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ORIGINAL REPORT

FIVE-YEAR MORTALITY AND RELATED PROGNOSTIC FACTORS AFTER INPATIENT STROKE REHABILITATION: A EUROPEAN MULTI-CENTRE STUDY

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Objective: **To determine 5-year mortality and its association with baseline characteristics and functional status 6 months post-stroke for patients who received inpatient rehabilitation.**

Design: **A prospective rehabilitation-based cohort study.**

Subjects: **A total of 532 consecutive stroke patients from 4 European rehabilitation centres.**

Methods: **Predictors were recorded on admission. Barthel Index was assessed at 6 months (BI6mths) and patients were followed for 5 years post-stroke. Survival probability was computed using Kaplan–Meier analysis and compared across 3 BI6mths-classes (0–60, 65–90, 95–100) (log-rank test). Significant independent predictors were determined using multivariate Cox regression analysis (hazard ratio (HR)).**

Results: **Five-year cumulative risk of death was 29.12% (95% confidence interval (CI): 22.86–35.38). Age (HR = 1.06, 95% CI: 1.04–1.09), cognitive impairment (HR = 1.77, 95% CI: 1.21–2.57), diabetes mellitus (HR = 1.68, 95% CI: 1.16–2.41) and atrial fibrillation (HR = 1.52, 95% CI: 1.08–2.14) were independent predictors of increased mortality. Hyperlipidaemia (HR = 0.66, 95% CI: 0.46–0.94), and higher BI6mths (HR = 0.98, 95% CI: 0.97–0.99) were independent predictors of decreased mortality. Five-year survival probability was 0.85 (95% CI: 0.80–0.89) for patients in BI6mths-class: 95–100, 0.72 (95% CI: 0.63–0.79) in BI6mths-class: 65–90 and 0.50 (95% CI: 0.40–0.60) in BI6mths-class: 0–60 ($p < 0.0001$).**

Conclusion: **Nearly one-third of rehabilitation patients died during the first 5 years following stroke. Functional status at 6 months was a powerful predictor of long-term mortality. Maximum functional independence at 6 months post-stroke should be promoted through medical interventions and rehabilitation. Future studies are recommended to evaluate the direct effect of rehabilitation on long-term survival.**

Key words: follow-up study; stroke; rehabilitation; prognosis; mortality.

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INTRODUCTION

In the past decade, the rate and prognostic factors for long-term mortality after stroke have been investigated in both community- and hospital-based studies. Cumulative mortality risk ranges from 5% to 28% at 1 month, 15% to 41% at 1 year, and 42% to 60% at 5 years post-stroke (1–10). Age (2, 3, 6, 7, 9), diabetes mellitus (6, 7, 9), atrial fibrillation (3, 9, 10), stroke recurrence (3, 7) and severity (3, 10) are well-recognized independent predictors of long-term mortality after stroke.

The long-term outcome of patients admitted to stroke rehabilitation units (SRU) has received less attention (11, 12). Lincoln et al. (11) reported 5-year mortality rates of 45% in 176 patients treated on a SRU, compared with 55% in 139 patients treated on conventional wards. For 110 patients treated in combined acute and rehabilitation wards, Indredavik et al. (12) reported 5-year mortality rate of 59% vs 71% for those in general wards. Studies investigating prognostic factors for long-term mortality in patients admitted to SRUs are lacking. Both from a clinical and economic point of view, knowledge of the prognostic factors for their long-term survival is of interest.

Results of both community- and hospital-based studies showed that functional outcome at 6 months post-stroke was associated with an increased risk of dying in the long term (9–13). It is unknown whether this association also applies to a stroke rehabilitation sample. For these patients, 6 months post-stroke is an important time-point. By then, the majority have been discharged from SRU and most motor and functional recovery has occurred (14).

