

Models containing age and NIHSS predict recovery of ambulation and upper limb function six months after stroke: an observational study

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Questions: What is the incidence of recovery of ambulation and upper limb function six months after stroke? Can measures such as age and the National Institutes of Health Stroke Scale (NIHSS) be used to develop models to predict the recovery of ambulation and upper limb function? **Design:** Prospective cohort study. **Participants:** Consecutive sample of 200 people with stroke admitted to a Sydney Hospital. **Outcome measures:** Ambulation was measured with item 5 of the Motor Assessment Scale (MAS); patients scoring ≥ 3 could ambulate independently. Upper limb function was measured with items 7 and 8 of the MAS; patients scoring ≥ 5 could move a cup across the table and feed themselves with a spoonful of liquid with the hemiplegic arm. **Results:** Of the 114 stroke survivors who were unable to ambulate initially, 80 (70%) achieved independent ambulation at six months. Of the 51 stroke survivors who could not move a cup across the table initially, 21 (41%) achieved the upper limb task at six months. Of the 56 stroke survivors who were unable to feed themselves initially, 25 (45%) could feed themselves at six months. Models containing age and severity of stroke (measured with NIHSS) predicted recovery of ambulation and ability to move a cup across the table, whilst a model containing severity of stroke predicted ability to feed oneself. All prediction models showed good discrimination (AUC 0.73 to 0.84). **Conclusion:** More than two-thirds of people after stroke recovered independent ambulation and less than half recovered upper limb function at six months. Models using age and NIHSS can predict independent ambulation and upper limb function but these prediction models now require external validation before use in clinical practice. [Kwah LK, Harvey LA, Diong J, Herbert RD (2013) Models containing age and NIHSS predict recovery of ambulation and upper limb function six months after stroke: an observational study. *Journal of Physiotherapy* 59: 189–197]

Key words: Recovery, Ambulation, Upper limb function, Stroke, Incidence, Prognosis

Introduction

Clinicians often have to make early predictions about patients' potential to walk independently or use their hemiplegic arm. Such predictions are necessary to provide information to patients, set realistic goals for therapy, and plan for discharge. Many prognostic studies of ambulation (Craig et al 2011, Meijer et al 2003) and upper limb recovery (Chen and Winstein 2009, Coupard et al 2012) have been published, but few have recruited representative cohorts early after stroke, reported predictive accuracy of models and used common predictors to develop models for external validation. If information from prognostic studies is to be used by clinicians to derive prognoses of patients early after stroke, it is important that prognostic studies recruit representative populations (Herbert et al 2005) seen early after stroke. These include consecutive cohorts from hospitals or cohorts from registries, rather than a select group of patients included in trials or referred for rehabilitation. It is also important that studies not only identify significant predictors but develop robust and clinically applicable models for external validation. Without external validation, it is not recommended for clinicians to use the prediction models in clinical practice (Moons et al 2009).

Studies that have recruited cohorts early after stroke have reported varying estimates of recovery of independent ambulation (41 to 85%) (Dallas et al 2008, Feigin et al

1996, Veerbeek et al 2011, Wade and Hewer 1987, Wandel et al 2000) and upper limb function (32 to 34%) (Au-Yeung and Hui-Chan 2009, Heller et al 1987, Nijland et al 2010). In addition, some researchers have conducted multivariate analyses of data from acute stroke cohorts. These studies reported that pre-morbid function (Wandel et al 2000), strength of leg muscles (Veerbeek et al 2011, Wandel et al 2000), sitting ability (Loewen and Anderson 1990, Veerbeek et al 2011), walking ability and bowel control (Loewen and Anderson 1990) predicted recovery of independent

What is already known on this topic: Many studies have identified predictors of recovery of ambulation and upper limb function after stroke. However, few have recruited representative cohorts early after stroke or developed prediction models suitable for external validation.

What this study adds: Within six months of stroke, over two-thirds of people who are initially non-ambulant recover independent ambulation but less than half of those who initially lack upper limb function recover it. Prediction models using age and NIHSS can predict independent ambulation and upper limb function six months after stroke. External validation of these models is now required.

ambulation. The same studies showed that strength of arm and hand muscles (Au-Yeung and Hui-Chan 2009, Nijland et al 2010, Smania et al 2007), sensation (Au-Yeung and Hui-Chan 2009, de Weerd et al 1987) and baseline measures of upper limb function (de Weerd et al 1987, Loewen and Anderson 1990) predicted recovery of upper limb function. However, only two of these studies recruited consecutive cohorts and reported predictive accuracy of their models (de Weerd et al 1987, Smania et al 2007). Non-representative sampling threatens the generalisability of the prediction models to a wider stroke cohort and failure to report accuracy of the prediction models brings into question whether the prediction models are robust enough to be externally validated prior to use in clinical practice.

