

Differential risk of Alzheimer's disease in MCI subjects with elevated Abeta

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ABSTRACT

Backgrounds: People with elevated beta amyloid have different risk and progress speed to Alzheimer's disease. **Purpose:** The research is to validate the risk classification of AD developed in the Shanghai mild cognitive impairment (MCI) cohort study using ADNI data. **Methods:** The risk classification of AD in MCI was based on several optimal cut-off points of a novel parameter Cog_Vol. **Results:** In total, 843 subjects with MCI were included, of whom 220 had elevated PET beta amyloid. 273 (32.3 %) and 70 (31.8 %) progressed to AD in all subjects and in those with elevated PET beta amyloid, respectively. The risk of AD in subjects whose Cog_Vol >340 was very low, while the risk for those with Cog_Vol less than 101 indicated a super high within 4 years of follow-up. **Discussion:** Risk classification using Cog_Vol at an optimal value was able to detect subjects among those with PET-amyloid-elevated MCI were at greater risk of developing AD and were unlikely to develop AD within 4 years of follow-up.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder in which the central symptoms include impairments in memory and cognition. So much progress has been achieved in the research field that the National Institute on Aging–Alzheimer's Association (NIA-AA) Research Framework have proposed that amyloid positivity, regardless of cognitive performance or other biomarker evidence, may be sufficient for classifying a person as being “in the Alzheimer's continuum” [1]. However, many researchers have also reported that PET elevated beta amyloid or cerebrospinal fluid (CSF) beta amyloid is not enough on its own to indicate progression from mild cognitive impairment (MCI) to AD. About 40–55 % of subjects with elevated brain PET beta amyloid progressed to the clinical endpoint of AD during a 26–60 month follow-up period [2–4]. Efficient early detection of AD remains a problem that needs to be resolved.

A combination of several tests can improve the prediction of conversion to AD in subjects with MCI [5–9]. Combining magnetic resonance imaging (MRI)-based markers (cortical thickness and volume of subcortical structures) with neuropsychological tests predicted conversion with 77 % accuracy at baseline (AUC = 0.855, 84 % sensitivity, 70 % specificity) [10]. Combining the plasma neurofilament light chain

(pNfL) marker with a simple dementia screen (mini-mental state examination, MMSE) can reliably predict whether a person with MCI is likely to progress to AD dementia within five years [8]. Studies combining structural MRI and PET achieved better classification accuracy overall than those using only one technology [11]. Machine learning algorithms can classify images from healthy subjects and those with MCI or AD with high levels of accuracy [12,13]. Combining plasma p-tau181 or p-tau217 with other measurements is also a potential approach to improve prediction [14]. Despite the rapid advances in these research fields, the challenge of translating research achievements into clinical practice remains. All risk classification addresses the population risk of AD in one specified population; however, it is still necessary to determine and predict whether and when people with MCI will progress to AD dementia or remain stable and not progress to AD. Another challenge is the generalizability of the classification using clinical data commonly available for clinicians and easy to use in the routine clinical practice.

In the Shanghai MCI cohort study, we developed a risk classification for AD in MCI that uses data available in clinical practice: the combination of ADAS13 (Alzheimer's Disease Assessment Scale, 13 items) with hippocampal volume was able to differentiate between higher, moderate and lower risk of AD in subjects with MCI^{15,16}. Because the Shanghai

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MCI cohort study did not include data on brain beta amyloid, in this study we use the Alzheimer's Disease Neuroimaging Initiative (ADNI) data, which includes PET scans for brain beta amyloid, to validate the findings of the Shanghai MCI study and establish a convenient and effective method for routine clinical practice, toward the early detection of AD in patients with MCI.

2. Methods

2.1. Subjects and data included

We selected subjects with MCI, including a sub-cohort of subjects who had elevated PET beta amyloid, in the ADNI1 and ADNI GO/2 obtained from the publicly available data repository, the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The data used in this article were downloaded from the ADNI website in May 2019, including data from florbetapir-PET scans to detect brain beta amyloid, structural MRI, APOE genotyping, and some cognitive and demographic information. For up-to-date information on specific inclusion and exclusion criteria, please see <http://adni.loni.usc.edu>.

