UTILITY OF CLOCK DRAWING TEST AND CUBE CONSTRUCTION IN DIAGNOSIS OF EARLY COGNITIVE IMPAIRMENT

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DM NEUROLOGY THESIS

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A THESIS SUBMITTED BY

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TO

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IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

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DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr. Sayooja Sachithanandan hereby certify that I had personally carried out the work depicted in the thesis titled, "Utility of clock drawing test and cube construction in diagnosis of Early cognitive impairment".

No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

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*Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

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LIST OF ABBREVIATIONS

S.No.	Abbreviation	Full form
1.	ECI	Early cognitive impairment
2.	MCI	Mild cognitive impairment
3.	ED	Early dementia
4.	MoCA	Montreal Cognitive Assessment
5.	RUDAS	Rowland Universal Dementia Assessment Scale
6.	ACE	Addenbrooke's Cognitive Examination ACE
7.	CDT	Clock drawing test CDT
8.	CCT	Cube construction test
9.	CN	Cognitively normal
10.	NPT	Neuropsychological tests
11.	CDR	Clinical Dementia Rating
12.	DSM	Diagnostic and Statistical Manual
13.	aMCI	Amnestic MCI
14.	NIAA	National Institute of Aging and the Alzheimer's Association
15.	VaMCI	Vascular MCI
16.	AD	Alzheimer's disease

17.	VaD	Vascular dementia
18	FTD	Frontotemporal dementia
19.	LBD	Lewy body dementia
20.	MMSE	Mini-Mental State Examination
21.	ACE	Addenbrooke's Cognitive Examination
22.	ADNI	Alzheimer's Disease Neuroimaging Initiative
23.	BNA	Behavioural Neurological Assessment
24.	HD	Huntington's disease
25.	PI	Principal Investigator
26.	ROC	Receiver operating characteristic
27.	AUC	Area under the receiver operating characteristic curve

SYNOPSIS

UTILITY OF CLOCK DRAWING TEST AND CUBE CONSTRUCTION IN DIAGNOSIS OF EARLY COGNITIVE IMPAIRMENT

Early cognitive impairment (ECI) which includes MCI and early dementia (ED) is regarded as pre dementia stage where involvement of cognitive domains does not result in functional disability. Several neurocognitive screening tools are effective in screening these population, however is limited by time consuming nature and requirement of expertise in performing. Clock drawing test (CDT) and cube construction test (CCT) are simpler tasks mainly focusing on the visuospatial and executive domains of cognition, which are easier to perform. This study aims to find out utility of clock drawing test (CDT) and cube construction in diagnosing early cognitive impairment (ECI), to determine correlation between CDT and Cube construction scores and other domain specific neuropsychological tests (NPT) used in diagnosis of ECI, to generate cut off scores of CDT and Cube construction scores which can be used in screening for ECI

This was a hospital based retrospective study. All subjects were recruited who fulfilled inclusion and exclusion criteria. CDT and CCT was analyzed and given quantitative and qualitative scores by the PI blinded to the final diagnosis as either CN, MCI or ED. CDT and CCT was compared among the three groups of CN, MCI and ED. Correlation between demographic variables and CDT, CCT were performed using Spearman's rank (Rho) correlation analysis. Utililty of CDT and CCT as screening tool for diagnosing ECI were estimated with ROC curves. Linear regression models were derived to develop a formula for total ACE score from demographic dependent variables, CDT and CCT scores. Statistical significance was taken at p value < 0.05

A total 228 participants with mean age of 69 ± 6.7 years, sex ratio of 1.25:1 (M:F) and mean number of years of education of 13 ± 3.6 were recruited in the study, among which 80 were CN, 77 had MCI and 71 had ED. The three groups were matched with regard to number of years of education and sex distribution, CN were younger compared to MCI and ED. Mean CDT and CCT scores were lower among ED and MCI compared to CN group. ECI had higher frequency of qualitative errors of CDT than CN. CDT and CCT had significant positive correlation with other neuropsychological tests such as ACE scores. Both the tests had negative correlation with age and positive correlation with number of years of education among CN subjects, which was lost in ECI. CDT cutoff scores at 12 good sensitivity (88%) and specificity(54%) and CCT cut off score at 22 had intermediate sensitivity (72%) and specificity (61%) in detecting ED from CN, however both the tests were not useful in diagnosing MCI from CN and ED from MCI. Using linear regression models, a formula was formed to derive total ACE scores from CDT, CCT and demographic variables, ACE = 61.84 + (-0.14 x age) + (0.15 x education) + (1.80 x CDT) + (0.26 x CCT)

CDT performed better than CCT as a useful screening tool in detecting ED from CN, however both the test were not useful in detecting MCI. Qualitative errors of CDT needs further exploration in detecting ECI

INTRODUCTION

The incidence of dementia is expected to rise significantly over the next decade (Lee et al., 2023). Clinical stage of dementia is preceded by a stage of early cognitive impairment (ECI) which includes mild cognitive impairment (MCI) and early dementia(ED) (Petersen et al., 2018; Pujol Domenech and Azpiazu Artigas, 2015). In recent years, the exponential rise in cases of MCI progressing to dementia has led to concern and interest in diagnostic measures for neuropsychological deficiencies. Recent research worldwide has emphasized on the importance of early diagnosis to delay or slow the progression of dementia.

Cognitive assessment tools, such as, the Montreal Cognitive Assessment (MoCA) ("Montreal Cognitive Assessment - an overview | ScienceDirect Topics," n.d.), the Rowland Universal Dementia Assessment Scale (RUDAS) ("Rowland Universal Dementia Assessment Scale (RUDAS) | Dementia Australia," n.d.), the Addenbrooke's Cognitive Examination (ACE)(Beishon et al., 2019) are useful in screening dementia. However, most of the cognitive assessment tools are time consuming and often requires help of a dedicated Neuropsychologist. Clock drawing test (CDT)(Eknoyan et al., 2012) and Cube construction test (CCT)(Mathew et al., 2018) are simple, comprehensive figure drawing test, which embrace visuospatial constructional abilities and executive functions, forming integral part of most of the cognitive assessment tools, and can be performed as bedside test quickly.

The CDT requires participants to draw a clock and set the hands to a particular time specified by the investigator(Shulman, 2000). In cube construction test, a three dimensional clock is drawn. Such a tasks requires higher levels of cognitive functioning (Eknoyan et al., 2012). While research has shown that the CDT and CCT can differentiate cognitively normal (CN) older adults from dementia populations(Charernboon, 2017; Kim et al., 2018), less research has explored whether the CDT can detect mild cognitive impairment (MCI), a transitional stage between normal aging and dementia.

Indian studies on CDT/ CCT and correlation with ECI are lacking in literature. This study was aimed to look at the utility of CDT and CCT as screening tool independent of other tools such as ACE in diagnosing ECI. It would also be interesting to look for potential correlation of qualitative parameters of CDT and final diagnosis of cognitive stage.

Aims and Objectives

Primary Objective:

- To compare clock drawing test (CDT) and Cube construction tests (CCT) scores among cognitively normal (CN) subjects and Early Cognitive Impairment (ECI).

Secondary objectives:

- To determine correlation between CDT and CCT scores and other domain specific neuropsychological tests (NPT)
- To generate cut off scores of CDT and CCT scores which can be used in screening for ECI

LITERATURE REVIEW

Dementia is one of the most common and burdensome diseases of the elderly, and diagnosis of dementia has an enormous impact on society and its healthcare systems(Lee et al., 2023). The estimated prevalence of dementia among adults aged more than 60 in India is 7.4%(Lee et al., 2023). The proportion of individuals aged 60 years or older is projected to increase to nearly 20% of the total Indian population by 2050 (319 million)(Lee et al., 2023). This demographic trend reflects rising longevity, as life expectancy in India has steadily increased from 42.9 years in 1960 to 70.4 years in 2020, which could be likely explanation for increase in the number of people with dementia, as age is the strongest and best-known risk factor for dementia. Prevalence of dementia among women is almost double that among men, and also much higher in rural than in urban areas. Finally, dementia is considerably more prevalent among individuals with lower educational level with individuals without formal education having much higher dementia prevalence relative to their more educated counterpart (Lee et al., 2023)

In higher income countries, prevalence is 5–10% in those aged above 65 years, usually greater among women than among men, mostly because women live longer than men. Within the US, higher prevalence has been reported in African American and Latino/Hispanic populations than in White nonHispanic populations

Prevalence is defined as a function of incidence and duration. Since most dementias are not completely curable, their duration reflects how long individuals live with their dementia. Thus, the public health burden of dementia depends both on the development of new cases and on the survival of those cases after onset; when considered incidence as constant, groups with longer life expectancy will have higher prevalence

Life expectancy is increasing across the planet, with population aging rising the most rapidly in the low- and middle-income countries, where the prevalence of dementia is therefore expected to increase.

Recent studies suggest that prevalence may be steadying off or even decreasing in the high-income countries(Hugo and Ganguli, 2014)

No single definitive diagnostic test exists for clinical syndromes such as dementia. Most of the diagnosis in clinical practice and research relies on a process of consensus which reviews detailed information on aspects of the clinical assessment of a given patient, discusses the findings, and renders a consensus diagnosis using standardized criteria, such as the Clinical Dementia Rating (CDR)(Morris, 1993)

Dementia is typically diagnosed when acquired cognitive impairment has become severe enough to compromise social and occupational functioning. Mild cognitive impairment (MCI) is a state intermediate between normal cognition and dementia, with essentially preserved functional abilities(Hugo and Ganguli, 2014). The American Psychiatric Association's Diagnostic and Statistical Manual (DSM-5) diagnosis of Major Neurocognitive Disorder, which corresponds to dementia, requires substantial impairment to be present in one or more cognitive domains("DSM-5," 2023). The impairment must be sufficient to interfere with independence in everyday activities. The diagnosis of Mild Neurocognitive Disorder, which corresponds to MCI, is made when there is modest impairment in one or more cognitive domains. The individual might still be independent in everyday activities, however with greater effort. The impairment should be documented both by history and by objective assessment as representing a decline from previously higher level. Further, the cognitive deficits must not occur exclusively in the context of a delirium or be better explained by another mental disorder

Early Cognitive Impairment

The spectrum of cognitive decline in older adults ranges from normal cognitive decline with aging to

subjective cognitive impairment (cognitive complaint with normal cognitive screening test) to MCI to dementia. Subjects with MCI and mild or early dementia (ED) are considered as having early cognitive impairment (ECI), where there is growing interest because of the fact that we may be able to identify the earliest clinical features before functional impairment is evidenced. The prevalence of early cognitive impairment is estimated to be ranging from 5.1% to 41.0%(Pais et al., 2020). Good quality scientific data on ECI are needed, both to identify groups at risk of developing cognitive changes at earliest stage and to identify the optimum time at which to implement preventive and corrective measures. A better understanding of ECI and its lifetime course is needed to define and implement strategies to both prevent initial cognitive impairment and either stop or delay its progression towards dementia once established.

The ability to rely on tests to identify ECI with high accuracy (sensitivity and specificity) is crucial for population studies and population interventions, as it is neither practical nor cost-effective to have a specialist neurological assessment of large numbers of unaffected individuals

MILD COGNITIVE IMPAIRMENT

Mild cognitive impairment (MCI) as a term was introduced in 1988(Reisberg et al., 1988), referring to the clinical state of individuals who are memory impaired but are otherwise functioning well and do not meet clinical criteria for dementia, represents the transitional stage of cognitive impairment between normal aging and early dementia(Petersen et al., 2001), subsequently classified as Global Deterioration Scale (GDS) stage 2 or 3 and as having a Clinical Dementia Rating (CDR) scale of 0 or 0.5(Morris, 1993).

