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Efficacy of combined use of three non-invasive atherosclerosis tests to predict vascular events in the elderly; carotid intima-media thickness, flow-mediated dilation of brachial artery and pulse wave velocity

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ABSTRACT

Background: Intima-media thickness (IMT) of the carotid artery, flow-mediated dilation (FMD) of the brachial artery, and pulse wave velocity of the central artery (PWV) have been widely used to evaluate progression of atherosclerosis. Our previous work has revealed that IMT, FMD and PWV are related to each other, and the combination of these measurements was useful in identifying patients with atherosclerotic disease. The aim of the present study was to investigate whether combination of these measurements would predict future cardiovascular events better than each test alone.

Methods and results: From November 2000 to March 2008, 274 consecutive elderly subjects (men/women; 114/160, mean age; 71 ± 12 years) were enrolled in this study. We measured IMT, FMD, and PWV in all of these subjects and followed them for a mean of 41 ± 28 months. During the follow-up period, vascular events occurred in 42 patients (15.3%). IMT (hazard ratio = 1.28 [95%CI, 1.09–1.50], $p = 0.002$ per 0.1 mm increase in mean IMT) and brachial-ankle (ba) PWV (hazard ratio = 1.06 [95%CI, 1.01–1.10], $p = 0.015$ per 1 m/s increase in baPWV) were independent predictors of future vascular events by Cox proportional hazard analysis, although FMD did not reach statistical significance (hazard ratio = 0.85 [95%CI, 0.72–1.01], $p = 0.062$ per 1% increase in %FMD). Importantly, the number of tests showing results in the worst tertile was a more powerful predictor (hazard ratio = 2.21 [95%CI, 1.42–3.43], $p = 0.0004$ for number of tests showing worst tertile) of future vascular events than either IMT, baPWV, or FMD alone. When both IMT and baPWV (with respective cut-off values of 0.98 mm and 19.1 m/s) were taken into consideration, the efficacy increased as compared with each test alone (odds ratio 4.9).

Conclusion: These results indicate that IMT and baPWV, especially when combined, are useful in predicting future vascular events in elderly subjects.

1. Introduction

Recently, noninvasive tests of atherosclerosis have been clinically available, such as common carotid intima-media thickness (IMT), flow-mediated dilation (FMD) of the brachial artery, pulse wave velocity (PWV), beta stiffness index, and systemic arterial stiffness [1]. Several epidemiologic studies have shown that IMT, PWV, and FMD are important, independent determinants of cardiovascular risk in patients with cardiovascular disease [2–5], or diabetes mellitus [6,7] and healthy adults [1,8–12]. These three tests assess different aspects of atherosclerosis; carotid IMT reflects structural changes in the artery wall [13], PWV reflects central arterial stiffness, and FMD reflects endothelial function. While the majority of previous studies utilized a single method to evaluate atherosclerosis, several recent studies showed that combination of two measurements may strengthen the predictive power for future cardiovascular events [14,15].

Consistent with these studies, our previous article showed that a combination of IMT, FMD and PWV was able to predict more reliably the prevalence of atherosclerotic disease in an elderly population than did each test alone [16]. However, it is not clear whether the combination of these three tests is more reliable in predicting future vascular events than is each single test. Thus, the purpose of the present study was to prove the hypothesis that the combination

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of the three different methods to evaluate atherosclerosis would strengthen the predictive power over each test alone. For this purpose, we followed vascular events in patients in whom IMT, FMD and PWV were measured in advance.

2. Methods

2.1. Subject background

From November 2000 to March 2008, 274 consecutive subjects from outpatients of the Department of Geriatric Medicine, Kyorin University Hospital (Tokyo, Japan) were enrolled in this study (Table 1). Three non-invasive atherosclerosis tests (IMT, FMD and PWV) were performed in these subjects for the study purpose. All participants gave written informed consent to the study, which was approved by our institutional ethics committee. The study was performed in compliance with the Helsinki declaration. We included all subjects who agreed to participate in the study, and in whom IMT, FMD and PWV were available.

Diabetes mellitus was defined as fasting glucose of 126 mg/dL or higher, or the use of hypoglycemic medication. Resting blood pressure was measured three times in the seated position, and the average of the second and third readings was recorded. Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or use of medication prescribed for hypertension. Body mass index was calculated as weight (kg)/height^2 (m^2). Total and high-density lipoprotein (HDL) cholesterol were measured in blood samples obtained after a 12-h fast. Low-density lipoprotein (LDL) cholesterol was estimated by the Friedewald equation. Framingham risk score was determined from age, sex, smoking, blood pressures, diabetes, total cholesterol and HDL cholesterol based on the report by Wilson et al. [11].

Table 1
Clinical characteristics of study subjects.

	Vascular event		
	With (n = 42)	Without (n = 232)	p
Sex (male/female)	24/18	90/142	0.026
Age, y/o	74 ± 12	71 ± 12	0.087
Body mass index (kg/m^2)	23 ± 4	23 ± 3	0.208
Number of risk factors	1.8 ± 1.1	1.6 ± 1.0	0.281
Hypertension, n (%)	31 (74)	126 (54)	0.019
Hyperlipidemia, n (%)	14 (33)	115 (50)	0.052
Diabetes mellitus, n (%)	12 (29)	57 (25)	0.582
Chronic pulmonary disease, n (%)	0 (0)	2 (0.9)	0.546
Kidney disease, n (%)	1 (2.4)	8 (3.4)	0.721
Chronic systemic inflammatory disease, n (%)	0 (0)	2 (0.9)	0.546
Smokers, n (%)			
Never	22 (52)	139 (60)	0.364
Past	17 (41)	69 (30)	–
Current	3 (7)	24 (10)	–
History of stroke, n (%)			
Cerebral infarction	7 (17)	14 (6)	0.295
Brain hemorrhage	0 (0)	3 (1)	–
Cerebral thrombosis	1 (2)	1 (0)	–
Cerebral infarction & hemorrhage	0 (0)	2 (9)	–
Multiple cerebral infarction	0 (0)	7 (3)	–
Transient ischemic attack	1 (2)	0 (0)	–
Unknown	2 (5)	6 (3)	–
History of IHD, n (%)			
Angina pectoris	3 (7)	7 (3)	0.560
Myocardial infarction	0 (0)	4 (2)	–
Unknown	0 (0)	3 (1)	–
Atherosclerosis measurements			
Mean IMT, mm	1.06 ± 0.21	0.94 ± 0.19	0.000
FMD, %	2.01 ± 1.71	2.83 ± 2.42	0.045
baPWV, m/s	22.5 ± 6.6	19.7 ± 6.5	0.018
Medication			
ACEI/ARB, n (%)	13 (33)	54 (24)	0.210
Ca blocker, n (%)	14 (35)	58 (16)	0.185
β-Blocker, n (%)	3 (8)	10 (4)	0.383
Statin, n (%)	5 (12)	38 (17)	0.426
Anti-platelet agent, n (%)	15 (38)	42 (19)	0.009

Data are expressed as mean ± SD. FMD, flow-mediated dilation of right brachial artery; IMT, intima-media thickness of common carotid artery; baPWV, brachial-ankle pulse wave velocity, IHD, ischemic heart disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; Smoker Never, no smoking history; Smoker Past, previously smoked and quit; Smoker Current, currently regularly smoking.
Student's t test for continuous variables and χ^2 test for categorical variables.

2.2. Participant follow-up and CV events

The occurrence of vascular events was investigated by inquiry to the attending doctor (n = 234), examining the patient's clinical record (n = 9), or inquiry to the patient and/or the family by either telephone (n = 13) or mail (n = 18). The majority of cardiovascular events (n = 243/274) was confirmed as follows: angina and myocardial infarction were confirmed by clinical symptoms and/or coronary arteriography; cerebral hemorrhage, subarachnoid hemorrhage, cerebral infarction and transient ischemic attack were confirmed by clinical symptoms followed by computed tomography, MRI and/or angiography; heart failure, renal failure and arteriosclerosis obliterans were diagnosed according to the clinical guidelines; and aortic dissection was confirmed by contrast computed tomography.

2.3. Measurements of atherosclerosis

Measurements of atherosclerosis were performed as previously described [16]. All examinations were performed by the same skilled technician throughout the study. The subject reclined on the examination table for at least 15 min before the examination to obtain hemodynamic stability.

2.3.1. Measurement of carotid IMT

Common carotid IMT was measured by ultrasound (PowerVision6000, Toshiba) with a 7.5 MHz linear-array transducer. The images were recorded on S-VHS videotape. IMT at the far wall of the common carotid artery was measured by B-mode scan within 10 mm proximal to the bifurcation. Four points were measured in one scan, and mean IMT was calculated [2,16]. The typical error as a coefficient of intra-observer variation in the measurement of IMT was 3.7%, and changes in mean were 2.0%.

2.3.2. Measurement of FMD of brachial artery

The diameter of the artery was measured by ultrasound (PowerVision6000, Toshiba) with a 7.5 MHz linear-array transducer. The images were recorded on S-VHS videotape. The mean diameter of the brachial artery was calculated from four cardiac cycles synchronized with the R-wave peaks on ECG. After a 10 min rest in the supine position, the right brachial artery was scanned. After recording the resting diameter, a cuff was placed around the forearm distal to the target artery and inflated to a pressure of 250 mmHg. Inflation was maintained for 5 min. Maximal vasodilation was observed 45–60 s after cuff release. The change in diameter caused by the restoration of blood flow was expressed as the percent change relative to the initial diameter [16–18]. The typical error as a coefficient of intra-observer variation in the measurement of FMD was 7.4%, and changes in mean were 0.1%.

2.3.3. Measurement of PWV

Brachial-ankle (ba) PWV was measured using an automated device (Form PWV/ABI, OMRON-COLIN, Japan). The average measurement of left and right baPWV was used for analysis. The typical error as a coefficient of intra-observer variation in the measurement of PWV was 2.0%, and changes in mean were 0.2%.

