

# Voxel-based specific regional analysis system for Alzheimer's disease utility as a screening tool for unrecognized cognitive dysfunction of elderly patients in diabetes outpatient clinics: Multicenter retrospective exploratory study

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## Keywords

Cognitive dysfunction, Elderly patients with diabetes, Magnetic resonance imaging

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## ABSTRACT

**Aims/Introduction:** An efficient screening strategy for identification of cognitive dysfunction remains a clinical issue in the management of elderly adults with diabetes. A magnetic resonance imaging voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) has been developed as an automated brain morphometry system that includes the hippocampus. We carried out a multicenter retrospective study to evaluate the utility of VSRAD for screening cognitive dysfunction in diabetes outpatient clinics.

**Materials and Methods:** We enrolled patients with diabetes aged >65 years who underwent brain magnetic resonance imaging scans for the purpose of a medical checkup between November 2018 and May 2019. Patients who were already suspected or diagnosed with mild cognitive impairment and/or dementia as well as those with a history of cerebrovascular disease were excluded.

**Results:** A total of 67 patients were enrolled. Five patients were diagnosed with mild cognitive impairment or dementia (clinical cognitive dysfunction). Patients with clinical cognitive dysfunction showed a significantly higher z-score in VSRAD analysis ( $2.57 \pm 0.47$  vs  $1.15 \pm 0.55$ ,  $P < 0.01$ ). The sensitivities and specificities for diagnosis of clinical cognitive dysfunction were 80 and 48% for the Mini-Mental State Examination, 100 and 89% for the z-score, and 100 and 90% for the combination of the Mini-Mental State Examination score and z-score, respectively.

**Conclusions:** VSRAD analysis can distinguish patients with clinical cognitive dysfunction in the elderly with diabetes, and also shows reasonable sensitivity and specificity compared with the Mini-Mental State Examination alone. Thus, VSRAD analysis can be useful for early identification of clinical cognitive dysfunction in the elderly with diabetes.

## INTRODUCTION

The prevalence of cognitive dysfunction has been increasing worldwide and has become a major public health concern. Since several population-based prospective studies have

reported that diabetes mellitus is associated with the risk of dementia, including Alzheimer's disease<sup>1–3</sup>, cognitive dysfunction is increasingly recognized as an important comorbidity of diabetes mellitus. In addition, cognitive dysfunction in elderly adults is often associated with severe hypoglycemia, which in turn impairs cognitive function<sup>4,5</sup>. In fact, the Japan Diabetes Society/Japan Geriatrics Society Joint Committee has provided

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a recommended glycated hemoglobin (HbA1c) target for elderly patients with diabetes based on their cognitive function status<sup>4</sup>.

As the hippocampus plays a pivotal role in specific aspects of memory and learning, declining cognitive performance can plausibly be linked to changes in hippocampal volume<sup>6</sup>. Diabetes mellitus is therefore a possible risk factor for hippocampal atrophy, which might precede clinical development of cognitive dysfunction<sup>7</sup>. In the Hisayama Study, a population-based prospective cohort study designed to evaluate the risk factors for lifestyle-related diseases in Japan, elderly individuals with diabetes had significantly lower ratios of hippocampal volume-to-total brain volume<sup>8</sup>. Thus, evaluating hippocampal volume in elderly patients with diabetes must be informative for physicians to facilitate early diagnosis of cognitive dysfunction and optimization of diabetes management.

Recently, a magnetic resonance imaging (MRI) voxel-based specific regional analysis system for Alzheimer's disease (VSRAD) was developed as a tool to automatically evaluate atrophy of the parahippocampal gyrus and has become widely available in medical checkup for neurological screening in Japan<sup>9,10</sup>. However, its usefulness for screening cognitive dysfunction of elderly patients with diabetes has not been examined in diabetes outpatient clinics.

We therefore carried out a multicenter retrospective study of elderly Japanese patients with diabetes who underwent brain MRI scanning using VSRAD. In the present study, we evaluated the utility of VSRAD for early identification of mild cognitive impairment (MCI) and dementia in elderly patients with diabetes in whom cognitive dysfunction had not been previously recognized. In addition, we also investigated clinical factors associated with VSRAD analysis.

