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RESEARCH ARTICLE

The Differential Diagnostic Value of the Callosal Angle and Evans Index in Mild Cognitive Impairment and Alzheimer's Disease

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Abstract: ***Background*:** Callosal angle (CA) and Evans index (EI) are considered as imaging biomarkers to diagnose normal-pressure hydrocephalus using traditional MR measurement methods.

***Objective*:** The current study aimed to evaluate the differential diagnostic value of CA and EI in mild cognitive impairment (MCI) and Alzheimer's disease (AD).

***Methods*:** Five-hundred and two subjects were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, which included 168 normal controls (NC), 233 MCI and 101 AD patients. The structural MR images were interactively applied with multiplanar reconstruction to measure the CA and EI.

***Results*:** CA presented no significant difference among NC, MCI and AD groups (H value = 3.848, *P* value = 0.146), and EI demonstrated higher value in MCI and AD groups than that in NC groups (*P* = 0.000 and 0.001, respectively). MCI group had significant larger EI (0.29±0.04) than (0.27±0.03) NC group in 70-75 years old sub-groups. ROC showed that the area under the curve was 0.704±0.045 for NC-MCI in 70-75 years old groups. The correlation analysis indicated that EI was significantly negatively related to MMSE scores of MCI patients (r = -0.131, *P* = 0.046).

***Conclusion*:** EI might serve as a screening imaging biomarker for MCI in 70-75 years old patients, and show limited differential value for the diagnosis of AD. CA could present no diagnostic value for MCI and AD in the current study.

ARTICLE HISTORY

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1. INTRODUCTION

Callosal angle (CA) is an imaging biomarker and a predictor of outcome in idiopathic normal-pressure hydrocephalus (NPH) [1], defined as the angle between medial superior borders of the left and right ventricle on the coronal images through the posterior commissure, perpendicular to the anterior-posterior commissure plane [2] while not one of the callosal structures [3-5]. In the early studies, CA was measured to evaluate the occult normal-pressure hydrocephalus by using pneumoencephalography, which was defined as the angle between the lateral margins of the roofs of the posterior and midportions of the lateral ventricles on the anteroposterior supine radiological films [6], and was also used to diagnose the ventricular enlargement [7]. Immediately following these, standard CA measurement based on 3D structural MR images was applied, which provided a new method to evaluate the normal-pressure hydrocephalus [2, 8]. Recently, CA has been applied to the differential diagnosis between NPH and Alzheimer's disease (AD) [2], with the consideration that CA is smaller in NPH than that in AD, and CA combined with Evans index could present 89.6%–93.4% accuracy in differentiating NPH patients from patients without NPH (*i.e.*, AD) [9]. However, it is not clear whether CA could be used to distinguish mild cognitive impairment (MCI), AD and normal controls (NC) from each other.

EI is an indirect linear measurement of ventricular size, and defined as the maximal width of the frontal horns divided by the maximal width of the inner skull on the axial images [2]. EI is normally smaller than 0.3 in adults, and could be considered as an objective biomarker to diagnose hydrocephalus [10] and ventriculomegaly [11], which is a requirement prior to the consideration of treatment with ventriculo-periteoneal shunt for the patients with idiopathic NPH(iNPH) [12]. EI is regarded as an indirect surrogate imaging biomarker for the ventricular volume (VV) that makes use of CT [13] and MRI [12]; the relationship [2, 14-16] and the reliability [15, 17] between EI and true VV have been evaluated and questioned. A recent study [18] demonstrated that the

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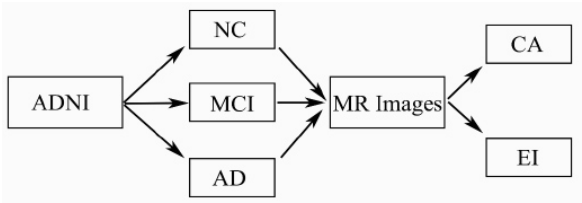

Fig. (1). Flowchart showing the study population and image processing. ADNI, Alzheimer's Disease Neuroimaging Initiative; NC, normal controls; MCI, mild cognitive impairment; AD, Alzheimer disease; CA, callosal angle; EI, Evans index.