2.4. Statistical analysis

All data are expressed as mean ± SD. Patients were classified according to the tertiles of IMT, %FMD and baPWV. Event rate was calculated using the Kaplan–Meier method, and the statistical significance of differences was investigated by log-rank test. A Cox proportional hazard model was used to determine the variables independently associated with vascular events. Odds ratio was calculated by logistic regression analysis to evaluate the association of event occurrence and each atherosclerosis measurement, with adjusted for age and sex as well as FRS. Receiver operating characteristic curve analysis was performed to estimate the best cut-off point in each test for predicting future vascular events. A p value <0.05 was considered statistically significant.

3. Results

3.1. Subjects

In the 274 patients, the mean duration of follow-up was 41 ± 28 months. During this time, 42 (15.3%) patients experienced vascular events: 14 (33.3%) had angina, 13 (31.0%) stroke, 10 (23.8%) heart failure, 6 (14.3%) renal failure, 3 (7.1%) myocardial infarction, 3 (7.1%) transient ischemic attack, 2 (4.8%) arteriosclerosis obliterans, 2 (4.8%) cerebral hemorrhage, 1 (2.4%) aortic dissection, and 1 (2.4%) subarachnoid hemorrhage.

As shown in Table 1, male sex and hypertension were more frequent in patients with vascular events than in those without events. In addition, patients with vascular events showed thicker mean IMT, smaller %FMD, and greater baPWV than those without events.

3.2. Tertiles and prognostic value of each test

With regard to IMT and baPWV, Kaplan–Meier analysis showed that patients in the worst tertile experienced a higher rate of vascular events than those in the other two tertiles (Fig. 1a, b). A similar trend was also found for %FMD, although not reaching statistical significance ($p = 0.052$ by log-rank test, Fig. 1c). Of note, patients in the three worst tertiles had a markedly higher rate of vascular events than those in the other groups (0, 1, and 2 in Fig. 1d).

In the Cox proportional hazard model, IMT, baPWV, and the number of results in the worst tertiles were significantly associated with vascular events. They remained significant after adjusting for age and sex (Table 2), and FRS (Table 3). FRS alone was not a significant predictive factor ($p = 0.203$, RR 0.987, 95%CI 0.966–1.007).

3.3. Test combination model and vascular events

Receiver operating characteristic curve analysis demonstrated that IMT of 0.98 mm (area under curve = 0.72, sensitivity = 83%, specificity = 57%) and baPWV of 19.1 m/s (area under curve = 0.67, sensitivity = 61%, specificity = 63%) were the best cut-off points for predicting future vascular events.

When the subjects were subdivided into four groups according to the cut-off values of IMT and baPWV, Kaplan–Meier curves showed a stepwise increase in the risk of vascular events (Fig. 2a). Patients with both IMT and baPWV above the cut-off values (group IV) showed the highest rate of vascular events. In addition, the odds ratio of vascular events in group IV was significantly higher than that in group I (Fig. 2b).

4. Discussion

Consistent with the hypothesis, the combination of the three atherosclerosis measurements (IMT, %FMD, and baPWV) was

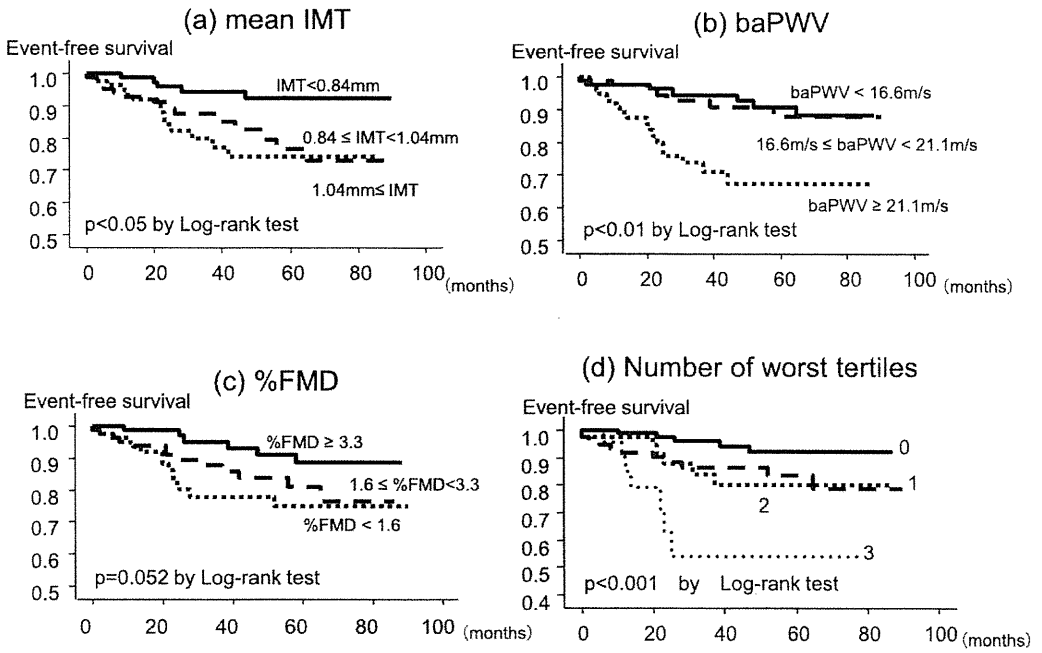

Fig. 1. Kaplan–Meier curves according to tertiles of (a) IMT, (b) baPWV, (c) %FMD, and (d) number of worst tertiles in atherosclerosis tests.

Table 2
Predictive value for future vascular events by Cox proportional hazard analysis adjusted by age and sex.

Variable	Unadjusted ($n = 274$)		Adjusted for age and sex ($n = 274$)	
	HR (95%CI)	p	HR (95%CI)	p
IMT, tertile (increase of 1)	1.836 (1.187–2.840)	0.0064	1.606 (1.002–2.753)	0.0489
IMT, 0.1 mm	1.279 (1.093–1.497)	0.0022	1.226 (1.034–1.454)	0.0191
baPWV, tertile (increase of 1)	2.191 (1.365–3.516)	0.0012	1.969 (1.115–3.476)	0.0195
baPWV, 1.0 m/s	1.055 (1.010–1.101)	0.0152	1.027 (0.970–1.088)	0.3552
FMD, tertile (increase of 1)	1.691 (1.090–2.624)	0.0190	1.631 (0.925–2.342)	0.1029
FMD, 1%	0.849 (0.716–1.008)	0.0615	0.903 (0.756–1.079)	0.2608
Number of worst tertiles	1.930 (1.353–2.754)	0.0003	1.891 (1.229–2.912)	0.0038

HR, hazard ratio; CI, confidence interval; other abbreviations are as in Table 1.

shown to be more powerful in predicting future vascular events as compared with each single test. This finding is consistent with our previous study showing that the combination of these three tests more reliably reflected the prevalence of atherosclerotic disease in the elderly population than did each test alone [16]. Here, IMT, baPWV, and %FMD (although less sensitively) were shown to predict future vascular events in the elderly population. This is in agreement with previous longitudinal studies showing that IMT was a predictor of future vascular disease [2,19], including a study of an elderly population [8], as well as central PWV in a study of subjects over 70 years old [4,11].

With regard to FMD, the present study did not show a significant association with the occurrence of vascular events. Considering the low value and small difference in FMD in the two groups with and without vascular events, one possible explanation for the non-significance is the floor effect. In support of this result, a significant relationship was found between baseline FMD and future cardiovascular events in middle-aged adults [9,10], whereas the prognostic power declined linearly with advancing age from the mid-40s, reaching nearly zero around 70 years of age [20]. Considering the subjects' age in the present study, the non-significance of FMD could be attributable to the advanced age of the patients.

An important point of the present study is that while IMT, baPWV, and %FMD were useful to predict future vascular events, combination of these tests increased the predictive power (Fig. 1d). This finding was consistent with those of our previous cross-sectional study showing that the result of a combination of the three tests was more strongly related to the prevalence of vascular disease in the elderly population than was that of each single test [16]. Several longitudinal studies have shown efficacy of the combination of two different atherosclerosis tests, such as FMD and ankle-brachial pressure index [14], plaque score of the common carotid artery and FMD [15], or carotid IMT and FMD [21], in predicting vascular events. The present study showed strong predictive power of combining three atherosclerosis tests for future vascular events. From our results, it is recommended that three tests should be combined in clinical work to evaluate vascular risk. However, when cost-effectiveness is taken into account, the combination of two tests (IMT and baPWV) would be sufficiently practical for event prediction in the elderly population because FMD requires much more skill and time than does IMT or baPWV. The same idea has been introduced in the recent guidelines from the ACCF/AHA for the assessment of cardiovascular risk in asymptomatic adults [22].

Table 3
Predictive value for future vascular events by Cox proportional hazard analysis adjusted by Framingham Risk Score (FRS).

Variable	Unadjusted ($n = 215$)		Adjusted for FRS ($n = 215$)	
	HR (95%CI)	p	HR (95%CI)	p
IMT, tertile (increase of 1)	1.704 (1.044–2.782)	0.0329	1.669 (1.018–2.735)	0.0422
IMT, 0.1 mm	1.277 (1.069–1.526)	0.0071	1.281 (1.064–1.544)	0.0090
baPWV, tertile (increase of 1)	2.675 (1.522–4.700)	0.0006	2.582 (1.445–4.614)	0.0014
baPWV, 1.0 m/s	1.065 (1.018–1.115)	0.0060	1.060 (1.011–1.111)	0.0166
FMD, tertile (increase of 1)	1.785 (1.072–2.973)	0.0260	1.669 (0.989–2.815)	0.0548
FMD, 1%	0.864 (0.716–1.043)	0.1281	0.888 (0.730–1.080)	0.2339
Number of worst tertiles	2.031 (1.350–3.055)	0.0007	1.991 (1.309–3.027)	0.0013

HR, hazard ratio; CI, confidence interval; other abbreviations are as in Table 1.

