IgG), anticardiolipin IgM antibodies (aCL IgM), anticardiolipin β_2-glycoprotein I antibodies (aCL β_2-GPI) and/or lupus anticoagulant on at least 2 examinations 6 weeks apart. The presence of aCL IgG and IgM isotypes was measured by a β_2-GPI-dependent enzyme-linked immunosorbent assay (ELISA; Mesacup Cardiolipin Test, Medical and Biological Laboratories Co., Nagoya, Japan). The aCL β_2-GPI titer was also measured by ELISA (aCL β_2-GPI kit, Yamasa, Choshi, Japan). Lupus anticoagulant activity was detected by coagulation assays utilizing activated partial thromboplastin time or kaolin clotting time, adhering to the Sapporo criteria. Forty consecutive aPL-negative stroke patients who were admitted during the same period were enrolled as controls.

We analyzed differences in gender, age, risk factors for stroke, hemostatic markers and radiological findings between the aPL-positive and aPL-negative groups. With regard to risk factors for stroke, prevalences of hypertension, hyperlipidemia and diabetes mellitus were compared between the two groups. We also compared neurological manifestations and associations of coagulopathy, venous thrombosis and systemic lupus erythematosus (SLE) and other collagen vascular diseases between the two groups.

Hemostatic markers examined in plasma were β-thromboglobulin (β-TG), platelet factor 4 (PF4), thrombin-antithrombin III complex (TAT) and D-dimer. β-TG was measured using an Asserachrom β-TG kit (Diagnostica Stago, Asnières, France). PF4 was also measured using an Asserachrom PF4 kit (Diagnostica Stago). TAT was measured using a TAT SRL kit (SRL, Tokyo, Japan), and D-dimer was measured using an Lpia-ace D-dimer kit (Mitsubishi Kagaku Iatron, Tokyo, Japan). These hemostatic markers were quantitated using ELISA.

Hypertension was defined as systolic blood pressure above 140 mm Hg or diastolic blood pressure above 90 mm Hg on admission, or a history of high blood pressure requiring medical treatment. The diagnosis of diabetes mellitus was made if a patient was treated with oral glucose depressants or insulin, or if their glycosylated hemoglobin levels were 6.5% or higher, based on the criteria of the Japan Diabetes Mellitus Society [3]. Hyperlipidemia was defined as an elevated fasting serum total cholesterol level more than 220 mg/dl or a history of hyperlipidemia requiring statin treatment.

In order to evaluate cardiac diseases such as valvular heart disease, arrhythmia and patent foramen ovale, we performed electrocardiography, Holter cardiac monitoring, transthoracic echocardiography and transesophageal echocardiography. Brain MRI was performed in all patients to determine the site and number of cerebral infarctions. Multiple cerebral infarctions were diagnosed when more than 3 infarcts were detected. Patients with more than 50% stenosis in the carotid and/or intracranial major arteries on either MR angiography or carotid duplex ultrasonography were defined as having large-artery lesions.

Differences between the two groups were analyzed using χ^2 tests for nominal variables with 5 or more possible values and Fisher's exact test for nominal variables with fewer than 5 possible values. Student's independent t test was used for comparing continuous variables. We also used the Mann-Whitney test for comparing hemostatic markers because of their skewed distributions. Two-sided p values were calculated, and $p < 0.05$ was chosen for statistical significance. Statistical analysis was performed using the SPSS software package (version 7.5, SPSS Inc., Chicago, Ill., USA).

Table 1. Gender, age and aPL in aPL-positive and -negative groups

	aPL		p value
	positive (n = 40)	negative (n = 40)	
Gender			0.007[1]
Men	12	25	
Women	28	15	
Mean age, years	46.9	66.2	<0.0001[2]
aCL IgG	13	0	
aCL IgM	16	0	
Lupus anticoagulant	14	0	
aCL β_2-GPI	12	0	

[1] χ^2 test.
[2] Student unpaired t test.

Results

Age, Gender and aPL

Age, gender and aPL of the two groups are shown in table 1. Distributions according to gender and age differed significantly between the groups. Stroke patients with aPL were significantly younger (46.9 vs. 66.2 years, $p < 0.0001$) and significantly more likely to be women (70 vs. 37.5%, $p = 0.007$) in comparison with stroke patients in the aPL-negative group.

Stroke Risk Factors

Differences in the prevalence of stroke risk factors between the aPL-positive and aPL-negative patients with acute ischemic stroke are shown in table 2. Diabetes mellitus was less frequent in the aPL-positive group (18%) than in the aPL-negative group (43%; $p = 0.028$). There were no significant differences in the prevalence of hypertension, hyperlipidemia or cardiac disease between the two groups. However, when the prevalence of valvular disease was analyzed separately from other cardiac diseases, its proportion differed significantly between the groups. Thus, in the aPL-positive group 58% of the patients had valvular disease, whereas only 13% of the patients in the aPL-negative group had valvular heart disease ($p = 0.0001$). The mean number of stroke risk factors per patient (other than aPL) differed significantly between the groups. The mean numbers of risk factors in the aPL-positive and aPL-negative groups were 1.0 and 1.65, respectively ($p = 0.007$). It is noteworthy that 20 patients (50%) in the aPL-positive group had

Table 2. Differences in prevalence of risk factors between aPL-positive and -negative patients with cerebral infarction

Risk factor	aPL		p value[1]
	positive (n = 40)	negative (n = 40)	
Hypertension	12 (30)	18 (45)	NS
Hyperlipidemia	6 (15)	12 (30)	NS
Diabetes mellitus	7 (18)	17 (43)	0.028
Heart disease	18/23 (90)	14/40 (35)	0.002
Arrhythmia	10 (43)	12 (30)	NS
Valvular disease	14 (61)	4 (13)	0.0001
Mean number of risk factors	1.00	1.65	0.007[2]

Figures in parentheses are percentages. NS = Not significant.
[1] χ^2 test.
[2] Student's unpaired t test.

Table 3. Differences in clinical features between aPL-positive and -negative patients with cerebral infarction

Clinical feature	aPL		p value[1]
	positive (n = 40)	negative (n = 40)	
Neurological complication[2]	18 (45)	0	0.0001
Hematological disorder[3]	12 (30)	3 (8)	0.022
Venous thrombosis	6 (15)	0	0.034
All collagen vascular diseases	9 (23)	3 (8)	NS
SLE	6 (15)	0	0.034

Figures in parentheses are percentages. NS = Not significant.
[1] χ^2 test.
[2] Includes epilepsy, myelitis and migraine.
[3] Includes protein S and C deficiencies and thrombocytopenia.

no risk factors other than aPL. In contrast, only 3 (7.5%) patients in the aPL-negative group had no stroke risk factors.

Neurological Manifestations

Differences in clinical features between the groups are shown in table 3. Eighteen (45%) patients in the aPL-positive group showed neurological complications other than stroke, such as epilepsy, myelitis or migraine, whereas no patient in the aPL-negative group had any neurological complications ($p < 0.0001$). Coagulopathies, including protein C and/or protein S deficiency and thrombocytopenia, were observed in 30 and 8%, respectively, in the aPL-positive and aPL-negative patients with acute ischemic stroke ($p = 0.022$). Six patients in the aPL-positive group, as opposed to none in the aPL-negative group, suffered from deep vein thrombosis ($p = 0.034$). Considering all collagen vascular diseases together, no significant difference was observed between the groups. However, SLE was present in 6 aPL-positive patients but in none of the aPL-negative patients ($p = 0.034$).

Hemostatic Markers

There was no significant difference in the mean value of β-TG, PF4 or D-dimer between the aPL-positive and aPL-negative groups (table 4). Only the mean value of TAT was significantly lower in the aPL-positive group than in the aPL-negative group (26.5 vs. 38.2 ng/ml, $p = 0.012$).

Table 4. Hemostatic markers (ng/ml) in aPL-positive and -negative patients with cerebral infarction

Markers	aPL		p value[1]
	positive (n = 40)	negative (n = 40)	
β-TG	138.6 ± 107	142.6 ± 125	NS
PF4	63.4 ± 77	61 ± 70	NS
TAT	5.8 ± 15	6.6 ± 6	0.012
D-dimer	53.0 ± 57	65.5 ± 99	NS

Data are shown as means ± 1 standard deviation. NS = Not significant.
[1] Mann-Whitney U test.