2.2. Neuropsychological testing

Results from MMSE and ADAS13 tests are included in the analysis.

2.3. PET scan and brain amyloid

Florbetapir-PET was performed according to the ADNI PET protocol, which is available online (<http://adni.loni.usc.edu/data-samples/pet>) and has been described by Landau [1,17]. Image processing was performed by the ADNI Core Laboratory. A PET scan was performed 50–70 min after florbetapir injection. Images were smoothed and aligned with MPRAGE anatomical images to obtain cortical segmentations. Mean cortical standardized uptake value ratios (SUVr) were obtained for the lateral and medial frontal, anterior and posterior cingulate, lateral parietal, and lateral temporal regions. The cut-off value for cortical florbetapir uptake at ≥ 1.11 was considered "elevated" or "positive" for cortical A β [2,17].

2.4. MRI

MRI was conducted using standardized protocols, as indicated by <http://adni.loni.usc.edu/data-samples/access-data/> [7,18], on 1.5 T MRI scanners with 3D T1-weighted sequences optimized for the different scanners. MRI measurements and imaging analysis were reconstructed using the FreeSurfer software program, as indicated by Fischl et al. [7,19]. The average cortical volume of the hippocampus and temporal lobe were included in the analysis. APOE genotyping was performed as described on the ADNI website (<http://adni.loni.usc.edu/data-sample/genetic-data/>).

2.5. Statistics

Wilcoxon's rank sum test was used for continuous variables. Fisher's exact test was used for categorical variables. The cut-off points for ADAS13 and hippocampal volume tests were generated by quantile values. Kaplan-Meier and log-rank tests were used to measure the cumulative conversion from MCI to AD in groups stratified by the combination of ADAS13 score and left hippocampal volume. Cutoff points were determined based on quartiles of ADAS_cog13 and quartiles of hippocampal volume. A new parameter Cog_Vol (CoV) was created using the ratio of hippocampal volume to ADAS13 score. Pearson correlation was used to explore the relationship between Cog_Vol and the time to conversion to AD from MCI or censoring. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc. Cary, NC, USA) and R version 3.6.1.

3. Results

In total, 843 subjects with MCI were included, of whom 273 (32.3 %) progressed to AD over an mean period of 2.76 (range 0.54–9.18) years of follow-up. PET beta amyloid was greater than 1.11 in 220 subjects, of whom 70 (31.8 %) progressed to AD and 150 were stable or normal. The baseline characteristics of APOE4 carrier status, cognition measured by MMSE and ADAS13, and left hippocampal volume in subjects who progressed were significantly different from those in subjects who were stable (Table 1).

Based on previous results, we chose several cut-off points for the ADAS13 score and left hippocampal volume to perform a risk classification for AD in subjects with elevated PET beta amyloid and MCI. We found that the combination of an ADAS13 score < 14 and left hippocampal volume > 3459 predicted no conversion to AD, and ADAS13 > 24 and left hippocampal volume < 2715 predicted 90 % conversion to AD (Figs. 1, 2).