Increased carotid IMT has been considered as a marker of subclinical atherosclerosis. Although the biological meaning of IMT remains to be debated, it seems more likely to represent target organ damage related to cardiovascular risk [13]. PWV is the mostly widely used index for evaluating central arterial stiffness. FMD is a tool that is proposed for the assessment of endothelial function and is related to cardiovascular risk, but is not yet a commonly applied method to assess CV risk. Our major finding that the combination of three tests was more predictive than each test alone may be attributable to the fact that each test reflects a different aspect of the progression of atherosclerosis.

The best cutoff value of IMT calculated from event prediction was 0.98 mm in the present study. This value was comparable to previously reported values; approximately ~1.00 mm in healthy adults in spite of populations of different ages; middle age [23–25], over 55 yearsold [26], and 60–74 years old [27]. Although the detailed methodologies were slightly different between studies, ~1.00 mm appears to be relevant to the occurrence of vascular events.

The cutoff value of baPWV calculated from the receiver operating characteristic curve was 19.1 m/s in the present study. This value is slightly higher as compared with values reported previously; that for major cardiovascular events in patients with acute coronary syndrome was 18.0 m/s [28], and that for re-hospitalization and cardiac death in patients with heart failure was 17.5 m/s [29]. On the other hand, the cut-off value for cardiovascular death in community-dwelling elderly people (LILAC study [30]) was higher (25 m/s) than that in the present study. This difference could be explained by the susceptibility to arteriosclerosis in different subjects depending on whether they have preexisting cardiovascular disease and how old they are.

Because of the efficacy of the cut-off values of baPWV and IMT, we investigated the significance of the combination of these two measurements. A stepwise increase in the risk of vascular events was evident by Kaplan–Meier analysis and calculated odds ratio. This is important because much higher predictability can be obtained by simple non-invasive tests. Although FMD did not reach statistical significance, the combination of even three tests would strengthen the predictive power. Indeed, our previous results showed higher prevalence of atherosclerotic disease by combining three tests. Considering the efficacy and simplicity of performance of the three tests, combination of baPWV and IMT (with cut-off values of 19.1 m/s and 0.98 mm, respectively) should be of value for prediction of future occurrence of vascular events in elderly patients.

5. Limitations

One of the limitations of this study was that our approach of three tests for atherosclerosis did not follow the most updated

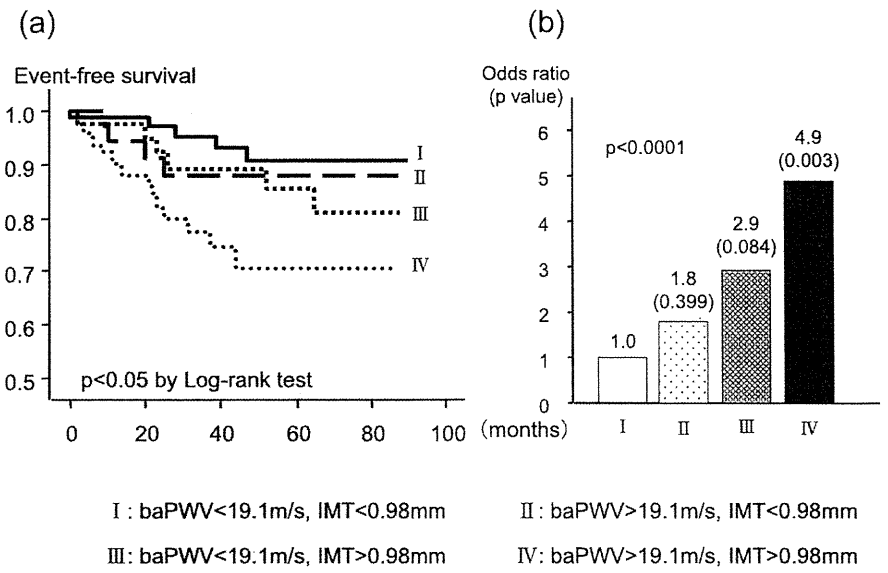

Fig. 2. (a) Kaplan–Meier curves and (b) adjusted relative risks of future vascular events according to cut-off values of baPWV and IMT. Odds ratio and *p* value, in parentheses, are indicated over the bar.

methodologies, because they were not fully established when we started this study. The most recent approaches may provide better predictive values for PWV and IMT, and statistical significance for FMD. Particularly, we manually held the echo probe for FMD measurement, which may have led to low intra-observer reproducibility and no statistical significance.

Second, despite the number of controls, the number of patients was very small.

Third, we included renal failure and heart failure as vascular events since these diseases are thought to be associated with progression of atherosclerosis in the elderly. However, it is possible that heart failure and renal failure may be caused by other etiologies such as collagen disease, infection, valvular disease, etc. Therefore, we also analyzed predictive values excluding heart failure and renal failure as vascular events, and obtained similar results. Thus, the effect of bias in selecting vascular events is considered to be small.

6. Conclusion

IMT, baPWV and, less significantly, FMD, especially when combined, are useful to predict future vascular events in elderly subjects. Because elderly people are at high risk for vascular disease, performing these simple and reliable non-invasive tests will add important clinical information.

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Respiratory dysrhythmia in dementia with Lewy bodies: a cross-sectional study

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ABSTRACT

Objectives: Dementia with Lewy bodies (DLB) is the second most common form of neurodegenerative dementia after Alzheimer's disease (AD). DLB is characterised by intracytoplasmic inclusions called Lewy bodies that are often seen in the brainstem. Because modulation of the respiratory rhythm is one of the most important functions of the brainstem, patients with DLB may exhibit dysrhythmic breathing. This hypothesis has not yet been systematically studied. Therefore, we evaluated the association between DLB and dysrhythmic breathing.

Design: In this cross-sectional study consecutive inpatients who were admitted for the evaluation of progressive cognitive impairment were enrolled. We assessed breathing irregularity using polysomnographic recordings on bed rest with closed eyes, without reference to the clinical differentiation among DLB, AD and having no dementia.

Setting: Single centre in Japan.

Participants: 14 patients with DLB , 21 with AD and 12 without dementia were enrolled in this study.

Primary outcome measures: The coefficient of variation (CV) of the breath-to-breath time was calculated. We also examined the amplitude spectrum A (f) obtained using the fast Fourier transform and Shannon entropy S of A(f) in patients with DLB compared with patients with AD and patients without dementia.

Results: The values of CV and entropy S were significantly higher in patients with DLB than in patients with AD and patients without dementia. No significant differences were observed between patients with AD and patients without dementia.

Conclusions: Patients with DLB exhibit dysrhythmic breathing compared with patients with AD and patients without dementia. Dysrhythmic breathing is a new clinical feature of DLB and the spectral analysis of breathing patterns can be clinically useful for the diagnostic differentiation of DLB from AD.

ARTICLE SUMMARY

Strengths and limitations of this study

- Dysrhythmic breathing is a completely novel topic in DLB.
- This study is a cross-sectional, small-sized pilot study.
- The patholocgical diagnosis of DLB could not be obtained.

INTRODUCTION

Dementia with Lewy bodies (DLB) is a neurodegenerative disease characterised by parkinsonism, visual hallucinations and cognitive fluctuations. DLB is now thought to be the second most common form of dementia after Alzheimer's disease (AD), affecting 15–25% of elderly demented patients.[1] The clinical diagnostic criteria for DLB were first published in 1996 and modified in 2005.[1 2] The central feature of DLB is progressive cognitive decline. The core features include recurrent visual hallucinations, spontaneous features of parkinsonism and fluctuating cognition with pronounced variations in attention and alertness. These diagnostic criteria require clinical evaluation by a trained neurologist and include few objective markers. Although Single Photon Emission CT (SPECT) and ^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy are useful for making the differential diagnosis of DLB,[3–5] these examinations are too expensive to be generally utilised. DLB is characterised by intracytoplasmic inclusions called Lewy bodies that consist of filamentous protein granules composed of α-synuclein and ubiquitin. Lewy bodies are often seen in the brainstem and in limbic and cortical neurons.[2] However, the brainstem serves as the connection among the cerebral hemispheres and the cerebellum, and is responsible for basic vital functions. Modulation of the respiratory rhythm is one of the most important functions of the brainstem. In cases of brain disorders, such as Wallenberg syndrome and brain tumours, it is known that respiratory patterns sometimes become ataxic. Because brainstem neurodegeneration is often

seen in patients with DLB, the respiratory patterns of patients with DLB might be dysrhythmic. However, this hypothesis has not yet been systematically studied and no controlled data have been published to date. The current investigation was performed in patients with DLB, AD and patients without dementia to assess and compare breathing patterns. In addition, we evaluated the usefulness of the measurement of breathing patterns as a novel tool to aid the differential diagnosis of dementia.

METHODS

Subjects

The study population comprised consecutive inpatients of the Department of Geriatric Medicine at the University of Tokyo Hospital, who were admitted for evaluation of progressive cognitive impairment. The patients underwent neuropsychological assessments, including the Mini-Mental State Examination (MMSE), blood tests and neuroimaging tests (MRI and SPECT). The diagnosis was performed at a consensus conference of physicians and neurologists. The diagnosis of DLB was based on the clinical diagnostic criteria proposed by McKeith *et al*.[2] And AD was diagnosed in accordance with the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association.[6] The group without dementia comprised patients who did not fit the criteria for dementia in the medical and neurological examinations. Between November 2010 and June 2012, 70 patients were enrolled in this study.

Exclusion criteria

We evaluated the breathing patterns of patients with DLB, with AD and patients without dementia. Patients with cognitive impairments other than AD or DLB (eg, normal pressure hydrocephalus and vascular dementia) were excluded.

Breathing irregularities are associated with certain environments such as high altitudes, medical conditions, such as heart failure and chronic obstructive pulmonary disease, and the usage of opioids or levodopa.[7 8] We excluded one patient who reported breathing problems, including dyspnoea. We also excluded four patients who were taking levodopa and dopamine agonists. No patients were using opioids. We excluded three patients whose recorded respiratory signal data were insufficient due to noise.

