ORIGINAL ARTICLE

Dynamic Aspect of Functional Recovery After Stroke Using a Multistate Model

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ABSTRACT. Pan SL, Lien IN, Yen MF, Lee TK, Chen THH. Dynamic aspect of functional recovery after stroke using a multistate model. Arch Phys Med Rehabil 2008;89:1054-60.

Objective: To estimate time to functional recovery and quantify the effects of significant prognostic factors affecting the dynamic change of 3-state functional outcome after stroke.

Design: Modeling of clinical predictions.

Setting: Referral center.

Participants: One hundred eleven patients with first-time ischemic stroke.

Interventions: Not applicable.

Main Outcome Measure: Serial Barthel Index scores at onset, 2 weeks, and 1, 2, 4, and 6 months poststroke. The severity of disability was classified into 3 functional states: poor functional state (PFS) for Barthel Index scores from 0 to 40, moderate functional state (MFS) for scores from 45 to 80, and good functional state (GFS) for scores greater than 80. A 3-state Markov regression model together with Bayesian acyclic graphic underpinning was used to estimate transition parameters and mean time to functional recovery between states and to predict the probability of functional recovery by using Gibbs sampling technique.

Results: The mean total recovery time was 3.1 months for patients with PFS at baseline and 1.3 months for patients with MFS at baseline. The mean recovery times to different functional states were also estimated. Age predominantly affected the probabilities of MFS to GFS transitions, younger patients had faster transition rates (rate ratio, 4.51; 95% confidence interval [CI], 2.72−7.40); but age had only borderline effects on PFS to MFS transitions. In contrast, infarct size exerted substantial effects on PFS to MFS transitions: small-size infarct correlated with a higher transition rate (rate ratio, 10.17; 95% CI, 5.25−20.13), whereas only a borderline effect on MFS to GFS transitions was found. The baseline functional state significantly affected the MFS to GFS transitions.

Conclusions: By using a multistate model, overall and patient-specific mean time to functional recovery to different functional states can be estimated and the effect of clinical predictors on functional transitions can be precisely quantified to predict patient-specific probability of functional recovery.

Key Words: Activities of daily living; Cerebrovascular accident; Markov chains; Rehabilitation; Risk factors; Stochastic processes.

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STROKE IS A LEADING CAUSE of disability and death worldwide. The neurologic impairments associated with stroke prevent patients from performing basic activities of daily living (ADLs) and lead to enormous social burden. It is therefore of paramount importance to estimate time to functional recovery at different states and to quantify the effects of relevant predictors. Although efforts have been made to investigate functional outcome in stroke patients, most previous studies on functional outcomes are subject to 2 limitations. First, functional outcomes were commonly measured at admission and reassessed at discharge[1-5] or at 1 predetermined time point after discharge[6-9] rather than a series of dynamic changes in functional status over time. Although some previous studies[10,11] did collect a series of longitudinal functional outcomes at successive time points, these studies could hardly identify significant predictors in association with various stages of functional recovery. Hence, little is known about the determinants related to such dynamic processes after first-time stroke, which are necessary to elucidate the underlying pathophysiologic mechanism.

The second limitation is related to the classification and data property of functional outcomes. Functional outcomes after stroke are frequently classified as a dichotomized status (eg, poor vs good function)[8,12] and therefore lose information on the change of intermediate functional states. Furthermore, because common assessment tools for measuring functional performance after stroke are characterized by ordinal rating scales, such as the Barthel Index, Modified Rankin Scale, and FIM instrument, it is inadequate to analyze such ordinal data using interval-scale based statistical methods. In the present study, we proposed a multistate model by translating the Barthel Index scores into 3 gradient functional states (poor, moderate, good) for assessing a series of functional recovery in patients with first-ever stroke and quantified the time-dependent transition probability between various functional states. Moreover, the effects of clinical prognostic factors on the probability of functional transitions were also investigated to construct a dynamic, probability-based model of functional recovery.

