



Predicting disease progression in acute stroke using the Barthel Index

Introduction and Objectives

At present there are no clinically effective drugs available for shielding the brain from the biochemical and neurological consequences of acute ischaemic stroke. Many candidate compounds have been evaluated but none have been successful, possibly due to suboptimal study designs¹ or statistically inadequate analytical techniques.² Current regulatory-approved practice is to contrast clinical assessment scale scores at a predefined endpoint, typically 90 days. Here, we demonstrate the generality of a recently-developed approach for longitudinally modelling non-monotonic clinical assessment scale data³ by applying it to data collected using the Barthel index of daily living (BI), a clinical assessment scale designed to rate motor recovery and functional independence in acute stroke⁴, in the hopes that it may be a useful solution to problems associated with current analytical techniques.

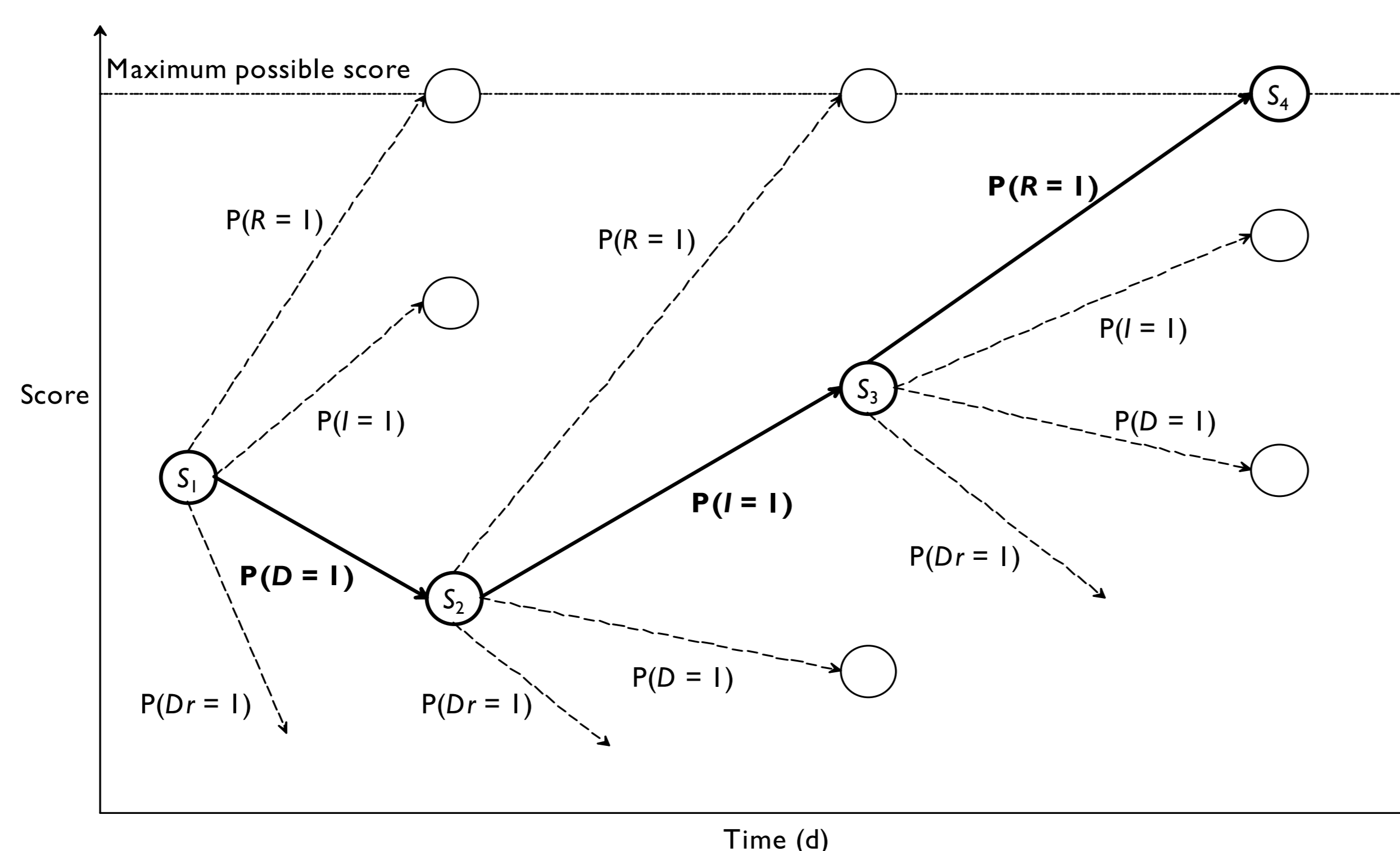


Figure 1. A flowchart illustrating the concept of the core probabilistic model. S_1 , S_2 , S_3 and S_4 are observed scores at observations 1, 2, 3 and 4, respectively. Empty circles indicate potential scores after each type of transition (which, in reality, could be any value between the score minimum and the last observation in the event of a score decline, between the last observation and one unit below the score maximum in the event of a score improvement, or the score maximum). Bold lines indicate actual score progression, whereas broken lines represent events that were possible, but did not take place, at every transition. $P(R = 1)$, $P(I = 1)$, $P(D = 1)$ and $P(Dr = 1)$ are the probabilities of reaching maximum score, improvement in score, decline in score, and dropout, respectively.