Recordings of respiration

The patients underwent 30 min or more of recordings of respiration on bed rest with closed eyes in the inpatient ward by using the device for polysomnography (Somnotrac Pro, CareFusion, San Diego, California, USA). The recordings included two EEG leads (C3-A2 and O2-A1), electro-oculogram and submental electromyogram (EMG). Oronasal thermistor channel and arterial oxygen saturation (finger oximetry) were also monitored. All recordings were scored visually by an experienced rater according to the standard criteria.[9]

Five consecutive minutes of stable respiratory signals measured while the patients were awake were extracted from the recordings. Stable respiratory signals during wakefulness were identified using the respiratory signals themselves, arterial oxygen saturation, EMG and EEG. Wakefulness was confirmed using EEG. When the amplitude of the EMG signal that detected any body movements was high, that part of the signal was considered to have occurred during movement and was determined to be inappropriate for analysis. Epochs including apnoeas and hypopneas were also excluded.

Analysis of respiratory signals

Five minutes of stable respiratory signals were analysed. The breath-to-breath time was calculated for each respiration. To assess breathing irregularities, the coefficient of variation, CV ((SD/mean)×100) for the breath-to-breath time was calculated. The respiratory rate was also calculated.

In addition, we examined the amplitude spectrum A(f) obtained using fast Fourier transform (FFT) for analysing oscillation patterns in the respiratory signals. A(f) represents the amplitude distribution as a function of frequency. To avoid the possibility of spectral leakage, the signals were windowed by multiplying them by a Hamming window (w(n)):

$$w[n] = 0.54 - 0.46\cos(2\pi n/N) \text{ for } n = 0, 1, 2, \ldots, (N-1)$$

Then, the amplitude spectrum of the respiratory signals was analysed using the FFT of the Hamming-windowed signal.[10] Furthermore, according to Shannon entropy, we determined the spectral entropy S based on normalised A (f) to assess breathing irregularities:

$$\text{Entropy } S = -\sum A(f) \times \log_2(A(f))$$

To reduce the influence of artifact in the respiratory signals and FFT, we restricted the frequency of analysing Shannon entropy. Based on the results of the breath-to-breath time analysis (1.7–7.6 s, namely 0.13–0.59 Hz), we determined the validated frequency of 0.1–0.6 Hz.

Statistical analysis

The distribution of data was examined using the Shapiro-Wilk test. If data were normally distributed, one-way analysis of variance with Games-Howell post hoc tests was applied for group comparisons. If the data deviated significantly from normality, the Kruskal-Wallis test was used, followed by evaluation with the Mann-Whitney U test for multiple comparisons, with the p values being corrected according to the Bonferroni method. In correlation analysis, the Spearman rank

correlation coefficient was used. The χ^2 test was used to compare categorical variables, such as gender.

The diagnostic cut-off points for the CV value and Shannon entropy S to discriminate between DLB and AD were estimated for each outcome by maximising the Youden index. The discrimination ability was assessed by the area under the curve (AUC). Using this threshold, the sensitivity and specificity were calculated.

All of the statistical analyses were performed using the SPSS software program (V.19.0, SPSS inc, Chicago, Illinois, USA). Statistical significance was defined as p values <0.05.

RESULTS

Patient characteristics

Fourteen patients with DLB, 21 with AD and 12 without dementia were enrolled in this study. Among the 14 patients in the DLB group, 9 patients had probable DLB and 5 patients had possible DLB. The diagnoses in the five possible DLB patients were all supported by the typical findings in SPECT: generalised low uptake, reduced occipital activity and relatively preserved hippocampal blood flow. Table 1 shows the characteristics of the patients. The age and sex distributions were not significantly different among the three groups. No significant difference was found between the DLB group and the AD group in the MMSE. The use of medications for hypertension, hyperlipidaemia and diabetes mellitus were similar between the groups. Four patients in the DLB group, five patients in the AD group and no patients in the group without dementia had taken donepezil.

Breathing patterns

Figure 1 shows examples of flow signals during wakefulness for a patient with DLB, with AD and without dementia. Figure 2 shows examples of the characteristic patterns of the amplitude spectrum A(f). The patient with AD and without dementia exhibited a sharp peak in the spectrum. However, the amplitude spectrum of the patient with DLB was distributed over the whole displayed frequency area. These tracings indicate the occurrence of more irregular breathing patterns in the patient with DLB compared with that observed in the patient with AD and the patient without dementia.

The respiratory rates calculated from the average breath-to-breath time in patients with DLB, with AD and patients without dementia were 16.2 (3.2), 17.7 (2.7) and 18 (2.3)/min, respectively (mean (SD)). These differences were not statistically significant. However, the CV value for the breath-to-breath time in patients with DLB was significantly higher than in either the patients with AD or the patients without dementia (13.5 (2.6), 10 (3) and 9.9 (2.8), respectively; figure 3A). To discriminate the patients with DLB from those with AD using the CV value, the most favourable diagnostic threshold was found to be 10.2 (AUC=0.79). This threshold had a sensitivity of 92.9% and a specificity of 61.9%.

The results of the comparison of Shannon entropy S are summarised in figure 3B. The values of Shannon entropy S were significantly higher in patients with DLB than in patients with AD and patients without dementia (6.35 (0.11), 6.11 (0.29) and 6.16 (0.19), respectively). To discriminate patients with DLB from those with AD using the Shannon entropy S value, the most favourable diagnostic threshold was found to be 6.18 (AUC=0.77). This threshold had a sensitivity of 100% and a specificity of 57.1%.

These findings indicate the diversity of breathing frequencies, that is, respiratory dysrhythmia, in patients with DLB.

Comparison of CV and Shannon entropy S

To assess breathing irregularities, we used two different methods, namely, we compare CV and Shannon entropy S. These two methods are independent approaches to the assessment of breathing patterns; however, a significant correlation (Spearman r=0.78, p<0.001) was observed between these two values (figure 4).

DISCUSSION

In this study, we observed that patients with DLB exhibit dysrhythmic breathing compared to patients with AD and patients without dementia.

Table 1 Characteristics of patients with DLB, with AD and without dementia

Characteristics Number of patients	Patients with DLB n=14	Patients with AD n=21	Patients without dementia n=12	p Value
Age (years)	81.5 (5.6)	79.6 (7.8)	78.5 (4.3)	n.s.
Sex (men/women)	6/8	7/14	4/8	n.s.
MMSE	21.0 (3.8)	21.2 (3.4)	27.8 (2.1)	<0.001*
Hypertension	4	9	3	n.s.
Hyperlipidaemia	2	1	0	n.s.
Diabetes mellitus	1	1	1	n.s.

Values expressed as mean (SD) or number.
*One-way analysis of variance with Games-Howell post hoc tests (DLB vs AD: n.s., DLB vs without dementia: p<0.001, AD vs without dementia: p<0.001)
AD, Alzheimer's disease; DLB, dementia with Lewy bodies; MMSE, Mini-Mental State Examination; n.s., not significant.

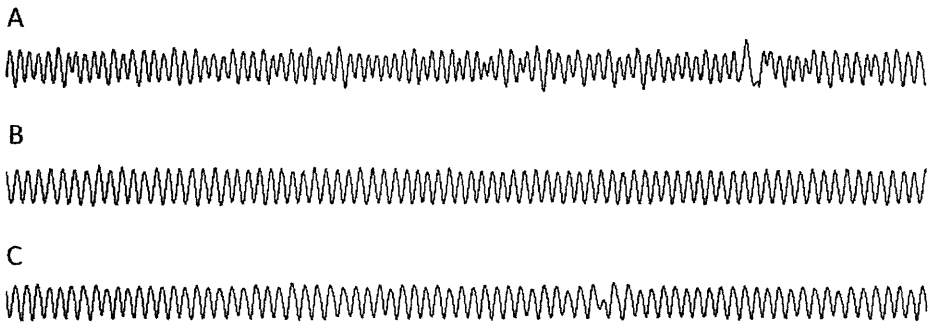

Figure 1 Typical flow patterns of a patient with DLB (A), a patient with AD (B) and a patient without dementia (C) observed in epochs of 5 min. Respiratory pattern is more irregular in the patient with DLB as compared with the patient with AD and the patient without dementia. AD, Alzheimer's disease; DLB, dementia with Lewy bodies.

The modulation of the respiratory rhythm is closely associated with the brainstem.[11] In particular, the pre-Bötzinger complex (pre-BötC) and the retrotrapezoid nucleus/parafacial respiratory group (RTN/pFRG) are thought to be very important for respiratory rhythm regulation.[12–14] For this reason, respiratory dysrhythmia may occur in cases of brainstem disorders, such as Wallenberg syndrome and brain tumours. In patients with DLB, Lewy bodies are often seen in the brainstem; however, it remains unknown whether the localisation and density of Lewy bodies are strongly associated with the symptoms of DLB. It is possible, considering the neurodegenerative aspects of DLB, that localisation of Lewy bodies in the brainstem causes respiratory dysrhythmia. One report has indicated that visual hallucinations are associated with increased numbers of Lewy bodies in the temporal lobe and amygdala, each of these areas being implicated in the generation of complex visual images.[15] In addition, concerning the association between respiration and DLB, Mizukami *et al*[16] reported the occurrence of decreased ventilatory responses to hypercapnia in patients with DLB. Furthermore, respiratory insufficiency, sleep-disordered breathing and central respiratory failure are known to occur in patients with multiple system atrophy,[17 18] which is an α-synucleinopathies, similar to DLB.