## MATERIALS AND METHODS

### Study population

The present multicenter retrospective study was carried out in the diabetes outpatient clinics in the four regional core hospitals in Japan: Kyoto University Hospital (Kyoto city, Kyoto, Japan), Shiga General Hospital (Moriyama city, Shiga, Japan), Koto Memorial Hospital (Higashiomi city, Shiga, Japan) and Hikone Municipal Hospital (Hikone city, Shiga, Japan). We enrolled patients with diabetes aged >65 years who underwent 1.5-T brain MRI scans for analysis with the VSRAD advance system (Eisai Co., Tokyo, Japan) for the purpose of a medical checkup between the period of 1 November 2018 and 31 May 2019. Those who had already been suspected of or diagnosed with MCI and/or dementia before the brain MRI scans and those who had a history of cerebrovascular diseases or apparent MRI finding of cerebrovascular diseases were excluded. We retrospectively collected clinical data from medical records including sex, age, type and estimated duration of diabetes, laboratory data, therapeutic agents, diabetic retinopathy and nephropathy, medical history (including hypertension, dyslipidemia and coronary artery disease [CAD]), and cognitive function. The protocol of this study was approved by the Kyoto University

Graduate School and Faculty of Medicine, Ethics Committee (registry no. R2023, 31 July 2019) and conforms to the provisions of the Declaration of Helsinki.

### Laboratory data

All patients underwent routine laboratory tests including fasting plasma glucose, C-peptide, HbA1c, serum triglycerides, serum high-density lipoprotein, serum low-density lipoprotein, serum creatinine, serum uric acid and hemoglobin. We collected the laboratory test data in the same month as the brain MRI scans were collected. We also calculated the C-peptide index, as well as the standard deviation adjusted for the number of HbA1c assessments and coefficient of variation<sup>11</sup> using 1-year data of HbA1c before the brain MRI scan, as HbA1c variability might affect cognitive function. As the Japan Diabetes Society/Japan Geriatrics Society Joint Committee has provided recommendations for glycemic control in elderly patients with diabetes<sup>4</sup>, we also assessed whether each patient achieved the recommended HbA1c levels during the study period.

### MRI analysis

In the present study, VSRAD advance software (Eisai Co.) was applied for analysis of the brain MRI images. Based on the computer-assisted voxel-based morphometry of MRI images, VSRAD analysis provided the mean values of positive *z*-scores in the target volume of interest as an indicator of atrophy of the parahippocampal gyrus by comparing a given individual's gray matter concentration voxel-by-voxel with that of the established reference database of Japanese healthy individuals. The 1.5-T MRI scanners and scan protocol were used for the brain scans to utilize the reference database for VSRAD analysis. According to the manufacturer's protocol and previous studies<sup>10,12</sup>, the three-dimensional sagittal sections of T1-weighted spin-echo images were used to evaluate brain and hippocampal atrophy; a *z*-score  $\geq 2$  was used to denote significant atrophy suggesting the possibility of cognitive dysfunction. In addition, all brain MRI images were also analyzed using FreeSurfer Software (version 6.0.0, <http://surfer.nmr.mgh.harvard.edu/>), and hippocampal volumes were calculated as previously reported<sup>13</sup>.

### Assessment and diagnosis of cognitive dysfunction

In the present study, we referred to MCI and dementia as 'clinical cognitive dysfunction'. After carrying out brain MRI scans, we additionally assessed cognitive function using the Mini-Mental State Examination (MMSE)<sup>14</sup>, the Dementia Assessment Sheet for Community-based Integrated Care System-21 items<sup>15</sup> and the Dementia Assessment Sheet for Community-based Integrated Care System-8 items<sup>16</sup>. The cut-off value of each test for suggesting clinical cognitive dysfunction was 27, 31 and 11, respectively<sup>14-16</sup>. These tests were carried out by well-trained diabetes educators and clinical psychotherapists in diabetes outpatient clinics. Separately, diagnosis of clinical cognitive dysfunction was made according to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders*<sup>17</sup> by

dementia specialists authorized by the Japan Geriatrics Society, Japan Society for Dementia Research and/or Japanese Psychogeriatric Society, using other evaluation tools, including the Japanese version of Montreal Cognitive Assessment (cut-off value, 25)<sup>18</sup>, Hasegawa dementia rating scale-revised (cut-off value, 20)<sup>19</sup>, and brain computed tomography and/or regional blood flow decrements in brain perfusion single-photon emission computed tomography<sup>20,21</sup>.

