Chapter 46

Predicting activities after stroke

Gert Kwakkel, Boudewijn J. Kollen, and John W. Krakauer

What do we mean by "prediction of activities after stroke?"

In this chapter we will focus on the evidence derived from prognostic research in predicting outcome of activities after stroke. To define activities, the World Health Organization (WHO) international classification of function, disability, and health (ICF) model [1] is used. This model provides a framework for classifying the effects of stroke rehabilitation on the individual (Figure 46.1) in terms of pathology (disease or diagnosis), body functions (i.e., impairments), limitations in activities (i.e., disability), and restriction in participation (i.e., handicap) [2]. The domain of activities (or functional outcome) is regarded as clinically meaningful for patients with stroke and is often targeted by the multidisciplinary stroke team [2]. This level of ICF refers to a patient's ability to be independent from his/her environment and supporting services and incorporates independence in activities of daily life/living (ADL), including gait and dexterity. The most relevant activities that may be affected after stroke are presented in the upper blue panel of Figure 46.1. These outcomes are captured mostly by assessments that validly measure a patient's ability to perform a particular activity. In this chapter, we focus on three main activities, namely basic ADLs, gait, and dexterity.

It is important to define prediction in this chapter. Because of the multifactorial nature of many deseases, the relationship between outcome and its different causes is explored frequently. This can be derived from a prognostic index from several explanatory variables for predicting outcome. These causes then can be established as risk factors for the occurrence of events or protective factors for the prevention of events. Multivariable regression analysis may be used to develop a prognostic model that provides information about the prognosis of a patient with a particular set of prognostic factors [3]. However, prognostic models provide valid estimates of risk only for patients with similar characteristics to those in the study population. Because data sets are samplings of the population, rather than the population itself, a slightly different sample is generated each time the population is resampled [4]. Studies aimed to investigate prediction of outcome (i.e., prognostic studies) may include clinical (observational) studies of variables that are predictive of future events as well as epidemiological studies of etiological risk factors [5]. Prediction of outcome commonly necessitates the development of a regression model to estimate the best (i.e., most important and most valid) subset of predictors and the corresponding best-fitting regression model for describing the relationship between a response variable and determinants. Prognostic validity refers to obtaining accurate estimates for the regression parameters in the model in order to make inferences about these parameters of interest. In other words, the objective is to quantify this relationship between dependent and one or more independent variables, controlling for the other variables [6]. This way, the strength, direction, and extent of the relationship between dependent and independent variables becomes clear. Normally, it will be impossible to predict with complete certainly, but prediction models provide estimated information about the mean value and the variability of the predicted value. While there is much overlap between prediction and forecast, a prediction may be a statement that some outcome is expected, while a forecast may cover a range of possible outcomes at activity level.

Strictly speaking, a predictive model should be able to determine future outcome for a particular measure in a single patient within an acceptable margin of error. However, accurate prognostic models with 100% certainty about the outcome or future of an individual stroke patient are not yet available in rehabilitation medicine. A clinical prognosis for an individual stroke patient is based on the examination of so-called "prognostic factors" ("markers" or "predictors") that are found to be associated with the final outcome in a representative sample of stroke patients. In most cases, these prognostic markers (i.e., predictors or determinants) are based on multivariate (or multivariable) regression models. However, the determinants derived from these regression or association models will never be 100% predictive. As a consequence, these determinants should be used as a marker for estimating a patient's future at a certain post-stroke time. In other words, using these

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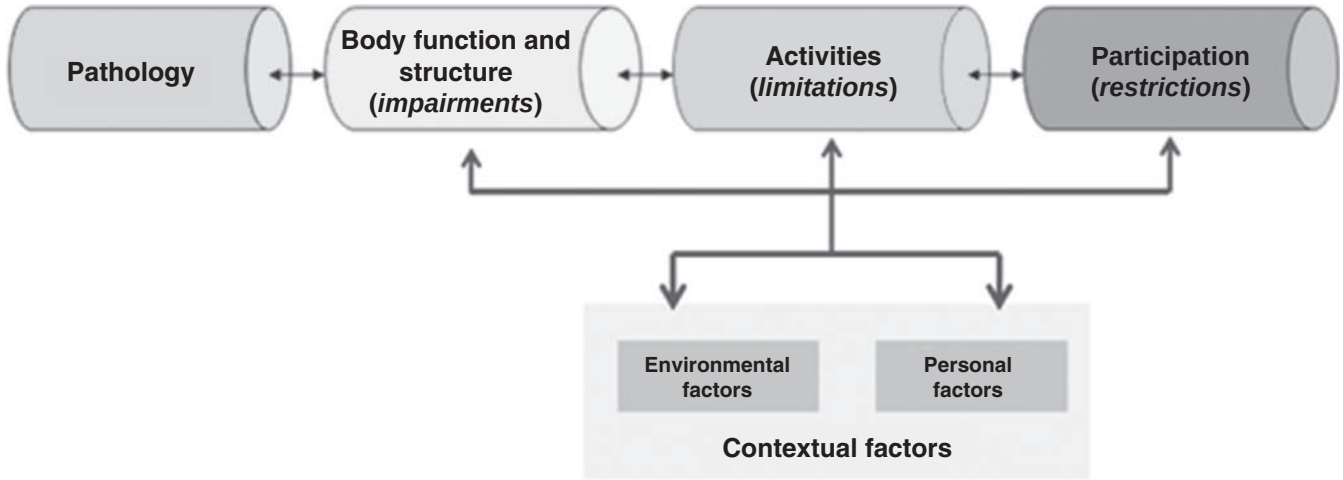

ICF model

Most relevant ICF categories affected after stroke*

Ischemic stroke (–80%):
Syndrome according to the Oxfordshire Community Stroke Project classification

Hemorrhagic stroke (–15%):
- Intracerebral (–10%)
- Subarachnoid (–5%)

Not otherwise specified (–5%)

Most relevant body functions and structures affected by stroke:

- Consolousness, orientation and intellectual functions
- Temperament and personality functions
- Sleep, attention and memory functions
- Psychomotor and perceptual functions
- Perceptual and cognitive functions
- Proprioceptive and touch functions
- Sensory function related to temperature
- Sensation of pain
- Articulation function
- Detecation and urinary (excretory) functions
- Sensations associated with urinary functions
- Sexual functions
- Mobility and stability of joint functions
- Muscle power and muscle tone and motor ref,ex
- Muscle endurance functions
- Control of voluntary movement and involuntary movement functions
- Gait pattern functions
- Sensations related to muscle and movements
- Protective functions of the skin

Most relevant structures affected

- Structure of the brain and cardiovascular system
- Upper and lower extremity
- Urinary system
- Areas of skin

Most relevant activities affected by stroke:

- Transferring oneself
- Maintaining body position
- Walking
- Mobility, other specified
- Toileting
- Dressing
- Moving around
- Moving around in different locations
- Washing oneself
- Hand and arm use
- Eating and drinking
- Selfcare, unspecified
- Prepare meals
- Reading and writing messages
- Speaking
- Using transportation

Most common affected contextual factors (i.e., environmental and personal):

- Technology and products for personal use
- Health professionals
- Health services, system, and polices
- Products or substances for personal communication
- House services, systems, and policies
- Support and relationships

Most relevant restrictions in participation affected by stroke:

- Acquistion goods and services
- Doing housework
- Preparing meals
- Basic interpersonal
- Recreation and leisure activities
- Remunerative employment

Classification of Outcome scales#

Diagnostics:

- CT or MRI scan (with or without contrast)
- Doppler
- ECG

Examination:

- History from patient and family
- Clinical examination
- Fundoscopic examination
- Auscultation
- Blood analysis (including pressure)

Body structure (impairments):

Neurological scales*

- GlasgowComa Scale
- Mini-Mental State Examination (MMSE)
- National Institutes of Health Stroke Scale (NIHSS)
- Scandination Stroke Scale (SSS)

