Title page:

Combining MMSE and brain MRI and SPECT indicators from the automated quantitative assessment applications VSRAD and eZIS improves accuracy of discrimination between mild cognitive impairment and early Alzheimer's disease.

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Key words:

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Abstract:

Background: Alzheimer's disease (AD) is assessed by carefully examining a patient's cognitive impairment. However, previous studies reported inadequate diagnostic accuracy for dementia in primary care settings. The automated quantitative evaluation called the Voxel-based Specific Regional analysis system for Alzheimer's Disease (VSRAD) that uses brain MRI data to evaluate brain morphological abnormalities

associated with AD, is used in many hospitals. Similarly, an automated quantitative evaluation application called the easy Z-score imaging system (eZIS), which uses brain SPECT data to detect regional cerebral blood flow decreases associated with AD, is widely used. These applications have several indicators, each of which is known to correlate with the degree of AD. However, it is not completely known whether these indicators work better when used in combination in real-world clinical practice.

Methods: We included 112 participants with mild cognitive impairment (MCI) and 128 participants with early AD participants in this study. All participants underwent MRI, SPECT, and the Mini-Mental State Examination (MMSE). Demographic and clinical characteristics were assessed in univariate analysis, and logistic regression analysis with a combination of MMSE and VSRAD and eZIS indicators was performed to verify whether the diagnostic accuracy in discriminating between MCI and early AD was improved.

Results: The area under the receiver operating characteristic curve (AUC) for the MMSE score alone was 0.835. Combining the MMSE score with two quantitative indicators from the VSRAD and eZIS that assessed the extent of brain abnormalities significantly improved the AUC to 0.870.

Conclusion: Compared with the MMSE score alone, combining the MMSE score with

the VSRAD and eZIS indicators significantly improved the accuracy of discrimination between patients with MCI and early AD. Implementing VSRAD and eZIS does not require professional clinical experience of treatment in dementia. Therefore, physicians may easily improve the accuracy of dementia diagnosis in real-world primary care settings.

Introduction:

Dementia is an important disease characterized by progressive cognitive impairment and social dysfunction [1]. In particular, Alzheimer's disease (AD) accounts for approximately 70% of dementia [2] and often occurs in patients in their 70s to 80s. It is also known that the prevalence increases exponentially with aging [2]. Diagnosis of dementia is assessed by carefully examining a patient's cognitive impairment and function in daily life according to international diagnostic criteria such as the International Statistical Classification of Diseases and Related Health Problems 10th edition (ICD-10)

and the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) [3]. More than half of patients with mild cognitive impairment (MCI) progress to dementia within 5 years, but some MCI patients may remain MCI stable or return to normal cognition over time [4]. For this reason, accurate discrimination between MCI and early AD is important [4-6], especially regarding therapeutic interventions and the prognosis of dementia [4, 6-7].

However, due to the rapid increase in the number of patients, diagnosis and treatment are not always performed only by doctors who are clinically accustomed to dementia. Therefore, the Mini-Mental State Examination (MMSE) is being developed as a screening tool to assist in the diagnosis of dementia [8]. This tool is a simple test consisting of questions asked by an evaluator and is often used in primary care settings. However, it is difficult to exclude cerebral organic diseases with only the MMSE, and it is inferior to the diagnostic accuracy of a specialist in distinguishing MCI from AD [9]. Therefore, it is necessary to try to improve the accuracy by combining it with other assessment methods.

At this point, brain imaging analyses are useful in the differential diagnosis of dementia and are often used in a qualitative manner to exclude organic disorders such as stroke, brain tumors, normal pressure hydrocephalus, and encephalitis. Recently, the

91 performance of brain imaging analyses have improved, and the quantitative analysis of
92 brain morphology and function has become possible, making it a powerful auxiliary tool
93 for dementia diagnosis [10-11].