Two prognostic models, one of ambulation and one of upper limb function, were recently developed by one group in the Netherlands and these are potentially at the stage of external validation (Nijland et al 2010, Veerbeek et al 2011). Even though the cohorts do not appear to have been recruited consecutively, recruitment from multiple acute stroke units and high follow-up rates in both studies may make these cohorts more representative than other non-consecutive cohorts. They also reported good predictive accuracy of their models (positive likelihood ratios = 5.24 to 5.59, negative likelihood ratios = 0.06 to 0.13, calculated from data in original reports), although external validation of their models is difficult in Australian cohorts as assessment tools such as the Trunk Control Test, Motricity Index and Fugl-Meyer Assessment (used in their prognostic models) are not commonly used in Australian stroke units (National Stroke Foundation 2010).

The research questions for this study were:

1. What is the incidence of recovery of independent ambulation and upper limb function in a representative acute stroke cohort six months after stroke?
2. Can measures such as age and the National Institutes of Health Stroke Scale (NIHSS) be used to develop models to predict the recovery of ambulation and upper limb function?

Method

Design

This was a secondary analysis of data that were prospectively collected for a cohort study investigating the incidence and prediction of contractures after stroke (Kwah et al 2012). Consecutive patients admitted between January 2009 and January 2010 to the accident and emergency department of St George Hospital with a diagnosis of stroke or transient ischaemic attack were screened. St George Hospital is a large teaching public hospital in Sydney, Australia, that admits more than 500 patients a year with stroke or transient ischaemic attack.

Participants

Patients were eligible to participate in the study if they were over 18 years old, had a medically documented stroke, were able to respond to basic commands, and understood English. Patients who received recombinant tissue plasminogen activator were included if they had remaining neurological symptoms 24 hours after receiving treatment. Patients with subarachnoid haemorrhages were included only if they satisfied the World Health Organization definition of stroke (WHO 1988).

Measurements

Baseline measurements of outcomes and predictors were obtained within the first four weeks after stroke. At six months patients were followed up at their discharge destinations to measure ambulation and upper limb function outcomes.

Outcomes. The outcomes of interest were independent ambulation, ability to move a cup across the table, and ability to feed oneself with a spoonful of liquid with the hemiplegic arm. These were measured with Item 5 (walking), Item 7 (hand movements), and Item 8 (advanced hand activities) of the Motor Assessment Scale (MAS), respectively (Carr et al 1985). Each item on the Motor Assessment Scale is scored on a scale from 1 to 6. For the purposes of prediction we dichotomised each item. Patients who scored $\geq 3/6$ on Item 5 were deemed able to walk independently. Patients who scored $\geq 5/6$ on Item 7 were deemed able to pick up a cup and move it across the table, and patients who scored $\geq 5/6$ on Item 8 were deemed able to feed themselves with a spoonful of liquid.

Predictors. Five candidate variables were used to predict ambulation: age, severity of stroke, standing up ability, pre-morbid function, and spasticity. Three candidate variables were used to predict upper limb function: age, severity of stroke, and combined motor function of the upper arm and hand. The number of candidate predictors was restricted so that the ratio of outcome events to predictors was at least greater than 10 to avoid problems of overfitting (Peduzzi et al 1996). Candidate predictors were chosen based on their clinical relevance, common use in the clinic, and availability at the time when the model is meant to be used (Moons et al 2009, Royston et al 2009).

Severity of stroke was measured using the National Institutes of Health Stroke Scale (NIHSS) (Brott et al 1989, Kasner 2006). NIHSS scores were obtained 24 hours after the administration of recombinant tissue plasminogen activator. Standing up ability was measured using Item 4 (sitting to standing) of the MAS (Carr et al 1985). Combined motor function of the arm was obtained by summing the scores of Items 6 (upper arm function), 7 (hand movements), and 8 (advanced hand activities) of the MAS (Carr et al 1985). Pre-morbid function was assessed with the Barthel Index (Collin et al 1988, Kasner 2006). Spasticity of the ankle plantarflexors was measured using the Tardieu Scale and was recorded as present if a catch or clonus was detected during fast-velocity limb movements (Patrick and Ada 2006). Validity and reliability of all assessment tools have been established (Carr et al 1985, Kasner 2006, Lannin 2004, Mehrholz et al 2005, Patrick and Ada 2006, Poole and Whitney 1988).

