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Association Between Disability Measures and Healthcare Costs After Initial Treatment for Acute Stroke

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Background and Purpose—The distribution of 3-month modified Rankin scale (mRS) scores has been used as an outcome measure in acute stroke trials. We hypothesized that hospitalization and institutional care home stays within the first 90 days after stroke should be closely related to 90-day mRS, that each higher mRS category will reflect incremental cost, and that resource use may be less clearly linked to the National Institutes of Health Stroke Scale (NIHSS) or Barthel index.

Methods—We examined resource use data from the GAIN International trial comparing 90-day mRS with total length of stay in hospital or other institutions during the first 90 days. We repeated analyses using NIHSS and Barthel index scores. Relationships were examined by analysis of variance (ANOVA) with Bonferroni contrasts of adjacent score categories. Estimated costs were based on published Scottish figures.

Results—We had full data from 1717 patients. Length of stay was strongly associated with final mRS ($P<0.0001$). Each mRS increment from 0 to 1–2 to 3–4 was significant (mean length of stay: 17, 25, 44, 58, 79 days; $P<0.0005$). Ninety-five percent confidence limits for estimated costs (£) rose incrementally: 2493 to 3412, 3369 to 4479, 5784 to 7008, 7300 to 8512, 10 095 to 11 141, 11 772 to 13 560, and 2623 to 3321 for mRS 0 to 5 and dead, respectively. Weaker relationships existed with Barthel and NIHSS.

Conclusions—Each mRS category reflects different average length of hospital and institutional stay. Associated costs are meaningfully different across the full range of mRS outcomes. Analysis of the full distribution of mRS scores is appropriate for interpretation of treatment effects after acute stroke and more informative than Barthel or NIHSS end points. (*Stroke*. 2007;38:1893-1898.)

Key Words: Barthel index ■ healthcare costs ■ modified Rankin Scale (mRS) ■ NIHSS ■ resource utilization

The recent paper published by Lees et al in the *New England Journal of Medicine* on results of the SAINT trial found that modified Rankin scale (mRS) scores at 90 days were significantly more favorable after acute stroke in those treated with NXY-059 compared with placebo (OR=1.20, 95% CI=1.01 to 1.42).[1] The benefit was more modest than some observers desired[2] and was not accompanied by significance on the secondary outcomes. It included benefits across the range 0 to 2 on mRS that have not previously attracted attention.[3] The distribution of National Institutes of Health Stroke Scale (NIHSS) scores,[4] which measure neurological examination, and of the Barthel index,[5] which measures activities of daily living, both showed similar trends to improvement, although differences were not significant at 90 days. However, variability in these latter scores is greater, and the mRs[6] has become the preferred end point for acute stroke trials.[7–9] Furthermore, stroke is a devastating

condition associated with vast economic cost,[10] and few patients are able to receive thrombolytic therapy. Because of this, modestly effective treatments may offer substantial clinical and economic benefits when delivered to a high proportion of patients.

Two important questions therefore arise: 1) How meaningful is improvement in mRS scores at 90 days in terms of social and economic cost? 2) In terms of resource utilization, are day 90 mRS scores a more robust measure than NIHSS and Barthel index scores?

Data on these 2 questions are limited. Previous work suggests that mRS categories are clinically distinct and are meaningful to both patients and drug-regulatory authorities.[11] Higher economic costs have been associated with higher disability levels on discharge as measured by the Rankin scale.[12–14] However, analyses have been dichotomized and based on crude splits in mRs score disregarding information

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about any difference in costs associated with Rankin categories 0 to 1 and 3 to 4 for example. Furthermore, the time of Rankin assessment in these studies was typically at discharge rather than after a predetermined interval, biasing the estimates and rendering extrapolation to trial data difficult.

Attempts to link resource use to Barthel index scores have yielded even weaker associations.[14–16] Equally, the Barthel index has recently been criticized as a trial outcome measure on grounds of its U-shaped distribution and ceiling effect both of which render it less sensitive to drug treatment effects.[7,9] The NIHSS was designed to assess severity at trial entry and not as an outcome measure.[4] The scoring rules for NIHSS are complex and restrictive. Patients who learn to live with their disability scored poorly on NIHSS, although their functional outcome measures improve. Patients who die of unrelated causes are awarded the theoretically worst possible score of 42, producing a bimodal and skewed distribution of "change" scores when compared with baseline stroke severity. This undermines the very attraction of such comparisons with baseline severity. Thus, the NIHSS score is informative early after stroke, but when correctly scored, it poorly reflects later outcome and, as yet, no link has been made between change in NIHSS score and socioeconomic costs.

