**Longitudinal Changes in Disability Rating Scale Scores: A secondary analysis Among Patients with Severe TBI enrolled in the Epo Clinical Trial**

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**Supplementary Material**

**Supplementary S.1 *Statistical modeling***

From previous literature we anticipated the possibility of modeling change in DRS as a polynomial function of time (McCauley et al., 2001). Graphical inspections of the DRS trajectories indicated curvilinearity along with the theoretical construct that a patient would likely have a higher DRS score (poorer outcome) closer to the time of injury and improve over time until leveling off by 180 days (Figure 1). Here, we represent a further elaboration of the modeling technique described in the methods of the body of the manuscript.

We began with the unconditional means model without predictors to describe the DRS outcome variation and unadjusted mean in sTBI patients. We then characterized the average DRS trajectory by fitting unconditional growth curve models to select the most suitable polynomial trajectory for change. With *TIME*, defined as day after injury (DAI), centered at 7 days, reported coefficients (e.g., intercepts and slopes) will be referenced at 1 week post-injury. Higher order fixed and random components were examined. For the random effects, an unstructured covariance structure was first specified, followed by more restrictive assumed structures in the presence of convergence issues. The extent and nature in which the individual quadratic and cubic effect varied across patients were investigated by specifying these terms as both fixed and random and exploring various covariance structures. Ultimately, the linear slope was assumed to vary across patients, while the instantaneous rate of change and deceleration were held constant. Parameter estimates, Akaike information criterion (AIC) and deviance statistics were evaluated and used to determine the characterization of DRS over time. The third step investigated randomization effects over time by comparing the likelihoods of two models: a) model allowing the trajectories to differ over time; b) allowing the intercepts only to differ (See Supplemental S2 for more details). Epo randomization groups [Epo v. Placebo; Hemoglobin transfusion threshold (TT) 10 g/dL v. 7 g/dL] were the primary independent variables of interest. Control variables for the current study were selected *a priori* adhering to pre-specified covariates used in the Epo clinical trial final outcomes article and included Injury Severity Score (*ISS)* and IMPACT prognostic scores classified into (lowest, medium, and highest risk), representing least, intermediate, and most sTBI groups. The nature in which these covariates interacted with time and inclusion into the final model were investigated. We began with a full model including all main effects and interactions that involved both randomization groups with sTBI groups and *ISS* independently (i.e. three-way interactions) at the intercept level and also related each main effect and interaction with time. Higher order interactions were tested first both at the intercept level and as related to polynomial time trajectories followed by two-way interactions in the same fashion, and finally the main effects on time, removing non-significant effects (based on Type III estimates) terms at each step. We only included up to highest significant polynomial in the model.

If a covariate was not related to time, we controlled for its effect at the intercept level only with the exception of a treatment group on time which remained as a primary question in the study. We also specified and formally tested (based on the visual inspection of the individual trajectories) that the variability in the intercepts differed across sTBI groups.

**Table S1. Estimation of growth parameters and the relationships between the growth parameters and covariates for the DRS.**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Effect | | Estimate | | Std. Error | | P-value | |
| Intercept | | 18.0064 | | 1.86 | | <.0001 | |
| Linear Change | | -0.3944 | | 0.05 | | <.0001 | |
| Quadratic Change | | 0.004356 | | 0.001 | | <.0001 | |
| Cubic Change | | -0.00001 | | 3.00E-06 | | <.0001 | |
| Intercept/TT7 | | -0.8231 | | 0.824 | | 0.3182 | |
| Intercept/Epo1 | | 0.9359 | | 2.19 | | 0.6694 | |
| Intercept/Epo2 | | 1.6916 | | 1.730 | | 0.3283 | |
| Intercept/Most sTBI | | 4.8077 | | 1.485 | | 0.0014 | |
| Intercept/Least sTBI | | -5.027 | | 1.665 | | 0.0029 | |
| Intercept/Injury severity score (ISS) | | 0.1244 | | 0.043 | | 0.0043 | |
| Intercept/Epo1\*Most sTBI | | -1.926 | | 2.750 | | 0.4839 | |
| Intercept/Epo1\*Least sTBI | | 1.8981 | | 3.133 | | 0.5447 | |
| Intercept/Epo2\*Most sTBI | | -3.2707 | | 2.275 | | 0.1509 | |
| Intercept/Epo2\*Least sTBI | | -1.3659 | | 2.643 | | 0.6055 | |
| Linear Change/TT7 | | -0.0219 | | 0.033 | | 0.5098 | |
| Quadratic/TT7 | | 0.000323 | | 0.001 | | 0.5508 | |
| Cubic Change/TT7 | | -1.27E-06 | | 2.10E-06 | | 0.5466 | |
| Linear Change/Epo1 | | 0.3036 | | 0.084 | | 0.0003 | |
| Linear Change/Epo2 | | 0.1331 | | 0.060 | | 0.0277 | |
| Quadratic Change/Epo1 | | -0.00475 | | 0.001 | | 0.0005 | |
| Quadratic Change/Epo2 | | -0.00305 | | 0.001 | | 0.0019 | |
| Cubic Change/Epo1 | | 0.000018 | | 5.31E-06 | | 0.0009 | |
| Cubic Change/Epo2 | | 0.000013 | | 3.79E-06 | | 0.001 | |
| Linear Change/Most sTBI | | 0.2364 | | 0.056 | | <.0001 | |
| Linear Change/Least sTBI | | 0.0266 | | 0.058 | | 0.6496 | |
| Quadratic Change/Most sTBI | | -0.00307 | | 0.001 | | 0.0008 | |
| Quadratic/Least sTBI | | -0.00026 | | 0.001 | | 0.7842 | |
| Cubic/Most sTBI | | 0.000011 | | 3.55E-06 | | 0.0024 | |
| Cubic/Least sTBI | | 9.20E-07 | | 3.69E-06 | | 0.8031 | |
| Linear Change/Epo1\*Most sTBI | | -0.3494 | | 0.109 | | 0.0014 | |
| Linear Change/Epo1\*Least sTBI | | -0.4831 | | 0.114 | | <.0001 | |
| Linear Change/Epo2\*Most sTBI | | -0.2181 | | 0.087 | | 0.0125 | |
| Linear Change/Epo2\*Least sTBI | | -0.1505 | | 0.092 | | 0.1025 | |
| Quadratic Change/Epo1\*Most sTBI | | 0.004977 | | 0.002 | | 0.0052 | |
| Quadratic Change/Epo1\*Least sTBI | | 0.006334 | | 0.002 | | 0.0007 | |
| Quadratic Change/Epo2\*Most sTBI | | 0.004064 | | 0.001 | | 0.0038 | |
| Quadratic Change/Epo2\*Least sTBI | | 0.003623 | | 0.001 | | 0.0155 | |
| Cubic Change/Epo1\*Most sTBI | | -0.00002 | | 6.93E-06 | | 0.0085 | |
| Cubic Change/Epo1\*Least sTBI | | -0.00002 | | 7.21E-06 | | 0.0023 | |
| Cubic Change/Epo2\*Most sTBI | | -0.00002 | | 5.43E-06 | | 0.0034 | |
| Cubic Change/Epo2\*Least sTBI | | -0.00002 | | 5.79E-06 | | 0.0085 | |