Measurements were performed by three experienced neurological physiotherapists who also received online training and certification to carry out the NIHSS. Therapists who performed outcome measures at follow-up were blinded to baseline measures. Patients received standard medical and allied health care according to the National Stroke Foundation guidelines in Australia. As this was a secondary analysis of a cohort study on contractures, sample size for the current study was not calculated *a priori*. However, 80 participants achieved independent ambulation and 21 participants achieved independent upper limb function, and we used five candidate predictors in the

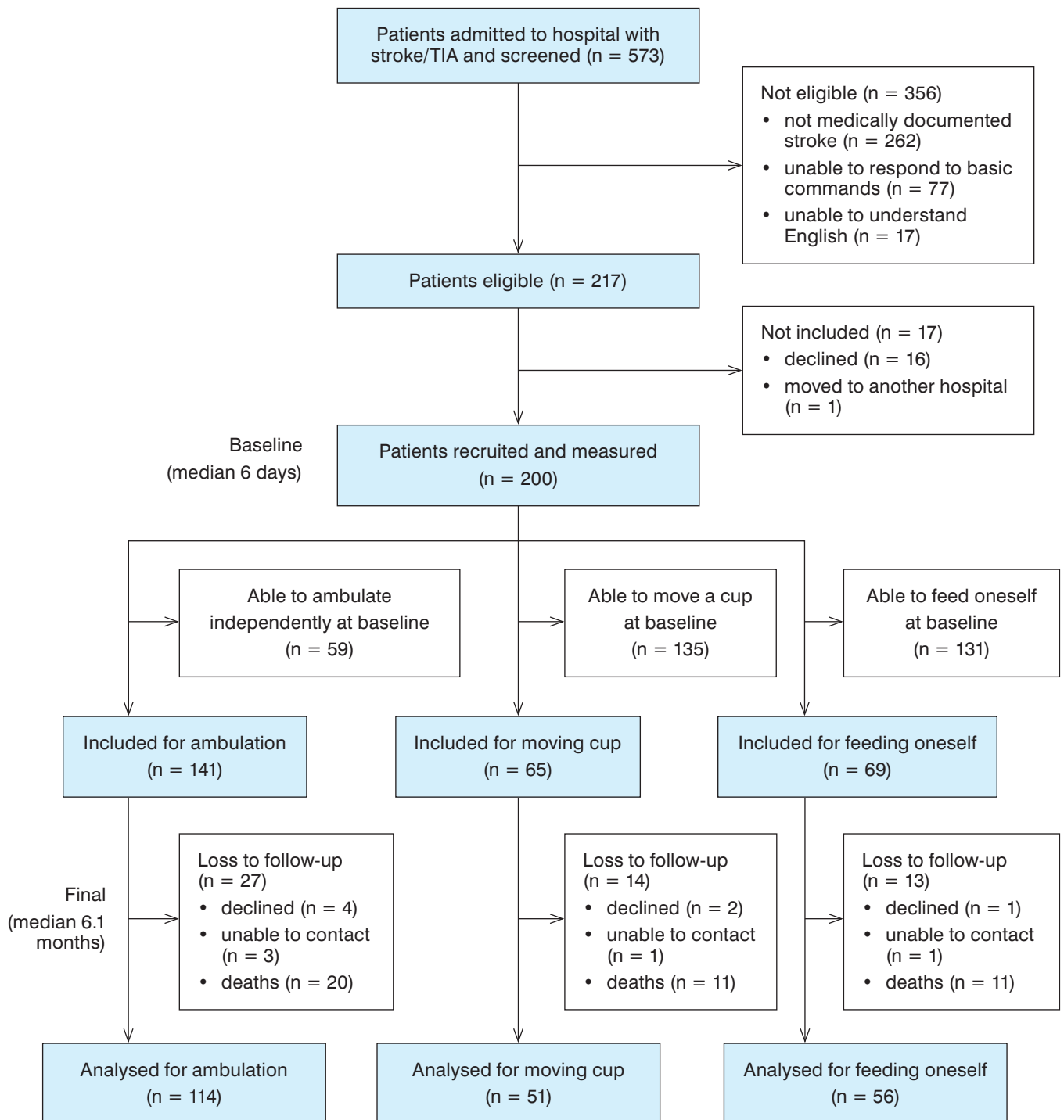


Figure 1. Flow of participants through the study. TIA = transient ischaemic attack.