By combining these two factors, hippocampal volume and ADAS13 score, we created a new parameter, Cog_Vol. A value of Cog_Vol less than 101 predicted 94.1 % conversion to AD within the first two years of follow-up, while a value greater than 266 predicted 4.16 % conversion to AD within four years of follow-up. Most conversion from MCI to AD happened in the first three years of follow-up, and the conversion rate after the third year was low. When subjects were categorized into groups according to Cog_Vol value, the conversion rate (94.1 %, 60 %, 39.2 %, 26.0 %, 10.3 % and 0) decreased with increasing Cog_Vol value (< 101 , 101–142, 142–193, 193–266, 266–340 and > 340 , respectively) over the whole follow-up period as well as in each follow-up year in subjects with MCI and elevated PET beta amyloid. In all subjects with MCI, the conversion rate was 78.1 % in the group with Cog_Vol < 101 and 3.2 % in those with Cog_Vol > 340 . Other groups had similar conversion rates to those in the corresponding elevated PET beta amyloid groups. The number of subjects developing AD among those with Cog_Vol > 340 was 0 within three years of follow-up and very low after four years of follow-up. For those with negative PET beta amyloid, the conversion rate was 17.24 % in MCI with Cog_Vol < 193 , and 3.1 % in the 193–340 group (Table 2, Figs. 3, 4 and Suppl. Table1). The smaller the value of Cog_Vol, the bigger the risk of AD in subjects with MCI, particularly in those with elevated PET beta amyloid. The Cog_Vol of group B in Fig. 1 is 266, and the Cog_Vol of group A in Fig. 2 is 108.

The cumulative conversion rate of each Cog_Vol group at each follow-up year was also calculated (data not shown). The conversion rate increased annually within the first 3 years of follow-up; however, it hardly increased at all after 3 years of follow-up in each group where Cog_Vol < 340 .

4. Discussion

The risk of progression to AD in subjects with MCI and a left hippocampal volume ≥ 3459 mm³ and ADAS13 < 14 , or Cog_Vol > 340 , was very low within a 4-year follow-up period. The risk increased slightly after 4 years of follow-up. A value of the parameter Cog_Vol less than 101 predicted a conversion rate of 94.12 % (16/17) to AD in subjects with MCI and elevated PET beta amyloid in the first two years of follow-up, while the corresponding rate was 78.1 % in all subjects with MCI. The smaller the value of Cog_Vol, the bigger the risk of AD in subjects with MCI. This classification, using data available in clinical practice, is able to detect groups of people with different levels of risk of progressing to AD within 4 years.

Elevation of PET beta amyloid is associated with an increase in progression to AD, but the rate of early detection using the single factor tau or beta amyloid for AD is not high at present. Some researchers using the non-amyloid based biomarkers A2M, ApoE, BNP, Eot3, RAGE and SGOT have identified panels that achieved sensitivity (SN) > 80 %, specificity (SP) > 70 % [20]. An automated speech-based artificial intelligence system predicted amyloid beta positivity (area under the

Table 1
Characteristics of subjects with MCI at baseline.

Factors	All MCI (N = 843)			MCI with elevated beta amyloid (N = 220)		
	Total	Conversion	Stable MCI	Total	Conversion	Stable MCI
Number of cases	844	273	570	220	70	150
Age (y, SD)	73.08(7.4)	74.05(7.1)	72.5(7.6)	72.9(6.5)	73.6(6.4)	72.6(6.5)
Education (y, SD)	15.96(2.82)	15.9(2.74)	16.0(2.86)	16.06(2.83)	16.2(2.59)	16.0(2.95)
Gender (male,%)	455	166(62.17)	289(57.57)	116	42(60.87)	74(49.3)
APOE4 (0)	377	90(33.7)	287(57.17)*	64	12(17.4)	47(31.3)*
MMSE (mean, SD)	27.58(1.81)	26.82(1.75)	27.94(1.2)*	27.65(1.81)	27.02(1.75)	27.91(1.8)*
ADAS13 (mean, SD)	16.56(6.77)	21.27(5.97)	14.3(5.9)*	16.86(6.89)	22.1(6.9)	14.5(5.4)*
PET amyloid AV45	1.22(0.22)	1.42(0.21)	1.17(0.20)*	1.38(0.17)	1.46(0.17)	1.35(0.16)*
LHV (mm ³ , SD)	3328.93(593.9)	3012.86(520.0)	3480.0(567.4)*	3387.47(540.4)	3105.8(426.8)	3514.7(539.3)*
Average follow-up time (y, SD)	2.76(1.87)	2.03(1.52)	3.15(1.93)*	2.27(1.13)	1.71(1.04)	2.53(1.09)*

* p < 0.05, LHV: left hippocampal volume.

