CI = 1.32–2.46), and having a higher ADL dependency was associated with the underuse of acetylcholinesterase inhibitors in those with dementia (low ADL function: OR = 0.13, 95% CI = 0.06–0.28). In older people with dementia or diabetes mellitus, those with heart failure were less likely to be prescribed acetylcholinesterase inhibitors (OR = 0.22, 95% CI = 0.05–0.94) and hypoglycemics (OR = 0.30, 95% CI = 0.10–0.94). In older people with dementia or depression, those with a history of CVD were less likely to be prescribed acetylcholinesterase inhibitors (OR = 0.67, 95% CI = 0.49–0.93) and antidepressants (OR = 0.48, 95% CI = 0.23–0.97). The presence of dementia was associated with the underuse of antithrombotic agents and hypoglycemic drugs in older people with a history of CVD (OR = 0.67, 95% CI, 0.49–0.93) and those with diabetes mellitus (OR = 0.48, 95% CI = 0.25–0.91).

Multivariable analysis showed that the oldest age group received fewer antithrombotic agents (OR = 0.53, 95% CI = 0.32–0.90), acetylcholinesterase inhibitors (OR = 0.21, 95% CI = 0.06–0.71), and antidepressants (OR = 0.33, 95% CI = 0.12–0.91) among older people with a history of CVD and those diagnosed with dementia and with depressive symptoms, respectively (Table 4). When a separate analysis was conducted of the participants with a history of stroke and those with a history of coronary heart disease, the oldest age group was less likely to be prescribed antithrombotic agents in subjects with a history of coronary heart disease (OR = 0.29, 95% CI = 0.09–0.91) but not with stroke (OR = 0.66, 95% CI = 0.37–1.19). Analysis also showed that women with a history of CVD were less likely than men with CVD to be prescribed antithrombotic agents (male: OR = 1.57, 95% CI = 1.08–2.30) and that having a low ADL function was associated with the underprescription of acetylcholinesterase inhibitors (low ADL function: OR = 0.07, 95% CI = 0.02–0.26) in older people with dementia. In older people with hypertension or diabetes mellitus, none of the factors studied were associated with the underprescription of antihypertensive or hypoglycemic drugs, respectively. In older people with depressive symptoms, those with a history of CVD were less likely to be prescribed antidepressants (OR = 0.45, 95% CI = 0.21–0.97).

DISCUSSION

In the present study, the presence of various chronic diseases, including congestive heart failure, coronary heart disease, and diabetes mellitus, was demonstrated to influence multiple medication use in community-dwelling frail older people. In contrast, participants with dementia were less likely to be prescribed multiple medications. Whether doctors prescribe differently for patients with cognitive impairment is a controversial issue. Some studies have shown that fewer drugs are prescribed for patients with dementia than for those without,[12,13] but other studies have demonstrated no significant difference between patients with and without dementia in the average number of medications prescribed.[14,15] Nevertheless, it is more important to know the influence of the presence of cognitive impairment on the use of beneficial medication for specific chronic diseases than that on the total number of prescribed medications. This study also showed, using a multivariate logistic regression model controlling for other confounding factors, that the oldest age group ($\geq$85) is less likely to be prescribed multiple medications. It is possible that these oldest patients do not see their primary care physician, even if they have chronic diseases or conditions, but this was found not to be true, because the number of visits they made to their primary physician per month was not a predictor of underuse of medication for chronic diseases and conditions (data not shown). These results prove the hypothesis that the rate of multiple medication use is lower in the oldest community-dwelling frail older people ($\geq$85) than in the younger old.

Previous studies have showed that nursing home residents aged 85 and older are less likely to be treated than those aged 65 to 74 for stroke secondary prevention[16] and that there is a marked underuse of aspirin in the treatment of older patients with documented prior myocardial infarction at the time of admission to a nursing home.[17] In agreement with these studies based at the nursing home, the present study targeting community-dwelling older people demonstrated that the oldest subjects with a history of CVD were less likely to be prescribed antithrombotic agents for secondary prevention. Nevertheless, when a separate analysis was conducted of the participants with a history of stroke and those with a history of coronary heart disease, older age was still a predictor of nonuse of antithrombotic agents in subjects with a history of coronary heart disease but not with stroke. In the present survey, hemorrhagic and ischemic stroke were not differentiated between in the stroke diagnosis. Although ischemic strokes account for 85% of all strokes of persons aged 65 and older according to the Japanese national survey, it is possible the inclusion of hemorrhagic stroke affected the analysis.

In the present study, the oldest group univariate and multivariate analyses indicated underuse of acetylcholinesterase inhibitors by older people with dementia. It is possible that a higher proportion of the oldest elderly might have a severe form of Alzheimer's disease and therefore not be eligible for treatment with acetylcholinesterase inhibitors. Few published studies on the use of antidepressants have focused on the older population, even though the prevalence of depression is high in community-dwelling elderly persons. In the present study, 57.2% of the participants had a GDS-15 score of 6 or higher, although only 2% of the subjects were diagnosed with depression in primary care settings, consistent with reports from other countries that the majority of older people with depression are not diagnosed in primary care.[18,19] Alternatively, potentially effective antidepressant medications are also used inadequately in older populations. According to the data from a national survey in Canada, the rate of antidepressant use was 3.1% in older people in the community. Of those who were depressed, 4.2% were taking an antidepressant.[20] In the current survey, only 5.9% of subjects who had depressive symptoms received antidepressants, and univariate analysis showed that the oldest old with depression were less likely to use antidepressants than those who were younger. The multivariate analysis confirmed this association.

Only several reports on the rate of drug treatment for diabetes mellitus in older people have been found. One cross-sectional study demonstrated that the likelihood of drug treatment for people with diabetes with insulin or oral

hypoglycemics declined substantially with increasing age.[21] In the present study, the use of hypoglycemic agents by older people diagnosed with diabetes mellitus was the lowest in the oldest persons, and in comparison with persons aged 65 to 74, the OR of hypoglycemic use in the oldest old was 0.53 using multivariable logistic regression analysis, although the *P*-value did not reach statistical significance ($P = .23$).

In this population of frail older people living at home, the nonuse of antihypertensive medication was relatively low in older people with hypertension, and no difference in the ratio of the prescription of antihypertensive drugs between age categories was found. Furthermore, no association was detected between the nonuse of antihypertensive medication and any factors tested, not only in the univariate analysis but also in the multivariate analysis. This is in contrast to previous studies showing that older people were likely to be undertreated for hypertension.[22,23]

It has been suggested that ADL impairment, cognitive impairment, and comorbid conditions are factors influencing the underprescription of beneficial agents in older people associated with chronic diseases: the underuse of antithrombotic agents by stroke patients with severe cognitive or physical impairment,[16,24] hypoglycemic agents underuse by older people with diabetes mellitus with higher levels of comorbidity,[21] and the underuse of antihypertensive medication by older people with cognitive impairment or comorbidity.[22,23] Nevertheless, in the current study, even after controlling for ADL dependency and the presence of dementia, age was still a significant predictor of the nonuse of antithrombotic agents by older people with a history of CVD, acetylcholinesterase inhibitors by older people with dementia, and antidepressants by older people with depression. In addition, the present study suggests that the influence of ADL dependency, cognitive impairment, and comorbid conditions on the underuse of beneficial medications was also dependent on each chronic disease/condition. The lowest category of ADL function was only associated with the nonuse of acetylcholinesterase inhibitors by the demented elderly using multivariable logistic regression analysis. The presence of dementia was associated with the nonuse of antithrombotic agents by the participants with a history of CVD in univariate analysis, but multivariate analysis did not confirm this association. Furthermore, no association was detected between the nonuse of antihypertensive medication and the presence of dementia in univariate and multivariate analysis. It is possible that, to avoid the risk of adverse drug reactions, physicians decide not to use beneficial medications for the oldest old, although multiple medication use may not always be a disadvantage for older people with comorbid conditions when drugs with proven efficacy in elderly patients are available. These results suggest again that it is not easy to predict the underuse of prescribed beneficial medication in older persons but is instead complex and dependent on each chronic disease/condition. The history of CVD was associated with the nonuse of acetylcholinesterase inhibitors by older people with dementia using univariate and multivariate logistic regression analysis. It is possible that the origin of dementia for most of them might be vascular.

There are many factors that contribute to the underuse of beneficial medications in the oldest old. The use of age as an indicator of benefit of care is imprecise, in that elderly persons differ appreciably in physical, mental, and cognitive status and in life expectancy. It is of concern that the very population that receives the most medications may not always have a favorable risk/benefit ratio. Physicians may decide not to use a medication, because patients may not benefit from treatment (e.g., the low use of acetylcholinesterase inhibitors by demented older people with the lowest ADL function). In fact, geriatric therapeutics must also take into account specific geriatric diseases (e.g., dementia, CVD) and syndromes (e.g., falls, gait and balance disturbances, incontinence, ADL impairment). As proposed by others,[25] the lack of high-quality evidence derived from clinical studies with relevance to treating older patients with multiple chronic medical conditions may be one of the factors that contribute to the underuse of beneficial medications in the oldest old. In fact, clinical evidence often does not provide a definitive answer on the benefits or risks of many drug therapies in older people, especially in those aged 75 and older.[26] Of a number of chronic diseases common in older people, the evidence for drug therapy has been accumulating in the field of hypertension faster than with other diseases. This may be one of the reasons that the highest prescription rate is for antihypertensive medication and the reason there is no restriction of treatment in the oldest patients.