We hypothesized that by using records of resource use from GAIN International,[17] we would be able to demonstrate that the healthcare costs associated with stroke vary according to the mRS category achieved by 90 days. Demonstration of such differences would inform interpretation of future acute stroke trials. We further hypothesized that if mRS is a more meaningful outcome measure than Barthel index or NIHSS, then it would exhibit the strongest association with healthcare costs.

Methods

We extracted and analyzed data from original records of the GAIN International trial conducted in 1998 to 1999 and first reported in 2000. GAIN was a multicenter randomized, double-blind, placebo-controlled trial of gavestinel after acute stroke. Patients were aged greater than 18 years old with symptoms of acute stroke, including limb weakness, who were previously independent and were randomized and treated within 6 hours of onset of stroke. Data extraction and preparation for analysis were performed by 2 researchers (T.P.C. and J.S.L.). Checks of resource use validity were undertaken by reference to vital status records and functional outcomes.

Collection of Outcome Data

In GAIN, a trial investigating a neuroprotective compound, mRS, Barthel index, and NIHSS scores were gathered at 1 month and 3 months from recruitment. Outcomes on mRS were assessed by local observers according to a standard scoring system. No formal training or certification was offered. To assist consistency, observers were offered advice on scoring of Barthel index in the form of a video demonstration but no certification procedure was in place. All observers had been trained and were certified in use of the NIHSS scoring system.

Collection of Resource Use Data

Resource use was recorded by trial staff at the 90-day follow-up visit based on interviews with patients or their relatives or caregivers and on review of hospital records. In particular, detailed data regarding duration of hospitalization or time spent in nursing facilities was gathered. Hospital bed occupancy was recorded in 6 categories: emergency room, intensive care, high dependency, general ward,

rehabilitation unit, or undefined. Nonhospital placement postdischarge was also collected in 6 categories: own home, relative's home, intermediate-care facility, nursing/convalescence home, rehabilitation facility, or undefined. For the purposes of this analysis, all high-dependency and medical bed-days were grouped together and considered separately from days spent in nursing or institutional residential care. Days spent in the patient's own home were grouped together with time spent in a relative's home; the remainder was classed as intermediate care. Length of stay was defined as the total time in the hospital and intermediate or nursing/institutional care (all places except the patient's or a relative's home).

Costs of hospital bed occupancy were taken from published Scottish Health Service statistics for 2005 (£207 per day for hospital care [or $408]).[18] Costs of subsequent institutional or nursing home care were based on £350 per week (or $689).[19] No additional cost was ascribed to care in the patient's own or a relative's home.

Only outcomes actually recorded at 90±7 days were used; missing data were not imputed. Resource use was censored at 90 days. When final follow up occurred earlier than 83 days in a patient who survived past 90 days, last known placement was extrapolated to 90 days; patients in whom dates of placement were not recorded were excluded from analysis. Deaths within 90 days were excluded from the primary statistical analysis on the grounds that resource use would inevitably be lower and that death is the least desirable health state; however, data are shown for completeness.

Statistical Methods

One-way ANOVA was used to assess outcome-related trends in resource use or costs for mRs scores, Barthel index, and NIHSS scores. After significant ANOVA results, adjacent categories of each scale were compared by Bonferroni testing. Analyses were conducted using StatsDirect statistical software version 2.4.5 (StatsDirect Ltd).

Results

Seventeen hundred eighty-eight patients were included within the intent-to-treat analysis of GAIN international of whom 56 withdrew from the study before 90 days for reasons other than death. Incomplete data on resource use or final outcome scores were available for a further 15 patients, leaving 1717 in our analysis population. Mean age (±SD) was 69.7±12.2 years. Mean baseline NIHSS score was 13.1±6.2 points. Seven hundred thirty-seven patients (42.9%) were female and 321 (18.7%) had primary intracerebral hemorrhage. Overall, our population spent a mean of 28 days in the hospital, 17 days in intermediate institutional care, and 31 days in domestic premises.