Radiological Findings

As shown in table 5, cerebral infarctions in the carotid system were less frequent in the aPL-negative patients as compared to the aPL-positive patients (21 vs. 33, i.e. 52.5 vs. 82.5%, $p = 0.009$). No significant differences were observed between the two groups in the prevalence of cortical and multiple infarcts. Large-artery lesions defined as more than 50% stenosis in the carotid and/or intracranial major arteries on either MR angiography or carotid ultrasonography were detected in 14 (35%) and 34 (85%) of the aPL-positive and aPL-negative patients, respectively ($p = 0.038$).

Table 5. Radiological findings in aPL-positive and -negative patients with cerebral infarction

Radiological finding	aPL		p value[1]
	positive (n = 40)	negative (n = 40)	
Infarction in carotid system	21 (53)	33 (83)	0.009
Infarction in vertebrobasilar system	18 (45)	15 (38)	NS
Cortical infarction	13 (33)	11 (28)	NS
Multiple infarcts	28 (70)	20 (50)	NS
Large-artery lesion[2]	14 (35)	34 (85)	0.038

Figures in parentheses are percentages. NS = Not significant.
[1] χ^2 test.
[2] More than 50% stenosis in the carotid and/or intracranial major arteries on either MR angiography or ultrasonography.

Discussion

aPL are frequently observed in patients with SLE and are associated with an increased risk of thrombosis. aPL are also detected in patients with other collagen vascular diseases, infectious diseases and malignancies. In addition, it has been reported that aPL can be positive even among 1–5% of the normal population [4]. Previous studies have reported that aPL are present in 9.7–29% of stroke patients without any collagen disease [5, 6]. The Antiphospholipid Antibodies in Stroke Study (APASS) Group [7] has shown that the odds ratio for stroke in patients with positive aPL is significantly higher than 1 (2.31) after adjustment for other stroke risk factors, indicating that aPL are an independent risk factor for stroke [8].

It is recognized that APS is a female-predominant disorder that tends to occur in relatively younger patients, and 13–30% of patients with APS develop stroke later [1, 9]. Levine et al. [10] showed that the mean age of patients with aPL-positive stroke was 43 years, and the male:female ratio was 1:2 in 48 patients. The mean age of aPL-positive stroke patients in the present study was 47 years, and 70% of them were women.

Common risk factors for stroke have been reported to be less frequent in aPL-positive than aPL-negative stroke patients [11]. In our study, diabetes mellitus was significantly less common in the aPL-positive than aPL-negative stroke patients. The mean number of risk factors was also significantly lower in the aPL-positive group. Furthermore, 50% of the aPL-positive patients in our study had no other stroke risk factors. Levine et al. [10] speculated that the immunological consequences of aPL might account for the development of stroke in this group of patients. Our results suggest that immune-mediated thrombogenesis arising from aPL increases stroke risk more than common risk factors for atherosclerosis in these patients.

Several mechanisms have been proposed for the development of thrombosis in APS. These mechanisms include fibrinolysis, antithrombin III, prostacyclin generation, platelet aggregability, functional alterations of protein C and complement activation [12, 13]. Furthermore, disruption of the annexin V antithrombotic shield is one of the interesting hypotheses proposed by Rand and Wu [14]. This hypothesis offers the first simultaneous explanation for prolonged coagulation time and thrombophilic tendency. Thus, it has been proposed that some of the above-mentioned mechanisms of thrombogenesis play distinct roles in the pathogenesis of stroke in aPL-positive patients.

The prevalence of cardiac disease, another risk factor for stroke, was significantly different between aPL-positive and aPL-negative stroke patients in the present study. In particular, the prevalence of valvular disease was significantly higher in the aPL-positive group. Vianna et al. [15] showed that 63% of patients with aPL-positive stroke had valvular disease. Khamashta and Hughes [16] showed that 23% of SLE patients had some valvular lesions, and these valvular diseases were strongly correlated with the presence of aCL. These reports suggest that aCL can be a risk factor for valvular heart disease in patients with SLE and APS. The pathogenesis of valvular disease has been hypothesized to involve fibrin thrombi on the valve and its organization leading to fibrosis and dysfunction, as in cases of Libman-Sacks endocarditis [17]. aPL, even without SLE, may play a role in valvular damage by thrombus formation on the endocardium [18].

Atsumi and Koike [19] reported that more than 90% of arterial events were cerebrovascular in APS patients [20]. Ischemic heart disease is rare, but valvular disease is frequent, which correlates with cerebrovascular thromboembolic complications in APS patients. By using transcranial Doppler ultrasound, Rademacher et al. [21] detected microembolic signals in 39% of patients with APS, whereas none were detected in those without APS among SLE patients. They concluded that microembolic signals may be a useful indicator of active APS and that subsequent stroke can be predicted by microembolic signals. Our results, together with these reports, imply that stroke in APS patients is caused not only by in situ im-

mune-mediated mechanisms linked to aPL, but also by cardioembolic mechanisms due to valvular disease. These conditions frequently coexist in aPL-positive patients. Thus, it should be emphasized that careful cardiac examination to detect sources of emboli is crucial for therapeutic decision making.

In the present study, stroke patients in the aPL-positive group had more frequent neurological complications such as epilepsy, myelitis or migraine than those in the aPL-negative group [22, 23]. The association of migraine and APS is controversial, with widely varying results from different series. In this study, 8 stroke patients in the aPL-positive group had migraine, but none in the aPL-negative group. Our results support a relationship between migraine and APS, although the sample size is small and statistical power is weak. Furthermore, one fourth of the aPL-positive patients in this study suffered from deep vein thrombosis, which is very common in patients with APS [24]. Up to half of these patients had pulmonary emboli [25]. Therefore, it is important for physicians to consider APS as a component of the differential diagnosis when patients with stroke present with one or more of the above-mentioned neurological symptoms.

Hematological abnormalities such as protein C and S deficiencies as well as thrombocytopenia were more frequent in our aPL-positive than aPL-negative patients. Some aPL-positive patients have antibody activity against protein C and protein S. Therefore, it is possible that thrombosis due to decreased protein C and protein S antigens, together with immunological mechanisms, might contribute to the development of stroke in patients with APS [26].

As for coagulation markers such as β-TG, PF4 and D-dimer, no significant differences could be seen between the aPL-positive and aPL-negative groups. Because platelet activation is frequently observed in the acute phase of stroke irrespective of aPL, increases in β-TG and PF4 are common in both aPL-positive and aPL-negative patients [27]. Such responses may explain why we found no significant differences in β-TG or PF4 between the groups. In contrast, the mean values of TAT differed between the two groups. TAT in the aPL-positive group was lower than that in the aPL-negative group. Yamazaki et al. [28] reported that there was no elevation of TAT in patients with APS. Ieko [29] speculated that the existence of abundant free thrombin due to inhibition of TAT formation could contribute to thrombosis in APS. Naitoh et al. [30] suggested that inhibition of the formation of TAT is caused mainly by aCL IgG. Shibata et al. [31] reported that aCL IgG antiheparin antibodies inhibit the heparin-accelerated formation of TAT. They concluded that antiheparan sulfate/heparin antibodies may be a cause of vascular thrombosis in APS. These studies support the results in our study. Our results revealed that many patients with aPL-positive stroke do not show any increase in TAT.

