



Model-based assessment of risks and benefits of tissue plasminogen activator treatment in acute ischemic stroke

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OBJECTIVE

Although thrombolysis with recombinant tissue plasminogen activator (t-PA) is licensed for treatment of stroke, it has been an important issue to manage the increased risk of treatment-related intra-cerebral hemorrhage. With this background, this work aimed to develop a quantitative tool to assess benefit and risks of t-PA treatment in ischemic stroke.

METHODS

Longitudinal NIHSS score changes for 337 acute stroke patients treated with t-PA at Severance hospital were collected from electronic medical record. Patients' age, weight, underlying diseases, medications, laboratory test results, stroke territory were collected also. Using item response theory (IRT)-based disease progression model, NIHSS scores for the period of 24h after treatment begins were analyzed, where, for IRT model, graded response and generalized partial credit response (GPCR) models were examined [1,2]. Model building proceeded sequentially using NONMEM 7.3 with Laplacian method, by first obtaining an item characteristic curve (ICC), consisting of slope, difficulty and baseline severity parameters then obtaining a disease progression model for time-varying severity by fixing ICC parameters at estimates from the first step. Model evaluation was performed using VPC, with equal-size binning due to inhomogeneity and heteroscedacity in data clustering [3].

RESULTS

A set of 13 test scores, with each test having the score of 0, 1 or 2 (3 categories), 0, 1, 2 or 3 (4 categories), or 0, 1, 2, 3 or 4 (5 categories), composed the aggregate NIHSS scores ranging from 0 to 42 [4]. Most observations occurred within 2 h post-treatment. 7 bins were chosen, with more bins located at early times. With GPCR model being selected and standard normal distribution for baseline severity, time-varying severity was modeled to be decreased exponentially with time, with half-life of 1.56 h. VPC showed estimated ICC and disease progression models predicted data adequately.

CONCLUSION

This preliminary result showed the feasibility of applying IRT model to assess t-PA treatment outcome. Observation mostly occurring within 2h post-treatment reflects the importance of model's predictability at early times and incorporating dropout model along with covariate model for prognosis factors, which is under development. Predicting the probability of having hemorrhagic event will be also incorporated in the model for assessing risks of t-PA treatment.

Figure 1.

Goodness of fit plot : of Item Characteristic Curve (Red solid line : estimated ICC, Blue solid line : smooth line (GAM), blue area : 95% CI of blue solid line, black closed dots : raw data DV (y-axis, 1=YES, 0=NO) with estimated severity(x-axis).

