

RESULTS

We registered 105 elderly in LTC, and assessed HRV from 24-hour Holter monitoring. The underlying diseases of elderly in LTC for rehabilitation were cerebrovascular disease (n=59, 56.2%), disuse syndrome (n=26, 24.8%), fracture (n=19, 18.1%), and dementia (n=1, 1.0%). The proportions of underlying diseases were similar to those reported in Japanese elderly in LTC (3).

The background data of this study are shown in Table 1. In LTC elderly, mean age was 86.5 ± 6.0 years, blood nutritional data including albumin, hemoglobin and total cholesterol were at the lower limit of the normal range, and physical function represented by FIM and Barthel index was significantly lower (46 ± 26 and 30 ± 31 , respectively) than that in elderly controls (116 ± 24 and 92 ± 16 , respectively). Scores for each FIM item were following, eating; 3.7 ± 2.2 , grooming; 2.6 ± 1.8 , bathing; 1.5 ± 1.1 , upper body dressing; 2.5 ± 1.7 , lower body dressing; 2.2 ± 1.6 , toileting; 2.7 ± 2.0 , bladder management; 2.6 ± 2.1 , bowel management; 2.4 ± 2.0 , bed to chair transfer; 3.0 ± 1.9 , toilet transfer; 2.4 ± 1.7 , shower transfer; 1.5 ± 1.4 , locomotion (ambulatory or wheelchair level); 2.0 ± 1.8 , stairs; 1.2 ± 0.8 , cognitive comprehension; 3.6 ± 2.2 , expression; 3.6 ± 2.2 , social interaction; 3.2 ± 2.2 , problem solving; 2.8 ± 1.9 and memory; 2.8 ± 1.9 . These score indicated that the overall subjects needed moderate care supporting physical and cognitive function. In addition, BMI, albumin, SDANN and LF/HF were significantly decreased in LTC elderly compared with elderly controls. After adjustment for covariance, of all HRV indices, only LF/HF was significantly lower in LTC elderly (Table 1). Data of HRV indices were obtained every 5 minutes, and averaged every three hours to examine the circadian rhythm in both LTC elderly and healthy controls. A significant decrease of LF/HF was observed in the nighttime in healthy controls, whereas there was a loss of circadian rhythm in LTC elderly (Figure 1).

Multiple regression analysis revealed that the associations between heart rate, SDANN and physical function (Barthel index and FIM) were independent of age, sex, and CVD. Moreover, albumin and hemoglobin were also correlated with heart rate and SDANN. In contrast, LF, HF and LF/HF were not significantly correlated with physical function and blood nutritional data (Table 2).

Next, we followed the survival of LTC elderly, and 23 people died among 105 LTC elderly during a mean follow-up period of 8.9 months. The major cause of

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5 death was pneumonia (n=12). There was no sign of stroke among study subjects, and
6 one subject with acute myocardial infarction was observed during follow-up period.
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8 Mortality according to HRV indices divided by the average is shown in Table 3. After
9 adjustment for covariates, of all HRV indices, only LF/HF was associated with
10 mortality. Kaplan-Meier survival curves also showed an association between decreased
11 LF/HF and high mortality (Figure 2). In addition to adjusted covariates, BMI, Barthel
12 index and blood nutritional data were not different between the high LF/HF group and
13 low LF/HF group (data not shown).
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DISCUSSION

In this study, we investigated the relationship between physical function, mortality and sympathetic nervous activity measured by HRV in Japanese LTC elderly, and it was demonstrated that LF/HF was significantly decreased in LTC elderly after adjustment for age, sex, CVD risk factors and FIM compared with elderly controls. In addition, the circadian rhythm of LF/HF was lost in LTC elderly, and low LF/HF was associated with overall mortality.

In a previous study, low LF/HF was associated with both frailty and mortality in community-dwelling people of whom one-third were frail elderly (9), and these associations were consistent with our data. Additionally, low LF/HF was also shown in LTC elderly, and was independent of physical function.