Results of previous radiological studies have suggested that stroke patients with APS often have multiple infarcts present in the white matter or basal ganglia, and in cortical or subcortical areas [32–34]. In the present study, neither the number of lesions nor the percentage of cortical infarcts differed significantly between the two groups. One possible explanation is that all patients in the control (aPL-negative) group required hospitalization due to relatively severe infarction compared with patients treated in an outpatient clinic. Specifically, patients in our control group tended to have multiple and/or large cortical infarcts, which might have obscured differences between the two groups. As for the location of infarcts, infarcts in the carotid system were less frequent in the aPL-positive group. This also means that infarcts in the vertebrobasilar system were more common in patients with aPL than in patients without aPL. Five patients in the aPL-positive group showed basilar syndrome that is probably attributable to a cardioembolic mechanism [19, 21]. There are several reports concerning angiographic findings in patients with APS [35, 36]. The APASS Group reported that 36.7% of APS patients had normal angiographic studies and 49.0% showed intracranial arterial lesions on cerebral angiography [9]. In the present study, we evaluated arterial lesions by using MR angiography and carotid duplex ultrasonography. Large arterial lesions were less frequent in the aPL-positive group. It has been suggested that thrombosis in APS is caused partly by oxidized low-density lipoprotein, which accelerates atherosclerosis [37]. However, if the stroke subtype in APS was cardioembolic, it may develop without progression of atherosclerosis in major arteries. In addition, according to the definition of APS, APS-induced stroke has to be stroke without underlying angiitis [2]. Therefore, our results indicate that stroke occurring without obvious arterial lesions is one of the relevant characteristics of APS.

In conclusion, stroke with aPL is associated with several patient characteristics: (1) a higher incidence in females than males and onset at a relatively young age, (2) frequent association with valvular heart disease, (3) less frequent prevalence of the common risk factors for stroke such as hypertension, hyperlipidemia and especially diabetes mellitus, (4) frequent neurological or hematological

complications such as epilepsy, myelitis, migraine, coagulopathy, deep vein thrombosis and thrombocytopenia, (5) less prominent elevation of TAT, (6) preferential involvement of the vertebrobasilar system and (7) less frequent large-artery lesions. The small size and potential bias that could exist in the aPL-positive stroke patients limit this study. Results of the present study should be further confirmed in a future study with a large patient population.

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Carotid Ultrasonographic Appearance of the Rupture of an Unstable Atheromatous Plaque in a Patient with Acute Ischemic Stroke

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Carotid Ultrasonographic Appearance of the Rupture of an Unstable Atheromatous Plaque in a Patient with Acute Ischemic Stroke

Key words: atheromatous plaque, artery-to-artery embolism, carotid artery, ultrasonography

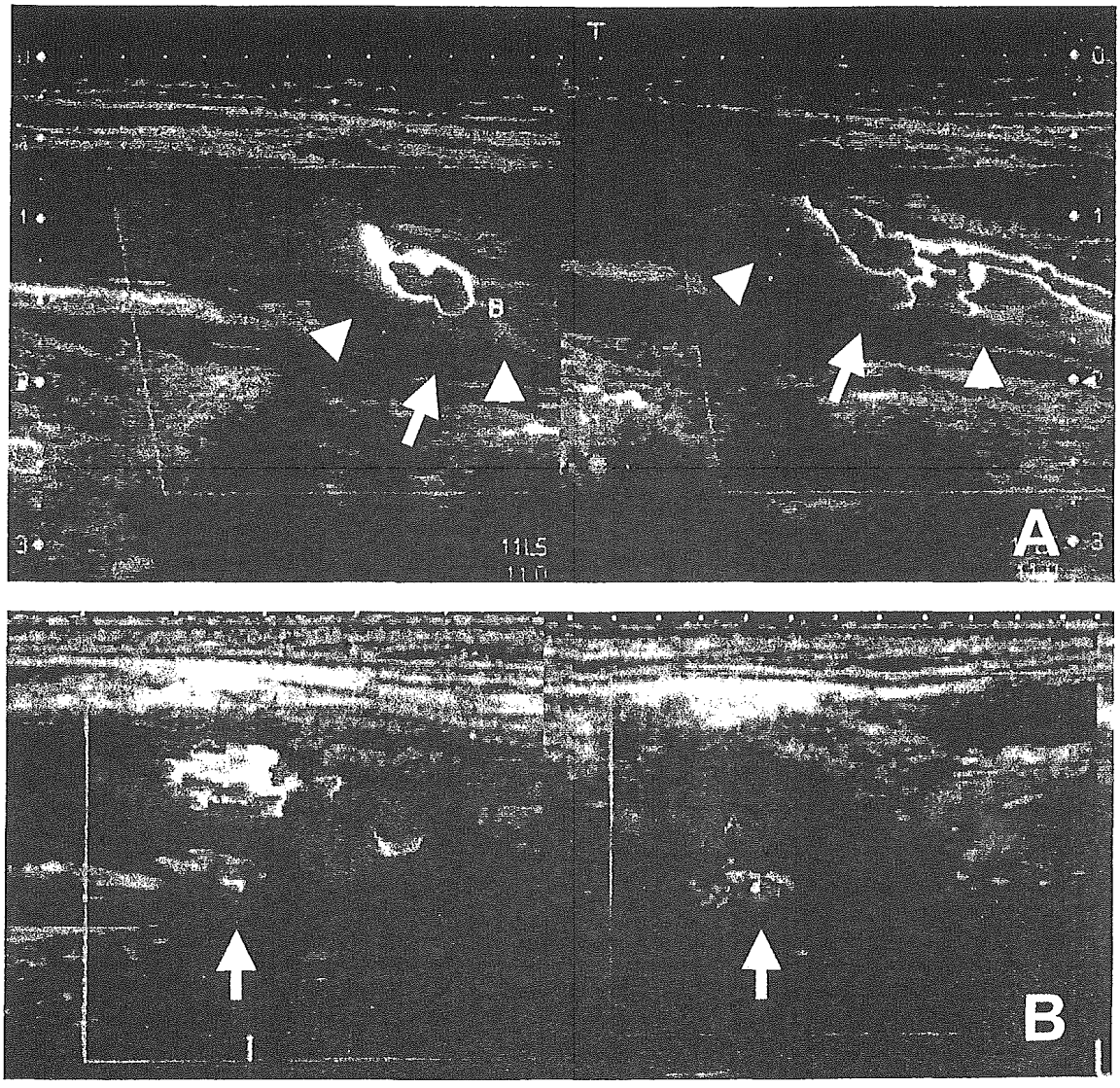

Figure 1. Color duplex flow imaging of the right ICA. A: On admission. A low echo plaque (arrowhead) with giant ulceration (arrow) (longitudinal sections). B: Three weeks later. A hole in the plaque (ulceration) connecting to the flow lumen of the right ICA (yellow arrow) (longitudinal and transversal sections).

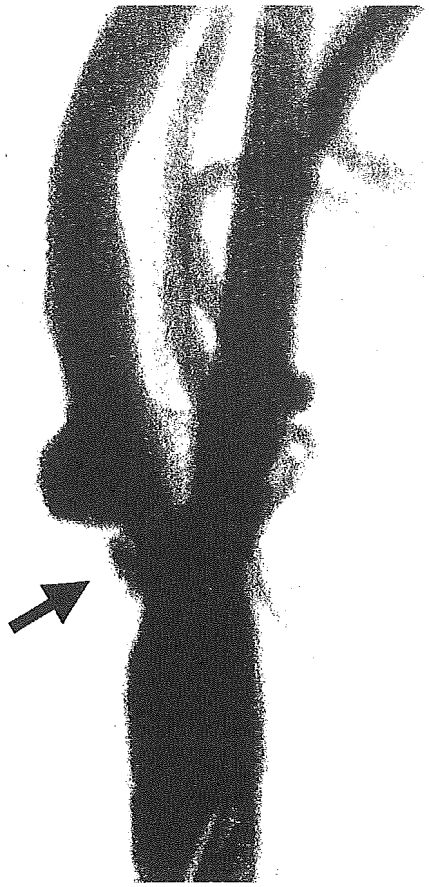

Figure 2. The ulceration with a hole (arrow) was detected by angiography of the right ICA.

A 66-year-old man was admitted because of left hemiparesis and dysarthria. He smoked 20 cigarettes a day for 20 years and did not receive treatment for his hypertension. MRI revealed an infarcted lesion in the territory of the right middle cerebral artery and brain MR angiography was negative. Carotid ultrasonography revealed a giant ulceration with low echo plaque in the right internal carotid artery (ICA). It was suggested that artery-to-artery embolism was attributable to the low echo plaque. He was placed on an anti-platelet agent. Three weeks later, ultrasonography showed a small hole in the low echo plaque and that communicated with the lumen of the right ICA (Fig. 1). Angiography also presented a hole in the plaque of the right ICA (Fig. 2). As we diagnosed that plaque rupture had occurred, carotid endarterectomy was performed. Serial carotid ultrasonographic studies were useful to reveal the rupturing of unstable plaque responsible for the artery-to-artery embolism.