94 It has been reported that medial temporal lobe atrophy is a characteristic morphological
95 change in AD. The automated quantitative evaluation application called the Voxel-based
96 Specific Regional analysis system for Alzheimer's Disease (VSRAD), which uses brain
97 magnetic resonance imaging (MRI) data to assess the brain morphological abnormalities
98 associated with AD, was developed by Dr. Matsuda and colleagues [12-13]. VSRAD
99 applies voxel-based morphometry (VBM), which is a method for superimposing plane
100 tomographic images from head MRI and dividing the entire brain into small cubes for
101 statistical analysis [14]. This free software application was updated into VSRAD advance
102 2 in May 2015, and it is being used in many hospitals. In particular, a Z-score of gray
103 matter atrophy in the volume of interest (VOI) relevant to AD, which measures the
104 severity of medial temporal atrophy, is a representative indicator of VSRAD [13, 15-16].

105 Furthermore, characteristic cerebral blood flow decreases in the parietal lobe and
106 posterior cingulate gyrus associated with AD can be assessed by single photon emission
107 computed tomography (SPECT) [17]. An automated quantitative evaluation application
108 called the easy Z-score imaging system (eZIS), which uses brain SPECT data to detect

the regional cerebral blood flow decrease in AD, is widely used in Japan [18]. The severity of regional blood flow decrease is the most representative quantitative indicator in eZIS.

These two applications have several indicators, each of which is known to correlate with the degree of AD [10]. However, previous studies have the limitation that the sample size is small, and it is not completely known whether these indicators work better in combination in real-world clinical practice. To approach this clinical question, it is necessary to perform multivariate analysis. Hence, we performed a binomial logistic regression analysis combining MMSE scores and VSRAD and eZIS indicators to verify whether the diagnostic accuracy for discriminating between MCI and early AD was improved.

Materials and Methods:

Ethical consideration

This study was conducted in accordance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects. Prior to the initiation of the study, the study protocol was reviewed and approved by the

institutional review board of the ethics committee of Towada City Hospital (No. 1-4, Approved 12 June 2020). Since this was a retrospective medical record survey, informed consent was exempted, but we instead released information on this research so that patients were free to opt out.

Participants

We recruited MCI and early AD participants from the outpatient department of Towada City Hospital between September 2016 and March 2020. All participants underwent MRI, SPECT, and a battery of laboratory tests including assessment of thyroid function and vitamin B12, folate and serum ammonia concentrations. Cognitive function was assessed with the MMSE [19], the Revised Hasegawa's Dementia Scale (HDS-R) [20], and the clock-drawing test (CDT) [21]. A diagnosis of AD was made based on the DSM-5 and ICD-10. A diagnosis of MCI was made according to Petersen's criteria [22]. We included patients in our study with MMSE scores of 20 or higher to exclude moderate to severe dementia [23]. The exclusion criteria were symptoms of depression, dementia with Lewy bodies, cerebrovascular disease, or any other psychiatric disorder.

MRI procedure

MRI was performed on a 1.5T system (GE Signa Explore, General Electric Co, Boston, USA). Axial, coronal and sagittal T1-weighted sequence (SE) images (repetition time [TR], 520 ms; echo time [TE], 12.0 ms; 5 mm slice thickness) and axial T2-weighted SE images (TR, 3800 ms; TE, 97.0 ms) were obtained for diagnosis. Then, 3D volumetric acquisition of a T1-weighted gradient-echo sequence produced a gapless series of thin sagittal sections using a magnetization-prepared rapid-acquisition gradient-echo sequence (TR, 12.3 ms; TE, 5.1 ms; flip angle, 15°; acquisition matrix, 256 × 256; 1.4-mm slice thickness).

