurol India. 2018 Apr;66(2):370–6.

97. Sheelakumari R, Sarma SP, Kesavadas C, Thomas B, Sasi D, Sarath LV, et al. Multimodality Neuroimaging in MCI: A Cross-sectional Comparison Study. Ann Indian Acad Neurol. 2018 Jun;21(2):133–9.

98. Thomas B, Sheelakumari R, Kannath S, Sarma S, Menon RN. Regional Cerebral Blood Flow in the Posterior Cingulate and Precuneus and the Entorhinal Cortical Atrophy

Score Differentiate MCI and Dementia Due to Alzheimer Disease. AJNR Am J Neuroradiol. 2019 Oct;40(10):1658–64.

99. Menon RN, Varghese F, Paplikar A, Mekala S, Alladi S, Sharma M, et al. Validation of Indian Council of Medical Research Neurocognitive Tool Box in Diagnosis of MCI in India: Lessons from a Harmonization Process in a Linguistically Diverse Society. Dement Geriatr Cogn Disord. 2020;49(4):355–64.

100. Menon R, Lekha V, Justus S, Sarma PS, Mathuranath P. A pilot study on utility of Malayalam version of Addenbrooke's Cognitive Examination in detection of amnestic MCI: A critical insight into utility of learning and recall measures. Ann Indian Acad Neurol. 2014;17(4):420–5.

101. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement J Alzheimers Assoc. 2011 May;7(3):263–9.

102. Pantoni L, Inzitari D. Hachinski's ischemic score and the diagnosis of vascular dementia: a review. Ital J Neurol Sci. 1993 Oct;14(7):539–46.

103. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011 Sep;134(9):2456–77.

104. McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor J-P, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology. 2017 Jul 4;89(1):88–100.

105. van Straaten ECW, Fazekas F, Rostrup E, Scheltens P, Schmidt R, Pantoni L, et al. Impact of White Matter Hyperintensities Scoring Method on Correlations With Clinical Data. Stroke. 2006 Mar 1;37(3):836–40.

106. Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren M, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. Stroke. 2001 Jun;32(6):1318–22.

107. Enkirch SJ, Traschütz A, Müller A, Widmann CN, Gielen GH, Heneka MT, et al. The ERICA Score: An MR Imaging-based Visual Scoring System for the Assessment of Entorhinal Cortex Atrophy in Alzheimer Disease. Radiology. 2018 Jul;288(1):226–333.

108. Cerebral Microbleeds: Imaging and Clinical Significance | Radiology [Internet]. [cited 2021 Aug 3].

109. Bean J. Rey Auditory Verbal Learning Test, Rey AVLT. In: Kreutzer JS, DeLuca J, Caplan B, editors. Encyclopedia of Clinical Neuropsychology [Internet]. New York, NY: Springer; 2011 [cited 2021 Aug 3]. p. 2174–5.

110. Chlebowski C. Wechsler Memory Scale All Versions. In: Kreutzer JS, DeLuca J, Caplan B, editors. Encyclopedia of Clinical Neuropsychology [Internet]. New York, NY: Springer; 2011 [cited 2021 Aug 3]. p. 2688–90.

111. Kolakowsky-Hayner SA. Wisconsin Card Sorting Test. In: Kreutzer JS, DeLuca J, Caplan B, editors. Encyclopedia of Clinical Neuropsychology [Internet]. New York, NY: Springer; 2011 [cited 2021 Aug 3]. p. 2719–20.

112. Snaith RP. The Hospital Anxiety And Depression Scale. Health Qual Life Outcomes. 2003 Aug 1;1:29.

113. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. The Gerontologist. 1969;9(3):179–86.

114. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology. 1993 Nov;43(11):2412–4.

115. Devanand DP, Pelton GH, Zamora D, Liu X, Tabert MH, Goodkind M, et al. Predictive utility of apolipoprotein E genotype for Alzheimer disease in outpatients with MCI. Arch Neurol. 2005 Jun;62(6):975–80.

116. Sarma PS, Sadanandan R, Thulaseedharan JV, Soman B, Srinivasan K, Varma RP, et al. Prevalence of risk factors of non-communicable diseases in Kerala, India: results of a cross-sectional study. BMJ Open. 2019 Nov 10;9(11):e027880.

117. Non Communicable Diseases (NCDs) – dhs [Internet]. [cited 2021 Aug 3]. Available from: https://dhs.kerala.gov.in/non-communicable-diseases-ncds/

118. Hulette CM, Welsh-Bohmer KA, Murray MG, Saunders AM, Mash DC, McIntyre LM. Neuropathological and neuropsychological changes in 'normal' aging: evidence for preclinical Alzheimer disease in cognitively normal individuals. J Neuropathol Exp Neurol. 1998 Dec;57(12):1168–74.

119. Fischer P, Jungwirth S, Zehetmayer S, Weissgram S, Hoenigschnabl S, Gelpi E, et al. Conversion from subtypes of MCI to Alzheimer dementia. Neurology. 2007 Jan 23;68(4):288–91.

120. Hamilton CA, Matthews FE, Donaghy PC, Taylor J-P, O'Brien JT, Barnett N, et al. Progression to Dementia in MCI with Lewy Bodies or Alzheimer Disease. Neurology. 2021 Jun 1;96(22):e2685–93.

121. de Mendonça A, Ribeiro F, Guerreiro M, Garcia C. Frontotemporal MCI. J Alzheimers Dis JAD. 2004 Feb;6(1):1–9.

122. Hallam BJ, Silverberg ND, LaMarre AK, Mackenzie IRA, Feldman HH. Clinical Presentation of Prodromal Frontotemporal Dementia. Am J Alzheimers Dis Dementias®. 2008 Dec 1;22(6):456–67.

