Identifying an Optimal Cutoff of the Montreal Cognitive Assessment to Predict Amyloid-PET Positivity in a Referral Memory Clinic

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Background: Brain amyloid- positron emission tomography (PET) imaging is highly sensitive for identifying Alzheimer disease. Currently, there is a lack of insight on the association between amyloid-PET status and the widely used Montreal cognitive assessment (MoCA). Studying this relationship may optimize the clinical use of amyloid-PET imaging.

Objectives: To evaluate the relationship between amyloid-PET status and MoCA scores and to identify a MoCA score cutoff that translates to amyloid-PET positivity.

Methods: Using retrospective chart review, patients from 2010 to 2017 with amyloid-PET scans (positive or negative) and MoCA test scores were included. We studied the relationship between amyloid-PET status and MoCA scores and the influence of age, sex, education, and race. A MoCA score cutoff for amyloid-PET positivity was estimated.

Results: Among the 684 clinic patients with dementia, 99 fulfilled inclusion criteria. Amyloid-PET positivity was associated significantly with lower MoCA scores (median = 19, $U = 847$, $P = 0.01$). The MoCA score cutoff (25) used for minimal cognitive impairment (MCI) predicted amyloid-PET positivity suboptimally (sensitivity = 94.6%, specificity = 13.9%). A MoCA score cutoff of 20 patients had optimal sensitivity (64.2%) and specificity (67.4%).

Conclusions: Amyloid-PET positivity is associated with lower MoCA scores. Clinical utility of amyloid-PET scan is likely to be suboptimal at the MoCA score cutoff for minimal cognitive impairment.

Key Words: neurocognitive testing, MoCA, amyloid, PET, dementia, Alzheimer disease

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Brain amyloid scanning by positron emission tomography (amyloid-PET) is a new modality instrumental in detecting Alzheimer disease (AD) pathology and is found to alter clinical diagnosis and management in 30% to 60% of patients.[1] Current recommendations for clinical use include: (1) progressive or persistent unexplained minimal cognitive impairment (MCI), (2) patients with atypically young-onset dementia (below 65 y), and (3) patients with atypical course or mixed clinical features.[2] Despite its increasing popularity, there is currently no recommendation for an ideal clinical use point along the continuum of decreasing cognitive test scores. There is a lack of definitive correlation between increasing amyloid burden and declining cognitive test scores such as the mini-mental state examination (MMSE) in longitudinal studies of patients with memory impairment.[3] The Montreal cognitive assessment (MoCA) is a newer clinical test demonstrated to have higher sensitivity (90% vs. 18%) and lower ceiling effect compared with MMSE in identifying an MCI and also in differentiating an MCI from AD.[4–6] Therefore, evaluating the association between MoCA test scores and amyloid-PET status (positive or negative) may provide insights into the influence of brain amyloid deposition on cognitive test performance. This may help optimize the use of amyloid-PET scanning in the memory clinic and improve the cost of dementia care. Amyloid and Tau biomarkers are also recognized to have immense potential in the enrichment of clinical trials in dementia because they optimize patient recruitment strategies and enable better prediction of study endpoints.[7,8] Therefore, identifying a MoCA cutoff for amyloid-PET positivity may contribute to the enrichment of dementia trials, which both utilize and study amyloid-PET imaging.

Prior evidence of the association between MoCA test scores and amyloid-PET imaging is limited. Jung et al[9] reported that amyloid-PET positivity is associated with lower MoCA scores in AD patients who presented with aphasia. Liu et al[10] showed that brain amyloid uptake correlates with both MMSE and MoCA scores in patients with poststroke and post-TIA cognitive impairment. Dao et al[11] also found similar results in their evaluation of patients with vascular cognitive impairment. In a larger study that analyzed the influence of sex on amyloid deposition in patients with impairment of verbal learning and memory, Caldwell et al[12] found significant amyloid to MoCA association, but included a truncated MoCA score in their analysis. To our awareness, there are no previous studies that primarily explore the relationship between total MoCA scores and amyloid-PET status in patients with memory impairment. We performed a retrospective analysis for a 7-year period in a sample of patients with memory impairment with the following objectives: (1) To study the association between brain amyloid-PET status (positive or negative) and MoCA scores (we hypothesized that patients with amyloid-PET positivity have lower MoCA scores). (2) To identify an optimal MoCA score cutoff that translates to amyloid positivity on PET imaging.