### Statistical analysis

Data are presented as the mean  $\pm$  standard deviation. Differences between the two groups were analyzed by the unpaired Student's *t*-test, Wilcoxon test or Fisher's exact probability test, as appropriate. The optimal cut-off point was determined by the Youden Index; that is,  $J = \max(\text{sensitivity} + \text{specificity} - 1)$ . We evaluated the association between the *z*-score in VSRAD analysis or age and other factors, including sex, history of CADs and MMSE score, by logistic regression analysis. To compare the sensitivity and specificity of the MMSE score and *z*-score for the diagnosis of clinical cognitive dysfunction, McNemar's test was applied. A *P*-value of  $<0.05$  was considered statistically significant. JMP Pro<sup>®</sup>, version 15.1 (SAS Institute Inc., Cary, NC, USA) was used to carry out the statistical analyses.

## RESULTS

### Characteristics of enrolled patients

A total of 67 patients aged  $>65$  years were enrolled in the present study. Importantly, they had not been suspected of clinical cognitive dysfunction before the brain MRI scans and VSRAD analyses. The profiles of all the enrolled patients are shown in Table 1. Of the 67 patients, 43 (64%) were men. All of the patients had graduated from high school. There were 63 patients with type 2 diabetes mellitus, three patients with type 1 diabetes mellitus and one patient with pancreatic diabetes mellitus. The mean age was  $73.0 \pm 5.7$  years; body mass index was  $24.3 \pm 3.6$  kg/m<sup>2</sup>; estimated duration of diabetes was  $13.0 \pm 10.9$  years; HbA1c was  $7.1 \pm 1.0\%$ ; estimated glomerular filtration rate was  $58.0 \pm 16.1$  mL/min/1.73m<sup>2</sup>; *z*-score in VSRAD analysis was  $1.16 \pm 0.65$ ; Dementia Assessment Sheet for Community-based Integrated Care System-21 items score was  $22.0 \pm 3.0$ ; MMSE score was  $27.0 \pm 2.2$ ; and hippocampal volume estimated with the FreeSurfer Software was  $6,056.1 \pm 691.4$  mm<sup>3</sup>. A total of 22 patients (33%) had a history of CAD. No segmentation errors were identified in VSRAD analysis. During the first year after the brain MRI scans, five (7%) patients were diagnosed with clinical cognitive dysfunction.

### Profile of patients diagnosed with clinical cognitive dysfunction

The characteristics of the patients diagnosed with clinical cognitive dysfunction in this study are shown in Table 2. The patients diagnosed with clinical cognitive dysfunction during

**Table 1** | Profile of all the enrolled patients

	All patients ( <i>n</i> = 67)
Age (years)	73.0 $\pm$ 5.7
Male (%)	64.2
Body mass index (kg/m <sup>2</sup> )	24.3 $\pm$ 3.6
Waist circumferences (cm)	90.0 $\pm$ 9.2
Type of diabetes (type 2/type 1/pancreatic) (%)	94.0/4.5/1.5
Duration of diabetes (years)	13.0 $\pm$ 10.9
Medication	
Insulin (%)	34.3
Sulfonylurea (%)	43.3
Metformin (%)	52.2
Complications	
Nephropathy (stage 1/2/3/4/5) (%)	59.1/28.4/9.1/3.0/0.0
Retinopathy (NDR/SDR/PPDR/PDR) (%)	69.2/13.8/3.1/13.8
Coronary artery disease (%)	32.8
Severe hypoglycemia (%)	6.0
Systolic blood pressure (mmHg)	130.0 $\pm$ 13.0
Diastolic blood pressure (mmHg)	70.0 $\pm$ 10.4
HbA1c (%)	7.1 $\pm$ 1.0
Plasma glucose (mg/dL)	150.0 $\pm$ 83.9
C-peptide index	1.43 $\pm$ 1.15
Hemoglobin (g/dL)	13.8 $\pm$ 1.4
Serum creatinine (mg/dL)	0.87 $\pm$ 0.27
Estimated glomerular filtration rate (mL/min/1.73 m <sup>2</sup> )	58.0 $\pm$ 16.1
Low-density lipoprotein cholesterol (mg/dL)	104.0 $\pm$ 27.1
High-density lipoprotein cholesterol (mg/dL)	54.0 $\pm$ 15.9
Triglyceride (mg/dL)	112.0 $\pm$ 44.9
MMSE (total score)	27.0 $\pm$ 2.2
DASC21	22.0 $\pm$ 3.0
DASC8	9.0 $\pm$ 1.4
<i>z</i> -score in VSRAD	1.16 $\pm$ 0.65