The aims of the study were: (*i*) to describe the mortality rate in the first 5 years after stroke in patients admitted to 4 rehabilitation centres in Europe; (*ii*) to determine the baseline prognostic factors for 5-year mortality post-stroke; (*iii*) to investigate the association between patients' functional status at 6 months and their 5-year mortality.

METHODS

Patients and settings

This prospective cohort study is a follow-up of the Collaborative Evaluation of Rehabilitation in Stroke across Europe (CERISE) project. This project aimed to compare stroke care and recovery patterns between 4 European rehabilitation centres (14): University Hospital Leuven, Belgium; Nottingham University Hospitals, UK; RehaClinic Zurzach, Switzerland and Fachklinik Herzogenaurach, Germany. In each centre, inpatient multidisciplinary care was provided in a SRU. Between March 2002 and September 2004, patients were recruited consecutively using the following inclusion criteria: first-ever stroke as defined by the World Health Organization (WHO) (15), age 40–85 years, and Rivermead Motor Assessment scores (16): Gross function ≤ 11, and/or Leg and Trunk function ≤ 8 and/or Arm function ≤ 12 on admission to the centre. Exclusion criteria were: other neurological impairments with permanent damage; stroke-like symptoms attributable to subdural haematoma, tumour, encephalitis or trauma; admission to the centre > 6 weeks after stroke; no informed consent; and pre-stroke Barthel Index (BI) < 50. The BI consists of 10 items (continence of bowels and bladder, feeding, dressing, grooming, toilet use, bathing, mobility, stairs, transfer) that measure a person's functional status. Scores range from 0 to 100, with lower scores indicating more dependence (17).

Baseline assessment and follow-up

In the CERISE project, a trained researcher in each SRU recorded the following 17 items on admission: age, gender, centre, never/ever smoked, type of stroke (ischaemic infarct, bleeding, unknown), initial BI, urinary incontinence (score < 10 on BI-bladder), swallowing problems (fluids must be thickened, diet must be modified, or patient requires non-oral feeding), aphasia (score > 0 on item 9 of the National Institute of Health Stroke Scale (18) (NIHSS)), dysarthria (score > 0 on NIHSS-item 10), cognitive impairment (score > 0 on item 1b and/or 1c of the NIHSS), diabetes mellitus, history of hypertension (systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 95 mmHg based on several measurements or on a 24-h recording and patients treated with anti-hypertensives), coronary heart disease, atrial fibrillation, history of myocardial infarction, hyperlipidaemia (total cholesterol > 200 mg/100 ml). At 6 months after stroke, BI was reassessed during clinical visits (BI6mths).

In the present study, a researcher in each centre contacted all patients approximately 5 years after the initial stroke. In cases of death, the date of death was obtained from a family member, general practitioner, registry or hospital database. Data collection was spread over 1 year (June 2008–2009). The researchers were familiarized with study protocol at a workshop. The project manager (LDW) visited each researcher to ensure standardized implementation of the research protocol. The study was approved by the ethics committee in each country.

Statistical analysis

Patients' characteristics are presented as means with standard deviations (SD), medians with interquartile ranges (IQR), or frequencies with percentages, as appropriate.

Kaplan–Meier product limit techniques were used to generate mortality probabilities at each consecutive year until 5 years after stroke. Survival times were censored at 5 years post-stroke. Cox regression analysis was used to examine the relationships between baseline variables and mortality over 5 years. The univariate relation was examined between all 17 baseline variables and mortality over 5 years. Alpha was set at 0.05. Multivariate analysis was then performed including all 17 baseline variables, regardless of their univariate significance. This full model approach was used because of the observational study design. We verified for multicollinearity by calculating variance inflation factors (VIF). The square root of VIF indicates how much of the standard error of the estimate is increased due to multicollinearity compared with a situation where the covariates are uncorrelated. Results were presented as hazard ratio with 95% confidence intervals (HR (95% CI)). Explained variance (R^2: range: 0–100%) was calculated for all variables separately and for the full model according to Royston's formula (19). To test the proportional hazard assumption, we verified the significance level of the interaction between each of the 17 baseline variables and time: only "initial BI × time" ($p = 0.02$), and "swallowing problems × time" ($p = 0.04$) proved significant in univariate, but not in multivariate analysis ($p > 0.05$). Therefore, both interaction terms were not retained in the final Cox regression model. In addition, there were no significant interactions between baseline variables and centre, indicating that a stratified Cox regression analysis per centre was not required.