Other scales used by the stroke team:

- Medical Research Council (MRC)
- Motricity Index (MI)
- Fugil-Meyer Motor Assessment (FMA)
- Motor Assessment Scale (MAS)
- Hospital Anxiety and Depression Scale (HADS)
- Hamilton Rating Scale for Depression

Activity (disability):

Global scales for independency in ADLs:

- Barthel Index (BI)
- Functional Independence Measure (FIM)
- Frenchay Activities Index (FAI)
- (modified) Rankin Scale (mRS)

Other scales used by the stroke team*

- Trunk Control Test (TCT)
- Timed Up-And-Go (TUG)
- Rivermead Mobility Index (RMI)
- 5 or 10 meter maximal or comfortable walking speed test
- Stair-climbing Test
- Frenchay Arm Test (FAT)
- Action Research Arm Test (ARAT)
- Toronto Bed-side Swallowing Screening Test (TOR-BSST)

Contextural factors:

- Caregiver Strain Index (CSI)
- Family Assessement Device (FAD)

Participation (handicap):

- Euroqol-SD
- Nottingham Extended Activities of Daily Living (NE-ADL)
- Nottingham Health Profile (NHP)
- General Health Questionnaire (GHQ)
- Stroke Impact Profile (SIP) (stroke adapted version)
- Medical Outcome Study Short Form 36
- Stroke-Specific Quality of Life (SS-QOL)

Figure 46.1. The WHO international classification of function, disability, and health framework for the effect of stroke on an individual. This figure summarizes the key features of this classification system [1], the most relevant categories affected after stroke, and examples of measurement scales used in those categories. After Langhorne et al, 2011 [2]. (For color image, see color plate section.)

determinants or predictors for individual stroke patients always should be used with a degree of skepticism, keeping in mind that exceptions to the prediction rules exist (see later in this chapter).

Finally, it is important to note that prediction of activities by using one of these outcome scales at activity level only measures the patient's ability to perform a certain task independently, at a certain post-stroke time. As a consequence, the term "outcome" differs from the term "recovery," which is more a reflection of the process of how patients improve in their body functions and activities over time. In Volume II, Chapter 2, which is focused on the mechanisms of recovery of activities after stroke, a detailed description is given about the term "recovery" as well as terms as "restitution," "substitution," and "compensation" in light of the ICF.

Why should we predict activities after stroke?

Stroke recovery is heterogeneous in terms of outcome, and it is estimated that 25%–74% of the 50 million stroke survivors worldwide require some assistance or are fully dependent on caregivers for ADL post-stroke [7]. In addition to medical management after acute stroke to prevent further cerebral damage, early stroke rehabilitation is initiated with the ultimate goal of achieving better recovery in terms of body functions and acivities in the first months after stroke and to reduce disability and handicap during the years that follow [7,8]. Knowledge about factors that determine final outcome of activities after stroke is important for early stroke management in order to set adequate rehabilitation goals, enable early discharge planning, and to inform patients and relatives correctly. The current trend to shorten the length of stay in hospital stroke units, as well as the increasing demand for efficiency in the continuity of stroke care, imply that knowledge about the prognosis for outcome of basic activities such as dressing, mobility, and bathing is crucial to optimize stroke management in the first months post-stroke. Knowledge about prognosis of activities (i.e., functional prognosis) is also important to design future trials in stroke rehabilitation adequately. In particular, identifying subgroups of patients that may benefit most from a particular intervention [9,10] and stratifying patients into prognostically comparable groups will prevent underpowered studies (i.e., type II error), keeping in mind that the contribution of stroke services is relatively small (i.e., 5%–10% of the variance of outcome) when compared to the variability across patients that are included in trials [11–13]. Moreover, a number of observational studies suggest that the degree of recovery in terms of impairments and activities after stroke is largely defined within the first days [14–16] after stroke onset [17–21]. This latter finding suggests that the effectiveness of a particular therapy is not only determined by the most effective therapy but is also dependent on selecting appropriate patients that show some potential for recovery of activities after stroke. Moreover, many evidence-based therapies such as constraint-induced movement therapy (CIMT) or modified versions of CIMT, body weight-supported treadmill training (BWSTT), neuromuscular stimulation, and early supported discharge policies by a stroke team are heavily dependent on an appropriate seletion of stroke patients [2]. With that, making adequate prognoses by a stroke rehabilitation team will increase the efficiency of stroke services and reduce costs. From a patient's perspective, adequate prognostics enables healthcare professionals to respond to changes that occur over time, to estimate the feasibility of the short-term and long-term treatment goals, and to provide correct information to patients and their partners [22].

Despite the earlier mentioned advandages, prognostic research has received little attention in neurology and rehabilitation medicine when compared to intervention research, and has not gained much acceptance in clinical practice, due to: (1) doubts about its predictive accuracy because of issues such as confounding and bias in observations, (2) problems with generalization of its results, and (3) the complexity of algorithms that hamper practical implementation [22–24]. Furthermore, a number of previous systematic reviews of prognostic research has shown that a high proportion of prognostic studies in stroke is of poor quality methodologically [22,23]. On the other hand, a positive trend is found, as the better quality studies are published in the most recent years [24]. This illustrates the growing awareness among investigators of the importance of meeting the methodological criteria for prediction model development.

What constitutes adequate prognostic research?

In contrast to the Consolidated Standards of Reporting Trials (CONSORT) statements [25], there are no strict methodological criteria for assessing quality of prognostic research. There are a number of key factors identified in clinical epidemiology that may confound, internally, the relationship between the independent variable of interest (i.e., determinant), on the one hand, and on the other hand, outcome or the dependent variable in the regression model. The development of the methodology of prognostic studies is ongoing [5,26,27], and guidelines for reporting observational studies according to the "strengthening of reporting of observational studies in epidemiology" (STROBE) statement have been established only recently [28].

Table 46.1 summarizes the main factors that affect internal, statistical, and external validity of adequate prognostic research. In this 27-item checklist, six major risks of bias are addressed: (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) statistical analysis, and (6) clinical performance [5,22,23,26,27,29]. As shown in Table 46.1 each item can be graded positive (sufficient information: low risk of bias, 1 point assigned), negative (sufficient information: potential risk of bias, 0 points assigned), or partial/unknown. A total score can be obtained by summing all items that were scored as positive. The main methodological factors