Elevated heart rate or low SDANN leads to cardiovascular disease and low physical function (17, 18), and the same relationship was also observed in LTC elderly. Furthermore, low albumin and low hemoglobin were observed in the high heart rate group, and limited physical function was observed in LTC elderly. These results are supported by a previous report (19). So it may be possible to improve the physical function of LTC elderly by maintaining their nutritional state. The high LF/HF group has been reported to show high physical function and muscle mass (4, 20), whereas our data did not show this association. One of the reasons for this discrepancy is thought to be the effect of aging. Aging generally attenuates LF/HF, and the patients in our study were older than those in other studies (9, 14). Another reason might be autonomic nervous system disturbance. In particular, the circadian rhythm of LF/HF was impaired in LTC elderly.

Circadian imbalance of LF/HF has been demonstrated in some disorders such as Parkinson disease, type 2 diabetes mellitus (T2DM) and ischemic stroke (21-23), and moreover, physical activity also influences HRV indices (24, 25). In this study, LTC elderly with Parkinson disease were excluded, and CVD risk factors including T2DM were matched between LTC elderly and healthy controls, as stroke and physical activity might affect LF/HF. However, the influence of both conditions on LF/HF is controversial. High physical activity and good posture led to high LF/HF activity (26), while it was also suggested that LF/HF was not affected by physical activity (13). The effect of LF/HF on stroke is also controversial (23, 27, 28). In ischemic stroke patients, LF/HF was higher than healthy controls in some studies (27, 28) whereas another study

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5 suggested that LF/HF was lower in patients (23). So the mechanism of LF/HF circadian
6 rhythm disturbance is not clear, though its recovery may be important to increase
7 physical function in LTC elderly. Other reasons why LF/HF and physical function did
8 not reveal correlation in LTC elderly might to be effects of stroke, insufficient exposure
9 to daylight and posture at daytime. All subjects were over 75 years old in this study, and
10 there is a possibility that asymptomatic lacunar infarction might be observed. It is also
11 suggested that lacunar infarction disturb autonomic nervous system such as decrease in
12 LF/HF and related value of autonomic nervous system, leading to disappearance of the
13 correlation between physical activity and LF/HF. In addition, exposure to daylight was
14 known to be one of the most powerful rhythmic regulator in environment (49). All
15 subjects in this study spent their time indoor for rehabilitation and care. Moreover, it is
16 known that supine position increases HF and decreases LF/HF (50), and LTC elderly
17 subjects who were at rehabilitation unit or health service facilities might spend more
18 time in bed compared with outpatient controls, leading to low LF/HF and disappearance
19 of the correlation between LF/HF and physical activity in this study.

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Recent studies revealed that decreased HRV indices including LF, HF and LF/HF were associated with CVD risk factors, and decreased LF was an independent predictor of death in elderly people (29, 30). However, our findings demonstrated that, of all HRV indices, only LF/HF was associated with mortality. This result is supported by a previous study in which, of HRV indices, LF/HF was associated with both frailty and mortality (9). The major difference between our and other studies is whether the subjects included frail, LTC elderly or not. All subjects were LTC elderly in our study and WHAS-I, which was reported by Varadhan et al and included one-third frail elderly, whereas in other studies the subjects were community-dwelling elderly with intact activities of daily living (ADL) and they did not consider physical function (14, 30, 31). These results suggest that the significance of LF/HF might differ between LTC elderly and elderly with intact ADL and physical function.

There is a discrepancy in the results derived from studies of LTC elderly and studies of elderly with intact physical function regarding the sympathetic nervous activity. Exercise activates the sympathetic nervous system, leading to an increase in blood pressure, muscle blood flow, and muscle strength by inducing muscle protein synthesis (32-35), suggesting that low sympathetic nervous activity is related to not only physical dysfunction but also inability to maintain muscle strength, leading to a