DASC-8, Dementia Assessment Sheet for Community-based Integrated Care System 8-items; DASC-21, Dementia Assessment Sheet for Community-based Integrated Care System 21-items; HbA1c, glycated hemoglobin; MMSE, Mini-Mental State Examination; NDR, no diabetic retinopathy; PDR, proliferative diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; SDR, simple diabetic retinopathy; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease.

1-year follow up showed significantly higher *z*-scores on VSRAD analysis (clinical cognitive dysfunction group vs non clinical cognitive dysfunction group;  $2.52 \pm 0.47$  vs  $1.15 \pm 0.55$ ,  $P < 0.01$ ) in accordance with significantly smaller hippocampal volumes calculated by the FreeSurfer Software ( $5704.0 \pm 264.2$  mm<sup>3</sup> vs  $6137.0 \pm 697.8$  mm<sup>3</sup>,  $P = 0.03$ ). In addition, patients diagnosed with clinical cognitive dysfunction showed a significantly higher age (clinical cognitive dysfunction group vs non-clinical cognitive dysfunction group;  $79.0 \pm 4.7$  years vs  $72.5 \pm 5.7$  years,  $P = 0.04$ ), significantly lower MMSE scores ( $25.0 \pm 2.7$  vs  $27.0 \pm 2.0$ ,  $P = 0.01$ ) and significantly higher frequencies of CAD (80 vs 29%,  $P = 0.04$ ; Table 2). The youngest

**Table 2** | Profile of patients categorized by cognitive function

	Clinical cognitive dysfunction (n = 5)	Non-clinical cognitive dysfunction (n = 62)	P-value
Age (years)	79.0 ± 4.7	72.5 ± 5.7	0.04
Male (%)	60.0	66.1	0.34
Body mass index (kg/m <sup>2</sup> )	26.8 ± 3.3	24.2 ± 3.6	0.18
Waist circumferences (cm)	96.0 ± 9.2	89.0 ± 9.2	0.43
Duration of diabetes (years)	8.0 ± 12.4	14.0 ± 10.8	0.52
Medication			
Insulin (%)	20.0	35.5	0.65
Sulfonylurea (%)	40.0	44.5	1.00
Metformin (%)	60.0	51.6	1.00
Complications			
Nephropathy (stage 1/2/3/4/5) (%)	80.0/20.0/0.0/0.0/0.0	57.4/29.5/19.8/3.3/0.0	1.00
Retinopathy (NDR/SDR/PPDR/PDR) (%)	40.0/20.0/0.0/40.0	71.7/13.3/3.3/11.7	0.37
Coronary artery disease (%)	80.0	29.0	0.04
Severe hypoglycemia (%)	0.0	8.1	1.00
Systolic blood pressure (mmHg)	126.0 ± 11.9	130.0 ± 13.2	0.95
Diastolic blood pressure (mmHg)	70.0 ± 5.6	69.5 ± 10.8	0.96
HbA1c (%)	6.6 ± 0.6	7.1 ± 1.0	0.16
Plasma glucose (mg/dL)	124.0 ± 23.0	157.0 ± 85.6	0.14
C-peptide index	2.10 ± 1.22	1.39 ± 1.16	0.18
HbA1c-AdjSD	0.35 ± 0.25	0.24 ± 0.29	0.43
HbA1c-CV	5.50 ± 3.08	3.39 ± 3.65	0.26
Achievement of HbA1c according to the recommended level (%)	40.0	32.3	1.00
Hemoglobin (g/dL)	13.3 ± 1.1	13.8 ± 1.4	0.45
Creatinine (mg/dL)	0.85 ± 0.20	0.88 ± 0.27	0.28
Estimated glomerular filtration rate (mL/min/1.73 m <sup>2</sup> )	60.0 ± 18.0	58.0 ± 16.1	0.52
Low-density lipoprotein cholesterol (mg/dL)	100.0 ± 16.4	105.0 ± 27.9	0.92
High-density lipoprotein cholesterol (mg/dL)	55.0 ± 6.8	53.0 ± 16.4	0.99
Triglyceride (mg/dL)	111.0 ± 18.2	113.0 ± 46.3	0.70
MMSE (total score)	25.0 ± 2.7	27.0 ± 2.0	0.01
Orientation for place (%)	40.0	12.9	0.16
Orientation for time (%)	60.0	19.4	0.07
Registration (%)	0.0	3.2	1.00
Attention and calculation (%)	80.0	48.3	0.36
Delayed recall (%)	40.0	46.8	1.00
Naming (%)	0.0	0.0	1.00
Repetition (%)	40.0	11.3	0.13
Following command (%)	0.0	3.2	1.00