Mild cognitive impairment or mild neurocognitive disorder is an intermediate state between normal aging and dementia. This state can progress to dementia, mostly in the form of Alzheimer's disease. The prevalence of MCI in adults older than 60 is approximately 6.7% to 25.2% and the incidence of ECI ranged from 22 to 215 per 1000 person-years, with a median incidence of 56.50 per 1000 person-years(Jongsiriyanyong and Limpawattana, 2018). It increases with age and lower level of education and

is more prevalent in men. The prevalence varies in different studies due to differences in definitions of MCI used in most studies. Formerly, MCI was defined by focusing mainly on memory loss, but it later includes a wider definition that covers either impairment in single-domain non amnestic or several cognitive domains with or without memory deficit. The annual rate of progression to dementia is approximately 5% to 17%(Jongsiriyanyong and Limpawattana, 2018).

Diagnosis of MCI

The diagnostic criteria for MCI include change in cognition, abnormal cognitive function in one or more domains, normal daily activity, and absence of dementia. A detailed interview regarding the patient's history from knowledgeable informants in order to detect the clinical clues is fundamental in making diagnosis. Adding appropriate cognitive screening tests is another crucial part for clinical evaluation of patients with MCI. The Montreal Cognitive Assessment (MoCA) with a cutoff point of 24/25 is the recommended cognitive screening tool for MCI. The sensitivity and specificity of the test have been found to be 80.48% and 81.19%, respectively(Jongsiriyanyong and Limpawattana, 2018). However, it is affected by educational level, lifestyle factors, and ethnic diversities.

Table 1: Original 1999 Mild Cognitive Impairment Criteria[a]

Criterion
Memory complaint, preferably corroborated by an informant
Memory impairment documented according to appropriate reference values
Essentially normal performance in nonmemory cognitive domains
Generally preserved activities of daily living
Not demented

[a]Based on information from Petersen et al(Petersen et al., 1999)

Although MCI can be the initial cognitive expression of Alzheimer disease (AD), it can also be secondary to other disease processes (other neurologic, neurodegenerative, systemic, or psychiatric disorders).The term amnestic MCI (aMCI) describes a syndrome in which memory dysfunction predominates. In nonamnestic MCI, impairment of other cognitive features (e.g., language, visuospatial, executive) is more prominent. Various definitions of MCI have been used over time, reflecting an evolution of thought from primarily focusing on amnesia to including other cognitive deficits. Because memory deficits are the clinical hallmark of AD, some descriptions used criteria for MCI that required the presence of memory deficits in isolation (aMCI) and others included a broader definition that included either single-domain nonamnestic deficits or deficits in multiple cognitive domains, either with memory impairment (multidomain aMCI) or without (multidomain nonamnestic MCI)(Petersen et al., 2018).

Amnestic MCI is more common than non-amnestic MCI by a ratio of about 2:1. Non-amnestic MCI may result from normal aging and have reversible causes, or it may be the result of a predementia stage of non-Alzheimer's disease such as frontotemporal lobar degeneration, dementia with Lewy bodies, Parkinson disease with dementia, vascular dementia, or primary progressive aphasia.

Table 2: Core Clinical Criteria of MCI[b]

Type of MCI	Description
MCI amnestic	MCI with only memory deficit
MCI single-domain nonamnestic	MCI without memory deficit and only 1 domain of deficit such as attention deficits, language impairments, visuospatial impairment, or

	dysexecutive functions
MCI multiple-domain amnestic	MCI with memory deficit and 1 or more domain(s) of deficit
MCI multiple-domain nonamnestic	MCI with more than 1 domain of deficit but preserved memory

[b]Based on information from Peterson et al(Petersen et al., 2018)

The National Institute of Aging and the Alzheimer's Association (NIAA) work group proposed a new diagnostic criterion for Alzheimer's disease, which can be applied to preclinical Alzheimer's disease, MCI due to Alzheimer's disease, and Alzheimer's disease dementia. Both the core clinical criteria and the biomarker criteria for MCI due to Alzheimer's disease are useful for diagnosis. The core clinical criteria are subjective or objective cognitive impairments in one or more domain(s) of cognitive function, which have not disturbed the patient's social or occupational functions with no other causes of cognitive impairment (neurologic, psychiatric, systemic disorders, metabolic dysfunctions, or medications)(Jongsiriyanyong and Limpawattana, 2018).

Vascular MCI (VaMCI) is a type of MCI that is unlikely to be due to Alzheimer's disease. It is commonly classified into 2 categories namely, poststroke- and nonstroke-related VCI. Vascular cognitive impairment consists of one or more cognitive impairments including executive/attention, memory, language, and visuospatial functions, ranging from MCI to dementia, caused by clinical features of vascular events or evidence of vascular damage found using neuroimaging. There are multiple domains of cognitive deficits in cases of VCI that have common presentations with dysexecutive syndrome. Concomitant motor signs with VCI include frontal gait disturbance, lower body Parkinsonism, apathy, depression, urinary incontinence, spasticity, hyperreflexia, and frontal release signs. Majority of VCI

would be mixed type, with the most common combined with Alzheimer's disease(Jongsiriyanyong and Limpawattana, 2018).

Appropriate diagnosis of MCI is important because MCI becomes increasingly common as individuals age and is associated with an increased risk of progression to dementia, suggesting that this condition reflects a pathologic disease state rather than normal cognitive aging. It is also important in to assess for reversible causes of cognitive impairment, to help patients and families understand the cause of their cognitive concerns, and to discuss the prognostic possibilities with the provider so they can plan accordingly, although sharing the diagnosis must be balanced with the potential harm of anxieties from diagnosing a patient with a condition that may not progress(Petersen et al., 2018). Although subjective cognitive complaints alone are insufficient to diagnose MCI, such complaints from either patients or their close contacts are core to most major MCI diagnostic criteria, as they may reflect a change in cognitive function.

Early Dementia

The diagnosis of dementia is intended to encompass the spectrum of severity, ranging from the mildest to the most severe stages of dementia. The differentiation of dementia from MCI rests on the determination of whether or not there is significant interference in the ability to function at work or in usual daily activities. This is inherently a clinical judgment made by a skilled clinician on the basis of the individual circumstances of the patient and the description of daily affairs of the patient obtained from the patient and from a knowledgeable informant(McKhann et al., 2011).

Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that(McKhann et al., 2011):

1. Interfere with the ability to function at work or at usual activities; and

2. Represent a decline from previous levels of functioning and performing; and

3. Are not explained by delirium or major psychiatric disorder;

4. Cognitive impairment is detected and diagnosed through a combination of

(a) history-taking from the patient and a knowledgeable informant and

(b) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.

5. The cognitive or behavioral impairment involves a minimum of two of the following domains:

a. Impaired ability to acquire and remember new information

b. Impaired reasoning and handling of complex tasks, poor judgment

c. Impaired visuospatial abilities

d. Impaired language functions

e. Changes in personality, behaviour, or comportment

Dementia is an overarching term that encompasses several forms, including Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal dementia (FTD) and Lewy body dementia (LBD). As knowledge and understanding has evolved, it has become increasingly dificult to distinguish between these dementia subtypes, as there is considerable clinical and pathological overlap between them.

Alzheimer's disease(AD) is the most common dementia subtype, accounting for 62% of all cases(McKhann et al., 2011). Probable AD dementia is diagnosed when the patient (McKhann et al., 2011)

1. Meets criteria for dementia described earlier in the text, and in addition, has the following characteristics:

A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;

B. Clear-cut history of worsening of cognition by report or observation; and

C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.

a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.

b. Nonamnestic presentations: Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present. Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

D. The diagnosis of probable AD dementia should not be applied when there is evidence of

(a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or

(b) core features of Dementia with Lewy bodies other than dementia itself; or

(c) prominent features of behavioral variant frontotemporal dementia; or

(d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or

(e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition

Vascular dementia is the second most common form, comprising 17% of all dementia cases. The prevalence of VD is reported to be lower than that of AD, but there are large variations among different studies, depending mostly on definition. It is associated with vascular risk factors and events (transient ischaemic attack, acute stroke), resulting in chronic small vessel disease and leading to sustained cerebral hypoperfusion and thus cognitive impairment). Deterioration in cognitive function would characteristically result in a stepwise decline in cognition, although a slow progression similar to that seen with Alzheimer's disease is also seen in vascular dementia secondary to small vessel disease, rather than discrete vascular events

Cognitive Screening Tools

Ideally, a cognitive screening test should be brief, easy to score, independent of educational/cultural/language confounders, psychometrically robust, and broad in its coverage of cognitive domains(Kim et al., 2018). The need for a wide range of intellectual and perceptual skills to complete a task makes for a good cognitive screening instrument. There is a strong demand for screening instruments for early cognitive impairment (ECI), as a pre-stage of dementia.

The objective assessment requires the administration of one or more standardized tests. Neuropsychological assessment of specific cognitive domains is preferred for detecting mild impairments. If neuropsychological assessment is unavailable, objective testing can consist of a global screening scale, such as the well-known Mini-Mental State Examination (MMSE)(Australia, 2022) the Montreal Cognitive Assessment (MoCA)(https://www.facebook.com/verywell, n.d.). Such tests are usually sensitive enough to detect dementia but not necessarily MCI. It is critically important that a patient's test performance be interpreted in accordance with norms for that patient's age and educational

level, and preferably for their cultural and linguistic group and region also. Screening tests can be used to target high-risk groups who are more likely to develop dementia (i.e. those over 65 years of age) and those who are presenting with memory complaints, or to screen wider, unselected populations who are not presenting with memory problems.

Addenbrooke's Cognitive Examination

The Addenbrooke's Cognitive Examination, is such a cognitive screening test that is widely available for use across a variety of healthcare settings(Beishon et al., 2019). It is a brief, bedside, cognitive screening test that takes approximately 15 to 20 minutes to deliver and it encompasses five major cognitive domains: attention, memory, language, visuospatial function, and verbal fluency(Beishon et al., 2019). It is composed of 21 cognitive tasks and has a total score of 100, where the common cut-offs for dementia and MCI are considered at scores lower than 82 and 88, respectively. Studies have demonstrated good sensitivity (93% to 100%) and specificity (96% to 100%) at these cut-offs(Beishon et al., 2019)

Clinical Dementia Rating scale:

The CDR is derived from a semi structured interview with the patient and an appropriate informant and rates impairment in each of six cognitive categories (Memory, Orientation, Judgment and Problem Solving, Community Affairs, Home and Hobbies, and Personal Care) on a five-point scale in which none = 0, questionable = 0.5, mild = 1, moderate 2, and severe = 3. From the six individual category ratings, the global CDR IS established by clinical scoring rules where, CDR 0 = no dementia and CDR 0.5, 1, 2, or 3 indicates questionable, mild, moderate, or severe dementia

CLINICAL DEMENTIA RATING (CDR):	0	0.5	1	2	3

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretense of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests slightly impaired	Mild but definite impairment of function at home; more difficult chores abandoned; more complicated hobbies and interests abandoned	Only simple chores preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Fully capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Requires much help with personal care; frequent incontinence

Figure 1- CDR scale

Clock Drawing Test

The value of the clock drawing test (CDT) as a screening instrument for global cognitive deficits has been recognized by many studies due to its ease of use and brief administration time for patients with mild cognitive impairment (MCI) and/or various types of dementia(Shulman, 2000). Proficiency in the CDT requires a wide range of cognitive domains, such as auditory comprehension, sustained attention, visuospatial ability, memory, abstract thinking, planning, motor execution, and executive function(Eknoyan et al., 2012). The CDT was made popular in 1983, when Goodglass and Kaplan incorporated it into the Boston Aphasia Battery ("The assessment of aphasia and related disorders - NLM Catalog - NCBI," n.d.). In the first systematic use of CDT, the procedure involved clock setting where the subject was given four pre drawn clock faces including short lines marked in the positions of the twelve numbers. The subject was then asked to denote four different times including 1:00, 3:00, 9:15 and 7:30. One point was awarded for each correct placement of a hand and one point each for correctly drawing the relative lengths of the minute and hour hand, thus three points could be achieved for each

clock with a maximum of 12 points on the test(“The assessment of aphasia and related disorders - NLM Catalog - NCBI,” n.d.)

