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A MATHEMATICAL LOG-LOGISTIC STEP STRESS MODEL FOR THE SECRETION OF LOW EARLY MORNING PLASMA CORTISOL IN POSTTRAUMATIC STRESS DISORDER WITH CO-MORBID DEPRESSION IN HUMAN BEINGS

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Abstract: The hypothalamic pituitary adrenal (HPA) axis is integral to the acute stress response. Although abnormalities in the entire HPA axis including regulation of cortisol secretion have been reported in chronic posttraumatic stress disorder (PTSD), a recent meta-analysis did not confirm significant differences in pooled cortisol levels between patients with PTSD and healthy controls. Continuous plasma cortisol measurement, particularly during the time of dynamic transition from nadir to peak levels (12 a.m. to 5 a.m.), therefore offers distinct advantages over single-point measures in assessing HPA axis abnormalities in stress-related disorders [8]. Preliminary evidence suggests that MDD, a common co-morbid condition [7] contributes to a distinct HPA axis profile in PTSD. The main purpose of this study is to evaluate serial overnight levels of plasma cortisol in participants with PTSD + MDD compared to PTSD – MDD and to non-traumatized healthy subjects. Here we assume that the model is a cumulative exposure model and the life distribution is log-logistic the corresponding cdf under simple step stress and the corresponding probability density function have been obtained. The application part is fitted to the mathematical model and we conclude that the functional value of $f_0(t)$, the plasma cortisol levels corresponding to PTSD + MDD decreases rapidly than the healthy controls and PTSD – MDD. The Fisher information matrix for the application part is also obtained.

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Keywords: PTSD, MDD, Depression, Cortisol, Accelerated life test, Cumulative exposure model, Fisher information matrix, Log-logistic life distribution, Step-stress test.

1. INTRODUCTION

Accelerated Life Tests (ALT) provide information quickly on the life distribution of the material or products by testing them at higher than usual level of stress such as high temperature, pressure, vibration, cycling rate, or load to induce early failures. The results obtained at the accelerated conditions are analyzed in terms of a model to relate life length to stress; they are extrapolated to the design stress to estimate the life distribution.

The problems of designing optimum step stress ALT, and making inferences, have been studied by several authors. Nelson [10] introduced step-stress ALT that allows test conditions to change during testing. In this type of testing, a unit is placed on test at an initial low stress; and if it does not fail in a predetermined time τ, stress is increased. If there is a single change of stress, the ALT is called a simple step-stress test. The cumulative exposure model defined by Nelson [10] for simple step-stress testing with stresses x_1 and x_2 is

$$F(t) = \begin{cases} F_1(t), & 0 \le t < \tau \\ F_2(t - \tau + \tau), & 0 \le t < \infty \end{cases} \tag{1}$$

where $F_i(t)$ is the c.d.f of the failure time at stress x_1 , τ, is the time to changing stress, and τ is the solution of $F_1(\tau) = F_2(\tau)$. The stress change time which minimizes the asymptotic variance of maximum likelihood estimate of the log mean life at the design condition [2, 3, 4]. Alhadeed & Yang [1] discussed the optimal simple step-stress plan for the Khamis-Higgins model [6]. Mostly, the step-stress accelerated life testing deals with the exponential, and Weibull distributions. In this paper, we propose a log-logistic step-stress model.

In a time-step stress test, units are initially placed on test at stress x_1, and run until time τ when the stress is changed to x_2. The test is continued until all the units run to failure. Such a test is called a simple step-stress test because it uses only two stresses.

2. ASSUMPTIONS

(i) Two stress levels are used: stresses x_1 and x_2 ($x_1 < x_2$).

(ii) For any level of stress, the life distribution of the test unit is log-logistic.

(iii) The median life of a test unit is a log-linear function of stress, i.e., $\log \lambda(x_i) = \lambda_0 + \beta_1 x_i$, $i = 0, 1, 2$, where β_0 and $\beta_1 (< 0)$ are unknown parameters depending on the nature of the product, and the method of test. The median life of a test unit at lower stress is longer than that at higher stress, i. e., $\lambda_0 > \lambda_1 > \lambda_2$.

(iv) A cumulative exposure model holds, i.e., the remaining life of a test unit depends only on the cumulative exposure it has seen [13].

(v) The lifetimes of test units are i.i.d.