**Table 2** (Continued)

	Clinical cognitive dysfunction (n = 5)	Non-clinical cognitive dysfunction (n = 62)	P-value
Reading (%)	0.0	0.0	1.00
Writing (%)	0.0	4.8	1.00
Visual construction (%)	20.0	3.2	0.21
DASC21	25.0 ± 3.8	22.0 ± 2.9	0.18
DASC8	9.0 ± 1.6	9.0 ± 1.4	0.22
z-score in VSRAD	2.52 ± 0.47	1.15 ± 0.55	<0.01
MoCA-J	23.0 ± 1.2	28.0 ± 1.8	<0.01
HDS-R	24.0 ± 1.6	27.0 ± 2.3	0.01
Hippocampal volume calculated in the FreeSurfer Software (mm <sup>3</sup> )	5704.0 ± 264.2	6137.0 ± 697.8	0.03

DASC-8, Dementia Assessment Sheet for Community-based Integrated Care System 8-items; DASC-21, Dementia Assessment Sheet for Community-based Integrated Care System 21-items; HbA1c, glycated hemoglobin; HbA1c-AdjSD, standard deviation adjusted for the number of HbA1c assessments; HbA1c-CV, coefficient of variation for the number of HbA1c assessments; HDS-R, Hasegawa dementia rating scale-revised; MMSE, Mini-Mental State Examination; MoCA-J, Japanese version of Montreal Cognitive Assessment; NDR, no diabetic retinopathy; PDR, proliferative diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; SDR, simple diabetic retinopathy; VSRAD, voxel-based specific regional analysis system for Alzheimer's disease.

patient diagnosed with clinical cognitive dysfunction was aged 73 years. In the logistic regression analysis adjusting for age, sex, history of CAD, z-score and MMSE score, the z-score was significantly associated with clinical cognitive dysfunction ( $P < 0.05$ ; Table 3). Consequently, we categorized the patients into two groups according to the z-score, and further investigated clinical factors that might be associated with the z-score.

#### Profile of patients categorized by z-score in VSRAD analysis

The clinical characteristics of patients whose z-scores in VSRAD analysis were  $>2$  and  $<2$  are shown in Table 4. A total of 12 patients (18%) were identified with a z-score  $>2$ . Patients with a z-score  $\geq 2$  showed significantly higher frequencies of clinical cognitive dysfunction (z-score  $\geq 2$  group vs z-score  $<2$  group; 42 vs 0%,  $P < 0.01$ ), significantly higher age (75.5 ± 5.9 years vs 72.0 ± 5.4 years,  $P = 0.02$ ), significantly lower MMSE scores (26.5 ± 2.3 vs 28.0 ± 2.0,  $P = 0.03$ ), significantly smaller hippocampal volumes calculated in the FreeSurfer Software (5611.1 ± 577.8 mm<sup>3</sup> vs 6151.6 ± 649.8 mm<sup>3</sup>,  $P < 0.01$ ) and significantly higher frequencies of CAD (58 vs 27%,  $P = 0.04$ ; Table 4). There were no significant differences between the two groups with respect to sex, body mass index, HbA1c or duration of diabetes. In logistic regression analysis adjusting for age, sex, history of CAD and MMSE score, the