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5 worse outcome in LTC elderly. Appropriate activation of the sympathetic nervous
6 system may prevent muscle wasting and improve overall mortality in LTC elderly.
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9 Activation of the sympathetic nervous system has been applied to aging or
10 sarcopenic model rats. The β 2-adrenergic agonists, clenbuterol and formoterol,
11 improved muscle mass and muscle strength and prevented muscle aging in aging, disuse
12 and sarcopenia (36-42) model rats. In contrast, inhibition of sympathetic nervous
13 activity with β -blockers was associated with a worse outcome in elderly people (43).
14 These findings also suggest the importance of preventing a sympathetic nervous activity
15 decline in LTC elderly.
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20 There are several study limitations. First, this was an observational study, and
21 cannot provide direct evidence of causality. So it will be necessary to carry out
22 randomized controlled trials to reveal whether high sympathetic nervous activity leads
23 to a good outcome or not. Second, excessive sympathetic nervous activity is associated
24 with cardiovascular risk factors such as hypertension, left ventricular myocardial
25 hypertrophy and old cerebrovascular disease (44, 45). In addition, the number of control
26 subject was relatively small in this study. Based on these results, it might be hard to
27 mention about general application of the findings to oldest old subjects. However, some
28 studies, particularly in the elderly, showed that decreased sympathetic nervous activity
29 was associated with a worse outcome (9). In addition to low physical activity, poor
30 handgrip strength and frailty are known to be important risk factors predicting death in
31 elderly people (2, 46-48), and few reports have focused on LTC elderly. So this study
32 has the possibility of providing evidence to improve physical function and mortality in
33 LTC elderly by means of maintaining or increasing LF/HF.
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43 In summary, our study demonstrated that LF/HF is a factor that distinguishes
44 LTC elderly from elderly controls independent of physical function. In addition, the
45 circadian rhythm of LF/HF was lost in LTC elderly. Moreover, low LF/HF was
46 associated with high mortality. For LTC elderly aged 75 years or over, LF/HF may be a
47 predictive biomarker of physical function and mortality.
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52 **Disclosure Statement:** There is no financial support or relationship that might pose
53 conflicts of interest.
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REFERENCES

1. Japanese Ministry of Health, Labor and Welfare. Changes in the number of people certified for long-term care/support need [cited 23 August 2011.] Available from: <http://www.mhlw.go.jp/english/wp/wp-hw3/dl/10-06.pdf>.
2. Fried LP, Tangen CM, Walston J et al. Frailty in older adults: Evidence for a phenotype. *J Gerontol* 2001; 56: M146-156.
3. Japanese Ministry of Health, Labor and Welfare. Welfare policy for the elderly with a focus on long-term care insurance system. [cited 23 August 2011.] Available from: <http://www.mhlw.go.jp/english/wp/policy/dl/04.pdf>.
4. Camillo CA, Pitta F, Possani HV et al. Heart rate variability and disease characteristics in patients with COPD. *Lung* 2008; 186: 393-401.
5. Muslumanoğlu L, Aki S, Turkdogan D, Us O, Akyuz G. Involvement of sympathetic reflex activity in patients with acute and chronic stroke: A comparison with functional motor capacity. *Arch Phys Med Rehabil* 2004; 85: 470-473.
6. Oka H, Morita M, Onouchi K, Yoshioka M, Mochio S, Inoue K. Cardiovascular autonomic dysfunction in dementia with Lewy bodies and Parkinson's disease. *J Neurol Sci* 2007; 254: 72-77.
7. Oka H, Yoshioka M, Morita M et al. Reduced cardiac 123I-MIBG uptake reflects cardiac sympathetic dysfunction in Lewy body disease. *Neurology* 2007; 69: 1460-1465.
8. Heart rate variability. Task force of the European Society of Cardiology and the North American Society of Pacing Electrophysiology. *Circulation* 1996; 93: 1043-1065.
9. Varadhan R, Chaves PHM, Lipsitz LA et al. Frailty and impaired cardiac autonomic control: New insights from principal components aggregation of traditional heart rate variability indices. *J Gerontol A Biol Sci Med Sci* 2009; 64: 682-687.
10. Alter P, Grimm W, Vollrath A, Czerny F, Maisch B. Heart rate variability in patients with cardiac hypertrophy - relation to left ventricular mass and etiology. *Am Heart J* 2006; 151: 829-836.
11. Smilde TDJ, van Veldhuisen DJ, van den Berg MP. Prognostic value of heart rate variability and ventricular arrhythmias during 13-year follow-up in patients with mild to moderate heart failure. *Clin Res Cardiol* 2009; 98: 233-239.

12. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: Relations to age and gender over nine decades. *J Am Coll Cardiol* 1998; 31: 593-601.
13. Greiser KH, Kluttig A, Schumann B et al. Cardiovascular diseases, risk factors and short-term heart rate variability in an elderly general population: the CARLA study 2002-2006. *Eur J Epidemiol* 2009; 24: 123-142.
14. Tsuji H, Venditti Jr FJ, Manders ES et al. Reduced heart rate variability and mortality risk in an elderly cohort. The Framingham Heart Study. *Circulation* 1994; 90: 878-883.
15. Keith RA, Granger CV, Hamilton BB, Sherwin FS. The functional independence measure: a tool for rehabilitation. *Adv Clin Rehabil* 1987; 1: 6-18.
16. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. *Md State Med J* 1965; 14: 61-65.
17. Graham I, Atar D, Borch-Johnsen K et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary: Fourth joint task force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (Constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2007; 28: 2375-2414.
18. Roach D, Wilson W, Ritchie D, Sheldon R. Dissection of long-range heart rate variability: controlled induction of prognostic measures by activity in the laboratory. *J Am Coll Cardiol* 2004; 43: 2271-2277.
19. Spurr GB, Barac-Nieto M, Maksud MG. Functional assessment of nutritional status: heart rate response to submaximal work. *Am J Clin Nutr* 1979; 32: 767-778.
20. David MDR, Martha ERR, Ernesto GR, David MDR, Martha EMDR. Sympathovagal imbalance assessed by heart rate variability correlates with percent body fat and skeletal muscle, independent of body mass index. *Cleve Clin J Med* 2011; 78: S91a
21. Niwa F, Kuriyama N, Nakagawa M, Imanishi J. Circadian rhythm of rest activity and autonomic nervous system activity at different stages in Parkinson's disease. *Auton Neurosci* 2011; 165(2): 195-200.
22. Boer-Martins L, Figueiredo VN, Demacq C et al. Relationship of autonomic imbalance and circadian disruption with obesity and type 2 diabetes in resistant hypertensive patients. *Cardiovasc Diabetol* 2011; 22: 10-24.

23. Juha T, Korpelainen KA, Sotaniemi HV et al. Circadian rhythm of heart rate variability is reversibly abolished in ischemic stroke. *Stroke* 1997; 28: 2150-2154.
24. Ino-Oka E, Sekino H, Ohtaki Y, Inooka H. Effects of daily physical activity level on the degree of sympathetic tone. *Intern Med* 2009; 48: 19-24.
25. Fortrat JO, de Germain V, Custaud MA. Holter heart rate variability: are we measuring physical activity? *Am J Cardiol* 2010; 106: 448-449.
26. Miyamoto S, Fujita M, Sekiguchi H et al. Effects of posture on cardiac autonomic nervous activity in patients with congestive heart failure. *J Am Coll Cardiol* 2001; 37: 1788-1793.
27. Dütsch M, Burger M, Dörfler C, Schwab S, Hilz MJ. Cardiovascular autonomic function in poststroke patients. *Neurology* 2007; 69: 2249-2255.
28. Colivicchi F, Bassi A, Santini M, Caltagirone C. Cardiac autonomic derangement and arrhythmias in right-sided stroke with insular involvement. *Stroke* 2004; 35: 2094-2098.
29. Stein PK, Brazilay JI, Chaves PH, Domitrovich PP, Gottdiener JS. Heart rate variability and its changes over 5 years in older adults. *Age Aging* 2009; 38: 212-218.
30. La Rovere MT, Pinna GD, Maestri R et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. *Circulation* 2003; 107: 565-570.
31. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; 59: 256-262.
32. Nakamura T, Mizushima T, Yamamoto M, Kawazu T, Umezu Y, Tajima F. Muscle sympathetic nerve activity during isometric exercise in patients with cerebrovascular accidents. *Arch Phys Med Rehabil* 2005; 86: 436-441.
33. Astrand PO, Cuddy TE, Saltin B, Stenberg J. Cardiac output during submaximal and maximal work. *J Appl Physiol* 1964; 19: 268-274.
34. Koopman R, Ryall JG, Church JE, Lynch S. The role of β -adrenoceptor signaling in skeletal muscle: therapeutic implications for muscle wasting disorders. *Curr Opin Clin Nutr Metab Care* 2009; 12: 601-606.
35. Lynch GS, Ryall JG. Role of beta-adrenoceptor signaling in skeletal muscle: implications for muscle wasting and disease. *Physiol Rev* 2008; 88: 729-767.