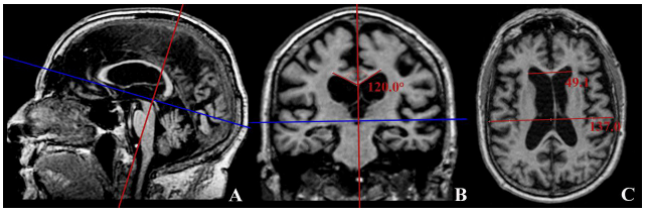

Fig. (2). 3D T1-weighed MR structural images were interactively reformatted to generate coronal images through the anterior and posterior commissure plane (blue line on **A**), perpendicular to the posterior commissure level (red line on B). CA was defined as the angle between the medial superior borders of the left and right ventricles on the coronal images (**B**). EI was defined as the largest left-to-right width of the frontal horns divided by the largest left- to-right extent of the skull on the axial images (**C**).

range of EI in healthy elderly was wide, and the cut-off value of 0.3 could not be used to distinguish normal ventricle from the enlarged ventricle, and iNPH from the other dementias [8].

In the early rare studies [2, 9], the CA and EI were used to evaluate the AD and NC. One previous study [2] demonstrated that CA presented no significant difference between AD (104±15) and NC (112±11) while EI was significantly larger in AD (0.283±0.033) than that in NC (0.259±0.025). The further analysis demonstrated that the combination of CA (threshold < 90°) and EI (threshold > 0.3) could provide an accuracy of 96%, a sensitivity of 97% and a specificity of 94% [2]. A new study [19] investigated a significant correlation between EI and Aβ and CA, Aβ and total tau, which suggested that EI and CA could be considered as rough estimates of biomarker levels in everyday clinical practice. Therefore, a detailed evaluation should be performed for the role of CA and EI in differentiating MCI, AD and NC from each other.

In the era of Volumetric MR Imaging, these traditional measurements (CA and EI) are easy to perform providing quick and high reliable measurements [20]; also, these are not time-consuming and do not require specialized software [9]. In the current study, we hypothesized that CA and EI could be used to differentiate MCI, AD and NC from each other. To address this hypothesis, five-hundred and two subjects were selected from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, including 168 NC, 233 MCI and 101 AD patients. Then CA and EI were measured on the structural images. Further, the diagnostic values of CA and EI were evaluated using one-way analysis of variance (ANOVA) and receiver operating characteristic curve (ROC) methods. By doing this, we aimed to investigate the differential diagnostic value of CA and EI in MCI and AD.

2. METHODS

2.1. Subjects

The normal controls (NC), the patients with mild cognitive impairment (MCI) and Alzheimer's disease were selected from Alzheimer's Disease Neuroimaging Initiative (ADNI) database (ADNI1_Annual_2_Yr_1.5T collection) (http://adni.loni.usc.edu/data-samples/access-data/). The subject accrual flowchart is displayed in (Fig. **1**). The included criteria were as follows: (1) The subjects performed 3D structural MR images (3D T1-weighted MPRAGE sequence); (2) The subjects evaluated with mini-mental state examination (MMSE) and the geriatric depression scale (GDS); (3) The MR images not having any MR artifacts. The excluded criteria were as follows: (1) The clinical neuropsychological evaluation not performed or not completed; (2) The patients with the periventricular leukomalacia and other brain lesions influencing the measurement of CA and EI.

2.2. Study Design

All the subjects were classified into three groups, including NC, MCI and AD groups. According to the previous study [18], each group was classified into three sub-groups as follows: (1) 70-75 years old, including 72 NC subjects, 72 MCI patients and 32 AD patients; (2) 76-80 years old, including 62 NC subjects, 56 MCI patients and 28 AD patients; (3) above 80 years old, including 27 NC subjects, 57 MCI patients and 23 AD patients.

2.3. MR Image Analysis

One observer was blinded to the clinical information and measured the CA and EI values two times at an interval of 1 week independently, and the mean value was regarded as the final CA and EI value. 3D T1-weighed MPR images were interactively reformatted to generate coronal images through the anterior and posterior commissure plane, perpendicular to the posterior commissure level. On the coronal images, CA was defined as the angle between the medial superior borders of the left and right ventricles (Fig. **2A**, **B**). EI was defined as the largest left-to-right width of the frontal horns divided by the largest left-to-right extent of the skull on the axial images (Fig. **2C**). These combined measurements required an average of 2 minutes per case. A Picture Archiving and Communication Systems in Medicine multiplanar reconstruction tool (AnyPacs V2.0, MEDICON DIGITAL ENGINEERING CO.LTD QINGDA, China) was used for three-dimensional reformatting.