Length of stay was strongly associated with final mRS score and with Barthel index category trichotomized into 0 to 55, 60 to 90, and 95 to 100. All categories of mRS significantly differed from their neighbor apart from mRS 4 and 5, which were indistinguishable (Figure 1; Table). In-hospital stay was greater for mRS category 5, however, and when estimated costs were included in the model, mRS 5 was found to consume significantly more resource than mRS 4 (Table).

Length of stay for Barthel categories could only be distinguished across the Barthel range 90 to 95–100 with other categories contributing little useful discriminating information (Figure 2). Costs could be distinguished only between Barthel 100 and 95.

Length of stay was significantly associated with 90-day total NIHSS score, but between-category differences were present only across the NIHSS ranges 0 to 1 and 4 to 5 (Figure 3) and only categories 0 to 1 could be distinguished
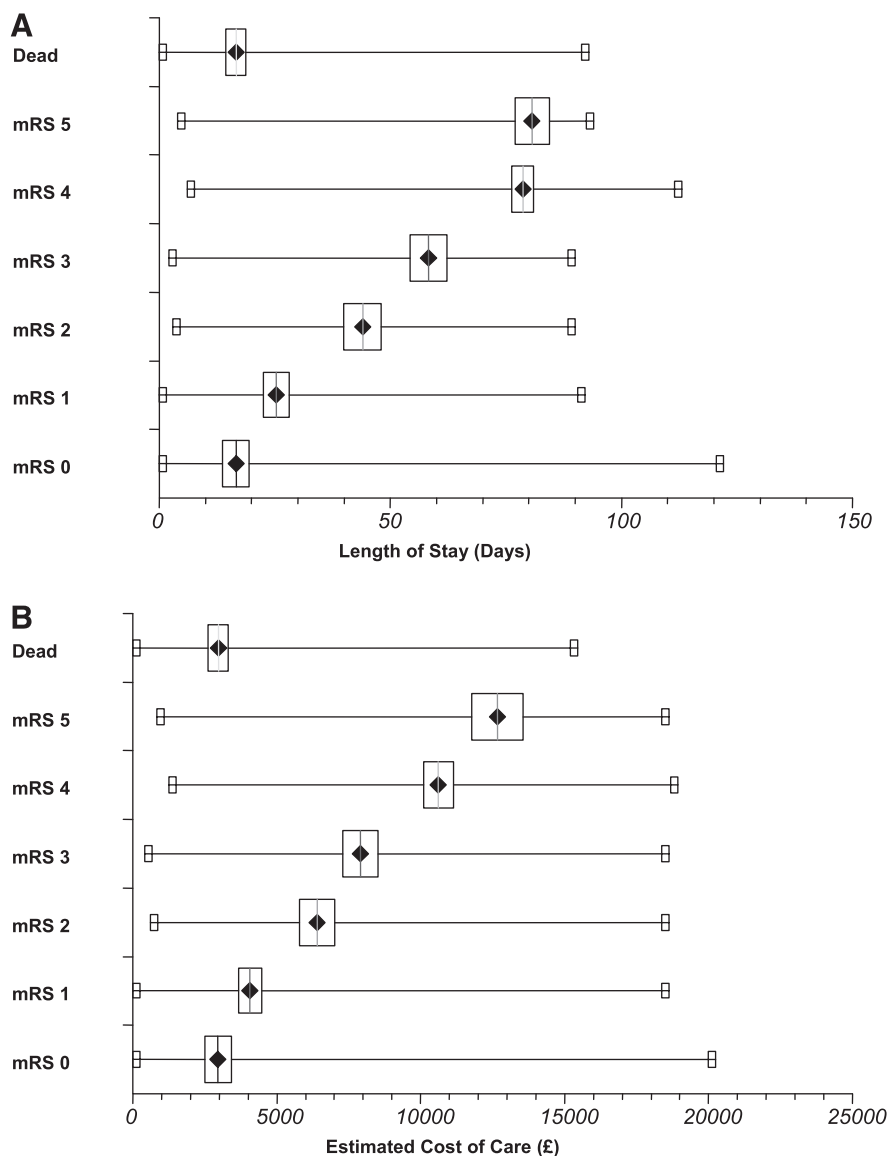
Figure 1. A, Length of stay during first 90 days after acute stroke according to final mRS. Each category is significantly different from its neighbor by ANOVA ($P<0.0001$) and subsequent Bonferroni testing (all $P<0.0005$), except that mRS categories 4 and 5 were not significantly different. Box plots represent the minimum, mean±95% CI, and maximum duration of institutional stay. B, Estimated cost of institutional stay during first 90 days after acute stroke according to final mRS. Each category is significantly different from its neighbor by ANOVA ($P<0.0001$) and subsequent Bonferroni testing (all $P<0.0005$ except mRS 0 versus mRS 1 ($P=0.023$) and mRS 2 versus mRS 3 ($P=0.0015$). Box plots represent the minimum, mean±95% CI, and maximum cost of institutional stay.

