Diagnostic Utility of Revised Addenbrooke's Cognitive Examination (ACE-R) for Discrimination of Types of Dementia and its Applicability in Parkinson's Disease Dementia (PDD)

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Abstract: Objectives: To evaluate the discriminative ability of Mini Mental State Examination; (MMSE), Clock-drawing test (CDT) and revised Addenbrooke' cognitive examination (ACE-R) for differentiation of demented patients from controls and between types of dementia.Patients & Methods: The study included 160 patients; 113 males and 47 females with mean age of 65.2±7.2 years. Patients were diagnosed as regards type and severity of dementia using the Clinical Dementia Rating (CDR) scale and were assessed as regards demographic and social variables. The study also included 40 age-matched controls, all patients and controls completed MMSE, CDT and ACE-R scoring systems.Results: Mean total and differential ACE-R scoring of dementia patients were significantly lower compared to controls. Alzheimer dementia (AD) patients showed significantly lower scores compared to other dementia patients. Vascular dementia (VD) patients had significantly lower total score compared to patients had Parkinson's disease dementia (PDD) and other types of dementia with significantly lower total scores in PDD patients. Receiver operating characteristic (ROC) curve analysis defined ACE-R as the significant discriminative scoring system between types of dementia with high screening ability for AD and VD with area under curve (AUC)=0.085 and 0.288, respectively and showed high diagnostic ability for PDD with AUC=0.711. ROC curve analysis defined ACE-R score in range of 61-63 to give the highest diagnostic yield with sensitivity and specificity rates of 90.2% and 62.2%, respectively with accuracy rate for the diagnosis of 65% for the three points. Conclusion: ACE-R is a valid and reliable screening modality for dementia and could significantly identify patients had PDD with sensitivity and specificity for the cutoff score range of 61-63 points. Moreover, ACE-R is easy to administer without need for difficult maneuvers and could be used as a screening test for other types of dementia with high sensitivity.

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1. Introduction

Dementia is a clinical syndrome whose main element is memory impairment; it is due to Alzheimer's disease in more than 75% of cases. Alzheimer's disease, on the other hand, is a neuropathological entity that is characterized by a protracted preclinical phase followed by the onset of slowly progressive dementia. About 60% of demented patients manifest the typical pathological findings of Alzheimer's disease—amyloid deposits and neurofibrillary tangles—, without any other abnormalities in the brain, while a further 15% have these findings accompanied by brain damage of vascular origin. Dementia due to vascular lesions alone is accounting for fewer than 15% of cases. Lewy-body dementia that is usually accompanied by parkinsonism and marked fluctuations of consciousness and frontotemporal lobar degeneration each account for about 5% of cases of dementia. According to epidemiological data, dementia is secondary to another disease in fewer than 5% of cases; causes in this category include endocrine disorders such as hypothyroidism and hyperpara-thyroidism **(Cavalieri & Schmidt, 2010; Song et al., 2011)**.

Parkinson's disease (PD) is a neurodegenerative disorder that affects some 3 million patients in Europe and North America and is characterized by a basic phenotype of motor deficits (akinesia, rigidity, tremor, and postural alterations) together with other neurological complications that develop over the long course of the disease. Among the most important of these complications are the cognitive, affective and behavioral alterations that can appear even during the early stages of the illness and that become more

difficult to deal with than the motor manifestations **(Pagonabarraga et al., 2007; Mena et al., 2008)**.

The prevalence of dementia in PD patients varies between 20 and 40%, whereas the risk of developing dementia during the course of the disease is between 4 and 6 times greater than in a control population of the same age. Moreover, many PD patients without dementia can present varying degrees of cognitive alterations that appear in the early stages of the illness or even in recently diagnosed patients. Mild cognitive impairment in Parkinson's disease tends to manifest initially with more or less subtle alterations of attention, memory, visuo-spatial functions and executive functions. A sub-group of patients may present language alterations already from the early stages of disease **(Caballol et al., 2007; Weintraub et al., 2008)**.

Considering progressive aging of general population, increasing prevalence of early-onset dementia, and increasing percentage of literacy and weak medical knowledge about symptoms of dementia, thus screening tests of susceptible persons became mandatory. Neuropsychometric assessment seems to be the best method to screen individuals; however, the lack of standardization of screening tools has to be recognized as a major issue in the estimation of the true burden. Standardization might not be readily achieved because of diversity of language, culture, and levels of literacy **(Borson et al., 2010; Siemers et al., 2011)**.