Table 46.1. Quality assessment of reports of prognostic studies

Outcome strategies		Scale	Criteria
Evaluation of study design			
D1	Source population and recruitment	Y/N/?	Positive when sampling frame (e.g., hospital based, community based, primary care) *and* recruitment procedure (place and time, method used to identify sample) are reported
D2	Inclusion and exclusion criteria	Y/?	Positive if both the inclusion and exclusion criteria are explicit and described
D3	Important baseline key characteristics of study sample	Y/?	Positive if the following key characteristics of the sample are described: gender, age, type, localization, number of strokes, stroke severity Number of strokes is adequate when at least "a history of stroke" or "recurrent stroke" is reported
D4	Prospective design	Y/N/?	Positive when a prospective design was used, *or* in the case of a historical cohort in which prognostic factors were measured before the outcome was determined
D5	Inception cohort	Y/N/?	Positive if observation started at a uniform time point within two weeks after stroke onset
D6	Information about treatment	Y/N/?	Positive if information on treatment during observation period is reported (e.g., [para]medical, usual care, randomized, etc.)
Study attrition			
A1	Number of loss to follow-up	Y/N/?	Positive if the number of loss to follow-up during period of observation did not exceed 20%
A2	Reasons for loss to follow-up	Y/N/?	Positive if the reasons for loss to follow-up are specified *or* if there is no loss to follow-up
A3	Methods dealing with missing data	Y/N/?	Positive if, in the case of missing values, the method of dealing with missing data is adequate (e.g., multiple imputation), *or* there are no missing values
A4	Comparison completers and non-completers	Y/N/?	Positive if the article mentions that there were no significant differences between participants who completed the study and who did not, concerning key characteristics gender, age, type, and severity, *and* candidate predictors and outcome, *or* if there were no loss to follow-up
Predictor measurement			
P1	Definition of predictors	Y/?	Positive if the article clearly defines or describes all candidate predictors (concerning *both* clinical and demographic features)
P2	Measurement of predictors reliable and valid	Y/N/?	Positive if $\geq$1 candidate predictors were measured in a valid and reliable way, *or* referral was made to other studies that have established reliability and validity
P3	Coding scheme and cutoff points	Y/N/?	Positive if the coding scheme for candidate predictors were defined, including cutoff points *and* rationale for cutoff points given, *or* if there were no dichotomization or classification
P4	Data presentation	Y/N/?	Positive if frequencies, percentages, mean (SD/CI), or median (IQR) are reported of all candidate predictors
Outcome measurement			
O1	Outcome(s) defined	Y/N/?	Positive when a clear definition of the outcome(s) of interest is presented
O2	Measurement of outcome(s) reliable and valid	Y/N/?	Positive when outcome was measured in a valid and reliable way, *or* there is reference to other studies that have established reliability and validity
O3	Coding scheme and cutoff points described	Y/N/?	Positive if the coding scheme of the outcome were defined, including cutoff points *and* rationale for cutoff points weres given, *or* if there were no dichotomization
O4	Appropriate end-points of observation	Y/N/?	Positive if observation were obtained at a fixed moment after stroke onset Negative when observation was obtained at discharge
O5	Data presentation	Y/N/?	Positive if frequencies, percentages, mean (SD/CI), or median (IQR) of the outcome measure are reported
Statistical analysis			
S1	Strategy for model building described	Y/N/?	Positive if the method of the selection process for multivariable analysis is presented (e.g., forward, backward selection, including P-value)

Table 46.1. (*cont.*)

Outcome strategies		Scale	Criteria
S2	Sufficient sample size	Y/N/?	Positive if, in logistic regression analysis, the number of patients with a positive or negative outcome (event) per variable is adequate, i.e., is equal to or exceeds 10 events per every variable in the multivariable model (events per variable), *or* in case of linear regression analysis, n ≥100
S3	Presentation univariable analysis	Y/N/?	Positive if univariate crude estimates and confidence intervals (β/SE, OR/CI, RR, HR) are reported Negative when only P-values or correlation coefficients are given, *or* if no tests were performed at all
S4	Presentation multivariable analysis	Y/N/?	Positive if, for the multivariable models, point estimates with confidence intervals (β/SE, OR/CI, RR, HR) are reported
S5	Continuous predictors	Y/N/?	Positive if continuous predictors are not dichotomized in the multivariable model
Clinical performance/validity			
C1	Clinical performance	Y/?	Positive if the article provides information concerning ≥1 of the following performance measures: discrimination (e.g., ROC), calibration (e.g., HL statistic), explained variance, clinical usefulness (e.g., sensitivity, specificity, PPV, NPV)
C2	Internal validation	Y/?	Positive if appropriate techniques were used to assess internal validity (e.g., cross-validation, bootstrapping), or if the negative split-sample method was used
C3	External validation	Y/?	Positive if the prediction model was validated in a second independent group of stroke patients

Y, positive, 1 point; N, negative, 0 points; ?, partial/unknown [5,22,23,26].

affecting the quality of reports of prediction studies are explained as follows.

Internal validity

Internal validity refers to the validity of inference for the source population of study subjects. It implies accurate measurement of effects apart from random errors [30]. Thus, internal validity is a measure of the inherent relationship between cause and effect, which are being studied. Adequate internal validity implies that the relationship between "independent variable" (or determinant that has preceded in time) and dependent variable (i.e., outcome of activity) is not based on systematic errors due to selection bias, information bias, or confounding. In order to generate such a relationship, first the measurement of outcome needs to be internally consistent among scale items, reproducable, valid, responsive, and interpretable. Reproducibility incorporates both reliability and agreement among observers. In addition, clinical predictors and outcomes should be defined clearly, validated, and cutoff values need to be justified.

Second, in initial prognostic research, an inception cohort is required, which is defined as a designated group of persons assembled at a common time early in the development of a specific clinical disorder (e.g., at first exposure to the putative cause or at initial diagnosis), who are followed thereafter. Measurements in a prospective inception cohort should be taken as early as possible after stroke onset and, in a repeated measurement design, at fixed intervals during the post-stroke course. Having a core group of patients followed from stroke onset allows investigators to get an idea about dropout rate as well as to assess the reasons for dropout, which is critical because dropout as a result of migration, death, or other reasons almost always is systematic rather than random and thereby increases the risk of bias [31]. In addition, an adequate period of observation for determining final outcome at fixed times post-stroke prevents the possibility of overly pessimistic or optimistic views on a patient's ability to recover. To prevent a pessimistic view on outcome, prognostic studies should follow patients for at least three months post-stroke when recovery from impairment may be close to plateau. To prevent too optimistic a view of a patient's ability to regain ADLs adequately, a follow-up of three to six months is probably adequate. Interestingly, more than 20%–30% of all stroke patients will deteriorate in their gait performance after six months post-stroke. For, example, in a sample of 264 stroke patients, it was found that 21% significantly deteriorated two points or more on the Rivermead mobility index (RMI) from one to three years post-stroke [32]. Finally, many studies in rehabilitation medicine start their prognostic research projects at the time of admission to a rehabilitation ward and use the measurement at discharge to determine study outcome. The problem is that both of these times–admission and discharge from the acute rehabilitation setting–are influenced heavily by non-brain recovery-related factors, such as bed availability, and economic considerations.

Statistical validity

Statistical validity refers to whether a statistical study is able to draw conclusions that are in agreement with statistical and scientific laws. This means if a conclusion is drawn from a

given data set after experimentation, it is said to be scientifically valid if it is scientific and relies on mathematical and statistical laws. Next to internal validity, statistically the strategy for model building should be described and the sample size of the cohort in relation to the number of variables should be adequate. The validity of the logistical model becomes problematic when the ratio of the numbers of events per variable analyzed becomes small. As a rule of thumb, the number with positive or negative (events) in the outcome variable should exceed 10 events per independent variable in the multivariable regression model. The derived prediction model as well as the bivariate estimates, including their confidence intervals observed for the candidate variables tested, should be presented in a table in the study.

External validity

The derived multivariable regression model should be investigated for its clinical performance that includes the discriminative properties, sensitivity, specificity, and positive and negative predicted values. In addition, the internal validity of the model preferably should be cross validated for its stability and representativeness based on bootstapping or split-sample methods. Finally, the claimed accuracy of the multivariable model should be validated in at least one and preferably several independent cohorts of patients (test cohort) that were not used to generate the model [23]. To date, there are only few validating studies performed that tested the model's predictive performance (e.g., calibration and discrimination) in other participants after stroke [23].

Validation studies can be restricted to a narrow sample of participants from the same institution, measured in the same manner by the same researchers, although at a later time, or in another single institution by different researchers, using perhaps slightly different definitions and data collection methods or a broad sample of participants obtained from various other institutions, or using wider inclusion criteria [27]. Testing the model with a second set of patients strengthens the validity of the model. However, it is not as strong a validation as testing the model on patients from different centers (i.e., case-mix), because a model usually does not perform as well under different circumstances. Finally, succesfull prediction models are applicable clinically if they are implemented easily and simple to use. With that, models preferably should be based on simple bed-side clinical tests without relying on complex algortithms that are difficult to use in practice.

