Is the proportional recovery rule applicable to the lower limb after a first-ever ischaemic stroke?

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ABSTRACT

Background and objective To investigate (a) the applicability of the proportional recovery rule of spontaneous neurobiological recovery to motor function of the paretic Lower Extremity (LE); and (b) the presence of fitters and non-fitters of this prognostic rule post stroke. When present, the clinical threshold for fitting nor non-fitting would be determined, as well as within-subject generalisability to the paretic Upper Extremity (UE).

Methods Prospective cohort study in which the Fugl-Meyer Assessment (FMA)-LE and FMA-UE were measured < 72 hours and 6 months post stroke. Predicted maximum potential recovery was defined as \[\text{FMA-LE}_{\text{max}} - \text{FMA-LE}_{\text{initial}} = 34 - \text{FMA-LE}_{\text{initial}}\]. Hierarchical clustering in 202 first-ever ischaemic stroke patients distinguished between fitting and not fitting the rule. Descriptive statistics determined whether fitters and non-fitters for LE were the same persons as for UE.

Results 175 (87%) patients fitted the FMA-LE recovery rule. The observed average improvement of the fitters was ~64% of the predicted maximum potential recovery. In the non-fitter group, the maximum initial FMA-LE score was 13 points. Fifty-one out of 78 patients (~65%) who scored below the identified 14-point threshold at baseline fitted the FMA-LE rule. Non-fitters were more severely affected than fitters. All non-fitters of the FMA-LE rule did also not fit the proportional recovery rule for FMA-UE.

Conclusions Proportional recovery seems to be consistent within subjects across LE and UE motor impairment at the hemiplegic side in first-ever hemispheric ischaemic stroke subjects. Future studies should prospectively distinguish between fitters and non-fitters within the subgroup of patients who have initial low FMA-LE scores. Subsequently, patients could be stratified based on fitting or not fitting the recovery rule, as this would impact rehabilitation management and trial design.
INTRODUCTION

It is suggested that about 90% of all neurological improvement during the first 6 months after stroke is defined by progress of time alone. However, the neurophysiological mechanisms driving neurobiological recovery are poorly understood. Prospective studies showed that the amount of neurobiological recovery of the paretic Upper Extremity (UE), VisuoSpatial Neglect (VSN), and speech is relatively fixed – ranging from 60 to 97% – and highly predictable. Proportional recovery is the percentage that a patient improves over time for a specific measure, such as the Fugl-Meyer Assessment (FMA) motor score, in relation to his or her theoretical maximum improvement on that specific measure. Patients with first-ever right hemispheric lesions who do not follow the proportional recovery rule (i.e. ‘non-fitters’, patients who improve to a lesser extent on a specific measure than would have been expected based on the proportional recovery rule) for one modality such as motor recovery of the upper limb are also likely not to follow the rule on other modalities such as VSN. This suggests that mechanisms driving spontaneous neurobiological recovery post stroke generalise across neurological impairments. Recently, in a small cohort of 32 patients, it was shown that the maximum proportional recovery rule is also applicable to motor function of the paretic Lower Extremity (LE). However, the lack of a non-fitter group in this cohort was an unsuspected finding, as all previous studies regarding proportional recovery identified such a cluster.

The present study therefore aimed to investigate the generalisability of the ‘proportional recovery rule’ for motor function of the paretic UE, measured with the Fugl-Meyer Assessment (FMA) UE subscale, to motor function of the paretic LE, measured with the FMA-LE subscale within 72 hours and at 6 months post stroke in a considerably larger cohort of first-ever ischaemic hemispheric stroke patients. This included investigating the presence of both fitters and non-fitters of the proportional recovery rule. When present, the secondary aims were to determine whether (a) there was a clinical threshold for the FMA-LE within 72 hours, separating non-fitters from fitters; (b) fitters and non-fitters could be distinguished based on demographic and clinical characteristics at baseline; and (c) fitters or non-fitters of the proportional recovery rule for the LE were the same patients who do or do not show proportional recovery for the paretic UE.
MATERIALS AND METHODS

Data from the prospective cohort of the Early Prediction of functional Outcome after Stroke (EPOS) study were used. Details of this study have been published elsewhere. Stroke patients were included when they met the following criteria: (1) first-ever ischaemic anterior circulation stroke in one hemisphere; (2) mono- or hemiparesis < 72 hours after onset; (3) premorbid Barthel Index score ≥ 19 out of 20; (4) aged ≥ 18; (5) no severe deficits of communication, memory, or understanding; and (6) written informed consent. For this study, only patients were included who had a FMA-LE motor score of less than 34 (i.e. a lower limb paresis), a FMA-UE motor score of less than 66 (i.e. an upper limb paresis) within 72 hours post stroke, and with available FMA-LE and UE scores at 6 months post stroke.