MRI: voxel-based morphometry

The voxel-based analysis system in the present study has been validated [12]. Currently, the software is distributed in Japan under the name Voxel-based Specific Regional Analysis System for Alzheimer Disease advance 2 (VSRAD advance 2, Eisai Co, Tokyo, Japan). VSRAD scores reflect the severity of gray matter loss across the entire brain because the software compares an image with the original normal database template. VSRAD advance 2 automatically calculates the four indicators of AD shown below:

(1) the Z-score of gray matter atrophy severity in the volume of interest of AD ("VSRAD VOI severity") = ((normal control average of voxel level – patient's voxel level)/normal control standard deviation)

(2) the extent of gray matter atrophy in the VOI of AD ("VSRAD VOI extent") = ((number of voxels judged to have a Z-score of more than 2/number of all voxels in the volume of the hippocampus) × 100%)

(3) the extent of gray matter atrophy in the whole brain ("VSRAD GM extent") = a percentage of voxels with a Z-score >2 compared with the whole brain.

(4) the ratio of the extent of gray matter atrophy in the VOI to the whole brain ("VSRAD VOI ratio") = ((number of voxels judged to have a Z-score of more than 2/number of all voxels in the volume of the whole brain) × 100%)

These four indicators of VSRAD have been explained in previous reports [13, 24].

SPECT procedure

The patient received a bolus injection of 99mTc-ethyl cysteinate dimer (ECD) (600 MBq, Fujifilm Toyama Chemical Co, Tokyo, Japan) via the right brachial vein in a comfortable supine position with eyes closed, in an awake state in quiet surroundings.

Twenty minutes after angiography, SPECT images were obtained using a rotating, two-head gamma camera (GE Infinia, General Electric Co, Boston, USA) with low energy high resolution and parallel hole collimators (128 × 128 matrix). The images were reconstructed using Butterworth and Ramp filters, and attenuation correction was performed according to Chang's method.

SPECT: the easy Z-Score Imaging System (eZIS)

This is a software-based application that first performs an anatomical standardization of SPECT images into a stereotactic space using SPM2 (Wellcome Department of Cognitive Neurology, London, United Kingdom). Subsequently, a voxel-based analysis is performed using a Z-score map calculated through a comparison of a patient's data with a control database after voxel normalization to global mean cerebral blood flow, Z-score = ([control mean] − [individual value])/(control SD).

The eZIS automatically calculates the following three indicators for characterizing regional cerebral blood flow (rCBF):

(1) The severity of rCBF decrease in a specific region showing rCBF reduction from the averaged positive Z-score in the voxels of interest (bilateral posterior cingulate cortices [PCC], precunei, and parietal cortices) (“eZIS severity”).

(2) The extent of a significant regional rCBF reduction in the voxel of interest was determined by calculating the percentage of coordinates with a Z-value exceeding the threshold value of 2 (“eZIS extent”).

(3) The ratio of the extent of a region showing significant rCBF reduction in the voxel of interest to the extent of a region showing significant rCBF reduction in the whole brain, which is also the percentage of coordinates with a Z-value exceeding the threshold value of 2 (“eZIS ratio”). This ratio indicates the specificity of the rCBF reduction in the voxel of interest compared with that in the whole brain.

These three indicators of eZIS have been explained in previous reports [18, 25].

Statistical analysis

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [26], which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria, version 3.5.2). More precisely, it is a modified version of R commander that was designed to add statistical functions frequently used in biostatistics.

First, all statistical tests were based on a two-sided significance level of $p < 0.05$.

Demographic and clinical characteristics were analyzed using the chi-square test and Mann–Whitney U test for differences between MCI and early AD patients. For multiple univariate analysis, the Benjamini-Hochberg procedure was used to determine whether each p-value was statistically significant.

Second, a forward-backward stepwise binomial logistic regression analysis based on Akaike's information criterion (AIC) was performed. MCI or early AD were included in the analysis as dependent variables, and sex, age, education year, MMSE score, VSRAD VOI severity, VSRAD VOI extent, VSRAD GM extent, VSRAD ratio, eZIS severity, eZIS extent and eZIS ratio were used as candidate independent variables. Factors showing significant differences in univariate analysis were included in the model by the stepwise method. The result of this calculation was named the "stepwise selection model".