METHODS

Data Sources

Data used in this study were part of a previous multicenter randomized controlled trial with the major objective of evaluating the relative efficacy of treatment using aspirin and nicametate citrate in reducing recurrent ischemic stroke and assessing prognostic factors associated with first recurrence of stroke. The results regarding the efficacy have been described in full

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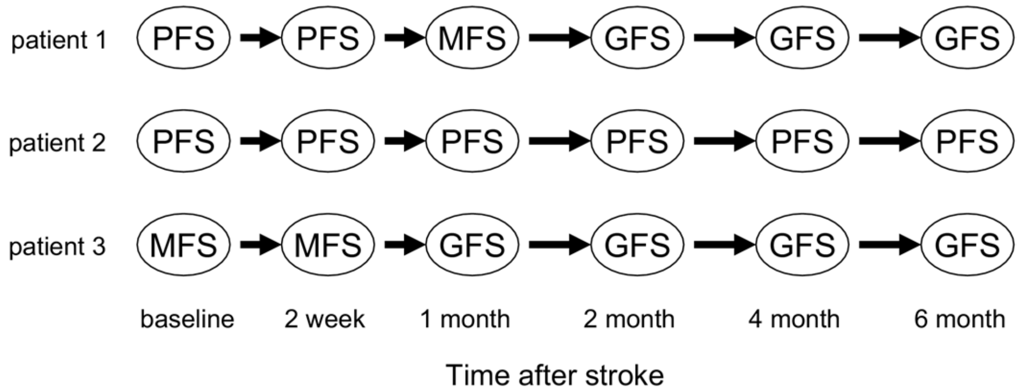

Fig 1. Hypothetic clinical scenario of the multistate model for functional recovery after stroke.

elsewhere.[13,14] In brief, a total of 466 patients who had a first noncardioembolic stable ischemic stroke were recruited from 13 medical centers in Taiwan from October 1992 through April 1995. Because it is difficult to follow participants in other hospitals, we collected only longitudinal data on 6-month repeated measurements of the Barthel Index for 111 subjects who were recruited in one of the largest specific centers in the following analysis.

Patient Eligibility and Follow-Up

The study was primarily designed to evaluate long-term outcomes after noncardioembolic ischemic stroke. This required exclusion of patients who had conditions associated with possible cardiogenic emboli, including atrial fibrillation, myocardial infarction within 6 months of stroke, valvular heart disease, and congestive failure. Patients with severe neurologic deficit (eg, coma) were excluded because severe neurologic impairment may impede the diagnosis of recurrent stroke. Subjects who were willing to participate in this study gave written informed consent, as approved by the research ethics committee. All patients started taking aspirin (acetylsalicylic acid) or nicametate at 3 to 6 weeks after the onset of the first stroke and continued taking the medication thereafter. They all underwent the regular rehabilitation training program during hospitalization, including physical therapy, occupational therapy, speech-language pathology, and nurse support. Both patients and health care professionals were blinded to the treatment assignment.

Data Collection

Each enrolled patient had computed tomography (CT) scanning of the brain. Magnetic resonance imaging (MRI) of the brain was administered only to patients who had brainstem lesions or those with equivocal findings on brain CT. The infarct size was determined by the largest diameter of the lesion on neuroimages. Brain MRI was used to measure the size of infarct in patients with brainstem lesion, and brain CT was used in other patients. The Barthel Index is a weighted, 100-point scale for measuring disability in ADLs, including performance in self-care (feeding, bathing, personal toilet, dressing, bowel and bladder care) and mobility (transfer, ambulation, stair-climbing).[15] The Barthel Index score of each patient was assessed by research assistants at the following 6 time points: within 3 days after stroke (baseline), at 2 weeks, and at 1, 2, 4, and 6 months.

Multistate Model for Functional Transitions

The severity of disability was classified into the following 3 functional states according to Barthel Index rating: poor functional state (PFS) for a Barthel Index score of 0 to 40, moderate functional state (MFS) for a Barthel Index score of 45 to 80, and good functional state (GFS) for a Barthel Index score greater than 80. This 3-state model can delineate the course of function recovery more comprehensively than a dichotomized classification (ie, poor function vs good function) model can. The cutoff points 40 and 80 on the Barthel Index were used to define the 3 groups of functional disability. These cutoff points are comparable to several previous trials and studies.[10,16-19]