Ethical approval was obtained before start of participant recruitment from the nationally certified Ethical Committee of the VU University Medical Center, Amsterdam, the Netherlands (https://www.vumc.nl/afdelingen/METc/METc/). Local feasibility was approved by the institutional review boards of the participating hospitals (AMC, Amsterdam; Erasmus MC, Rotterdam; LUMC, Leiden; UMC Sint Radboud, Nijmegen; UMC Utrecht; Amphia Hospital Breda; Diaconessen Hospital, Leiden; Franciscus Hospital, Roosendaal) and nursing homes (Sint Jacob, Amsterdam; Zonnehuis, Amsterdam; Cordaan/Berkenstede, Amsterdam; Laurens Antonius Binnenweg, Rotterdam; Reumaverpleeghuis, Rotterdam; Albert van Koningsbruggen, Utrecht; Wiekendaal, Roosendaal). The capacity to consent was determined during the screening and consent visits. This was based on the patients’ ability to (1) understand the participant information (oral and written); (2) explain why they were admitted to the hospital; and (3) follow two-staged commands as requested in the Mini-Mental State Examination.

The FMA-LE (score range 0–34) and FMA-UE (score range 0–66) subscales were measured within 72 hours and at 6 months after onset. The FMA quantifies limb impairment in terms of synergistic (in)dependent motor control. Observed motor recovery of the lower extremity was defined as $\Delta FMA-LE = FMA-LE_{6\text{ months}} - FMA-LE_{\text{initial}}$ and predicted maximum potential recovery as $FMA-LE_{\text{max}} - FMA-LE_{\text{initial}} = 34 - FMA-LE_{\text{initial}}$.

Hierarchical clustering analysis based on the average pairwise Mahalanobis distances method was used to classify patients into fitters and non-fitters of the proportional recovery rule (Matlab’s Statistic toolbox, version 8.1, Matlab version 2013a, Mathwords Inc, Natwick, MA). We selected the Mahalanobis distance method and not the more common used Euclidian
distance with circular boundaries, as it also takes co-variances into account and leads to elliptic decision boundaries. Fitters were defined as patients who showed a comparable amount of predicted maximum potential and observed improvement on the FMA-LE. Patients who did not show this comparable amount of predicted maximum potential and observed improvement were considered non-fitters. Goodness-of-fit was assessed by the cophenetic correlation and the Spearman correlation between the Mahalanobis and cophenetic distances obtained from the dendrogram. Linear regression was applied to determine the percentage of the predicted maximum potential recovery ($R^2$) that explained the observed change of the LE in the fitter subgroup. Normality of data was checked by visual inspection of histograms. Patient characteristics were analysed by descriptive statistics. Differences between fitters and non-fitters by the independent $t$-test for parametric data, Pearson's $X^2$ test for categorical data, and the Mann-Whitney U test for nonparametric data.

To assess the threshold value on the initial FMA-LE for not fitting the proportional recovery rule, the highest score of the initial FMA-LE in the non-fitter subgroup was taken. The sensitivity, specificity, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) of this threshold were determined. In a next step, characteristics were compared between patients who scored below this threshold value but still fitted the rule and those who did not. SPSS (version 22) was used unless indicated otherwise and a 2-tailed $p$-value $< .05$ was considered statistically significant.

Predicted maximum potential recovery and observed change for the upper extremity were defined as $[FMAUE_{\text{max}} - FMAUE_{\text{initial}} = 66 - FMAUE_{\text{initial}}]$ and $[\Delta FMAUE = FMAUE_{\text{6 months}} - FMAUE_{\text{initial}}]$. Subsequently, $\Delta FMA$-LE and $\Delta FMA$-UE were expressed as percentages of their maximum possible scores in order to compare the distribution of maximum potential and observed recovery. Descriptive statistics were used to determine whether fitters and non-fitters were the same persons for both outcomes.