A recent study indicated that the cost of prescription drugs is another problem contributing to the undertreatment of diseases in older people.[27] These cost-related problems seem to be dependent on health insurance systems, which vary between countries. In Japan, universal mandatory health insurance, which covers nearly all regular health care, including prescription drugs, covers the entire population. Elderly health insurance for people aged 75 and older or aged 65 and older with some impairments covers health care, including prescription drugs, with a 10% copayment. Therefore, it is unlikely that cost problems influenced these results or that their influence, if any, was great.

The major limitation of this study was that diagnoses of chronic diseases were based solely on information available in the care-managing centers' records, which were based on the data provided by primary care physicians every 6 months. The accuracy of the diagnosis of chronic diseases by these physicians was not evaluated. It was also not discovered how severe these chronic conditions, which included dementia, diabetes mellitus, and hypertension, were. The results may not be representative of frail older Japanese in the community as a whole, because the subjects in this study represented an urban population. In addition, these findings may not be generalizable to other populations given that health practices, ethnic attitudes about treating very old people, and cost/access to medications may influence these results. Because of the small numbers of participants with each chronic condition, these observations cannot be commented on conclusively. The findings of this study need to be reproduced in a larger sample of practices.

In summary, it was demonstrated that, among community-dwelling frail older people, the rate of multiple medication use is lower in the oldest persons than in the younger ones. In addition, the underuse of beneficial medication for the oldest persons in this group was observed: antithrombotic agents by subjects with a history of CVD,

acetylcholinesterase inhibitors by subjects with dementia, and antidepressants by subjects with depression. Nevertheless, the oldest persons with diabetes mellitus and hypertension were not associated with the underuse of hypoglycemic and antihypertensive agents, respectively. Thus, the underuse of prescribing medication for chronic diseases/conditions of frail older people living in the community is common but not for all conditions.

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ORIGINAL ARTICLE

Lack of correlation between total lymphocyte count and nutritional status in the elderly

Masafumi Kuzuya*, Shigeru Kanda, Teruhiko Koike, Yusuke Suzuki, Akihisa Iguchi

Department of Geriatrics, Graduate School of Medicine, Nagoya University, 65 Tusruma-cho, Showa-ku, Nagoya 466-8550, Japan

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KEYWORDS
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Summary *Background & aims*: Malnutrition is a widespread but largely unrecognized problem in aged people. Although absolute total lymphocyte count (TLC) has been proposed as a useful indicator of nutritional status, there is little evidence that low TLC levels reflect malnutrition in the elderly. To examine whether TLC is a suitable marker of malnutrition in the elderly.

Methods: A total of 161 elderly subjects (44 males and 117 females, mean age±SD: 77.9±7.4; range: 65–95 years) were enrolled from geriatric clinical settings. The participants were categorized according to severely low, low, or normal TLC. Anthropometry measurements, serum albumin, total cholesterol levels, and total score on the mini-nutritional assessment (MNA) were determined.

Results: There were no significant differences among the three TLC groups with regard to anthropometry measurements, serum albumin, total cholesterol levels, or MNA score. There was a significant negative correlation of TLC with age, but not with other nutritional markers. The clinical nutritional screening tool, MNA score, was well correlated with all of the nutritional parameters used in the present study except for TLC.

Conclusion: TLC is not a suitable marker of malnutrition in the elderly.

Introduction

Malnutrition is a common finding in the elderly, not only in institutionalized populations but also in community-dwelling elderly, with prevalence rates ranging from 12% to 85%.[1,2] Malnutrition is associated with increased hospitalizations, increased susceptibility to infection, decreased wound healing, reduced quality-of-life, and increased mortality in the elderly.[3,4] However, it remains difficult to define malnutrition for the elderly precisely. Therefore, malnutrition is

*Corresponding author. Tel.: +81 52 744 2364; fax: +81 52 744 2371.
E-mail address: kuzuya@med.Nagoya-u.ac.jp (M. Kuzuya).

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often unrecognized and subsequently goes untreated.

Anthropometry measurements such as body mass index (BMI), mid-arm circumference (MAC), calf circumference (CC), and skin fold thickness are generally considered as the single most easily obtainable, inexpensive, and noninvasive method by which to assess nutritional state. Biochemical measurements such as serum albumin and total cholesterol are also well known as markers for the protein energy malnutrition (PEM), and are the most commonly used laboratory tests.[5,6]

Multidimensional screening tools for nutritional assessments in the clinical situation have been developed. Among those, the mini-nutritional assessment (MNA) is a simple clinical scale for the evaluation of the nutritional status of frail elderly subjects.[7,8] It has been validated in various countries by comparing its results with a clinical assessment performed by expert geriatric nutritionists.

Total lymphocyte count (TLC) has been also proposed as a useful indicator of nutritional status and outcome. It has been proposed that TLC decreases with progressive malnutrition and correlates with morbidity and mortality in hospitalized patients.[5,6] It has also been proposed that regardless of age, a decrease in TLC to less than 1500/mm^3 or less than 900/mm^3 reflects malnutrition or severe malnutrition, respectively.[5,6] Although TLC is one of the most commonly obtained nutritional markers, there is little evidence that low TLC levels reflect malnutrition in the elderly, and it remains uncertain whether TLC can be used as a marker of malnutrition in elderly subjects.

In the present study, we evaluated the relationship of TLC with other nutritional markers including MNA score, anthropometry measurements, serum albumin, and total cholesterol levels as an indicator of nutritional status in the Japanese elderly.

Methods

Subjects

We enrolled 235 elderly subjects (67 males and 168 females, mean age $\pm$SD: 78.6$\pm$7.6; range: 65–95 years) from our geriatric outpatient clinic ($n = 69$), a nursing home ($n = 56$), geriatric hospitals ($n = 72$), and home care patients ($n = 38$). All participants provided written informed consent. Subjects diagnosed with infection, inflammation, liver disorders, kidney disorders, cancer, or bone marrow proliferative disorders were not included in the 235 participants. The analysis on TLC described herein was limited to the 161 (44 male and 117 female) participants (mean$\pm$SD: 77.9$\pm$7.4 years; range: 65–95 years) whose TLC measurements were obtained, since some participants did not approve blood sampling for TLC measurement.

Anthropometric measurements and biochemical markers

BMI is defined as weight in kilograms divided by height in meters squared. Triceps skinfold (TSF) was measured with Harpenden callipers over the triceps muscle at the midway point between the acromion and the olecranon process. MAC and CC were measured on the left arm and calf with a tape measure. Three repeat measurements were taken to the nearest 0.5 mm, with the mean taken as the true value. All anthropometric measurements were taken at least twice by two different investigators, and the reported values are the means of the repeated measurements. Blood samples were collected after an overnight fast. Serum albumin and total cholesterol levels were determined using automated analysers. Blood was collected into tubes containing EDTA, and TLC was measured with use of a Coulter counter.

Definition of malnutrition

A BMI of less than 20 is widely accepted to indicate that the subject is underweight, particularly in well-developed countries, and 18.5 is recommended as a practical lower limit for most populations.[9] Therefore, a diagnosis of malnutrition was made when BMI was less than 18.5 kg/m^2. Serum albumin and total cholesterol levels were used as the biochemical markers of undernutrition: levels less than 3.5 g/dl of albumin or 150 mg/dl of total cholesterol were taken to indicate malnutrition. Participants were categorized into three groups according to lymphocyte count, as follows: severely low lymphocyte ($<$900 count/mm^3), low lymphocyte (900–1499 count/mm^3), and normal lymphocyte count ($\geqslant$1500 count/mm^3). The relationship of each group to various respective nutritional markers has been examined. In addition, participants were classified according to the cutoff of each nutritional parameter and comparisons were made among groups in terms of anthropometric markers, nutritional proteins, and MNA score.

MNA, a comprehensive, noninvasive, well-validated screening tool for malnutrition in elderly persons, has been also used as an indicator of

malnutrition. The MNA includes 18 items, including the anthropometrical measurements BMI, MAC, and CC, weight loss, a global assessment (six questions related to lifestyle, medication, and mobility), a dietary questionnaire (eight questions related to the number of meals, types of food, and fluid intake), and a subjective assessment (self-perception of health and nutrition). The MNA assigns points on nutritional adequacy with a maximum score of 30 points.[7] The MNA score distinguishes between elderly patients with adequate nutrition (scores of 24 and up), protein-calorie undernutrition (lower than 17), and risk of malnutrition (between 17 and 23.5).[7]

Statistical analysis

Differences between groups (TLC: <900, 900–1499, ⩾1500) were determined by one-way analysis of variance, Chi-square test or the Kruskal–Wallis test, as appropriate. The Kolmogorov–Smirnov test was used to check the normal distribution of variables. Chi-square test, Mann–Whitney *U* test, or Student's unpaired *t*-test was used to test differences between normal and malnutrished groups, as appropriate. Partial rank correlation coefficients adjusted for age were used to measure the relationships between TLC and variables, or between MNA score and variables. The significance level was set at 0.05. Data evaluation was carried out using the SPSS software package (SPSS Inc., Chicago, USA).