2.4. Statistical Analysis

The data with normal distribution have been presented as means ± SD, and non-normal distribution data presented

Table 1. Demographic Characteristics and neuropsychiatric scale assessment.

Group	N(M/F)	Age(years)	MMSE†	GDS‡
NC	168(85/83)	76.03±5.11	29(25,30)	0(0,5)
MCI	233(154/79)	74.88±7.00	27(23,30)	1(0,5)
AD	101(52/49)	75.32±7.39	23.20±1.93	1(0,6)

†MMSE presented significant different among each group (H value = 305.141, $P = 0.000$)
‡GDS presented significant differences in NC-MCI and NC-AD groups (H value = 44.677, $P = 0.000$)
NC, normal control; MCI, mild cognitive impairment; AD, Alzheimer disease; N, number; M, male; F, female; MMSE, mini-mental state examination; GDS, geriatric depression scale

Table 2. The Comparison of CA and EI among NC, MCI and AD patients*.

-	NC	MCI	AD	F/H Value*	*P* Value
All subjects	-	-	-	-	-
CA(°)	119.83±11.33	120.0(63.45,144)	115.92±14.54	3.848	0.146
EI	0.27±0.04	0.29(0.17,1.43)	0.29±0.04	19.443	0.000[a]
70-75 Y/O	-	-	-	-	-
CA(°)	120.04±10.95	118.67±11.67	116.48±13.44	1.031	0.359
EI	0.27±0.03	0.29±0.04	0.28±0.04	9.518	0.000[b]
76-80 Y/O	-	-	-	-	-
CA(°)	119.25±12.74	120.67±12.21	113.61±17.43	2.609	0.077
EI	0.28±0.04	0.28±0.04	0.29±0.05	0.932	0.396
>80 Y/O	-	-	-	-	-
CA(°)	120.07±10.39	112.40±18.82	115.8±15.57	2.037	0.136
EI	0.28±0.04	0.30±0.04	0.30±0.04	2.537	0.084

* F value for one-Way ANOVA; H value for Kruskal-Wallis one-way ANOVA
[a]Significant difference was demonstrated in NC-MCI ($P = 0.000$) and NC-AD ($P = 0.001$) groups
[b]Significant difference was demonstrated in NC-MCI ($P = 0.000$)
CA, callosal angle; EI, Evans index; NC, normal control; MCI, mild cognitive impairment; AD, Alzheimer disease; Y/O, years old

as median (minimum, maximum). The reliability was evaluated using the intraclass correlation coefficient (ICC). The variables with normal distribution were analyzed with one-way analysis of variance (ANOVA) and Post Hoc multiple comparisons (Equal Variance assumed: LSD method, Equal Variance not assumed: Tamhane's T2 method), and the variables with non-normal distribution were analyzed with Kruskal-Wallis one-way analysis of variance (ANOVA) among each group. The receiver operating characteristic curve (ROC) was used to compare the diagnostic value of CA and EI between the compared groups. Area under the curve (AUC) more than > 0.7 was defined as having reasonable diagnostic value [21]. Statistically significant difference was set at a *P* value of less than 0.05. Statistical analysis was performed using the PASW Statistics Software Version 18.0 (SPSS Inc., Chicago, IL, USA) and MedCalc for Windows, version 11.4.2.0 (MedCalc Software, Ostend, Belgium).

3. RESULTS

3.1. Test-retest Reliability of CA and EI

ICC showed a good reliability score for CA (ICC, 0.920; 95% confidence interval: 0.891, 0.941) and CA (ICC, 0.943; 95% confidence interval: 0.923, 0.958).

3.2. Demographic Characteristics of the Subjects

The subjects included 168 NCs (M/F = 85/83), 233 MCI patients (M/F = 154/79) and 101 AD patients (M/F = 52/49) (Table **1**). The age presented no significant different among each group ($P = 0.226$). MMSE scores showed significant difference among each group (H value = 305.141, $P = 0.000$). GDS scores were significantly higher in MCI and AD groups than in the NC group (H value = 44.677, $P = 0.000$).