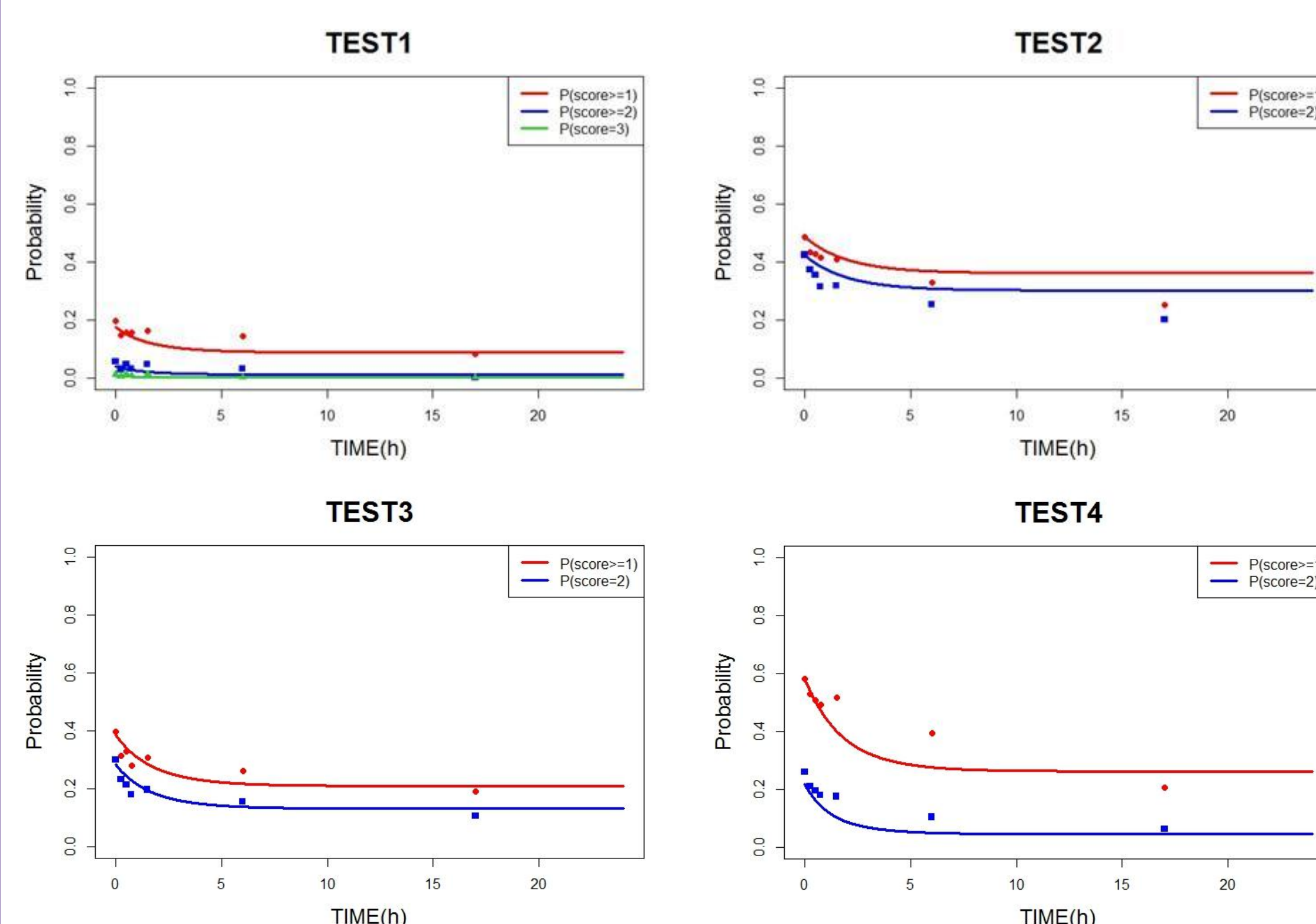
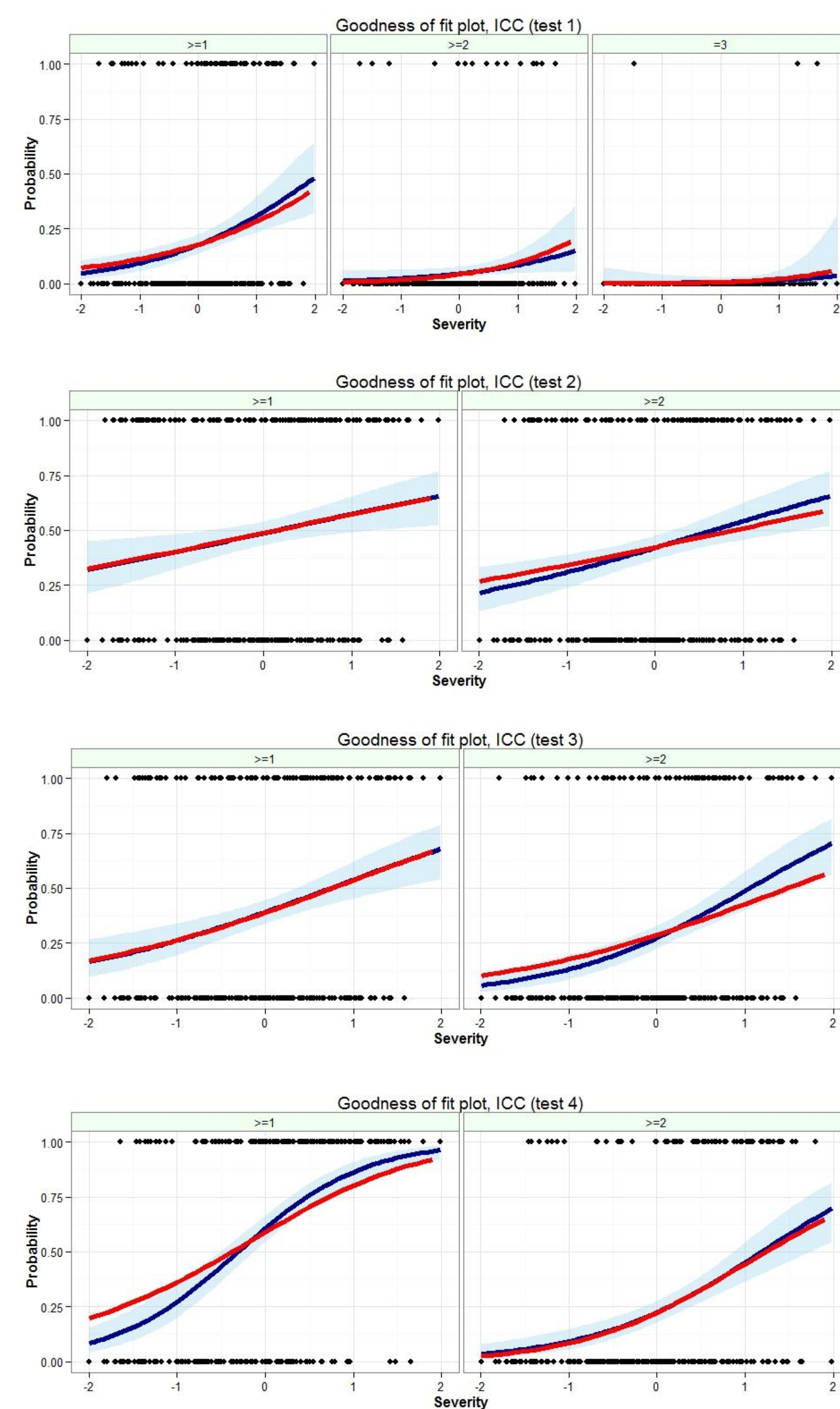


Figure 2.