Results

Table 1 shows the mean results of variables, which are expressed according to the classification of lymphocyte count (< 900, 900–1499, ⩾1500). There were significant differences between classes with regard to MAC, but there was no trend toward greater MAC values in the group with 900–1499 TLC compared to those in the <900 TLC group. No significant differences were observed between classes in terms of age, BMI, TSF, CC, serum albumin, total cholesterol, or MNA score. There was a weak but statistically significant negative correlation between lymphocyte count and age ($r = -0.21$, $P = 0.0006$). There were no correlations between TLC and any other nutritional indices.

When levels of less than 18.5 kg/m^2 of BMI, 3.5 g/dl of albumin or 150 mg/dl total cholesterol, and 17 points on MNA score were taken to indicate malnutrition, the relationship among these parameters and anthropometric measurements were examined (Table 2). The groups with <18.5 kg/m^2 of BMI, <3.5 g/dl of serum albumin, <150 mg/dl of total cholesterol, and <17 of MNA score had significantly lower values than those of the well-nourished groups with respect to most of the nutrition-related variables except for lymphocyte count.

The score on MNA, a commonly used comprehensive malnutrition screening for the elderly, was correlated with BMI, MAC, TSF, CC, serum albumin, and total cholesterol levels ($r = 0.52$, 0.36, 0.26, 0.28, 0.61, and 0.34, respectively; $P \leqslant 0.0001$

Table 1 Lymphocyte count and nutritional characteristics.

	Lymphocyte (count/mm^3)			*P*-value*
	<900	900–1499	⩾1500	
n	9	51	101	
Men/women	1/8	12/39	31/70	0.343
	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	79.1 (9.8)	79.1 (6.4)	77.2 (7.7)	0.287
BMI (kg/m^2)	21.8 (3.1)	21.2 (3.9)	22.6 (3.7)	0.074
MAC (cm)	25.0 (2.8)	23.6 (3.1)	25.2 (3.2)	0.013
TSF (mm)	10.6 (4.9)	11.4 (8.2)	14.6 (8.6)	0.052
CC (cm)	30.3 (2.2)	31.2 (3.8)	31.5 (4.0)	0.666
Albumin (g/dl)	4.0 (0.4)	4.1 (0.3)	4.1 (0.5)	0.526
Total cholesterol (mg/dl)	186.4 (38.3)	203.8 (33.8)	205.3 (41.3)	0.380
MNA score	20.9 (2.3)	20.6 (4.2)	21.0 (4.1)	0.901

BMI: body mass index; MAC: midarm circumference; TSF: triceps skinfold; CC: calf circumference; MNA: mini-nutritional assessment.

*One-way analysis of variance was conducted except for the gender difference (χ^2-test) and MNA score (Kruskal–Wallis test).

Table 2 Comparison among various nutritional markers.

	BMI (m/kg^2), $n = 235$			Albumin (g/dl), $n = 179$			Total cholesterol (mg/dl), $n = 177$			MNA score, $n = 235$		
	<18.5	⩾18.5	*P*-value*	<3.5	⩾3.5	*P*-value	<150	⩾150	*P*-value	<17	⩾17	*P*-value
Men/women	14/29	53/139	0.549	7/14	41/117	0.473	6/8	41/122	0.150	18/39	49/129	0.514
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
Age (years)	79.9 (7.5)	78.3 (7.5)	0.188	82.1 (7.9)	77.9 (7.3)	0.017	77.6 (8.5)	78.4 (7.4)	0.700	80.2 (8.1)	78.1 (7.3)	0.065
BMI (kg/m^2)	16.4 (1.6)	23.2 (3.3)	<0.0001	19.1 (4.8)	22.1 (3.9)	0.002	19.5 (3.9)	22.0 (4.1)	0.035	19.1 (3.6)	22.8 (3.8)	<0.0001
MAC (cm)	20.3 (2.3)	25.4 (3.0)	<0.0001	22.1 (4.7)	24.7 (3.3)	0.002	22.6 (3.9)	24.5 (3.6)	0.053	21.6 (3.4)	25.2 (3.2)	<0.0001
TSF (mm)	8.18 (6.6)	14.3 (8.4)	<0.0001	7.8 (6.3)	13.8 (8.8)	0.003	7.8 (6.4)	13.5 (8.8)	0.018	8.1 (6.1)	14.4 (8.4)	<0.0001
CC (cm)	28.6 (4.7)	31.5 (3.6)	<0.0001	27.1 (4.4)	31.4 (3.9)	<0.0001	26.0 (3.7)	31.3 (4.0)	<0.0001	28.9 (4.5)	31.6 (3.5)	<0.0001
Albumin (g/dl)	3.7 (0.9)	4.1 (0.4)	<0.0001	3.1 (0.3)	4.2 (0.3)	<0.0001	3.1 (0.5)	4.1 (0.4)	<0.0001	3.6 (0.6)	4.2 (0.3)	<0.0001
Total cholesterol (mg/dl)	187 (44)	204 (38)	0.026	152 (32)	207 (36)	<0.0001	129 (19)	206 (35)	<0.0001	175 (42)	208 (36)	<0.0001
MNA score	15.2 (4.8)	21.3 (3.7)	<0.0001	12.0 (5.1)	21.1 (3.7)	<0.0001	12.1 (4.9)	20.8 (4.3)	<0.0001	13.0 (3.4)	21.9 (2.7)	<0.0001
Lymphocyte (count/mm^3)	1620 (577)	1789 (680)	0.244	1890 (692)	1754 (666)	0.513	2016 (742)	1749 (664)	0.273	1829 (630)	1748 (675)	0.557

*Student's, *t* test was conducted except for the gender difference (χ^2-test) and MNA score (Mann–Whitney *U*-test).

except for TSF ($P = 0.001$)), but not with TLC ($P = 0.524$).

Discussion

Although the TLC is one of the most commonly used markers for assessing nutritional status, so far little evidence exists as to whether TLC reflects the nutritional status of the elderly. In the present study, we concluded that TLC is not a suitable marker of malnutrition in the elderly. This conclusion was based on the observation that no correlation was detected between TLC and other well-known nutritional parameters including anthropometric measurements, biochemical markers, and MNA score, a comprehensive nutritional screen tool for the elderly. In addition, MNA score was correlated with all of the nutritional markers used in the present study except for TLC. This result is consistent with the previous observation of Goodwin JS that no significant correlation was observed between lymphocyte count and blood levels of specific nutrients including serum albumin in the independently living healthy elderly.[10]

It has been shown that the serum albumin and total cholesterol levels, both of which are commonly used as nutritional markers, are sometime discordant with clinical assessments of malnutrition, largely because these biomarkers are influenced by factors such as inflammatory activity, hemoconcentration, and various diseases such as liver cirrhosis and nephritic syndrome. However, in the present study, these biochemical markers for malnutrition were well correlated with anthropometric measurements as well as with MNA score.

There is no general agreement of the effect of aging on TLC. Divergent data have been reported concerning age-related changes in total lymphocyte number.[5,11,12] This may be due to the heterogeneity of the aging immune system. The present study suggested that TLC was correlated with aging in subjects between 65 and 90 years old, indicating that TLC appears to be reflective of age rather than of nutritional status. Our results that TLC is not a suitable marker of malnutrition in the elderly does not indicate that malnutrition is not a risk factor for the impairment of immune function. In fact, nutritional status has long been recognized as a major factor in age-related immune impairment, and a number of studies have already demonstrated that malnutrition is associated with decreased lymphocyte proliferation, reduced cytokine release, and lower antibody response to vaccines.[12,13] In addition, an important modification in T lymphocyte subsets is known to occur in aged people.[14] In fact, it has been demonstrated that a low lymphocyte count is associated with an increased mortality risk in older persons.[15]

There are several limitations to this study. First, the study group might have consisted of elderly who had comorbid diseases, given that they were enrolled from clinical settings. Therefore, our results may apply only to the elderly in ill health. The possibility of an association between TLC and nutritional status in the healthy elderly cannot be excluded. Second, the effect of medication on TLC was not considered in this study, due to the fact that medication data were not available.

In conclusion, we found that TLC is not suitable as a marker of nutritional status in the elderly. TLC appears to be reflective of age rather than of nutritional status.

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Evaluation of Mini-Nutritional Assessment for Japanese frail elderly

Masafumi Kuzuya, M.D., Ph.D.*, Shigeru Kanda, M.D., Ph.D., Teruhiko Koike, M.D., Ph.D., Yusuke Suzuki, M.D., Ph.D., Shosuke Satake, M.D., Ph.D., Akihisa Iguchi, M.D., Ph.D.

Department of Geriatrics, Nagoya University Graduate School of Medicine, Nagoya, Japan

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Abstract

Objective: We evaluated the Mini-Nutritional Assessment (MNA) test and the short-form MNA as screening tools for malnutrition in the Japanese elderly population.

Methods: A cross-sectional study of 226 elderly Japanese patients (78.6 ± 0.5 y of age, mean ± standard deviation; 67 men and 159 women) in various settings was carried out. Nutritional assessment included MNA, anthropometric measurements, and biochemical markers.