Third, another binomial logistic regression analysis was performed with MCI or early AD as dependent variables, and MMSE, VSRAD VOI severity and eZIS severity were forced entry into the model as independent variables, because VSRAD VOI severity and eZIS severity were the most representative indicators in each modality. The result of this calculation was named the "forced entry model".

Fourth, receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) analysis for the discrimination between MCI or early AD was performed for each

VSRAD indicator, each eZIS indicator, the stepwise selection model, and the forced entry model.

Result:

Patient characteristics and univariate analysis

A total of 411 individuals (112 with MCI and 299 with AD) were found as candidates for the participants. After excluding individuals with MMSE < 20, we included 240 participants. There were 112 participants with MCI (68 women and 44 men; median age was 77.5 years old) and 128 participants with early AD (89 women and 39 men; median age was 78 years old). The median MMSE score for those with MCI was 26 and for those with early AD was 23. The median education years those with MCI was 12 and those with early AD was 11. Regarding the results of the VSRAD indicators, the MCI and early AD groups showed median scores of 0.95 and 1.77 for VSRAD VOI severity, 4.38 and 32.22 for VSRAD VOI extent, 3.16 and 4.19 for VSRAD GM extent, and 1.53 and 6.10 for VSRAD ratio, respectively. Regarding the results of the eZIS indicators,

the MCI and early AD groups showed median scores of 1.10 and 1.25 for eZIS severity, 9.23 and 13.70 for eZIS extent, and 1.64 and 2.13 for eZIS ratio, respectively. As a result of univariate analysis applying the Benjamini-Hochberg procedure, there were no statistically significant differences in gender distribution, age, education year or eZIS ratio between participants with MCI and early AD. There was a statistically significant difference between the MCI and early AD groups in MMSE scores, VSRAD VOI severity, VSRAD VOI extent, VSRAD GM extent, VSRAD ratio, eZIS severity and eZIS extent. Table 1 shows demographic and clinical data for participants.

Table 1: demographic and clinical data for participants.

Factor	MCI	early AD	p.value
N	112	128	
gender distribution (%): women	68 (60.7)	89 (69.5)	0.174
gender distribution (%): men	44 (39.3)	39 (30.5)	
age (median [range])	77.5 [60, 90]	78 [64, 94]	0.428
education year (median [range])	12 [6, 16]	11 [6, 16]	0.683
MMSE (median [range])	26 [20, 30]	23 [20, 30]	<0.001
VSRAD VOI severity (median [range])	0.95 [0.03, 4.82]	1.77 [0.31, 5.44]	<0.001
VSRAD VOI extent (median [range])	4.38 [0.00, 98.10]	32.22 [0.00, 98.71]	<0.001
VSRAD GM extent (median [range])	3.16 [0.86, 11.28]	4.19 [1.27, 16.03]	<0.001
VSRAD ratio (median [range])	1.53 [0.00, 20.45]	6.10 [0.00, 26.06]	<0.001
eZIS severity (median [range])	1.10 [0.53, 2.11]	1.25 [0.67, 3.13]	0.002
eZIS extent (median [range])	9.23 [0.08, 45.10]	13.70 [0.13, 51.33]	0.004
eZIS ratio (median [range])	1.64 [0.01, 7.19]	2.13 [0.02, 6.23]	0.03

Abbreviation in Table 1: mild cognitive impairment, MCI; Alzheimer’s disease, AD; Voxel-based Specific Regional analysis system for Alzheimer's Disease, VSRAD; Volume of interest, VOI; gray matter atrophy in the whole brain, GM; easy Z-Score Imaging System, eZIS