123. Mez J, Cosentino S, Brickman AM, Huey ED, Manly JJ, Mayeux R. Dysexecutive versus amnestic Alzheimer's disease subgroups: Analysis of demographic, genetic, and vascular factors. Alzheimer Dis Assoc Disord. 2013;27(3):218–25.

124. Preclinical, Prodromal, and Dementia Stages of Alzheimer's Disease [Internet]. Practical Neurology. Bryn Mawr Communications; [cited 2021 Aug 3].

125. Lengthy Prodromal Phase of MCI and Alzheimer's Disease [Internet]. Medscape. [cited 2021 Aug 3].

126. Reinvang I, Grambaite R, Espeseth T. Executive Dysfunction in MCI: Subtype or Early Symptom. Int J Alzheimerx2019s Dis. 2012 May 30;2012:e936272.

127. Karantzoulis S, Galvin JE. Distinguishing Alzheimer's disease from other major forms of dementia. Expert Rev Neurother. 2011 Nov;11(11):1579–91.

128. El Sankari S, Gondry-Jouet C, Fichten A, Godefroy O, Serot JM, Deramond H, et al. Cerebrospinal fluid and blood flow in MCI and Alzheimer's disease: a differential diagnosis from idiopathic normal pressure hydrocephalus. Fluids Barriers CNS. 2011 Feb 17;8(1):12.

129. Weinstein G, Beiser AS, DeCarli C, Au R, Wolf PA, Seshadri S. Brain Imaging and Cognitive Predictors of Stroke and Alzheimer Disease in the Framingham Heart Study. Stroke J Cereb Circ. 2013 Oct;44(10):2787–94.

130. Raghavan S, Reid RI, Przybelski SA, Lesnick TG, Graff-Radford J, Schwarz CG, et al. Diffusion models reveal white matter microstructural changes with ageing, pathology and cognition. Brain Commun. 2021 May 19;3(2):fcab106.

131. Talamonti D, Koscik R, Johnson S, Bruno D. Predicting Early MCI with Free Recall: The Primacy of Primacy. Arch Clin Neuropsychol. 2020 Feb 20;35(2):133–42.

132. National Family Health Survey [Internet]. [cited 2021 Aug 4]. Available from: http://rchiips.org/nfhs/factsheet_nfhs-4.shtml

133. Census of India: Sample Registration [Internet]. [cited 2021 Aug 4]. Available from: https://censusindia.gov.in/vital_statistics/srs/sample_registration_system.aspx

134. Jia L, Du Y, Chu L, Zhang Z, Li F, Lyu D, et al. Prevalence, risk factors, and management of dementia and MCI in adults aged 60 years or older in China: a cross-sectional study. Lancet Public Health. 2020 Dec 1;5(12):e661–71.

135. Jak AJ, Bondi MW, Delano-Wood L, Wierenga C, Corey-Bloom J, Salmon DP, et al. Quantification of five neuropsychological approaches to defining MCI . Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry. 2009 May;17(5):368–75.

136. Jak AJ, Preis SR, Beiser AS, Seshadri S, Wolf PA, Bondi MW, et al. Neuropsychological Criteria for MCI and Dementia Risk in the Framingham Heart Study. J Int Neuropsychol Soc JINS. 2016 Oct;22(9):937–43.

137. Wong CG, Thomas KR, Edmonds EC, Weigand AJ, Bangen KJ, Eppig JS, et al. Neuropsychological Criteria for MCI in the Framingham Heart Study's Old-Old. Dement Geriatr Cogn Disord. 2018;46(5–6):253–65.

Plagiarism Checker X - Report

Originality Assessment

Overall Similarity: **13%**

Date: Aug 1, 2021

Statistics: 2194 words Plagiarized / 16819 Total words

Remarks: Low similarity detected, check your supervisor if changes are required.

APPENDICES -1-MCI DEFINITION (PETERSEN ET AL)

PETERSEN'S CRITERIA FOR DEMENTIA & SUBTYPING

NAME:	_____	HOSP. NO.:	_____
D.O.B.:	_____	TESTING DATE(S):	_____
AGE:	_____	EDUCATION (YEARS):	_____
Handedness:	_____	Tested in (Language):	_____
Gender:	PTNO :	Urban / Rural:	

Petersen's Criteria for MCI (fulfilled? Yes 1, no 0) ☐

1) presence of subjective memory complaints	☐
2) preserved general intellectual functions as estimated by performance on a vocabulary test	☐
3) demonstration of memory impairment by cognitive testing and no impairment on tests of other cognitive functions	☐
4) intact ability to perform activities of daily living	☐
5) absence of dementia	☐

APPENDICES -2 - DEMENTIA (DSM-4 CRITERION)

A1 - Memory impairment

A2 - One of the following

-Aphasia

-Apraxia

-Agnosia

-Disturbance in executive function

The cognitive deficits in A1 and A2 each cause significant impairment in social or occupational function and represent a significant decline from previous level of functioning

The cognitive deficits do not occur exclusively during the course of delirium.

APPENDICES -3 -ALZHEIMER's DEMENTIA (Mc KHANN et al 2011)

CRITERIA FOR CLINICAL DIAGNOSIS OF AD

NAME:		HOSP. NO.:	
D.O.B.:		TESTING DATE(S):	
AGE:		EDUCATION (YEARS):	
Handedness:		Tested in (Language):	
Gender:		Urban / Rural:	Rater:

CRITERIA FOR CLINICAL DIAGNOSIS OF AD: (No=0; Probable=1; Possible=2) ☐

For the following use CODE: yes = 1 & no = 0

1	The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:		☐
	A	dementia established by clinical examination and documented	☐
	B	deficits in two or more areas of cognition	☐
	C	Progressive worsening of memory and other cognitive fns	☐
	D	no disturbances of consciousness	☐
	E	Onset between ages 40 and 90, most often after age 65	☐
	F	absence of systemic disorders or other brain diseases	☐
2	The diagnosis of PROBABLE Alzheimer's disease is supported by		☐
	A	Progressive deterioration of specific cognitive functions such as language,motorskills	☐
		and perception	☐
	B	Impaired activities of daily living and altered patterns of behaviour	☐
	C	Family history of similar disorders, particularly if confirmed neuropathologically; and	☐
	D	Laboratory results of:	
		1 normal lubar puncture as evaluated by standard techniques	☐
		2 normal pattern or nonspecific changes in EEG	☐
		3 evidence of cerebral atrophy on CT with progression documented	☐
3	Other clinical features with the diagnosis of PROBABLE AD after exclusion		☐
	A	plateaus in the course of progression of the illness	☐
	B	symptoms of depression,insomnia,incontinence,delusions,	☐
		illusions,hallucinations,catastrophic outbursts,sexual disorders,	
		weight loss;increased muscle tone, myoclonus,or gait disorder	
	C	seizures in advanced age	☐
	D	CT normal for age	☐
4	Features that make the diagnosis of PROBABLE AD uncertain or unlikely		☐
	A	sudden, apoplectic onset	☐
	B	focal neuro findings such as hemiparesis, sensory loss, visual	☐
		field deficits and incoordination early	
	C	seizures or gait disturbances at the onset or very early	☐
5	Clinical diagnosis of POSSIBLE AD		☐
	A	made on the basis of the dementia syndrome, in the absence of	☐
		other neurologic, psychiatric, or systemic disorders sufficient to	
		cause dementia, and in the presence of variations in the onset, in	
		the presentation, or in the clinical course	
	B	may be made in the presence of a second systemic or brain	☐
		disorder sufficient to produce dementia, which is not considered	
		to be the cause of the dementia	
	C	Should be used in research studies when a single, gradually	☐
		progressive severe cognitive deficit is identified in the absence of	
		other identifiable cause.	

AD ☐

Non AD ☐

APPENDICES -4-CLINICAL PROFORMA

NAME: _____	Pt No.: _____
D.O.B.: _____	TESTING DATE(S): _____
Age / Gender: _____	EDUCATION (YEARS): _____
Handed: _____	Tested in (Language): _____
Diagno: _____	Hosp No.: _____
Urb/Rur:	Tested By:

Participation		(yes 1; no 0)	
if not participating then main reason for not participating			
dementia too advanced to participate		(yes 1; no 0)	
Other medical problems prevent participation: Stroke/ Parkinsonism/ General debility		(yes 1; no 0)	
participant available but not interested		(yes 1; no 0)	
participant is not alive		(yes 1; no 0)	
participant is not available at the given address		(yes 1; no 0)	
Present history			
Memory difficult not present earlier or impairing daily activity		(yes 1; no 0)	
Forgets recent events	(അടുത്തകാലത്ത് സംഭവിച്ച കാര്യങ്ങൾ മറന്നു പോവുക.)		
Forgets to pass on telephone messages	(ടെലിഫോൺ സന്ദേശങ്ങൾ പറയാൻ മറന്നു പോവുക.)		
Forgets names of people, money matters etc.	(പണസംബന്ധമായ കാര്യങ്ങളും, ആളുകളുടെയും പേര് മറന്നു പോവുക.)		
Language problems		(yes 1; no 0)	
Word finding difficulty	(വാക്കുകൾ കിട്ടുവാനുള്ള ബുദ്ധിമുട്ട്.)		
Comprehension difficulty	(കാര്യങ്ങൾ മനസ്സിലാക്കുവാനുള്ള ബുദ്ധിമുട്ട്.)		
Circumlocutory speech, paraphasias	(കാര്യങ്ങൾ വളച്ചുകെട്ടി പറയുക.)		
Attention/Concentration difficulty		(yes 1; no 0)	
cannot follow conversations	(സംഭാഷണങ്ങൾ മനസ്സിലാവാതിരിക്കുക.)		
Needs repetition to understand instructions	(നിർദ്ദേശങ്ങൾ വീണ്ടും വീണ്ടും ആവർത്തിക്കേണ്ടി വരിക.)		
Tends to talk out of context	(ചർച്ചാവിഷയങ്ങളിൽ നിന്നും വേറിട്ടുള്ള സംസാരം.)		
Visuospatial orientation		(yes 1; no 0)	
Getting lost in familiar ways outside house	(വീടിനു പുറത്ത് പരിചിതമായ വഴികൾ തെറ്റാറുണ്ട്.)		
Restrict to known path: fear of getting lost	(വഴിതെറ്റും എന്ന ഭയത്താൽ പരിചിതമായ വഴികളിലൂടെ മാത്രം സഞ്ചാരം)		
Looses way inside the house	(വീടിനകത്തു വഴി തെറ്റുക.)		
Dysexecutive symptoms		(yes 1; no 0)	
recent change in behaviour, temperament	(സ്വഭാവത്തിൽ അടുത്തകാലത്ത് കാര്യമായ മാറ്റം വരിക, ദേഷ്യപ്പെടുക.)		
Persevaration- verbal or motor	(ആവർത്തനം- സംസാരം, പ്രവർത്തികൾ)		
impaired social judgment, insight,	(സാമൂഹിക തീരുമാനങ്ങളെടുക്കുന്നതിലും, ഉൾക്കാഴ്ചയിലുമുള്ള കുറവ്.)		
Other cognitive symptoms		(yes 1; no 0)	
mistakes in calculation- shopping/banking	(കണക്കുകൾ കൂട്ടുന്നതിൽ തെറ്റു സംഭവിക്കുക-കടയിൽ,ബാങ്കുസംബന്ധമായ)		
mistakes in dressing: needs rectification	(വസ്ത്രധാരണത്തിൽ വരുന്ന പിഴവുകൾ തിരുത്തേണ്ടി വരിക.)		
misidentifying relatives by face	(ബന്ധുക്കളെ കണ്ടാൽ തിരിച്ചറിയാതിരിക്കുക)		
Neuropsychiatric Symptoms		(yes 1; no 0)	
Paranoid ideations	(സംശയരോഗം)		
Hallucinations: visual or verbal	(മതിഭ്രമം - കാഴ്ചയിലും, സംസാരത്തിലും)		
Delusions	(മിഥ്യാധാരണ)		
Depression	(വിഷാദം)		
Mood (sadness)	മനോഭാവം (ദുഃഖം)		
Loss of Interest	(താത്പര്യമില്ലായ്മ)		
Death wish (suicidal Ideation)	മരണം ആഗ്രഹിക്കുക (ആത്മഹത്യാ പ്രവണത)		
Worthlessness/hopelessness	(തന്നെ കൊണ്ടൊരു പ്രയോജനവുമില്ലായെന്ന തോന്നൽ/പ്രതീക്ഷയില്ലായ്മ)		
Anxiety or agitation	(ഉത്കണ്ഠം/മനഃക്ഷോഭം)		
Illusions	(വ്യാമോഹം)		
Chronic headaches (in past 1 year)	(ദീർഘകാലമായിട്ടുള്ള തലവേദന)	(yes 1; no 0)	
Incontinence	(രോഗി അറിയാതെയുള്ള മലമൂത്രവിസർജ്ജനം)	(yes 1; no 0)	
Gait abnormality	(നടക്കുന്നതിൽ എന്തെങ്കിലും അസ്വാഭാവികത)	(yes 1; no 0)	
Falls (in past 1 year)	(വീഴ്ച്ച)	(yes 1; no 0)	