with regard to estimated cost. When the change in NIHSS score from baseline was examined (ie, 90-day score minus baseline score), no significant differences were found and results showed considerable scatter (data not shown).

In total, the mean 90-day cost of stroke, excluding specific rehabilitation costs, was £6603±5424.

Discussion

We have found that a significant and graded relationship exists between 90-day mRS score and hospital, intermediate or institutional care bed occupancy, confirming that even

short-term costs are substantially affected by the degree of recovery at 3 months after stroke. When translated into estimated care costs, excluding specific rehabilitation input, we have found that each increment in mRS score adds significantly to the 90-day cost of care. We can speculate that such differences will accumulate substantially through time over longer-term follow up.

We have demonstrated that certain categories on Barthel index are also associated with changing bed occupancy and cost but that the relationship is not graded across the entire scale as it is with mRS. Apart from the range 90 to 100,

Length of Stay and Estimated Costs Across the 6 mRS Categories in Survivors

	mRS 0 (n=197)	mRS 1 (n=268)	mRS 2 (n=205)	mRS 3 (n=214)	mRS 4 (n=366)	mRS 5
Median, mean LOS	9, 17	17, 25‡	37, 44‡	64, 58‡	90, 79‡	90, 81
Mean hospital: intermediate LOS	14: 3	18: 7	27: 17	32: 26	43: 36	55: 26
Estimated costs: 95% CI	2493 to 3412	3369 to 4479*	5784 to 7008‡	7300 to 8512†	10 095 to 11 141‡	11 772 to 13 560‡

*$P<0.025$, †$P<0.005$, ‡$P<0.0005$ for difference when compared with preceding column.
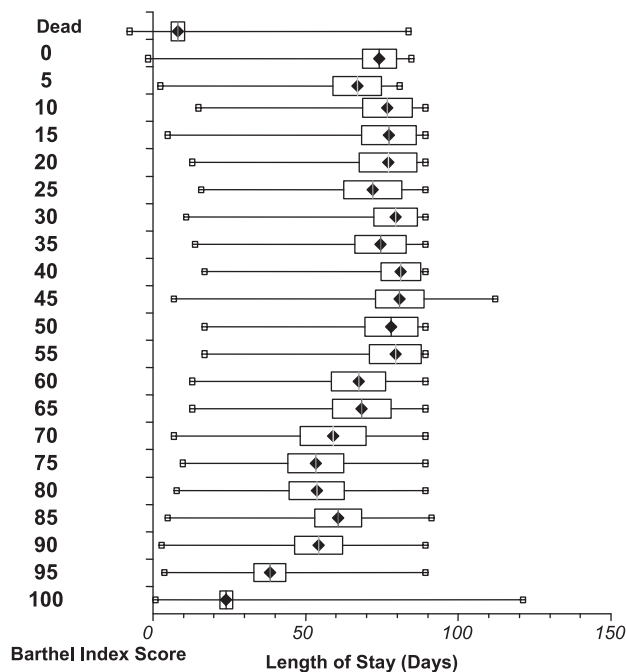LOS indicates length of stay.

Figure 2. Length of stay during first 90 days after acute stroke according to final Barthel score. Duration of stay was associated with Barthel index (*P*<0.0001 by ANOVA), but on Bonferroni testing of adjacent categories, significant differences were found only within the range 90 to 95–100. However, if Barthel scores were grouped (0 to 55, 60 to 90, and 95 to 100), then each group differed significantly from its neighbor (data not shown).

Barthel index scores offer little useful information in this regard. Our study has only examined resource use in terms of bed occupancy over the first 90 days. It remains possible that Barthel index scores would be more informative in predicting longer-term use of other types of support services.