ambulation models and two candidate predictors in the upper limb models. Therefore the sample size was sufficient to satisfy the widely used criterion of 10 cases per candidate predictor (Peduzzi et al 1996).

Statistical analysis

Participants who had achieved independent ambulation and upper limb function at baseline had already recovered, so they were excluded from subsequent analyses. Participants who died were also excluded from subsequent analyses.

Thus the incidence of independent ambulation and upper limb function is the incidence amongst those who had not already recovered at baseline, conditional on survival. As there were very few missing data (<6%; 10 missing for Item 7 of MAS, 11 missing for Item 8 of MAS), a complete case analysis was undertaken. For participants with bilateral strokes, measures from the initially worse side were chosen for analysis – if both sides were the same, one side was randomly selected.

If predictors were highly correlated ($r > 0.6$), the predictor that was more widely used and had fewer missing data was used. Univariate associations between predictors (at baseline) and outcomes (at six months) were quantified with odds ratios and their 95% CIs. All predictors except spasticity were treated as continuous variables in the logistic regression (Royston et al 2009). The predictors were entered in the initial model for multivariate analysis. Initially we used a bootstrap variable selection procedure that retained those variables selected with backwards stepwise regression (p to remove = 0.2) in at least 80% of bootstrap samples. Regression coefficients were zero-corrected to reduce bias (Austin 2008). However, two of the three bootstrap models obtained in this way had poor calibration (Hosmer-Lemeshow $p < 0.05$). We therefore used, instead, a conventional backwards stepwise regression variable selection procedure (p to remove = 0.05) to develop our final models. Discrimination (how well the model can identify patients with and without outcomes) was quantified with area under the receiver-operating curves (AUC). Calibration (how well observed probabilities agree with predicted probabilities) was evaluated by inspecting the slope of the observed-predicted graphs and with the Hosmer-Lemeshow statistic (Royston et al 2009). All analyses were conducted using Stata 11.1.

Results

Compliance with the study protocol

The flow of participants through the study is shown in Figure 1. Baseline measures were obtained at a median of 6 days (IQR 3 to 11) after stroke. Final outcome measures were measured at a median of 6.1 months (IQR 5.9 to 6.4) after stroke. Patients who were able to ambulate independently

($n = 59$), or move a cup ($n = 135$), or feed themselves ($n = 131$) with the hemiplegic arm at baseline were excluded from subsequent analyses of recovery in these abilities, respectively. Twenty of the remaining participants died, four declined re-assessment, and three could not be contacted (Figure 1). Consequently the overall rate of follow up was 81% for ambulation, 78% for moving a cup, and 81% for feeding. In participants who survived, the rate of follow up was 94% for ambulation, 94% for moving a cup, and 97% for feeding. Characteristics of patients are shown in Table 1.

Incidence of independent ambulation and upper limb function

Of the 114 stroke survivors who were unable to ambulate initially, 80 (70%, 95% CI 62 to 79) were able to do so at six months. Of the 51 stroke survivors who were unable to move a cup across the table initially, 21 (41%, 95% CI 27 to 55) were able to do so at six months. Of the 56 stroke survivors who were unable to feed themselves with a spoonful of liquid initially, 25 (45%, 95% CI 31 to 58) were able to do so at six months.

Prediction of independent ambulation and upper limb function

Results of univariate analyses are shown in Table 2. Odds ratios are associated with a one-unit increase in the predictor. Both severity of stroke and motor function (standing up ability and combined motor function of arm) were significantly associated with recovery of ambulation and feeding oneself. A one-unit increase in the NIHSS was associated with a 15% reduction in odds of recovering ambulation. A one-unit increase in Item 4 of MAS was associated with a 2.8-fold increase in the odds of ambulation recovery.

Table 1. Baseline characteristics of all patients and subgroups of patients at baseline.