**RESULTS**

A total of 202 patients met the present inclusion criteria (Figure 4.1). The mean age of the total sample was $66.62 \pm 13.97$ years, 106 (52.5%) subjects were male, and the mean National Institutes of Health Stroke Scale (NIHSS) score within 72 hours was $9.27 \pm 5.78$ points. Hierarchical clustering analysis showed that 175 patients (86.6%) fitted the FMA-LE proportional recovery rule (Figure 4.2). The goodness-of-fit was $c = 0.73$ (i.e. cophenetic
correlation coefficient) and $r_s = 0.80$ (Spearman correlation). Two patients had high predicted maximum potential recovery and observed recovery (data points at the top right corner of Figure 4.2). These patients were also characterized as ‘outliers’ in the hierarchical cluster analysis. However, as their predicted and observed recovery matched, they were added to the ‘fitters’ group. Note that there were patients who had lower scores at follow-up, in comparison to their initial FMA-LE score, which resulted in a negative $\Delta$FMA-LE (see Figure 4.2). As these patients were part of the groups based on the hierarchical clustering analysis and the decline in FMA-LE score was within the measurement error of the FMA-LE, we did not exclude these patients from analyses.
For the fitters, the median FMA-LE maximum potential recovery was 12 (interquartile range, IQR = 6–22) points and ΔFMA-LE was 8 (IQR = 3–14). For the non-fitters, these were 30 (IQR = 25–32) and 3 (IQR = 0–6), respectively. The observed improvement of the fitters was ~64% (95% confidence interval, CI = 59–69%) of the predicted maximum potential recovery (i.e. proportional recovery). At baseline, fitters had significantly lower neurological impairments and less motor impairment when compared to non-fitters ($p < .001$; Table 4.1). In addition, predicted maximum potential recovery of both FMA-LE and FMA-UE was significantly higher in fitters ($p < .001$).
The maximum initial FMA-LE score within the non-fitter group \((N = 27)\) was 13 points (38% of the total score). Overall, 78 patients had a FMA-LE score of 13 points or lower at baseline. In this subgroup, 51 patients (~65%) fitted the rule for the lower extremity and 27 (~35%) did not.

The sensitivity was 0.71 (95% CI = 0.63–0.77), the specificity 1.00 (95% CI = 0.84–1.00), the positive predictive value 1.00 (95% CI = 0.96–1.00), and the negative predictive value 0.34 (95% CI = 0.24–0.46). The non-fitters were more severely affected than the fitters, as
indicated by the initial NIHSS (17 (IQR = 15–20) and 13 (IQR = 9–17), respectively; \( p = .001 \)) and Bamford classification (LACI = 1, PACI = 13, TACI = 13 vs. LACI = 20, PACI = 15, TACI = 16, respectively; \( p = .008 \)).

Comparing fitters and non-fitters for both the predicted maximum potential and observed \( \triangle \)FMA-LE showed the same pattern as for the maximum potential and observed \( \triangle \)FMA-UE (Figure 4.3). All non-fitters of FMA-LE (\( N = 27 \)) also did not fit the rule for FMA-UE. Thirty-eight (21.7%) of the FMA-LE fitters did not fit the rule for FMA-UE. Conversely, none of the patients that were non-fitters on FMA-UE fitted the rule for FMA-LE.

**DISCUSSION**

The present prospective cohort study confirmed that the proportional recovery rule is generalisable to motor function of the paretic lower extremity in patients with a first-ever ischaemic hemispheric stroke. Patients who fitted this rule improved on average 64% (95% CI = 59–69%) of their predicted maximum potential recovery. In addition, the present study

![Image](image-url)
shows that also for motor function of the LE, there seems to be a subgroup of patients who did not fit the proportional recovery rule (i.e. non-fitters). These non-fitters are characterized by having more neurological impairments such as hemianopia, VSN, and sensory loss, when compared to patients who did follow the rule (i.e. fitters). Importantly, all patients who had an initial FMA-LE score of 14 points or higher within 72 hours post stroke did follow the proportional recovery rule, whereas only 35% of the patients with scores below this critical threshold failed to follow the expected amount of spontaneous neurobiological recovery. This finding also suggests that even stroke patients with a very severe lower extremity deficit (i.e. below 14 points on a FMA-LE) at stroke onset may show a tremendous amount of spontaneous neurobiological improvement of up to 20 out of 34 points on the FMA-LE. This proportion of non-fitters was about 13% (N = 27) of our total cohort. This critical threshold of 14 points is in line with the threshold found for non-fitters of the FMA-UE (i.e. < 17 points) and suggests that there are common threshold-dependent mechanisms which define proportional recovery within the first days after a first-ever ischaemic stroke. Moreover, hemiplegic patients who were non-fitters of motor function of the paretic LE (N = 27) were also non-fitters on the proportional recovery rule of the paretic UE.