Clinical Proforma

NAME: _____ Pt No.: _____

D.O.B.: _____ TESTING DATE(S). _____

Age / Gender: _____ EDUCATION (YEARS): _____

Handed: _____ Tested in (Language): _____

Diagno: _____ Hosp No.: _____

Urb/Rur: Tested By:

Risk Factors	Present or not (no 0; definite 1; possible 2)	1st Onset age	Quantity	Stopped (yrs. ago)	Under regular M
DM (പ്രമേഹം)					
HT (രക്തസമ്മർദ്ദം)					
Brain Fever/ Meningitis/ Encephalitis (മസ്തിഷ്ക ജ്വരം)					
Psychiatric Illness (മാനസിക രോഗം)					
Heart Attacks (ഹൃദയാഘാതം)					
Seizures / Epilepsy (ജന്നി/അപസ്മാരം)					
Tobacoo Use (പുകയിലയുടെ ഉപയോഗം)					
Cigarretts (nos./day)					
Beedis (nos./day)					
Tobacoo Chewing (times/day)					
Snuff (times/day)					
Alcohol (മദ്യപാനം)					
Frequency (upto 3 times/month =1;4-6 times/month =2; >7 times/month=3)					
Quantity (small =1; medium =2; large =3)					
Drug abuse (മയക്കുമരുന്ന് ഉപയോഗം)					
Head injury with LOC (mild=1; mod.=2; severe=3)					
(അപായാവസ്ഥ ഉണ്ടാകത്തക്ക രീതിയിൽ തലക്ക് പരിക്കേറ്റിട്ടുണ്ട്)					
Over the counter medications					

(ഡോക്ടറുടെ അനുവാദമില്ലാതെ ദീർഘകാലമായി മരുന്ന് കഴിക്കാറുണ്ട്)

Strokes (Sudden onset)	(no 0; definite 1; possible 2)	
Transient or lasting weakness on one side or of face/ Incoordination of hands or legs		
(കൈകാലുകൾക്ക് സ്വാധീനക്കുറവോ,ഒരുവശം തളർന്നു പോവുകയോ, വായ് കോട്ടമോ ഉണ്ടായിട്ടുണ്ട്)		
Number of strokes		
Known toxin exposures (വിഷവാതകങ്ങളുമായി ബന്ധപ്പെട്ടിട്ടുണ്ട്)	(no 0; definite 1; possible 2)	
Education		
Highest Grade (ഉയർന്ന വിദ്യാഭ്യാസ യോഗ്യത)		
Performance as a student (വിദ്യാർത്ഥി ആയിരിക്കുമ്പോഴുള്ള പ്രകടനം)	(poor 1, average/ good 0)	
Vocation (Classification of type of job)		
(1Unemployed, 2 House wife, 3 Unskilled labour, 4 Skilled labour, 5 Buisness, 6 Professional, 999 DNK)		
Frequency of job change (ഇടക്കിടക്കുള്ള ജോലി മാറ്റം)		
Problems with job (ജോലിയുമായി ബന്ധപ്പെട്ട പ്രശ്നങ്ങൾ)		

Family history (In siblings, parents =1; cousins or siblings of parents= 2)		(no 0; definite 1; possible 2)
epilepsy (അപസ്മാരം)		
dementia (ഡിമെൻഷ്യ/ഭ്രമാക്ഷയം)		
strokes (പക്ഷാഘാതം)		
Psychiatric illness (മാനസിക രോഗം)		
HT (രക്തസമ്മർദ്ദം)		
DM (പ്രമേഹം)		
Heart attacks (ഹൃദയാഘാതം)		

Clinical Proforma

NAME: _____	Pt No.: _____
D.O.B.: _____	TESTING DATE(S): _____
Age / Gender: _____	EDUCATION (YEARS): _____
Handed: _____	Tested in (Language): _____
Diagno: _____	Hosp No.: _____
Urb/Rur:	Tested By:

General Examination

BP (sitting/supine)		
Thyromegaly/nodules	(yes 1; no 0)	
Lymphadenopathy	(yes 1; no 0)	
Dermatitis ? Nutritional	(yes 1; no 0)	
apthous ulcers	(yes 1; no 0)	
bald tongue	(yes 1; no 0)	
cataract	(yes 1; no 0)	
V/A left (News paper headlines reading)		
right		
neck stiffness	(yes 1; no 0)	