The Mini-Mental State Examination (MMSE) is the screening tool most widely used and validated in dementias. However, this tool presents major difficulties for the detection of dementia in its initial stages. First of all, changes in memory and language are the initial symptoms in Alzheimer's disease (AD) and MMSE presents low sensitivity in the detection of these deficits. Secondly, the MMSE also presents low sensitivity for the objective detection of executive deficits, which are characteristic of other high prevalence dementias, such as frontotemporal dementia. In order to overcome the weaknesses of the MMSE, **Mathuranath et al. (2000)** developed Addenbrooke's Cognitive Examination (ACE) as a cognitive screening tool that was, in addition to brief (between 15 and 20 min) and easily administered, sensitive for the detection and differentiation of the most prevalent dementias **(Stokholm et al., 2009, Rosness et al., 2011)**.

Over these years, the ACE has gained great popularity in clinical practice and has been adapted to several languages. In addition, it has been administered in different clinical populations and has been shown to be capable of detecting cognitive impairment **(Sarasola et al., 2005; García-Caballero et al., 2006)**. In order to improve the original version, a new version of the test was developed in 2006: the Addenbrooke Cognitive Examination-Revised (ACE‑R). The ACE‑R incorporated changes based on the experience of the group of ACE authors following the repeated use of their original version. The changes in the design were made to facilitate administration and the amendments to the content were aimed at permitting an easier trans-cultural use of the test and at increasing its levels of sensitivity and specificity **(Mioshi et al., 2006, Stokholm et al., 2009)**.

The current prospective study aimed to evaluate the discriminative ability of MMSE, CDT and ACE-R for differentiation of demented patients from controls and for differentiation between types of dementia.

Patients and Methods

This prospective multi-center study was conducted at Neurology and Psychiatry Departments, Hospitals, KSA since Jun 2010 till Jan 2012 so as to include dementia patients with varied types and severity attending the Neurology outpatient clinic for follow-up. Patients were diagnosed as regards type and severity of dementia using the Clinical Dementia Rating (CDR) scale **(Morris et al., 1997)**. All patients underwent routine laboratory investigations including complete blood count, random blood glucose levels, renal function and liver function tests and thyroid hormone profile; then CT or MR imaging according to need.

All patients underwent evaluation of the following demographic and social variables: age assessment included 5-year age grouping, gender, marital status, and level of education (illiterate or educated), occupation and living arrangement. Smoking status was categorized as "nonsmoker," "ex-smoker," and "current smoker." General health status was evaluated as regards past and present history of chronic diseases with special regards to cardiac or cerebrovascular diseases, Parkinson's disease, diabetes mellitus, or cancer, all were signed arbitrarily as "yes" or "no" and then general health status was categorized into "poor/fair," "good," and "very good/excellent."

All patients were assessed for neuropsychatric manifestations including presence of signs of extra-pyramidal, pyramidal, cerebellar affection. Presence of paranoid or other delusional ideation, hallucinations, psychomotor activity disturbances, aggressiveness or affective disturbances was assessed. All clinical and radiological data were evaluated for categorization of dementia patients according to type of dementia

The study also included 40 age-matched controls selected from patients admitted to General

Surgery Department for minor surgical procedures with CDR rate ranging between 0 and 0.5 and were neurologically free.

All patients and controls completed a Mini Mental State Examination; total and sub-scores was conducted and the score determined according to the guidelines for the standardized MMSE **(Folstein et al., 1975; Molloy & Clarnette, 1999)**. Clock-drawing test (CDT): to minimize the effect of education a simple scoring system **(Roth et al., 1986)** was used and all patients were allowed see a large-sized wall watch prior to drawing and turn away from it to start drawing. The following three items were evaluated: correctly drawn clock shape, all numbers in the correct position and hands of the clock set to the correct time, a score of 1 was assigned for each of these items; thus, the score could range from 0 (all items incorrect) to 3 (all items correct). The presence of bizarre drawings was scored 0 and 1 otherwise. Therefore, final possible scores ranged between 0 (the worst) and 4 (the best).

Then, all patients and controls completed the ACE-R examination which comprises a total of six subtests measuring almost the full range of major cognitive functions and yielding a total score of 100 points. These tasks include orientation/attention (max 18 points), memory (max 26 points), verbal fluency (max 14 points), language (max 26 points) and visuospatial (max 16 points). Test of memory contains a subtest to measure verbal short-term memory composed of seven items administered over three trials, in addition to a delayed-recall trial. Language assessment includes 10 object-naming items, two word-generation tasks and wider assessment of other basic language functions, such as comprehension, reading and repetition are included **(Mathuranath et al. 2000)**.