Our findings are in line with previous studies about the proportional recovery rule of motor function of the upper\textsuperscript{3-6} and lower extremity,\textsuperscript{9} speech,\textsuperscript{8} and VSN.\textsuperscript{7} However, in contrast to the recent published study of Smith and co-workers,\textsuperscript{9} the present larger cohort did include also some more severely affected hemiplegic stroke patients with an unfavourable prognosis for recovery of gait.\textsuperscript{10} Obviously, a number of these patients with a poor prognosis for gait did not follow the proportional recovery rule (i.e. non-fitters) of spontaneous neurobiological recovery after stroke. With that, we suggest that spontaneous neurobiological recovery is a consistent intra-hemispheric phenomenon that seems to occur irrespective of affected neurological impairments post stroke. In addition, this ‘70% recovery rule’ is not fixed, but may show variance ranging from 64% for motor recovery of the paretic LE (95% CI = 59–69%) in the present study to 97% (95% CI = 82–112) for VSN.\textsuperscript{7} At least, the result from the current and previous cohort studies in this field further confirm that proportional recovery is inherent to acute stroke and reflects common underlying mechanisms of spontaneous neurobiological recovery.

The key challenge is to disentangle the underlying causes that define the 10 to 30% of the stroke patients that did not follow the proportional recovery rule, irrespective of initial lower or upper extremity motor deficit and irrespective of the involved neurological modality opposite of the hemispheric lesion.\textsuperscript{7} Although stroke volume could intuitively
be thought of as an important cause of not showing proportional recovery, Prabhakaran and colleagues showed that subcortical infarct volume was significantly related to change in FMA-UE scores in both fitters and non-fitters. Other studies showed that there is no significant relation between lesion volume and proportional recovery of UE motor function and language. It is suggested that the metabolic cascade (initially starting with energy failure due to hypoperfusion) that causes the intrinsic degeneration of distal axons, known as Wallerian degeneration, is fundamental to absence of spontaneous neurobiological recovery, as mechanisms that suppress spontaneous neurobiological recovery early after stroke are highly associated with disruption of the corticospinal tract. However, one may also suggest that ‘abnormal network interactions’ suppress spontaneous neurobiological recovery, such as a deactivation to an anatomically related intact area or the changes in connectivity with this remote brain area (i.e. diaschisis). It could be hypothesized that, for example, when the connectivity in the brain network is not normalized, motor recovery is negatively influenced and patients do not show proportional recovery. In addition, potential factors that may limit neurobiological recovery are polymorphisms of the Brain-Derived Neurotrophic Factor (BDNF) gene, as well as blood-brain barrier dysfunction that is associated with vasogenic oedema. We therefore advocate that the focus of future research should not only be on validating the proportional recovery rule and its intra-hemispheric generalisability for other affected modalities, but also on understanding underlying mechanisms of spontaneous neurobiological recovery. The ability of innovative pharmacological interventions to influence the proportion of non-fitters should be investigated as well. Examples are immunotherapy targeting the neurite growth-inhibitory protein Nogo-A, therapies enhancing phasic GABA inhibition, and neural network modulating therapies. Specifically, GABA (gamma-aminobutyric acid) is an inhibitory neurotransmitter that contributes to cortical functions, including motor control. Pharmacological agents may modulate phasic (synaptic) GABA signaling, which is suggested to enhance brain repair and plasticity related recovery after stroke. In addition, pharmacological agents are also suggested to modulate non-invasive brain stimulation-induced network reorganization. However, at this moment, we do not know which of these interventions are effective. Keeping in mind the suggested critical time window of recovery, these interventions should preferably be initiated within the first days post stroke. Furthermore, research is needed to identify factors that hamper neurobiological recovery and which may lead to a relatively higher proportion of patients who do not follow the expected proportional recovery after stroke. For example, one may assume that high doses of early mobilisation enhances orthostatic variation in penumbral and oligemic brain
areas early post stroke, and with that, may increase neurological damage early after stroke onset. Therefore, neuro-imaging and neurophysiological determinants such as the quality of collateral blood flow defining early regional perfusion within the first 24 hours post stroke, the integrity of the affected corticospinal tract and its (a)symmetry index, stroke location (grey matter versus white matter), and dynamics in brain connectivity should be taken into account when investigating neurobiological markers of proportional recovery. However, a recent systematic review showed that studies that use neurological biomarkers of brain impairment for prediction of motor recovery post stroke such as diffusion tensor imaging, structural MRI, and transcranial magnetic stimulation need to improve their methodological quality in terms of cross-validation, considering the minimally clinical important difference of motor recovery, and recruitment of a large enough sample to provide sufficient statistical power. In light of these recent findings, there is a need to underpin the added value of these neurological biomarkers next to behavioural markers in improving the predictive accuracy (i.e. true and false negatives) of fitters and non-fitters of the proportional recovery rule.