Finally, the association between BI6mths and long-term mortality was examined using Cox regression analysis including only those patients for whom BI6mths was assessed. All 17 baseline variables were compared between patients who retained in the study and those who dropped out at 6 months. If BI6mths proved a significant univariate predictor, the association was further explored. Therefore, patients were divided into 3 classes based on their BI6mths score: 0–60, 65–90, and 95–100. A cut-off of 60/100 was chosen, as the score of 60 is reported to be the cut-off point between independence and some dependence (20). Furthermore, patients are considered to be totally functionally independent when scoring ≥ 95/100 on the BI. Kaplan–Meier curves were calculated for each BI6mths class and compared using a log-rank test. *Post-hoc* pairwise class comparisons were carried out with a Šidák multiple testing correction. Finally, BI6mths was added to the baseline model to verify its multivariate association. All statistical analyses were carried out with SAS, version 9.2.

Table I. *Patients' characteristics on admission to the rehabilitation centre (*n = *532)*

Age at stroke onset, years, mean (SD)	69.5 (10.3)
Barthel Index, median (quartile 1–3)	55 (30–80)
Female gender, *n* (%)	249 (46.8)
Ever smoked, *n* (%)	260 (48.9)
Centre, *n* (%)	
Belgian	127 (23.9)
British centre	135 (25.4)
Swiss centre	135 (25.4)
German centre	135 (25.4)
Type of stroke, *n* (%)	
Bleeding	76 (14.3)
Ischaemic infarct	446 (83.8)
Unknown	10 (1.9)
Urinary incontinence, *n* (%)	182 (34.2)
Swallowing problems, *n* (%)	106 (19.9)
Aphasia, *n* (%)	178 (33.5)
Dysarthria, *n* (%)	223 (41.9)
Cognitive impairment, *n* (%)	147 (27.6)
Diabetes mellitus, *n* (%)	118 (22.2)
History of hypertension, *n* (%)	354 (66.5)
Coronary heart disease, *n* (%)	135 (25.4)
Atrial fibrillation, *n* (%)	104 (19.6)
History of myocardial infarction, *n* (%)	68 (12.8)
Hyperlipidaemia, *n* (%)	219 (41.2)

SD: standard deviation.

RESULTS

A total of 532 patients were included in CERISE and in the present follow-up study. Patients' characteristics are shown in Table I. Mean follow-up time was 5.63 years (SD 0.63) (range: 4.06–7.31). At the time of follow-up, 338 patients were alive; 167 had died and 27 could not be contacted (Fig. 1).

These 27 patients were known to be alive at 6 months post-stroke and contributed to the Kaplan–Meier calculations, with their survival time censored at 6 months post-stroke. Date of death was unknown for 4 patients. The midpoint of the interval between the moment they were last known to be alive and 5-year follow-up, was considered as date of death in the Kaplan–Meier calculations. Table II shows the risk of death in each consecutive year. Five-year cumulative risk of death was 29.1%.