The GAIN International trial included a wide range of patients considered to be representative of the usual acute stroke population. The data on resource use were collected during end point assessment and were monitored and verified against source data. A limited number of patients withdrew consent for follow up and there were few missing observations. These were not of a frequency or nature that would influence the conclusions. International variation in clinical practice will influence total length of stay and the proportion in various categories. Costs of hospital and intermediate institutional care will also vary. We have therefore chosen not to subdivide types of hospital or intermediate care in our analysis, but have supplied sufficient data within our report for reinterpretation based on alternative estimates of costs. We used £207 as our cost for hospital care, which was based on the cost of a medical day bed. Total costs will have been underestimated for those who required high dependency or intensive care, but this will only have attenuated the relationship we have seen. Costs in Scotland may be lower than in other countries, in particular the United States, but the proportional changes should be similar. The definitions used also explain why the lengths of stay appear long. For

example, a median and mean length of stay of 9 and 17 days, respectively, was seen in those with a day 90 mRS of 0. Importantly, these figures include stays in rehabilitation units and therefore provide a more meaningful measure of impact and cost of stroke than, for example, duration of stay in acute medical or high-dependency beds; the time taken to attain full recovery is often underestimated.

Previous studies have shown a relationship between resource utilization and level of handicap, in particular when the mRs is used. However, these were limited in size and follow-up periods were uncontrolled. Ninety days has become the standard time for end point assessment in acute stroke trials. Furthermore, prior reports typically divided their populations for these analyses into Rankin 0 to 2 versus 3 to 6 disregarding information about the costs associated with individual Rankin categories, especially in the range 0 to 2.[3] We elected not to do this in our study. Also, direct comparisons between different measures of functional outcome have not been made with regard to resource use. Establishing the relationship between 90-day outcome and resource use and exploring whether one outcome measure is more clearly associated is of direct relevance to, and would aid interpretation of, clinical trial data.

We have now shown in an independent population that there are significant differences in resource use in terms of institutional bed occupancy and estimated institutional costs that are strongly associated with mRs scores and with each incremental increase in score, even in the range 0 to 1–2. The finding that estimated institutional care costs are significantly related to 90-day Barthel index is not a surprise, but the lack of a convincing graded influence of the Barthel index may surprise proponents of the scale. However, this has been suggested by other groups.[14–16] Our results suggest that, when compared with the mRs, the Barthel index is less clearly related to outcomes that matter to patients and to healthcare providers, which reaffirms the belief that mRS outcomes and nondichotomized methods of analysis should be used. Our results also suggest that changes in disability level not captured by traditional dichotomized analyses are both clinically and economically significant and that small shifts from mRs category 4 to 3 in particular are likely greatly to reduce care costs. Because mRS categories are loosely described and because there is variation among observers in scoring an individual patient, further attempts to improve its reliability such as the formal training and certification program developed in Glasgow should be used.