Figure 1 illustrates the dynamic aspect for 3 hypothetic cases to account for how data were applied to modeling the transitions between these 3 states. At the baseline assessment after stroke, patient 1 was in the PFS state. Patient 1 stayed in PFS and then progressed from PFS to MFS at 1 month and from MFS to GFS at 2 months after stroke. The observed states at the initial assessment were PFS for patient 2 and MFS for patient 3. As shown in figure 1, patient 2 stayed in PFS for the total follow-up of 6 months; patient 3 stayed in MFS initially and then progressed to GFS at 1 month. The dwelling times in each state were therefore estimated by modeling the time between initial assessment and each transition for each person. To elucidate the course of functional recovery after stroke, we proposed a 3-state Markov model that assumes each transition between states follows the "no memory" property of the exponential distribution, which facilitates the estimation of mean functional recovery time by taking the inverse of the transition rate. The statistical analyses were performed according to the method proposed by Chen et al.[20] In the present study, because no subjects showed deteriorated changes in functional states (eg, backward transition from MFS to PFS), the probabilities of backward transition were set as zero. The GFS was defined as the absorbing state (ie, no possibility of further transition).

Clinical Correlates

To investigate the effects of various prognostic factors on each transition relating to step-by-step progression of functional states, we incorporated individual clinical correlates into the multistate model to estimate 1-month transition probabilities between various functional states defined as above. These included (1) treatment modality (ie, aspirin and nicametate treatment), (2) demographic factors (including age, sex), (3) size of infarct, (4) laterality of infarct, and (5) location of infarct. Because it has been reported that basal ganglia lesions may be associated with unfavorable functional outcome,[21,22] we grouped the location of infarct according to the involvement of basal ganglion. Univariate analysis was performed for each variable at 1 time. Because the rates of functional recovery may vary across subjects, depending on baseline functional states of

Table 1: Demographic and Clinical Characteristics of 111 Patients With Stroke

Variable	n (%)
Age (y)	
<70	56 (50.4)
≥70	55 (49.6)
Sex	
Female	49 (44.1)
Male	62 (55.9)
Treatment	
Nicametate citrate	33 (29.7)
Aspirin	78 (70.3)
Size of infarct (cm)	
<1	80 (72.1)
≥1	31 (27.9)
Laterality of infarct	
Left	52 (46.8)
Right	59 (53.2)
Location of infarct	
Basal ganglion	17 (15.3)
Nonbasal ganglion	94 (84.7)
Baseline functional state	
Poor	71 (64.0)
Moderate	25 (22.5)
Good	13 (11.7)
Unknown	2 (1.8)

PFS and MFS, stratified analyses of transitional probability were performed in light of baseline functional state. Parameters for the effects of individual covariates were estimated using programs developed by Winbugs[a] software.[23,24] The mean values of estimates and the corresponding standard deviations (SDs) were calculated using Markov chain Monte Carlo methods. The significance of a predictor was determined using the Wald test statistic, which is the difference in transition probability between groups divided by its standard error (square root of the sum of the 2 variances). The effects of predictors on the transition rates were quantified by rate ratio, with a ratio greater than 1 indicating a positive effect on the transition rate. A variable is considered statistically significant if the *P* value is less than .05.

RESULTS

Descriptive Findings

A total of 111 patients with first-time stroke were enrolled in the study. Table 1 summarizes the demographic- and outcome-related characteristics of patients with stroke. The mean age at the time of stroke was 68.0±11.2 years, and the proportion of women was 44.1%. The numbers of patients in each functional group at baseline were 71 for PFS, 25 for MFS, and 13 for GFS. The distributions of functional states at serial time points are presented in figure 2. The portion of PFS decreased rapidly in the first 1 month and then decreased at a slower rate during subsequent follow-up. By contrast, the portion of GFS increased quickly at the initial time and reached a plateau after 2 months or so. The portion of MFS increased in the first 2 weeks and then declined after because of steady transition from MFS to GFS.