For statistical purposes, equalization of groups was intended so as to enroll equal number of patients having the same type of dementia with maximal number for each group of 40 patients.

Statistical analysis

Obtained data were presented as mean±SD and ranges. Results were analyzed using Wilcoxon ranked test for unrelated data (Z test) and Chi-square test (X^2 test). Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. P value <0.05 was considered statistically significant.

3. Results

The study included 160 patients; 113 males (70.6%) and 47 females (29.4%) with mean age of 65.2±7.2; 51-79 years. Forty-three patients (26.9%) were free of medical co-morbidities, while 117 patients (73.1%) had additional medical co-morbidities with diabetes mellitus was the most frequent among these co-morbidities. Seventy-one patients (44.4%) had good-excellent general health, 59 patients (36.8%) had good general health, while 30 patients (18.8%) had poor-fair general health. Patients' enrollment criteria are shown in table 1.

Total mean MMSE score of enrolled patients (18.9±1.6) was significantly ($p<0.001$) lower compared to control subjects. Differentially according to type of dementia, the recorded MMSE estimates were significantly lower ($p<0.001$) compared to control group. Patients had vascular dementia had significantly lower MMSE compared to those had Alzheimer dementia ($Z=2.388$, $p=0.017$) and Parkinsonian disease dementia ($Z=2.41$, $p=0.016$), but with non-significant ($p>0.05$) difference among patients had AD, PDD, and other types of diagnoses, (Table 2, Fig. 1).

The frequency of higher CDT scores was significantly ($X^2=5.44$, $p<0.05$) lower in patients compared to control subjects with significantly lower mean total score compared to control subjects (2.07±0.97 vs 3.58±0.7, respectively). Differentially, mean CDT scores determined in AD and variant types-group were significantly higher compared to patients had VD and PPD with non-significant difference between VD and PPD groups, (Table 2, Fig. 2).

Mean total ACE-R scoring of dementia patients (62.4±2.8; range: 56-69) was significantly lower ($Z=5.513$, $p<0.001$) compared to ACE-R scoring of controls (89.7±3.3; range: 83-96), (Fig. 3). Consequently, mean total ACE-R scores of dementia patients categorized according to type of dementia was significantly lower compared to control scores. Patients had AD showed the lowest scores that were significantly lower compared to scores of other dementia patients. similarly, patients had VD had significantly lower total ACE-R score compared to those had PDD and other types of dementia with significantly lower total ACE-R scores detected in PDD patients compared to patients had other types of dementia, (Table 3, Fig. 4).

Differentially, orientation/attention and visuospatial scoring were significantly higher in patients had PDD and other dementia types compared to those had AD or VD with significantly higher scores recorded in patients had VD compared to those had AD, but non-significantly lower scores of both items in patients had PDD compared to those had other dementia types. As regards memory, fluency and language scoring, patients had other dementia types showed significantly higher scores compared to those had AD, VD and PDD with significantly higher fluency and language scores in PDD patients compared to AD and VD patients. Memory scores were significantly higher in PDD patients compared

to those had AD and VD with non-significant difference in favor of VD patients, (Table 3).

Using ROC curve analysis for evaluation of the diagnostic yield of the studied scoring systems for differentiation between types of dementia; defined ACE-R as the significant discriminative scoring system between types of dementia with high screening ability for AD with AUC=0.085 that showed significant difference compared to the null hypothesis that AUC=0.5, while the other scoring systems showed AUC=0.565 and 0.515 for MMSE and CDT, respectively which is non-significant versus the null hypothesis (Fig. 5). For VD, ACE-R also showed high screening ability with AUC=0.288 that showed significant difference compared to the null hypothesis, while MMSE and CDT showed AUC=0.438 and 0.500, respectively with non-significant difference versus the null hypothesis (Fig. 6). For PDD, ACE-R showed high diagnostic ability with AUC=0.711 that showed significant difference compared to the null hypothesis, while both of MMSE and CDT showed AUC=0.521 and 0.441, respectively which is non-significant versus the null hypothesis, (Table 4, Fig. 7).