Different scoring system

Different instructions and methodologies are used to administer the CDT to cognitively impaired patients. These include using a pre-drawn circle, additional copying or time-reading commands, as well as free-drawing, which is the most commonly used method(Shulman, 2000). In addition, several different scoring systems have been used, such as the two-point system in the Saint Louis University Mental Status; the 3-point system in the Montreal Cognitive Assessment (MoCA)(https://www.facebook.com/verywell, n.d.); the five-point system in the Alzheimer's Disease Neuroimaging Initiative (ADNI)'s cognitive assessment; the 15-point system in the Behavioural Neurological Assessment (BNA)(Maeshima et al., 1997); and the 20-point system in the Mendez's scoring system. Although there is no consensus on which CDT scoring system is the most effective, studies suggest that simpler scoring systems are better because of their ease of use and their strong correlations with more complex systems(Kim et al., 2018)

The 15 point quantitative scoring system is widely used in CDT, where subject is instructed to draw a clock and correctly mark the time as ten past five

Figure 2: Representative CDT

Neural correlates of CDT

The most commonly utilized system of qualitative clock drawing categorizes six types of errors 1) size; 2) graphic difficulties; 3) stimulus-bound response; 4) conceptual deficit; 5) spatial and/or planning deficit; and 6) perseveration (Rouleau et al., 1992).

Size of the Clock: A clock-drawing is considered small if it measures less than 1.5 inches, and large if it measures more than 5 inches. Patients with Huntington's disease (HD) have a higher incidence of small clocks, whereas patients with AD have a higher incidence of large clocks (Rouleau et al., 1992). The small clocks seen in HD may be due to the micrographia seen in disorders that involve the basal ganglia and large clocks seen in AD may be a result of poor visuospatial planning due to impairment of executive (frontal lobe) and visuospatial (right parietal lobe) functioning (Eknoyan et al., 2012).

Graphical difficulties: Are present when lines are not precise, resulting either in distortions of the clock face or in numbers that are difficult to read. The hands are not straight and sometimes fail to connect in the middle. The overall performance may appear inaccurate and clumsy, but the drawing is still usually recognizable as a clock. Graphical errors are more common in HD and in moderate vascular dementias than in AD (Rouleau et al., 1992). Graphical difficulties are likely a result of secondary disruption of frontostriatal circuits necessary for coordinating fine motor control and planning (Eknoyan et al., 2012).

Stimulus-bound response: Is the tendency of the drawing to be dominated or guided by a single stimulus, most often related to the time-setting instructions (Rouleau et al., 1992) which is related to impairment in frontostriatal circuits, commonly found in AD and PD dementia (Eknoyan et al., 2012).

Conceptual deficits: defined as a loss or impairment in accessing knowledge of the attributes, features, and meaning of a clock, can be due to a drawing that does not look like a clock (i.e., misrepresentation of the clock) or drawing with hands that do not communicate a time (i.e., misrepresentation of time)

(Rouleau et al., 1992). Conceptual errors are more common in patients with mild cognitive impairment (MCI) than in normal subjects, and are likely due to impairment in semantic memory, a primary function of the lateral temporal lobes (Eknoyan et al., 2012).

Spatial and/or Planning Deficits: are due to errors in the layout of numbers on the clock-drawing (e.g., neglect of the left hemispace, deficit in planning resulting in gaps in number spacing, deficit in spatial layout of numbers in absence of a specific pattern in spatial disorganization, numbers written outside the clock face, numbers written counter-clockwise) (Rouleau et al., 1992). Spatial/planning deficits have been found to be more common in AD than in frontotemporal dementia or schizophrenia, likely due to greater parietal lobe involvement in AD (Eknoyan et al., 2012). Clock drawing errors due to spatial/planning deficits are due to impairment in the nondominant right hemisphere, especially the right parietal lobe. Frontoparietal circuits likely play a role in coordinating the visuospatial understanding of a clock and frontostriatal circuits the executive functions that result in an accurate clock face (Eknoyan et al., 2012).

Perseveration: defined as the continuation or recurrence of activity without an appropriate stimulus. In clock-drawing, this can be due to perseveration of hands (e.g., presence of more than two hands, reflecting a failure to terminate the ongoing set of tracing the hands) or perseveration of numbers (e.g., abnormal prolongation of numbers, such as writing beyond 12 or inappropriate recurrence of the same numbers) (Rouleau et al., 1992). Perseveration errors are more common in AD than in normal subjects, and are likely due to impairment of executive function in the prefrontal area of the frontal lobe (Eknoyan et al., 2012)

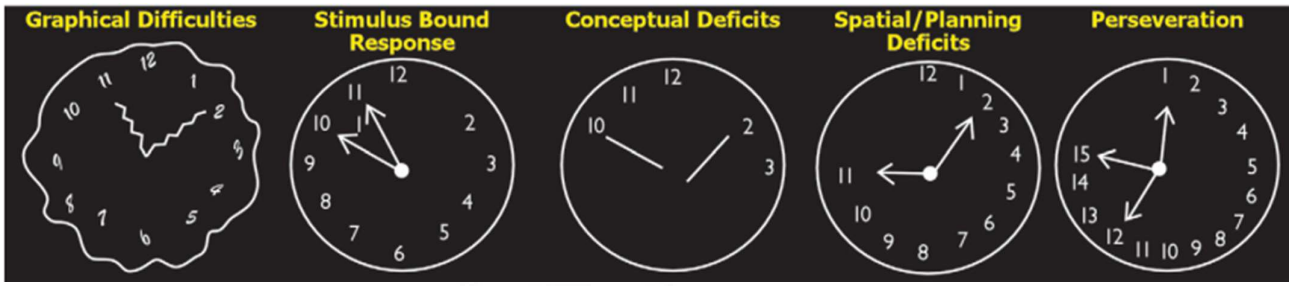


Figure 3: Representative illustrations of common types of clock drawing errors

Factors influencing CDT scoring

The utility of the CDT for screening patients with dementia as compared to normal participants has been widely accepted, and many studies have found that the positive and negative predictive values of the CDT are good(Rouleau et al., 1992). Additionally, the value of the CDT for differentiating patients with MCI from those with dementia has been recognized in many studies(Kim et al., 2018). However, there have been inconsistent findings regarding the utility of the CDT in discriminating between MCI and healthy normal controls.

Considering the subtypes of MCI, no difference was found in the performances on the CDT between amnestic mild cognitive impairment (aMCI) and vascular mild cognitive impairment (VaMCI) patients. However, to date, no studies have examined the validity of the CDT in differentiating these two MCI groups.

Cube Construction Test

Combined perceptual-motor, cognitive, and sociocultural components converge in drawing the cube. Construction involves a receptive component (visuoperceptual) and executive (practical) component along with selective attention which is affected in AD. Figure-copying tests require analysis of a visual

stimulus followed by its reproduction using motor executive skills. Analysing a visual image requires two different streams, namely, a ventral stream projecting to the inferior temporal cortex for object perception and a dorsal stream connected to the parietal cortex for visuospatial control of movement. An impairment in drawing without any compromise in intelligence, visual, or motor capabilities can be caused by parietal lesions involving either of the hemispheres(Maeshima et al., 1997). Therefore, it is reasonable to infer that the motor executive skills involved in cube copying may be a reflection of parietal lobe function. Prior studies have shown that, along with other factors, the constructional ability in cube-copying is also related to verbal intelligence(Bremner et al., 2000). In addition, drawing tasks are also a measure of executive function in dementia screening(Mathew et al., 2018)

Scoring systems

Modified scoring system of cube construction has total score of twenty eight(Mathew et al., 2018). The task consist of drawing a three-dimensional (3D) wire-cube. The form of oblique projection is known as 'cabinet oblique'. In this projection, equal length is maintained of the horizontal and vertical lines; while, the oblique lines were half in length. This form of projection is preferred because maintaining the true length in oblique lines results in suppression of elongation in the third dimension. The length of the vertical line was 2.5 cm.

There are scores for each of the three elements in the figure, i.e., the number of corners (total eight), parallel lines (total twelve), and parallel faces (total six). The overall 3D concept in the figure to capture if the information on the depth of the model was conveyed in the figure (total two). A corner was defined as a point at which three lines meet to form a vertex, and lines more than 3 mm off the intersection point were considered as being inaccurate.

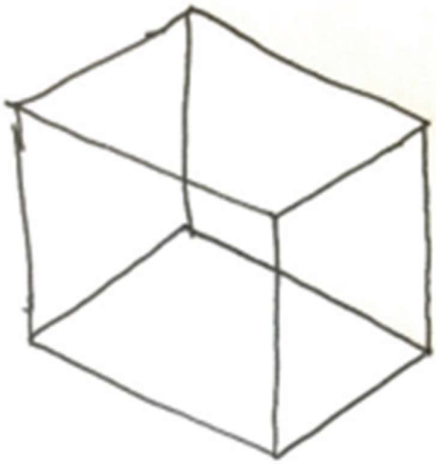


Figure 4: Representative image of CCT

MATERIALS AND METHODS

Study design:

This was a hospital based retrospective observational study. Subject details recorded in the database at Department of Cognitive and Behavioral Neurology, SCTIMST between 2012- 2021, were selected by the Clinician and provided to principal investigator. Target population consists subjects of age more than 60 years, who had at least 8 years of formal education, who had underwent CDT and CCT as a part of detailed neuropsychological evaluation with ACE scoring.

Participants:

Eligibility:

Inclusion criteria

- Age more than 60 years
- At least 8 years of formal education
- Underwent CDT and CCT as a part of detailed neuropsychological evaluation with ACE scoring

Exclusion criteria

- Moderate to advanced dementia
- Major medical comorbidity- major visual /hearing/motor deficits impairing task performances
- Clinically significant anxiety /depression/ psychiatric comorbidity
- Stroke patients with strategic infarcts

After meeting inclusion and exclusion criteria, 228 subjects were recruited for the study.

Definition:

The study participants were diagnosed by the Clinician, into cognitively normal (CN) control group, MCI and ED based on following criteria

- Controls- Cognitively normal (CN) elderly adults. Eighty subjects met inclusion and exclusion criteria
- Minimal Cognitive Impairment (MCI) subjects diagnosed by Peterson criteria(Petersen et al., 2018), with ACE scores more than 85 and CDR less than 0.5. Seventy seven subjects met inclusion and exclusion criteria
- Early dementia (ED) subjects diagnosed based on the criteria described by DSM-5 ("DSM-5," 2023), the National Institute on Aging-Alzheimer's Association (NIA-AA) workgroups(McKhann et al., 2011) and Pantoni's criteria for vascular dementia(Pantoni and Inzitari, 1993), with CDR less than 1. Seventy one subjects met inclusion and exclusion criteria

MCI and Early dementia were grouped as early cognitive impairment. The final diagnosis of the subjects was blinded to the principal investigator (PI) during initial phase of data collection

Data Collection Procedures:

Data collection was performed as two stages. During the first stage of data collection, Clock drawing test (CDT) and Cube construction (CCT) which are routinely performed as part of ACE were provided by the Clinician to the PI who was blinded to the final diagnosis and ACE scores of each subject. During ACE scoring by Neuropsychologist, subjects are instructed to draw a clock with time marked as ten past 5 (Figure 2) and to draw a three dimensional cube (figure 4). CDT was scored by the PI both quantitatively(Rouleau et al., 1992) and qualitatively (Rouleau et al., 1992) and CCT was scored quantitatively (Mathew et al., 2018). In the second stage of data collection, final diagnosis and ACE scores were revealed by the Clinician, after the PI had scored CDT and CCT. Subsequently data regarding demographics, ACE scores and final diagnosis were collected using structured proforma.