In this study, we also analysed the breathing patterns of patients without dementia. The CV for

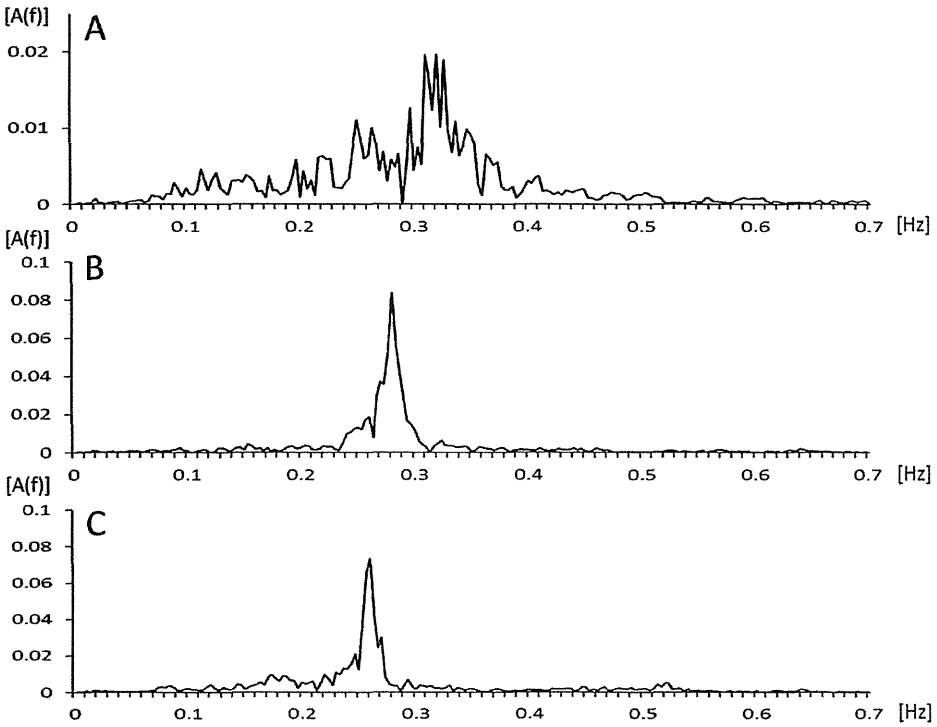

Figure 2 The typical power spectrum of a patient with DLB (A), a patient with AD (B) and a patient without dementia (C) obtained by fast Fourier transform. The amplitude spectrum of the patient with DLB is distributed over the whole displayed frequency. AD, Alzheimer's disease; A(f), amplitude spectrum; DLB, dementia with Lewy bodies.

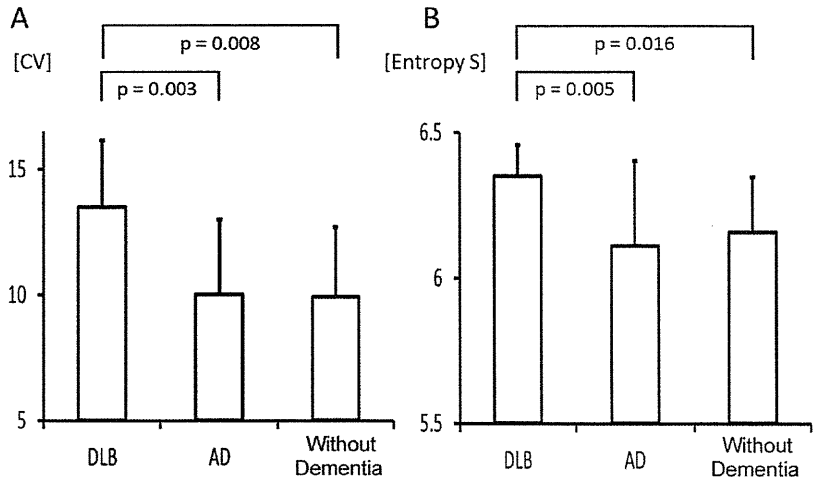

Figure 3 (A) Coefficient of variation for breath-to-breath respiratory time in patient with DLB, patient with AD and patients without dementia. One-way analysis of variance with Games-Howell post hoc tests; significant differences in DLB versus AD (p =0.003) and DLB versus without dementia (p=0.008). (B) The comparison of Shannon entropy S in DLB patients, AD patients and patients without dementia. One-way analysis of variance with Games-Howell post hoc tests; significant differences in DLB versus AD (p=0.005) and DLB versus without dementia (p=0.016). Values are mean±SD. AD, Alzheimer's disease; CV, coefficient of variation; DLB, dementia with Lewy bodies; n.s., not significant.

breath-to-breath time in patients without dementia was not significantly different from that reported in previous studies of control patients.[19 20] Although the complication with hypertension was greater in AD group than in DLB group, no significant differences were found in the measures of breathing patterns between patients with hypertension and the patients without hypertension (data not shown).

Patients with DLB exhibit many clinical features other than dementia, visual hallucinations and parkinsonism. For example, Rapid Eye Movement sleep behaviour disorder, severe autonomic dysfunctions, such as orthostatic hypotension, repeated syncope and systematised delusions, can be seen in patients with DLB.[21] Furthermore, in a previous study, we reported a high frequency of periodic limb movements in patients with DLB.[22] The results of the current study indicating that DLB patients exhibit dysrhythmic breathing compared with normal patients suggest that irregular breathing patterns may be a new clinical feature of DLB.

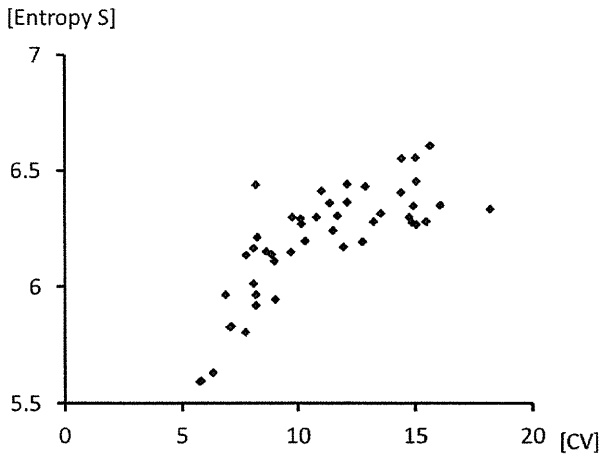

Figure 4 Scatter plot showing the relationship between the coefficient of variation for breath-to-breath respiratory time and the value of Shannon entropy S. A significant correlation (r=0.78, p<0.001) was found between the coefficient of variation (CV) and the Shannon entropy S.

Currently, DLB and AD are diagnosed according to their respective clinical diagnostic criteria,[2 6] and differentiation of these two diseases is frequently difficult. Our findings of different breathing patterns between patients with DLB and AD suggest the usefulness of the spectral analysis of breathing for discriminating patients with DLB from those with AD. Because the diagnostic threshold had a high sensitivity in our study, the spectral analysis of breathing may be useful for making an exclusive diagnosis. While the utilisation of SPECT and MIBG myocardial scintigraphy are limited to well-equipped hospitals, the spectral analysis of breathing can be performed more easily and with lower expenses. As a screening tool for the diagnosis of DLB, the spectral analysis of breathing patterns may be cost-effective and useful.

The FFT is an important tool for digital signal processing of the information commonly encoded in the sinusoids that form the signal. Additionally, the important information to be evaluated is the frequency and amplitude of the component sinusoids. To reduce spectral noise, a Hamming window is used that involves the multiplication of the signal by a smooth curve. The result is plotted graphically in terms of amplitude and frequency. In addition, we used Shannon entropy in this study to quantify the variability of the amplitude spectrum, namely breathing irregularities. This measure has been widely used in a range of biological applications in which quantitative descriptions of data regularity are

required.[23 24] The Shannon entropy indicates the degree of uncertainty and is higher when the variability of the parameter is greater.

There are several limitations to the current study. First, we included patients with possible DLB and probable DLB in the same DLB group. In addition, we did not make a pathological diagnosis of DLB or AD. A prospective investigation on the course of breathing patterns and cognitive impairment, including the eventual pathological diagnosis, should be examined in a future study. Second, no arterial blood gas analyses were performed. Therefore, a possible effect of hypercapnia or hypocapnia on breathing cannot be excluded. To evaluate more precisely, arterial blood gas analyses should be examined in a future study, as well. Third, we could not make the raters of respiratory measures completely blinded to the clinical symptoms of the patients, although the final diagnosis of dementia had been made independently, and the analysis of respiratory measures had been performed objectively according to the predetermined protocol. Finally, the number of patients in each group was relatively small. We could not rule out the contribution of other comorbid factors to irregular breathing. However, our data provide the first evidence of irregular breathing in DLB patients. In a future study, an additional investigation involving a larger number of patients should be performed.

In conclusion, we found that DLB patients exhibit dysrhythmic breathing compared with that observed in AD patients and patients without dementia. Ataxic breathing may be a new clinical feature of DLB, and the spectral analysis of breathing patterns may be clinically useful for the diagnostic differentiation of DLB from AD.

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Contributors SH was involved in design, analysis, interpretation and drafting of the article. YY was responsible for conception, design, analysis, interpretation and drafting of the article. YU-K and KI were involved in design. MT and TM were involved in analysis. MA and YO were involved in design and interpretation. All authors had full access to the data and take responsibility for its integrity and the accuracy of the analysis.

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Competing interests None.

Patient consent Obtained.