Cut-offpoint1 Selection				
	Hipp. Vol.			
	3459 <	≤3459		
Total ADAS	14 <	C	A	
	≤14	B	D	

Number of censored and non-censored subjects				
Stratify Group	Total	AD	Censored	Censored%
1 A	101	51	50	49.5
2 B	41	0	41	100.00
3 C	30	7	23	76.67
4 D	48	12	36	75.00
Total	220	70	150	68.18

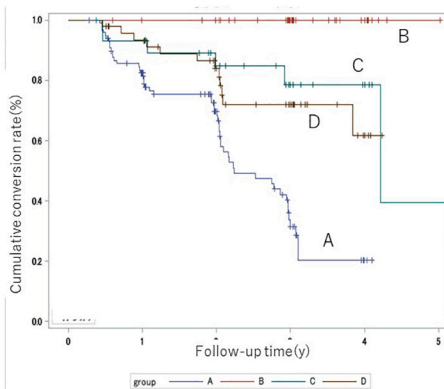


Fig. 1. Kaplan Meier curves of conversion rates at cut-off1. Hipp.:hippocampus, Vol.:Volume. ADAS: Alzheimer's Disease Assessment Scale—cognitive subscale.

Hippo.Vol.				
	2715 ≤		<2715	
Total ADAS	24 ≤	C	A	
	<24	B	D	

The number of censored and non-censored				
Stratify group	Tot.	AD	censored	censored%
1 A	11	10	1	9.09
2 B	168	36	132	78.57
3 C	13	4	9	69.23
4 D	28	20	8	28.57
Total	220	70	150	68.18

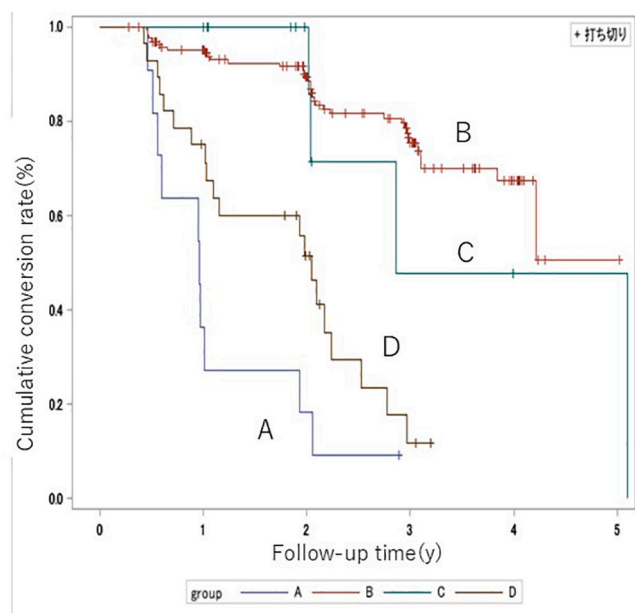


Fig. 2. Kaplan Meier curves of conversion rates at cut-off 2. Hipp.:hippocampus, Vol.:Volume. ADAS: Alzheimer's Disease Assessment Scale—cognitive subscale.

curve = 0.77) in the full sample [21,22]. However, none of these methods increased the early detection rate of AD in MCI compared with brain PET beta amyloid.

The detection of both PET beta amyloid and tau in the brain implies a diagnosis of AD, but in those people with elevated beta amyloid, the question of who will have elevated tau protein and when this will

happen is yet to be resolved. ADNI4 started in November 2022 to attempt to answer this question. Atrophy of hippocampal volume is associated with neurodegeneration. Impairment of cognition indicates the risk of dementia symptoms [23]. Before a method for early diagnosis is established using simultaneously PET beta amyloid and tau, a simple and effective method to detect AD risk that can be used in all clinical

Table 2
Conversion rate from MCI to AD classified by Cog_Vol (Cog_Vol) group.