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36. Carter WJ, Dang AQ, Faas FH, Lynch ME. Effects of clenbuterol on skeletal muscle mass, body composition, and recovery from surgical stress in senescent rats. *Metabolism* 1991; 40: 855-860.
 37. Carter WJ, Lynch ME. Effect of clenbuterol on recovery of muscle mass and carcass protein content following dietary protein depletion in young and old rats. *J Gerontol* 1994; 49: B162-168.
 38. Chen KD, Alway SE. Clenbuterol reduces soleus muscle fatigue during disuse in aged rats. *Muscle Nerve* 2001; 24: 211-222.
 39. Ryall JG, Plant DR, Gregorevic P, Sillence MN, Lynch GS. Beta 2-agonist administration reverses muscle wasting and improves muscle function in aged rats. *J Physiol* 2004; 555: 175-188.
 40. Ricart-Firinga C, Stevens L, Canu MH, Nemirovskaya TL, Mounier Y. Effects of beta(2)-agonist clenbuterol on biochemical and contractile properties of unloaded soleus fibers of rat. *Am J Physiol Cell Physiol* 2000; 278: C582-588.
 41. Stevens L, Firinga C, Gohlsch B, Bastide B, Mounier Y, Pette D. Effects of unweighting and clenbuterol on myosin light and heavy chains in fast and slow muscles of rat. *Am J Physiol Cell Physiol* 2000; 279: C1558-1563.
 42. Ryall JG, Scherzer JD, Lynch GS et al. Attenuation of age-related muscle wasting and weakness in rats after formoterol treatment: Therapeutic implications for sarcopenia. *J Gerontol* 2007; 62A: 813-823.
 43. Peters R, Beckett N, Burch L et al. The effect of treatment based on a diuretic (indapamide) +/- ACE inhibitor (perindopril) on fractures in the Hypertension in the Very Elderly Trial (HYVET). *Age Ageing* 2010; 39: 609-616.
 44. Lucini D, Mela GS, Malliani A, Pagani M. Impairment in cardiac autonomic regulation preceding arterial hypertension in humans: insights from spectral analysis of beat-by-beat cardiovascular variability. *Circulation* 2002; 106:2673-2679.
 45. Burns J, Sivananthan MU, Ball SG, Mackintosh AF, Mary DA, Greenwood JP. Relationship between central sympathetic drive and magnetic resonance imaging-determined left ventricular mass in essential hypertension. *Circulation* 2007; 115: 1999-2005.
 46. Stessman J, Rozenberg RH, Cohen A, Mor EE, Jacob JM. Physical activity, function, and longevity among the very old. *Arch Intern Med* 2009; 169: 1476-1483.

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6 47. Rantanen T, Voipato S, Ferrucci L, Heikkinen E, Fried LP, Guralnik JM. Handgrip
7 strength and cause-specific and total mortality in older disabled women: exploring
8 the mechanism. *J Am Geriatr Soc* 2003; 51: 636-641.
9
10 48. Ling CHY, Taekema D, de Craen AJM, Gussekloo J, Westendorp RGJ, Maier AB.
11 Handgrip strength and mortality in the oldest old population: the Leiden 85-plus
12 study. *CMAJ* 2010; 182: 429-435.
13
14 49. Appenzeller O, Oribe E. *The Autonomic Nervous System. An Introduction to Basic*
15 *and Clinical Concepts*, 5th edn. UK: Elsevier Science Publishers, 1997.
16
17 50. Huikuri HV, Niemelä MJ, Ojala S, Rantala A, Ikäheimo, MJ, Airaksinen KE.
18 Circadian rhythms of frequency domain measures of heart rate variability in healthy
19 subjects and patients with coronary artery disease. Effects of arousal and upright
20 posture. *Circulation* 1994; 90: 121-126.
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5 **Figure legends**
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8 **Figure1**