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Model Specification and Testing of Outcome Indicators Used for Assessment of Healthcare Service for Home-Care Neurology Patients

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In order to assess the effectiveness of healthcare services for home-care neurology patients and families, an outcome indicator was developed based on the degree of difficulty in performing daily life activities. Furthermore, using structural equation modeling (SEM) and general linear model, we examined the indicators' construct validity and predictive validity. To test the construct validity of the outcome indicators, we examined whether the second-order factor model was established or not using SEM. The outcome indicators consisted of five sub-indicators: 1) Anxiety about disease and disability indicator, 2) Family care burden and strain indicator, 3) Motor dysfunction indicator, 4) Appearance of symptom indicator, and 5) Interference in social network utilization indicator, resulting in high construct validity. The result of multiple indicators model indicated that all of the indicators influenced the HRQOL (SF-36) two years after baseline survey. The aspect of SF-36 on which outcome indicators have their influences was different for each indicator. Based on whether the scores of outcome indicators were improved or not in two years, the subjects whose degree of difficulty in performing daily living activity increased in the two years showed a remarkable decrease of SF-36 domains relating to role and physical functioning.

Key words: outcome indicator, validity testing, health-related quality of life, quality of home care, neurology patients

Introduction

The growth in home health care services in Japan since the 1990s and the enactment of long-term care insurance (April 2000) have resulted in a large increase in the number of home-care beneficiaries, primarily diagnosed with neurological and cerebrovascular diseases. With the shift of care from public facilities to the home milieu, the critical need to assess the effectiveness of home care services in our society has been underscored. In particular, because neurology patients and their family caregivers have a variety of difficulties performing daily living activities, and suffer from long-term diseases, it is important to assess the effectiveness of the home care services provided to these patients and their families over a long period of time.

In recent years, the quality of services has been an increasing focus in the US health care system. This emphasis has included efforts to quantify and analyze the outcome of care[1)]. For home care, the focus on outcome has resulted in new federal requirements that home health agencies participating in Medicare collect and report patient data using a single core set of measures specified in the outcome assessment and information set (OASIS; Health Care Financing Administration 1999)[2)]. In contrast, only a few studies in Japan have reported on the outcome of home care for the client, and explored an

evaluation method for the effectiveness of home care in practice[3)4)].

Most home care services under Medicare in the US, however, are subject to providing short-term care, because of the strictness of Medicare's eligibility criteria for coverage[5)]; OASIS is, therefore, designed to assess the outcome for the client at 60-day intervals. Although most home care in our society is long-term care and most home-care patients have chronic conditions such as neurological diseases, it is necessary to develop a new instrument for assessing the outcome of care in the long term.

Thus, in order to assess the effectiveness of health care services for home-care neurology patients who are receiving long-term care, and their families, we developed a multi-dimensional outcome indicator based on the degree of difficulty performing daily living activities. Furthermore, using psychometric methods and structural equation modeling (SEM), we examined the indicators' reliability, construct validity and predictive validity.

Subjects and Methods

Procedure of data collection

In the current study, a two-fold postal survey for home-care neurology patients and their families, consisting of a baseline survey and a follow-up survey 2 years later, was carried out. For each survey, we mailed a cover letter and a set of questionnaires, with a postage-paid reply envelope. The cover letter explained the purpose and procedures of the current study and the option to refuse to participate. A document of informed consent was also sent to the individuals, and written consent was obtained. Return of the questionnaire was also considered as consent to participate. In addition, telephone contact was used to instruct individuals who required assistance in responding to the questionnaires. The questionnaires returned were linked with medical records regarding diagnosis and treatment status. Before the actual research was conducted, this survey project was approved by the ethics committee board of Tokyo Women's Medical University.

Sample characteristics

We conducted the baseline survey by mail for patients over 20 years of age, who were discharged from the Neurology Word at a university hospital between April 1995 and March 2000, and their families. As shown in the flowchart (Fig. 1), 504 responses were received, resulting in a participant rate of 49% and the measurement of 463 respondents, excluding the cases of patients whose deaths were confirmed during the survey period and of insufficient response content, were used for analysis. Of the 463 respondents, 54.4% were men with a mean age of 63.4 (range = 20 to 94, SD = 15.3) and 45.6% were women with a mean age of 57.7 (range = 20 to 92, SD = 16.1). When comparing the profiles of the respondent group and non-respondent group from the baseline survey, the ages of the non-respondent group with a mean age of 56.3 (SD = 19.0) at the time of survey were significantly younger than those of the respondent group ($p<0.001$), whereas there was no statistical significance for number of days in the hospital, gender, and the proportion of profiles of each disease group between the respondent and non-respondent groups. The breakdown of diseases for the respondent group was: cerebrovascular diseases, 28.4%; degeneration and demyelinating diseases such as amyotrophic lateral sclerosis, Parkinson's disease, spinocerebellar degeneration and multiple sclerosis, 21.9%; peripheral nerve diseases and myopathy such as polyneuropathy, myositis and severe myasthenia gravis, 19.9%, and others, 29.8%.

Two years after the baseline survey, we conducted a follow-up survey (response rate: 51.6%) on the same subjects who agreed to participate in the survey, and used the data from 201 responses for analysis. Of the 201 subjects, 52.7% were men with a mean age at the baseline survey of 63.2 (range = 21 to 83, SD = 13.8) and 47.3% were women with a mean age of 59.6 (range = 20 to 84, SD = 14.1). There were no statistically significant differences between the 201 respondents and non-respondents on the variables of gender, age, length of hospitalization, and the proportion of profiles of each disease group, whereas the level of physical disability measured by the activities of daily living (ADL) scale was lower in non-respondents compared with respon-

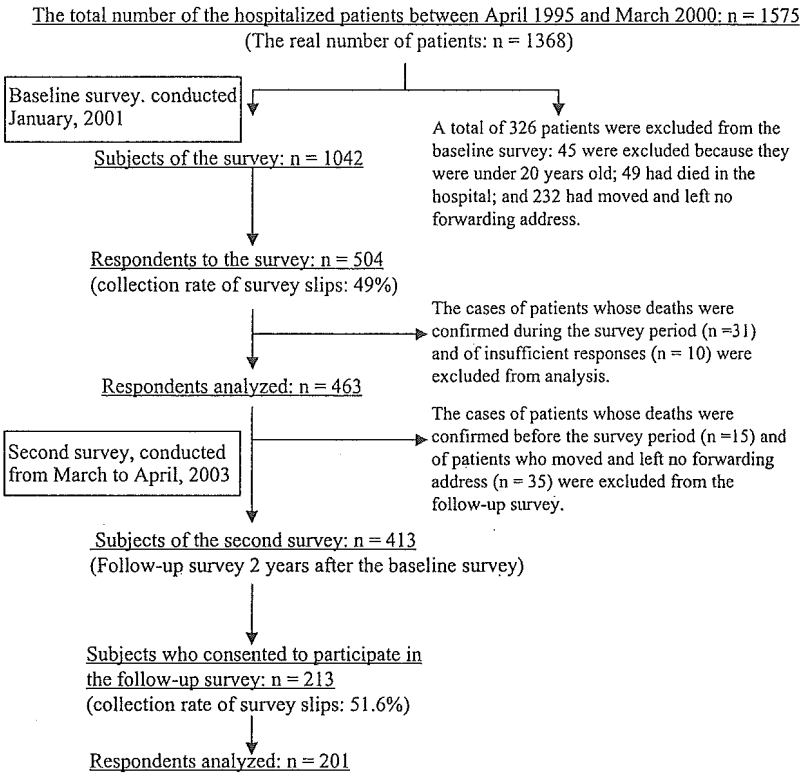

Fig. 1 Flowchart of the baseline and the follow-up surveys

dents ($p = 0.038$).