It is important to realize that prediction models usually do not perform as well with new data as with the original data. This is because the model maximizes the probability of obtaining the values of the original outcome data. Unless the new data are exactly the same as the original data, it would be surprising for a model based on maximizing the original data to perform as well on the new data. It is important to know how large the decrement in performance is. In the case of a small decrement, the model is considered to be validated. Several methods of validation are employed in the literature, that is, to collect new data or divide the existing data (split-group, jack-knife, or bootstrap method). The best way is to collect more data from a different center and test the performance of the initial model with the new model. Validating data externally is by far superior to validating data internally; that is, because a model may not perform as well under a different set of circumstances. Subsequently, a comparison can be made between the probability of the predicted values of the derivation set and the predicted values of the observed values in the validation set, in a line chart using mean predicted values and their 95% confidence intervals. If the validation is perfect, all mean predicted values would fall exactly on the diagonal line that originates from ($y = x = 0$), and which indicates perfect validation. Once a model has been validated, multiple samples are combined or split samples reunited for the final model. Results are judged primarily on the strength of the methods that have been used, but also on the biological plausibility of the results and prior findings in the area [4].

What do we know about the pattern of stroke recovery in terms of body functions and activities?

The time course of body functions (i.e., impairments) and activities (i.e., disabilities) after stroke is characterized by a large diversity. Some patients show almost no improvement even in the long term, whereas others recover fully within hours or days after stroke. Even though the outcome of stroke patients is heterogeneous by nature and individual recovery patterns differ, strong mathematical regularities (i.e., logistics and sigmoidal) have been found in these nonlinear patterns of recovery, making the outcome of body functions and activities highly predictable [15,16,31,33–35]. Figure 46.2 shows a common, hypothetical pattern of stroke recovery in a patient with a first-ever ischemic middle cerebral artery (MCA) stroke.

In addition, a number of cohort studies has shown that the initial severity of disability as well as the extent of improvement observed within the first days or weeks post-stroke are important indicators for the outcome at six months after stroke [17,36–39]. As shown in Figure 46.3, the time course after stroke is characterized by larger improvements during the first weeks post-stroke when compared to post-acute phases beyond three months after stroke, reflecting common underlying mechanisms known as "spontaneous neurological recovery," as illustrated [2,37,40–42].

Another striking feature that underpins the existence of a predefined biological pattern in time is the observation that the sequence of progress in activities assessed, for example with the Barthel index (BI), is almost fixed in time. For instance, hierarchical scaling procedures of the BI show that in about 80% of all patients with a first-ever MCA stroke, progress of activities follows the same sequence of items on the BI [33,43].

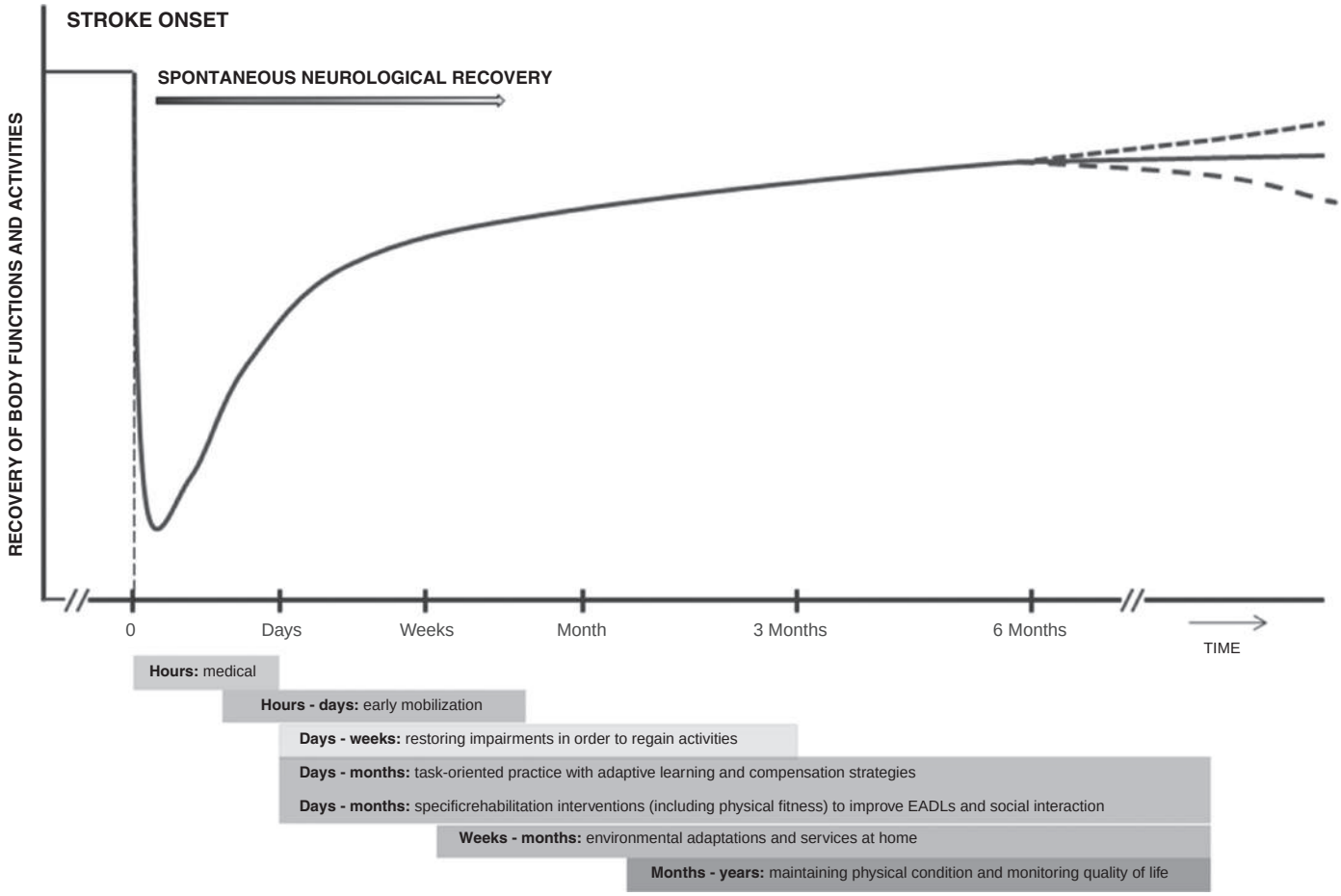

Figure 46.2. Hypothetical pattern of recovery after stroke with timing of intervention strategies. After Langhorne et al., 2011 [2]. (For color image, see color plate section.)

As shown in Figure 46.3, skills that allow compensation strategies, such as grooming, recover earlier than more complex skills, such as dressing and climbing stairs. The observed sequence in this small sample of patients was confirmed recently by a number of studies using Rasch analysis. In Rasch analysis, the probability of achieving a certain milestone is determined on the basis of the patient's ability and item difficulty [44,45]. In a larger study involving 556 stroke patients [43], the same hierarchical sequence was found according to the BI. It should be noted, however, that not all items of the BI measure the same underlying concept. Indeed, items that measure body functions (i.e., bladder and bowel control) in the BI [43] and the functional independence measure (FIM) [46,47] are not suitable for a Rasch analysis, because these items assess different (impairment-related) constructs.