Overall and Patient-Specific Transition Probabilities

The estimated 1-month transition probabilities for progression from PFS to MFS, from PFS to GFS, and from MFS to GFS are presented in table 2. Note that the 1-month transition probability for PFS to GFS was imputed by 2-step transitions, from the first transition—PFS to MFS—and the subsequent one—MFS to GFS—within a 1-month interval. In the null model without considering clinical correlates (see table 2, row 1), the 1-month transition probabilities in subjects with a baseline state of PFS were .54 for PFS to MFS, .35 for MFS to GFS, and .15 for PFS to GFS, whereas the transition probability for MFS to GFS in subjects with a baseline state of MFS was .54. The estimated 1-month MFS to GFS probability for subjects with a baseline state of PFS tended to be lower than that for subjects with a baseline state of MFS (95% confidence interval [CI], .27−.43 vs .39−.69, respectively).

The estimated transition probabilities for each variable are listed in table 2. Treatment, sex, and laterality of infarct showed no significant effect on the transitions between functional states, whereas statistical significance was observed for age, size of infarct, and location of infarct, all of which were then included in the subsequent multivariate analysis. Because the MFS to GFS transition probability for subjects with a baseline state of MFS tended to be higher than that for subjects with a baseline state of PFS, as shown in table 2, the baseline functional state was also considered as a prognostic factor when analyzing the MFS to GFS transition. The results of multivariate analysis are presented in table 3. The effect of age on the PFS to MFS transition was of borderline statistical significance, whereas a significant effect was seen for the MFS to GFS transition with a 4.5-fold higher transition rate in patients aged less than 70 years compared with those aged 70 years or above. The small-size infarct group had a 10-fold higher rate of showing the improvement from PFS to MFS but showed no significant effect on the MFS to GFS transition. These findings indicate that age predominantly affects the MFS to PFS, whereas infarct size affects PFS to MFS. We found that the baseline functional state significantly affected the MFS to GFS transition rates. Subjects with a baseline state of MFS had 2 times higher transition rates for MFS to GFS compared with those with a baseline state of PFS. The effect of location of infarct on functional transitions was not statistically significant in the multivariate analysis after controlling for other variables.

Clinical Applications

Functional recovery time. By translating monthly transition rates based on exponential distribution, mean recovery

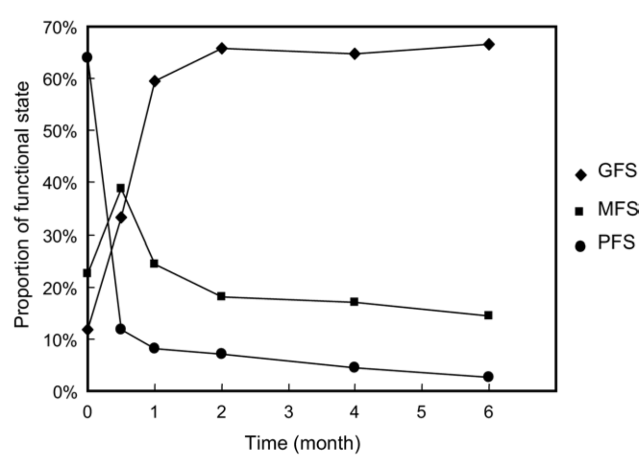

Fig 2. Distribution of serial functional states after stroke. Data points are percentages of total subjects.

Table 2: Univariate Analysis of Factors Affecting the 1-Month Transition Probabilities

	1-Month Transition Probability							
	Baseline State: PFS*						Baseline State: MFS	
	PFS to MFS		MFS to GFS		PFS to GFS		MFS to GFS	
Variables	Estimate (SD)	*P*	Estimate (SD)	*P*	Estimate (SD)	*P*	Estimate (SD)	*P*
Overall	.54 (.04)		.35 (.04)		.15 (.02)		.54 (.08)	
Treatment								
Nicametate citrate	.54 (.05)	.972	.35 (.05)	.547	.14 (.03)	.598	.51 (.08)	.430
Aspirin	.54 (.07)		.38 (.07)		.17 (.04)		.66 (.17)	
Sex								
Female	.48 (.06)	.274	.41 (.07)	.274	.17 (.04)	.577	.60 (.12)	.430
Male	.57 (.05)		.31 (.05)		.14 (.03)		.48 (.10)	
Age (y)								
<70	.42 (.05)	.039	.58 (.07)	<.001	.27 (.05)	.001	.91 (.07)	<.001
≥70	.59 (.06)		.22 (.05)		.09 (.02)		.33 (.09)	
Size of infarct (cm)								
<1	.72 (.04)	<.001	.32 (.05)	<.001	.24 (.04)	.305	.72 (.09)	<.001
≥1	.23 (.05)		.44 (.10)		.08 (.03)		.25 (.11)	
Location of infarct								
Basal ganglion	.68 (.09)	.163	.20 (.08)	.963	.32 (.10)	.393	.90 (.12)	.004
Nonbasal ganglion	.51 (.04)		.35 (.05)		.15 (.03)		.48 (.08)	
Laterality of infarct								
Left hemisphere	.51 (.06)	.682	.45 (.07)	.085	.21 (.05)	.086	.68 (.11)	.086
Right hemisphere	.54 (.05)		.29 (.05)		.12 (.03)		.43 (.10)	