Outcome indicators for assessing the effectiveness of home care service for neurology patients

1) Definition of outcome indicator

The outcome indicator was defined by three types of outcome, according to Shaughnessy et al[6]: end-result outcome, intermediate-result outcome, and utilization outcome. End-result outcomes refer to changes in functional ability, physiologic condition, symptom distress, and emotional condition. Intermediate-result outcomes reflect a quantified non-functional outcome of care and can be pivotal in attaining certain end-result outcomes (e.g., a dichotomy reflecting change in the extent of family caregiver strain is an intermediate-result outcome). Utilization outcomes are a quantification of the health services that are potentially attributable to home care under consideration.

2) Scale development

We started the formulation of a questionnaire, including items indicating multi-dimensional outcomes, from a hypothetical measurement scale. As the first procedure, we started with the content analysis of qualitative data obtained from our previous study[7], which was related to the problematic events which neurology patients and family members experienced while giving home care. Based on the degree of difficulty in performing daily living activities obtained from these analytical results, and the relevant literature by Kramer[8] which presented a conceptual framework of Medicare quality indicators of home health care for neurological conditions, we created a measurement scale for multi-dimensional outcome indicators consisting of 30 items in total which were designed tentatively to cover five dimensions. The five dimensions for assessing the effectiveness of home care services for neurological patients and their family caregivers are changes in: 1) functional status measured by ADL and instrumental activities of daily living (IADL), 2) health status signs and symptoms, 3) family/caregiver strain, 4) unmet needs, and 5) utilization. The category of satisfaction was not included in the initial items, since global satisfaction

measures tend to be influenced by many factors unrelated to the quality of home health care services[9].

The measurement scale, consisting of 30 items, used a four-point Likert-type response format, scored as: 1 = no problem, 2 = small problems, 3 = considerable problems and 4 = big problems for each item, for the clarity and ease of administration of both patients and their families. It was designed to show a higher degree of difficulty performing daily living activities with higher scores.

Measures

The following measurement scale for ADL was included to assess the functional status of neurology patients. Health-related quality of life (HRQOL) measurement was also included to assess the predictive validity of the newly developed outcome indicators.

1) Measurement of activities of daily living

Independence in ADL was determined by a partially modified Katz's index of independence in ADL developed by Katz[10] to measure the physical ability to function of the study participants. Katz's index is the most widely used of all functional assessment indices in studies determining the condition of ambulatory patients[11]. For the current study, independence was determined in six activities: bathing, dressing, waking, communication, continence, and feeding. Although through a series of questions from the original scale, participants were rated on a 3-point scale of independence for each activity, we revised the scoring system to count the number of activities in which the individual was dependent, measured on a scale of 0 to 6 (0 = independent in all six functions, 6 = dependent in all six functions).

2) Health-related quality of life measurement

HRQOL was assessed using the Medical Outcome Study 36-Item Short Form Health Survey, version 1.2 (SF-36)[12]. The SF-36 is a generic, self-administered survey, which has been widely used for varying chronic conditions, such as neurological diseases. This questionnaire consists of 36 questions, from which eight different domains can be calculated: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). The time frame is given as 'during the past 4 weeks'. Scores of the SF-36 range from 0 to 100, with the maximum score of 100 indicating the best possible health state and 0 indicating the worst health. The reliability and validity of the Japanese version of this scale have been supported by several studies[13][14]. Published sex and age-specific norms of the SF-36 are available from the general population in Japan.

Statistical analysis

All statistical analyses were performed with SAS statistical software package version 8.2[TM 15] and SPSS version 11.5[16] for Windows. In descriptive statistics, frequencies, means, and standard deviations were computed to obtain a sample profile on demographic and disease-related variables. Continuous variables were compared using student's t-test. To compare the categorical data, chi square test with Yates' correction was used. Pearson product-moment correlation coefficient was also used for this analysis. For each statistical analysis, cases with missing values were deleted from relevant analysis. A significance level of 0.05 was used for statistical tests, unless otherwise stated.

1) Internal consistency reliability

The internal consistency reliability of the outcome indicators was determined by calculating Cronbach's alpha coefficient, which provides an indication of the degree of convergence among different items hypothesized to represent a unified construct. Scales with reliabilities of more than 0.70 are recommended for the purpose of comparing groups of patients, whereas a higher reliability criterion of 0.90 is recommended for greater precision in analyzing individual patient scale scores[17].

2) Factorial validity

To analyze the scale structure of the outcome indicators, we used the psychometric method and explanatory factor analysis (EFA) with oblique promax rotation accompanied by the maximum likelihood method. Before EFA, in order to enhance internal consistency, unnecessary items were excluded; items with a manifestation frequency of less than 5% or more than 95% were eliminated from

this analysis. An item of either which showed a correlation coefficient of more than 0.70 between two items was also eliminated. The number of factors in our procedure using EFA was fixed at five according to the initial hypothesis.

3) Construct validity

SEM and maximum likelihood estimation procedures using the CALIS procedure of SAS were employed to examine the construct validity of the outcome indicators. In order to test the construct validity of the outcome indicators, we examined whether the second-order factor model was established or not using SEM. In addition, to test homogeneity of the second-order factor model constituted above, we prepared the six datasets that divided each into two groups according to the three kind of patient's profiles: gender, age-class (under 65 years old/65 years old and over), and disease group (neurological/cerebrovascular). Parameter estimates and values of fit indices for each of the six datasets were computed based on the second-order factor model constituted from SEM. The reason SEM was used is that it is the best model for implementing factor analysis and regression analysis simultaneously, and that it allows investigators to test a prespecified a priori relationship and to determine if a reasonable fit exists between the five factors model and the raw data. SEM also has the ability to incorporate latent variables, which are hypothesized and unobserved concepts that can only be approximated by observed or measured variables, into the analysis[18].

A standardized coefficient was used to estimate causal effects. Standardized coefficients allow comparison of variables with different units of measurement. In the present study, five different fit indices are reported; chi-square likelihood ratio statistic (Chi-square/d. f.), goodness of fit index (GFI), adjusted goodness of fit index (AGFI), root mean square error of approximation (RMSEA) estimate, and the comparative fit index (CFI) were used to estimate overall model fit.

Chi-square likelihood ratio statistic[19] assesses the magnitude of the discrepancy between the sample and fitted covariance matrices. The chi-square statistically tests the lack of fit. A non-significant chi-square is desired because it indicates agreement between the proposed model and the data. That is, there is no significant discrepancy between the sample and the fitted model[20].

GFI indexes the relative amount of observed variance and covariance accounted for by the model[21]. AGFI is goodness of fit index adjusted for degrees of freedom. Both GFI and AGFI range from 0 to 1.00, with the former indicating the absence of model fit and the latter indicating perfect model fit; Values of 0.90 or above usually indicate good model fit.

RMSEA is a measure of the discrepancy between the observed and model implied covariance matrices per degree of freedom, suggesting that values of RMSEA of 0.05 or less indicate good fit, and less than 0.08 indicate an adequate fit[22][23].

CFI ranges from 0 to 1.00, with 0 indicating a poor fit, 1.00 indicates a perfect fit, and is derived from the comparison of a restricted model with a null model (one in which each observed variable represents a factor). CFI also provides a measure of complete covariation in the data, and a value larger than 0.90 indicates a psychometrically acceptable fit to the data[24].

In addition to assessing overall model fit, SEM also permits investigators to assess the degree of variance accounted for in each dependent variable and to determine whether individual path loadings are significantly different from 0. If calculated t values exceed the value of 1.96, then the parameter estimate is statistically significant[25].

4) Predictive validity

The predictive validity of the outcome indicators was tested using the multiple indicators model which is a sub-model of SEM, and the general linear model (GLM)[15]. The multiple indicators model is a regression analysis model explaining the relationship among latent variables as constructs. This model allows the investigators to deal with distinguishing three kinds of measurement errors: those of independent variables, those of dependent variables and the error for describing the causal relation among constructs, whereas the generally used

regression analysis assumes an error term only in the dependent variable. In the present study, two latent variables, those of the outcome indicator and the HRQOL, were used for examining the causal relation between these constructs. The multiple indicators model was constructed, supposing that each indicator of the baseline survey would have its influence on each subject's SF-36 score after two years.