METHODS

With the approval of the internal review committee, we performed a retrospective observational chart review study (Fig. 1). The study was conducted at the Alzheimer Disease Center, a suburban neurology center serving the south shore of Boston, MA.

All patients evaluated in our memory clinic from 2010 to 2017 with MoCA testing and amyloid-PET imaging were

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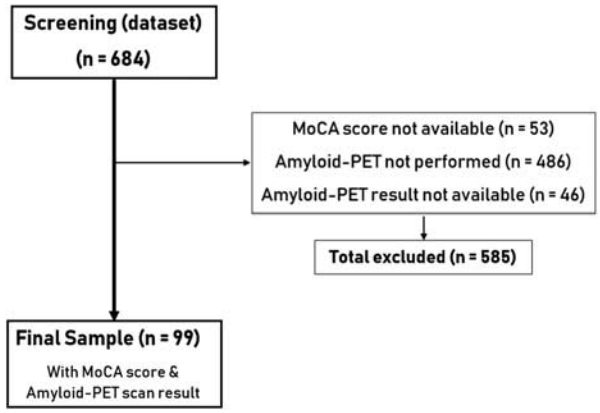

FIGURE 1. Study flowchart. MoCA indicates Montreal cognitive assessment; PET, positron emission tomography.

included in the study. From our database, we excluded patients who did not have an available MoCA score, patients who did not warrant amyloid-PET imaging during clinical care, and patients whose amyloid-PET imaging result could not be retrieved (research-protocol based amyloid-PET imaging).

We obtained the results of the amyloid-PET imaging that was performed over the 7-year period (2010 to 2017). During this period, amyloid imaging was offered to patients for the following indications as per the current appropriate use recommendations: progressive or persistent unexplained MCI, atypically young-onset dementia (below 65 y), and patients with atypical course or mixed clinical features.[2] Informed consent was obtained from eligible patients who were then referred to different imaging centers in the region, all well-versed in amyloid imaging in both clinical and research scenarios. Imaging was performed using 3 tracers: Florbetapir (^{18}F), Flutemetamol (^{18}F), and Florbetaben (^{18}F). Imaging had therefore been performed using different tracers on different scanners as is common in the clinical setting. Our study being a retrospective chart analysis of amyloid-MoCA association, adherence to a particular tracer, protocol, or machinery was not possible. Scans were reported using the visual read method by certified nuclear imaging experts experienced in brain amyloid imaging and scan results were dichotomized as positive and negative. We included the binary positive or negative result in our analysis. Semiquantitative analysis using standardized uptake value ratio (SUVR) and centiloid measurements to establish amyloid-PET status was not performed.

From our clinical database, first-visit total MoCA scores of patients were included for analysis. The next-nearest available MoCA score was included for patients without a first-visit MoCA score. As is usual in the memory clinic, sometimes alternative tests such as MMSE and self-administered gerocognitive examination were administered at the first visit. The clinic corrects for the level of education in MoCA scores by adding 1 point to the MoCA score for individuals with $\leq$12 years of education. All MoCA tests were administered by the clinical staff experienced in neurocognitive testing. Other variables included for analysis were age (age at first visit), sex, total years of education, and race.

As this is a study primarily aimed at analyzing overall association between brain amyloid status and MOCA scores, we did not stratify our sample to estimate amyloid-MoCA association by the following variables, which were not included in our analysis—tracer and imaging protocol used, indications for which amyloid-PET was performed, and severity of memory impairment.

Statistical Analysis

After summarizing the variables, all statistical analysis was conducted using the statistical software "R," version 3.3.3. Normality testing of variables was done with the Shapiro-Wilk test. After normality testing for distribution of variables, age, MoCA score, and total number of years of education were expressed as mean $\pm$ SD or median and interquartile ranges (IQRs). Sex and race were recorded as numbers and percentages. Amyloid-PET status (positive or negative) was expressed as numbers and percentages. To assess selection bias, the differences between included and excluded patients was analyzed using the χ^2, independent samples t test, and Mann-Whitney U test. Univariate analysis of the relationship of MoCA score and amyloid-PET status to age, sex, education, and race was also performed using the χ^2 test, independent samples t test, and Mann-Whitney U test. Pearson and Spearman analysis was used to assess the correlation between continuous variables. Logistic regression analysis was performed for the outcome of amyloid-PET status. Predictor variables included in the model were MoCA score, age, sex, years of education, and race. Sensitivity, specificity, and cutoff estimation for amyloid positivity was done by receiver operating characteristic curve (ROC) analysis (DeLong method). P-value of 0.05 was considered statistically significant.