Characteristics	All patients ($n = 200$)	Unable to ambulate ($n = 114$)	Unable to move a cup ($n = 51$)	Unable to feed oneself ($n = 56$)
Age (yr), median (IQR)	78 (65 to 84)	78 (67 to 83)	74 (61 to 82)	75 (61 to 81)
Gender, n male (%)	98 (49)	53 (47)	25 (49)	27 (48)
Thrombolysis, n (%)	19 (10)	12 (11)	8 (16)	9 (16)
Side of hemiplegia, n (%) ^a				
right	94 (47)	52 (46)	22 (43)	28 (50)
left	89 (45)	50 (44)	26 (51)	26 (46)
both	17 (9)	12 (10)	3 (6)	2 (4)
Type of stroke, n (%) ^a				
ischaemic	134 (67)	78 (68)	35 (69)	42 (75)
intracerebral haemorrhage	42 (21)	24 (21)	14 (28)	12 (21)
subarachnoid haemorrhage	7 (4)	1 (1)	0 (0)	0 (0)
unknown	17 (9)	11 (10)	2 (3)	2 (4)
Pre-morbid function (BI ≤ 95), n (%)	47 (24)	27 (24)	9 (18)	11 (20)
Severity of stroke (NIHSS), n (%) ^a				
mild (0 to 5)	107 (54) ^b	49 (43)	7 (14)	12 (21)
moderate (6 to 13)	59 (30) ^b	43 (38)	25 (49)	24 (43)
severe (14 to 42)	33 (17) ^b	22 (19)	19 (37)	20 (36)

IQR = Interquartile range, BI = Barthel Index, NIHSS = National Institutes of Health Stroke Scale. ^aPercentages do not add to 100% due to the effects of rounding. ^bThere was one missing observation for NIHSS, hence the denominator for NIHSS proportions is 199 patients.

Table 2. Univariate and multivariate associations between candidate predictors and outcomes.

Candidate predictors	Univariate analysis	Multivariate analysis (backwards selection)	
	Odds ratios ^a (95% CI)	Odds ratios ^a (95% CI)	Regression coefficients (95% CI)
Predictors for independent ambulation			
age (10 years)	0.54 ^c (0.35 to 0.82)	0.35 ^c (0.20 to 0.62)	-0.11 ^c (-0.16 to -0.05)
severity of stroke (NIHSS, 0 to 42)	0.85 ^c (0.78 to 0.92)	0.78 ^c (0.70 to 0.87)	-0.24 ^c (-0.35 to -0.13)
standing up (MAS, 0 to 6)	2.77 ^c (1.52 to 5.08)	–	–
pre-morbid function (BI, 0 to 100)	1.04 ^b (1.01 to 1.07)	–	–
spasticity in ankle (1 = yes, 0 = no)	0.52 (0.19 to 1.43)	–	–
constant	–	–	11.03 ^c (5.91 to 16.14)
Predictors for moving a cup across table			
age (10 years)	0.66 (0.42 to 1.04)	0.59 ^b (0.36 to 0.97)	-0.05 ^b (-0.10 to 0)
severity of stroke (NIHSS, 0 to 42)	0.91 (0.82 to 1.00)	0.88 ^b (0.79 to 0.99)	-0.12 ^b (-0.24 to -0.01)
combined motor function of arm (MAS 0 to 18)	1.04 (0.99 to 1.10)	–	–
constant	–	–	4.82 ^b (0.67 to 8.96)
Predictors for feeding oneself with spoon			
age (10 years)	1.17 (0.79 to 1.74)	–	–
severity of stroke (NIHSS, 0 to 42)	0.80 ^c (0.70 to 0.91)	0.80 ^c (0.70 to 0.91)	-0.23 ^c (-0.35 to -0.10)
combined motor function of arm (MAS 0 to 18)	1.12 ^c (1.05 to 1.20)	–	–
constant	–	–	2.09 ^c (0.74 to 3.43)

NIHSS = National Institutes of Health Stroke Scale, MAS = Motor Assessment Scale, BI = Barthel Index. ^aOdds ratios are the increase in odds associated with a 1-unit increase in the predictor, ^b $p < 0.05$, ^c $p < 0.01$

Results of the multivariate analysis are shown in Table 2. Combined motor function of the arm was not entered into the multivariate prediction models for upper limb function because there was a high correlation between severity of stroke and combined motor function of the arm (correlation between NIHSS and sum of MAS Items 6, 7, and 8 were $r = 0.64$ in the model for moving a cup, and $r = 0.70$ in the model for feeding oneself). Age and NIHSS were statistically significant ($p < 0.05$) predictors of recovery in ambulation and moving a cup. For recovery in feeding oneself, only NIHSS was statistically significant. The final multivariate models (Table 2) were used to estimate probabilities of recovery in ambulation and functional use of the arm. The probabilities are shown graphically in Figure 2.

