Supplementary Data

Supplementary Material: Techniques

Methods

To determine the best fitted regression modeling for examining the effect of hours of therapy on motor FIM change, a series of statistical analytical techniques was applied starting with a nonparametric version of linear regression that is part of the generalized additive model (GAM).[1]

GAM

Suppose that Y is a response random variable and $X_1, \ldots, X_p$ is a set of predictor variables. A regression procedure can be viewed as a method for estimating how the value of Y depends on the values of $X_1, \ldots, X_p$. Given a sample of values for Y and X, estimates of β_0, $\beta_1,\ldots,\beta_n$ are often obtained by the least squares method. One of the most commonly used statistical models in medical research is the multiple linear regressions for continuous data. It is used here as a specific illustration of a GAM. Linear regression models (and many other techniques) illustrate the effects of independent variables χ_i in terms of a linear predictor of the form $\sum x_j\beta_j$, where β_j are parameters. The GAM replaces $\sum x_j\beta_j$ with $\sum f_j(x_j)$ where f_j is a nonparametric function. This function is estimated in a flexible manner using a scatter plot smoother. The estimated function $\hat{f}_j(x_j)$ can reveal possible nonlinearity in the effect of the x_j. In this application, y is a response or outcome variable (motor FIM change), and x is an independent factor (hour of rehabilitation). We want to fit a smooth curve $f(x)$ that summarizes the dependence of y on x. We seek the function $f(x)$ that minimizes

$$\sum(y_i - f(x_i))^2 + \lambda \int f''(x)^2 \quad (1)$$

Notice that $\int f''(x)^2$ measures the ‘‘curvature'' of the function f; λ is a nonnegative smoothing parameter that has a direct relation with ‘‘degree of freedom (df),'' and numerical search should be used to determine the value of λ.[2]

Table S1 provides analytical results from the GAM, including estimation for the linear part of the model and smoothing components. Variables AIS A, AIS B, and high cervical were found to have a significant relationship with motor FIM change, in that patients with any of these injury characteristics would have experienced less motor FIM change. The variable pneumonia was marginally statistically significant. Analysis of deviance indicated that total hour of therapy had a nonlinear statistically significant effect on FIM change. This model was the final model after testing nonlinearity on age and rehabilitation onset. Generalized cross validation was used to choose degree of freedom. Based on the general trend in the smoothing component plot, a second-order polynomial regression of total hour of therapy was used next.

Generalized linear models

To determine whether linear term (THT) or quadratic term of total hour of therapy ($THT + THT^2$) would provide more accurate modeling, two generalized linear models (GLM) with each term were compared using lack-of-fit criteria. Results indicated (partial F-test = 21, $p = 0.001$) that the quadratic form should be used, from which similar to results from GAM, AIS A, AIS B, high cervical, pneumonia, and THT were found to be significant variables (Table 3).

Analysis was repeated for the AIS D subgroup because pattern-based analysis revealed that this group had a different pattern of motor FIM improvement than the other groups. Table S2 shows that, similar to the results for the entire group, total hour of therapy had a nonlinear relation with outcome ($p = 0.0099$). Nonlinear form for all continuous variables (age and rehabilitation onset) was applied, but only total hours of therapy remained significant.

A similar trend in the smoothing component plot was also observed for the AIS D subgroup, and second-order polynomial regression of total hour of therapy was used in the regression model. In a similar comparison with the lack-of-fit criteria between a GLM model with the linear term of the variable and that with the quadratic form (Table 4), results indicated (partial F-test = 6.1, $p = 0.015$) that the quadratic form of model should be used. Further, results from the regression model showed that both linear and quadratic form should be used for prediction of outcome ($p = 0.001$) and that the effect of time for patients with AIS D was stronger than whole sample ($\beta = 0.61$ vs. $\beta = 0.40$).

References

1. Hastie, T., and Tibshirani, R. (1990). Exploring the nature of covariate effects in the proportional hazards model. Biometrics 46, 1005–1016.
2. Hastie, T., Tibshirani, R., and Friedman, J. (2009). The elements of statistical learning. New York, NY: Springer New York.