Using ROC curve analysis to define the diagnostic cutoff point of ACE-R scores for diagnosis of PDD, score value at 62 provided the highest diagnostic yield with AUC=0.632, (Fig. 8). Test validity characters defined the range of 61-63 on ACE-R scoring system as the value to give the highest yield with sensitivity rate of 90.2% at 16 and specificity rate of 62.2% and accuracy rate for the diagnosis of 65% for the three points, (Table 5).

Table (1): Patients enrollment data

			Number (%)	Mean±SD
Age (years)	Strata	<60	41 (25.6%)	56.8±1.6 (52-59)
		60-65	49 (30.6%)	62.1±1.4 (60-65)
		>65-70	21 (13.1%)	67.5±1.3 (66-70)
		>70-75	26 (16.3%)	73.2±1 (71-75)
		>75-80	23 (14.4%)	76.2±0.8 (76-79)
	Total			64.3±7.2 (52-79)
Gender	Males		113 (70.6%)	
	Females		47 (29.4%)	
Marital Status	Married		79 (49.4%)	
	Divorced		24 (15%)	
	Widow		38 (23.8%)	
	Single		19 (11.8%)	
Educational level	illiterate		17 (10.6%)	
	Educated	Pre-high school	22 (13.8%)	
		High school	61 (38.1%)	
		College	45 (28.1%)	
		Post-college	15 (9.4%)	
		Total	143 (89.4%)	
Smoking	Never		21 (13.1%)	
	Ex-smoker		89 (55.6%)	
	Still		50 (31.3%)	
Care provision	Living alone with the other partner		79 (49.4%)	
	Living with the family		30 (18.7%)	
	Living care provider		16 (10%)	
	Living in elderly home		24 (15%)	
	Living alone with family member		11 (6.9%)	

Data are presented as numbers & mean±SD; percentages & ranges are in parenthesis

Table (2): Results of MMSE and CDT of studied patients categorized according to type of dementia and compared to control subjects

			Control	AD	VD	PDD	Other types
MMSE score			28.4±1.3 (26-30)	19.4±1.8*† (16-24)	18.7±1.9* (16-23)	19.1±1.6*† (17-23)	18.8±1.5* (15-21)
CDT	Scores	4	27 67.5%)	4 (10%)	2 (5%)	1 (2.5%)	3 (7.5%)
		3	9 (22.5%)	11 (27.5%)	13 (32.5%)	10 (25%)	14 (35%)
		2	4 (10%)	16 (40%)	16 (40%)	19 (47.5%)	15 (37.5%)
		1	0	6 (15%)	5 (12.5%)	7 (17.5%)	5 (12.5%)
		0	0	3 (7.5%)	4 (10%)	3 (7.5%)	3 (7.5%)
	Total score		3.58±0.7	2.18±1.06*†‡	2.1±1.03*	1.98±0.92*	2.18±1*†‡

Data are presented as numbers & mean±SD; ranges & percentages are in parenthesis

*: significant versus control group †: significant versus VD group ‡: significant versus PPD group

Table (3): Results of ACE-R of studied patients categorized according to type of dementia and compared to control subjects

	Control	AD	VD	PDD	Other types
Orientation/attention (max 18)	17.5±0.6	13.3±2.4*	14.4±1.1*†	14.9±1.3*†‡	15.2±1.6*†‡
Memory (max 26)	20.6±2.2	11.9±3.6*	12.7±3.8*	13.8±2.2*†	16.6±3.5*†‡#
Verbal fluency (max 14)	12.4±1.6	7.3±1.4*	7.7±1.6*	9.4±1.2*†‡	10.5±1.3*†‡#
Language (max 26)	23.8±1.2	9.9±2.9*	12.2±2.6*†	17.8±3.8*†‡	20.1±3.6*†‡#
Visuospatial (max 16)	15.3±0.8	9.3±1.5*	10.4±1*†	10.9±1*†‡	11.2±1.5*†‡
Total (max 100)	89.7±3.3	51.7±6.5*	57.5±4.9*†	66.8±4.8*†‡	73.5±6.9*†‡#

Data are presented as mean±SD max: maximum score *: significant versus control group
†: significant versus VD group ‡: significant versus PPD group #: significance versus PDD group

Table (4): ROC curve analysis of diagnostic yield of the studied scoring systems for differentiation of types of dementia