The fact that recovery of activities after stroke follows a fixed hierarchy of activities is not specific outcomes of ADLs measured with the BI or FIM, for example [47], but is also found for the stroke impact scale [48], the National Institutes of Health stroke scale (NIHSS in acute stroke) [49], as well as for the recovery of the upper limb function measured with the ABILHAND questionnaire [50] or the action research arm test (ARAT) [51]. These findings support the notion that defining

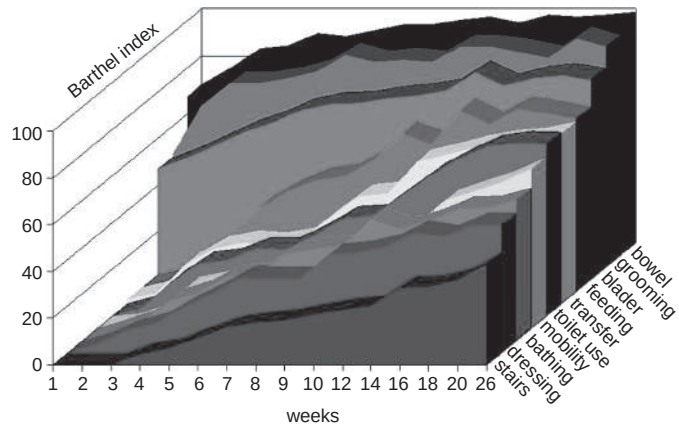

Figure 46.3. Skills of patients progress in a fixed sequence on the Barthel index (BI), with earlier recovery for relatively less complex skills that allow compensation strategies, such as feeding and grooming, and later recovery for more complex skills, such as dressing and climbing stairs. As illustrated in this figure, patients showed an almost consistent sequence of recovery, with bowel control to be restored first, followed by grooming, bladder control, feeding, transfer, toilet use, mobility, bathing, dressing, and finally climbing stairs. Based on the so-called Guttmann scaling procedure, a coefficient of scalability ranging from 0.72 for week 26 to 0.85 for week 3 post-stroke was found, suggesting that about 80% of the patients progressed through this fixed sequence in time. (For color image, see color plate section.)

milestones may serve as an important part of multidisciplinary stroke management [52–54] in order to define realistic attainable treatment goals. Future studies should investigate whether the observed natural sequence of milestones can be changed by offering patients task-oriented training programs with a variety of intensities and treatment goals.

What is the impact of spontaneous biological recovery on outcome of activities?

Longitudinal regression modeling of change scores has shown that most motor recovery is almost completed within four to 10 weeks post-stroke [31]. This finding is in agreement with the patterns observed in a number of prospective cohort studies [17,20,21,38,39]. For example, Duncan and colleagues showed that, between four and 12 weeks after stroke, the recovery of motor impairments (assessed with the Fugl–Meyer [FM] motor score) and of ADL (assessed with BI) levels off [40]. What all these studies and others have in common, regardless of the applied measure, is the observation that the largest gains occur within the first three months after stroke. That the most motor recovery occurs in a limited time window after injury is entirely congruent with observations in animal models, in which converging data at the molecular, cellular, physiological, and behavioral level suggest a limited time-window of heightened plasticity and increased receptivity to training regimens [55]. At a body function level, spontaneous biological (or neurological) recovery can be defined as the amount of neurological improvement of body functions, such as synergism, attention, strength etc., that is generated by the progress of time alone [31]. Due to these spontaneous nonlinear changes in impairments within the first four to eight weeks post-stroke, activities will show concomitant instantaneous changes as well. This definition does not preclude the possibility that heightened homeostatic plasticity in the spontaneous recovery time-window could also allow for faster learning of compensatory strategies that is not dependent on recovery from impairment [55].

The mechanisms and predictors of spontaneous biological recovery in the first weeks post-stroke have been surprisingly under-investigated in humans [31,56]. Understanding the intrinsic, spontaneous recovery after stroke onset is paramount and has important clinical implications. First, knowledge about the extent and duration of spontaneous recovery allows clinicians to predict outcome early after stroke, enabling realistic and attainable treatment goals to be set and proper discharge planning to take place. Second, knowledge about the time window during which spontaneous return may be expected allows therapists to choose whether they will focus their therapy on reduction of impairment or on compensatory strategies at the activity level [33]. Third, the mechanisms of spontaneous neurological recovery induce some recovery in almost all patients, irrespective of whether they receive rehabilitation therapy. This finding emphasizes the necessity for conducting appropriate randomization procedures when studying early-applied therapeutic interventions post-stroke and confirms the general rule that stroke outcome data should be reported only when the observations of experimental and control groups are made at the same time interval after stroke onset [41,57]. Fourth, it is only through knowledge of the expected magnitude of spontaneous biological recovery, and its attendant mechanisms, that we can develop treatments that will go beyond what is predicted from spontaneous biological recovery alone.

Are we able to measure the impact of spontaneous biological recovery on improvement of activities post-stroke?

Unfortunately, there is no uniform definition of spontaneous biological recovery and no methods to measure its contribution to the overall recovery directly. Nevertheless, one may define spontaneous biological recovery as the amount of improvement in terms of body functions and activities that is determined by the progress of time alone. Using this concept, there are two ways of demonstrating the contribution of progress of time on the nonlinear recovery pattern after stroke. First, by applying an individual curve-fitting analysis, and second, by using random coefficient analysis of change scores [58].

The best model to fit the (growth) curve of the BI in the first 26 weeks after stroke was a logistic regression model capturing time series [33]. In this study, both time of fastest recovery as well as extent of recovery observed in the first weeks were strongly associated with the final plateau phase of the BI at six months post-stroke. This suggests that the amount of progress as well as the time at which these changes occur relative to stroke onset are important predictive factors for the expected outcome at six months [33,59]. In a similar way, a close fit was shown between logarithmic modeling for predicting ADL in stroke patients according to the FIM and the actual FIM scores [34]. Based on two initial time-points assessed between two and six weeks post-stroke, mathematical modeling explained 94% of the variance of the actually observed outcomes assessed with the FIM [34].

Another way of investigating the impact of spontaneous biological recovery on the observed time-dependent change of functions and activities is by applying longitudinal regression analysis on observed change scores [60–62]. For this purpose, we recently introduced a new longitudinal first-order, regression model in stroke rehabilitation [60–62]. In this model based on the within-subject change scores, the contribution of progress of time in recovery of body functions and activities post-stroke was investigated.

When studying the impact of the progress of time in 102 MCA stroke victims, assessed 18 times in the first year post-stroke, it was shown that at least 80% of the observed improvements in body functions and activities can be explained by progress over time alone, measured during the first 10 weeks

post-stroke [31]. For example, progress of time, corrected for age, gender, type and hemisphere of stroke, and type of intervention accounted for 8 points (or 40%) change with respect to the total BI score. In other words, adding 8 points on the initial BI measured at the fifth to seventh day post-stroke will produce a valid conservative estimate of the final BI at six months post-stroke [14,31]. This latter finding further underpins the close relationship between, on the one hand, initial deficit in terms of activities, and on the other hand, the final outcome at six months post-stroke. The same 40% gain was found by Ng and colleagues [63] in 2213 subjects, between admission FIM and FIM at discharge. This 40% gain was irrespective of vascular territory (anterior, middle, or posterior; cerebellar and brainstem), age risk factors, or hemisphere. Patients with multiple strokes in more than one vascular territory did not follow this rule and showed less improvement on the motor and cognitive FIM [63].

Do activity profiles plateau in the chronic phase after stroke?

Although long-term prospective cohort studies after stroke are scarce [24,64–66], it is generally accepted that, on average, patients seem to "plateau" in their recovery three to six months after onset. Furthermore, the Copenhagen stroke study showed that recovery of activities according to the Barthel index was completed in 12.5 weeks from stroke onset in 95% of the patients (n=1197) [17]. The time course of body functions followed a pattern similar to that of activities; however, body functions preceded the pattern of recovery of activities by two weeks on average and showed a plateau phase sooner. This cohort study suggests that a reliable prognosis can be made within the first three months post-stroke and that even in patients with severe strokes, recovery of body functions and activities should not be expected after the first five months. It generally is accepted that the chronic phase starts after the first six months after stroke onset.

Using more sensitive measurement instruments such as gait speed, analysis of individual recovery patterns shows that about 10%–30% of all patients significantly deteriorate or improve in their performance of activities beyond the 95% limits of measurement error after six months. This finding suggests that absence of a signifcant change on average in a stroke population does not reflect adequately the possible changes within individuals in which some patients may show a significant improvement and others a significant deterioration in the long term [67]. However, this finding also suggests that development of a plateau phase is caused as well by the ceiling effects of measurement of outcome used.