*Baseline state denotes the functional state measured within 3 days after stroke.

times to different functional states were estimated and are listed in table 4. For patients with PFS at baseline, the overall recovery times on average were 3.1 months for PFS to GFS (total recovery time), 0.8 month for PFS to MFS, and 2.3 months for MFS to GFS. For patients with MFS at baseline, the overall mean recovery time for MFS to GFS was approximately 1.3 months.

By considering age and infarct size, the mean total recovery time ranged from 1 month to 11 months. By splitting into 2 transition processes (PFS to MFS, MFS to GFS), the mean recovery time ranged from 1 week to 4 months for the PFS to MFS transition step and ranged from 1 month to 7 months for MFS to GFS transition step, depending on age and infarct size.

Predictive probability of recovery. Figures 3 and 4 present the estimated probabilities of transition over time by 4 groups according to their age and infarct size. For subjects with an initial state of PFS as shown in figure 3, group A (age <70y; size <1cm) had the most favorable prognosis with an estimated probability of .98 for the transition from PFS toward higher functional states at 1 month, whereas group D (age ≥70y; size ≥1cm) showed the slowest functional recovery. Figure 4 shows the estimated transition probability curves for subjects with a baseline state of MFS. Group A subjects in MFS had a probability of .72 to enter GFS at 1 month compared with a probability of .16 for group D subjects. These results also suggest that group A subjects had the most favorable prognosis. It should be pointed out that although figure 3 shows that group B (age ≥70y; size <1cm) had faster transition than group C (age <70y; size ≥1cm), figure 4 indicates that group C was superior to group B in terms of functional recovery. These findings are compatible with the results presented in table 3, which indicate that infarct size played a more important role in PFS to MFS transition, whereas age predominantly affects MFS to GFS transition.

DISCUSSION

It is of interest to investigate the recovery time and odds of recovering from PFS to MFS and from MFS to GFS for patients after stroke. Very few studies have attempted to quantify the mean recovery times corresponding to step-by-step progression varying with different clinical attributes such as infarct size and personal characteristics like age. The proposed model in our study was tailored for throwing light on 2 novel notions: functional recovery time and predictive probability of recovery. Providing such information is very useful for clinical consultation for patients after first stroke.

The results of multivariate analysis showed that the prognostic roles of infarct size and age tended to vary with different stages of functional recovery. This multistate model is not only able to identify prognostic factors but also to quantify the

Table 3: Multivariate Analysis of Prognostic Factors Affecting the Rates of Functional Transitions After Stroke

Factors	PFS to MFS	MFS to GFS
Baseline transition rate (/mo)	0.27 (0.13–0.49)	0.14 (0.06–0.25)
Ratio of transition rate		
Age (y)		
<70	1.73 (0.96–3.14)	4.51 (2.72–7.40)
≥70	1	1
Size (cm)		
<1	10.17 (5.25–20.13)	1.82 (0.97–3.42)
≥1	1	1
Baseline functional state		
MFS	NA	2.41 (1.37–4.10)
PFS	NA	1

NOTE. Values are mean (95% CI).
Abbreviation: NA, not applicable.