Ethics approval The study was approved by the Institutional Review Board of the Graduate School of Medicine, University of Tokyo, and written informed consent was obtained from all participants before the study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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Original Study

Priorities of Health Care Outcomes for the Elderly

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Keyword:
Geriatrics
quality of care
health care policy

A B S T R A C T

Objectives: Physicians are uncertain about what medical services should be provided to older and/or disabled patients. Better understanding of health outcome prioritization among health care providers and recipients may help the process of decision- and policy-making. For this purpose, surveys were conducted on priorities of health care outcomes for the elderly.
Design: Survey research.
Setting: Four groups of health care providers and four groups of health care recipients.
Participants: A total of 2512 health care providers and 4277 recipients.
Measurements: Questionnaires were sent to more than 8000 health care providers and more than 9000 health care recipients: geriatricians, physicians who commonly see older patients or work in long term care facilities, staff members and participants in adult day care, patients in outpatient geriatric clinics, family members of patients with dementia, and community-dwelling older adults. The questionnaire asked the subjects to rank 12 measures of health care outcomes.
Results: The mean response rate was 49%. All health care provider groups considered "improvement of quality of life" the most important. In contrast, in health care recipient groups, "effective treatment of illness," "improvement of physical function," and "reduction of carer burden" were given high priority, whereas "improvement of quality of life" was perceived as less important. All the groups, including health care providers and recipients, ranked "reduction of mortality" the least important, followed by "avoiding institutional care." Stratification analysis showed that the results did not differ by sex, nursing care level, or the existence of relatives who required nursing care, whereas age slightly influenced the order of high-ranked measures.

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Conclusion: Priorities of health care services and their differences between providers and recipients should be taken into account in the health care of older patients and the design of health care policies and research.

Japanese society has been rapidly aging owing to long life expectancy and a low birth rate.[1] People older than 65 comprised 23.8% of the population in 2012, which is expected to rise to 31.8% in 2030[2] and will be by far the highest in the world. Japanese physicians have been exposed to a high load of older patients, and management of older patients remains a major challenge. There are several reasons for this difficulty. Evidence is still largely lacking for older patients, especially for those older than 75 years, who account for 11.8% of the Japanese population.[2,3] Older patients are likely to have multimorbidities, or co-occurrence of two or more chronic conditions,[4] but application of disease-specific guidelines to older patients with multimorbidities may result in polypharmacy, an increased risk of adverse drug reactions, and poor outcomes.[5,6] At the same time, however, older patients are at increased risk of underuse of necessary medication, for fear of polypharmacy or complications.[7,8]

In an attempt to help optimize prescribing for older patients, investigators have devised numerous tools to guide clinicians, such as lists of indicated, beneficial medication or medication with high potential for harm.[9,10] Although these tools are helpful in reducing exposure of older patients to inappropriate medication and risk of adverse drug events,[11] they do not provide more general considerations, such as when or how to discontinue potentially inappropriate medications, how to balance risks and benefits of unlisted medication, or how to manage medication in special circumstances, such as palliative and hospice care where symptom control is of higher priority. Therefore, the process of determining the medication regimen is inevitably subjective and individualized, taking into account patients' cognitive, physical, and social function, remaining life expectancy, and the goals of care.

Unfortunately, few studies have examined the priorities of health care perceived by health care providers and recipients in geriatric medicine. One small study conducted in England more than 15 years ago showed that geriatricians and patients similarly gave high priority to reducing disability and improving quality of care, and low priority to reducing mortality.[12] However, the serious question of whether there may be a gap in priorities of health care between health care providers and recipients has been raised.[13,14]

Better understanding of health outcome prioritization among health care providers and recipients in geriatric medicine is necessary to help physicians, older patients, and their family members discuss the goals of care and to assist health policy makers in effectively using resources to address the needs of older patients. In this study, we aimed to obtain a comprehensive picture of the views of groups with an important stake in geriatric health care services (geriatricians, physicians who commonly see older patients or work in long term care facilities, staff members and participants in adult day care, patients in outpatient geriatric clinics, family members of patients with dementia, and community-dwelling older adults) on the relative priorities of different outcome measures that are relevant to geriatric clinical practice and health care policy.

Methods

Between September 2010 and October 2011, surveys were conducted in the following eight groups:

(1) All geriatricians (approximately 1500) board certified by the Japan Geriatrics Society
(2) A total of 5000 physicians randomly selected from the list of board-certified physicians in five subspecialties (two internal medicine subspecialties, two surgical subspecialties, and one other) with high exposure to older patients
(3) Physicians working in 800 long term care facilities that were randomly chosen from the nationwide list of long term care facilities
(4) Staff members working in adult day care at 400 randomly chosen long term care facilities as mentioned previously
(5) Participants in adult day care at the same 400 long term care facilities as mentioned previously
(6) Patients in geriatric outpatient clinics at five university teaching hospitals (the University of Tokyo, Kyorin University, Nagoya University, Kyoto University, and Tohoku University)
(7) Family members of patients with dementia who had been seen in geriatric outpatient clinics at four university teaching hospitals (Tohoku University was excluded because of the Tohoku Earthquake at the time of this survey)
(8) A total of 6000 community-dwelling, functionally independent (ie, not requiring nursing care provided by long term care

Table 1
Survey Methods and Number of Valid Answers in 8 Groups

Groups	Time of Survey	Survey Methods	No. of Questionnaires Sent	No. (%) of Valid Answers*
Health care providers				
Geriatricians	2010, Sep	By post	1500	619 (41)
Physicians in 5 subspecialties	2011, Oct	By post	5000	1305 (26)
Physicians in long term care facilities	2011, Oct	By post	800	384 (48)
Adult day care staff	2010, Sep	By post for each facility	400 facilities (2 per facility)	204†
Health care recipients				
Adult day care participants	2010, Sep	By post for each facility	400 facilities (5–10 per facility)	795†
Patients in geriatric outpatient clinics	2010, Sep	Distributed by physicians and returned by post	950	512 (55)
Family members of patients with dementia	2011, Oct	Distributed by physicians and returned by post	542	333 (61)
Community-dwelling older adults	2010, Sep	By post	6000	2637 (44)

*Responses with missing items or invalid answers were excluded.
†For adult day care staff members and participants, questionnaires were sent to each facility by post, where 2 staff members and 5 to 10 participants were offered the questionnaire; 123 facilities (31%) returned the completed questionnaires.

insurance) older adults randomly drawn from the community registers of two target areas (Kashiwa, Chiba Prefecture, a city close to Tokyo, and Sabae, Fukui Prefecture, a provincial city), from which men and women, 65 to 74 years and older than 75 years, were equally selected

Postal questionnaires were sent to all groups of physicians and community-dwelling old adults. For adult day care staff members and participants, questionnaires were sent to each facility, where two staff members and 5 to 10 participants were offered the questionnaire, to be completed on a voluntary basis. The completed questionnaires were gathered at each facility and then returned to us. Patients and family members of patients with dementia received the questionnaires from their physicians (Table 1).

The questionnaire asked about the relative priorities of 12 health care measures that were derived from a literature review and a previous Internet-based survey conducted by the National Center for Geriatrics and Gerontology in 2009 (in Japanese; http://www.ncgg.go.jp/pdf/itaku/21hokoku/20si-3.pdf). Each item was expressed as several words so as to help health care recipients understand the meaning. The respondents were asked to rank the measures in order of priority from 1 (most importance) to 12 (least important). To facilitate ranking the outcomes in order, they were prompted to choose and rank the three most important outcomes, then the three least important outcomes, and last, the six middle outcomes. Ties, or the same ranks, were not allowed.

To examine whether variation in the question wording could affect the results, we devised another version of the questionnaire with different wording for four items and sent that version to a randomly selected subset of participants; however, the results were almost identical (data not shown). We also tested whether the order of health care measures that appeared in the questionnaire would affect the results in a random subset of participants, but the responses to the reverse order questionnaire were similar to those of the original version (data not shown). Therefore, we analyzed the responses from different versions (wording and order) together.

The following information was also collected using the questionnaire: age and sex for all participants; specialty (internal medicine, surgery, psychiatry, or others) and years of experience for physicians; qualification and years of experience for adult day care staff; nursing care level (level of required nursing care: relatively independent, limited impairment, needing extensive help, or severely dependent) for adult day care participants; nursing care level and the existence of relatives who required nursing care for patients in geriatric outpatient clinics; nursing care level, morbid conditions, and the existence of relatives who required nursing care for community-dwelling older adults.

The study protocol was approved by the Ethics Committee of the Graduate School of Medicine, The University of Tokyo. Ethical approval for the surveys on patients in geriatric outpatient clinics and family members of patients with dementia was also obtained from the participating institutions.

Results

The mean response rate for the eight groups was 49%, which varied from 28% for board-certified physicians to 68% for family members of patients with dementia (Table 1). The analytic sample included a total of 2512 health care providers and 4277 recipients.

Tables 2 and 3 show the relative priorities of 12 measures of health care services from the highest importance to the lowest, with mean and 95% CI, perceived by health care providers and recipients, respectively.

All physician groups considered "improvement of quality of life" the most important, and the low mean value for this item across physician