The present study is a retrospective study using the data already collected for clinical use and other purposes. Thus, informed consents from the participants was waivered.

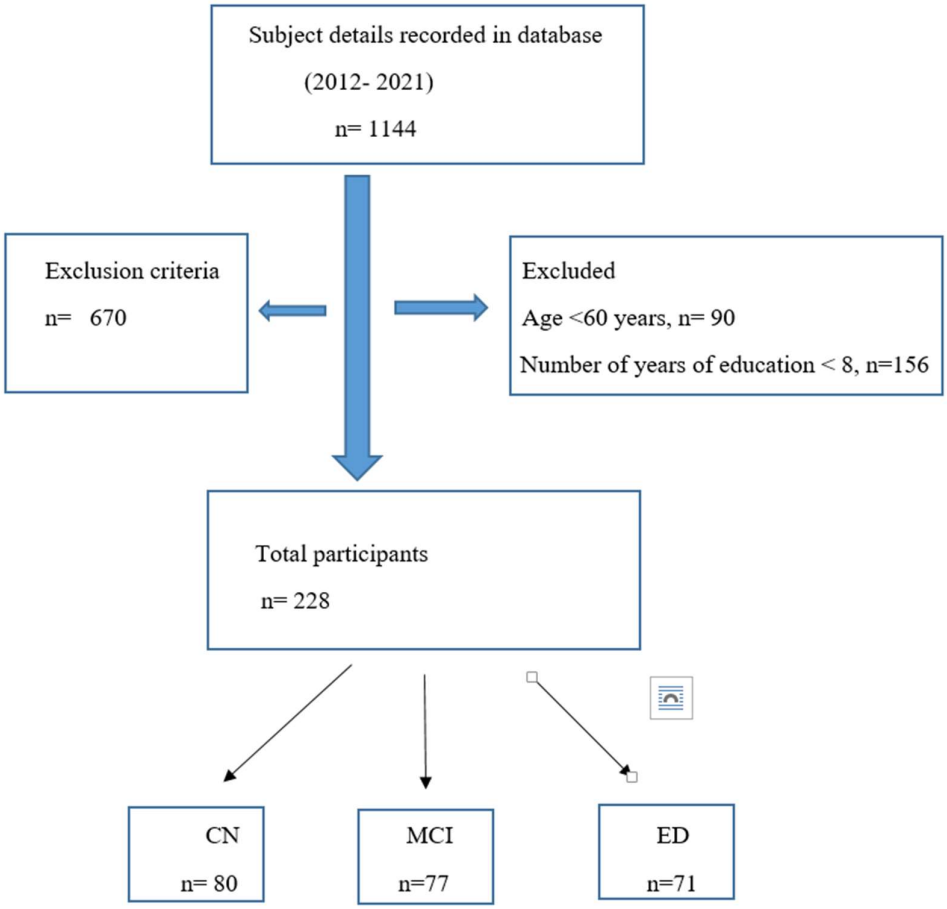


Figure 5: Patient recruitment flowchart

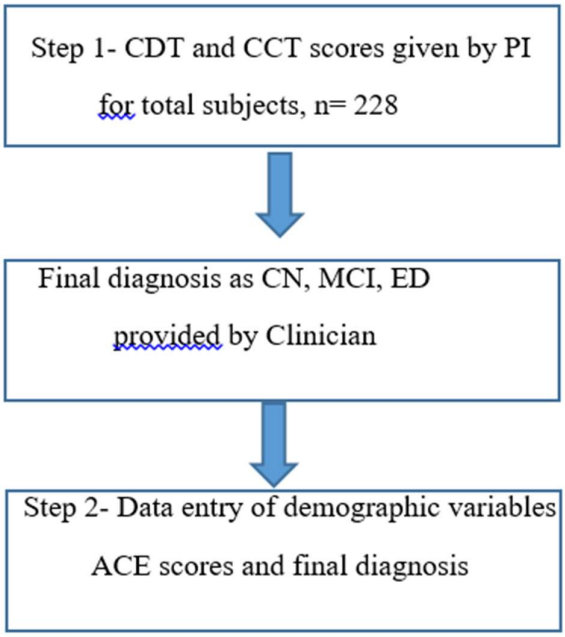


Figure 6: Step wise data collection procedure

Table 3: Quantitative scoring system of CDT

Parameters	Scoring criteria	Total score
Contour	Contour is closed or within 3 mm of closure and is not too small to contain all numbers Contour is circular with the ratio of the shortest diameter no greater than 1:1.5	1 1

Numbers	Numbers 1 to 12 are all present without additional numbers Numbers are in the corrected order All numbers are within the clock contour Numbers are approximately in the correct position Numbers are represented by either Arabic numerals alone or by Roman numerals alone not by a combination of both Paper not rotated	1 1 1 1 1
Hands	Two and only two hands are present Hour target number indicated in some manner Minute target number indicated in some manner Hands in correct proportion No superfluous markings on the clock face Hands overlap or join within 12 mm	1 1 1 1 1 1
Centre	Centre drawn or inferred	1

Table 4: Qualitative scoring of CDT (Modified Rouleau clock drawing scale)

Parameters	Scoring criteria	Score given
Size of the Clock	Small (less than 1.5 inches in diameter) Large (more than 5 inches in diameter)	1 1
Graphic Difficulties	Lines imprecise resulting in distortions of the clock face or resulting in numbers that are difficult to read Hands not straight or fail to connect in the middle Overall performance appears inaccurate or clumsy Mild: some distortions of clock face and/or hands and/or numbers. Overall performance was adequate Moderate: distortions evident, but overall performance remained interpretable Severe: distortions evident and severe, possibly resulting in a non-interpretable drawing	1 2 3
Stimulus-Bound Responses	The tendency for the drawing to be dominated or guided by a single stimulus Time is written (in letters/numbers) beside the 1 or between the 4 and the 5 Hands are pointed toward 4 or 5, or hands are absent	1 1
Conceptual Deficits	Errors reflect a loss/deficit in accessing the knowledge of the attributes, features, and meaning of a clock Misrepresentation of the clock itself (clock without numbers, no outer circle) Misrepresentation of the time (hands absent or inadequately represented, incorrect length of hands or hands the same length, time written on the clock) Numbers out of order or missing (starting sequence with 1 in the "12" position, number sequence finishes early or does not reach 12, numbers missing in the sequence)	1 1

		1
Spatial and/or Planning Deficits	Deficits in the layout of the numbers on the clock face Neglect of left hemi-space Deficit in planning, with gap before 12, 3, 6, or 9 Deficit in spatial planning of numbers, without any specific pattern in disorganization Numbers written outside of the clock face, or numbers written on the outer circle Numbers written counterclockwise	1 1 1 1 1
Perseveration	The continuation or recurrence of activity without an appropriate stimulus Perseveration of hands: presence of more than 2 hands Perseveration of numbers: abnormal prolongation of numbers (e.g., writing numbers beyond 12, or repeating the same numbers)	1 1

Total Number of Errors = _____ Total Score (16 - number of errors) = _____

Table 5: Scoring system for cube construction test

Parameter	Score given
Number of pairs of parallel sides 12 Number of faces 6 Number of corners 8 Degree of three-dimensional concept 2 Total	12 6 8 2 28

Data analysis:

The data was entered using MS Excel and analysed with the help of SPSS 26 trial version for windows (IBM Corp). The data is represented as percentages or mean +/- standard deviation as defined appropriate for qualitative and quantitative variables respectively.

Univariate analysis was undertaken to examine relationship of various factors. Crude odds ratio with 95% confidence interval was reported. Multivariate analysis/ logistic regression was used to evaluate the independent and joint effect of the variable of interest on the outcome. Statistical significance was assessed using p value

Receiver operating characteristic (ROC) curve analyses were performed in order to examine the ability of the CDT (quantitative) and CCT scoring systems to differentiate MCI and ED from CN. Areas under the receiver operating characteristic curves (AUCs) for the CDT and CCT were compared with those for the ACE to ensure that they were comparable with the ACE as a cognitive screening instrument. Using multivariate linear regression models, prediction formula for ACE was derived from CDT and CCT.

RESULTS

Baseline demographics:

A total of 228 subjects with mean age of 69 ± 6.7 years, sex ratio of 1.25:1 (M:F) and mean number of years of education of 13 ± 3.6 were recruited to the study. They were categorized into 3 groups: 80 cognitively normal (CN), 77 subjects with minimal cognitive impairment (MCI) and 71 subjects with early dementia (ED) based on clinical criteria

Demographic variables among control, MCI and ED are detailed in Table 1.1 and 1.2. The level of education and sex distribution among the groups were comparable. However, the control group was younger (mean age 67 years) than MCI (mean age 70 years) and ED (mean age 70 years) groups (p=0.007), after Bonferroni correction

Table 6 : Comparison of demographics between subjects

	CN (n=80)	**MCI (n=77)**	**Early dementia (n=71)**	**Total (n=228)**	**p value**
Age, mean (SD)	67.44(±6.32)	70.53 (6.50)	70.66 (5.95)	69.49 (6.42)	0.239
Age group, n (%) Less than 65 years	32 (40)	14 (18.2)	14 (19.7)	60 (26.3)	**0.004**
66-70 years	24 (30)	24 (31.2)	18 (25.4)	66 (28.9)	
More than 71 years	24 (30)	39 (50.6)	39 (54.9)	102 (44.7)	
Sex, n (%) Male	49 (61.2)	43 (55.8)	35 (49.3)	127 (55.7)	0.336
Female	31 (38.8)	34 (44.2)	36 (50.7)	101 (44.3)	

Education (in years), mean (SD)	13.30 (± 3.83)	13.17 (3.67)	12.9 (3.29)	13.13 (3.60)	0.656
Education (In years), n (%) Less than 12 years	43 (54.4)	42 (55.3)	39 (55.7)	124 (55.1)	0.987
More than 13 years	36 (45.6)	34 (44.7)	31 (44.3)	101 (44.9)	

Table 7: Comparison of demographic variables between subjects (Post hoc correction)

				Bonferroni corrected p value		
Variables	CN (n=80)	MCI (n=77)	ED (n=71)	MCI vs CN	ED vs CN	ED vs MCI
Age, mean (SD)	67.44(±6.32)	70.53(±6.50)	70.66(±5.95)	**0.007**	**0.006**	1
Education (in years), mean (SD)	13.30(±3.83)	13.17(±3.67)	12.9(±3.29)	1	1	1
Sex, n (%) Male	49 (61.2)	43 (55.8)	35 (49.3)			

Test variables

CDT(Quantitative), CCT, ACE and CDR among three groups

ED group scored lowest in mean CDT, CC and ACE values, and had highest CDR compared to MCI and

control group (Table 8)

Table 8: Comparison of CDT, CC, ACE and CDR among three groups

				Bonferroni corrected p value		
	CN (n=80)	**MCI (n=77)**	**ED (n=71)**	**CN vs MCI**	**MCI vs ED**	**CN vs ED**
CDT, mean (SD)	13.52 ± 2.33	12.30 ± 2.46	10.08 ± 3.99	**0.03**	**<0.001**	**<0.001**
CCT, mean (SD)	22.96 ± 7.87	22.26 ± 8.81	16.18 ± 10.15	**<0.001**	**<0.001**	**<0.001**
ACE, mean (SD)	90.60 ± 5.98	79.68 ± 9.63	73.11 ± 10.55	**<0.001**	**<0.001**	**<0.001**
CDR, mean (SD)	0.18 (±0.27)	0.47 (±0.20)	0.66(±0.26)	**<0.001**	**<0.001**	**0.001**

Comparison of Qualitative variables of CDT among groups

Further evaluation of the individual clock drawing errors examined using the Modified Rouleau criteria revealed qualitative differences between the CN, MCI, and AD groups. Six qualitative variables/errors (Size, graphic errors, stimulus bound responses, conceptual errors, spatial errors and perseveration) were compared among the subjects. As depicted in table 9, with the exception of size, all other errors were demonstrated to be at higher frequency among the cognitively impaired group. ED group had significantly higher error rate, particularly graphic errors, stimulus bound responses, conceptual errors and spatial errors compared to MCI and CN. MCI group had higher rate of error of perseveration compared to CN and ED group.