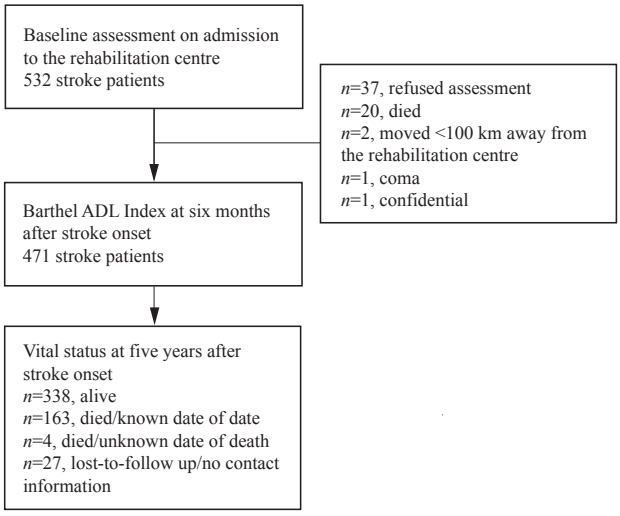

Fig. 1. Study flowchart.

Risk factors for long-term mortality after stroke (Table III)

Univariate analyses. Age ($p < 0.0001$), urinary incontinence ($p < 0.0001$), swallowing problems ($p < 0.0001$), aphasia ($p = 0.04$), dysarthria ($p = 0.003$), cognitive impairment ($p < 0.0001$), diabetes mellitus ($p = 0.007$), coronary heart disease ($p < 0.0001$), atrial fibrillation ($p < 0.0001$), and history of myocardial infarction ($p = 0.02$) were associated with increased mortality. Hyperlipidaemia ($p = 0.006$) and higher initial BI score ($p < 0.0001$) were associated with decreased mortality. R^2-values of parameters with significant associations ranged between 1.57% (aphasia) and 19.47% (age).

Multivariate analysis. The VIF scores of all 17 baseline variables were low (range 1.07–2.34), indicating that the full model approach was appropriate. Independent predictors of increased mortality were age ($p < 0.0001$), cognitive impairment ($p = 0.003$), diabetes mellitus ($p = 0.006$) and atrial fibrillation ($p = 0.02$). Hyperlipidaemia ($p = 0.02$) was associated with reduced mortality. Urinary incontinence, swallowing problems, aphasia, dysarthria, coronary heart disease, history of myocardial infarction and initial BI score were not significant in the multivariate model ($p > 0.05$). R^2 of the full model was 42.27%.

Association between functional outcome 6 months post-stroke and long-term mortality.

BI6mths could not be assessed in 61 patients (Fig. 1). Baseline variables did not differ between the 61 drop-outs and 471 patients remaining in the study, except for swallowing problems ($p = 0.02$) and aphasia ($p = 0.01$). In the 471 patients, median BI6mths equalled 90 (IQR: 70–100). Higher BI6mths-score was univariate significantly associated with decreased mortality (HR = 0.98, 95% CI: 0.97–0.98, $p < 0.0001$). R^2 of BI6mths equalled 28.52%. Patients were classified into 3 classes based on their BI6mths-score: 106 patients (23%) were classified in the lowest (0–60), 131 (28%) in the middle (65–90) and 234 (49%) in the highest class (95–100). Kaplan–Meier curves for the 3 BI6mths classes are shown in Fig. 2.

Estimated 5-year survival probability was 0.85 (95% CI: 0.80–0.89) for patients in BI6mths class 95–100, 0.72 (95% CI: 0.63–0.79) in BI6mths class 65–90 and 0.50 (95% CI: 0.40–0.60) in BI6mths class 0–60 (log-rank, $p < 0.0001$). BI6mths proved a significant independent predictor ($p < 0.0001$), after adding this parameter to the full model.

Table II. *Kaplan–Meier estimates of the risk of death within defined time intervals after stroke onset (*n = *532)*

	Years after stroke				
	<1	1–<2	2–<3	3–<4	4–<5
At risk, *n*	522[a]	470[a]	448	423	368[a]
Deaths, *n*	42	22	25	32	31
Cumulative deaths, *n*	42	64	89	121	152[b]
Risk of death, % (95% CI)	8.05 (5.72–10.38)	4.68 (2.77–6.59)	5.58 (3.46–7.70)	7.57 (5.04–10.10)	8.42 (5.58–11.26)
Cumulative risk of death, % (95% CI)	8.05 (5.75–10.38)	12.26 (9.50–15.02)	17.05 (13.35–20.75)	23.18 (18.43–27.93)	29.12 (22.86–35.38)

[a]"Number at risk" is influenced by censored observations.
[b]Another 15 patients died after 5 years.
CI: confidence interval.