**Supplemental S.2 Modeling the Covariance**

AIC comparisons and as reported in a previous study (McCauley et al., 2001), results from Table S.2 verify that DRS trajectories follow a cubic pattern with intercepts varying across patients (random intercept) at week 1 post injury and linear slopes varying across patients (Model D) and used throughout the remainder of this study to analyze individual change in DRS. Fixed effects in the unconditional growth model represent the instantaneous rate of change (TIME), the deceleration rate (TIME2), and change in the rate of deceleration (TIME3). The average DRS score at week 1 post injury (initial starting point) is 21.8 (*p*<.0001), falling within the moderately severe, severe, and extremely severe category of disability with a negative linear slope (b=-.30, *p*<0.0001) indicating initial improvement (or instantaneous rate of change of .3 points per day) and a deceleration in this initial change (i.e., initially decreased and then begins to decrease) that is incrementally smaller (.003; *p*<.001). The negative cubic effect indicates that this deceleration gradually plateaus over time (*p*<.0001) (Individual trajectories in Figure 1). These TBI patients vary in their initial DRS score (variance: 52.61, *p*<0.0001) and in their instantaneous rate of linear change (.002, *p*<.0001).

Variability in DRS scores at 7 days (intercept) is quite different depending on injury severity group (statistics not presented). Variability among those with least sTBI is ~2x that of those with most sTBI (40.6 v. 22.5) and among the intermediate sTBI was ~1.5 times higher than those with most sTBI. However, variability in slopes were similar (range: .0015-.0022).

**Supplementary Table S2. Modeling the covariance: Results from unconditional means and unconditional growth models.**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | Parameter | Model A  No Change | Model B  Linear Change | Model C  Quadratic  Change | Model D  Cubic  Change |
| Fixed Effects |  |  |  |  |  |  |
| Composite Model | Intercept ( week 1 status) |  | 16.8\*\*\* | 19.44\*\*\* | 20.84\*\*\* | 21.75\*\*\* |
|  | *TIME* (linear term) |  |  | -0.06\*\*\* | -0.17\*\*\* | -.30\*\*\* |
|  | *TIME2* (quadratic term) |  |  |  | 0.0006\*\*\* | .003\*\*\* |
|  | *TIME3* (cubic term) |  |  |  |  | -.000\*\*\* |
| Variance components |  |  |  |  |  |  |
| Level-1 | Within-person |  | 33.57\*\*\* | 12.52\*\*\* | 8.88\*\*\* | 8.182\*\*\* |
| Level-2 | In 1st week status |  | 53.82\*\*\* | 50.04\*\*\* | 51.87\*\*\* | 52.61 |
|  | *Linear term* |  |  |  |  |  |
|  | Variance |  |  | 0.002 | 0.002\*\*\* | .002\*\*\* |
|  | Covar w/1st week status |  |  | .045 | 0.036 | .03\*\*\* |
|  | *Quadratic term* |  |  |  |  |  |
|  | Variance |  |  |  |  |  |
|  | Covar w/1st week status |  |  |  |  |  |
|  | Covar w/linear term |  |  |  |  |  |
| Goodness-of-fit | Deviance statistic |  | 8618.6 | 7786.1 | 7481.5 | 7413.2 |
|  | AIC |  | 8624.6 | 7798.1 | 7495.5 | 7429.2 |
|  | BIC |  | 8634.5 | 7817.9 | 7518.6 | 7455.6 |

**Supplemental S.3. Trajectories of Disability Rating Scale by randomizations group and injury severity (Figures S1-S3).**

**Figure S1.** Individual trajectories of Disability Rating Scale (DRS) scores across patients in the EPO randomization trial (n=193) by Epo Randomization Groups. \*Thick black line indicates the *average change trajector*y for the entire sample.



**Figure S2.** Individual trajectories of Disability Rating Scale (DRS) scores across patients in the Epo randomization trial (n=193) by transfusion threshold Groups. \*Thick black line indicates the *average change trajector*y for the entire sample.



**Figure S3.** Individual trajectories of Disability Rating Scale (DRS) scores across patients in the Epo trial (n=193) by injury severity groups. \*Thick black line indicates the *average change trajector*y for the entire sample.