Table 9: Comparison of Qualitative variables of CDT among groups

Qualitative variable	Control N= 80 (%)	MCI N= 77 (%)	ED N= 71 (%)	Chi square(p value)
Size	7 (8.8%)	2 (2.6%)	4 (5.6%)	2.76 (0.25)
Graphic errors	38(47%)	62(80%)	61 (85%)	32.24 **(<0.001)**
Stimulus bound response	6(7.5%)	11(14%)	18 (22%)	9.32 **(0.009)**
Conceptual errors	28(35%)	40 (59%)	51 (72%)	20.45**(<0.001)**
Spatial errors	24(30%)	48 (62%)	49(69%)	26.99 **(<0.001)**
Perseveration	13(16%)	26(33%)	21(21%)	6.74 **(0.034)**

Comparison of CDT, CCT scores among subtypes of dementia

Among the MCI, amnestic MCI was present in 23 (29.9%), rest of them were either non amnestic MCI 16 (20.8%) or diagnosis not available in 38 (49.3%). Whereas among the ED, diagnosis was due to AD in 58 (81.7%), VaD 9 (12.7%), FTD 2 (2.8%), unclassified dementia in 2 (2.8%)

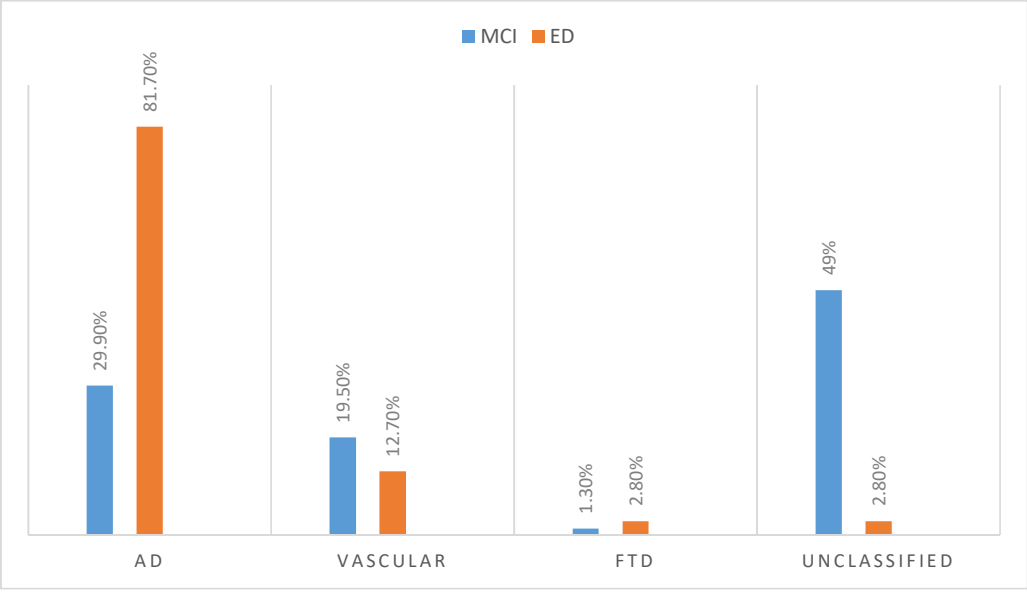


Fig 7: Distribution of clinical final diagnosis among MCI and ED groups

The mean CDT, the types of qualitative errors in CDT and mean CCT scores were comparable among various clinical diagnosis of cognitive impairment like Alzheimers, vascular or frontotemporal lobar degeneration, as demonstrated by Mann Whitney U test for quantitative variables and Chi square test for qualitative variables.

Table 10: Comparison of mean CDT, and CC among subtypes of dementia

Variable	AD (n= 81)	FTD (n= 3)	VaD (n= 24)	p value
CDT score, mean (SD)	10.8± 3.9	10 ±2.64	11.04 ±3.26	0.545
CCT score, mean (SD)	19.38± 9.5	12.6± 9.2	15.04± 10.9	0.809
Size abnormality, frequency (%)	2 (2.5)	0 (0)	2 (8.3)	0.59
Graphic errors, frequency (%)	64 (79)	2(66)	22(91)	0.341
Stimulus, frequency (%)	20 (24)	1 (33)	2 (8)	0.244
Conceptual, frequency (%)	54(66)	3(100)	15(62)	0.106
Spatial, frequency (%)	51(63)	3(100)	16(64)	0.59
Perseveration, frequency (%)	24(29)	2(66)	6(25)	0.39

Correlation between variables and outcomes

Correlation between demographic variables and CDT scores

The correlation between age, number of years of education, and CDT was studied using Spearman's rank correlation test (Rho). A significant ($p < 0.05$) negative correlation between age and CDT scores were found among CN and total population, which was lost among MCI and ED groups.

Table 11: Correlation of age and number of years of education with CDT scores

Population	Variables	Rho	p value
Total (n=228)	Age	-0.167	**0.011**
	Education	0.073	0.276
CN (n=80)	Age	-0.224	**0.046**
	Education	0.223	**0.048**
MCI (n=77)	Age	0.082	0.478
	Education	-0.051	0.661
ED (n=71)	Age	-0.082	0.495
	Education	0.018	0.880

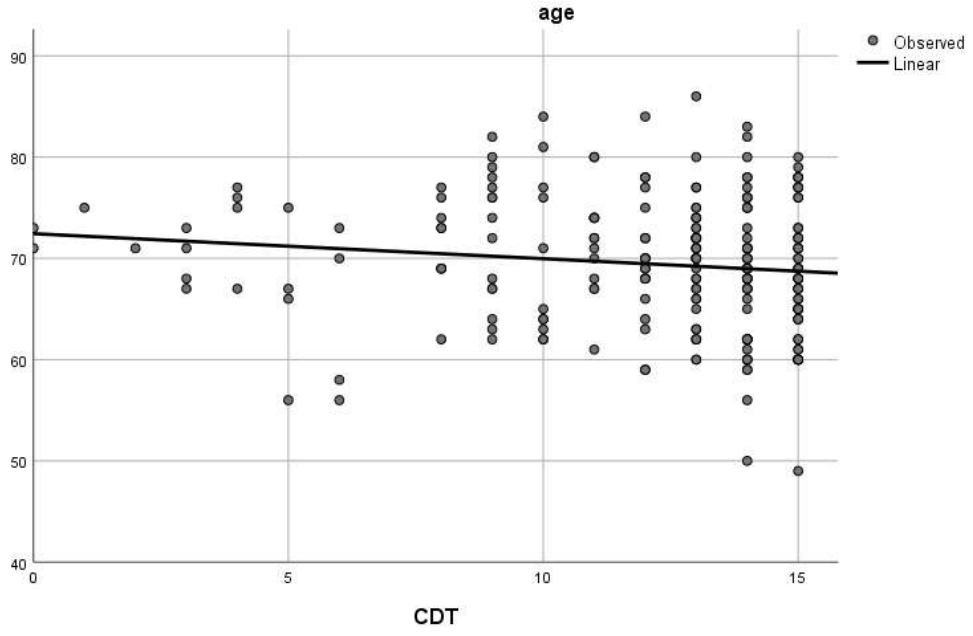


Figure 8: Correlation of age with CDT scores among total population

Number of years of education had significant ($p< 0.05$) positive correlation with CDT scores only in cognitively normal subjects, which is cancelled in diseased population. Irrespective of educational levels, when population shifts from normal to MCI/ ED, CDT scores are affected.

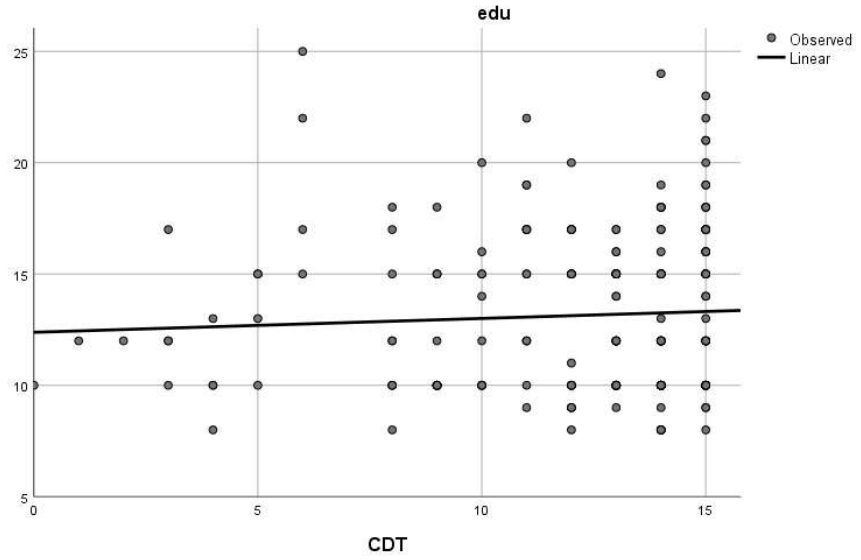


Figure 9: Correlation of number of years of education and CDT scores among CN subjects

Correlation between demographic variables, CDT score and CCT scores

The correlation between age, number of years of education and CDT scores with CCT scores was studied using Spearman's rank correlation test. There was significant ($p < 0.05$) correlation between CDT scores and CCT scores across all population groups

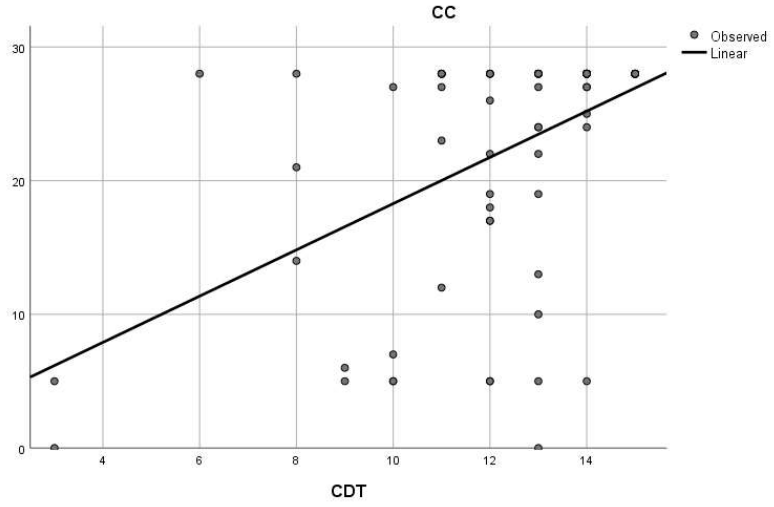


Figure 10: Correlation of CDT to CCT among total population, CN, MCI and ED groups

Age did not have correlation with CCT scores among total population or CN, MCI and ED groups separately. Number of years of education had significant ($p<0.05$) positive correlation with CCT scores among CN and MCI, which was lost in ED group