Mood

Normal for the situation	(yes 1; no 0)	
Sadness	(yes 1; no 0)	
Elation	(yes 1; no 0)	
Lability	(yes 1; no 0)	
Fluctuations	(yes 1; no 0)	

Other HMF

judgment: sealed letter with address on the street (മേൽവിലാസമെഴുതിയ ഇല്ലാത്ത് റോഡിൽ കിടക്കുന്നതു കണ്ടാൽ എന്തുചെയ്യും)	(abn 1; nor 0)	
insight	(abn 1; nor 0)	
abstract: all that glitters is not gold (മിന്നുന്നതെല്ലാം പൊന്നല്ല.)	(abn 1; nor 0)	
perseveration	(abn 1; nor 0)	
2 similarities: chair and table (കസേരയും മേശയും തമ്മിലുള്ള സാമ്യം.)	(abn 1; nor 0)	
language	(abn 1; nor 0)	
fluency ☐ naming ☐		
paraphasia ☐ grammar ☐		
praxis	(abn 1; nor 0)	
blow out a burning match stick (കത്തികൊണ്ടിരിക്കുന്ന തിരി ഊതി കെടുത്തുക.)	☐	
use a key (give a key in hand) (താക്കോൽ എങ്ങനെയാണ് ഉപയോഗിക്കുന്നത്.)	☐	
show how you light a match stick (തീപ്പെട്ടി തിരി എങ്ങനെ കത്തിക്കാം എന്ന് കാണിക്കൂ)	☐	
gnosis:	(abn 1; nor 0)	
simultaneous touch on both arms ☐ identify coin by feel (give in hand) ☐		
Completed MMSE items in ACE	(yes 1; no 0)	

Neurological Examination

Hemianopia	(yes 1; no 0)	
Eye movements		
saccades (vertical/horizontal)	(abn 1; nor 0)	
pursuits (vertical/horizontal)	(abn 1; nor 0)	
Release reflexes	(yes 1; no 0)	
jaw jerk	☐	
palmo mental	☐	

Focal Motor Deficit (yes 1; no 0)	☐	Gait abnormality (yes 1; no 0)	☐
Focal Sensory Abnorma (yes 1; no 0)	☐	Incontinence (yes 1; no 0)	☐
Involuntary Movement (yes 1; no 0)	☐	Ataxia (yes 1; no 0)	☐
Tone (abn 1; nor 0)	☐	Other signs (yes 1; no 0)	☐

APPENDICES -5-NEUROPSYCHOLOGY TESTS

MMSE

- It is probably the most widely used test for bedside memory testing.
- It has sensitivity and specificity of 70% with a cut off score of 26.
- The scores of 26 (in non educated individuals) and 28 (in educated individuals) warrant further assessment, follow up and surveillance for MCI.
- Addition of a recall after a longer delay improves the sensitivity and specificity to >80%.

Addenbrooke's Cognitive Examination

The ACE encompassed tests of five cognitive domains: attention/orientation, memory, language, verbal fluency, and visuospatial skills.

It is scored out of 100, with a higher score denoting better cognitive function.

The ACE also incorporated the MMSE, such that this score (out of 30) might also be generated.

The current version of the test is the Addenbrooke's Cognitive Examination-III (ACE-III). This consists of 19 activities which test five cognitive domains: Attention, Memory, Fluency, Language and Visuospatial processing

Attention

Attention is tested by asking the patient for the date including the season and the current location; repeating back three simple words; and serial subtraction. An example is something like "subtract seven from 100 and then continue subtracting seven away from each new number."

Memory

Memory is tested by asking the patient to recall the three words previously repeated; memorising and recalling a fictional name and address; and recalling widely known historical facts. The memory section is split into five sections scattered throughout the tests.

Fluency

Fluency is tested by asking the patient to say as many words as they can think of starting with a specified letter within one minute; and naming as many animals as they can think of in one minute. An example of this would be the tester asking the test taker to list every word they can think of that starts with the letter C.

Language

Language is tested by asking the patient to complete a set of sequenced physical commands using a pencil and piece of paper such as "place the paper on top of the pencil"; to write two grammatically-complete sentences; to repeat several polysyllabic words and two short proverbs; to name the objects shown in 12 line drawings, and answer contextual questions about some of the objects; and to read aloud five commonly-mispronounced words. Language involves ascribing meaning to words and statements so this section consists of simple directions that may involve movements, such as the example of placing the paper on top of the pencil, to see how well they apply meaning. Because language is valuable and important to functioning in society, this section is the longest consisting of seven separate parts.

Visuospatial

Visuospatial skills are used almost daily to remember directions, addresses, and layout of familiar places. Visuospatial abilities are tested by asking the patient to copy two diagrams; to draw a clock face with the hands set at a specified time; to count sets of dots; and to recognize four letters which are partially obscured.

Scoring

The results of each activity are scored to give a total score out of 100 (18 points for attention, 26 for memory, 14 for fluency, 26 for language, 16 for visuospatial processing). The score needs to be interpreted in the context of the patient's overall history and examination, but a score of 88 and above is considered normal; below 83 is abnormal; and between 83 and 87 is inconclusive.