9 * $p < 0.05$, mean \pm SEM, The activity of LF/HF in long-term cared elderly and controls.
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11 The RR interval data were measured every 5 minutes, and the graph shows averaged
12 every 3 hours.
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16 **Figure2**

17 Kaplan-Meire survival curves for death according to LF/HF. Mortality was significantly
18 higher for patients with low LF/HF group than for patients with high LF/HF group.
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20 Mean follow up period was 8.9 months.
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Table 1. Characteristics of long-term cared elderly and healthy elderly controls

	LTC elderly	controls	p
No. of subjects	105	17	
Age, years	86.5±6.0 (75-100)	86.3±9.1 (75-103)	0.311
Sex, male (%)	29 (27.6)	6 (35.3)	0.999
Body mass index	19.5±3.3	22.0±3.5	0.009
Cardiovascular risk factors, n (%)			
Hypertension	57 (54.3)	11 (64.7)	0.590
Diabetes mellitus	13 (12.4)	2 (11.8)	0.999
Hyperlipidemia	14 (13.3)	3 (17.6)	0.921
Chronic heart failure	12 (11.4)	1 (5.9)	0.792
Ischemic heart disease	15 (14.3)	1 (5.9)	0.572
Physical function			
FIM	46±26	116±24	<0.001
Barthel index	30±31	92±16	<0.001
Blood nutritional data			
Albumin, g/dl	3.5±0.5	3.9±0.3	<0.001
Hemoglobin, g/dl	12.0±1.8	12.4±2.2	0.188
Total cholesterol, mg/dl	177±40	175±34	0.892
Heart rate variability indices			
SDANN	85.0±34.3	112.1±27.2	0.001
Heart rate, beat/min	73.1±12.1	71.5±7.4	0.878
LF, ms ²	36.1±25.3	42.4±37.5	0.274
HF, ms ²	65.9±56.3	60.7±52.3	0.813
LF/HF	0.69±0.27*	0.87±0.31	0.023

Values are mean ± standard deviation. FIM, function independent measure; SDANN, standard deviations of the all NN intervals in all 5-minute segments of the entire recording; LF, low frequency; HF, high frequency.

*After adjusted with age, sex, cardiovascular risk factors and FIM, LF/HF were significantly lower in long-term cared elderly than healthy controls (p=0.049).

Table 2. Multiple regression analysis of heart rate variability indices with physical function and blood nutritional data after adjusted age, sex and cardiovascular risk factors.

	HR	SDANN	LF	HF	LF/HF
FIM	-0.25*	0.28*	0.19	0.15	-0.08
Barthel index	-0.27*	0.29*	0.08	0.04	0.00
Body mass index	-0.05	0.05	0.00	-0.08	0.19
Albumin	-0.21*	0.25*	0.05	-0.02	0.11
Hemoglobin	-0.20*	0.27*	0.12	0.12	0.05
Total cholesterol	-0.01	-0.05	-0.13	-0.17	0.03