Analysis of covariance (ANCOVA), which is the main technique used in the GLM procedure, was also used to assess the predictive validity; the influences on SF-36 extended by the change in outcome indicators in two years were analyzed. In addition, least squares means (LSM) of SF-36 scores adjusted values for each outcome indicator of the baseline survey were also computed, to remove the influence of confounding variables.

5) Clinical relevancy

To assess the clinical relevancy of the outcome indicators, we examined the relationship between each outcome indicator and the subjects' profiles: gender, age, and ADL. Furthermore, we calculated the rate of patient improvement and stabilization for each outcome indicator for three disease categories, cerebrovascular diseases, demyelinating and degenerative diseases, peripheral nerve disorders and myopathy, based on scores of the changes in outcome indicators in two years. The rates of improvement and stabilization were calculated according to the methodology of the Outcome-Based Quality Improvement System in Medicare[6].

Results

1. The scaling structure in the outcome indicators

Before EFA, five unnecessary items were excluded. Five factors were extracted from the 25 remaining items by EFA using an oblique promax rotation accompanied by the maximum likelihood method (Table 1).

According to our results, the first factor consisted of seven items concerning needs, problems with the progression of the disease/disorder and anxiety, which the present health care system has difficulty covering, and which were interpreted as "anxiety about disease and disability indicator". The second factor consisted of four items concerning the caretaker, and was interpreted as "family care burden and strain indicator". The third factor consisted of five items showing IADL problems centering on movement ability, and was interpreted as "motor dysfunction indicator". The fourth factor consisted of five items concerning ADL problems and complaints of disturbed comfort, and it was interpreted as "appearance of symptoms indicator". The fifth factor consisted of four items concerning problems receiving consultation in a specialized hospital, necessitated by worsening of the disease, and specialist advice for treatment, and was interpreted as "interference in social network utilization indicator". The results of EFA indicated that the outcome indicators could be divided into five factors with comparatively simple structures and with high factor loadings held in items included in each subindicator.

The results of EFA, using the oblique promax rotation method, also show an inter-factor correlation coefficient. The maximum value of the inter-factor correlation coefficient was between the first and second factors ($r = 0.784$), and the minimum value was between the fourth and the fifth factors ($r = 0.417$). Regarding the reliability coefficient, Cronbach's alpha of five factors was between 0.78 and 0.92 and fulfilled the acceptance criteria, whereas the reliability coefficient of the fourth outcome indicator was slightly low.

2. Second-order factor model structure of outcome indicators by structural equation modeling

Figure 2 shows the second-order factor model of the outcome indicators. As the observed variables structuring the hypothetical model, three observed variables with high factor loading and comparatively simple structures of relevant factors based on the results of EFA were allocated to each factor. The reason is that one of the limitations of this model involves the maximum number of indicator variables that can be effectively studied[26]. For this measurement, we decided to acknowledge the residual covariance between error variables within a logically valid range, and examined the second-order factor model's goodness of fit.

Table 1 Factor pattern coefficients[†] of outcome indicators consisting of 25 items

Item	Factor					Communality
	1	2	3	4	5	
1) Feels anxious because medicines always need to be kept on hand.	**.364**	−.216	.150	.343	.160	.473
2) Feels that there is no way to cope with disease because sees no marked improvement.	**.868**	−.040	.103	.058	−.143	.754
3) Feels anxious about how to cope with a disease which is difficult to cured.	**.855**	.044	.121	.026	−.148	.812
4) Has difficulty working because of occasional symptoms.	**.642**	−.062	.032	.056	.069	.486
5) Feels anxious because of a lack of knowledge about the disease.	**.449**	.151	−.012	−.017	.239	.508
6) Feels anxious and conflicted after being discharged from the hospital.	**.656**	.218	.037	−.034	.069	.751
7) Has to live concealing disease.	**.493**	−.082	−.184	.016	.236	.258
8) Family caregiver cannot get enough sleep because of the need for constant care.	−.129	**.746**	−.146	.401	.002	.701
9) Family caregiver feels uneasy about caregiving.	.098	**.875**	.059	−.067	−.025	.876
10) Family caregiver hardly has any spare time to go out.	−.157	**.774**	.164	−.002	.051	.710
11) Family caregiver feels strong anxiety and conflict toward caregiving.	.180	**.703**	.087	−.080	.077	.820
12) Takes time to go to hospital and tires easily.	.075	−.070	**.598**	.147	.066	.540
13) Has difficulty with daily living activities such as preparing food and eating because of insufficient recovery.	.290	.115	**.533**	−.023	−.109	.605
14) Has a problem being accompanied by a family member when going to the hospital and for rehabilitation.	−.078	.199	**.621**	.076	.058	.665
15) Has difficulty in daily living activities because of walking difficulty.	.054	.093	**.844**	−.021	−.054	.836
16) Has difficulty going to the hospital because of problems of waking up and down stairs and riding in trains or other vehicles.	−.028	.003	**.907**	−.061	.044	.777
17) Has problems excreting and often has to a use laxative to fight constipation.	−.108	.002	.309	**.415**	.085	.396
18) Has difficulty urinating and a frequent desire to urinate.	−.062	.139	.231	**.407**	.129	.513
19) Has difficulty swallowing food because of dry mouth and problems swallowing.	.005	.335	.240	**.341**	−.166	.505
20) Cannot get enough sleep.	.160	−.033	−.123	**.710**	−.012	.494
21) Cannot have a long conversation because of breathing difficulties.	.127	.324	−.087	**.355**	−.017	.367
22) There is no special hospital for emergency consultation when feeling sick.	.003	−.020	.146	.072	**.584**	.495
23) Has no one to consult about how to cope with problems.	.383	−.018	−.140	.009	**.633**	.668
24) Has difficulty keeping in touch with the hospital from which he/she was discharged.	−.088	.059	.014	.015	**.755**	.568
25) Needs and desires for rehabilitation are not fulfilled.	.099	.241	.313	−.166	**.373**	.634
Eigen value for each factor	12.179	1.705	1.233	1.171	0.947	—

[†]: explanatory factor analysis using an oblique promax rotation with maximum likelihood method.

Analysis by SEM showed that the fit of the model was adequate at chi-square/d.f. = 0.621 ($p > 0.05$), GFI = 0.936, AFGI = 0.906, CFI = 1.000 and RSMEA estimate = 0.001. The standardized path coefficient was positive for the five latent variables (first-order factors) from the observed variables (0.520–0.926). The standardized coefficient was also positive for the second-order factor (overall outcome indicator) from the five first-order factors (0.716–0.929). The coefficients of determination (R-Square) of the five latent variables ranged from 0.512 to 0.864. The 15 observed variables ranged in R-Square from 0.428 to 0.858, except item No. 11 which had a coefficient of determination of 0.270. As shown in Table 2, the observation of homogeneity of the second-order factor models which were constituted from six deferent datasets divided by the patient's profiles, indicated that the fit of the model was also adequate, judging from the values of each parameter estimates and fit indices, whereas the value of fit indices for the dataset of cerebrovascular group showed insufficient model fit. It was suggested that the five indicators showing each aspect of the degree of difficulty in performing daily living activities could possibly be integrated in one factor as an overall outcome indicator.