Rey Auditory Verbal Learning Test, RAVLT

- The Rey Auditory Verbal Learning Test (RAVLT) is a neuropsychological assessment designed to evaluate verbal memory in patients, 16 years of age and older.
- It can be used to evaluate the nature and severity of memory dysfunction and to track changes in memory function over time.
- The test is designed as a list-learning paradigm in which the patient hears a list of 15 nouns and is asked to recall as many words from the list as possible. After five repetitions of free-recall, a second ‘‘interference’’ list (List B) is presented in the same manner, and the participant is asked to recall as many words from List B as possible.
- After the interference trial, the participant is immediately asked to recall the words from List A, which she or he heard five times previously. After a 20 min delay, the participant is asked to again recall the words from List A. After this ‘‘delayed recall’’ task, a list of 50 words is presented containing all of the words from Lists A and B, in addition to 20 phonemically and/or semantically similar words. This trial directly tests recognition memory, as opposed to free-recall.
- The multiple memory processes assessed by the RAVLT provide rich data regarding memory abilities.
- The multiple recall trials for List A can be represented as a learning curve, demonstrating relative memory capacity.
- In addition, the correct number of recalled words from List B, the recall of immediate-delayed words from List A, and the delayed-recall words from List A are also recorded to assess for interference and retention.
- The RAVLT may be particularly useful for comparing specific memory processes within an individual.
- The number of words recalled on the first five repetitions of List A provides a measure of immediate memory span.
- The change over these five trials provides a learning curve, with the slope of the curve representing verbal learning.

- The delayed recall score compared to the number of words recalled on trial one asses the participant's retention skill.
- The recognition task allows the clinician to distinguish between retrieval in initial encoding and retention of information.
- Overall recall patterns can also be evaluated for primacy and recency effects, intrusion errors, and semantic or phonetic confusions

Digit Span Test

- The Digit Sequencing Test, alternatively called the Digit Span Test is a key tool for working verbal memory. Usually, the examiner reads a list of numbers as the digit sequencing, and the participant repeats them until an incorrect answer is given.
- The test was originally designed to test working memory and attention, as part of the Wechsler Intelligence Scale.
- Usually, the examiner reads a list of numbers, and the participant repeats them until an incorrect answer is given. Sometimes the participant is asked to repeat the sequence of digits backward.
- The Digit Sequencing test measures one's verbal working memory and attention. After the examiner has presented the digits, the participant must recall them – until they can't remember the complete sequence, or until they repeat it incorrectly. Usually, the trials are presented twice.
- The Digit Sequencing test can be administered backward, which means that the subject has to repeat the digits in reverse order. This variation requires the participant to hold the digits longer in their working memory.
- Thus, it's believed that the ability to perform well on this additional difficulty of the task can be linked to general intelligence.

Trail Making Test

- The **Trail Making Test** is a neuropsychological test of visual attention and task switching.
- It consists of two parts in which the subject is instructed to connect a set of 25 dots as quickly as possible while still maintaining accuracy.

- The test can provide information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning.
- It is sensitive to detecting cognitive impairment associated with dementia, for example, Alzheimer's disease.
- The task requires a subject to connect a sequence of 25 consecutive targets on a sheet of paper or computer screen, in a similar manner to a child's connect-the-dots puzzle.
- There are two parts to the test: in the first, the targets are all numbers (1, 2, 3, etc.) and the test taker needs to connect them in sequential order; in the second part, the subject alternates between numbers and letters (1, A, 2, B, etc.).If the subject makes an error, the test administrator corrects them before the subject moves on to the next dot.
- The goal of the test is for the subject to finish both parts as quickly as possible, with the time taken to complete the test being used as the primary performance metric.
- The error rate is not recorded in the paper and pencil version of the test; however, it is assumed that if errors are made it will be reflected in the completion time.
- The second part of the test, in which the subject alternates between numbers and letters, is used to examine executive functioning. The first part is used primarily to examine cognitive processing speed.

Wisconsin Card Sorting Test

- The Wisconsin Card Sorting Test (WCST) is a neuropsychological test of "set-shifting", i.e. the ability to display flexibility in the face of changing schedules of reinforcement.
- The Wisconsin Card Sorting Test requires subjects to discover the principle according to which a deck of cards must be sorted.
- The standard material consists of cards bearing geometric figures that vary in colour (red, green, blue, or yellow), shape (triangle, star, cross, or circle) and number (1, 2, 3, or 4 items).
- Four reference cards are aligned in front of the subject throughout the test. Another deck of cards serves as response cards.

- The subject is instructed to place each response card in front of 1 of the 4 reference cards, wherever he thinks it should go. After each response, he is told whether the response was "right" or "wrong," but not where the card should have gone.
- The goal for the subject is to get as many "right" responses as possible.

Initially, cards must be sorted according to, say, colour. When performance is successful, the sorting rule is changed, for example from colour to shape; the subject must notice the change and find the new correct rule.

Wechsler Memory Scale (WMS)

The Wechsler Memory Scale is a neuropsychological test that can be used with people from age 16 to 90. The WMS or WMS-R contains sub-tests like Logical Memory Passage, Visual Reproduction and Paired Associate Learning. Logical Memory Passage is a test of paragraph or prose recall and has an immediate recall and delayed recall. The examiner reads two stories, stops after each reading, and asks for an immediate free recall. After a delay of 30 minutes, delayed recall is taken as an attempted verbatim recitation. Story 1 contains 24 memory units and Story 2, 23 memory units. The total score is the total number of ideas recalled for both stories together. The WMS-R Visual Reproduction Subsets requires the subject to draw from memory simple geometric figures. Each of the visual reproduction cards is shown for ten seconds. Following each presentation, immediate recall is tested. The subjects then draw from memory what they remember of the design. A delayed recall is taken after 30 minutes.