For example, in a prospective cohort study of 264 young stroke victims, it was found that nearly one-fifth of all patients showed significant deterioration in terms of mobility status measured with the RMI between one and three years after stroke [32], whereas about 7% of all young stroke victims (with a mean age of 58 years) showed significant improvement of at least 2 points (out of 15) on the RMI. In particular, patients who had a poor level of activity and self-initiative, suffered from cognitive problems and depression, and complained about fatigue at one year after stroke, were more susceptible to deterioration in their mobility status during these two years than those who did not suffer from such symptoms. On the basis of these four determinants, it was possible to identify 80% of the patients who were susceptible to deterioration [32]. These previously mentioned findings from longitudinal research strongly suggest that chronic stroke patients need to be monitored on a regular basis for possible changes, such as "learned non-use," over time.

Why patients experience a plateau phase is largely unknown. However, understanding the development of this phase post-stroke is critical for adequate stroke management. At least a number of factors are involved in the gradual development of an individual's plateau phase post-stroke, such as reversal of processes underlying spontaneous biological recovery, inability of patients to compensate their neurological deficits, restrictions in the patient's physical condition, as well as ceiling effects of applied measures of outcome.

Are we able to predict ADL independency after stroke?

Knowledge about robust and unbiased factors that predict outcome of ADL is paramount in early stroke management. After systematically reviewing 48 studies aimed to predict outcome of ADL, the BI and modified Rankin scale (mRS) were the two activity level outcome measures that were used most frequently in prognostic stroke studies. Despite the fact that only a small proportion (i.e., six out of the 48 studies; 12.5%) of the included studies was of high quality [24], strong evidence was found for age and scales to assess severity of neurological deficits in the early post-stroke phase, such as the NIHSS and the Canadian neurological scale, which are associated strongly with final basic ADL outcome beyond three months post-stroke [68]. For example, we found in a prospective cohort study, in 159 stroke victims with a mild to moderate first-ever ischemic hemispheric stroke, that when measured within 72 hours post-stroke, the NIHSS score is associated strongly with the final outcome of ADL independency measured with the Barthel index at six months.

The discriminative properties as well as the accuracy of prediction with NIHSS at baseline seem to be robust and hardly influenced by the timing of assessment in the first nine days after stroke onset [14]. The area under the curve ranged from 0.789 (95% CI: 0.715–0.864) for measurements on day 2 to 0.804 (95% CI: 0.733–0.874) and 0.808 (95% CI: 0.739–0.877) for days 5 and 9, respectively [14].

The systematic review of 48 prognostic studies also showed that gender and the presence of risk factors for stroke, such as atrial fibrillation, did not predict outcome of basic ADL. Conspicuously, imaging data for the prediction of ADL outcome was shown to be of limited value when compared to the

contribution of clinical variables alone [24]. In a previous prospective study in 75 first-ever MCA stroke survivors, we found that age and the initial Barthel index measured at day 5 post-stroke predicted 84% of the area under the curve in predicting outcome of ADL indepenency one year post-stroke. For this purpose, patients were classified as ADL-independent if they had a score of 19 or 20 points on a BI. However, adding MRI findings at 11 days post-stroke, such as the presence of white matter lesions, hemisphere of stroke, cortical or subcortical, and lesion as well as stroke volume, increased the area under the curve from 0.84 to 0.87 in the surviving patients. In line with other studies in this field that investigated the impact of stroke lesion volumes on outcome of ADL [69,70], this prospective cohort study suggests that neuroimaging variables from conventional MRI scans did not increase the accuracy in predicting ADL long-term [69,70].

In addition to the predictive validity of neurological scales such as NIHSS and the Canadian neurological scale, a number of prospective cohort studies has shown that the baseline value of the BI (or FIM) assessed within two weeks post-stroke, is associated strongly with the final BI (or FIM) measured at six months post-stroke [29,33]. However, the predictive accuracy of the initial BI seems to be time-dependent [14]. For example, a prospective cohort study in which the diagnostic accuracy of the BI in 206 hemispheric stroke patients was investigated [14], showed a significantly higher accuracy in predicting outcome of the BI at six months when assessed at five or nine days than at two days post-stroke. The area under the curve ranged from 0.785 on day 2 to 0.837 and 0.848 on days 5 and 9, respectively, suggesting that the assessment on day 5 proved to be the earliest post-stroke time for making an optimal prediction of final outcome of ADL (Figure 46.4) This finding suggests that, preferably, the BI should be measured at the end of the first week in hospital-based stroke units for adequate stroke rehabilitation management. This time-dependency in predictability may be explained by several putative mechanisms. The first is that two days is too early for patients to begin to develop compensatory strategies that will be used to carry out ADLs. At one week, in contrast, the core compensatory abilities may be present already. The second possibility is that subjects may have a greater tendency to perform below their true maximal capacity early after stroke. The third option is that edema and metabolic factors, which have their maximal influence in the first 72 hours, could mask the capacity for recovery.

The less than optimal prediction of BI at six months for patients assessed within 72 hours may be caused by the instability of neurological deficits, as manifested by some neurological worsening during the first 24 to 48 hours after stroke, observed in approximately 25% of all patients [71]. However, as concluded from the study running parallel and focused on the timing of assessment of neurological deficits by NIHSS in the same population, there was no significant differences between day 2, 5, or 9 [14], which makes neurological worsening within this period unlikely (Figure 46.5). A more plausible explanation could be that observers find it difficult to determine the patient's actual performance in basic ADLs when the patient is still bedridden. As a consequence, an assessment within 72 hours post-stroke will underestimate the actual patient's performance. In line with the recommendation of Kasner [72], the present findings suggest that, even in individuals with a minor stroke who are bedridden in the first few days after stroke, the BI will underestimate outcome scores, hence making the BI not a suitable instrument to measure disability within the first three days post-stroke.

Other determinants reported in valid prospective cohort studies suggest that, in addition to baseline ADLs factors such as sitting balance, urinary incontinence, severity of hemiplegia, comorbidity, consciousness at admission, cognitive status, and depression,there are independent factors that contribute to outcome of ADL beyond six months [22,23,29,73].

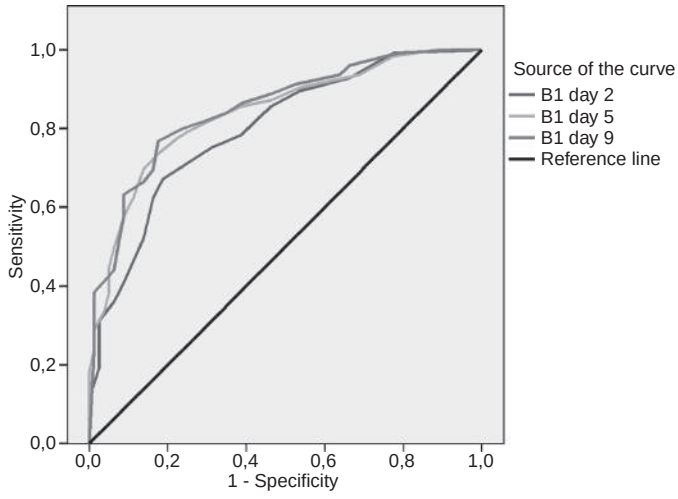

Figure 46.4. Graphic presentation of ROC analyses of timing of assessment of BI at day 2, 5, and 9, for outcome of dichotomized BI (≥19) after six months (n=206). (For color image, see color plate section.)