Table 2
Health Care Providers' Priorities for Health Care Outcome

Rank Order	Geriatricians (n = 619) Outcome	Mean	95% CI	Physicians from 5 Relevant Subspecialties (n = 1305) Outcome	Mean	95% CI	Physicians in Long Term Care Facilities (n = 384) Outcome	Mean	95% CI	Adult Day Care Staff (n = 204) Outcome	Mean	95% CI
1	Improvement of quality of life	2.62	2.45–2.80	Improvement of quality of life	3.09	2.96–3.22	Improvement of quality of life	2.88	2.62–3.14	Improvement of quality of life	4.29	3.88–4.71
2	Patient satisfaction with care	4.37	4.15–4.58	Patient satisfaction with care	4.34	4.19–4.49	Patient satisfaction with care	4.60	4.32–4.88	Maintaining a high level of activity	4.35	3.96–4.73
3	Effective treatment of illness	4.80	4.53–5.07	Maintaining a high level of activity	4.64	4.48–4.80	Improvement of physical function	4.68	4.39–4.97	Reduction of carer burden	4.80	4.42–5.17
4	Maintaining a high level of activity	4.92	4.69–5.15	Improvement of physical function	5.25	5.08–5.42	Maintaining a high level of activity	4.73	4.43–5.03	Resolution of assessed problems	5.15	4.74–5.55
5	Improvement of physical function	4.94	4.71–5.18	Effective treatment of illness	5.32	5.13–5.52	Improvement of mental health	5.50	5.29–5.71	Improvement of mental health	5.26	4.86–5.65
6	Improvement of mental health	6.04	5.87–6.20	Reduction of carer burden	5.93	5.79–6.07	Resolution of assessed problems	5.77	5.51–6.04	Patient satisfaction with care	5.43	5.03–5.83
7	Resolution of assessed problems	6.39	6.17–6.61	Resolution of assessed problems	6.12	5.97–6.27	Reduction of carer burden	6.10	5.84–6.37	Improvement of physical function	5.83	5.42–6.25
8	Reduction of carer burden	6.45	6.27–6.64	Improvement of mental health	6.39	6.26–6.52	Effective treatment of illness	6.22	5.87–6.57	Improvement of social functioning	7.17	6.79–7.55
9	Efficient use of resources	7.83	7.67–8.00	Efficient use of resources	7.50	7.37–7.62	Efficient use of resources	8.15	7.95–8.35	Effective treatment of illness	7.41	6.95–7.87
10	Improvement of social functioning	8.80	8.62–8.98	Improvement of social functioning	8.69	8.56–8.82	Improvement of social functioning	8.20	7.95–8.44	Efficient use of resources	7.43	7.04–7.81
11	Avoiding institutional care	10.28	10.15–10.42	Avoiding institutional care	10.24	10.14–10.34	Avoiding institutional care	10.31	10.13–10.50	Avoiding institutional care	9.97	9.71–10.23
12	Reduction of mortality	10.56	10.37–10.76	Reduction of mortality	10.49	10.36–10.62	Reduction of mortality	10.85	10.67–11.04	Reduction of mortality	10.92	10.66–11.17

CI, confidence interval.

Table 3
Health Care Recipients' Priorities for Health Care Outcome

Rank Order	Community-Dwelling Older Adults (n = 2637)			Family Members of Patients With Dementia (n = 333)			Patients in Geriatric Outpatient Clinics (n = 512)			Adult Day Care Participants (n = 795)		
	Outcome	Mean	95% CI	Outcome	Mean	95%CI	Outcome	Mean	95% CI	Outcome	Mean	95% CI
1	Effective treatment of illness	4.23	4.11–4.36	Effective treatment of illness	3.04	2.76–3.32	Effective treatment of illness	2.79	2.58–3.00	Improvement of physical function	3.64	3.42–3.86
2	Reduction of carer burden	4.56	4.44–4.67	Improvement of physical function	4.49	4.19–4.78	Improvement of physical function	4.06	3.84–4.29	Effective treatment of illness	4.33	4.11–4.55
3	Improvement of physical function	5.24	5.13–5.36	Maintaining high level of activity	5.11	4.76–5.45	Improvement of quality of life	5.46	5.19–5.73	Reduction of carer burden	5.40	5.18–5.63
4	Maintaining high level of activity	5.88	5.76–5.99	Reduction of carer burden	5.29	4.98–5.61	Reduction of carer burden	5.52	5.28–5.77	Improvement of quality of life	6.08	5.86–6.30
5	Resolution of assessed problems	5.91	5.76–6.05	Improvement of mental health	5.53	5.24–5.82	Improvement of mental health	5.81	5.58–6.04	Maintaining high level of activity	6.12	5.88–6.37
6	Improvement of mental health	6.26	6.15–6.36	Improvement of quality of life	5.80	5.48–6.13	Maintaining high level of activity	5.97	5.66–6.28	Improvement of mental health	6.38	6.17–6.58
7	Improvement of quality of life	6.36	6.23–6.49	Resolution of assessed problems	5.98	5.69–6.27	Resolution of assessed problems	6.17	5.93–6.42	Patient satisfaction with care	6.44	6.24–6.64
8	Patient satisfaction with care	6.81	6.70–6.92	Patient satisfaction with care	6.01	5.70–6.31	Patient satisfaction with care	6.72	6.47–6.96	Resolution of assessed problems	6.45	6.26–6.65
9	Efficient use of resources	6.91	6.81–7.02	Efficient use of resources	7.49	7.21–7.76	Efficient use of resources	7.46	7.24–7.69	Efficient use of resources	6.57	6.36–6.77
10	Improvement of social functioning	7.44	7.32–7.56	Improvement of social functioning	9.17	8.90–9.45	Improvement of social functioning	8.42	8.18–8.65	Improvement of social functioning	8.22	8.03–8.42
11	Avoiding institutional care	8.43	8.31–8.56	Avoiding institutional care	9.86	9.60–10.12	Avoiding institutional care	9.39	9.16–9.62	Avoiding institutional care	8.61	8.41–8.81
12	Reduction of mortality	9.98	9.87–10.08	Reduction of mortality	10.23	9.99–10.48	Reduction of mortality	10.22	10.00–10.44	Reduction of mortality	9.75	9.55–9.95

CI, confidence interval.

groups indicated physicians' strong preference for this item. All the physician groups also considered "patient satisfaction," "maintaining a high level of activity," and "improvement of physical function" important after "improvement of quality of life," with some variation in the order of their preferences. Geriatricians ranked "effective treatment of illness" the third most important, in contrast to the other two physician groups that ranked this item lower. Adult day care staff ranked "improvement of quality of life" and "maintaining a high level of activity" first and second, respectively, but placed "reduction of carer burden" the third most important, unlike physicians.

With regard to the receiving side of health care, "effective treatment of illness," "improvement of physical function," and "reduction of carer burden" were given high priority, whereas "improvement of quality of life" tended to be perceived as less important.

All the groups, including both health care providers and recipients, ranked "reduction of mortality" the least important, followed by "avoiding institutional care," "improvement of social functioning," and "efficient use of resources," except for the adult day care staff who ranked "improvement of social functioning" higher than "effective treatment of illness."

Stratification analysis demonstrated that the results from physicians were not influenced by sex (male vs female, data not shown); however, physicians older than 60 years tended to rank "effective treatment of illness" and "improvement of physical function" higher compared with younger physicians, who appeared to prioritize "patient satisfaction" and "maintaining a high level of activity." Physicians with more than 30 years' experience, most of whom were older than 60 years, showed a similar tendency, prioritizing "effective treatment of illness" and "improvement of physical function." The results from adult day care staff were identical across groups stratified by age, years of experience, and qualification (data not shown).

The results from the health care recipients did not differ by nursing care level (relatively independent vs limited impairment or higher, or limited impairment vs needing extensive help or higher) for adult day care participants and patients in geriatric outpatient clinics, the existence of relatives who required nursing care (present vs absent) for patients in geriatric outpatient clinics, study site for patients in geriatric outpatient clinics and community-dwelling older adults, or sex for all health care recipient groups (data not shown). Although stratification by age showed that the three measures given highest priority were the same across the age groups (65 to 74 vs older than 75) in community-dwelling older adults, the younger group ranked "reduction of carer burden" first, whereas the older group ranked "effective treatment of illness" first (data not shown).

Discussion

This study is, to our knowledge, the largest survey ever conducted to describe health outcome prioritization in geriatric medicine. We aimed to obtain a comprehensive picture of the views of those involved in decision-making processes in geriatric medicine and compare views between health care providers and recipients. We chose four groups each from providers and recipients that are considered relevant to our purpose. The mean response rate was close to 50%, which was good for a large-scale postal survey and ensured the representative nature of our respondents.

This survey demonstrated that there may be an important gap in health outcome prioritization between health care providers and recipients in geriatric medicine. All health care provider groups, notably physicians, expressed a strong preference for improvement in quality of life (QOL) as a priority of care, whereas health care recipients gave the highest priority to effective treatment of diseases and tended to put lower importance on QOL. In the context of clinical medicine, QOL is often used as a nonspecific, all-encompassing term to describe

nonmortality outcomes averaged over multiple domains (ie, physical, social, and psychological functioning and well-being). Consideration of QOL is essential for the selection of a treatment option, particularly when conditions are noncurative and chronic.[15] Therefore, it is not surprising that physicians who regularly see older patients with multiple chronic conditions consider QOL the most important health care outcome. On the other hand, the term QOL may not be familiar to many health care recipients, and we cannot exclude the possibility that QOL might be confused with other terms, such as standard of living.

Most health care recipients ranked effective treatment of diseases as the most important, suggesting that patients are concerned about their own particular symptoms rather than nonspecific QOL, arguing for efforts to examine the symptoms most concerning to patients. The high importance of effective treatment of diseases ascribed by health care recipients, but not physicians, also implies the significance of the often-neglected aspect of inappropriate prescribing in older adults: underuse of medication likely to be beneficial to older adults. Increased evidence has suggested that failure to prescribe indicated, beneficial medication is common in older adults,[7,8,16] and recent attempts to provide an explicit list of appropriate, indicated medication for older adults are justified.[10]

Interestingly, views on patient satisfaction were also different. All physician groups ranked patient satisfaction as the second top priority, whereas health care recipients considered this to be less important. This tendency has been demonstrated in a prior small study in England more than 15 years ago.[12] Recently, patient satisfaction has been increasingly used to measure health care qualities and compare health plans or physicians.[17] However, our finding may argue against the value of patient satisfaction as a performance measure in geriatric medicine, especially in light of recent evidence suggesting that higher patient satisfaction is accomplished at the sacrifice of increased use of health care resources and may not be directly associated with technical quality of care or improved outcome.[17,18]

We observed agreement on several items between health care providers and recipients. The importance of physical and mental function, such as maintaining activity or improving physical function, was expressed by both health care providers and recipients. This finding was consistent with prior studies in older adults with multiple chronic conditions[12,19] or terminal conditions,[20,21] suggesting that physical and mental function should be an essential factor to consider as a health care outcome in various care settings for older patients.

Reduction in mortality was given the lowest priority by all the groups in health care providers and recipients alike. This view is similar to that observed in previous studies.[12,19] This finding supports the contention that treatment interventions should be assessed in terms of reduced morbidity and improved QOL in addition to reduced mortality.