RESULTS

Participants and Demographic Data

Six hundred eighty-four patients attended the memory clinic from July 2010 to December 2017 and had analyzable data. We excluded 585 patients based on the exclusion criteria stated above. Ninety-nine patients who had an available brain amyloid-PET result and a MoCA score were included for analysis (Fig. 1).

The mean age of the sample was 71.3 $\pm$ 9 years. Forty-nine patients were male (49.49%) and 50 were female (50.51%). The patients were racially distributed as 94 Caucasian (95.9%) and 4 African American. One patient had missing race information. Median (IQR) years of education was 12 (12 to 16) years. Median (IQR) MoCA score of the sample was 18 (13 to 23). Fifty-six tested positive for amyloid deposition (56.6%; Table 1).

We also explored differences in demographic variables between included (N = 99) and excluded patients (N = 585) to assess for possible bias (Table 2). No significant difference

TABLE 1. Descriptive Data of Included Patients (N = 99)

Parameters	Mean $\pm$ SD/Median (IQR)/n (%)
MoCA score	18 (13-23)
Age (y)	71.3 $\pm$ 9*
Education (y)	12 (12-16)
Sex (male)	49 (49.49)
Race (Caucasian)†	94 (95.9)
Amyloid-PET positive	56 (56.57)

*Normally distributed variable (Shapiro-Wilk test).
†One person had missing race information.
IQR indicates interquartile range; MoCA, Montreal cognitive assessment; PET, positron emission tomography.

TABLE 2. Comparison Between Included and Excluded Patients

Parameters	Included (99) MoCA Score and Amyloid-PET Result Available	Excluded (585) MoCA and/or Amyloid-PET Result Not Available	*P*
Age (mean ± SD)	71.3 ± 9	71.1 ± 14	0.51
Sex (males), n (%)	49 (49.49)	252 (43.07)	0.27
Race (Caucasian), n (%)	94 (95.9)*	524 (93.5)*	0.41
Education [median (IQR)]	12 (12-16)	12 (12-14)†	0.04

*Race information available for 98 patients in sample included and 560 patients in excluded.

†Education information available for 559 patients in excluded.

IQR indicates interquartile range; MoCA, Montreal cognitive assessment; PET, positron emission tomography.

in age ($U = 27752$, $P = 0.51$), sex ($\chi^2_1 = 0.24$, $P = 0.27$), and race ($\chi^2 = 02.91$, $P = 0.41$) was observed, but the level of education was higher in the included patients (median = 12, $U = 24171$, $P = 0.04$).

Main Results

In our assessment of the factors influencing amyloid-PET status, MoCA scores, and the association between them, we found that higher age was associated with amyloid-PET positivity ($t_{97} = -2.484$, $P = 0.01$) and lower MoCA scores ($r_s = -0.43$, $P < 0.001$; Table 2). Male patients were found to have lower MOCA scores (median = 20, $U = 914$, $P = 0.03$), but no difference was observed between male and female patients with respect to amyloid-PET status ($\chi^2 = 0.47$, $P = 0.49$). Level of education was found to correlate positively with MoCA scores ($r_s = 0.25$, $P = 0.01$), but had no influence on amyloid-PET status ($U = 1177$, $P = 0.84$). No racial differences were observed with respect to MOCA scores ($U = 135$, $P = 0.34$) or amyloid-PET status ($\chi^2 = 0.09$, $P = 0.77$).

We compared MoCA scores between amyloid positive (N = 56) and negative (N = 43) patients and found that amyloid-PET positivity was associated with lower MoCA scores (median = 19, $U = 847$, $P = 0.01$; Table 2). This was further evident in the logistic regression model which showed that amyloid-PET status was predicted singularly by MoCA test scores [odds ratio = 0.89, 95% confidence interval (CI), 0.80-0.99; $P < 0.05$] among the other predictor variables (Table 3). Goodness-of-fit of the regression model was confirmed by Hosmer-Lemeshow testing ($\chi^2 = 10.67$, $P = 0.22$).