Methods

Underlying disease processes may precipitate the exit of a subject from the study before the endpoint is reached, with the result that one or more data points for that subject are missing. In acute stroke, such dropout is informative, providing information relating to unseen disease processes.

BI scores are non-monotonic and erratic, in that they may change in both positive and negative directions relative to previous observations, over time. Disease progression in acute stroke may be seen as a series of discrete transitions from one score to another, or from a previous score to dropout. Each transition has a probability, and a score change magnitude, associated with it (see Figure 1).

The model was developed using a dataset composed of BI scores obtained from 775 acute stroke patients. The data were transformed into a format suitable for modelling: reaching a maximum score (R), improvement (I), and dropout (Dr) were assigned variables which were set to 1 if true, and 0 if not. Decline (D) was assumed where R , I and Dr were equal to 0. Score change magnitudes were transformed to constrain estimates to the scale.

Logit-transformed linear functions were used to describe the probabilities of reaching a maximum score, improvement, and dropout, as well as relative improvement and decline. These five functions were modelled simultaneously using NONMEM VIb.

References

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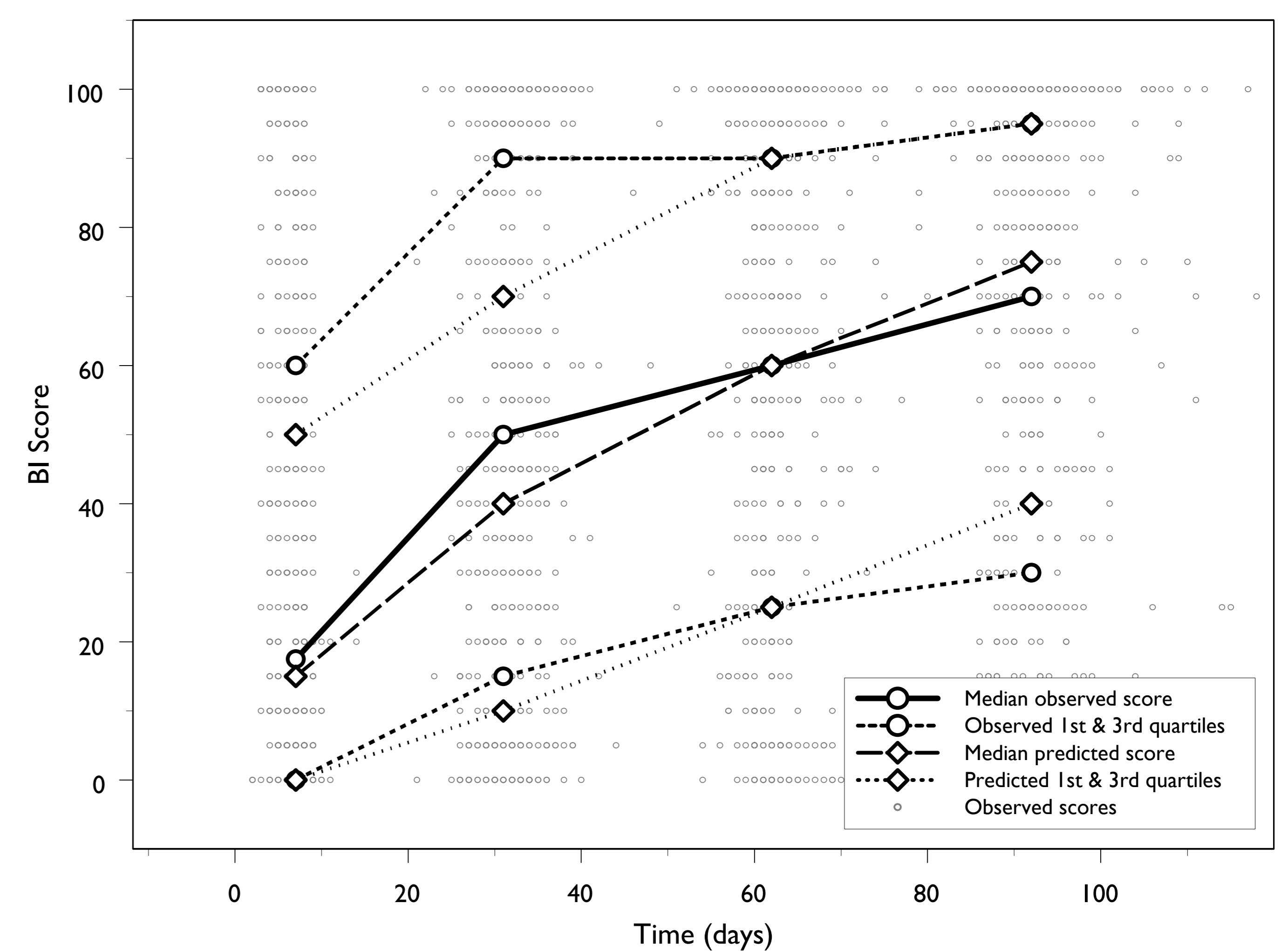