Table III. *Univariate and multivariate Cox regression analyses of baseline predictors for long-term mortality after stroke (*n = *532)*

Parameters	Univariate analysis HR (95% CI)	R^2	Multivariate analysis HR (95% CI)
Age at stroke onset	1.07 (1.05–1.09)***	19.47	1.06 (1.04–1.09)***
Female gender	0.95 (0.70–1.29)	0.03	0.80 (0.56–1.11)
Ever smoked	1.07 (0.79–1.45)	0.08	1.26 (0.89–1.78)
Centre		1.48	
Belgian vs German centre	0.86 (0.54–1.37)		0.64 (0.38–1.07)
British vs German centre	1.30 (0.85–1.98)		0.80 (0.49–1.32)
Swiss vs German centre	1.19 (0.78–1.83)		0.80 (0.48–1.32)
Initial Barthel Index (0–100)	0.99 (0.98–0.99)***	8.93	0.99 (0.98–1.00)
Type of stroke	0.73 (0.45–1.18)	0.62	0.91 (0.55–1.50)
Urinary incontinence	1.95 (1.44–2.65)***	6.47	1.07 (0.68–1.70)
Swallowing problems	2.00 (1.43–2.80)***	5.21	1.21 (0.81–1.82)
Aphasia	1.40 (1.02–1.91)*	1.57	1.00 (0.67–1.48)
Dysarthria	1.58 (1.17–2.14)**	3.14	1.07 (0.74–1.53)
Cognitive impairment	2.14 (1.57–2.92)***	7.74	1.77 (1.21–2.57)**
Diabetes mellitus	1.58 (1.13–2.20)*	2.44	1.68 (1.16–2.41)**
History of hypertension	1.31 (0.93–1.83)	0.92	1.24 (0.86–1.80)
Coronary heart disease	1.90 (1.39–2.60)***	5.32	1.46 (0.98–2.16)
Atrial fibrillation	2.35 (1.70–3.25)***	8.56	1.52 (1.08–2.14)*
History of myocardial infarction	1.65 (1.10–2.47)*	1.87	1.20 (0.74–1.96)
Hyperlipidaemia	0.60 (0.43–0.83)**	3.63	0.66 (0.46-0.94)*

*$p < 0.05$, **$p < 0.01$, ***$p < 0.0001$.
R^2 full model: 42.27%.
HR: hazard ratio; CI: confidence interval; R^2: explained variance according to formula of Royston.

DISCUSSION

The main findings of this study are that nearly one-third of stroke rehabilitation patients died in the first 5 years following stroke; age, cognitive impairment, atrial fibrillation, and diabetes mellitus were independent predictors of increased mortality, whereas hyperlipidaemia was associated with reduced long-term mortality after stroke; and a lower functional status at 6 months was both univariate and multivariate significantly associated with an increased long-term mortality.

The 5-year cumulative mortality risk of 29% was considerably lower than that reported in the Framingham study (40–48%) (21), other community- and hospital-based studies (42–60%) (1–10), and the rehabilitation-based studies of Lincoln et al.