Cumulative probability plots which were calculated by IRT model and disease progression model.

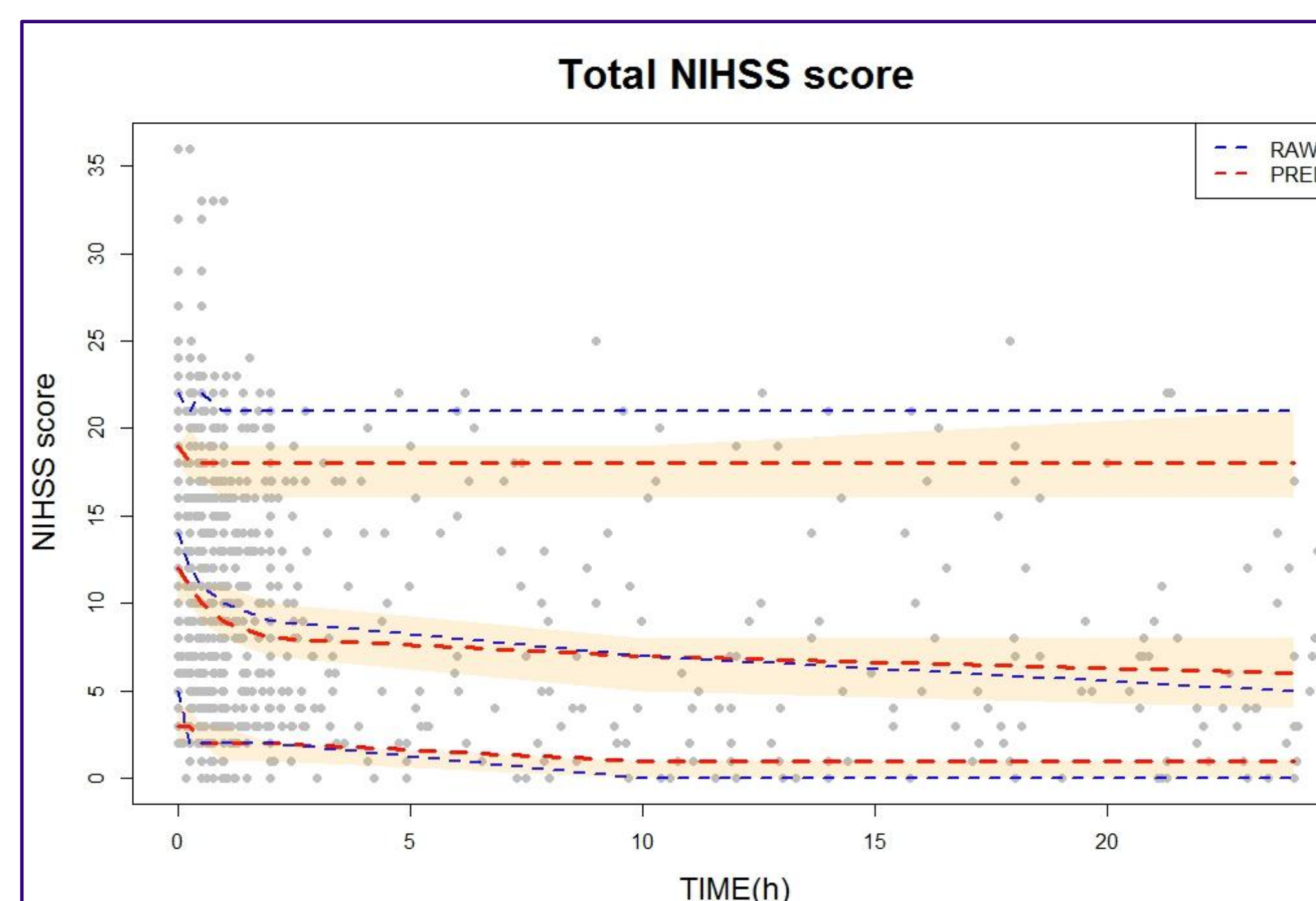


Figure 3.

VPC plot for NIHSS score. (Red dotted line : predicted 5th, 50th, 95th percentile value, blue dotted line : observed 5th, 50th, 95th percentile, shaded areas : 95% confidence interval of predicted lines)

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