Table 4: Estimated Recovery Time (in months) Grouped by the Clinical Correlates

Clinical Correlates			Individual Transition Step		Recovery to GFS
			PFS to MFS	MFS to GFS	
Baseline State	Size (cm)	Age (y)	Mean Recovery Time	Mean Recovery Time	Mean Total Recovery Time
PFS	Overall		0.84	2.32	3.16
	≥1cm	≥70	3.67	7.29	10.96
	≥1cm	<70	2.16	1.64	3.80
	<1cm	≥70	0.38	4.16	4.54
	<1cm	<70	0.22	0.93	1.15
MFS	Overall		NA	1.27	1.27
	≥1	≥70	NA	3.02	3.02
	≥1	<70	NA	0.67	0.67
	<1	≥70	NA	1.70	1.70
	<1	<70	NA	0.38	0.38

Abbreviation: NA: not applicable.

magnitude of influence of significant predictors (eg, age, infarct size, baseline function) on the step-by-step process of functional recovery after stroke. Doing so can aid health policymakers and clinicians predict subject-specific risk rather than population-average risk. As mentioned in the introduction, most previous studies assessed functional outcome with static time property. The functional outcomes were commonly measured at 2 time points, for example, at admission and 6 months after stroke.[6] Because the information within the follow-up period is lacking, determinants related to the dynamic step-by-step process of functional recovery over time cannot be quantified for some useful information like the mean time to functional recovery and the predictive probability for transition to different functional outcomes. Our results showed that for subjects with a baseline state of PFS, small-size infarct (<1cm) was associated with a higher probability for the PFS to MFS transition. Because smaller infarct size indicates less neural damage, it may lead to less neurologic deficit and faster functional recovery.[25,26] Nevertheless, the infarct size showed only a borderline effect on MFS to GFS transitions. This suggests that size of infarct predominantly affects the early stage of functional recovery and favors an underlying mechanism that could occur within a relatively short period—for instance, resolution of focal brain edema.

Previous studies[22,27,28] have reported that age is a predictor of functional outcome. Our results showed that young subjects have higher probability for MFS to GFS transitions, whereas only a borderline effect of age was seen on transitions from PFS toward higher functional states. Considering the effects of infarct size and age together, for stroke patients with a baseline state of PFS, infarct size significantly affected the rate of functional recovery at the initial stage (ie, PFS to MFS), but age played a less important role implicated at this stage. Once the patients entered MFS, the contribution of lesion size decreased, whereas the effects of age became more distinct. These findings imply that functional recovery at a later stage of stroke is mainly affected by age-related factors. It has been reported that elderly subjects have lower potentials for neural reorganization,[29] which may lead to less functional recovery. Furthermore, elderly patients are likely to have a higher risk of subsequent complications, which may also impede the functional improvement after stroke.[22]

Baseline Barthel Index score after stroke reflects the severity of neurologic impairment in the acute phase of stroke; it has

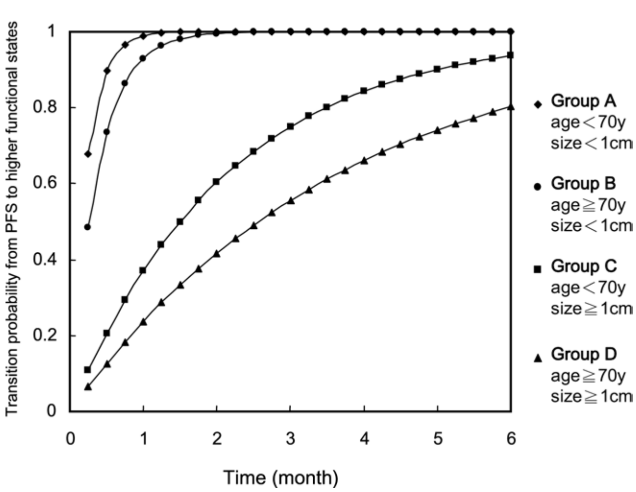

Fig 3. Estimated probabilities for transitions from PFS toward higher functional states over time, stratified by age and infarct size.