Performance of models

All three multivariate backwards prediction models had good discrimination (ability to differentiate between participants who did and did not recover). The AUC for the prediction models were 0.84 (95% CI 0.77 to 0.92) for ambulation, 0.73 (95% CI 0.59 to 0.87) for moving a cup, and 0.82 (95% CI 0.70 to 0.94) for feeding oneself. The Hosmer-Lemeshow test was not statistically significant for any model (0.70 for ambulation, 0.74 for moving a cup, 0.38 for feeding oneself), indicating that there was no evidence of a failure of fit. However with the sample size used here the Hosmer-Lemeshow test lacks the statistical power needed to provide a strong test of goodness of fit. Calibration curves are shown in Figure 3.

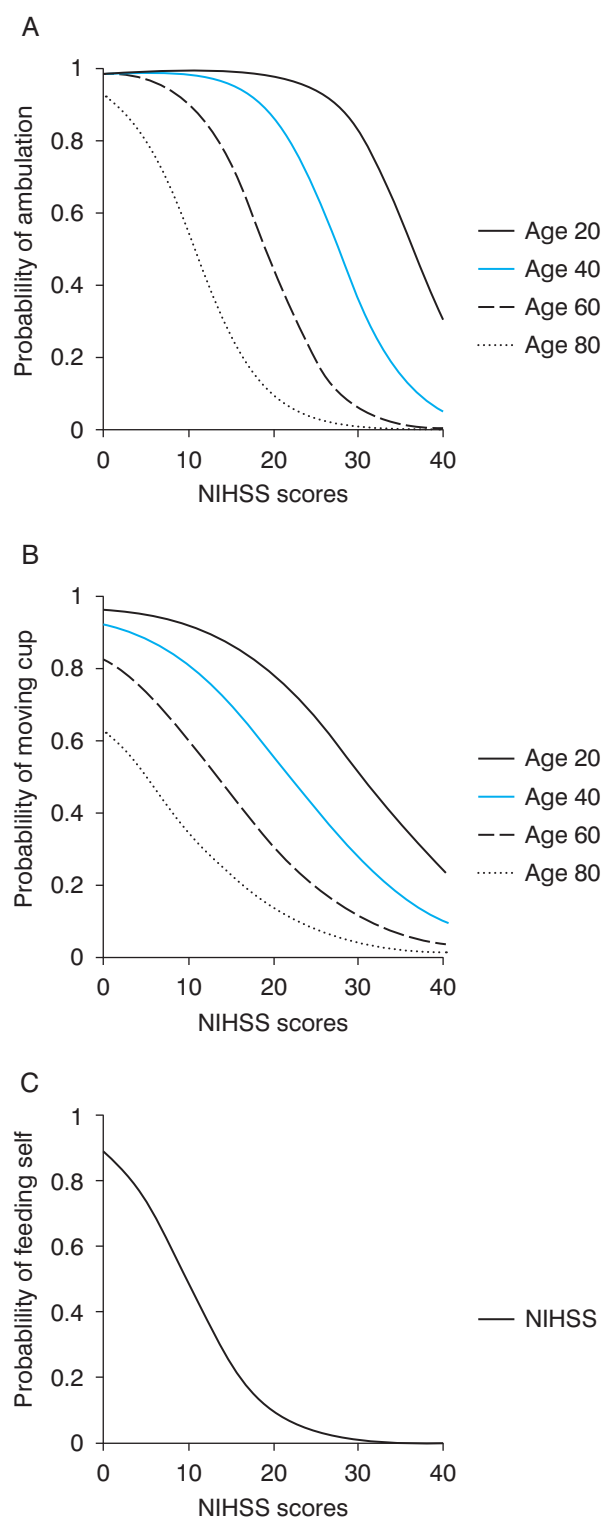


Figure 2. Probability of recovery in (A) independent ambulation, (B) moving a cup across table, and (C) feeding oneself with spoonful of liquid, as a function of age and NIHSS scores.