Clinical Dementia Rating (CDR) Scale

- It considers six domains - memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.
- Score of 0.5 on this scale is of diagnostic importance for MCI, according to Peterson’s modified criteria.
- American Academy of Neurology (AAN) accepts this score as equivalent to the presence of MCI.
- It has a high inter-rater reliability and appears to be a reliable and valid tool for assessing and staging dementia

IADL

- Instrumental Activities of Daily Living (IADL) Scale was developed to assess more complex activities (termed “instrumental activities of daily living”) necessary for functioning in community settings (e.g., shopping, cooking, managing finances).
- The capacity to handle these complex functions normally is lost before basic “activities of daily living” (e.g., eating, bathing, toileting) which are measured by ADL scales.
- Therefore, assessing IADLS may identify incipient decline in older adults or other individuals who are otherwise capable and healthy

APPENDICES -6-SENSITIVITY AND SPECIFICITY OF CONVERSION SCORE (YOUNDEN'S J MAX)

Test Result Converter_Score			
Positive if Greater Than or Equal To[a]	Sensitivity	Specificity	Youden's J
-5.4170	1.000	0.000	0.000
-4.1910	1.000	0.019	0.019
-3.9615	1.000	0.038	0.038
-3.6170	1.000	0.057	0.057
-2.9590	0.929	0.057	-0.015
-2.4610	0.929	0.075	0.004
-2.2360	0.929	0.094	0.023
-2.1640	0.929	0.113	0.042
-2.0680	0.929	0.132	0.061
-1.8740	0.929	0.151	0.080
-1.7340	0.929	0.170	0.098
-1.6460	0.929	0.189	0.117
-1.4940	0.929	0.208	0.136
-1.3820	0.929	0.226	0.155
-1.3345	0.929	0.245	0.174
-1.3130	0.929	0.264	0.193
-1.2785	0.929	0.283	0.212
-1.2455	0.929	0.302	0.230
-1.1840	0.929	0.321	0.249
-1.1085	0.929	0.340	0.268
-1.0365	0.929	0.358	0.287
-0.8120	0.929	0.377	0.306
-0.5865	0.929	0.396	0.325
-0.4815	0.929	0.415	0.344
-0.3140	0.929	0.434	0.363
-0.1735	0.929	0.453	0.381
-0.1450	0.929	0.472	0.400
-0.0745	0.929	0.491	0.419
0.0145	0.929	0.509	0.438
0.0770	0.929	0.528	0.457

0.0770	0.929	0.528	0.457	
0.1650	0.929	0.547	0.476	
0.2135	0.929	0.566	0.495	
0.2355	0.929	0.585	0.513	
0.3505	0.929	0.604	0.532	
0.4520	0.929	0.623	0.551	
0.5185	0.929	0.642	0.570	
0.6525	0.929	0.660	0.589	
0.7485	0.929	0.679	0.608	
0.7875	0.929	0.698	0.627	
0.8770	0.929	0.717	0.646	
0.9990	0.857	0.717	0.574	
1.0870	0.857	0.736	0.593	
1.1520	0.786	0.736	0.522	
1.1885	0.786	0.755	0.540	
1.2090	0.786	0.774	0.559	
1.4040	0.786	0.792	0.578	
1.6275	0.786	0.811	0.597	
1.6730	0.786	0.830	0.616	
1.7035	0.786	0.849	0.635	
1.7740	0.786	0.868	0.654	
1.8480	0.714	0.868	0.582	
1.9060	0.714	0.887	0.601	
2.0160	0.714	0.906	0.620	
2.1060	0.714	0.925	0.639	
2.2295	0.714	0.943	0.658	
2.3895	0.714	0.962	0.677	
2.6105	0.714	0.981	0.695	Jmax
2.7950	0.643	0.981	0.624	
2.8430	0.571	0.981	0.553	
3.0740	0.571	1.000	0.571	
3.3215	0.500	1.000	0.500	
3.4025	0.429	1.000	0.429	
3.6065	0.357	1.000	0.357	
4.0665	0.286	1.000	0.286	
4.6585	0.214	1.000	0.214	
5.0220	0.143	1.000	0.143	
5.4150	0.071	1.000	0.071	
6.7540	0.000	1.000	0.000	

APPENDICES-7 (MRI PARAMETERS ACROSS GROUPS AT BASELINE)

		N	Mean	Std. Deviation	Minimum	Maximum		
e54_GM	Nonconverter	43	548.3474	45.42042	455.89	637.00		
	Converter	16	561.3369	56.55029	480.00	710.39		0.365
WM	Nonconverter	43	451.0602	54.91220	334.87	649.21		
	Converter	16	456.2156	68.86217	379.00	649.14		0.766
CSF	Nonconverter	43	488.4449	115.17863	286.00	779.76		
	Converter	16	534.2894	112.76993	358.00	788.00		0.177
TIV	Nonconverter	43	1488.5279	145.79646	1141.00	1767.36		
	Converter	16	1552.4400	171.27102	1259.00	1900.00		0.159
e57_HL	Nonconverter	44	2.953983	0.732489	1.789612	4.811264		
	Converter	17	2.764542	0.852465	1.568300	4.210000		0.391
e58_HR	Nonconverter	44	3.147965	0.585582	1.989471	4.754204		
	Converter	17	3.044058	0.798186	1.787400	4.430000		0.578
e59_AL	Nonconverter	44	0.902487	0.318750	0.421632	2.300000		
	Converter	17	0.857547	0.295907	0.300153	1.280000		0.617
e60_AR	Nonconverter	44	0.913595	0.344223	0.452416	2.500000		
	Converter	17	0.871291	0.361967	0.207017	1.350000		0.673