An ROC curve for estimation of a MoCA score cutoff to predict amyloid-PET positivity (Fig. 2, Table 4) showed that a cutoff of 20 had optimal sensitivity (64.2%) and specificity (67.4%) for identifying amyloid-PET positivity (AUC = 0.65, 95% CI, 0.54-0.76). At a MoCA score cutoff of 25 that is used for the clinical diagnosis of minimal cognitive impairment, prediction of amyloid-positivity was suboptimal (specificity 13.9%, sensitivity 94.6%; Table 4).[4]

DISCUSSION

Amyloid-PET imaging is a sensitive tool for identification of AD.[1] Although MMSE scores correlate to amyloid positivity, there is no clear correlation between increasing amyloid burden and progressive decline in the MMSE scores in previous longitudinal studies.[3] Current guidelines do not recommend a specific MMSE score to perform amyloid imaging. The higher sensitivity of the MoCA test provides an opportunity to identify the relationship between biomarker imaging and cognitive testing.[4] We proposed to examine the association between MoCA test scores and amyloid-PET status and also aimed to identify a MoCA cutoff score for amyloid-PET positivity, which can be validated in future studies as an optimal clinical point to perform the PET scan.

We identified that lower MoCA scores are associated with amyloid-PET positivity. Previous research demonstrates amyloid-MoCA association, but focuses on atypical presentations, non-AD pathology, and truncated MoCA-domain scores.[9–12] In our study, we included patients with total MoCA scores who were primarily evaluated for AD. We found that the MoCA score was the only significant predictor of amyloid-PET positivity in the regression model that included age, sex, education, and race. We could not compare these findings with other samples due to the paucity of data on amyloid-MoCA association. In other studies which analyzed amyloid-MMSE correlation, lower MMSE scores were similarly found to be associated with amyloid-PET positivity.[3,13] The persistence of amyloid-MoCA association observed in our regression model, among other variables, possibly conveys the efficiency of the sensitive MoCA test in identifying cognitive decline due to amyloid deposition.

Exploring the influence of demographic variables, we found that higher age was associated with both amyloid-PET positivity (Table 3) and lower MoCA scores in univariate analysis, although the influence of age on amyloid status was not found to persist in the regression model. Increasing age is expected to result in lower cognitive scores and amyloid-PET positivity, but previous research demonstrates varying effect of age on MoCA scores.[14] However, in studies primarily involving patients with dementia, MoCA score is found to be influenced by age.[15] Prior evidence shows that amyloid-PET positivity is also influenced by higher age and this may lead to lower specificity of the PET scan for diagnosing AD with increasing age.[2] As our study mostly included patients with significant cognitive impairment (median MoCA of 18), it is reasonable to postulate that the low MoCA scores played a more significant role compared with age in the logistic regression model for predicting amyloid-PET positivity.

TABLE 3. Univariate Analysis and Logistic Regression Model for the Outcome of Amyloid-PET Positivity

		Logistic Regression Analysis		
Variables	Univariate Analysis by Amyloid-PET Status	Odds Ratio	95% Confidence Intervals	*P*
MoCA score	Median = 19, $U = 847$, $P = 0.01$*	0.89	0.80-0.99	0.04*
Age	$t_{97} = -2.484$, $P = 0.01$*	1.04	0.98-1.09	0.17
Education	$U = 1177$, $P = 0.84$	1.10	0.92-1.32	0.30
Sex	$\chi^2 = 0.47$, $P = 0.49$	0.89	0.37-2.14	0.79
Race	$\chi^2 = 0.09$, $P = 0.77$	0.54	0.06-4.86	0.58

*Clinically significant variable for amyloid-PET positivity.

MoCA indicates Montreal cognitive assessment; PET, positron emission tomography.

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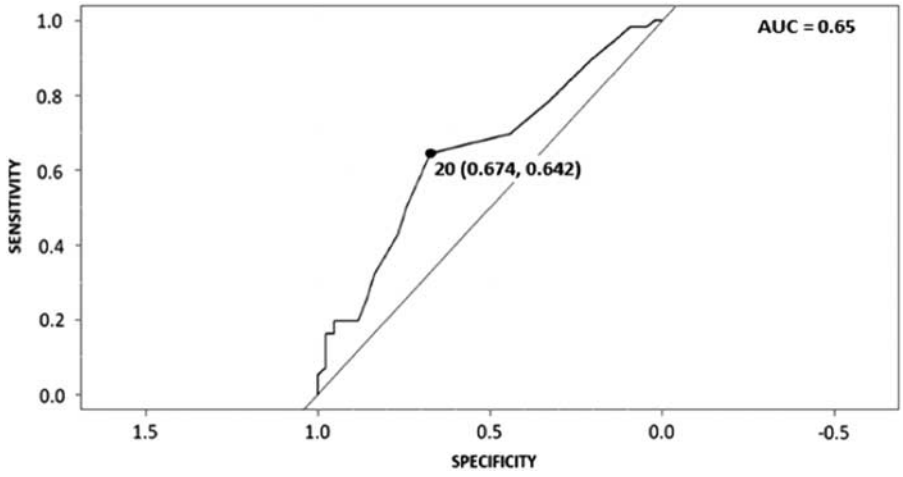