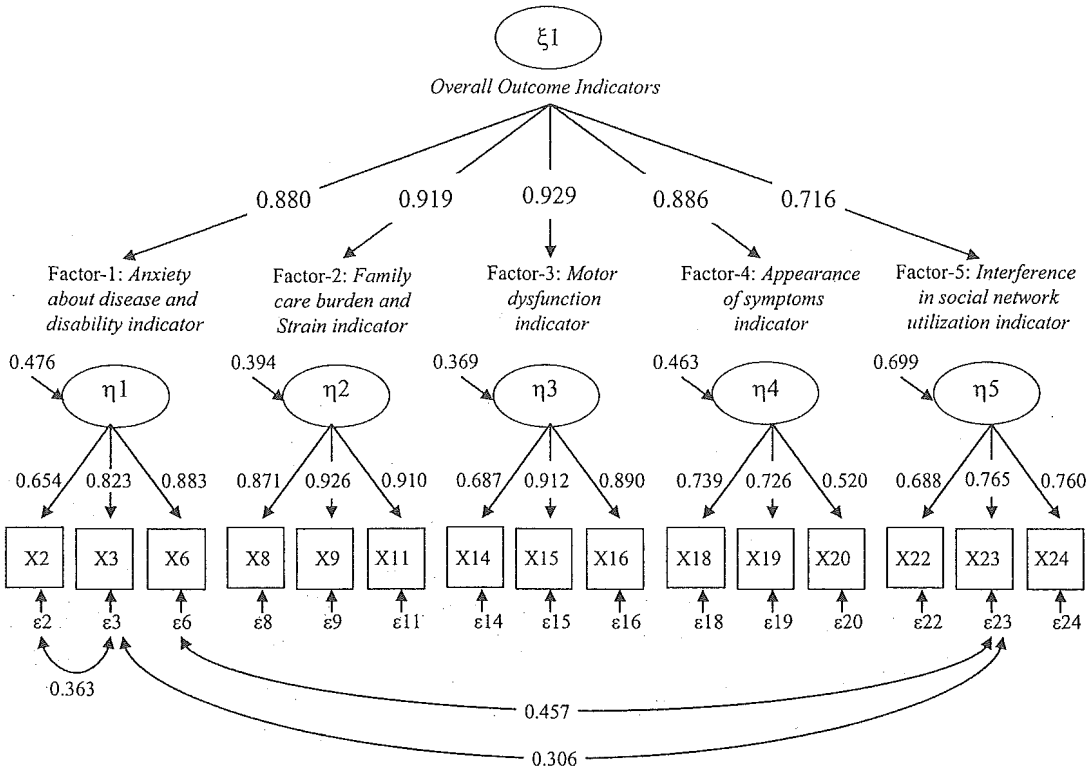

Fig. 2 Second-order factor structural model of the outcome indicators using structural equation modeling of PROC CALIS
All loadings are significant at the 0.05 level. Overall model fit: chi-squares/d. f. = 0.621, goodness of fit index (GFI) = 0.936, adjusted goodness of fit index (AGFI) = 0.906, root mean square error of approximation (RMSEA) estimate = 0.001, comparative fit index (CFI) = 1.000. An elliptical shape: latent variables, A box: observed variables (see Table 1 for a variable number.), ξ : exogenous variables, η : endogenous variables, ε : the residual for observed variables.

3. Relationship between the scores of outcome indicators and patient's profiles

With regard to the difference of gender, the degree of difficulty for females in the third outcome indicator for "motor dysfunction" was significantly high ($p<0.001$). The correlation coefficient between age and each indicator is low, ranging from − 0.064 to 0.171. Accordingly, these indicators were considered to be applicable regardless of age. The correlation coefficient between ADL and each indicator was moderate, ranging from 0.431 to 0.720.

4. Patient improvement and stabilization of the outcome indicators

As shown in Table 3, when calculating the rates of improvement and stabilization of the outcome indicators over two years among patients, the rate of improvement ranged from 0.258 to 0.398 and that of stabilization ranged from 0.561 to 0.700 in all diseases. The rate of improvement in the group of cerebrovascular diseases was lower, compared with that in the demyelinating and degenerative diseases, peripheral nerve disorders and myopathy groups. In particular, low improvement of the second indicator for "family care burden and strain" was observed in the cerebrovascular diseases group.

5. Assessment of the predictive validity of the outcome indicators

1) Assessment using Multiple Indicators Model

As noted, we conducted the follow-up survey for the same subjects as the first one, and analyzed the responses from 201 participants 2 years after the baseline survey. For the first, we constructed a multiple indicators model, supposing that each indicator

Table 2 Parameter estimates based on second-order factor model using SEM for each of patient's profiles

Parameters	Gender		Age-class		Disease category	
	Man (n† = 252)	Woman (n = 211)	under 65 (n = 235)	65 & over (n = 228)	Neurological (n = 329)	Cerebrovascular (n = 128)
Factor loadings						
ξ_1						
$\gamma_{1,1}$	0.885	0.876	0.873	0.909	0.863	0.937
$\gamma_{2,1}$	0.912	0.931	0.888	0.963	0.914	0.936
$\gamma_{3,1}$	0.937	0.925	0.946	0.887	0.917	0.988
$\gamma_{4,1}$	0.909	0.878	0.872	0.897	0.903	0.931
$\gamma_{5,1}$	0.682	0.762	0.717	0.728	0.674	0.837
η_1						
$\kappa_{2,1}$	0.824	0.822	0.845	0.790	0.820	0.812
$\kappa_{3,1}$	0.674	0.642	0.630	0.688	0.631	0.687
$\kappa_{6,1}$	0.866	0.904	0.921	0.844	0.887	0.866
η_2						
$\kappa_{8,2}$	0.922	0.923	0.937	0.914	0.918	0.952
$\kappa_{9,2}$	0.882	0.864	0.872	0.880	0.857	0.916
$\kappa_{11,2}$	0.933	0.885	0.914	0.903	0.911	0.929
η_3						
$\kappa_{14,3}$	0.902	0.880	0.917	0.877	0.893	0.875
$\kappa_{15,3}$	0.819	0.590	0.882	0.529	0.828	0.452
$\kappa_{16,3}$	0.923	0.895	0.898	0.925	0.908	0.903
η_4						
$\kappa_{18,4}$	0.730	0.752	0.732	0.747	0.714	0.777
$\kappa_{19,4}$	0.777	0.646	0.683	0.769	0.756	0.661
$\kappa_{20,4}$	0.545	0.479	0.461	0.571	0.447	0.667
η_5						
$\kappa_{22,5}$	0.615	0.758	0.740	0.613	0.662	0.756
$\kappa_{23,5}$	0.776	0.750	0.738	0.843	0.764	0.789
$\kappa_{24,5}$	0.838	0.697	0.760	0.758	0.780	0.724
Errors in equations						
ζ_1	0.466	0.482	0.487	0.416	0.506	0.348
ζ_2	0.411	0.364	0.459	0.271	0.406	0.353
ζ_3	0.349	0.379	0.325	0.461	0.398	0.155
ζ_4	0.416	0.478	0.490	0.442	0.430	0.365
ζ_5	0.731	0.648	0.697	0.685	0.739	0.547
Correlated measurement errors						
ε_1-ε_2	0.530	0.223	0.254	0.535	0.294	0.587
ε_2-ε_{14}	0.276	0.350	0.405	0.154	0.332	0.237
ε_3-ε_{14}	0.449	0.493	0.485	0.354	0.453	0.411
Values of fit indices						
GFI	0.903	0.894	0.919	0.889	0.919	0.839
AGFI	0.859	0.844	0.881	0.838	0.881	0.765
Chi-Square/d.f.	1.049	1.112	0.825	1.131	0.804	1.952
RMSEA	0.025	0.034	0.001	0.036	0.001	0.098
CFI	0.995	0.990	1.000	0.989	1.000	0.937

ξ: the second-order factor (exogenous variable), η: the first-order factor (endogenous variables), γ: the structural coefficient linking the latent variables (ξ, η), κ: the coefficients from the endogenous variables to the observed variables, ζ: the residual for endogenous variables, ε: the measured error for observed variables. †: cases with missing values were deleted from this analysis.

of the baseline survey would have an influence on each subject's HRQOL (SF-36) after two years. The multiple indicators model was constructed assuming that the outcome indicators with structural concepts consisting of three variables would have an influence on HRQOL with structural concepts consisting of eight domains of SF-36. Figure 3 shows the strength of the first indicator on HRQOL. The path coefficient from the first indicator was − 0.640; the increase in the degree of difficulty in performing

Table 3 Change in outcome indicators by neurological disease categories two years after the baseline survey