Binomial logistic regression analyses

First, a forward-backward stepwise binomial logistic regression analysis (stepwise selection model) based on AIC was performed with MCI and early AD as the dependent variables. Statistically significant factors in the univariate analysis (MMSE score, VSRAD VOI severity, VSRAD VOI extent, VSRAD GM extent, VSRAD ratio, eZIS severity and eZIS extent) were used as independent variables for stepwise binomial logistic regression analysis. As a result of this analysis, we found that a lower MMSE score (odds ratio = 0.561; $p < 0.001$), higher VSRAD VOI extent (odds ratio = 1.025; $p < 0.001$) and higher eZIS extent (OR 1.039; $p = 0.033$) were associated with early AD. Second, another binomial logistic regression analysis (forced entry model) was performed with MCI and early AD as the dependent variables, and MMSE, VSRAD VOI severity and eZIS severity were forced entry into the model as independent

variables. In this analysis, a lower MMSE score (OR = 0.567; $p < 0.001$), higher VSRAD VOI severity (OR 1.999; $p < 0.001$) and higher eZIS severity (OR 2.994; $p = 0.045$) were associated with early AD. These results are described in Table 2.

Table2: Results of the binomial logistic regression analyses.

	B	SE	Wald	OR (95% CI)	P-value
Stepwise selection model					
Intercept	13.127				
MMSE	-0.578	0.086	45.056	0.561 (0.474-0.664)	<0.001
VSRAD VOI extent	0.024	0.007	13.124	1.025 (1.011-1.038)	<0.001
eZIS extent	0.039	0.018	4.573	1.039 (1.003-1.077)	0.033
Forced entry model					
Intercept	11.585				
MMSE	-0.567	0.085	44.799	0.567 (0.481-0.670)	<0.001
VSRAD VOI severity	0.693	0.199	12.058	1.999 (1.352-2.955)	<0.001
eZIS severity	1.097	0.546	4.033	2.994 (1.027-8.732)	0.045

Abbreviation in Table 2: Mini-Mental State Examination, MMSE; Voxel-based Specific Regional analysis system for Alzheimer's Disease, VSRAD; Volume of interest, VOI; easy Z-score imaging system, eZIS; regression coefficient, B; standard error, SE; odds ratio, OR; confidence interval, CI.

294 Receiver operating characteristic (ROC) curve analysis

295 Table 3 shows the results of the ROC curve analysis for the discrimination between MCI
296 and early AD. The AUC using MMSE scores alone was 0.835. On the other hand, the
297 AUC obtained from the stepwise selection model that combined MMSE, VSRAD VOI
298 extent and eZIS extent was 0.870. The AUC obtained from the forced entry model
299 combining MMSE score, eZIS severity and VSRAD VOI severity was 0.868. A chi-
300 square test of these AUCs revealed that the stepwise selection model had a statistically
301 significantly larger area than the MMSE score alone ($p = 0.012$), and the forced entry
302 model also had a statistically significantly larger area than MMSE score alone ($p = 0.010$),
303 although there was no statistically significant difference between the stepwise selection
304 model and forced entry model based on AUC ($p=0.584$). The results of the ROC analysis
305 are described in Table 3 and Figure 1.

306

307 (Figure 1: Receiver operating characteristic (ROC) curve analyses.
308 Figure Legends: The results of the ROC analysis for the discrimination between MCI and
309 early AD. The area under the receiver operating characteristic curve (AUC) using MMSE
310 scores alone was 0.835. On the other hand, the AUC obtained from the stepwise selection
311 model that combined MMSE, VSRAD VOI extent and eZIS extent was 0.870. A chi-

square test of these AUCs revealed that the stepwise selection model had a statistically significantly larger area than the MMSE score alone ($p = 0.012$).)

Table3: Results of the receiver operating characteristic curve analyses.

	Cutoff point	FPF	TPF	AUC	SE
MMSE	23	0.143	0.695	0.835	0.026
VSRAD VOI severity	1.35	0.250	0.625	0.710	0.033
VSRAD VOI extent	33.54	0.125	0.492	0.708	0.033
VSRAD GM extent	3.51	0.402	0.703	0.649	0.036
VSRAD ratio	5.66	0.223	0.531	0.677	0.034
eZIS severity	1.3	0.250	0.469	0.616	0.036
eZIS extent	13.8	0.277	0.500	0.607	0.037
eZIS ratio	1.8	0.438	0.617	0.581	0.037
Stepwise selection model	0.517	0.179	0.828	0.870	0.023
Forced entry model	0.535	0.170	0.813	0.868	0.024

Abbreviation in Table 3: Mini-Mental State Examination, MMSE; Voxel-based Specific Regional analysis system for Alzheimer's Disease, VSRAD; Volume of interest, VOI; gray matter atrophy in the whole brain, GM; easy Z-score imaging system, eZIS; regression coefficient, false positive fraction, FPF; true positive fraction, TPF; area under the curve, AUC; standard error, SE.