3.3. Comparisons of CA and EI Among NC, MCI and AD Groups

Table **2** indicates that CA presented no significant difference among NC, MCI and AD groups (H value = 3.848, *P* value = 0.146) (Fig. **2**). In the MCI and AD groups higher EI values were observed than in NC group ($P = 0.000$ and 0.001, respectively), while there was no significant difference between MCI and AD groups ($P = 1.000$) (Fig. **3**).

Further sub-group analysis indicated significantly higher EI value in the MCI group than in the NC group ($P = 0.000$), and CA showed no significant difference among NC, MCI and AD groups in 70-75 years old sub-groups ($P = 0.359$) (Table **2** and Fig. **4**). There was no significant difference for CA and EI among each group in 76-80 years old and >80 years old sub-groups ($P > 0.05$).

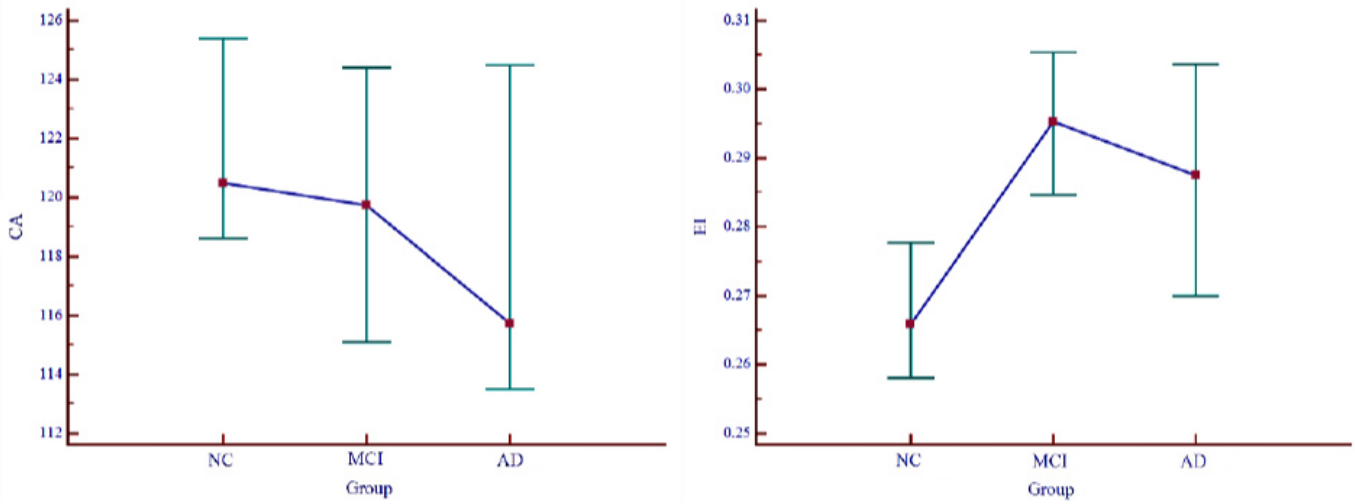

Fig. (3). Multiple comparison graph of callosal angle (CA) and Evans index (EI) between normal controls (NC) and mild cognitive impairment (MCI) and Alzheimer disease (AD) groups. The significant difference for EI was demonstrated in NC-MCI and NC-AD compared groups.