Results: According to the original cutoff point of the full MNA, 19.9% of those assessed were malnourished, 58.0% were at risk of malnutrition, and 22.1% were well nourished. Significant correlations were found between full MNA scores and age ($r = -0.14$), body mass index ($r = 0.59$), serum albumin ($r = 0.60$), total cholesterol ($r = 0.36$), midarm circumference ($r = 0.50$), and triceps skinfold ($r = 0.37$). The sensitivity and specificity of the full MNA score (<17) for hypoalbuminemia were 0.810 and 0.860, respectively. With a cutoff point lower than 18, sensitivity and specificity hypoalbuminemia were 0.857 and 0.815, respectively. Using a short-form MNA score 12 and higher as normal, its sensitivity and specificity for predicting undernutrition were 0.859 and 0.840, respectively.

Conclusions: The full and short forms of the MNA were useful tools to identify elderly Japanese patients with malnutrition or risk of malnutrition. However, the full MNA cutoff point for malnutrition should be modulated for this population.

Keywords: Elderly; Malnutrition; Nutritional assessment; Mini-nutritional assessment; Anthropometric measurements

Introduction

Malnutrition is a frequent and serious problem in geriatric patients. Malnutrition in ill elderly subjects is one of the most common and least-heeded problems in hospitals, nursing homes, and home care [1–4]. Different studies have suggested that malnutrition is an important predictor of morbidity and mortality in the elderly [5,6]. In addition, malnutrition has been shown to prolong hospital stays, thereby imposing enormous costs on health services [7,8]. To identify malnourished elderly or subjects at risk of malnutrition, a conventional malnutrition assessment tool is required [9,10]. Anthropometric measurements such as body mass index (BMI), midarm circumference (MAC), calf circumference (CC), and triceps skinfold (TSF) are essential parts of any nutritional assessment. Biochemical measurements including serum albumin and cholesterol are also frequently used as nutritional parameters, although at present there are no generally accepted criteria for the diagnosis of malnutrition in the elderly. The Mini-Nutritional Assessment (MNA) is a simple clinical scale for the evaluation of the nutritional status of frail elderly subjects. It has been validated in Europe and the United States by comparing its results with a clinical assessment performed by expert geriatric nutritionists [11,12]. Although the MNA was developed specifically for frail older people, it has been validated in a healthy older population [11,12].

The MNA has been demonstrated to be useful in predicting long-term mortality for the institutionalized elderly and acute hospital admission for the elderly living at home [6,13–15]. Recently, the MNA short form (MNA-SF) has been devised as the first step of a two-step process (screen-

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* Corresponding author. Tel.: +81-52-744-2364; fax:+81-52-744-2371.

E-mail address: kuzuya@med.nagoya-u.ac.jp (M. Kuzuya).

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ing with the MNA-SF followed by assessment, if needed, by the full MNA) [16]. The MNA has proved to be a simple, noninvasive, well-validated screening tool for malnutrition in elderly persons in Europe and the United States. Despite the fact that Japan has an aging society and ranks first in the world for life expectancy at birth [17], the MNA has not been validated in the Japanese elderly, and whether the MNA and its established cutoff points for the diagnosis of malnutrition and at-risk status are applicable to the Japanese elderly remain unknown.

In the present study we examined whether the MNA can screen and diagnose for malnutrition and risk for malnutrition in the Japanese elderly.

Materials and methods

Subjects

We enrolled 226 elderly (67 men and 159 women; mean age ± standard deviation = 78.6 ± 0.5 y; age range = 65–95 y) from our geriatric outpatient clinic (n = 68), a nursing home (n = 53), geriatric hospitals (n = 72), and home care patients (n = 33). Sixty-eight consecutive outpatients were living at home independently or with mild decline in activities of daily living. Fifty-three residents and 72 inpatients with mild to severe dependency in activities of daily living were randomly chosen from one private nursing home and two geriatric hospitals, respectively. Thirty-three patients living at home and receiving home care services were also eligible for the study. Subjects diagnosed with infection, inflammation, liver disorders, kidney disorders, cancer, or bone marrow proliferative disorders were excluded by physicians. All participants provided written informed consent.

MNA characteristics

The MNA is a two-step procedure: (1) the MNA-SF is used to screen for malnutrition and risk of malnutrition and (2) the full MNA is used to assess nutritional status [16]. The MNA includes 18 items, including anthropometric measurements: BMI, MAC, CC, weight loss, a global assessment (six questions related to lifestyle, medication, and mobility), a dietary questionnaire (eight questions related to number of meals, food, and fluid intake), and a subjective assessment (self-perception of health and nutrition). The MNA-SF comprises 6 of the 18 items. The maximum possible score of the MNA-SF is 14. Scores 12 and above indicate satisfactory nutritional status. A screening score 11 and below suggests possible malnutrition and a need to proceed to the assessment stage of the MNA [16]. The assessment stage has 12 questions, with a maximum possible score of 16 (total = 30 points). The MNA score distinguishes between elderly patients with adequate nutrition (score ≥ 24), protein-calorie undernutrition (score < 17), and risk of malnutrition (score = 17–23.5) [12].

Anthropometric measurements and biochemical markers

BMI is defined as weight in kilograms divided by height in meters squared. A BMI less than 20 kg/m^2 is widely accepted as underweight [18], particularly in well-developed countries, and 18.5 kg/m^2 is recommended as a practical lower limit for most populations [19]. Therefore, the diagnosis of malnutrition was made when BMI was less than 18.5 kg/m^2. TSF was measured with Harpenden calipers over the triceps muscle at the midway point between the acromion and the olecranon process. MAC and CC were measured on the left arm and calf, respectively, with a tape measure. Three measurements were taken to the nearest 0.5 mm, with the mean taken as the true value. All anthropometric measurements were taken at least twice by two different investigators, and the reported values are the means of the repeated measurements (interrater reliability with Pearson's correlation coefficient, r = 0.923, P < 0.0001). Blood samples were collected after an overnight fast. Serum albumin or total cholesterol levels were determined by kinetic immunonephelometry or enzymatically, respectively. Blood was collected into tubes containing ethylene-diaminetetra-acetic acid, and total lymphocyte count was measured with use of a Coulter counter. Serum albumin and total cholesterol levels were used as biochemical markers for undernutrition: levels lower than 3.5 g/dL of albumin or 150 mg/dL of total cholesterol were taken to indicate malnutrition.

Statistical analysis

Differences between groups (MNA total scores <17, 17–23.5, and ≥24) were determined by analysis of variance or the Kruskal-Wallis test, depending on the distribution of the analyzed variable. Partial rank correlation coefficients adjusted for age were used to measure the relations between MNA total score, MNA-SF, anthropometric measurements, and biochemical markers. To identify optimal threshold values for predicting malnutrition, receiver operating characteristic (ROC) curve analysis was performed by computing the sensitivity and specificity of the different tests at various cutoff levels [20]. The area under the ROC curve was also evaluated. A value of 0.5 under the ROC curve indicates that the variable performs no better than chance, whereas a value of 1.0 indicates perfect discrimination. A larger area under the ROC curve represents a greater reliability and discrimination of the scoring system [21]. Cutoff values can be set depending on the purpose for which the scales are used. For screening purposes, a high sensitivity and a high negative predictive value are required, whereas diagnosis requires a high specificity and a high positive predictive value. Sensitivity, specificity, positive predictive value, and negative predictive value for predicting malnu-

Table 1
MNA score, anthropometric measurements, and clinical chemistry in Japanese elderly

	MNA total score			
	<17	17–23.5	≥24	Analysis of variance (*P*)
n	45	131	50	
Men/women	16/29	40/91	11/39	0.220*
Age (y)†	80.2 (8.0)	78.5 (7.4)	76.9 (7.3)	0.157
BMI (kg/m^2)†	18.5 (3.2)	22.2 (3.8)	24.6 (3.0)	<0.0001
MAC (cm)†	21.6 (3.4)	24.8 (3.2)	26.2 (2.8)	<0.0001
TSF (mm)†	8.1 (6.2)	13.9 (8.2)	15.9 (9.1)	<0.0001
CC (cm)†	27.5 (4.7)	31.2 (3.1)	32.0 (3.3)	<0.0001
Albumin (g/dL)†	3.6 (0.6)	4.1 (0.3)	4.4 (0.3)	<0.0001
Total cholesterol (mg/dL)†	174.0 (42.5)	203.3 (35.4)	217.5 (35.1)	<0.0001
Lymphocyte (/μL)†	1825.0 (641.1)	1750.5 (725.5)	1744.1 (560.6)	0.805

BMI, body mass index; CC, calf circumference; MAC, midarm circumference; MNA, Mini-Nutritional Assessment; TSF, triceps skinfold
* Kruskal-Wallis test.
† Mean (standard deviation).

trition based on the various nutritional markers were also calculated for different cutoff points. The best Youden index (sensitivity + specificity −1) was used to determine the best cutoff point [22]. The Youden index is used to compare the proportion of cases correctly classified. The higher the Youden index, the more accurate the prediction (higher true positive and true negative and fewer false positive and false negative) at the cutoff point. The Kolmogorov-Smirnov test was used to check the normal distribution of variables. The statistical significance level was set at 0.05. Data evaluation was carried out with SPSS software (SPSS Inc., Chicago, IL, USA).