Discussion:

Our study revealed that the diagnostic accuracy that distinguished MCI from early AD was statistically significantly improved by combining quantitative data from psychological tests with brain morphological and functional image analyses. The AUC with the MMSE scores alone was 0.835, but the AUC was improved to 0.870 by adding the VSRAD VOI extent and eZIS extent to the MMSE scores. VSRAD and eZIS are useful applications that automatically quantify cerebral atrophy and blood flow decreases based on the data obtained from MRI and SPECT, so physicians may improve the diagnostic accuracy of dementia regardless of clinical experience.

For these applications, “VSRAD VOI severity” and “eZIS severity” are the most representative indicators. However, interestingly, the factors selected in the stepwise selection model were “VSRAD VOI extent” and “eZIS extent”.

According to Braak staging [27-28], which explains the pathological changes in AD, the burden of tau protein spreads as the stage progresses. In addition, gray matter loss in the medial temporal lobe has already been recognized in MCI, and it is known that the loss area expands when conversion to AD [29]. Mizumura *et al* stated that studying the “extent” of the region of abnormal blood flow that causes functional disorder is more rational than assessing the “severity” of the blood flow abnormality that reflects local tissue

343 degeneration. [30]. Their discussion confirmed the results of our study. Therefore, on
344 brain MRI and SPECT, the "extent" of the lesion may be more important for
345 distinguishing MCI from AD than the "severity" of local atrophy and decreased regional
346 cerebral blood flow. Since cognitive function was evaluated not only for memory but also
347 for social and emotional function, we thought patients with relatively widespread
348 neuronal loss and decreased cerebral blood flow were more likely to progress to dementia.
349 On the other hand, we also calculated binomial logistic regression analysis with a forced
350 entry model that included “MMSE”, "eZIS severity" and "VSRAD VOI severity" as
351 independent factors. Consequently, the AUC for the forced entry model was 0.868. There
352 was no statistically significant difference in AUC between the stepwise selection model
353 and forced entry model. However, it was revealed that the odds ratio for the indicators in
354 the forced entry model was higher than that on the stepwise selection model. Therefore,
355 it was suggested that the statistical impact and clinical influence of each indicator may be
356 different.
357 In our study, we compared participants with MCI and those with early AD, but VSRAD
358 and eZIS had lower AUC for each indicator than previous studies comparing healthy
359 volunteers with early AD [18, 31]. MCI may have some similar findings with early AD,
360 so there may have been relatively poor discrimination accuracy for discriminating MCI

and early AD.

There are several assessment tools for dementia, but it is not fully understood which combinations work better. A previous study on positron emission tomography (PET) and MRI stated that it was important to combine modalities to assess AD from different perspectives [32]. Another study reported that the diagnostic accuracy of dementia was improved by combining two different neuropsychological tests, the MMSE and clock-drawing test [33]. Now, we have shown that the combination of a neuropsychological test and brain imaging evaluation, based on logistic regression analysis, improves the diagnostic accuracy of discriminating MCI from early AD in a statistically significant manner compared with independently applying each test.

When predicting diagnostic accuracy by combining multiple different indicators, it is important to select statistically significant indicators and weight them by the multivariate analysis results. In our study, we included a sufficient sample of patients, more than 10 times the independent variables [34]. For this reason, we could identify statistically significant independent variables not only by univariate correlation analysis but also by binomial logistic regression analysis.