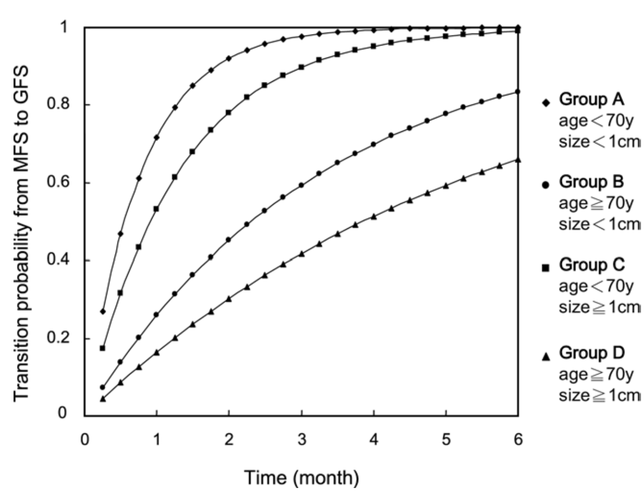

Fig 4. Estimated probabilities for transitions from MFS to GFS over time, stratified by age and infarct size.

been shown to be a predictor for functional outcome.[11] We also found that baseline functional state after stroke correlated with the MFS to GFS transition rate. Nevertheless, even after adjusting the effect related to baseline functional status, age remained a significant predictor for determining the MFS to GFS transition rate

Miyai et al[21] suggested that patients with basal ganglion and internal capsule lesion had persistently poor ambulation performance. Lenticulostriate infarct had also been reported to correlate with less favorable outcome.[22] However, other researchers[30,31] reported no significant association between infarct location and functional outcome. In our study, the results of multivariate analysis showed that basal ganglion lesion was not a significant predictor after adjusting other prognostic factors. It has been suggested that stroke location can explain only a small portion of variability of functional outcome.[2] In addition, Reding and Potes[32] reported that patients with pure motor deficits have more favorable outcomes than those with motor plus sensory plus visual deficit. It is possible that effect of lesion location on functional outcome might become evident only when the characteristics of type and severity of impairment are comparable across the patient groups.

The application of a multistate model would be very informative to clinical consultation for stroke patients. Taking the predictive probability curves in figure 3, for example, both groups A and B (ie, subjects with small infarct size) have high probability (>0.9) of having functional improvement. In other words, most stroke patients in this study who had an infarct less than 1cm in size would have functional recovery within 1 month. In contrast, groups C and D (ie, subjects with infarct size >1cm) had slower rates of functional recovery: the 1-month probabilities of improvement were .37 and .24, respectively. The functional recovery pattern could also be assessed by estimating the time required for achieving the chance of functional recovery. For instance, to reach a 50% chance of functional improvement, 1.5 months would be taken for group C, whereas 2.5 months would be needed for group D.

Probability-based multistate approaches would be valuable for clinical management and resource allocation. The expected number of those staying at PFS in a given stroke cohort can be imputed by using these individualized predicted transition probabilities. Doing so can help health policy-makers determine the expected demand for long-term care for patients after first stroke. Moreover, our proposed model also can be adapted to assess the effectiveness of certain rehabilitation programs for patients after first stroke by examining how the distribution of functional states across time has been modified after the introduction of the program. One can also assign measures of quality of life to various functional states and compare quality-adjusted life-years saved by the introduction of specific rehabilitation program.

Study Limitations

There are several concerns that should be addressed. First, although no recurrent stroke was noted in the dataset, it should be pointed out that a patient can have a subsequent stroke, in which case a new process of functional transitions would begin; our multistate model can be applied to such data. Second, concerning the predictive validity of the current model, we used the chi-square goodness-of-fit test to evaluate the final model. The lack of difference between the observed and the expected values (P=.67) indicates a good fit of the model. However, the applicability of this model still needs to be further validated in a set independent sample other than ours. Third, this study only recruited nonembolic ischemic stroke patients with mild or moderate severity from a single medical center. The generalizability of the results is therefore limited. Moreover, adjustment was made for only a few of the clinical variables that affect recovery; other potential predictors such as incontinence, visual inattention, dementia, and the intensity or duration of rehabilitation therapy were not included in the analysis. Therefore, although the model presented in the study may be useful for clinical reasoning and resource allocation, it should be considered as an additional tool and not be used alone for these purposes. Further research is required to confirm the findings and expand to a larger population across a broader spectrum of stroke severity.

CONCLUSIONS

The dynamic aspect of functional recovery in patients with first-ever ischemic stroke, classified as poor, moderate, and good states, has been studied by using a multistate model to estimate the mean time to functional recovery between transitions among the 3 functional states. The effects of 2 established factors, age and infarct size, have been precisely quantified to predict patient-specific probabilities for step-by-step processes of functional recovery.

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