Cog_Vol	Risk	All MCI (N = 843)			MCI with elevated beta amyloid (N = 220)		
		Conv.	Stable	Conv. rate (%)	Conv.	Stable	Conv. rate (%)
≤101	super high	50	14	78.1	16	1	94.1
101 < Cog_Vol ≤142	High	82	54	60.3	18	12	60.0
142 < Cog_Vol ≤193	High-moderate	76	106	41.5	20	31	39.2
193 < Cog_Vol ≤266	Moderate	49	129	27.6	13	37	26.0
266 < Cog_Vol ≤340	Mild	10	87	10.3	3	27	10.0
>340	Low	6	180	3.2	0	42	0
Total		273	570	32.3	70	150	31.8

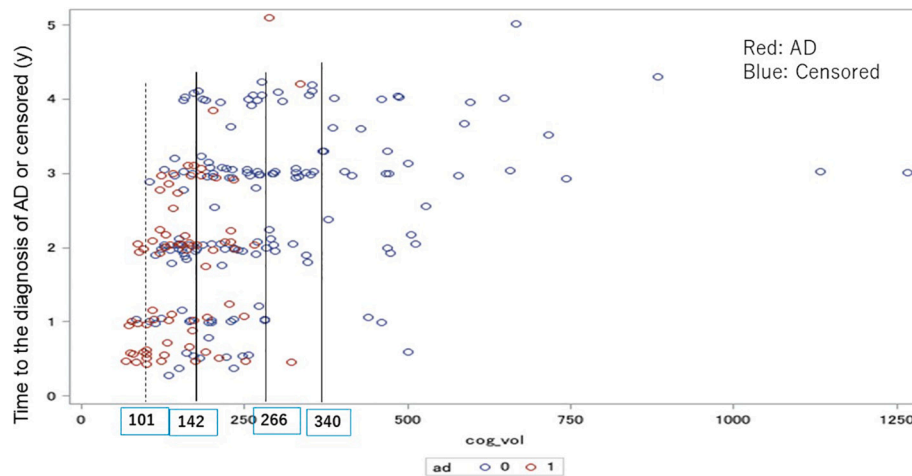


Fig. 3. Correlation of Cog_Vol with time of AD diagnosis or censored in MCI with elevated PET Abeta.

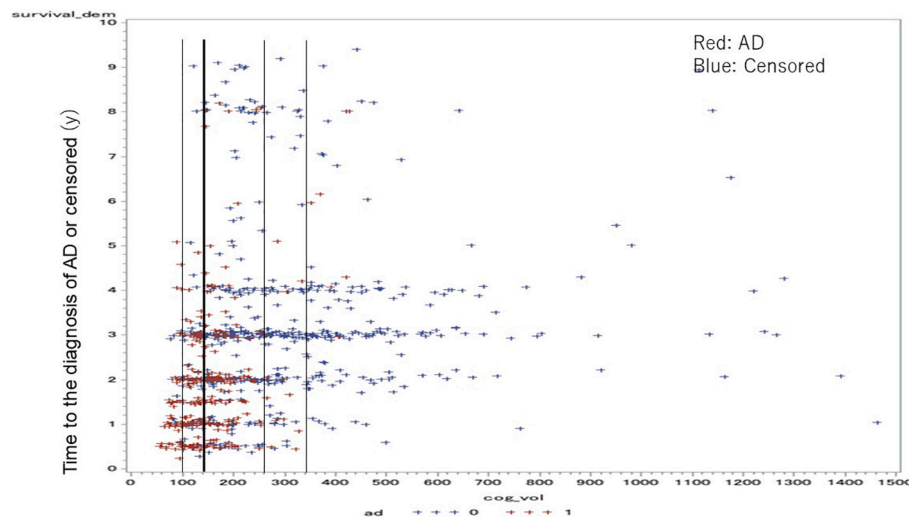


Fig. 4. Correlation of Cog_Vol with time of AD diagnosis or censored in all MCI.

settings is a solution.