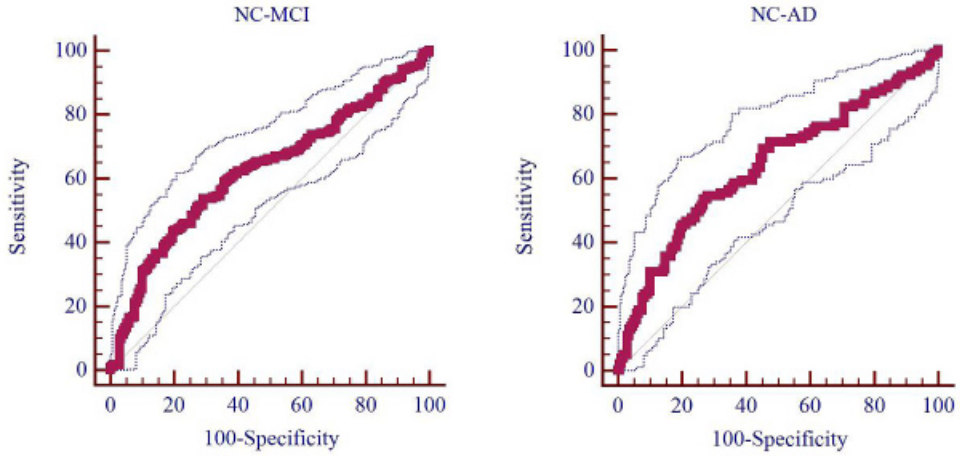

Fig. (4). Multiple comparison graph of callosal angle (CA) and Evans index (EI) between normal controls (NC) and mild cognitive impairment (MCI) and Alzheimer disease (AD) in 70-75 years old sub-groups. The significant difference for EI was demonstrated in NC-MCI groups.

3.4. ROC Analysis of EI in NC-MCI and NC-AD Groups

ROC analysis demonstrated area under the curve (AUC) to be 0.622±0.028 and 0.636±0.036 for NC-MCI and NC-AD groups, respectively. The cut-off value of EI was set at 0.287 with a sensitivity of 53.65% and a specificity of 70.83% for the NC-MCI group, and at 0.290 with a sensitivity of 53.47% and a specificity of 73.21% for NC-AD group (Table **3** and Fig. **5**).

Further ROC analysis of the sub-groups demonstrated that only NC-MCI compared groups had relatively large AUC (0.704±0.045) with a sensitivity of 61.11% and a specificity of 79.17% (Fig. **6**), and the other compared sub-groups presented a small AUC (< 0.700).

3.5. Correlation Analysis between the Clinical Variables and MRI Measurements

CA presented no significant correlation with MMSE and GDS scores for MCI and AD patients ($P > 0.05$) (Table **4**). EI showed significantly negative correlation with MMSE score for MCI patients (r = -0.131, P value = 0.046) and no significant correlation for AD patients (r = -0.128, P value = 0.201). EI also showed no significant correlation with GDS scores for MCI and AD patients ($P > 0.05$).

4. DISCUSSION

Although neuropsychological assessment and qualitative evaluation could be considered as a useful evaluating tool

Table 3. ROC analysis of Evans index in NC-MCI and NC-AD groups.

Group	AUC	Cut-off Value	Sensitivity	Specificity
All subjects	-	-	-	-
NC-MCI	0.622±0.028	0.287	53.65%	70.83%
NC-AD	0.636±0.036	0.290	53.47%	73.21%
70-75 Y/O	-	-	-	-
NC-MCI	0.704±0.045	0.287	61.11%	79.17%
NC-AD	0.658±0.063	0.291	50.00%	84.72%
76-80 Y/O	-	-	-	-
NC-MCI	0.535±0.054	0.310	30.36%	85.48%
NC-AD	0.612±0.067	0.269	78.57%	46.77%
>80 Y/O	-	-	-	-
NC-MCI	0.684±0.064	0.297	57.89%	74.07%
NC-AD	0.604±0.084	0.282	69.57%	59.26%

CA, callosal angle; EI, Evans index; NC, normal control; MCI, mild cognitive impairment; AD, Alzheimer disease; AUC, area under the curve; Y/O, years old