Figure 2. Simulated scores plotted against observed data for the Barthel index.

Results

The logit-transformed linear models for relative score change (C_{ij}) depended largely on Markovian predictors:

$$(C_{ij} | I = 1) = \theta_{IM} + \theta_{PIM} \cdot (BI_{i,j-1} - \theta_{BP}) + (\theta_{TIM} \cdot T_{ij}) + \eta_i + \varepsilon_{ij} \quad (1)$$

$$(C_{ij} | R, I, Dr = 0) = \theta_{PDE} \cdot (\theta_{BP} - BI_{i,j-1}) + (\theta_{TDE} \cdot T_{ij}) + \eta_i + \varepsilon_{ij} \quad (2)$$

In (1), the model for relative magnitude of improvement in score, θ_{IM} was constant improvement, θ_{PIM} was the effect of previous score ($BI_{i,j-1}$), θ_{BP} was a breakpoint for previous score, θ_{TIM} was the effect of time elapsed since the previous observation (T_{ij}), η_i was interindividual variability, and ε_{ij} was residual variability. Similarly, in (2), the model for relative score decline, θ_{PDE} described the effect of $BI_{i,j-1}$ and θ_{TDE} described the effect of T_{ij} .

$$(\lambda_{ij})_R = \theta_R + \theta_{PR} \cdot (BI_{i,j-1} - \theta_{BP}) + \theta_{TR} \cdot T_{ij} \quad (3)$$

$$(\lambda_{ij})_I = \theta_I + (\theta_{TI} \cdot T_{ij}) + \theta_{IAGE} \cdot (Age_i - Age_{med}) \quad (4)$$

$$(\lambda_{ij})_{Dr} = \theta_{Dr} \quad (5)$$

The linear function describing the probability of reaching a maximum score, $(\lambda_{ij})_R$, is defined in terms of a constant (θ_R), previous score (via θ_{PR}), and T_{ij} (via θ_{TR}). In (4), describing the probability of improvement, $(\lambda_{ij})_I$, θ_I is a constant, θ_{TI} reflects the effect of T_{ij} , θ_{IAGE} defines the effect of normalized age, Age_i is age in years of individual i , and Age_{med} is population median age. $(\lambda_{ij})_{Dr}$, the probability of dropout, is a constant (θ_{Dr}).

Discussion and Conclusions

We have developed a model for disease progression (or recovery) in acute stroke, as measured on the BI, that is both descriptive and predictive.

Simulations (Figure 2) demonstrate that the model mimics the distribution of observed scores over time, indicating that it will be possible to use it for simulating clinical trials. Drug effects may be included in the model without difficulty, and, based upon prior experience, it seems likely that use of modelling methods such as this may allow reductions in trial sample sizes without sacrificing power, enabling an increase in efficiency and cost-effectiveness.

Acknowledgments

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