Table 12: Correlation of demographic variables, CDT and CC scores

Population	Variables	Rho	p value
Total (n=228)	Age	0.072	0.278
	Education	0.212	**0.001**
	CDT	0.052	**<0.001**
Control (n=80)	Age	0.038	0.739
	Education	0.353	**0.001**
	CDT	0.344	**0.002**
MCI (n=77)	Age	0.174	0.131
	Education	0.298	**0.009**
	CDT	0.471	**<0.001**
ED (n=71)	Age	0.150	0.212
	Education	0.012	0.922
	CDT	0.471	**<0.001**

The mean CDT and CCT scores among males and females were studies across the three groups of CN, MCI and ED using ANOVA. CCT scores among males and females were comparable among each of the groups. However, among the ED population, women had significantly lower mean CDT scores compared to men, irrespective of age and number of years of education

Table 13: Mean CDT and CCT scores of males and females among groups

Variable	CN (n=80)	MCI (n=77)	ED (n=71)
Mean CDT score	M: 13.6 ± 1.62 F: 13.26 ± 3.172 p = 0.42	M: 12.23 ± 1.95 F: 12.38 ± 3.01 p 0.79	M: 11.23 ± 3.23 F: 8.97 ± 4.3 **p= 0.016**
Mean CCT score	M: 23.96± 7.06 F: 23.39± 8.96 p= 0.156	M: 22.3± 8.04 F: 21.41± 9.76 p= 0.57	M: 16.86± 10.84 F: 15.53± 9.51 p= 0.58

Correlation between CDT, CCT scores and total ACE scores

Standard neuropsychological tests like ACE scores were strongly correlated with CDT and CCT scores among total population as well as across CN, MCI ad ED groups

Table 14: Correlation between CDT, CCT scores and total ACE scores

Population	Variables	Rho	p value
Total (n=228)	CDT	0.586	**<0.001**
	CC	0.447	**<0.001**
CN (n=80)	CDT	0.318	**0.002**
	CC	0.430	**<0.001**
MCI (n=77)	CDT	0.256	**0.010**
	CC	0.230	**0.022**
ED (n=71)	CDT	0.701	**<0.001**
	CC	0.48	**<0.001**

Utility of CDT and CC as screening test for diagnosing early cognitive impairment

Sensitivity and specificity of CDT, CC, ACE in diagnosing MCI from CN

Using Youden's J maximum statistics, CDT cut off score of 14 had optimal sensitivity (68%) and specificity (63%), with area under ROC (AUC) of 0.63 ($p < 0.001$). CCT cut off score of 25 had optimal sensitivity (65%) and specificity (36%), with AUC of 0.51 ($p<0.001$).

Table 15: Diagnostic accuracy of CDT, CCT in detecting MCI from CN

Modality	Cut off score	AUC	Sensitivity	Specificity
CDT	14	0.7033	68.75	63.64
CCT	25	0.51	65.00	36.36
ACE	85	0.85	87.5	57.14

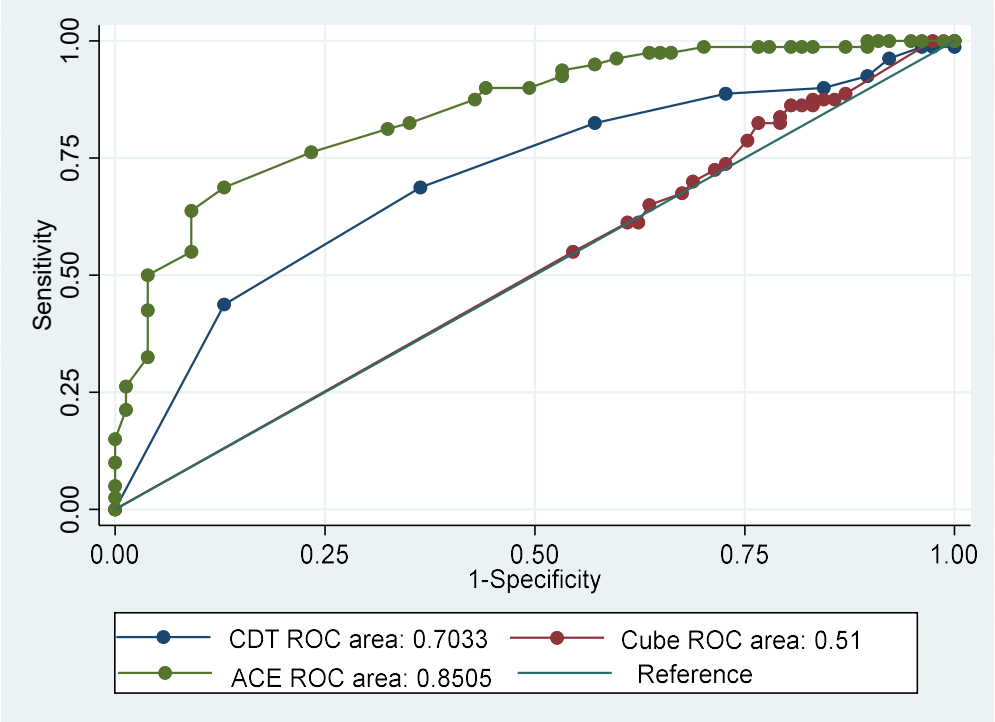


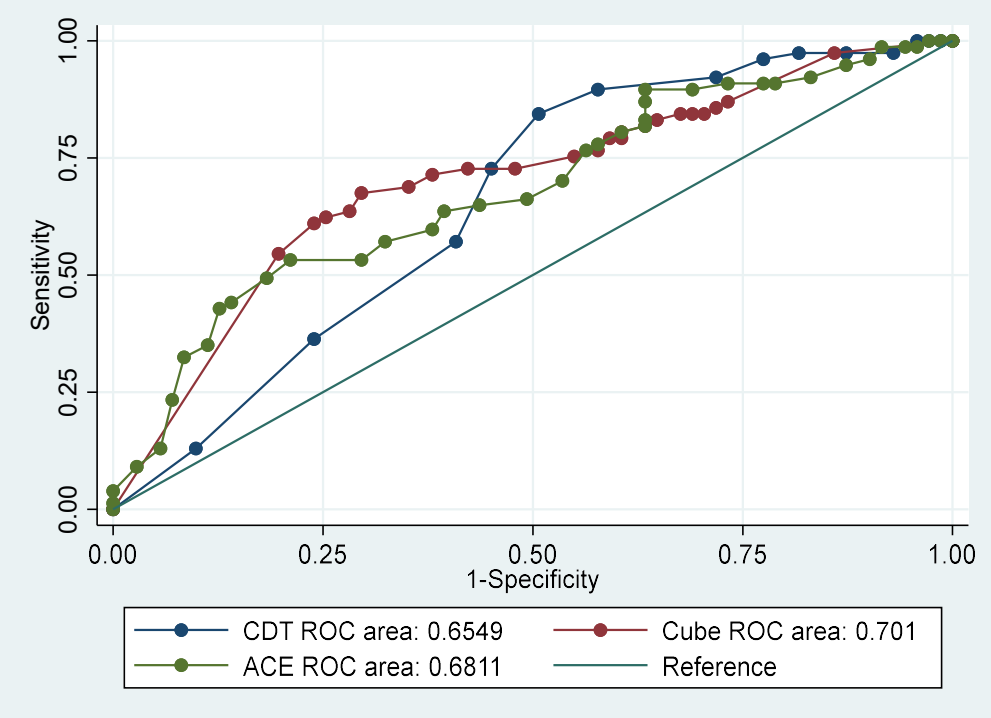
Figure 11: ROC curve: CN Vs MCI

Sensitivity and specificity of CDT, CC, ACE in diagnosing ED from MCI

Using Youden's J maximum statistics, CDT cut off score of 12 with sensitivity (72.73%) and specificity (54.93%), and CCT cut off score of 22 with sensitivity (71.43%) and specificity (61.97%), did not have statistical significance (p= 0.59)

Table 16: Diagnostic accuracy of CDT, CCT in detecting ED from MCI

Modality	Cut off score	AUC	Sensitivity	Specificity
CDT	12	0.655	72.73	54.93
CCT	22	0.701	71.43	61.97
ACE	73	0.681	77.92	42.25



P value = 0.5892

Figure 12: ROC curve: ED vs MCI

Sensitivity and specificity of CDT, CC, ACE in diagnosing ED from CN

Using Youden's J maximum statistics, CDT cut off score of 12 had optimal sensitivity (88.75%) and specificity (54.93%), with AUC of 0.79 ($p < 0.001$). CCT cut off score of 22 had optimal sensitivity (72.5%) and specificity (61.97%), with AUC of 0.72 ($p < 0.001$).

Table 17: Diagnostic accuracy of CDT, CCT in detecting ED from CN

Modality	Cut off score	AUC	Sensitivity	Specificity
CDT	12	0.79	88.75	54.93
CCT	22	0.72	72.50	61.97
ACE	84	0.93	90.00	85.92

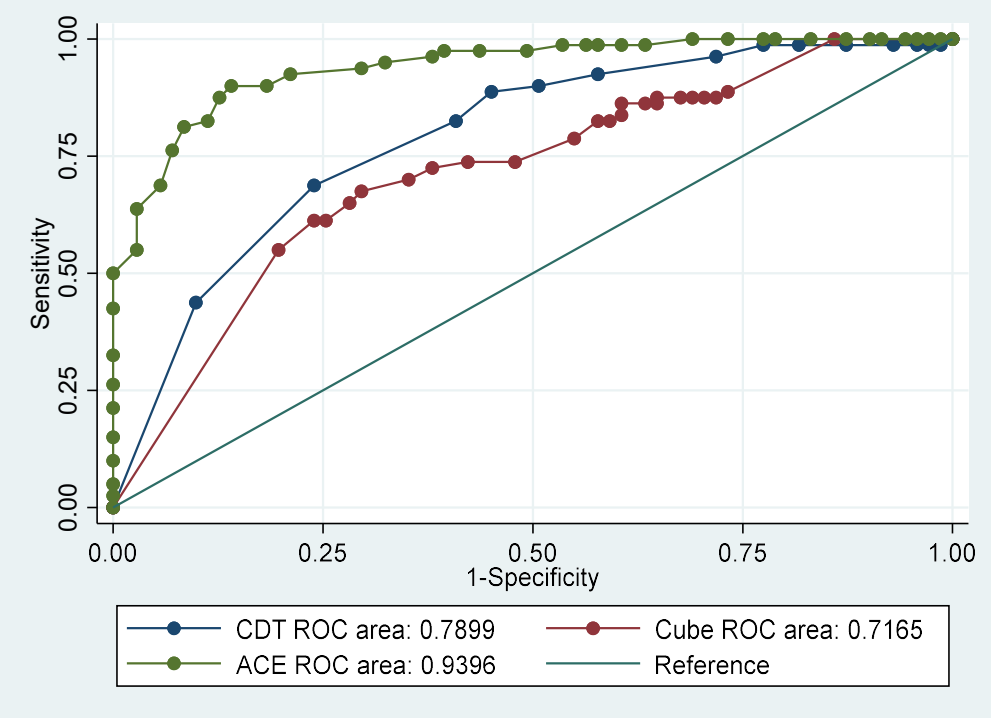


Figure 13: ROC curve – CN vs ED

The results suggest the utility of quantified CDT and CCT scores to differentiate ED from CN and intermediate utility to distinguish MCI from controls wherein a global screening instrument such as ACE has high sensitivity.