Results

Subjects' average age was 77.8 ± 13.8 y (mean ± standard deviation). MNA total scores averaged 20.2 ± 4.6 and ranged from a minimum of 4.0 to a maximum of 27.5, with a median at 21.0. Table 1 lists the mean results of variables, which are expressed according to the classification of the MNA. According to the original cutoff point of the full MNA, 19.9% (45 of 226) had an MNA score lower than 17, 58.0% (131 of 226) had an MNA score between 17 and 23.5, and 22.1% (50 of 226) had a score of at least 24. There were significant differences between classes with regard to BMI, MAC, TSF, CC, serum albumin, and total cholesterol levels, but not to age ($P = 0.157$) and lymphocyte count ($P = 805$). There was a weak but statistically significant, negative correlation between MNA total score and age (Table 2). There were relations between MNA total score and BMI, MAC, and CC, which are included as anthropometric markers in the MNA. In addition, MNA total score showed good correlation with TSF and serum albumin and total cholesterol, which are not included in the MNA, but no correlation between MNA score and lymphocyte number.

The ROC curves shown in Fig. 1A plot the sensitivity versus 1-specificity for MNA total score in predicting low serum albumin (<3.5 g/dL), total cholesterol (<150 mg/dL), and low BMI (<18.5 kg/m^2) as markers of malnutrition. The area under the ROC curves, which represent the overall accuracy of the MNA total score as a test for malnutrition, was found to be 0.916 (95% confidence interval = 0.846 to 0.985) for albumin ($P < 0.0001$), 0.912 (95% confidence interval = 0.850 to 0.974) for total cholesterol ($P < 0.0001$), and 0.855 (95% confidence interval = 0.801 to 0.908) for BMI ($P < 0.0001$), indicating that the MNA test is relatively accurate. The sensitivity, specificity, Youden index, positive predictive value, and negative predictive value of the MNA total score at the selected threshold MNA score are presented in Table 3. Based on biochemical markers (serum albumin or total cholesterol) or BMI as the indicator of malnutrition, the sensitivity and

Table 2
Correlation between MNA total or MNA-SF score and nutritional parameters in Japanese elderly

	No. of subjects	Correlation with MNA total score*		Correlation with MNA-SF score*	
		r	*P*	*r*	*P*
Age	234	−0.14	0.036†	−0.16	0.012†
BMI	233	0.59	<0.0001	0.57	<0.0001
MAC	227	0.50	<0.0001	0.33	<0.0001
TSF	225	0.37	<0.0001	0.24	0.003
CC	225	0.28	<0.0001	0.31	<0.0001
Albumin	179	0.60	<0.0001	0.56	<0.0001
Total cholesterol	177	0.36	<0.0001	0.30	<0.0001
Lymphocyte	161	0.01	0.930	0.04	0.96
MNA total score	226			0.88	<0.0001

BMI, body mass index; CC, calf circumference; MAC, midarm circumference; MNA, Mini-Nutritional Assessment; MNA-SF, Mini-Nutritional Assessment, Short Form; TSF, triceps skinfold
* Partial rank correlation coefficients adjusted for age were used to measure the association between MNA or MNA-SF score and nutritional parameters except for age.
† Spearman's rank correlation.

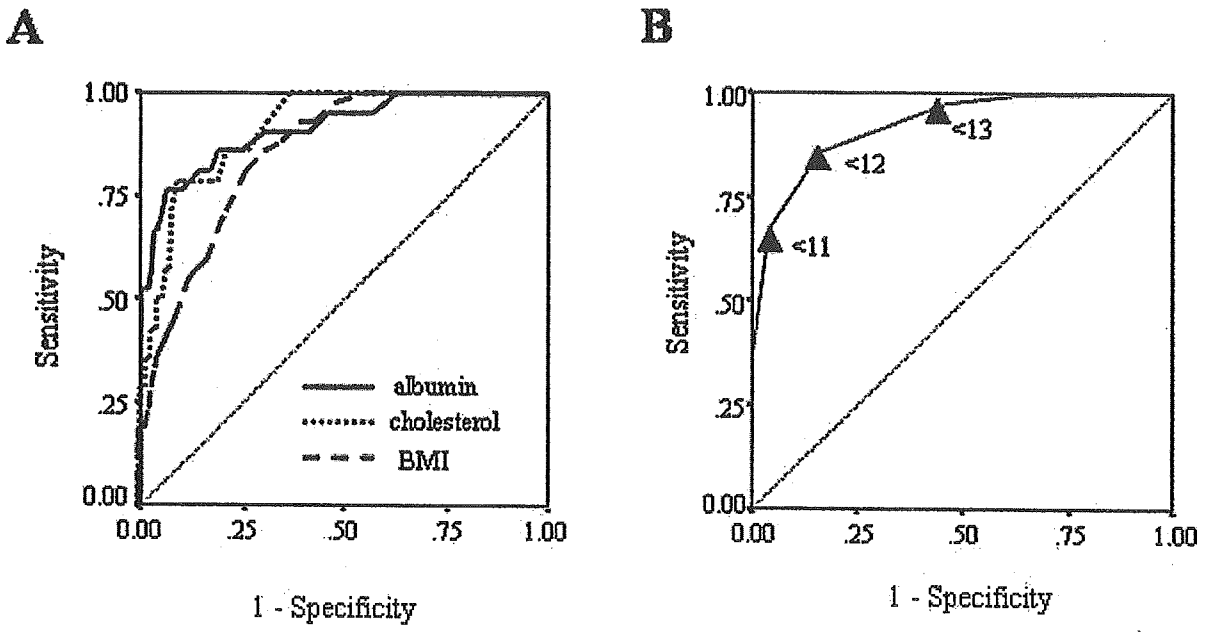

Fig. 1. Receiver operating characteristics (ROC) curve for the (A) full Mini-Nutritional Assessment (MNA) and (B) the MNA short form (MNA-SF) in the Japanese elderly. (A) ROC for MNA as a predictor of albumin levels lower than 3.5 g/dL, total cholesterol levels lower than 150 mg/dL, or BMI lower than 18.5 kg/m^2. (B) ROC for MNA-SF as a predictor of an MNA score below 24. BMI, body mass index.

specificity of the MNA total score were 0.810 and 0.860 for albumin, 0.786 and 0.822 for total cholesterol, and 0.558 and 0.839 for BMI, respectively, with a cutoff point lower than 17 indicating malnutrition. This suggests that 19% of elderly persons with hypoalbuminemia would be missed (sensitivity), and that 14% without hypoalbuminemia would be classified as malnourished (specificity).

Maximal discrimination between malnutrition and risk of malnutrition is by definition reached at the cutoff point that has the highest Youden index (sensitivity + specificity −1). As presented in Table 3, a cutoff point below 15.5 has the highest Youden index, based on hypoalbuminemia and hypocholesterolemia. With a cutoff point below 15.5, the sensitivity and specificity for hypoalbuminemia (<3.5 g/dL) were 0.762 and 0.936, respectively. The figures for hypocholesterolemia and low BMI (<18.5 kg/m^2) showed a

Table 3
Validity values of the MNA total score for malnutritional markers in Japanese elderly

	Threshold for MNA total score							
	<15	<15.5	<16	<16.5	<17	<17.5	<18	<18.5
Albumin (<3.5 g/dL)								
Sensitivity	0.714	0.762	0.762	0.762	0.810	0.810	0.857	0.857
Specificity	0.949	0.936	0.924	0.904	0.860	0.834	0.815	0.777
YI	0.663	0.698	0.686	0.666	0.670	0.644	0.672	0.634
PPV	0.625	0.593	0.552	0.500	0.425	0.386	0.375	0.333
NPV	0.943	0.967	0.967	0.966	0.971	0.970	0.977	0.976
Total cholesterol (<150 mg/dL)								
Sensitivity	0.714	0.786	0.786	0.786	0.786	0.786	0.857	0.857
Specificity	0.914	0.902	0.890	0.871	0.822	0.804	0.785	0.748
YI	0.628	0.688	0.676	0.657	0.608	0.590	0.642	0.605
PPV	0.417	0.407	0.379	0.344	0.275	0.256	0.255	0.226
NPV	0.974	0.980	0.980	0.979	0.978	0.978	0.985	0.984
BMI (<18.5 kg/m^2)								
Sensitivity	0.395	0.419	0.442	0.465	0.558	0.581	0.605	0.674
Specificity	0.902	0.891	0.881	0.870	0.839	0.824	0.798	0.772
YI	0.297	0.310	0.323	0.335	0.397	0.405	0.403	0.446
PPV	0.472	0.462	0.452	0.444	0.436	0.424	0.400	0.397
NPV	0.870	0.873	0.876	0.880	0.895	0.898	0.901	0.914

BMI, body mass index; MNA, Mini-Nutritional Assessment; NPV, negative predictive value; PPV, positive predictive value; YI, Youden index

similar pattern when 15.5 rather than 17 was used as the threshold MNA score; the sensitivities were unchanged or decreased and the specificities increased. With a cutoff point below 18, the sensitivity and specificity for hypoalbuminemia were 0.857 and 0.815, respectively; in this case, the sensitivity of the MNA total score increased but the specificity decreased, as did the positive predictive value.