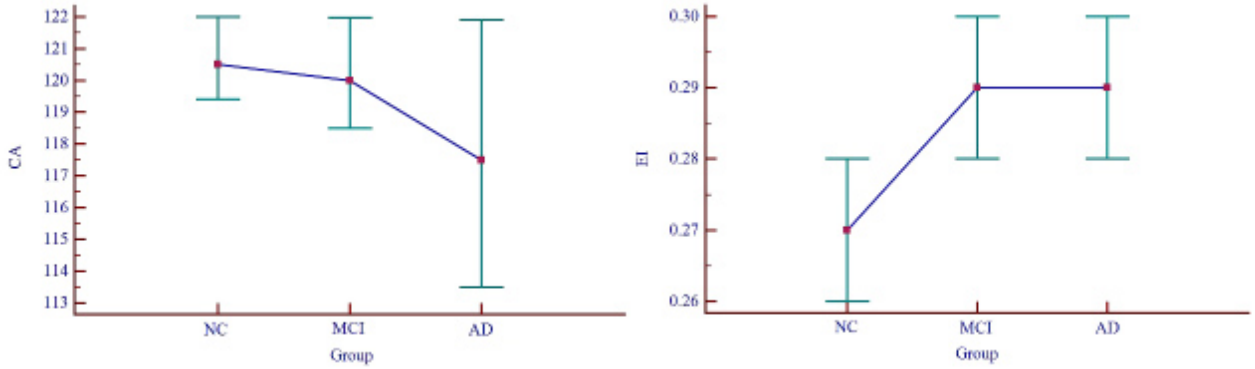

Fig. (5). Receiver operating characteristic (ROC) curve of Evans index (EI) in NC-MCI (AUC: 0.622±0.028) and NC-AD (AUC: 0.636±0.036) groups for all the subjects. NC, normal control; MCI, mild cognitive impairment; AD, Alzheimer disease; blue dotted line, 95% confidence bounds.

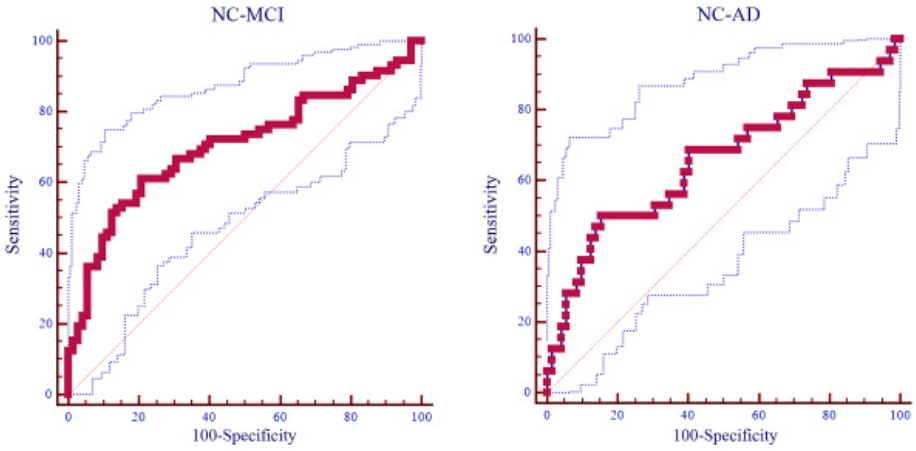

Fig. (6). Receiver operating characteristic (ROC) curve of Evans index (EI) in NC-MCI (AUC: 0.704±0.045) and NC-AD (AUC: 0.658±0.063) groups for the subjects with age 70-75 years. NC, normal control; MCI, mild cognitive impairment; AD, Alzheimer disease; blue dotted line, 95% confidence bounds.

Table 4. The Correlation analysis of CA and EI in MCI and AD patients.

-	CA		EI	
	r value	***P* value**	**r value**	***P* value**
MMSE				
MCI	0.050	0.453	**-0.131**	**0.046**
AD	-0.002	0.981	-0.128	0.201
GDS				
MCI	-0.003	0.966	0.079	0.230
AD	0.106	0.292	-0.012	0.909

CA, callosal angle; EI, Evans index; MCI, mild cognitive impairment; AD, Alzheimer disease; MMSE, mini-mental state examination; GDS, geriatric depression scale; r, Spearman's correlation coefficient

for the iNPH patients [22], CA and EI are still considered the traditional measurements to evaluate the ventricular size, and are widely used to diagnose the NPH [1, 9, 15, 18] and evaluate the treatment effect of the ventriculo-periteoneal shunt for NPH patients [12]. However, the studies using CA and EI to investigate AD are relatively rare [2, 9], especially for MCI. Therefore, the current study aimed mainly at investigating the values of CA and EI to differentiate NC, MCI and AD patients from each other.

In this study, CA and EI were manually measured on coronal and axial images using 3D structural MR images interactively to assure the exact linear position. Repeat measurement could decrease the subjective bias. The test-retest reliability analysis indicated that CA and EI presented excellent reliability according to Koo and Li's research [23].