Type of dementia	Scoring system	AUC	Std error	Sig.	95% CI	
					Lower	Upper
AD	MMSE	0.565	0.052	p>0.05	0.462	0.667
	CDT	0.516	0.054	p>0.05	0.410	0.622
	ACE-R	0.085	0.022	<0.001	0.043	0.128
VD	MMSE	0.438	0.057	p>0.05	0.326	0.550
	CDT	0.500	0.053	p>0.05	0.396	0.604
	ACE-R	0.288	0.039	<0.001	0.211	0.364
PDD	MMSE	0.521	0.052	p>0.05	0.419	0.622
	CDT	0.441	0.050	p>0.05	0.342	0.540
	ACE-R	0.711	0.039	<0.001	0.635	0.787

AUC: area under curve Std error: standard error Sig.: significance CI: Confidence interval

Table (5): Test validity characters of the predetermined cutoff points of ACE-R for screening and diagnosis of PDD

Score cutoff point	Sensitivity	Specificity	PPV	NPV	Accuracy
61	90.2%	57.1%	42%	94.4%	65.6%
62	82.9%	58.8%	41%	90.9%	65%
63	73.2%	62.2%	40%	87.1%	65%

PPV: positive predictive value NPV: negative predictive value

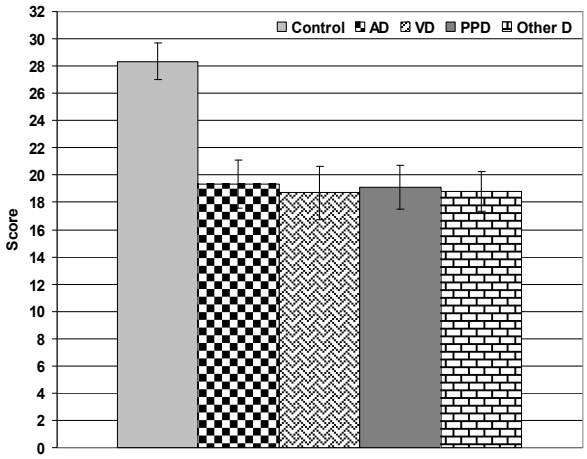

Fig. (1): MMES of studied patients categorized according to type of dementia and compared to control subjects

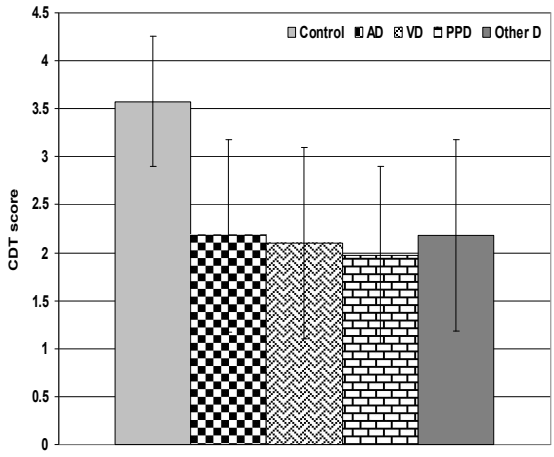

Fig. (2): Mean CDT scores of studied patients ctegorized according to type of dementia and compared to controls

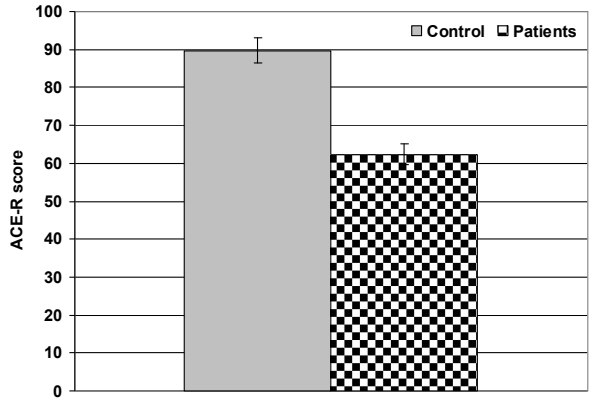

Fig. (3): Mean total ACE-R scores determined in dementia patients compared to controls