MNA-SF scores averaged 9.8 ± 0.2 and ranged from a minimum of 1 to a maximum of 14. Although MNA-SF contains only BMI as an anthropometric marker, Table 2 presents the significant correlations between MNA-SF score and age, BMI, MAC, CC, TSF, serum albumin, total cholesterol, or MNA total score. However, the higher degree of correlation existed between these nutritional markers and MNA total score. According to MNA criteria (≥24) used to define "well nourished," only 22.1% of subjects were assessed as such. Thus, 77.9% were malnourished or at risk of malnutrition. The correlation between MNA-SF and MNA total scores was high ($r = 0.88$, $P < 0.0001$). The sensitivity, specificity, Youden index, and positive and negative predictive values for different cutoff points for MNA-SF are presented in Table 4. For MNA-SF, the optimal cutoff point was lower than 12 (sensitivity = 0.861, specificity = 0.840, and Youden index = 0.701). This point can be also determined visually from the ROC curve (Fig. 1B).

Discussion

In the present study, the MNA was validated in the Japanese elderly. We demonstrated that the MNA total score showed a good correlation with anthropometric markers and biochemical markers including serum albumin and total cholesterol. The full MNA contains anthropometric indices including BMI, MAC, and CC. To date, no ethnic-specific anthropometric targets exist; rather, these targets are derived from populations of United States or European origin and are inappropriately applied to men and women of Asian descent. Ethnicity has been recognized as a significant modifier in anthropometric measurements [23]. In addition, MNA contains dietary patterns that may differ across ethnicities [24]. Therefore, the MNA or cutoff point for malnutrition may not be a good fit for the Asian, including Japanese, elderly.

Table 4
Validity values of the MNA-SF score for the risk of malnutrition

	Threshold for MNA-SF score				
	<9	<10	<11	<12	<13
Sensitivity	0.385	0.529	0.679	0.861	0.973
Specificity	1.000	0.980	0.960	0.840	0.540
YI	0.385	0.509	0.639	0.701	0.513
PPV	1.000	0.990	0.984	0.953	0.888
NPV	0.303	0.358	0.444	0.618	0.844

MNA-SF, Mini-Nutritional Assessment, Short Form; NPV, negative predictive value; PPV, positive predictive value; YI, Youden index

Several investigators have dealt with the problem of establishing nutritional parameters for the elderly. In the present study we used anthropometric measurements including BMI, MAC, TSF, and CC and biochemical markers such as serum albumin and total cholesterol as nutritional parameters. Although there are no currently, generally accepted criteria for the diagnosis of malnutrition, these parameters have been widely used to evaluate nutritional status. It should be noted that in the present study cutoff points below 3.5 g/dL for serum albumin and below 150 mg/dL for total cholesterol were considered as undernutrition markers. With aging there may be a small decrease in serum albumin [10]. Total cholesterol levels increase with age in healthy individuals and reach a peak between sixth and ninth decades, only to decrease afterward [10]. The cutoff points used in this study for undernutrition markers are widely accepted even in the elderly [10].

We also showed that the MNA is accurate, based on observation of the ROC curve. These results suggested that the MNA is a useful tool to assess the nutritional status of the Japanese elderly. In the elderly populations in Europe and the United States, an MNA total score cutoff point below 17 as an indicator of protein-calorie undernutrition was found to have a sensitivity of 96%, specificity of 98%, and positive predictive value of 97% [11]. However, the same cutoff point yielded a much lower sensitivity and specificity among the Japanese elderly.

For screening purposes, a malnutrition cutoff point below 18 appears to be better than one below 17 for the Japanese elderly, even though higher cutoff points were associated with lower predictive values. However, if MNA is used as a diagnostic tool, a cutoff point below 15.5 is the best for detecting malnutrition in the Japanese elderly because diagnosis requires a high specificity and a high positive predictive value. MNA is a screening tool mainly for malnutrition. MNA results must be confirmed by other anthropometric, biochemical, and dietary parameters to have a complete nutritional status evaluation and malnutrition diagnosis. Therefore, sensitivity is much more important than specificity, and a cutoff point below 18 appears to be more accurate for the Japanese elderly.

We also demonstrated that there were significant correlations between the MNA-SF score and nutritional parameters in addition to the full MNA score, although these correlations were somewhat stronger in MNA total score than in MNA-SF. When a full MNA score of at least 24 was considered the cutoff point for "normal nutrition" in the Japanese elderly, the optimal MNA-SF cutoff point was at least 12, a finding identical to that in the original report [16]. These results suggest that MNA-SF, which comprises six items, allows a quick screening to determine malnutrition and risk of malnutrition in the Japanese elderly. It has been demonstrated that an MNA score between 17 and 23.5, corresponding to "at risk of malnutrition," can identify older persons with mild malnutrition [25]. In addition, subjects "at risk of malnutrition" had higher mortality rates than did

subjects with a higher MNA score (≥24, corresponding to "normal nutrition") [13], suggesting that the identification of the elderly "at risk of malnutrition" is very important for clinical practice. It should be noted that, because the present study was a cross-sectional study, the threshold score between "normal nutrition" and "at risk of malnutrition" could not be determined. The category of "at risk of malnutrition" should be defined by longitudinal observation. In addition, the study group might have consisted of frail Japanese elderly who had comorbid diseases, given that they were enrolled from clinical settings. Therefore, it is hard to consider this sample representative of the elderly Japanese population, and our results may apply only to the elderly in ill health.

We believe this is the first study to examine whether the MNA is useful in identifying undernutrition in a non-Caucasian elderly population. However, because the MNA is used mainly as a screening tool for malnutrition among the Japanese elderly, the MNA total cutoff point shifts to a higher point, namely below 18. Further studies are required to evaluate the cutoff point for the "at risk of malnutrition" group. In addition, further investigation should be conducted to determine whether the MNA can correctly identify those elderly who are likely to benefit from nutritional support.

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Original Article

High Morning Home Blood Pressure Is Associated with a Loss of Functional Independence in the Community-Dwelling Elderly Aged 75 Years or Older

Masanori NISHINAGA, Jun TAKATA, Kiyohito OKUMIYA*,
Kozo MATSUBAYASHI**, Toshio OZAWA***, and Yoshinori DOI

To elucidate the relationship between home systolic blood pressure (SBP) and functional impairment in the elderly 75 years or older, 461 community-dwelling subjects (192 men, 269 women, mean age: 80 years) were studied. Home blood pressure was measured twice in the morning and twice in the evening for 5 consecutive days with an automatic cuff-oscillometric device. Total/high-density lipoprotein cholesterol and several functional assessments were evaluated. A subject was determined to exhibit a loss of independence according to the activities of daily living (ADL) score in a study conducted in 2001. Based on the mean home SBPs (mSBP) and morning–evening SBP differences (dSBP), the subjects were classified into 4 groups as follows: hypertensive/morning-dominant (HM; mSBP≥135 mmHg, dSBP≥15 mmHg), hypertensive/sustained (HS; mSBP≥135 mmHg, dSBP<15 mmHg), normotensive/morning-dominant (NM; mSBP<135 mmHg, dSBP≥15 mmHg), and normotensive/controlled (NC; mSBP<135 mmHg, dSBP<15 mmHg). There were no differences in sex, cholesterol levels, history of stroke, other cardiovascular diseases (CVDs), and cognitive function, but there were significant differences in age, antihypertensive medications, the neurobehavioral test scores, and ADL scores. There were no significant differences in terms of mortality and CVD events. In the survivors, HM and HS were independent risk factors for a loss of independence, after adjustments were made for onset of stroke, age, antihypertensive therapy, history of CVD, as well as neurobehavioral test scores and ADL scores (odds ratio [OR]: 12.2 and 3.78, respectively). After the same adjustments as those mentioned above were made, HM and HS were found to be negative determinants of survival and maintenance of independence (OR: 0.082, 0.270, respectively). In conclusion, high home SBP (≥135 mmHg) and high dSBP (≥15 mmHg) were found to be important in determining the levels of disability for the very elderly. (*Hypertens Res* 2005; 28: 657–663)

***Key Words*: home blood pressure, elderly, morning hypertension, independence, successful aging**

Introduction

Recently there have been rapid increases in both the population and life span of the elderly in developed countries, which has resulted in a considerable increase in the number of frail elderly people. "The project to reduce the number of dependent elderly persons" has been promoted as an important

From the Department of Medicine and Geriatrics, Kochi Medical School, Kochi, Japan; *Research Institute for Humanity and Nature, Kyoto, Japan; **South-East Asia Research Center, Kyoto University, Kyoto, Japan; and ***Tokyo Metropolitan Geriatric Hospital, Tokyo, Japan.
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Address for Reprints: Masanori Nishinaga, M.D., Ph D., Department of Medicine and Geriatrics, Kochi Medical School, Kohasu, Oko-cho, Nankoku 783–8505, Japan. E-mail: nishinam@med.kochi-u.ac.jp
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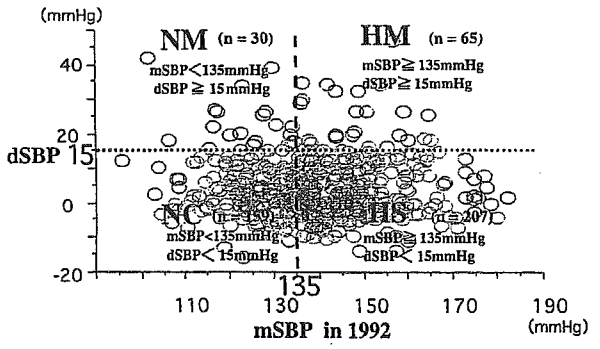