This study firstly compared CA and EI values among NC, MCI and AD groups. The results identified that CA showed no significant difference among each group, which was consistent with the previous study [2]. The previous studies [2, 9] confirmed that CA was < 90° in NPH and >90° in AD patients, which could be associated with "tight convexity" in NPH and "widen convexity" in brain atrophy [24]. Among NC, MCI and AD patients, CA was >90° and it was relatively difficult to distinguish these patients from each other. Therefore, CA could not be used to differentiate the disorder with brain atrophy (*i.e.*, AD and MCI) from NC.

CA is located in the transition between the frontal lobes and parietal lobes, while the symptoms of cognitive function might be related to the more anteriorly located area, such as frontal lobes. Hence, CA played a limited role in differentiating MCI and AD. Anterior callosal angle (ACA) is defined as the angle between medial superior borders of the left and right ventricle on the coronal images through the anterior commissure, perpendicular to the anterior-posterior commissure plane, which could be used to explain cognitive dysfunction [25]. A previous study had identified that ACA presented high accuracy, sensitivity and specificity in distinguishing AD patients from healthy controls [25], while MCI has not been investigated using ACA up to now. Therefore, ACA should further be explored to differentiate MCI, AD and NC in the future study.

EI is well-known as an imaging biomarker for NPH [1, 2, 9], and indirectly evaluates the ventricular volume [17]. In the current study, EI presented a higher value in AD groups compared with NC, which was also consistent with the previous study [2]. Besides this, the current study also confirmed that MCI patients also had a higher EI value compared with normal controls. However, ROC analysis indicated AUC to be in the range of 0.6-0.7, which indicated a lower diagnostic efficacy [26]. In order to avoid the bias from the aging factor, a sub-groups analysis was also performed according to age distribution [18].

In the current study, the subjects' age was applied with histogram analysis, and the high relative frequency was focused on 70-75, 76-80 and >80 years old. According to the previous study [18], the patients were classified into three groups based on age stratification, and multiple comparisons and ROC analysis were performed among each group. Over the whole compared groups, only MCI presented significantly higher EI value than NC while AD showed no significant difference for EI value compared with NC in the sub-groups with age 70-75 years. The reason for the difference of EI in MCI and AD might be attributed to EI with a decreased trend in AD, and its true mechanism should further be investigated.

ROC analysis also demonstrated that EI had the highest AUC value for NC-MCI groups in the sub-groups having age 70-75 years, and AUC value in the other compared groups was < 0.7, which indicated a low discriminative value [26]. Therefore, it was reasonable to conclude that EI is relatively much more sensitive in differentiating MCI than in AD, which could be explained by its negative correlation with MMSE scores in MCI patients in the current study. Besides this, EI was measured at the level of the frontal horns while the CA was measured at the level of the posterior commissure, and the cognitive dysfunction might be associated with the frontal lobes. Therefore, EI might play a relatively more important role in differentiating MCI, AD and NC compared with CA.

The limitations of the current study include the following: (1) All the images were the multiplanar reconstruction images with non-parametric non-uniform intensity normalization (N3) technique and B1 correction and not raw MR structural images. (2) The sample size was relatively small for the sub-groups after performing the age stratification; (3) The advanced volumetric MR imaging analysis was not performed in the current study.

CONCLUSION

In conclusion, CA presented no significant difference among NC, MCI and AD groups, and EI presented higher values in MCI and AD groups than the NC group, especially in 70-75 years old sub-groups. Therefore, CA could not be used to differentiate MCI, AD and NC while EI could be regarded as a pilot imaging biomarker for the differential diagnosis of MCI from NC.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's disease
ADNI	=	Alzheimer's Disease Neuroimaging Initiative
CA	=	Callosal Angle
EI	=	Evans Index
MCI	=	Mild Cognitive Impairment
GDS	=	Geriatric Depression Scale
MMSE	=	Mini-Mental State Examination
NC	=	Normal Controls
NPH	=	Normal-Pressure Hydrocephalus
VV	=	Ventricular Volume

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The image data was obtained from Alzheimer's Disease Neuroimaging Initiative (ADNI) database (ADNI1_Annual_2_Yr_1.5T collection) (http://adni.loni.usc.edu/data-samples/access-data/). The ethics approval and consents are not available.

HUMAN AND ANIMAL RIGHTS

Reported experiments on humans were in accordance with the ethical standards of the committee responsible for human experimentation (institutional national), and with the Helsinki Declaration of 1975, as revised in 2013 (http://www.wma.net/). No animals were used in this study.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIAL

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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