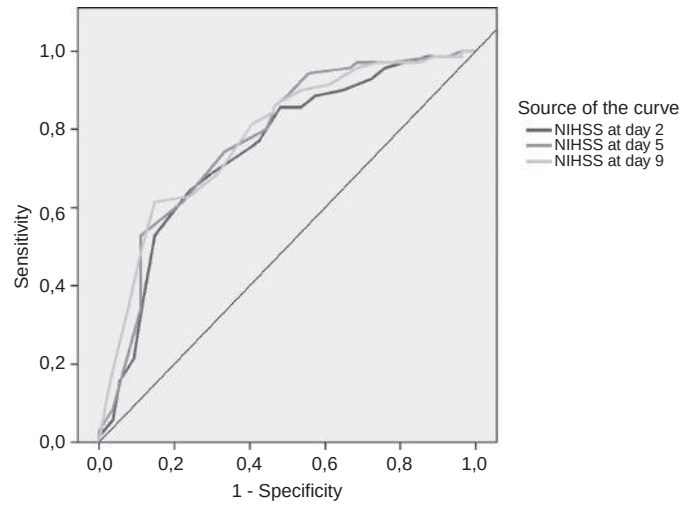

Figure 46.5. Graphic presentation of ROC analyses of moment of timing of assessment of NIHSS for outcome of BI (≥19) at six months after stroke. (For color image, see color plate section.)

Who regains walking ability?

Regaining independent gait is considered a primary goal in stroke rehabilitation. A number of prospective cohort studies have shown that approximately 60% [17,58] to 80% [74] of stroke patients are able to walk independently at six months post-stroke. A number of prognostic studies suggest that age [75,76], severity of sensory and motor dysfunction of the paretic leg [76,77], homonymous hemianopia [76,77], incontinence for micturition [21,75], sitting balance [18,21,78–80], initial disability in ADL and ambulation [17,18,21], level of consciousness on admission [75], and the number of days between stroke onset and first assessment [16] are associated independently with gait outcomes six months after stroke [24]. For example, the early prediction of outcome after stroke (EPOS) study involving 154 first-ever ischemic stroke patients who were unable to walk independently showed, based on multivariate (or multivariable) logistic modeling, that accurate prediction within 72 hours is attainable at hospital stroke units by means of two simple bedside tests, namely sitting balance and muscle strength of the paretic leg. Independent gait was defined as 4 points or more on the functional ambulation categories (FAC), suggesting that patients could be classified as safe walkers able to walk independently on flat surfaces. Those non-ambulatory patients who regained their sitting balance as assessed by the trunk control test (TCT) and developed some voluntary movement of the hip, knee, and/or ankle as assessed by the MI leg score ($\geq$25 points) within the first 72 hours post-stroke, had about a 98% chance of regaining independent gait within six months. In contrast, those patients who were unable to sit independently for 30 seconds and were hardly able to contract the muscles of the paretic lower limb within 72 hours had a probability of about 27% of achieving independent gait. Early reassessment of sitting balance and lower limb strength on days 5 and 9 showed that if sitting ability and lower limb strength failed to recover, the probability of regaining independent gait declined to 23% when assessed on day 5 and 10% when assessed on day 9 post-stroke. The increasing accuracy of prediction over time may reflect underlying intrinsic neurological mechanisms of recovery such as elevation of diaschisis after stroke [33]. Comparing these findings with those of other studies is difficult due to the lack of prognostic studies investigating the accuracy of prediction within 72 hours. However, a number of prospective studies have shown that muscle strength of the hemiplegic leg [76,77] and sitting balance [21,79], when measured in the second to fourth week after stroke, are associated significantly with improvement of walking ability [18] and achieving independent gait [18,80] at six months. Obviously, the early control of sitting balance as a prerequisite for regaining standing balance and gait at six months is an important factor for the final outcome [80]. The importance of balance control for gait is also supported in the study by Kollen and colleagues [58], who showed that improvement in standing balance was the most important variable associated with improvement of gait performance as measured with the FAC [58].

Because the proportion of false positives (≈7%) was clearly smaller than the proportion of false negatives (≈27%) within two days post-stroke, the present study suggests that our model generally is somewhat pessimistic, and illustrates that some patients with an initially poor sitting balance and a severe paresis of the hemiplegic limb, nevertheless, will regain independent gait [18]. This latter finding is supported by a number of recent longitudinally conducted studies showing that gait recovery is closely related to learning to use compensatory movement strategies [81–83]. For instance, patients learn to keep their balance by shifting their center of gravity to the non-paretic side [82,84], while significant change in motor control on the paretic side is almost lacking [81,83]. In the same vein, longitudinal studies with repeated measurments in time show that the contribution of the non-paretic side to increase comfortable and maximal walking speed is relatively larger than the contribution of the paretic side [67]. To date, all longitudinally conducted studies suggest that patients learn to cope with existing neurological deficits when regaining standing balance [82,84,85] and independent gait after stroke [81,83,86] (see [87] for a review). Obviously, previously mentioned adaptation strategies start as soon as patients learn to accomplish tasks within the first weeks post-stroke.

Who regains dexterity after stroke?

Although prospective epidemiological studies are lacking, findings of a number of prospective cohort studies suggest that 33%–66% of stroke patients with a paretic upper limb do not show any recovery of upper limb function and manual dexterity six months after stroke [88,89]. Depending on the outcome measures used, 5%–20% achieve full recovery of manual dexterity of the paretic upper limb at six months. [19,38,88,89].

The importance of selecting patients with a similar potential for recovery of activities is relatively easy to illustrate by studying the prediction of dexterity as a function of time, for example [19]. It was found that about one-third of the patients with an MCA stroke showed some ability of the paretic limb on the ARAT, measured at six months post-stroke. For this purpose, dexterity was defined as scoring 10 points or more on the ARAT.

In order to understand prognosis of manual dexterity better (i.e., skill acquisition with the paretic upper limb) at six months, we tested the probability by using logistic regression analysis in patients with an almost flaccid upper limb in the first week post-stroke and absence of dexterity on the FM arm score, as shown in Figure 46.6. We found that at least some motor recovery is needed in the upper paretic limb. Patients showing some (synergistic) movement in the upper limb within four weeks post-stroke had a probability of 94% for regaining some dexterity on ARAT, whereas for those who failed to show return of motor control, the probability remained below 10% [19] (Figure 46.6).

At the least, this study with repeated measurements over time suggests that there is a critical time window in which the final outcome of dexterity is largely defined. In fact, it is the

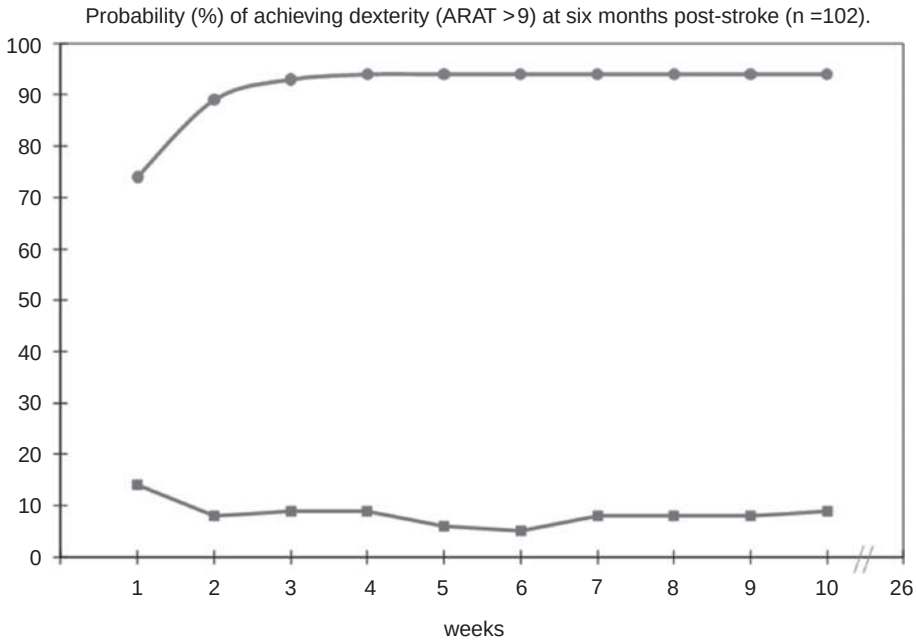

Figure 46.6. Probability of achieving some dexterity at six months post-stroke. Within the first three to four months, a critical time window was present, in which outcome of dexterity (dichotomized into ARAT <10 or ARAT ≥ 10 points) was defined. Optimal prediction was based on the Fugl–Meyer scores of the paretic arm and Motricity index score of the leg (MI-leg). After Kwakkel et al., 2003 [19]. (For color image, see color plate section.)

same time-limited window that is found in animal studies for an up-regulation of growth promoting factors, resulting in synapse strengthening and activity-dependent rewiring of neuronal networks to compensate for tissue lost to injury [55].