Predictability of CDT, CC in early cognitive impairment

Odd's ratio was estimated using binary logistic regression models, p value of <0.05 was taken as statistically significant. Number of years of education, CDT scores, qualitative variables of CDT (spatial planning, perseveration), CCT scores were associated with increased risk of early cognitive impairment (OR >1)

Table 18: Binary logistic regression model

Variable	Category	Adjusted OR (95% CI)	p value
Age	-	0.98 (0.92-1.04)	
Sex	M (Reference) F	1 0.93 (0.44-1.96)	
Education	-	1.02 (0.91-1.13)	
CDT score	-	1.24 (1.04-1.49)	**0.01**
Size	0 (Reference) 1	1 0.91 (0.13-6.40)	
Graphic errors	0 (Reference) 1	1 0.56 (0.53-4.61)	
Stimulus bound responses	0 (Reference) 1	1 0.59 (0.23-1.58)	
Conceptual deficits	0 (Reference) 1	1 0.93 (0.34-2.56)	

Spatial planning	0 (Reference) 1	1 1.88 (0.79- 4.47)	
Perseveration	0 (Reference) 1	1 1.96 (0.82-4.70)	
CC score	-	1.06 (1.01-1.11)	**0.01**

Linear regression models were used to generate coefficients, for predicting ACE scores from available variables. Age, number of years of education, CDT scores, CCT scores were analyzed in linear regression model, which had significance (p value <0.001)

A formula was developed using simple linear regression that related CDT scores, CCT scores, age and number of years of education with the ACE as follows:

ACE = α + (ß X variable), where α is the constant and ß is the coefficient for a given variable

Table 19: Linear regression model

Variable	α	ß	p value
Age	96.4	-0.121	**<0.001**
Education	76.7	0.11	**<0.001**
CDT score	54.9	0.63	**<0.001**
CC score	69.6	0.47	**<0.001**

Adjusted coefficients in multivariable linear regression,

ACE = 61.84 + (-0.14 x age) + (0.15 x education) + (1.80 x CDT) + (0.26 x CCT)

Where, α = 61.84

ß1 = -0.14

ß2 = 0.15

ß3 = 1.8

ß4 = 0.26

Coefficient of determination, (R^2) = 0.43

DISCUSSION

Our study aimed to examine whether CDT and CCT differed in performance among subjects with ECI and if they could independently be used as screening tool to diagnose MCI and ED from cognitively normal subjects. This is the first study from India addressing visual construction impairment in MCI and ED which has shown its utility as a screening instrument for early diagnosis of cognitive impairment. Both quantitative scores and qualitative errors in CDT were significantly impaired among the MCI and ED. CDT scoring was more objective and scored better as a screening tool than CCT for diagnosing MCI and ED from CN. The tests are more useful to distinguish ED from CN and to some extent MCI from CN, however not MCI from ED. In addition, relationships between the CDT, CCT and other neuropsychological measures as well as demographic variables were evaluated through correlational analyses. Finally, using a linear regression model, a prediction classifier for ACE value was derived from CDT, CCT and demographic variables.

Demographic Variables

All three groups (CN, MCI, ED) were homogenous in terms of demographic variables like sex distribution and number of years of education. However the control group were slightly younger (mean age of 67 years) compared to MCI and ED (mean age of 70 years), which was almost similar compared to previous studies(Kim et al., 2018). It is important to balance basic demographic variables among the groups before comparison of test variables as the visuospatial abilities can vary according to age and number of years of education(Ardila et al., 1989; Osterweil et al., 1994)

Comparison Of Test Variables

Our study demonstrated significantly lower mean CDT scores and CCT scores, as well as increased frequency of qualitative errors of CDT among subjects with MCI and ED compared to cognitively normal controls.

Consistent with severity of diagnosis, ED followed by MCI group had highest CDR scores and poor performance in ACE scoring as expected. Mean CDT scores were following similar trends with highest contrast demonstrated among MCI vs ED and CN vs ED group. Though the differences of mean CDT among CN vs MCI were statistically significant, absolute values (13.52 vs 12.30 respectively) were too close to be useful in demonstrating utility as screening tool. This result was similar to previous studies, were difference were maximum among ED vs CN than MCI vs CN(Charernboon, 2017; Kim et al., 2018), using different scoring methods. We used 15 point scoring system for CDT which evaluates various aspects of visuospatial abilities, in contrast to 5 point scoring system used in (Charernboon, 2017). Another study has compared three different scoring systems of CDT (3 point, 5 point and 15 point) among CN, MCI and ED(Kim et al., 2018) and found that 15 point scoring system best discriminated ED due to AD from MCI and CN, hence 15 point scoring system was adopted in our study.

Concerning errors identified by the Modified Rouleau CDT scoring system, graphic difficulties, stimulus bound responses, conceptual deficits, and spatial-planning errors were the most commonly committed error types across all groups. When the error performances of the CN and MCI group were compared, those occurring at highest frequency among MCI were that of graphic errors, conceptual errors and spatial errors. Whereas no significant differences emerged for the stimulus-bound and perseveration error categories. This result may suggest that these errors either are not frequently committed in the earliest stages of dementia or occur no more often than that seen with CN controls.

When compared to the MCI and the CN groups, the AD group exhibited greater difficulties in all error categories except size of clock, with highest error rate in graphic, conceptual and spatial catagories. The results regarding the CDT errors among MCI and ED so far were consistent with that of previous

studies(Parsey and Schmitter-Edgecombe, 2011).

However, errors with regard to size of the clock were spuriously higher among the CN than in MCI or ED. As size abnormality included both smaller and bigger sizes, which were not further analysed in the current study due to relatively smaller sample size, reason for cognitively normal elderly population having more error rate in size could be better clarified with further studies analysing the same concern. If the size errors are found to be those related to bigger size, possible presence of primary visual impairment among the CN elderly population could explain the higher rate of size errors.

Mean CCT scores were also significantly lower among ED and MCI with maximum difference in absolute values between ED and rest of the population, which was consistent to that in previous studies(Charernboon, 2017; Mathew et al., 2018).

Only few studies were reported in literature comparing the performance of CDT among various subtypes of cognitive impairment like amnestic MCI(aMCI), vascular MCI(VaMCI), AD or vascular dementia(VaD)(Kim et al., 2018), which demonstrated that the aMCI group exhibited significantly higher scores than the VaD, although the VaMCI did not demonstrate any differences with the AD or VaD groups. Our study however showed that mean CDT, the types of qualitative errors in CDT and mean CCT scores were comparable among various clinical diagnosis of cognitive impairment like Alzheimers, vascular or frontotemporal lobar degeneration. However the results could not be commented adequately in view of the smaller sample size when categorizing into subgroups as most of the final diagnosis regarding final etiology were not completed. No Indian studies so far to the best of our knowledge has looked into variation of qualitative errors in CDT and CCT scores among the subgroups.

Correlation Of Demographics And Standard Neuropsychological Tests With CDT And CCT

CDT scores and CCT scores were strongly correlated with standard neuropsychological tests like

total ACE scores which was used in the clinical classification of total population into CN, MCI and ED groups which was at par with results obtained in previous studies(Mathew et al., 2018). The geometric copying and handwriting skills are known to be decreased in direct proportion to decreased cognitive functioning, and failure in copying a cube has been shown to be useful in differentiating between normal and AD participants(Gaestel et al., 2006). The visuospatial impairment may be particularly important to identify during the initial examination because this problem may be associated with difficulties in walking and other aspects of functional limitations.

In our study, CDT scores had negative correlation with age and positive correlation with number of years of education among the cognitively normal subjects, which was not observed among MCI and ED groups. Similar results were observed in previous studies(Parsey and Schmitter-Edgecombe, 2011). This would indicate that as diseased stage advances from cognitively normal individuals to MCI and ED, visuospatial abilities are affected proportionately irrespective of the age and educational status. Also among cognitively normal subjects and ECI, interpretation of visuospatial constructional tools has to be used with caution as they are influenced by the age and educational status of the individual(Osterweil et al., 1994). Usefulness of CDT among illiterates is of limited value and minimum number of years of education sufficient for adequate copying skills are 6 to 8 years of formal education(Ardila et al., 1989). Hence, age and education specific cut-off values are needed for the appropriate interpretation of performance.

CDT scores were uniformly correlating with CC scores across all groups of population, irrespective of the age and educational status, which was expected as both tests embrace the visuospatial abilities. Similar to the CDT, number of years of education had positive correlation with CCT scores among CN and MCI, which was lost in ED. However, age did not have a significant correlation with CCT.

Previous studies have shown that gender influences clock drawing and cube construction

performance along with other visuospatial parameters, with male subjects showing a better performance(Ardila et al., 1989). Our study showed that mean CDT and CCT scores did not differ significantly between men and women, among CN and MCI subjects. However, among the ED group, women had lower mean CDT score compared to men irrespective of age and educational status. More studies are required to comment on explanation for the possible additional effect of gender on visuospatial constructional skills as disease advances. Probably the disease pathology hits harder on women, as evidenced by female gender being a risk factor for Alzheimers(McKhann et al., 2011) giving rise to poorer performance on cognitive tests.

Utility Of CDT And CCT As Screening Instrument

For demonstrating the utility in diagnosing ECI, cut off scores for CDT and CCT at optimal sensitivity and specificity were estimated by plotting ROC curves for CN vs MCI, MCI vs ED and CN vs ED.

Regarding detection of MCI from CN, participants with MCI had only slightly lower scores than CN in CDT (cut off score 14) and CCT (cut off score 25) leading to low sensitivity ranging from 65% (CCT) to 68% (CDT).

For detecting ED from CN, CDT (at cut off score of 12) showed good sensitivity (88.75%) and specificity of 54.93%. CCT at cut off score of 22 had intermediate sensitivity of 72% and specificity of 61%. Hence among the two tests, CDT had better diagnostic accuracy as screening test than CCT. The ROC curve plotted for detection of ED from MCI did not yield a statistically significant result.

These results suggest that the tasks are not sensitive detectors of cognitive impairment in MCI. Consequently, using these tasks alone are not recommended for screening of MCI. This result confirms other studies(Charernboon, 2017) that CDT and CCT does not appear to be a valid screening tool for detecting MCI. However, it could distinguish between normal aging and early dementia

In a multivariate regression analysis, variables such as age, number of years of education, CDT score and CCT score were used to derive the final ACE score using the formula

ACE = 61.84 + (-0.14 x age) + (0.15 x education) + (1.80 x CDT) + (0.26 x CCT)

Where, $\alpha = 61.84$, $ß1 = -0.14$, $ß2 = 0.15$, $ß3 = 1.8$, $ß4 = 0.26$, Coefficient of determination, $(R^2) = 0.43$

From a clinical perspective the clock drawing and cube construction test provides an easy to use visual record of cognitive function that is appealing to busy clinicians. Generally it takes less than a minute to conduct and score and appears to have achieved general acceptability on the part of patients

Strengths:

1. The principal investigator was blinded to the final diagnosis during the period of data analysis of CDT and CCT
2. This is the first Indian study looking into utility of CDT and CCT in diagnosing MCI and early dementia
3. We also looked into qualitative errors in CDT analysis

Limitation:

1. This was a retrospective study with relatively small sample size
2. There was no longitudinal follow up for final diagnosis in terms of etiology (Alzheimers/ vascular/ Frontotemporal lobar degeneration/ others) for all the patients

CONCLUSION

Robust screening tools for detection of MCI and early dementia is need of the hour. Clock drawing test and cube construction are simple to administer tasks which when analysed qualitatively along with quantitatively gives valuable insights into stage of dementia and can possibly be used as screening tools in place of standard neuropsychological tests like ACE. These tasks which utilise visuospatial abilities of individual were found to be performing better in diagnosing ED from CN, than MCI from CN. CDT scored better as screening tool than CCT possibly due to better objectivity in the scoring system. Level of education is a limiting factor in interpreting these results however. Further studies on different ethnicities and focussing more on qualitative errors of these tests would be useful.