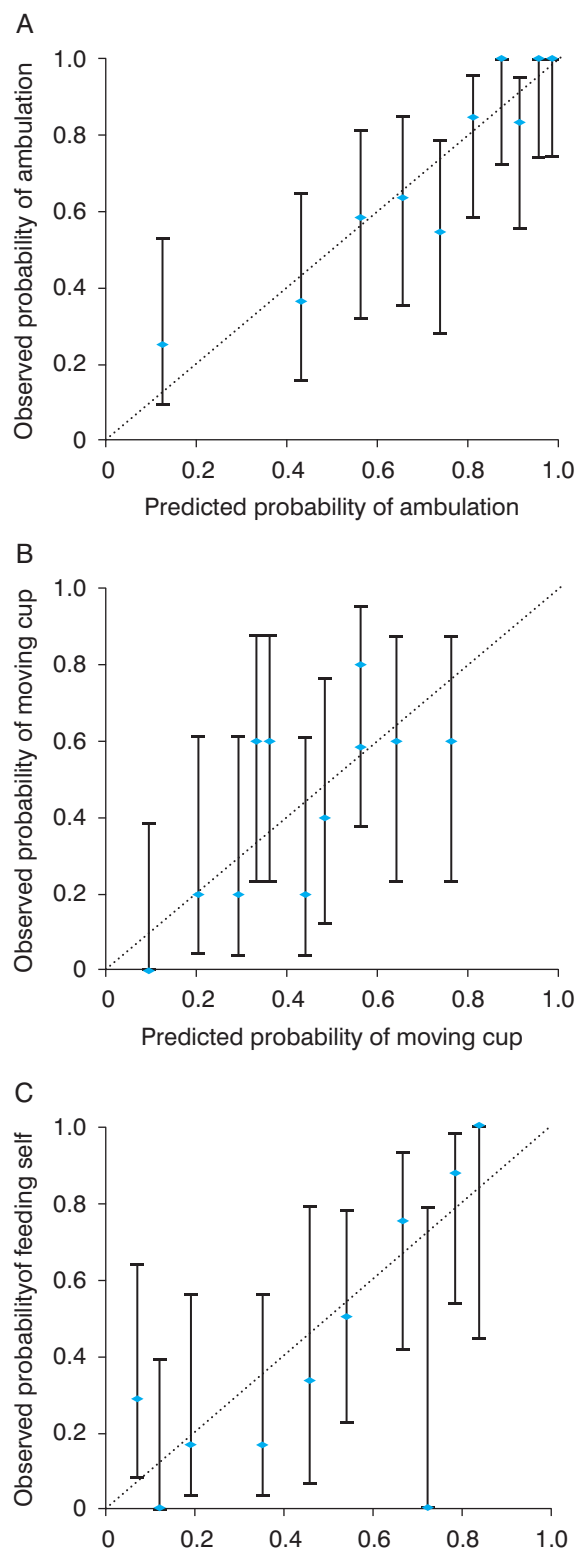


Figure 3. Calibration graphs of the final models for (A) ambulation, (B) moving a cup across table, and (C) feeding oneself with spoonful of liquid. Perfect calibration is represented by the diagonal dotted line; vertical lines represent 95% CIs.

Discussion

This study provides estimates of incidence of recovery in independent ambulation and upper limb function in a representative acute stroke cohort six months after stroke. Using age and NIHSS, we were able to develop models to predict independent ambulation and upper limb function six months after stroke.

Our estimates of recovery in independent ambulation (70% of those initially unable to ambulate) and upper limb function (41 to 45% of those initially without upper limb function) are broadly consistent with previous estimates from acute stroke cohorts. In studies that followed patients up six months after stroke, 79–85% of patients have been reported to recover independent ambulation (Veerbeek et al 2011, Wade and Hewer 1987) with a smaller proportion of patients (32–34%) recovering upper limb function (Au-Yeung and Hui-Chan 2009, Nijland et al 2010). The small differences between our estimates and those from these previous studies may be due to differences in the characteristics of cohorts or differences in the definitions of recovery in upper limb function. For example, recovery of upper limb function has been defined by others as a minimum score of 35/57 (Au-Yeung and Hui-Chan 2009) or maximum score of 57 (Nijland et al 2010) on the Action Research Arm Test, while we defined upper limb functional recovery by a minimum score of 5/6 on Items 7 and 8 of the MAS, as these scores reflected independence in important upper limb functional activities. It is important to note that in all these studies, including ours, 'recovery' in ambulation and upper limb function does not necessarily imply complete recovery. Many patients deemed to have recovered motor function using our operational definitions may still have had significant limitations in higher levels of mobility or more complex upper limb functional tasks.