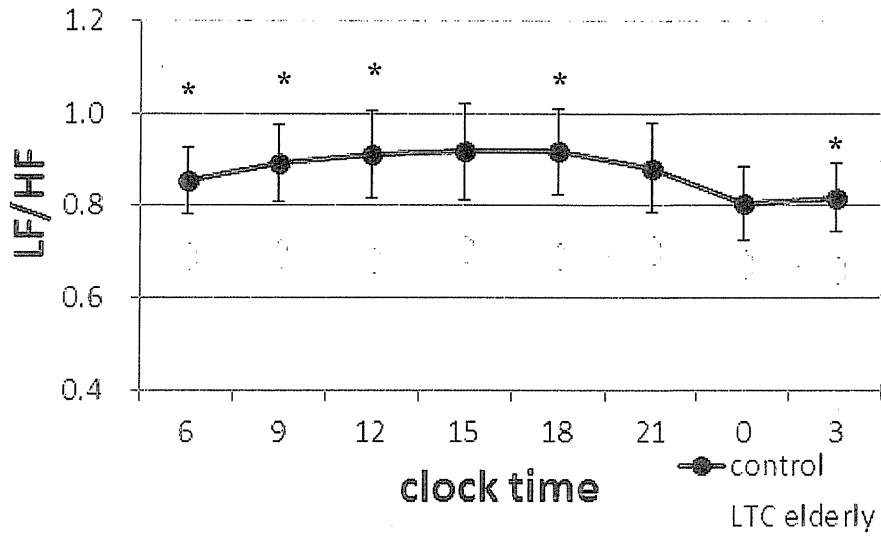
* $p < 0.05$, Analyzed in 105 long-term cared elderly. FIM, function independent measure; HR, heart rate; SDANN, standard deviations of the all NN intervals in all 5-minute segments of the entire recording; LF, low frequency; HF, high frequency.

Table 3. Proportional hazards regression analysis of the impact of heart rate variability measure on overall mortality.

	Hazard Ratio*	95% Confidence Interval	<i>P</i>
Unadjusted			
SDANN, ms	1.84	0.77–4.38	0.171
LF, ms ²	1.61	0.59–4.38	0.353
HF, ms ²	2.14	0.72–6.34	0.169
LF/HF	4.73	1.59–14.06	0.005
Age, sex and cardiovascular risk factors adjusted for association with mortality			
SDANN, ms	1.53	0.60–3.86	0.372
LF, ms ²	1.65	0.57–4.78	0.357
HF, ms ²	2.60	0.82–8.22	0.105
LF/HF	3.37	1.02–11.07	0.046
Age, sex, FIM and cardiovascular risk factors adjusted for association with mortality			
SDANN, ms	1.19	0.44–3.17	0.736
LF, ms ²	1.49	0.50–4.41	0.475
HF, ms ²	2.85	0.83–9.83	0.097
LF/HF	3.61	1.08–12.10	0.038

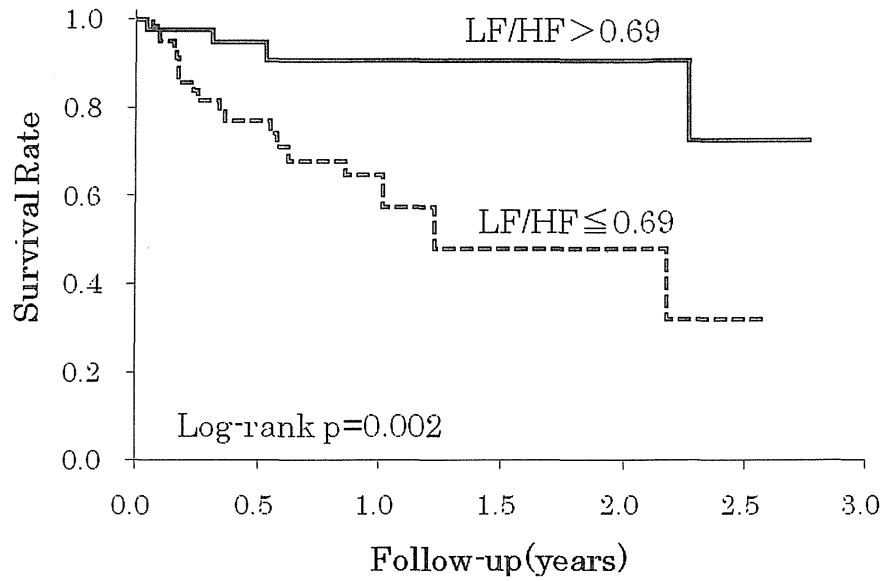
Based on 23 deaths among 105 subjects. Mean values of heart rate variability measure are in Table 1. *Hazard ratio of death rates of subjects whose heart rate variability are less than average.