FIGURE 2. ROC curve demonstrating a MoCA score of 20 as the cutoff point with optimal sensitivity and specificity for amyloid positivity. MoCA indicates Montreal cognitive assessment; ROC, receiver operating characteristic curve.

The study had a comparable percentage of males (N = 49) and females (N = 50). Males were found to have lower MoCA scores in our analysis. Normative data from large Italian and Portuguese studies indicate that MoCA is independent of sex.[16,17] However, studies including primarily AD patients show that women have faster rates of disease progression and higher cognitive decline measured by MMSE scores.[18,19] In our study, amyloid-PET status was not found to differ between males and females. Results from the community-based ARIC study demonstrated higher amyloid-PET positivity in females, but another major meta-analysis reported that amyloid status did not vary between sexes in both AD and non-AD dementias.[13,20]

We found that the level of education (years) correlates positively to MoCA scores, but not with amyloid-PET status. Education-corrected MoCA scores (+1 point in MoCA for education ≤ 12 y) were used in our analysis. Studies reveal that correlation persists between MOCA scores and education despite correcting for low levels of education, although further increase in compensation for decreasing education levels seems to nullify its effect on MoCA in early AD patients.[21,22] We found no influence of education on amyloid-PET status in our analysis. Similar findings were reported in the amyloid-PET meta-analysis which observed no association between amyloid-PET status and education in both AD and non-AD dementias.[13] We found no racial differences with respect to MoCA scores and amyloid-PET status in our study. We could not compare our finding with other samples considering that our study population was predominantly Caucasian (95.9%).

We estimated an ideal MoCA score cutoff to identify amyloid-PET positivity by ROC analysis. At the MoCA threshold (25) used to diagnose MCI, we found that identification of amyloid-PET positivity was sensitive (94.6%) but nonspecific (13.9%). We observed that a MoCA threshold of 20 carried optimal sensitivity (64.2%) and specificity (67.4%) for amyloid-PET positivity. We also found reasonable accuracy (AUC = 0.65, 95% CI, 0.54-0.76) at this cutoff for prediction of amyloid-PET positivity. As stated previously, the MoCA cutoff from our study provides an opportunity for optimal clinical use of the amyloid-PET scan. Identifying a high-yield point of use along the continuum of decreasing cognitive test scores would improve diagnostic accuracy and cost-effectiveness.

We also attempted to understand the significance of our MoCA score cutoff with respect to the current literature on disease severity, similar cognitive tests, and the pathologic progression of amyloid deposition in AD. In a previous study

TABLE 4. Sensitivity and Specificity Values at Different MoCA Scores for Amyloid-PET Positivity

MoCA Score	Sensitivity (%)	Specificity (%)	MoCA Score	Sensitivity (%)	Specificity (%)
28	98.2	4.65	17	32.1	83.7
26	98.2	9.30	16	25	86
25†	94.6	13.9	15	19.6	88.4
24	89.3	20.9	14	19.6	88.4
23	78.6	32.5	13	16.1	95.3
22	69.6	44.1	12	16.1	97.7
21	66.1	60.4	11	12.5	97.7
20*	64.2	67.4	10	7.14	97.7
19	50	74.4	9	5.35	1
18	42.8	76.7	8	1.78	1

*MoCA score cutoff with optimal sensitivity and specificity.
†MoCA score cutoff for MCI diagnosis.
MoCA indicates Montreal cognitive assessment; PET, positron emission tomography.

that validated MoCA against MMSE for MCI diagnosis, it was reported that a MoCA score of 17 to 19 ideally signifies the lower values of the MCI range, with some overlap between severe MCI and early AD.[5] A reasonable MMSE-MoCA equivalence scale was also reported in this study by which MoCA score of 20 translated to an MMSE score of 26.[5] Extrapolating our MoCA score cutoff (20) for amyloid-PET positivity to corresponding MMSE scores (26) observed in the aforementioned study certainly requires additional evidence from future studies which directly compare cutoffs for amyloid positivity between the cognitive tests. With respect to a possible relationship with pathologic amyloid deposition, it was often considered that amyloid burden may have already reached peak levels at the time of MCI diagnosis; however, recent longitudinal studies show that amyloid deposition progresses and peaks well into the MCI stage and plateaus in the later stages of dementia.[23] With the MoCA cutoff identified in our study at the lower thresholds of MCI, it is reasonable to postulate that prediction of amyloid-PET positivity might be optimal at MoCA scores corresponding to the peak of amyloid deposition. Further research is essential to explore these hypotheses.