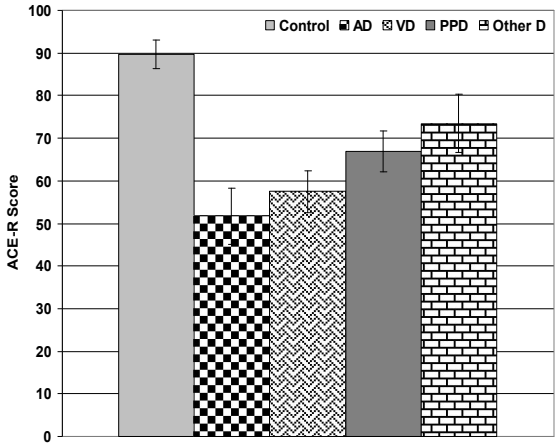

Fig. (4): Mean total ACE-R scores of studied patients categorized according to type of dementia and compared to control subjects

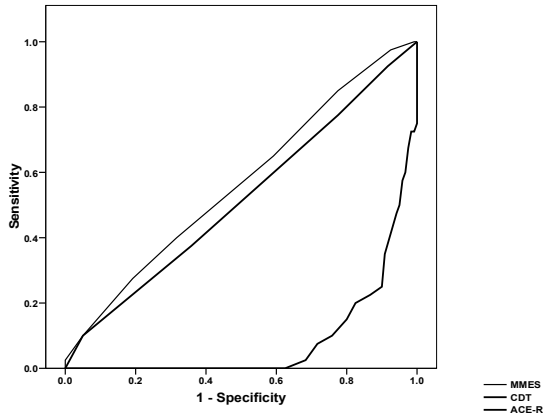

Fig. (5): ROC curve analysis for MMSE, CDT and ACE-R for differentiation of patients with AD among dementia patients

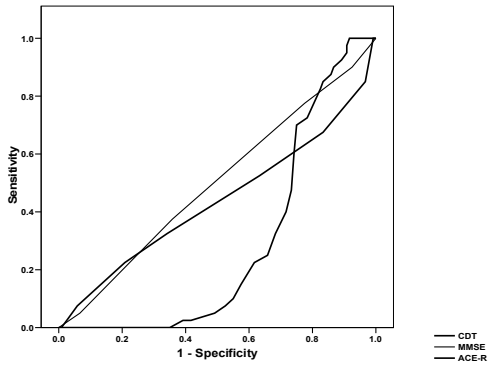

Fig. (6): ROC curve analysis for MMSE, CDT and ACE-R for differentiation of patients with VD among dementia patients

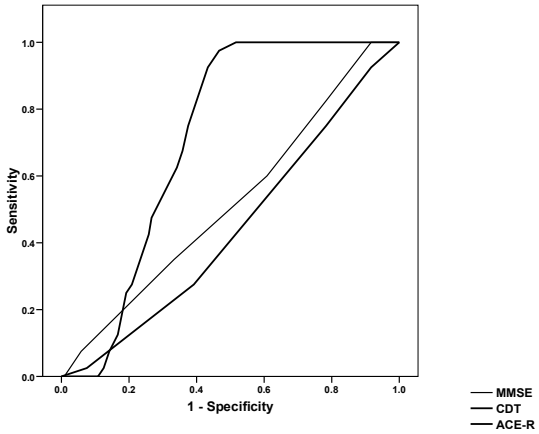

Fig. (7): ROC curve analysis for MMSE, CDT and ACE-R for differentiation of patients with PDD among dementia patients

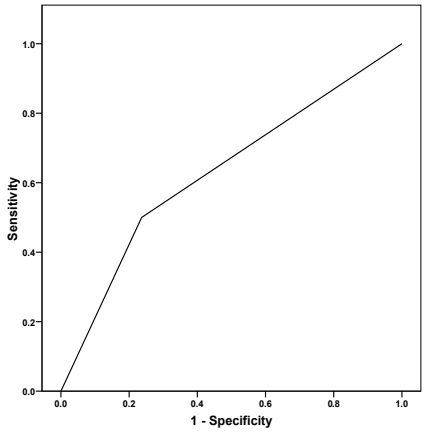

Fig. (8): ROC curve analysis for ACE-R at cutoff point of 62 for identification of patients with PDD among dementia patients

4. Discussion

The current study tried to evaluate the diagnostic yield of ACE-R examination for discrimination of demented patients from controls

and for differentiation between types of dementia. For comparative purposes, the study included equal number of patients of each dementia type and relied on two other scoring systems; the Mini Mental State and Clock-drawing test; both are validated tests for evaluation of cognitive changes accompanying dementia and impact of different types of dementia on their outcome. In hand with the validity of both tests for the defined target, ***de Guise et al., (2011)*** compared the performances of patients with mild, moderate, and severe traumatic brain injury on the CDT and MMSE and reported that the CDT and MMSE in combination have the potential for prediction of outcome in traumatic brain injury population.