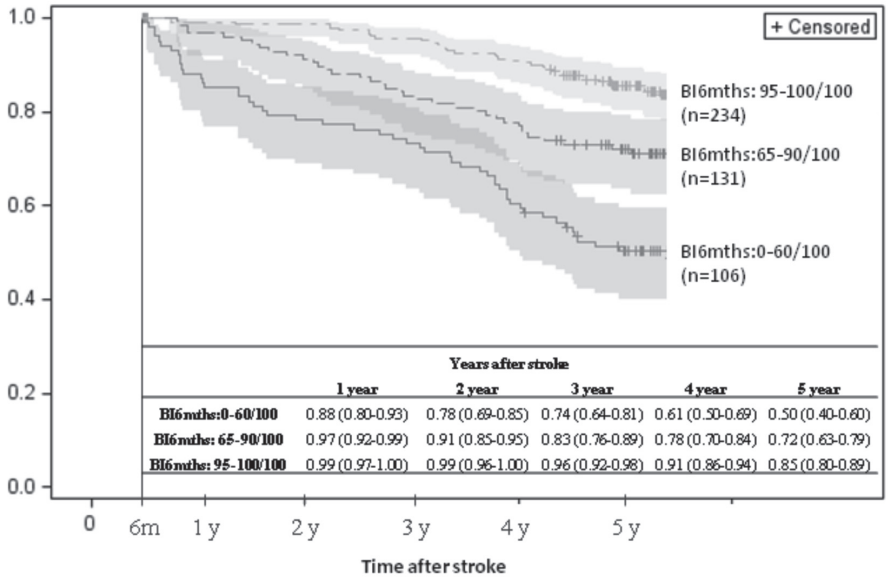

Fig. 2. Kaplan–Meier survival curves for stroke patients according to their functional status at 6 months after stroke onset ($n = 471$). BI6mths: Barthel Index at six months after stroke (0–100), log-rank test: $p < 0.0001$.

(45%) (11) and Indredavik et al. (59%) (12). This seems to be consistent as we recruited patients with a mean of 20 (SD 9) days post-stroke. Hence, we did not observe the high acute mortality rate in the first critical days, as observed in community and hospital-based studies (1–10) and by Indredavik et al. (12) who recruited patients from a combined acute- and rehabilitation stroke unit. Moreover, in the majority of the reported studies (1–4, 6–8, 10–12), patients were recruited in the late 1980s and early 1990s. There are indications that survival rate after stroke has increased since the 1990s, probably due to better stroke prevention strategies (13).

In line with community- and hospital-based studies (3, 6, 7, 9, 10), we found that age, diabetes mellitus, and atrial fibrillation were independently associated with long-term mortality post-stroke. The association with cognitive impairment has been investigated in two other studies, with conflicting findings (3, 8). Hyperlipidaemia was associated with reduced long-term mortality, which is in line with the findings of another study (22). This opposite finding may simply indicate that a low cholesterol level is associated with increased long-term mortality. It is possible that lower cholesterol in these relatively elderly patients may reflect underlying illness and poor nutritional status, which could predispose to a poor outcome after stroke. In future studies, the complex association between cholesterol level and mortality after stroke needs further attention.

For certain variables, HRs differed drastically between univariate and multivariate analysis. Urinary incontinence, swallowing problems, aphasia and dysarthria can each be considered as an indicator for stroke severity, as is the initial Barthel Index. Their HRs became insignificant in the multivariate model where initial Barthel Index was presented with a borderline significance of $p = 0.06$ (p-value is not shown in results). The same was true for coronary heart disease and history of myocardial infarction on the one hand and patients' age on the other hand. Finally, HR altered drastically in the between-centre comparisons. HR ("British vs German centre") and HR ("Swiss vs German centre") indicate that, although not significant, the risk of dying was higher (HR > 1) in patients from British and Swiss centres compared with the German patients in univariate analysis. The opposite (HR > 1) was true in the multivariate analysis. Patients in both the British and Swiss centre were significantly older compared with patients in the German centre (14). Age is an important predictor of mortality, explaining the higher risk of dying for patients in the Swiss and German centre (HR >1 in univariate analysis). When including age into the multivariate model, this effect disappeared.