		N	Mean	Std. Deviation	Minimum	Maximum		Sig.
e54_GM	Stable	40	551.1298	44.46422	457.30	637.00		0.8667242
	Progressor	19	553.4284	57.45022	455.89	710.39		
WM	Stable	40	450.0050	54.20316	334.87	649.21		0.6439232
	Progressor	19	457.6232	67.80514	378.51	649.14		
CSF	Stable	40	486.3023	118.68091	286.00	779.76		0.1610991
	Progressor	19	531.5616	104.54490	358.00	788.00		
TIV	Stable	40	1488.1630	149.34043	1141.00	1767.36		0.2037685
	Progressor	19	1543.1168	161.88400	1259.00	1900.00		
e57_HL	Stable	41	2.9213473	0.7424846	1.7896121	4.8112640		0.7710614
	Progressor	20	2.8598609	0.8283229	1.5683000	4.2100000		
e58_HR	Stable	41	3.1285477	0.5986023	1.9894709	4.7542040		0.8705256
	Progressor	20	3.0994492	0.7513706	1.7874000	4.4300000		
e59_AL	Stable	41	0.8909125	0.3269739	0.4216317	2.3000000		0.9730726
	Progressor	20	0.8880151	0.2826586	0.3001530	1.2800000		
e60_AR	Stable	41	0.9011748	0.3533066	0.4524161	2.5000000		0.9839826
	Progressor	20	0.9030976	0.3418402	0.2070170	1.3500000		

KEY TO MASTERCHART (APPENDICES-8)

BASELINE AND FINAL FOLLOW UP

Sex	1. Male	2. Female
Death	0. No	1. Yes
Death Cause	0. Alive 2. Other Medical	1. Advanced Dementia
Educational history	1. Illiterate 3. Middle School 5. Intermediate diploma 7. Professional degree/diploma	2. Primary 4. High School 6. Graduate
Occupation	1. Unemployed 3. Semiskilled worker 5. Clerical /shop /farm 7. Professional	2. Unskilled worker 4. Skilled worker 6. Semi Profession
Socioeconomic status	1. Lower 3. Lower middle 5. Upper	2. Upper lower 4. Upper middle

Family h/o	0. Absent	1. Present	
Family history	0. Absent 2. Two first degree 4. Third degree	1. One first degree 3. One first degree, one seconds deg	
Comorbidities	1. Absent 4. Dyslipidemia 7. POVD	2. Diabetes 5. CAD 8. Others	3. Hypertension 6. Stroke
Diabetes	0. Absent	1. Present	
Hypertension	0. Absent	1. Present	
Dyslipidemia	0. Absent	1. Present	
CAD	0. Absent	1. Present	
Stroke	0. Absent	1. Present	
POVD	0. Absent	1. Present	
Head injury	0. Absent	1. Present	
OSACS	0. Absent 2. Moderate	1. Mild 3. Severe	
Thyroid	0. Absent	1. Hyopothyroidism	2. Hyper

Respiratory	0. Absent	1. Asthma	2. COPD
Renal dys	0. Absent	1. Present	
History of Neuropsychiatric illness		0. None	1. Depression
		2. Anxiety	3. Psychosis

History of seizures	1.Present	2. Absent	
Deficits in attention	1.Present	2. Absent	
Memory deficits	1. Present	2. Absent	
Type of memory problem	1. Immediate	2. Recent	3. Remote
Type of Language deficit	0.None	1. Naming of items	
	2.Comprehension	3.Repitition	4.Fluency
	5.Reading	6.Writing	7 word finding

Language deficits	1. Present	2. Absent
Executive function	1. Absent	2. Present
Difficulty in performing familiar task	1. Present	2. Absent
Poor or decreased judgement	1. Present	2. Absent
Problems with abstract thinking	1. Present	2. Absent
Misplacing things	1. Present	2. Absent
Changes in mood and behaviour	1.Present	2. Absent
Changes in personality	1. Present	2. Absent
Loss of initiative	1. Present	2. Absent
Praxis	1. Normal	2. Impaired
Visuospatial functions	1. Normal	2. Impaired

Eye movements	1.Normal	2. Hypometric saccades
	3.Opthalmoplegia	
Speech disturbances	1.None	2.Flaccid dysarthria
	3. Spastic dysarthria	4. Ataxic speech
Extrapyramidal symptoms	1. Absent	2. Dystonia
	3. Tremor	4. Chorea
	5. Myoclonus	
Sensory	0. None	1. Upper limbs
	2. Lower limbs	3. Objective

Parkinsonism	1. Present	2. Absent
Tremor	1. Present	2. Absent
Sphincter disturbance	0. Normal	1. Bladder
	2. Bowel	3. Impotence

RBD	1. Present	2. Absent	
Sleep	0. Normal	1. Sleep disturbances)	
Serum Vitamin B12	0. Normal	1. Abnormal	2. ND
Comorbidities	1. Absent	2. Diabetes	3. Hypertension
	4. Dyslipidemia	5. CAD	6. Stroke
	7. POVD	8. Others	

MCI status at baseline
0- normal
1- MCI amnestic
2- MCI dysexecutive
3- MCI multidomain
4- MCI behavioral (anxiety/depressioN)
5- early dementia

MCI status on final follow up
0- normal
1- MCI amnestic
2- MCI dysexecutive
3- MCI multidomain
4- MCI behavioral (anxiety/depressioN)
5- early AD
6- Moderate AD
7- Advanced AD
8- FTD
9- DLBD
10- VaD
11- Mixed dementia
12- CBD
13- PSP
14- IPD

MCI Final follow up status
0- Converted to normal
1- MCI stable/improving
2- MCI progressor (single to multidomain)
3- Dementia convertor

MCI final status	1. Non converter	2. Convertor	
Flup available	0. No	1. Yes	
FAZEKA score	0.Nil	1.Mild	
	2.Moderate	3 .Severe	
Atrophy	0. Nil	1. Focal	2. Diffuse
Microbleed	0. Absent	1. Sup	2. Deep
ERIKA score	0. Normal	1. Mild	

2. Moderate 3. Severe

Quantitative MRI Variables
GM
WM
CSF
TIV
Left Hippocampus
Right Hippocampus
Left Amygdala
Right Amygdala
Cerebral microbleed number

-NEUROPSYCHOLOGY BATTERY (BASELINE (N=95) AND FOLLOW UP-TWO VISIT-N=68 ,THREE -N=37)

-OUTCOME MEASURES -BASELINE AND FOLLOW UP VISITS (FOUR TIME POINTS)