The results from our Shanghai MCI cohort study [16] showed that using ADAS13 and the volume of the hippocampus can increase the rate of detection of the group at high risk of developing AD. We adjusted the cut-off points for ADAS13 and hippocampal volume in this analysis, because the population was different from that in Shanghai MCI cohort study. We previously used several factors to find the people who are at high risk of AD [16]. Now, using one parameter we could find the population who will progress to AD within three years and those who will not progress to AD within 4 years. Although we determined that the risk of AD in subjects with MCI and $142 < \text{Cog_Vol} < 266$ was about 60

%, this cannot be used for individual diagnosis of AD. Further research is needed to determine the factors affecting progression to AD in people with MCI whose Cog_Vol is between 102 and 266. Although changes in hippocampal volume and impairment of cognition do not happen very early in the AD continuum, the use of the parameter Cog_Vol is currently an easy and practicable tool that can detect some patients who will develop 2–3 CE years in advance. In turn, this will facilitate the management of people with MCI in memory clinics and also the design of clinical trials in research and development of anti-AD drugs and medical devices. Certainly, the method we did still needs to be modified, and some factors need to be added to improve the detection of AD in groups

located between the high and low risk groups.

We compared results from two datasets, one including MCI subjects with elevated Abeta and the other including the entire MCI subjects with and without Abeta information. There were differences in conversion rates between the super-high-risk and low-risk groups, while conversion rates were essentially the same for the other groups. The conversion rate in low-risk group in data set including MCIs with elevated Abeta is 0, however it is 3.2 % (6/186) in data set including entire MCIs. Since Abeta information is unknown, it is not certain whether the 6 event AD converted from 186 MCIs are pathological AD. The new parameter Cog_Vol can be equivalent to Abeta when Abeta information is not available within a specified range from 101 to 266.

The clinical trial results for Lecanemab on early AD and MCI did not show an effect on prevention of AD in MCI and the effect size was small in cognition improvement [24]. As discussed in many articles, aggregation of both α -synuclein (α -SYN) and TAR DNA-binding protein 43 (TDP-43) together with beta amyloid and tau protein are regulated events in the pathogenesis of AD [25–28]. However their influence on the clinical trial results is not clear because there is limited understanding of the mechanisms that lead to aggregation of α -SYN and TDP-43 and their related toxicity in AD. Another factor is the heterogeneity of MCI, including some subjects who will not progress to AD. It is important to target the population with a high conversion rate in preventive clinical trials.

Hippocampal volume is usually associated with tau and Ptau accumulation in the brain [29,30]. And now Ptau217 is a potential candidate for an early diagnostic biomarker of AD [15,31]. In this study, we have not included information about Ptau217, so we do not know whether the subjects at very high and high risk of developing AD with elevated beta amyloid also have elevated tau or Ptau217. These issues including some other biomarkers [32] will be studied in the next stage of our research to improve detection. Regarding the conversion rates of 3.2 % and 1.15 % in those with Cog_Vol >340 in all MCI and those with negative PET beta amyloid, respectively, we are not sure whether these numbers are due to the misdiagnosis or not, because the brain PET beta amyloid is negative. A limitation of this study is that Cog_Vol cannot be used for individual diagnosis yet, but it could be used to identify groups at different risk of developing AD. In the very high risk group, 94.1 % would develop AD with 3 years. Further research is still needed to analyze the risk factors that modulate the speed of progression from MCI to AD, and to validate this research in different populations.

5. Conclusion

The novel parameter Cog_Vol can be used to identify groups at different risk of AD in people with MCI corresponding to different Cog_Vol values, of which the highest risk is about 94.1 % in MCI with Cog_Vol <101 and 60 % with 142 < Cog_Vol < 266 within four years of follow-up. This is a simple, feasible and efficient method to help evaluate the risk of AD and manage routine clinical work in the memory clinic and could also facilitate the design of clinical trials.

CRedit authorship contribution statement

Bin Zhou: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Masanori Fukushima:** Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization.

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Ethical statement

The data is from a public database. Ethical statement is not

applicable.

Appendix A. Appendix

Collaborator: ADNI—*Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the present analyses or the writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

Appendix B. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jns.2024.123319>.

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