Fig. 1. *Classification of four groups according to the distribution of mean home SBP (mSBP) and morning–evening home SBP differences (dSBP). HM, hypertensive/morning-dominant; HS, hypertensive/sustained; NM, normotensive/morning-dominant; NC, normotensive/controlled.*

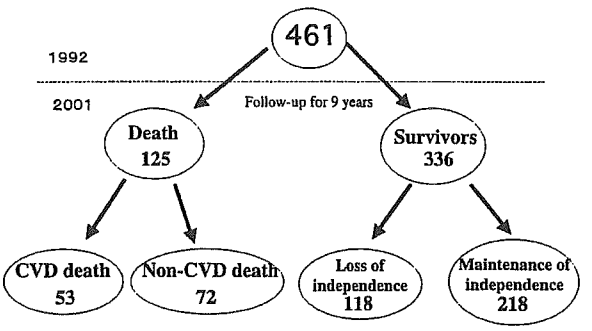

Fig. 2. *Outcome after a 9-year follow-up period. CVD, cardiovascular disease, including stroke.*

issue not only from the medical, but also from the socioeconomic point of view. This project should be considered a top priority, and appropriate measures should be taken to improve the current situation (*1*). Although stroke is a major cause of mortality and disability in the elderly (*2–4*), the management of hypertension in the community has contributed to an outstanding reduction in the incidence of stroke (*5, 6*).

In many previous epidemiological studies on blood pressure (BP) in the elderly, the mortality and morbidity associated with stroke and other cardiovascular diseases (CVDs) have been selected as the endpoint (*7–9*). There have been also several epidemiological studies of the relationship between hypertension and dementia (*10, 11*). However, assessments of functional abilities, the most important factor for elderly persons and their caregivers, have been rarely conducted.

Improving the management of BP for the prevention of stroke and other CVDs has led to the popularization of home BP monitoring devices among the general public (*12, 13*). However, there have been few reports concerning home BP values in the elderly. Increased BP in the morning is considered as a strong risk factor for stroke and other CVDs (*14–17*). It remains to be clarified whether such an elevation in BP in the morning is also a risk factor for a loss of functional independence in the elderly.

In the present study, we recruited community-dwelling elderly people 75 years of age or older, and conducted medical and functional assessments. We followed the subjects for 9 years. The purpose of our study was to clarify the relationship between home BP values and functional disabilities, as well as that between home BP and the mortality/incidence of stroke. Furthermore, we studied morning–evening home BP differences in this very elderly sample.

Methods

Subjects

The study subjects were elderly people, aged 75 years or older, who resided in Kahoku Town, Kochi Prefecture, Japan in 1992. All subjects applied to participate in the home BP monitoring program. Subjects with atrial fibrillation were excluded because of the potential inaccuracy of their home BP measurements. A total of 461 people were recruited as the subjects of our study (192 men, 269 women, mean age: 81 years).

Home BP Measurement

Home BP was measured in 1992 with an automatic device (HEM-755C; OMRON Life Science Co., Ltd., Kyoto, Japan) based on the cuff-oscillometric method. The validity of BP measurement according to this method has been reported in several studies (*18–20*). The subjects and their caregivers were taught by community nurses how to measure the BP at home using this device. According to a previously reported method (*21*), BP was measured in the non-dominant arm after taking at least a 5-min rest in a sitting position, twice in the morning (6–7 AM) and twice in the evening (8–9 PM), for 5 consecutive weekdays.

We obtained the data regarding the total mean systolic BP (mSBP), morning and evening systolic BP (SBP), morning and evening diastolic BP (DBP) and pulse rates (PR). The mean morning–evening SBP differences (dSBP) were calculated. We defined subjects with mSBP≥135 mmHg as hypertensive or poorly controlled subjects, according to the Japanese Society of Hypertension (JSH) Guidelines for the Self-Monitoring of Blood Pressure at Home (*12*). We also divided our subjects into two groups by using mean+1SD of the dSBP. There were no subjects whose mean DBP values alone exceeded 85 mmHg.

Table 1. Basic Characteristics (1992)

	NC (n=159)	NM (n=30)	HS (n=207)	HM (n=65)
Age (years)*	80.3±4.5	81.5±5.1	80.5±5.1	81.4±5.3
Men (n [%])	74 (46.5)	13 (43.3)	79 (38.1)	26 (40.0)
SBP (mmHg)**	125±8	124±8	148±11	150±10
DBP (mmHg)**	72±7	73±9	80±11	81±9
PR(/min)*	68±8	67±7	69±8	68±12
Morning SBP (mmHg)**	126±9	135±9	149±12	162±11
Evening SBP (mmHg)**	123±9	113±9	148±12	138±11
Total cholesterol (mg/dl)	190±35	210±39	186±38	195±42
HDL cholesterol (mg/dl)	48±14	56±10	45±13	44±12
ADL (full score: 21)	20.4±1.9	20.8±0.8	20.2±2.6	20.2±1.9
MMSE (full score: 30)	27.2±4.4	28.4±2.2	27.3±3.2	27.5±3.2
Up and Go test (s)	13.0±3.2	13.0±2.8	14.1±4.6	14.9±5.4
Antihypertensive drugs** (Yes, n [%])	38 (23.9)	10 (33.3)	89 (43.0)	40 (61.5)
History of CVD (Yes, n [%])	16 (10.0)	1 (3.3)	13 (6.3)	4 (8.1)

NC, normotensive/controlled; NM, normotensive/morning-dominant; HS, hypertensive/sustained; HM, hypertensive/morning-dominant; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; HDL, high-density lipoprotein; ADL, activities of daily living; MMSE, mini-mental state examination; CVD, cardiovascular disease, including stroke. *ANOVA, $p<0.05$, **ANOVA, $p<0.01$.

Annual Self-Administered Questionnaire

In the baseline survey (1992), the self-administered questionnaire was addressed to the study subjects to obtain information about characteristics potentially related to their BP, mortality, and disability; the data collected included a history of stroke, heart disease, and bone disease or arthropathy, antihypertensive medications, current and past cigarette smoking, current intake of alcohol, and activities of daily living (ADL). All of the response sheets submitted by the subjects were reviewed by community nurses to ascertain their information.

Assessment of ADL, Cognitive Function, Neurobehavioral Function, Mood and Serum Lipid Analysis

The questionnaire regarding the ADL was conducted in 1992 and 2001 in the same manner as was used in our previous study (*22*). Briefly, ADL were assessed with respect to the following seven items: walking, ascending and descending stairs, feeding, dressing, using the toilet, bathing, and grooming. Each ADL item was scored on a 0–3 scale: 0 = completely dependent, 1 = needs a lot of help, 2 = needs some help, and 3 = completely independent. The scores for these seven items were summarized to obtain a total ADL score ranging from 0 to 21. When a subject did not maintain a score of 21 or 20 points in 2001, he or she was defined as a person that was losing independence.

The mini-mental state examination (MMSE) was used to evaluate each subject's level of cognitive functioning (*23*). The Up and Go test was used to evaluate neurobehavioral function (*24*). This latter test measures, in s, the time it takes the subject to stand up from an armchair, walk a distance of 3 m, walk back to the chair, and sit down again. This simple test is a comprehensive evaluation of the subject's balance, gait speed, and functional ability. Since Okumiya and co-workers (*25*) reported its usefulness in predicting a decline in ADL in the Japanese community-dwelling elderly, the test has been widely accepted for this purpose in many fields. The Geriatric Depression Scale 15 (GDS 15) was also used to evaluate the mood of the subjects (depressive state) (*26*). Total serum cholesterol and serum high-density lipoprotein (HDL) cholesterol were analyzed in 1992.

During the period between 1992 and 2001, a total of 125 subjects (66 men, 59 women) died. In addition, the information regarding the events of stroke, myocardial infarction, congestive heart failure, and bone/joint diseases as causes of disability were collected by checking the responses provided on the annual questionnaire and the subjects' medical records.

Written informed consent was obtained from each subject at the time of the annual questionnaire. Our study was approved by the Research Ethics Committee of Kochi Medical School, Kochi University, Japan.

Statistical Analysis

All of the values were expressed as mean±SD. Mean values among the groups were compared using ANOVA. A χ^2 test was used to compare the 4 groups with respect to total mortality and incidence of stroke, as well as other CVDs. A logistic multivariate analysis was used to identify the factors that predicted a loss of functional independence or the survival and maintenance of functional independence 9 years after the initial assessment, using Stat View 5.0 for Windows (SAS Institute Inc., Cary, USA).