Supplementary Table 1. Generalized Additive Model for American Spinal Injury Association Impairment Scale A,B,C,D Groups

Parameter	*Outcome–Motor FIM change*			
	Parameter estimate	*Standard error*	*t value*	*Pr > [t]*
Intercept	33.79	6.99	4.83	< 0.0001
Age at injury	–0.07	0.06	–1.10	0.27
Gender				
Female	1.38	3.09	0.45	0.6550
Male (reference)	-	-	-	
ASIA Impairment Scale (AIS)				
AIS A	–12.47	3.59	–3.48	**0.0006**
AIS B	–12.55	4.53	–2.77	**0.0061**
AIS C	2.87	3.53	0.81	0.4166
AIS D (reference)	-	-	-	-
Neurological level of injury				
High cervical (C1–4)	–10.86	3.08	–3.53	**0.0005**
Low cervical (C5–8)	–3.86	3.13	–1.24	0.2176
Thoracolumbar (T1–S5) (reference)	-	-	-	-
Pressure ulcer				
Yes	2.56	2.69	0.95	0.34
No (reference)	-	-	-	-
Pneumonia				
Yes	–8.45	4.39	–1.92	0.0557
No (reference)	-	-	-	-
Urinary tract infection				
Yes	1.92	2.50	–0.77	0.4426
No (reference)	-	-	-	-
Rehabilitation onset	–0.04	0.02	–1.72	0.0872
Total hours of therapy - linear	0.07	0.02	3.14	**0.0019**
Component	*Smoothing parameter*	*DF*	*GCV*	*Num*
Smoothing Model Analysis—Fit Summary for Smoothing Components				
Spline (total hours of therapy)	0.999971	5	273.46598	245
Source		*DF*	*F Value*	*Fr>F*
Smoothing Model Analysis—Approximate Analysis of Deviance				
Spline (total hours of therapy)		5	9.59	<0.0001

FIM, Functional Independence Measure; ASIA, American Spinal Injury Association; AIS, American Spinal Injury Association (ASIA) Impairment Scale; DF, degree of freedom; GCV, generalized cross validation.

Supplementary Table 2. Generalized Additive Model for American Spinal Injury Association Impairment Scale D Group

Parameter	*Outcome–Motor FIM Change*			
	Parameter estimate	*Standard error*	*t value*	*Pr > [t]*
Intercept	22.99	6.76	3.40	0.0008
Age at injury	0.0005	0.06	0.01	0.9937
Gender				
Female	0.54	3.22	0.17	0.8658
Male (reference)	-	-	-	-
Neurological level of injury				
High cervical (C1–4)	−7.85	2.99	−2.63	**0.0092**
Low cervical (C5–8)	−2.47	2.97	−0.83	0.4057
Thoracolumbar (T1–S5) (reference)	-	-	-	-
Pressure ulcer				
Yes	−1.43	2.66	−0.54	0.5913
No (reference)	-	-	-	-
Pneumonia				
Yes	−9.94	4.57	−2.17	**0.0309**
No (reference)	-	-	-	-
Urinary tract infection				
Yes	−0.47	2.54	−0.19	0.8527
No (reference)	-	-	-	-
Rehabilitation onset	−0.06	0.02	−2.51	**0.0126**
Total hours of therapy - linear	0.05	0.02	2.60	**0.0099**
Component	*Smoothing parameter*	*DF*	*GCV*	*Num*
Smoothing Model Analysis—Fit Summary for Smoothing Components				
Spline (total hours of therapy)	0.999953	7.5	305.18626	245
Source		*DF*	*F Value*	*Fr>F*
Smoothing Model Analysis—Approximate Analysis of Deviance				
Spline (total hours of therapy)		7.5	5.97	< 0.0001

FIM, Functional Independence Measure; ASIA, American Spinal Injury Association; AIS, American Spinal Injury Association (ASIA) Impairment Scale; DF, degree of freedom; GCV, generalized cross validation.