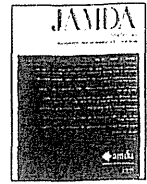
Figure 1. Circadian rhythm of LF/HF.



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Figure 2. Kaplan-Meier survival curves of LF/HF.





Original Study

Priorities of Health Care Outcomes for the Elderly

Masahiro Akishita MD, PhD^{a,*}, Shinya Ishii MD^a, Taro Kojima MD^a, Koichi Kozaki MD, PhD^b, Masafumi Kuzuya MD, PhD^c, Hidenori Arai MD, PhD^d, Hiroyuki Arai MD, PhD^e, Masato Eto MD, PhD^a, Ryutaro Takahashi MD, PhD^f, Hidetoshi Endo MD, PhD^g, Shigeo Horie MD, PhD^h, Kazuhiko Ezawa MD, PhDⁱ, Shuji Kawai MD, PhDⁱ, Yozo Takehisa MD, PhD^j, Hiroshi Mikami MD, PhD^k, Shogo Takegawa MSc^l, Akira Morita BPS^m, Minoru Kamata DMEⁿ, Yasuyoshi Ouchi MD, PhD^a, Kenji Toba MD, PhD^g

^a Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

^b Department of Geriatric Medicine, Kyorin University School of Medicine, Mitaka, Japan

^c Department of Geriatric Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan

^d Department of Human Health Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan

^e Department of Geriatric Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan

^f Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology, Tokyo, Japan

^g National Center for Geriatrics and Gerontology, Obu, Japan

^h Department of Urology, Teikyo University School of Medicine, Tokyo, Japan

ⁱ Japan Association of Geriatric Health Services Facilities, Tokyo, Japan

^j Japan Association of Medical and Care Facilities, Tokyo, Japan

^k Japan Medical Association, Tokyo, Japan

^l Graduate School of Humanities and Sociology, The University of Tokyo, Tokyo, Japan

^m Faculty of Law, Gakushuin University, Tokyo, Japan

ⁿ Institute of Gerontology, The University of Tokyo, Tokyo, Japan

A B S T R A C T

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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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* Address correspondence to Masahiro Akishita, MD, PhD, Department of Geriatric Medicine, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.

E-mail address: akishita-ky@umin.ac.jp (M. Akishita).

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.
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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 2030² 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	Outcome	Geriatricians (n = 619)			Physicians from 5 Relevant Subspecialties (n = 1305)			Physicians in Long Term Care Facilities (n = 384)			Adult Day Care Staff (n = 204)		
		Mean	95% CI	Outcome	Mean	95% CI	Outcome	Mean	95% CI	Outcome	Mean	95% CI	Outcome
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	10.37–10.75	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)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
1	4.23	4.11–4.36	3.04	2.76–3.32	2.79	2.58–3.00	3.64	3.42–3.86
2	4.56	4.44–4.67	4.49	4.19–4.78	4.06	3.84–4.29	4.33	4.11–4.55
3	5.24	5.13–5.36	5.11	4.76–5.45	5.46	5.19–5.73	5.40	5.18–5.63
4	5.88	5.76–5.99	5.29	4.98–5.61	5.52	5.28–5.77	6.08	5.86–6.30
5	5.91	5.76–6.05	5.53	5.24–5.82	5.81	5.58–6.04	6.12	5.88–6.37
6	6.26	6.15–6.36	5.80	5.48–6.13	5.97	5.66–6.28	6.38	6.17–6.58
7	6.36	6.23–6.49	5.98	5.69–6.27	6.17	5.93–6.42	6.44	6.24–6.64
8	6.81	6.70–6.92	6.01	5.70–6.31	6.72	6.47–6.96	6.45	6.26–6.65
9	6.91	6.81–7.02	7.49	7.21–7.76	7.46	7.24–7.69	6.57	6.36–6.77
10	7.44	7.32–7.56	9.17	8.90–9.45	8.42	8.18–8.65	8.22	8.03–8.42
11	8.43	8.31–8.56	9.86	9.60–10.12	9.39	9.16–9.62	8.61	8.41–8.81
12	9.98	9.87–10.08	10.23	9.99–10.48	10.22	10.00–10.44	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