Disease categories	Outcome indicator[§]				
	1	2	3	4	5
Rate of improvement[†]					
Overall diseases	0.398	0.316	0.358	0.258	0.325
Cerebrovascular diseases	0.333	0.125	0.286	0.294	0.200
Demyelinating and degenerative diseases	0.444	0.375	0.441	0.265	0.343
Peripheral nerve disorders and Myopathy	0.462	0.400	0.320	0.136	0.350
Rate of stabilization[‡]					
Overall diseases	0.561	0.700	0.560	0.536	0.593
Cerebrovascular diseases	0.500	0.706	0.542	0.604	0.608
Demyelinating and degenerative diseases	0.643	0.583	0.600	0.432	0.514
Peripheral nerve disorders and myopathy	0.586	0.824	0.546	0.533	0.630

[†]: If the patient's outcome improves between the baseline and follow-up point, this outcome measurement takes on a value of 1; otherwise it is 0. Patients who cannot improve (do not have problems relevant to the outcome indicator between the two points) are excluded from the computation of this measurement. [‡]: If the patient's outcome does not worsen between the baseline and follow-up point, this outcome measurement takes on a value of 1; otherwise it is 0. Patients who cannot worsen (are already the most severe level of the relevant outcome indicator between the two points) are excluded from the computation of this measurement. For all the analyses, missing values were excluded from the computation of these measurements. [§]: Outcome indicator, 1; anxiety about disease and disability indicator, 2; family care burden and strain indicator, 3; motor dysfunction indicator, 4; appearance of symptom indicator, 5; interference in social network utilization indicator.

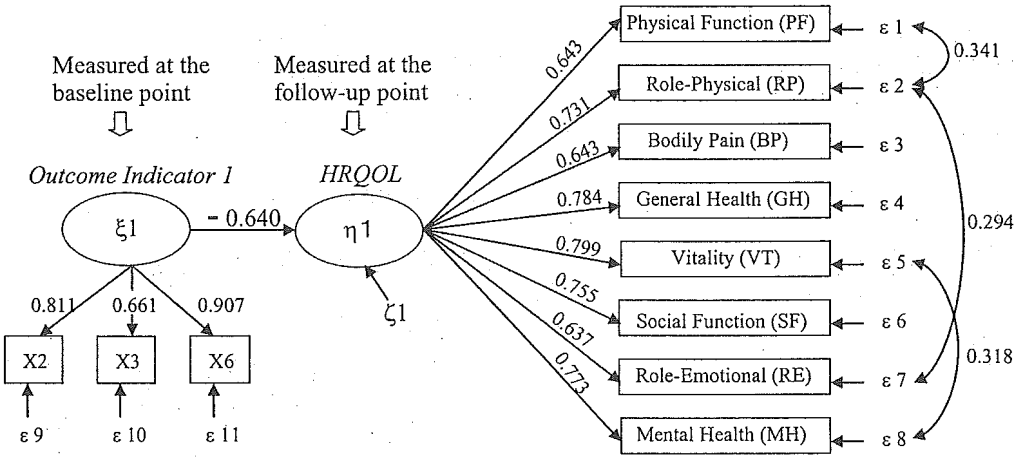

Fig. 3 The causal relationship from indicator 1 at the baseline survey point to HRQOL using the multiple indicators model constructed from structural equation modeling
All loadings are significant at the 0.05 level. Overall model fit: chi-square/d.f. = 1.141, goodness of fit index (GFI) = 0.925, adjusted goodness of fit index (AGFI) = 0.878, root mean square error of approximation (RMSEA) estimate = 0.038, comparative fit index (CFI) = 0.991. An elliptical shape: latent variables, A box: observed variables (see Table 1 for a variable number), ξ : exogenous variables, η : endogenous variables, ζ : the residual for endogenous variables, ε : the residual for observed variables.

daily living activities tended toward lowering HRQOL. The remaining four path coefficients from the second indicator, the third indicator, the fourth indicator and the fifth indicator were −0.542, −0.576, −0.492 and −0.498, respectively. Thus all indicators had influenced the HRQOL conditions

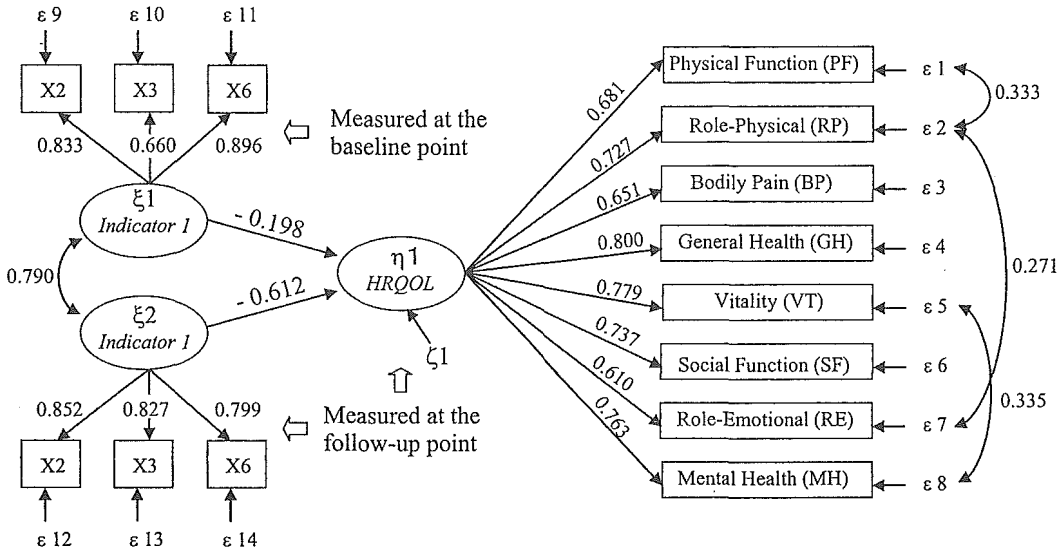

Fig. 4 The causal relationship from indicator 1 of the baseline survey and follow-up survey to HRQOL using the multiple indicators model constructed from structural equation modeling (SEM)
All loadings are significant at the 0.05 level. Overall model fit: chi-square/d.f. = 1.014, goodness of fit index (GFI) = 0.906, adjusted goodness of fit index (AGFI) = 0.868, root mean square error of approximation (RMSEA) estimate = 0.012, comparative fit index (CFI) = 0.999. An elliptical shape: latent variables, A box: observed variables (see Table 1 for a variable number), ξ : exogenous variables, η : endogenous variables, ζ : the residual for endogenous variables, ε : the residual for observed variables.

two years after the baseline survey. In particular, the first indicator for "anxiety about disease and disability" influenced HRQOL the most.

Secondly, the predictive validity was tested by a constructed model in which outcome indicators of both the baseline survey and the follow-up survey influenced HRQOL. In Fig. 4, the upper left side shows the outcome indicators determined at the baseline survey, and the lower part shows the same indicators determined by the follow-up survey. In this model, there is a correlation between structural concepts expressing indicators, and each indicator influences HRQOL. This model shows that the influence on HRQOL extended from outcome indicators determined at the baseline survey was comparatively low (path coefficient: from − 0.009 to − 0.098). On the other hand, the influence on HRQOL extended from the first, second, third, fourth and fifth outcome indicators determined with the second survey were − 0.612, − 0.611, − 0.783, − 0.309 and − 0.740, respectively. Generally, the outcome indicators determined from the follow-up survey, excluding the fourth indicator, had large influences on HRQOL, and among them, the third indicator for "motor dysfunction" and the fifth indicator for "interference in social network utilization" were shown to have large influences on HRQOL.

2) Assessment by using general linear model

Figure 5 shows the analysis of influence on HRQOL extended by the change in outcome indicators in two years using GLM. Because the scores of outcome indicators determined at the baseline time point might possibly become confounding variables which extend their influence on both the change in the scores of outcome indicators in two years and HRQOL at the same time, the influence of the scores of outcome indicators at the baseline time point were adjusted. In this measurement, the GLM was constructed using each SF-36 domain as a dependent variable and the change in outcome indicators in two years as explanatory variables.

The results of GLM indicated that the aspect of HRQOL which outcome indicators influence was different for each indicator. Based on whether the