Mean total and differential ACE-R scoring of dementia patients were significantly lower compared to controls. The ability of ACE-R to discriminate dementia types was evident and manifested as AD patients showed significantly lower scores compared to other dementia patients, VD patients had significantly lower total score compared to patients had PDD and other types of dementia with significantly lower total scores in PDD patients. Moreover, ROC curve analysis defined ACE-R as the significant discriminative scoring system between types of dementia with high screening ability for AD and VD and high diagnostic ability for PDD.

In hand with the discriminative ability of ACE-R between controls and demented patients and among various types of dementia, ***Crawford et al., (2012)*** conducted a systematic search that identified nine studies relating to the ACE/ACE-R for review and suggested that the ACE/ACE-R is capable of providing information on a range of cognitive domains and of differentiating well between those with and those without cognitive impairment and may be a tool that distinguishes between dementia subtypes and mild cognitive impairment. ***Hodges, (2012)***, documented that ACE-R is proven as a useful brief assessment tool for the early detection of a range of neurodegenerative disorders including AD and FTD and it also appears to be helpful in predicting those with mild cognitive impairment who will progress to frank dementia. ***Pendlebury et al., (2012)*** studied the relationship between Montreal Cognitive Assessment (MoCA), ACE-R, MMSE in patients with cerebrovascular disease and mild cognitive impairment (MCI) and found the sensitivity and specificity for MCI were optimal with MoCA <25 (sensitivity=77%, specificity=83%) and ACE-R <94 (sensitivity=83%, specificity=73%) and both tests detected amnestic MCI better than nonamnestic single-domain impairment.

ROC curve analysis defined ACE-R score in range of 61-63 to give the highest diagnostic yield with sensitivity and specificity rates of 90.2% and 62.2%, respectively with accuracy rate for the diagnosis of 65% for the three points. In line with these data, ***Law et al., (2012)*** evaluated how much the ACE-R improves the estimate of cognitive ability from the MMSE in people with AD and found that ACE-R and MMSE total scores are highly correlated and in people with established AD, for an MMSE score of 24, the predicted ACE-R score was 67.9. ***McColgan et al., (2012)*** investigated the utility of ACE-R for detecting mild cognitive impairment in PD and the relationship between performance on this instrument and behavior and quality of life and reported that ROC curve analysis revealed an AUC of 0.81 and cut off <89 gave a sensitivity of 69% and specificity of 84% for identification of parkinsonism patients with mild cognitive impairment and concluded that ACE-R is a useful screening tool for PD-MCI and poor performance is significantly related to impaired behavior and quality of life.

The differences reported in literature concerning the ACE-R cutoff point and their validity characters could be attributed the differences in population studied, the scale of enrolled patients, type of associated neurological deficit and the desired high validity character; sensitivity or specificity. In hand with this attribution, ***Torralva et al., (2011)*** tried found that with a cut-off score of 85 points, sensitivity and specificity of ACE-R for the detection of dementia was 97.5% and 88.5%, respectively and that the ACE-R showed higher sensitivity than the MMSE for the detection of dementia. ***Dos Santos Kawata et al., (2012)*** found that the cut-off score of 80 showed a sensitivity of 94% and a specificity of 94% for detection of dementia and concluded that the ACE-R is a reliable and valid test for the detection of dementia. On the other hand, ***Kaszás et al., (2012)*** reported that the cut-off score for ACE to identify PDD was 80 points providing sensitivity and specificity of 74% and 78.1%, respectively, but the specificity and sensitivity of Mattis Dementia Rating Scale was better than those of Frontal Assessment Battery, ACE and MMSE in Hungary and concluded that the types of applied screening instruments might differ from movement disorder clinic to clinic within a country, determination of the most specific and sensitive test for the given population remains to be an important task and further studies with larger sample size and more uniform criteria for participation are required to determine the most suitable screening instrument for cognitive impairment.

The obtained results and review of literature allowed concluding that ACE-R is a valid and reliable screening modality for dementia and could significantly identify patients had PDD with

sensitivity and specificity for the cutoff score range of 61-63 points. Moreover, ACE-R is easy to administer without need for difficult maneuvers and could be used as a screening test for other types of dementia with high sensitivity. However, wider-scale selective studies of patients had Parkinsonism are mandatory for identifying patients at risk of developing cognitive changes.

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