The MoCA cutoff estimated in our study may also facilitate the enrichment of clinical trials. Amyloid-PET imaging is an accurate diagnostic tool for AD and is therefore used in a research scenario to guide optimal patient recruitment both in observational studies of dementia and in therapeutic antiamyloid trials.[8] The accurate baseline identification of amyloid positive patients may enable better achievement of proposed study endpoints in these longitudinal studies. The MoCA cutoff identified in our study enables prediction of amyloid positivity and may therefore be studied for use in the above situations that include amyloid-PET imaging. It may then be possible to identify appropriate patients for amyloid imaging and predict amyloid positivity using the MoCA test in the clinic. Due to the immense cost of dementia care and research, trial enrichment is viewed as an essential factor for impactful research.[24]

Our study had an adequate sample size to test amyloid-MoCA association. We did not exclude patients or stratify our sample based on the different tracers, clinical presentations, or severity of cognitive impairment. These features of our study enable a good real-world extrapolation of the amyloid-MoCA association. Our study also had some limitations. MoCA scores during first visit to clinic were not available for all patients and the next available MoCA score was included for analysis. This resulted in MoCA scores not being obtained in a cross-sectional manner for the 99 patients and lower MoCA scores (first available MoCA) being recorded at later visits for some patients. The possible variation in the median MoCA score of the sample that may have occurred due to this time lag could not be assessed.

Amyloid-PET status was reported in our study by experts using the visual read method. Quantitative estimation of SUVR and determination of amyloid-PET positivity using SUVR cutoffs was not done. Recent studies indicate varying results for different tracers in the comparison of SUVR and visual read methods for establishing amyloid-PET status, but SUVR estimation was found to augment the consistency of early amyloid detection using Florbetapir (^{18}F) in a study by Harn et al.[25–27] Pontecorvo et al[28] also showed that the addition of quantitative method to visual read enhances the accuracy of identifying amyloid-PET positivity. Other findings from a meta-analysis of amyloid-PET imaging, which mostly included patients with PiB (^{11}C) imaging, suggest that the assessment method employed does not influence the prevalence of amyloid positivity.[13] Despite the variability seen between tracers and studies, the lack of quantitative assessment in our patients could have possibly impacted the accuracy of amyloid-PET status. From our study, we are also not certain about the possible effect of different amyloid tracers and protocols on amyloid-MoCA association, although this simulates a real-world setting. Recent meta-analysis and other individual studies report reasonable concordance between PiB (^{11}C), Florbetapir, Flutemetamol, and Florbetaben in identifying amyloid-PET positivity.[13,29,30] This provides an indication that the rates of amyloid-PET positivity may not have varied across different tracers in our study and may have similar MoCA cutoffs. We intend to explore this relationship in future studies of this topic because we are unable to provide the tracer information of patients at this time.

Other limitations of our study include possible selection bias and the lack of generalizability. Our study sample had a higher level of education compared to the excluded patients. Level of education is an established confounder of MoCA scores and higher education in the included patients (Table 2) could have possibly resulted in higher MoCA scores and in turn, higher MoCA cutoff for amyloid-PET positivity. There is also a potential lack of generalizability of our findings because MoCA scores are also influenced by ethnicity.[31] The predominantly Caucasian study sample (95.9%) in a suburban location may have contributed to a MoCA cutoff for amyloid-PET positivity that is not generalizable to populations with varying ethnicities.

In conclusion, our retrospective study shows that amyloid-PET positivity is associated with lower MoCA scores. Clinical use of PET scan to identify amyloid-PET positivity is suboptimal at the MoCA cutoff used for MCI and may yield optimal results if performed at the lower thresholds for MCI. Confirmation of this ideal use point for amyloid-PET imaging identified in our study requires further research and may have potential implications in dementia care and clinical trial enrichment.

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