Several acute stroke studies have considered age (Dallas et al 2008, de Weerd et al 1987, Hu et al 2010, Loewen and Anderson 1990, Meldrum et al 2004, Veerbeek et al 2011, Wandel et al 2000), and severity of stroke (Au-Yeung and Hui-Chan 2009, Dallas et al 2008, Hu et al 2010) in their multivariate analyses to identify predictors of ambulation or upper limb function. Only one study has found age and severity of stroke as significant predictors of ambulation. This study recruited patients from a stroke intensive care unit. Patients were included in that study only if they were referred for rehabilitation (Hu et al 2010). Another study that investigated the benefits of constraint-induced movement therapy in people six months after stroke also reported that age was a predictor for upper limb function (Fritz et al 2006). In these two studies, the cohorts might not be representative of patients seen early after stroke.

Age and NIHSS have previously been shown to be strong predictors of mortality (Konig et al 2008, Weimar et al 2004), disability (Johnston et al 2007), and independence with activities of daily living (Johnston et al 2007, König et al 2008, Weimar et al 2004) in acute stroke cohorts. Consequently these predictors appear to have broad predictive utility. Their routine use in acute stroke units will facilitate external validation of our prediction models in other cohorts. One limitation of the NIHSS is that it is a complex assessment that requires training to administer

(Reid et al 2010). This potentially undermines its clinical usefulness. However online training and access to the scale (Kasner 2006) have overcome some of these problems. An advantage of the NIHSS is that it provides information on a variety of stroke-related impairments that can be used by various health professionals in the acute stroke setting (Kasner 2006). The NIHSS can also be administered to patients who do not have good cognition or language, whereas this can be problematic with the MAS. We therefore recommend the use of the NIHSS in future prediction models of ambulation and upper limb recovery after stroke.

The strengths of our study include the consecutive recruitment of patients seen early after stroke, the minimal loss to follow-up, the low risk of over-fitting of the prediction model, and the strong performance of the prediction models (discrimination and calibration results). The main limitation of our study is that, after the exclusion of patients who had already achieved independent ambulation and upper limb function at baseline, the sample size was modest. This precluded consideration of other candidate predictors, especially in the upper limb prediction models. A second limitation to consider is the timing of our baseline measurements. We collected baseline measurements of predictors within the first four weeks of stroke as it was difficult to recruit participants and carry out measurements quickly in an acute stroke cohort where patients were very unwell. Measurement of predictors should be made early in the first few days after stroke if prediction models are to be used early to guide clinicians' decision-making in goal setting, therapy selection, and discharge planning (Nijland et al 2010, Veerbeek et al 2011). Even though our baseline measurements were taken at a median of 6 days (IQR 3 to 11) after stroke, the models may have had more clinical utility if all measurements had been obtained within this timeframe or if all measurements had been obtained earlier than 6 days. Third, our prediction models only allow the prediction of recovery in ambulation and upper limb function six months after stroke. Functional recovery has been reported to extend beyond six months (Kollen et al 2005). It is possible that patients who were predicted not to recover independent ambulation or functional use of their arms recovered after six months. Future studies could follow patients over a longer time period to capture a more accurate picture of recovery in ambulation and upper limb function. Lastly, despite its broad inclusion criteria, the cohort was recruited from only one hospital in Australia. This hospital may not be representative of all hospitals across Australia because it only admits patients from its surrounding geographical area and it may provide slightly different care to other hospitals. External validation of our prediction models in cohorts from other hospitals is required before the prediction models can be used in clinical practice (Konig et al 2007).

More than two-thirds of those who are initially non-ambulant recover independent ambulation, but less than half of those who initially lack upper limb function recover functional use of their upper limbs six months after stroke. Prediction models using age and NIHSS can predict independent ambulation and upper limb function six months after stroke, although these models require external validation. ■

Ethics: The local Human Research Ethics Committee (South Eastern Sydney and Illawarra Area Health Service) approved the study. All participants or guardians gave written informed consent before data collection began.

Competing interests: None

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