Previous studies have reported inadequate diagnostic accuracy for dementia in primary care settings [35]. That is, the diagnosis of early AD may be delayed and may lead to

379 underestimation of cognitive impairment [35]. In Japan, the number of dementia patients
380 will exceed 6 million in 2020 due to the rapid aging of the population [36]. In addition,
381 previous research estimated that the social cost of dementia in Japan will have reached
382 approximately 14.5 trillion yen per year in 2014 [37]. It is known that early diagnosis of
383 dementia and appropriate intervention not only improve the quality of life of patients and
384 their families but also reduce socioeconomic costs [38]. Therefore, we also considered it
385 important from the viewpoint of public health to combine psychological tests and
386 quantitative brain imaging data to improve the accuracy and reproducibility of dementia
387 diagnoses.

388 As imaging modalities evolve and examination costs decrease, it is expected that the
389 number of diagnostic support tools will increase. PET is a useful biomarker as well as
390 MRI and SPECT among the brain imaging assessment tools [32], however the use of PET
391 for the detection of dementia has not yet been accepted for reimbursement in the National
392 Health Insurance system in Japan. Hence, MRI and SPECT are widely applied in patients
393 with cognitive impairment in Japan [39]. New biomarkers for the diagnosis of AD,
394 including the measurement of cerebrospinal fluid β-amyloid 42 and tau proteins [40], are
395 being clinically applied. It is necessary to continue conducting research on better test
396 combinations that take cost performance and insurance adaptation into account.

There are several limitations of our study. Our research was a single-center, retrospective, cross-sectional study. It can explain the diagnostic accuracy of the test, but the causal relationship between the results and the disease remain unknown. In addition, our study did not randomize the patient population, which may lead to sampling bias. Furthermore, although the site and extent of atrophy differ based on the subtypes of AD [41], heterogeneity in the AD population may have been high because our study did not identify these subtypes.

Conclusion:

We found that combining the MMSE score with two indicators from automated quantitative assessment applications using brain MRI and SPECT, called VSRAD and eZIS, respectively, significantly improved the accuracy of discrimination between MCI and early AD compared with MMSE scores alone. Implementing VSRAD and eZIS does not require professional clinical experience of treatment in dementia. Therefore, physicians may easily improve the accuracy of dementia diagnosis in real-world primary care settings.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects. Prior to the initiation of the study, the study protocol was reviewed and approved by the institutional review board of the ethics committee of Towada City Hospital (No. 1-4, Approved 12 June 2020).

Consent for publication

Since this study was a retrospective medical record survey, informed consent was exempted; however, we instead released information on this research so that patients were free to opt out.

Data availability

Ethical restrictions prevent public sharing of data. Data may be obtained by contacting the corresponding author. (furukori@dokkyomed.ac.jp)

Competing interests

Norio Yasui-Furukori has been a speaker for Dainippon-Sumitomo Pharmaceutical, Mochida Pharmaceutical, and MSD. Kazutaka Shimoda has received research support from Meiji Seika Pharma Co., Pfizer Inc., Dainippon Sumitomo Pharma Co., Ltd., Daiichi Sankyo Co., Otsuka Pharmaceutical Co., Ltd., Astellas Pharma Inc., Novartis Pharma K.K., Eisai Co., Ltd., Takeda Pharmaceutical Co., Ltd. and honoraria from Mitsubishi Tanabe Pharma Corporation, Meiji Seika Pharma Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., Takeda Pharmaceutical Co., Shionogi & Co., Ltd., Daiichi Sankyo Co., Pfizer Inc. and Eisai Co., Ltd. The companies had no role in the study design, the data collection and analysis, the decision to publish, or the preparation of the manuscript. The remaining authors declare that they have no competing interests to report.

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Authors' contributions

KT designed the study, contributed to the data analysis and wrote the manuscript. KT, KY and JT diagnosed and treated the patients. NT, TN, and YT conducted brain imaging tests. NS, NYF and KS contributed to the interpretation and critically reviewed the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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