Finally, we found a strong association between low functional status 6 months post-stroke and increased long-term mortality. The univariate predictive value of BI6mths was 28.5%. This was considerably higher than any baseline variable, making it the most important observed univariate predictor. In multivariate analysis, BI6mths remained significantly associated with long-term mortality. These findings are consistent with other studies (9, 13). In a community-based study, Slot et al. (13) found a significant association between a higher modified Rankin scale (mRS) (more dependency) at 6 months and an increased risk of death. In a hospital-based study, Eriksson et al. (9) found that the mRS at 3 months was a significant independent predictor for long-term survival. The present study indicates that the association between functional disability and survival was also present in a sample of stroke patients who received inpatient rehabilitation. Based on a meta-analysis, Kwakkel et al. (23) reported that minimum 16 h of additional exercise therapy time is required in the first 6 months after stroke to obtain a significant 4–5% improvement in independency for activities of daily living, reflecting a 5-point increase (5%) in BI-outcome. Applying this to the current study sample, a 5% increase in BI6mths-score would produce a shift of 36 patients (7% of total group) to a higher BI6mths class and an accompanying increasing survival chance. Twenty-one percent ($n = 28$) of patients in the middle class would shift to the highest BI6mths class, potentially increasing their 5-year survival probability from 0.72 to 0.85. Eight percent of patients in the lowest class would shift to the middle BI6mths class, potentially increasing their 5-year survival probability from 0.50 to 0.71. Of note, the effect of rehabilitation on survival as such was not evaluated in the present study. Future trials should focus on the effect of additional exercise therapy time on functional outcome and survival.

The importance of our study rests upon the fact that we studied stroke patients who received inpatient rehabilitation. The long-term survival of this specific patient group has received little attention, which is surprising given the healthcare resources consumed by inpatient stroke care. To our knowledge, the current patient sample is larger than any other rehabilitation-based study reporting long-term mortality after stroke (11, 12). Patients were recruited from 4 European rehabilitation centres that were selected because of their established reputation for stroke rehabilitation. Baseline data are detailed and complete. Follow-up was prospective with minimal drop-out at 6 months and 5 years post-stroke. To investigate the association between 6 months functional status and mortality, we could not include 61 patients. Swallowing problems and aphasia occurred significantly more in the drop-out group. Both parameters were significant in univariate, but not in multivariate Cox regression analysis. We believe that the exclusion of these 61 patients is not substantially influencing our findings regarding the effect of 6 months functional status on long-term mortality. In addition, a crude sensitivity analysis (i.e. single imputation of BI6mths values) resulted in only marginally different results that did not alter any of the conclusions. This is reassuring and strengthens our findings. In large cohort studies, weak associations may become significant due to the large sample size. The explained variance (R^2) indicates the strength/weakness of the association between the independent and dependent variable and puts results into perspective. R^2 of the full model was 42.27%, indicating that approximately 58% of the variation in mortality in the first 5 years after stroke was not explained by the baseline model. This unexplained variance may be attributed to unmeasured baseline factors (e.g. cancer) and factors that developed after baseline (e.g. co-morbidities, extent of secondary prevention, etc.). In

previous studies, R^2 was not reported preventing comparison (2, 3, 6, 7, 9, 10). The lack of detailed medical information is a limitation of the study. No detailed information was available on type of medication, blood cholesterol levels, or cognitive impairment. We considered patients to have hyperlipidaemia if blood cholesterol concentration > 200 mg/100ml, based upon a single blood measurement on admission. Serum cholesterol levels in blood samples taken in the morning from fasting patients are more reliable for diagnosis. NIHSS was used to define cognitive impairment. In addition, we were unable to document recurrent strokes in the deceased patients.

In conclusion, nearly one-third of stroke rehabilitation patients died during the first 5 years following stroke. Functional status at 6 months was a powerful predictor of long-term mortality. Interventions that improve post-stroke functional status may have a protective effect on mortality. Maximum functional independence at 6 months post-stroke should therefore be promoted through medical interventions and rehabilitation. Future trials to investigate the effect of additional exercise therapy time on functional outcome and survival are recommended.

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