It is clear from our results that "change from baseline in the NIHSS" has serious statistical disadvantages as an outcome measure, but an examination of the relationship between NIHSS scores and robust measures of outcome such as duration of care remains of interest. We find in this independent sample that change in NIHSS score relates poorly to duration of institutional stay over the first 90 days after stroke and to estimated resource use. This adds to the evidence that change in NIHSS appears to be an inappropriate end point for acute stroke trials. Final total NIHSS score may experience fewer disadvantages. The relation between 90-day total NIHSS score and institutional care was statistically signifi-
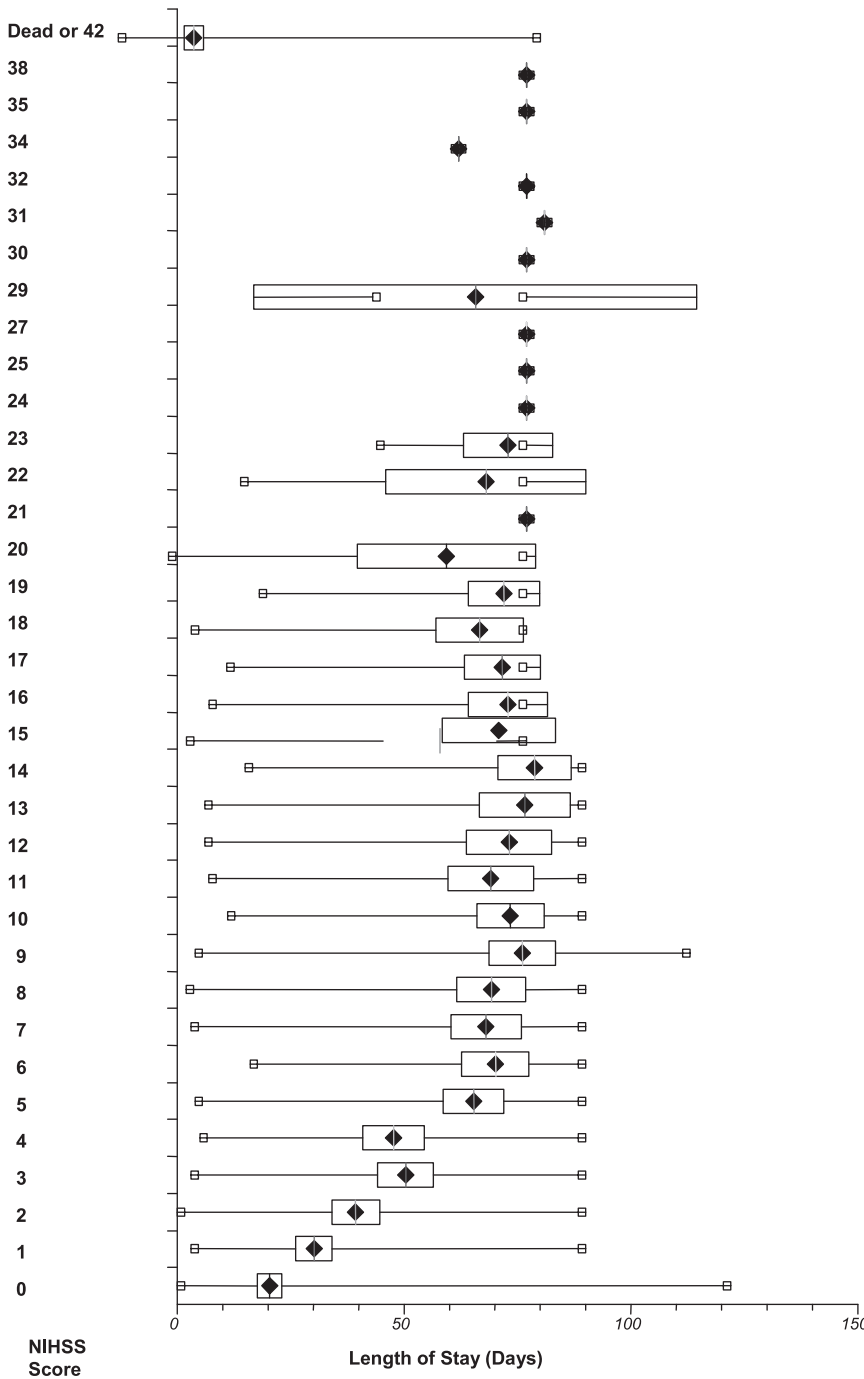
Figure 3. Length of stay during first 90 days after acute stroke according to final total NIHSS score. There is an overall difference among categories by ANOVA ($P<0.0001$), but significant differences between adjacent categories were present only within the ranges 0 to 1 and 4 to 5.

cant but mainly restricted to final scores in the range of 0 to 5. NIHSS therefore appears to have similar weaknesses to use of the Barthel index.

The results of our study are widely applicable. Although the GAIN International trial was reported 4 years ago, it included a similar range of countries and sites, a similar patient group, and recorded outcomes in a similar manner as recent and ongoing trials. Also, detailed records were prospectively collected regarding resource use. Clinical practice may have changed since the GAIN trial was conducted, especially in regard to thrombolytic therapy with recombinant tissue-type plasminogen activator. This is likely to influence functional outcomes but should not alter the relation among

functional recovery, bed occupancy, and associated costs. If outcomes are improved overall by modern care, then resource use within the first 90 days will assume even greater relevance.

In conclusion, mRS at 90 days is strongly associated with institutional bed occupancy over the preceding 3 months and with estimated care costs. Each grade on the mRS carries a different cost in terms of resource use, including the distinction between mRS 0 (no symptoms) and mRS 1 (symptoms but no disability). The mRS is thus a useful scale to assess outcome after acute stroke outcome and has several advantages over the Barthel index or NIHSS, including its relation to institutional resource use and discrimination.

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Disclosures

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