Table 2. Total/CVD Death and Non-Fatal Stroke

	NC (n=159)	NM (n=30)	HS (n=207)	HM (n=65)
Total death (%)*	36 (22.6)	3 (10.0)	62 (30.0)	24 (36.9)
Non-fatal stroke(%)	16 (10.1)	1 (3.3)	12 (5.8)	4 (6.2)
CVD death (%)	17 (10.7)	1 (3.3)	24 (11.6)	11 (16.9)
CVD events (%)	33 (20.8)	2 (6.7)	36 (17.4)	15 (23.1)

NC, normotensive/controlled; NM, normotensive/morning-dominant; HS, hypertensive/sustained; HM, hypertensive/morning-dominant; CVD, cardiovascular disease, including stroke. *ANOVA $p<0.1$.

Results

The distribution of mSBP and dSBP are shown in Fig. 1. The subjects were classified into the following 4 groups:

Hypertensive/morning-dominant (HM: mSBP≥135 mmHg, dSBP≥15 mmHg; n=65), hypertensive/sustained (HS: mSBP≥135 mmHg, dSBP<15 mmHg; n=207), normotensive/morning-dominant (NM: mSBP<135 mmHg, dSBP≥15 mmHg; n=30), and normotensive controlled (NC: mSBP<135 mmHg, dSBP<15 mmHg; n=159). The NC group, which was expected to be the lowest risk group because both the mSBP and the dSBP were lower than others, was used for reference.

A total of 461 elderly subjects, who were 75 years of age or older in 1992, were followed for 9 years until 2001 (Fig. 2). During that interval, 125 (27%) subjects died; 53 of these subjects had died of stroke and other CVDs. A total of 336 of the subjects were alive 9 years later (2001). One hundred-eighteen subjects had undergone a loss of their functional independence (HM, 17 [41%]; HS, 65 [45%]; NM, 7 [26%]; NC, 29 [24%]).

The basic characteristics of the 4 groups in 1992 are shown in Table 1. The subjects in the NC group were younger than those in the other 3 groups. The percentage of subjects who were taking antihypertensive agents was also the lowest in the NC group. There were no significant differences in terms of sex, PR, total serum cholesterol, HDL cholesterol, the scores of ADL, MMSE, the Up and Go test, or history of CVD among the 4 groups. There were also no differences in the scores on the GDS 15, history of bone/joint diseases, current and past cigarette smoking, and current intake of alcohol (data not shown).

Table 2 shows the total number of deaths, the number and percentage of deaths caused by stroke and other CVDs, and the incidence of non-fatal stroke during the 9-year follow-up period in the 4 groups. Although there was a difference in the total number of deaths among the 4 groups before adjustment for age, the significance of this difference disappeared after adjustment for age. There were no significant differences in the percentage of deaths from stroke or other CVDs. Although 33 subjects suffered from symptomatic strokes, no significant differences were seen in the incidence of strokes among the 4 groups.

The risk factors for loss of functional independence are shown in Table 3. Although a non-fatal event of stroke was one of the most important risk factors for loss of functional independence, HM and HS were also important risk factors, even after adjustment for age, sex, antihypertensive therapy, scores on the Up and Go test in 1992, and the ADL scores in 1992. The adjusted odds ratio (OR) of the HM group (12.2) was significantly higher than that of the HS group (3.78). Therefore, values of mSBP≥135 mmHg and dSBP≥15 mmHg were independent risk factors for a loss of functional independence (Fig. 3).

The factors associated with successful aging that contributed to the survival and maintenance of functional independence, even among the most elderly (age of 84 or older), are shown in Table 4. Although the non-fatal event of stroke was a significantly negative determinant, the HM and HS also remained as significant independent negative determinants of successful aging, after adjustment for age, sex, antihypertensive therapy, scores on the Up and Go test in 1992, and ADL scores in 1992.

As regards the elderly people aged 75 years or older living in the community, values of mSBP≥135 mmHg and dSBP≥15 mmHg were independent determinants of a loss of functional independence or successful aging, even when non-fatal stroke and these home SBP variables were simultaneously incorporated into a logistic multivariate analysis model.

In addition, since many of our subjects with morning hypertension had high home SBP, we added dSBP (≥15 mmHg) to the same model of multivariate logistic analysis, in order to elucidate whether dSBP was an independent determinant of a loss of functional independence or alive and independence. dSBP remained a significant determinant of a loss of independence (adjusted OR: 3.84, 95% confidence interval [CI]: 1.003–14.73), or alive and independence (adjusted OR: 0.46, 95% CI: 0.183–0.973), in our hypertensive subjects.

Discussion

Our prospective longitudinal study evaluating the maintenance of independence in the elderly aged 75 years or older demonstrated that a mean home SBP of ≥135 mmHg was a significantly important risk factor for a loss of functional independence. In addition, morning hypertension was an

Table 3. Independent Risk Factors for Loss of Independence in 336 Survivors

Factors	Adjusted odds ratio	95% CI	*p*
Stroke	17.4	3.67–82.8	0.0003
HM	12.2	3.00–50.0	0.0005
HS	3.78	1.45–9.83	0.0064
Age	1.17	1.05–1.30	0.0036

Data were adjusted for sex, antihypertensive therapy, Up and Go score, and activities of daily living (ADL) score in 1992. CI, confidence interval; HM, hypertensive/morning-dominant; HS, hypertensive/sustained.

Table 4. Independent Negative Factors for Survival and Maintenance of Independence (n=461)

Factors	Adjusted odds ratio	95% CI	*p*
Stroke	0.058	0.012–0.273	0.0003
HM	0.082	0.020–0.334	0.0005
HS	0.271	0.104–0.704	0.0073
Age	0.855	0.768–0.951	0.0038

Data were adjusted for sex, antihypertensive therapy, Up and Go score, and activities of daily living (ADL) score in 1992. CI, confidence interval; HM, hypertensive/morning-dominant; HS, hypertensive/sustained.

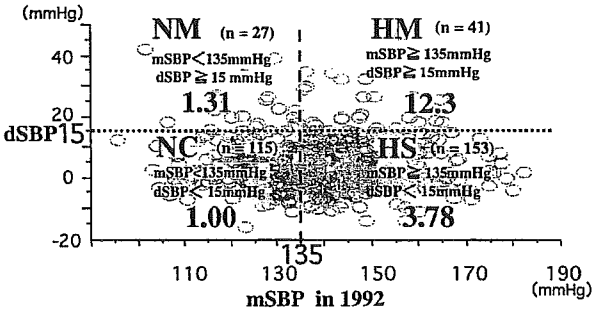

Fig. 3. *Adjusted odds ratios for loss of independence among the 4 groups. The abbreviations are the same as those introduced in Fig. 1.*

important independent predictor for the functional prognosis of our elderly subjects. The significance of dSBP should be further evaluated.

There were no differences in mortality and incidence of non-fatal stroke among the 4 groups. However, when a loss of functional independence was selected as the endpoint, significant differences were found among these groups. Home BP monitoring in the morning and in the evening was useful in predicting functional prognosis in elderly subjects aged 75 years or older.

Recent large clinical trials have clarified the importance of BP control, even among the elderly (*7–9*). However, the optimum home BP value for the elderly has not been established, and further prospective studies on the elderly will be necessary to define an adequate home BP value (*27*).

In the present study, there was no significant difference in the incidence of CVD death, stroke, and other CVD events among the 4 groups. Although the reason for this result is uncertain, further studies with a larger number of subjects may resolve this ambiguity.

Since a relationship between elevation of BP in the morning and stroke and other CVD events (*14–17*) has been reported, the importance of morning BP has been emphasized in studies of home BP monitoring (*28, 29*). However, in most of these studies the mortality and morbidity of stroke and other CVDs, as well as organ damage, were selected as the endpoints. Functional independence, which is important for the elderly as well as for the social economy, is not mentioned in these previous studies. Thus, in our present study, we added a loss of functional independence and successful aging as two new endpoints for geriatric study. Furthermore, we evaluated morning–evening home BP differences in terms of the usefulness of this information for the prognosis of the elderly aged 75 years or older.

Skoog *et al.* (*30*) reported the relationship between the presence of hypertension at the age of 70 and the development of dementia 10 to 15 years later. In subsequent large studies including SCOPE (*10*), the association between impaired cognitive function and BP values has been evaluated, although sufficient data on the relationship between BP control and cognitive function have yet to be accumulated. In our previous study (*31*), a J-curve phenomenon was demonstrated with respect to the profile of the association between BP values and cognitive function 3 years later in an elderly sample. Those findings indicate that BP exerted an effect on cognitive function, not only in the group with high BP, but also in the group with low BP. In our previous study, casual BP was measured twice with the subject in the supine position at the time of physical examination. Here, to avoid the inclusion of various other factors affecting BP measurements, we used 20 home BP measurements in order to calculate the mean value. This method of measurement appeared to have eliminated some of the potential problems with BP monitoring.

Because the follow-up period was so long (9 years), it was difficult to reexamine cognitive function in all of the subjects examined in 2001; some subjects were too old for us to obtain reliable data from them (*i.e.*, among those at least aged 84 years of age and older). Due to our small sample size in the MMSE evaluation (n=64, 19%), we did not observe any significant differences between the group with high home BP values (≥135 mmHg) and the group with normal home BP values (<135 mmHg). There were also no significant differences in dSBP (≥15 mmHg). Evaluation of the cognitive functions (MMSE) of the most elderly subjects included in the sample was difficult; thus, an appropriate, reliable method