**Table 3** | Outcomes of cognitive dysfunction with logistic regression analysis

Independent variable	Odds Ratio	95% Confidence intervals	P-value
Age	0.93	0.0001–130.51	0.57
Sex (male/female)	0.59	0.04–8.11	0.69
Mini-Mental State Examination	0.69	0.30–1.60	0.39
z-score in VSRAD	16.24	1.03–256.91	<0.05
Coronary artery disease	4.51	0.26–78.61	0.30

level of z-score was predicted by history of CAD ( $P = 0.04$ ); age, sex and MMSE score were not identified as statistically significant predictors of z-score ( $P = 0.06, 0.31, 0.81$ , respectively).

### Predictors of clinical cognitive dysfunction in elderly patients with diabetes mellitus

To evaluate the utility of VSRAD analysis for screening of cognitive dysfunction in elderly patients with diabetes, we evaluated the sensitivity and specificity of MMSE score, z-score, age, a history of CAD and combinations of them. The sensitivity and specificity for diagnosis of clinical cognitive dysfunction during 1-year follow up were 80 and 48% for MMSE (cut-off value, 27), 100 and 89% for z-score (cut-off value, 2.00; vs MMSE,  $P = 0.32, <0.01$ , respectively), 100 and 45% for age (cut-off value, 72 years), and 80 and 71% for a history of CAD. For the combination of MMSE score and z-score, the sensitivity and specificity were 100 and 90%. For the combination of MMSE score, z-score and age, the sensitivity and specificity were 100 and 92%. For the combination of MMSE score, z-score, age and a history of CAD, the sensitivity and specificity were 100 and 97%.

### DISCUSSION

In clinical management of elderly patients with diabetes, cognitive dysfunction has a pivotal role, as it can threaten patient self-management of glycemic control, which increases the frequency of hospital admissions, occurrence of cardiovascular events and death<sup>4,22</sup>. Although early vigilance for cognitive dysfunction in the elderly with diabetes is required, an efficient screening strategy for identification of patients with the potential for MCI and/or dementia remains an issue in diabetes clinics<sup>4,5</sup>. In the present study, we evaluated the utility of VSRAD, a structural MRI-based morphometry software, for screening unrecognized cognitive dysfunction in elderly patients with diabetes. Patients with clinical cognitive dysfunction showed significantly higher z-scores than those without cognitive dysfunction (Table 2); the z-score in VSRAD analysis was significantly associated with clinical cognitive dysfunction by logistic regression analysis (Table 3). In addition, VSRAD analysis was especially sensitive (100%) at the specificity level of 89%.

Hippocampal atrophy has a pathophysiological role as well as diagnostic value in clinical cognitive dysfunction, including MCI and dementia<sup>6</sup>. As it is known that hippocampal atrophy

might precede the development of declining cognitive dysfunction clinically<sup>7</sup>, hippocampal morphometry using MRI images is essential for early vigilance of clinical cognitive dysfunction<sup>9,10</sup>. Because conventional manual hippocampal segmentation has limited use due to test–retest reliability<sup>23</sup>, recent advances in image analysis algorithms, such as the VSRAD system, can be used to provide more definitive automated hippocampal morphometry using brain MRI images<sup>9,10</sup>. In the present study, the z-score in VSRAD analysis was shown to discriminate patients with clinical cognitive dysfunction from those without cognitive dysfunction (Table 2 and 4). Furthermore and surprisingly, a total of five patients were newly diagnosed for clinical cognitive dysfunction (Table 2), which shows the value of early detection of cognitive dysfunction in diabetes outpatient clinics; none of the enrolled patients in the present study had been suspected of cognitive dysfunction, and none had a history of cerebrovascular diseases. Although a previous study using the VSRAD system found potential hippocampal atrophy in type 2 diabetes mellitus patients compared with healthy individuals<sup>24</sup>, the clinical value of assessing the degree of hippocampal atrophy by VSRAD system in the elderly with diabetes remains to be discussed in real-world clinical practice. In particular, the applicability of the VSRAD system to clinical screening for cognitive dysfunction has not been investigated in diabetes care. This is the first report to evaluate the utility of the VSRAD system as a screening tool for clinical cognitive dysfunction in the elderly with diabetes.