In this survey, respondents' characteristics, except age, had limited influence on their views on health outcome prioritization within each group. Geriatricians older than 60 years and community-dwelling adults older than 75 years gave higher priority to effective treatment of diseases compared with their younger counterparts. This suggests that health outcome priorities may not be stable, and can change as respondents age or differ from generation to generation. The cross-sectional design of our survey prevented us from separating the age effect from the secular trend, and further studies will be required to examine the time- or setting-dependent variability of health outcome prioritization.

This study has several limitations. First, although the average response rate was high for a postal survey, it was lower in physician groups than in health care recipient groups (26% to 48% vs 44% to 61%, Table 1). Thus, selection bias cannot be excluded. Second, it was not sure that health care recipients, particularly adult day care participants, correctly understood the study terminology. Third, some of the items used in the survey were not mutually exclusive. Nevertheless, a similar trend in priorities of outcome measures according to either side of health care providers or recipients suggests that the overall results were not significantly affected by these limitations.

Conclusion

We demonstrated that there was significant agreement and disagreement of health outcome prioritization between health care providers and recipients in geriatric medicine. Health care providers and recipients agreed on high priority for function and low priority for reduction in mortality, but there was obvious disagreement in how they perceived QOL, treatment effect, and patient satisfaction as goals of care. Such disagreement necessitates better communication between providers and recipients to reach goals of care that are mutually understandable and tailored to meet patients' specific needs. The low importance of reduction in mortality and patient satisfaction ascribed by health care recipients may question the value of these outcomes as a way to assess treatment interventions and quality of care. We propose that the priorities of health care outcomes and their differences between providers and recipients demonstrated in this study should be taken into account in the health care of older patients and the design of health care policies and research.

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Postcard intervention for depression in community-dwelling older adults: A randomised controlled trial

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ABSTRACT

Depression in older adults erodes their health, quality of life and the economy. Existing interventions are not feasible for broad application at the community. Postcard intervention only requires a few resources, and previous studies have shown its effectiveness for patients following drug overdose, self-harm and hospitalisation for major depression. The purpose of the present study is to evaluate the effectiveness of a postcard intervention. Participants were community-dwelling individuals, aged 65 or older, who eat meals alone and with the score of 4 or higher on the 15-item Geriatric Depression Scale (GDS-15). We enrolled 184 eligible participants, with 93 in the intervention and 91 in the control arm. Postcards were sent to participants once a month for eight months. Primary outcome was the GDS-15 score at post-intervention. Secondary outcomes were quality of life and activities of daily living. There was no significant difference in primary and secondary outcomes between completers of the intervention and the control arm. However, most of the participants who received intervention thought the intervention was effective. The postcard intervention for depression in community-dwelling elderly people in Japan is neither feasible nor effective. However, the descriptive results suggest that the intervention may be effective given different parameters.

1. Introduction

The United Nations reports that nearly all the countries of the world face population aging (United Nations, 2013). Currently in Japan, one out of four people is over 65 years old, and it is estimated that one out of three people will be over 65 years old in twenty years' time (Statistics Breau in Japan, 2014). Future problems related to the aging population will be even more serious than the present situation.

Depression is one of the most serious problems in elderly people. It erodes their health and quality of life (QOL) and imposes huge economic costs on the society. The mortality rate of people with depression is 1.8 times greater than that of non-depressed subjects, due to suicide, unhealthy habits, and medical illnesses (Cuijpers and Schoevers, 2004). QOL of elderly people with depression is lower than those with many other chronic diseases (Unutzer, 2009). Depression deteriorates elderly patients' well-being, perceived physical functioning, bodily pain, and general health perceptions (Saarijärvi et al., 2002). It is reported that the additional medical cost per one depressed older adult is USD 686 for 1 year and USD 5271 for 4 years (Unutzer et al., 1997). Depressed older adults use more outpatient resources than those without depression, including frequent appointments and laboratory and radiographic tests. They also have more nonspecific medical complaints, and this is associated with increased total ambulatory care costs (Luber et al., 2001).

Furthermore, the prevalence of depression in elderly people is high, with poor prognosis. A review of community prevalence of depression in later life reported that the proportion of individuals reporting depressive symptoms is 2.8–35% (Beekman et al., 1999). A 6-year follow-up study showed that 76% of elderly patients with depressive disorder follow either an unfavourable fluctuating or a severe chronic course of depression, and only 23% of patients experience full remission (Beekman et al., 2002).

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However, no simple and effective interventions currently exist for depression in the community-dwelling elderly population (Cole, 2008). Existing interventions are for patients seen in clinics or hospitals, and they require considerable time and personnel (Burns et al., 2007; Gilden et al., 1992; Haight et al., 1998; Kennedy and Sherazi, 2005; Phillips, 2000; Raphael, 1977; Rovner et al., 2007).

A postcard intervention is the simple and effective intervention for several disorders. It was first conducted in the United States in 1976 for suicide prevention in major depression patients discharged from the hospital. Researchers sent 24 letters over five years and reported that this intervention significantly decreased suicide rates for the first two years and tended to lower suicide rates up to 13 years in total (Motto, 1976; Motto and Bostrom, 2001). Three more postcard intervention trials were conducted in Israel and Australia in 2005, 2010, and 2011, focusing on the prevention of drug overdose or self-harm. The results showed a significant decrease in the number of drug overdose episodes, as well as the rates of suicidal ideation and suicide attempts (Beautrais et al., 2010; Carter et al., 2005, 2007; Hassanian-Moghaddam et al., 2011).

One advantage of the postcard intervention is its low personal and financial cost; it only requires paper, pencil, and postage. Therapists are not required to visit the participants, and vice versa. If the postcards do not contain medical and related information, a wide range of people, such as elementary school students, can take part in the intervention programme.

The present study aimed to examine the effectiveness of a postcard intervention for the improvement of depressive symptoms, quality of life (QOL) and activities of daily living (ADL) and to assess the acceptability of the postcard intervention for community-dwelling older adults (aged 65+ years), reporting symptoms of depression and limited social support.

2. Methods

2.1. Design overview

This was a randomised controlled trial using Zelen's design, in which consent was obtained after the randomisation only from participants in the intervention arm (Zelen, 1979, 1990). An intention-to-treat analysis was used, based on group allocation. Results presented in this paper have been obtained by following the published study protocol (Imai et al., 2013). The trial was registered before recruitment (UMIN000010529).

2.2. Setting

The study was conducted in a town in Japan. It has a population of 4407, of whom 1711 (38.8%) were aged 65 years or older in 2013. Our study team has conducted a longitudinal observational study in this community since 2004, where we administer comprehensive geriatric assessments. This observational study has been approved by the IRB of the Graduate School of Medicine, Kyoto University (E-18), and written informed consent has been obtained from all the participants.

2.3. Participants

We selected participants by using data collected in 2013 as part of our annual observational study. Participants were included if they (1) were 65 years of age or older, (2) exhibited symptoms of depression, had a score of ≥ 4 on the self-rated 15-item Geriatric Depression Scale (GDS-15), and (3) reported that they eat meals alone, considered to be an indicator of isolation. Participants were excluded if they could not understand and sign the informed consent form or currently resided in a hospital or institution.

2.4. Zelen's design and ethical consideration

The study used a randomized controlled trial with the single consent version (Zelen's design) (Zelen, 1979, 1990). This is a variation of the standard randomized controlled design in which participants are randomized to intervention or control arm before consent is sought. Consent is obtained from the intervention group only after the randomisation. The advantage of this method is that participants know the intervention they will receive at the time of consent. In a conventional randomisation, participants who agree to join the study may retract their consent or continue participation with reluctance after finding out their assigned intervention, whereas the Zelen's method requires a decision only on the allocated intervention. The main ethical concern is that consent is obtained only from the intervention group. To overcome this point, the revised Zelen's method has been proposed (Campbell et al., 2005). This method is a combination of an observational study and a randomized controlled trial. Eligible participants first consent to an observational study, and then they are randomly assigned to intervention and control groups; those in the intervention group are asked to consent to participate in the study. Those in the control arm are not informed of this, but will be followed in the observational study if they agreed. Our study followed this method.

2.5. Randomisation and allocation

Eligible participants were randomised to either the intervention or the control group at a 1:1 ratio using computer-generated random numbers. Randomisation was stratified by gender and self-rated depression scale score (more or less than six

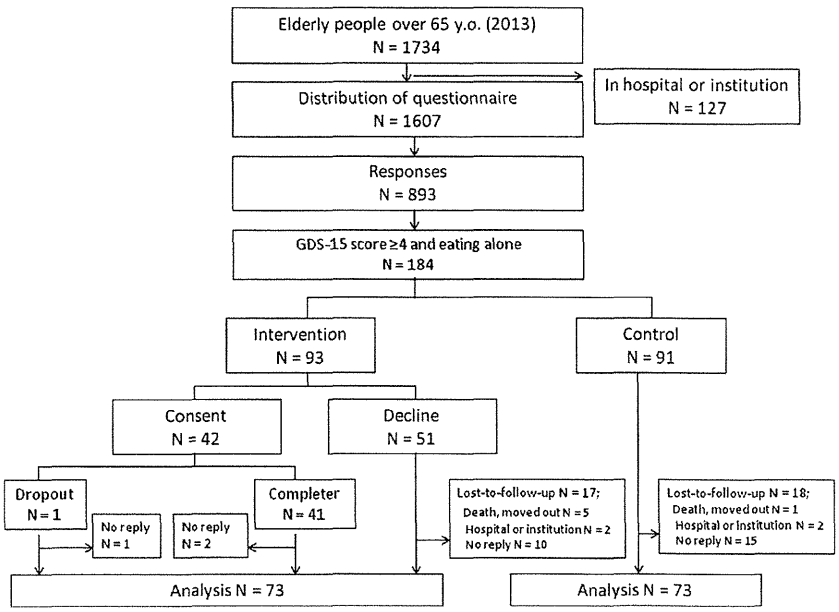

Fig. 1. CONSORT flow diagram of the present study. GDS-15: 15-item Geriatric Depression Scale.