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ANNEXURES

1. CV of Principal Investigator- Dr Sayooja Sachithanandan

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Date of Birth (dd/mm/yy) 04/12/1989		Sex FEMALE
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Academic Qualifications (Most recent qualification first)		
Degree/Certificate	Year	Institution, Country
MD GENERAL MEDICINE	2019	GOVERNMENT MEDICAL COLLEGE, THIRUVANANTHAPURAM, KERALA, INDIA
MBBS	2014	GOVERNMENT MEDICAL COLLEGE, THIRUVANANTHAPURAM, KERALA, INDIA

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration: TRAVANCORE COCHIN MEDICAL COUNCIL

REGISTRATION NUMBER: 52138

YEAR OF REGISTRATION: 2014

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
JANUARY, 2021	SENIOR RESIDENT, NEUROLOGY	SCTIMST, INDIA

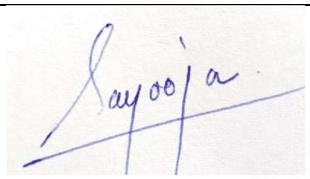
Brief summary of relevant research experience:

Observational study: CT angiographic imaging patterns differentiate pseudo occlusion from true occlusion of proximal ICA in acute ischemic stroke

Observational study: Autism spectrum disorder with and without epilepsy: a comparative study on clinical, developmental, electrophysiological and radiological profile

Current project/s at hand:

	Date: 25/08/2023 Place: Trivandrum

Signature: 	

Last Name: Menon	First Name: Ramshekhar	Middle Name: N
Date of Birth (dd/mm/yy) 25/09/1978		Sex M
Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator) PrincipalInvestigator		
Professional Mailing Address (Include Institution name)	Study Site Address (Include Institution name)	

Epilepsy Office, 4th floor , Block 2, SCTIMST, Trivandrum-11	Department of Neurology, SCTIMST, Trivandrum 11
Telephone (Office): 0471- 2524481	Mobile Number: 9946916769
Telephone (Residence):0471- 2734040	Email: rsnmenon@sctimst.ac.in

Academic Qualifications (Most recent qualification first) Epilepsy Fellowship, DM, DNB, MD, MBBS

Degree/Certificate	Year	Institution, Country
MBBS	2002	University of Pune, India
MD, DNB Medicine	2006	University of Mumbai, India
DM Neurology	2009	Maharashtra University of Health Sciences, India
Epilepsy Fellowship	2010	SCTIMST

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration- TCMC- 30958/2002

Current and previous positions (most recent position first) Professor, Department ofNeurology

Month and Year	Title	Institution/Company, Country
2017-2022	Additional Professor	SCTIMST

2015-2017	Associate Professsor	SCTIMST
2011-2015	Assistant Professor	SCTIMST

Brief summary of relevant research experience:

Research and clinical experience in epilepsy, cognitive neurology, autoimmune disorders, status epilepticus and general neurology

No. of publications and book chapters: 61No. of extramural funded projects: 15

Current project/s at hand:

PI: Effect of yoga on neuropsychological functions and brain connectivity networks in mild cognitive impairment and cognitively normal subjects.3 years. Commenced on 30/07/2016; Status ongoing.

Project PI: The influence of sleep architecture on the severity of memory disruption in amnesticMCI-Funded by Kerala State Council for Science, Technology and Environment. INR 8,41,500. Status completed in November 2016.

Project PI: Validation of memory fMRI paradigms and its utility in pre-surgical evaluation of patients with refractory TLE. Funded by Department of Science & Technology. INR 14,85,000. Status- completed on 31/03/2017

Site Project PI: Development and validation of a comprehensive clinical and neuropsychologicaltest battery for use in the Indian context for patients with Vascular Cognitive Impairment. Funded by ICMR. INR 14,00,000. Status completed on 31/12/2015

Project PI: The human brain mapping project- a resting state fMRI study of healthy controls andpatients with MCI & AD. Funded by cognitive science initiative of DST. INR 18, 77,600. Status ongoing.

Technology development- Site Project PI: Biomedical signal analyzer for seizure prediction, in collaboration with Centre for development of Advanced Computing, Trivandrum. Funded by Department of Electronics & Information Technology. INR 4,62,000 out of INR 30,38,000. Commenced on 30/06/2014. Pilot phase completed on 30/06/2015

Collaboration with BMT wing projects- Development of intracranial electrodes for use in acute and chronic electrocorticography for periods up to 15 days.- Clinical PI

Co-PI: Non-linear analysis of EEG signals in Alzheimer's Disease through DST funding provided to collaborating centre, NIT Kozhikode. Commenced on 04/07/14. Status completed on 30/06/2015

Co-PI: Biochemical and functional investigation of dorsolateral prefrontal cortex in mild cognitiveimpairment using functional magnetic resonance spectroscopy and functional magnetic resonance imaging. Commenced on 2/7/2016;INR 14,40,000 (DST-SERB); status completed on 01/07/2018.

Co-PI: A resting state fMRI and task based fMRI study: Optimization, language lateralization, memory lateralization and connectivity in normal subjects versus patients with epilepsy. Commenced on 1/7/2014; Status Ongoing; DBT

Co-investigator: In vitro beta-amyloid uptake by peripheral blood macrophages: predictor for progression of mild cognitive impairment to Alzheimer's disease. Commenced on 1/3/2015; ICMR- Rs. 40,99,400; Status Ongoing.

Co-investigator: Study of genetic risk factors associated with inflammation, autophagy and oxidative stress in Alzheimer's Disease and Frontotemporal Dementia; DST-SERB Postdoc fellowship- INR 19,20,000	
 Signature: Ramshekhar N Menon	Date: 03/09/2021 Place: Trivandrum

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1882/MAY/2022 14.09.2022

Dr. Sayooja Sachithanandan
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Sayooja Sachithanandan,

The Institutional Ethics Committee held on 13th May, 2022, reviewed and discussed your application to conduct the study titled **"UTILITY OF CLOCK DRAWING TEST AND CUBE CONSTRUCTION IN DIAGNOSIS OF EARLY COGNITIVE IMPAIRMENT"** (IEC/1882).

The following members of the Ethics Sub-committee were present at the meeting held on 13th May, 2022.

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
2.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
3.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
4.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
5.	Adv. Priya Kaimal	LLM, MBL	Female	Legal Expert	No
6.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
7.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. *Checklist Form*
2. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 03.09.2021*
3. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 02.09.2021 from Dr. Rakmshekhar N Menon, Additiona Professor, Department of Neurology, SCTIMST*
4. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 02.09.2021 from Dr. Sylaja PN, Professor, Department o Neurology, SCTIMST*
5. *IEC Application Form*
6. *Project Proposal*
7. *Declaration Form*
8. *Informed Consent in English and Malayalam*
9. *Subject Information in English and Malayalam*
10. *CV of PI and Co-PI*
11. *Proforma*
12. *SRC Recommendation Letter*

Revised submission

1. *Responses/Amendments made on the Reviewer's comments*
2. *Checklist Form*
3. *Glossary*
4. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 12.09.2021*
5. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 12.09.2021 from Dr. Rakmshekhar N Menon, Additional Professor, Department of Neurology, SCTIMST*
6. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 12.09.2021 from Dr. Sylaja PN, Professor, Department of Neurology, SCTIMST*
7. *IEC Application Form*
8. *Project Proposal*
9. *Declaration Form*
10. *CV of PI and Co-PI*
11. *Proforma*

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Dr. G. Srinivas
Member Secretary, IEC

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM

MEMBER SECRETARY

PROFORMA

AGE: **SEX:**

EDUCATIONAL QUALIFICATION:

OCCUPATION:

HANDEDNESS:

MEDICAL COMORBIDITIES: DIABETES/ HYPERTENSION/HYPOTHYROIDISM

DISABILITY IF ANY: VISUAL/ HEARING IMPAIRMENT, MOTOR OR SENSORY DEFICITS.

PSYCHIATRIC COMORBIDITIES: DEPRESSION/PSYCHOSIS/ ANXIETY/ DRUG ABUSE

HISTORY OF STROKE: YES/NO

DIAGNOSED/SUSPECTED PRIMARY PROGRESSIVE APHASIA: YES/NO

COGNITIVE DOMAINS INVOLVED:

MMSE:

ACE SCORE:

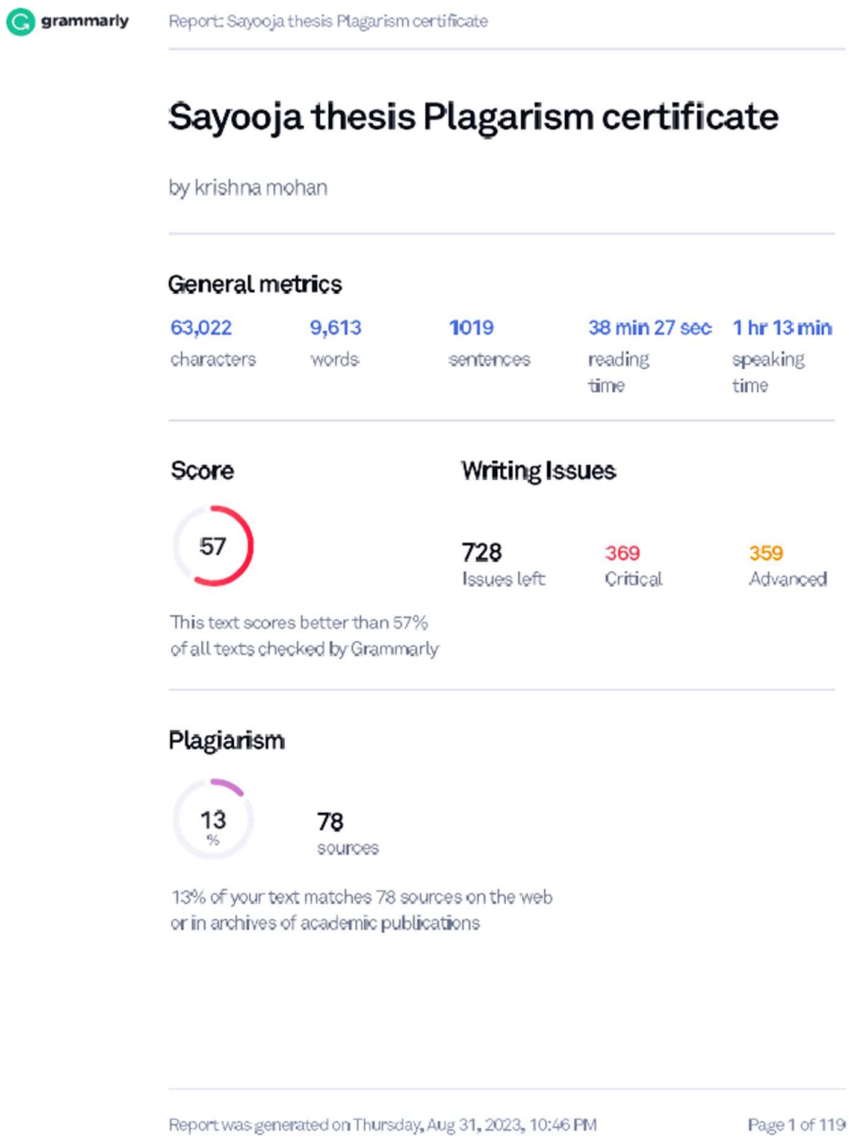
CLINICAL DEMENTIA RATING:

CLOCK DRAWING TEST SCORE:

CUBE CONSTRUCTION TEST SCORE:

FINAL DIAGNOSIS:

PLAGARISM CERTIFICATE



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Sayooja thesis Plagarism certificate

by krishna mohan

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Issues left	Critical	Advanced

Plagiarism

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