Additionally, the sensitivity and specificity for the diagnosis of clinical cognitive dysfunction were high for the z-score in VSRAD analysis (sensitivity, 100%; specificity, 89%). The z-score in VSRAD analysis showed comparable sensitivity and higher specificity than the MMSE score alone, whereas the combination of z-score and MMSE score only slightly improved the specificity.

Finally, a history of CAD might be a major factor in screening for cognitive dysfunction in the elderly with diabetes. In the present study, the patients diagnosed with clinical cognitive dysfunction showed significantly higher frequencies of CAD (Table 2), although a history of CAD was not significantly associated with clinical cognitive dysfunction in the logistic regression analysis (Table 3). The z-score  $\geq 2$  group showed significantly higher frequencies of CAD (Table 4), and the level of z-score was significantly predicted by a history of CAD in logistic regression analysis. This might suggest an influence of diabetes-induced vascular damage and arteriosclerosis on hippocampal atrophy. Taken together with the influence of CAD on cognitive decline and the higher prevalence of CAD in patients with diabetes as previously reported<sup>25,26</sup>, a history of CAD can be especially informative for determining the necessity of cognitive function screening for the elderly with diabetes.

There were several limitations to the present study. First, this was a multicenter retrospective exploratory study. Further large-scale prospective investigation of the VSRAD utility for clinical screening of cognitive dysfunction in the elderly with

**Table 4** | Profile of patients categorized by z-score

	z-score $\geq 2$ (n = 12)	z-score $< 2$ (n = 55)	P-value
z-score in VSRAD	2.42 $\pm$ 0.40	1.07 $\pm$ 0.33	
Age (years)	75.5 $\pm$ 5.9	72.0 $\pm$ 5.4	0.02
Male (%)	50.0	67.2	0.32
Body mass index (kg/m <sup>2</sup> )	24.0 $\pm$ 3.3	24.5 $\pm$ 3.7	0.98
Waist circumferences (cm)	89.0 $\pm$ 7.6	90.0 $\pm$ 9.5	0.89
Duration of diabetes (years)	11.5 $\pm$ 12.0	14.0 $\pm$ 10.7	0.99
Medication			
Insulin (%)	33.3	34.5	1.00
Sulfonylurea (%)	41.7	43.6	1.00
Metformin (%)	50.0	52.7	1.00
Complications			
Nephropathy (stage 1/2/3/4/5) (%)	50.0/33.3/8.3/8.3/0.0	60.0/27.2/9.1/1.8/1.8	0.58
Retinopathy (NDR/SDR/PPDR/PDR) (%)	50.0/16.7/0.0/33.3	70.9/12.7/3.6/9.1	0.22
Coronary artery disease (%)	58.3	27.3	0.04
Systolic blood pressure (mmHg)	130.0 $\pm$ 9.2	130.0 $\pm$ 13.8	1.00
Diastolic blood pressure (mmHg)	70.5 $\pm$ 8.7	69.0 $\pm$ 10.8	0.28
HbA1c (%)	7.0 $\pm$ 0.6	7.1 $\pm$ 1.0	0.18
Plasma glucose (mg/dL)	153.0 $\pm$ 87.6	129.5 $\pm$ 58.0	0.17
C-peptide index	1.54 $\pm$ 1.13	1.40 $\pm$ 1.16	0.40
HbA1c-AdjSD	0.25 $\pm$ 0.19	0.24 $\pm$ 0.31	0.64
HbA1c-CV	3.93 $\pm$ 2.51	3.43 $\pm$ 3.83	0.45
Achievement of HbA1c according to the recommended level (%)	41.7	30.9	0.50
Hemoglobin (g/dL)	14.1 $\pm$ 1.4	13.7 $\pm$ 1.4	0.20
Creatinine (mg/dL)	0.77 $\pm$ 0.37	0.90 $\pm$ 0.24	0.16
Estimated glomerular filtration rate (mL/min/1.73 m <sup>2</sup> )	69.5 $\pm$ 19.0	57.0 $\pm$ 15.5	0.26
Low density lipoprotein cholesterol (mg/dL)	98.5 $\pm$ 27.9	106.0 $\pm$ 27.0	0.59
High density lipoprotein cholesterol (mg/dL)	54.5 $\pm$ 20.2	53.5 $\pm$ 14.9	0.80
Triglyceride (mg/dL)	110.5 $\pm$ 66.1	112.5 $\pm$ 39.5	0.46
MMSE (total score)	26.5 $\pm$ 2.3	28.0 $\pm$ 2.0	0.03
Orientation for place (%)	33.3	20.0	0.44
Orientation for time (%)	33.3	10.9	0.07
Registration (%)	0.0	3.6	1.00
Attention and calculation (%)	66.7	47.2	0.34
Delayed recall (%)	58.3	43.6	0.52
Naming (%)	0.0	0.0	1.00
Repetition (%)	25.0	10.9	0.35
Following command (%)	0.0	3.6	1.00
Reading (%)	0.0	0.0	1.00
Writing (%)	0.0	5.5	1.00