These findings strongly build on results of previous prospective studies that were initiated after the first post-stroke week [90–93]. For example, Smania et al. [93] showed, in a sample of 48 stroke patients, that active finger extension at day 7 post-stroke is an early valid indicator of a favorable outcome in terms of upper limb function, measured with the nine-hole peg test, the FM arm test, and the MI arm test. In addition, Katrak et al. [91] reported that initial shoulder abduction, measured about 11 days after stroke, is an early predictor of good hand function at one and two months after stroke. These findings also suggest that the selection of patients in terms of a poor or favorable prognosis for upper limb recovery is an important component of adequate stroke rehabilitation. To date, all evidence-based therapies that have been shown to be effective for the upper limb, including CIMT, selected patients with a favorable prognosis. In contrast, reports of evidence-based therapies for those patients with an unfavorable prognosis for regaining dexterity are lacking in the literature.

In a more recent prospective study in 188 stroke patients, we investigated if outcome in terms of paretic upper limb function at six months can be predicted within 72 hours after stroke onset [15]. In addition, the effect of the timing of assessment on the accuracy of prediction was reinvestigated by reassessing observed clinical determinants at days 5 and 9 after stroke. It was found that those patients with some finger extension and some visible shoulder abduction on day 2 after stroke onset had a 98% probability of achieving some dexterity at six months. In contrast, patients who did not show this voluntary motor control had a probability of 25% in this regard [15]. It is also remarkable that 60% of the patients with some finger extension within 72 hours had regained full recovery of upper limb function according to the ARAT score at six months.

This finding confirms the substantial predictive value of finger extension as a positive sign for a favorable outcome for the paretic upper limb in the acute phase after stroke. Retesting the model on days 5 and 9 showed that the probability of regaining dexterity remained 98% for those with some finger extension and shoulder abduction, whereas the probability decreased from 25% to 14% for those without this voluntary control [15]. Obviously, the preservation of some voluntary finger extension reflects the necessity of some fibers of the corticospinal tract system in the affected hemisphere to remain intact in order to activate distal arm and hand muscles [94–96] assuming that the forearm and hand lacks bilateral innervation from both hemispheres [97]. To date, transcranial magnetic stimulation (TMS) [97,98] and diffusion tensor imaging [99,100] studies further confirm this hypothesis. For example, van Kuijk et al. [101] showed that in patients with an initial paralysis of the upper limb, the presence or absence of a motor-evoked potential in the abductor digiti minimi, measured with TMS at the end of the first week after stroke, is highly predictive for final outcome of dexterity at six months. However, the presence or absence of a motor-evoked potential in the abductor digiti minimi has similar predictive values when compared to clinical assessment alone and suggests that TMS measurements should investigate the predictive validity of motor-evoked potentials of the finger extensors in particular, rather than finger flexors or the abductor digiti minimi alone [102].

In the same vein, similar to findings from TMS studies, but in contrast to the predictive value of volume of MRI for outcome of ADL, we found in 75 MCA victims that lesions of the internal capsule, according to MRI, were associated with a significantly lower probability of return of isolated hand motor function more

than superficial lesions of the cortex, subcortex, and corona radiata [103]. The probability of regaining hand function declined from 54% if the corticofugal tract was only partly affected, and to 13% if both motor cortex and internal capsule were affected. Again, this latter study shows that the return of hand function one year after stroke depends largely on the preservation of neuroanatomical areas known to represent the corticofugal tract of the upper limb. Obviously, the involvement of structures with a greater density of dysfunctional corticofugal tract fibers such as the internal capsule, are associated with poor recovery of hand motor function at one year post-stroke [103].

Knowledge about the early prediction of final outcome of dexterity of the paretic upper limb is paramount for the implementation of adequate stroke management. In particular, subsequent multidisciplinary rehabilitation services may be optimized, based on the probability for regaining some dexterity, in the realization that many evidence-based therapies for the paretic upper limb, including CIMT, may require some return of voluntary wrist and finger extension [104,105]. This latter finding also suggests that evidence-based practice is not only a matter of applying the most effective therapy for a particular patient but is also about selecting the appropriate patients to be subjected to that specific therapy.

How should we proceed?

Findings of prognostic research in the field of stroke rehabilitation might improve early stroke management decisions like discharge and multidisciplinary intervention planning at (sub)-acute stroke units. As a consequence, subsequent multidisciplinary rehabilitation services may be optimized based on the probability for reducing impairment, or regaining ADLs, walking ability, or upper limb function. However, determinants of prediction models derived from multivariate regression methods should be regarded, at best, as gross indicators for the prognosis of a stroke patient with similar characteristics and abnormalities as the ones in the model. In reality, the likelihood of finding individual patients with a perfect match in demographic and neurological proportion is remote. For this reason, it is important to reiterate that clinical decisions should not be based solely on the outcomes of prediction models but should also incorporate clinical expertise of the specialist and patient values. Certain statistical techniques may individualize risk factors further, but again, these outcomes will never fit a particular stroke patient perfectly. In addition to meeting the key methodological criteria for valid prognostic research and using more dynamic models to predict outcome, future studies should focus on improving the accuracy of prognosis. This may be achieved by considering the capacity of the motor system for functional reorganization in response to therapy, in addition to the extent of stroke-related damage. Findings from the EPOS study also suggest that future studies should investigate the optimal timing of clinical assessments at hospital stroke units as well as gaining insight into recovery profiles in this early post-stroke period [58,61]. The critical time window found in prognostic research in which outcome is still not defined fits with neurobiological findings from recent animal studies in which an up-regulation of growth promoting factors (e.g., BDNF) is found in the first three weeks post-stroke. This period of heightened neuroplasticity is followed by an up-regulation of growth inhibiting factors (e.g., NOGO) in the subsequent weeks [55]. In order to identify how these changes in neuroplasticity are related to stroke recovery and final outcome, cohort studies should use an intensive repeated-measures design, allowing clinicians to increase their understanding of the early-observed changes in body functions, like coordination and compensation strategies, preferably by including kinematic and EMG measures in their model.

Greater predictive power could be obtained by combining simple measures of motor impairment with neuroimaging, genotyping, and neurophysiological measures of neural plasticity [96]. In particular, variations in the genotype for BDNF and other genes may play an important role in the relationship between neural plasticity and recovery of motor function after stroke [55,96]. In addition, futures studies should consider the capacity of the patient's brain to recover function based on neural plasticity. For example, recent work has shown that common polymorphisms of the gene for BDNF decreased neural plasticity and motor learning in healthy adults, suggesting that genetic factors strongly influence neural plasticity [96].

Predicting recovery of motor function after stroke for individual patients is likely to become more accurate with the development of algorithms to guide the sequential combination of measures, starting with those that are relatively quick and simple, such as bedside tests of motor impairment, and progressing to more sophisticated measures required to reduce uncertainty. This progression could involve neurophysiological and neuroimaging measures of motor system integrity, as well as genetic testing. Future studies are needed in which these approaches with clinical bedside tests alone are mutually compared in order to determine their relative accuracy and combined predictive value [35].

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