The first and main limitation of the present study is the exclusive use of clinical measures. Combining clinical with neuropsychological markers may improve prediction of neurobiological outcome, but further research needs to assess the cost-benefits of neuro-imaging measures in addition to clinical measures in predicting functional outcomes post stroke. Second, prediction of LE recovery following the FMA is less precise than for the UE. Although the reliability of the FMA has been described as excellent, the measurement error for the LE subscale is 6.4 points, resulting in a reliability change index of about 19% of the maximum score. In contrast, the measurement error for the UE is 7.2 points, which is about 11% of the maximum score. Consequently, this lack of precision makes the distribution of fitters and non-fitters along the estimated regression line in Figure 4.2 wider and more scattered when compared to the one for the paretic UE. In addition, due to the more scattered data points, using a different method to differentiate between fitters and non-fitters may have resulted in slightly different groups. Third, we included only patients with a first-ever ischaemic hemispheric stroke resulting in mild to moderate/severe neurological impairments at stroke onset. These patients may differ in the amount of pre-stroke comorbidities, as comorbidity is suggested to negatively influence outcome. In addition, research by Ng and colleagues found that patients with multiple infarcts show spontaneous neurobiological recovery to a lesser extent than patients with a first-ever stroke, suggesting that quality of vascularisation is an important issue for recovery. Contrary, a recent prospective cohort study did show that patients with previous or haemorrhagic strokes may also show proportional
recovery of the UE.\textsuperscript{38} Fourth, although our patients received usual care according to prevailing guidelines, rehabilitation may have differed in intensity and type of therapy.\textsuperscript{39} However, till so far, a number of studies failed to find evidence that type of therapy or intensity of practice interacts with spontaneous mechanisms of recovery.\textsuperscript{1,6,40} Being more positive, high quality trials are needed to investigate if very early applied intensive therapies are able to affect the proportion of fitters and non-fitters of the proportional recovery rule.

Prospectively being able to identify patients who will fit or not fit the proportional recovery rule would influence both trial design and rehabilitation management dedicated to investigate the impact of services for the LE.\textsuperscript{38,41} We already showed that stratifying patients based on expected spontaneous neurobiological recovery would have large consequences for the statistical power in stroke upper extremity trials as well as the choice for rehabilitation interventions.\textsuperscript{41} For the LE, we showed that all patients who scored 14 points or more on the FMA-LE at baseline followed the proportional recovery rule. However, also 51 out of the 78 patients who scored less than 14 points showed proportional recovery for the LE. Consequently, this cut-off cannot simply be used to stratify patients. Due to the lack of statistical power for a multivariable regression analysis, we were not able to develop a clinical prognostic model within this subgroup of patients with an initial FMA-LE score below 14 points. Therefore, we recommend to further investigate this subgroup of patients with initially severe strokes and pool the current data with other (sub)cohorts with FMA-LE baseline scores below 14 points. Subsequently, factors could be identified that are able to distinguish between fitters and non-fitters. This will enable stratification of patients based on proportional recovery and with that, investigating the impact of stratification in trials on LE outcomes post stroke. Ideally, the 70\% proportional recovery rule should be used in intervention trials by investigating interaction effects; aiming to increase the slope of the regression line (i.e. a higher percentage of proportional recovery) or to decrease the proportion of non-fitters. Above aims are in line with the recently published recommendations for improving stroke recovery and rehabilitation trials.\textsuperscript{42} In parallel, our understanding of underlying mechanisms of spontaneous neurobiological recovery should be increased. Therefore, we need more translational research in which clinical, neuroimaging, molecular, and neurophysiological biomarkers of spontaneous neurobiological recovery are combined.\textsuperscript{42}
Acknowledgements

The authors thank all EPOS assessors in the stroke units of the participating university centres and local hospitals (AMC Amsterdam; Erasmus MC Rotterdam; LUMC Leiden; UMC Sint Radboud; UMC Utrecht; VUmc Amsterdam; Amphia Hospital Breda; Diakenessen Hospital Leiden; Franciscus Hospital Roosendaal) and in the affiliated nursing homes (i.e. St. Jacob, Zonnehuis and Cordaan/ Berkenstede in Amsterdam, Laurens Antonius Binnenweg and Reumaverpleeghuis in Rotterdam, Albert van Koningsbruggen in Utrecht and Wiekendaal in Roosendaal) for performing the measurements. The authors also thank the patients who participated in the study.

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