**Table 4** (Continued)

	z-score $\geq 2$ (n = 12)	z-score $< 2$ (n = 55)	P-value
Visual construction (%)	16.7	1.8	0.08
DASC21	23.0 $\pm$ 3.1	22.0 $\pm$ 3.0	0.73
DASC8	8.0 $\pm$ 0.9	9.0 $\pm$ 1.4	0.16
Hippocampal volume calculated in the FreeSurfer Software (mm <sup>3</sup> )	5611.1 $\pm$ 577.8	6151.6 $\pm$ 649.8	<0.01
Clinical cognitive dysfunction (%)	41.7	0.0	<0.01

DASC-8, Dementia Assessment Sheet for Community-based Integrated Care System 8-items; DASC-21, Dementia Assessment Sheet for Community-based Integrated Care System 21-items; HbA1c, glycated hemoglobin; HbA1c-AdjSD, standard deviation adjusted for the number of HbA1c assessments; HbA1c-CV, coefficient of variation for the number of HbA1c assessments; MMSE, Mini-Mental State Examination; NDR, no diabetic retinopathy; PDR, proliferative diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; SDR, simple diabetic retinopathy.

diabetes is warranted, including comparison between the conventional screening tests, such as MMSE, even though the sensitivity and specificity of MMSE in the present study were found to be comparable with previous reports<sup>27,28</sup>. Furthermore, in the context of screening for cognitive dysfunction by MCI in elderly patients with diabetes<sup>29</sup>, comparison with the Montreal Cognitive Assessment would be informative in future investigations. Second, although the z-score in VSRAD analysis showed reasonable sensitivity as a screening tool in the present study, some of the patients with the z-score  $\geq 2$  were not diagnosed with clinical cognitive dysfunction. In those patients, an additional follow-up study might show consequent development of cognitive dysfunction, as hippocampal atrophy can precede the development of cognitive dysfunction<sup>7</sup>. In addition, pathophysiological classification of cognitive dysfunction was not carried out in the present study; the purpose of this study was screening for cognitive dysfunction in the elderly with diabetes in real-world diabetes outpatient clinics. Additionally, as CAD can have an influence on cognitive decline, as previously reported<sup>25</sup>, the relatively high frequency of CAD history in our enrolled patients might affect the results, even though patients having a history of cerebrovascular diseases were excluded from the present study. Finally, due to a relatively small number of the patients clinically diagnosed with MCI/dementia in this study, over/underdiagnosis of one patient might affect the statistical calculations.

In conclusion, in the present multicenter retrospective study, VSRAD analysis in elderly patients with diabetes identified those with clinical cognitive dysfunction who had not been previously suspected of cognitive decline. VSRAD analysis also showed a superior predictive value for clinical cognitive dysfunction compared with that with MMSE alone. Thus, VSRAD

analysis can be useful for early identification of clinical cognitive dysfunction in the elderly with diabetes.

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## DISCLOSURE

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