3. A CUMULATIVE EXPOSURE MODEL

(i) All n units are initially placed on low stress x_1, and run until τ when the stress is changed to x_2. At x_2, testing continues until all remaining units fail.

(ii) n_i failure times $\tau_{i,j}$, $j = 1, 2, ..., n_i$ of test units are observed while testing at stress x_i, $i = 1, 2$.

Further, the model is a cumulative exposure model, and the life distribution is log-logistic, the cdf of a test unit under simple step-stress test is given from (1) where τ' is the solution of $F_1(\tau) = F_2(\tau')$. Because $F_i(t)\left(\frac{t}{\lambda}\right)^{\alpha} \Big/ \left(1+\left(\frac{t}{\lambda}\right)^{\alpha}\right)$ therefore $\lambda' = (\lambda_2/\lambda_1)\tau$. Thus the pdf of a test unit is

$$f_0(t) = \begin{cases} \dfrac{\dfrac{\alpha}{\lambda_1}\left(\dfrac{t}{\lambda_1}\right)^{\alpha-1}}{\left(1+\left(\dfrac{t}{\lambda_1}\right)^{\alpha}\right)^2}, & t < \tau \\ \dfrac{\dfrac{\alpha}{\lambda_1}\left(\dfrac{t}{\lambda_1}\right)^{\alpha-1}}{\left(1+\dfrac{t^{\alpha}-\tau^{\alpha}}{\lambda_2^{\alpha}}+\dfrac{\tau^{\alpha}}{\lambda_1^{\alpha}}\right)^2}, & t \geq \tau \end{cases} \tag{2}$$

Now, the likelihood function from observations t_{ij}, $i = 1, 2$, $j = 1, 2, ..., n_i$, is

$$L(\lambda_1, \lambda_2) = \prod_{j=1}^{n_1}\left[\frac{\frac{\alpha}{\lambda_1}\left(\frac{t}{\lambda_1}\right)^{\alpha-1}}{\left(1+\left(\frac{t}{\lambda_1}\right)^{\alpha}\right)^2}\right] \times \prod_{j=1}^{n_2}\left[\frac{\frac{\alpha}{\lambda_1}\left(\frac{t}{\lambda_1}\right)^{\alpha-1}}{\left(1+\frac{t^{\alpha}-\tau^{\alpha}}{\lambda_2^{\alpha}}+\frac{\tau^{\alpha}}{\lambda_1^{\alpha}}\right)^2}\right] \tag{3}$$

By substituting for λ_i, $i = 1, 2$ in (1); the log likelihood function is a function of unknown parameters β_0 and β_1, and is given by

$$\begin{aligned} \log L(\beta_0, \beta_1) = \prod_{j=1}^{n_1} & [\log\alpha - (\beta_0 - \beta_1 x_1) + (\alpha-1)\log t_{1j} \\ & - (\alpha-1)(\beta_0+\beta_1 x_1) - 1\log(1+t_{1j}^{\alpha} e^{-\alpha\beta_0 - \alpha\beta_1 x_1})] \\ & + \prod_{j=1}^{n_2} [\log\alpha - (\beta_0 - \beta_1 x_2) + (\alpha-1)\log t_{2j} - (\alpha-1)(\beta_0+\beta_1 x_1) \\ & - (\alpha-1)(\beta_0+\beta_1 x_1) - 2\log(1+t_{2j}^{\alpha} - \tau^{\alpha}) e^{-\alpha\beta_0 - \alpha\beta_1 x_2} + \tau^{\alpha} e^{-\alpha\beta_0 - \alpha\beta_1 x_1}] \end{aligned} \tag{4}$$

The maximum likelihood estimates for β_0, β_1 can be obtained by solving the following equations.

$$\frac{\partial \log L}{\partial \beta_0} = -\alpha n + 2\alpha \sum_{j=1}^{n_1}\left[\frac{e^{-\alpha\beta_0-\alpha\beta_1 x_1} t_{1j}^{\alpha}}{1+e^{-\alpha\beta_0-\alpha\beta_1 x_1} t_{1j}^{\alpha}}\right] + 2\alpha \sum_{j=1}^{n_2}\left[\frac{e^{-\alpha\beta_0-\alpha\beta_1 x_1}\tau^{\alpha} + e^{-\alpha\beta_0-\alpha\beta_1 x_2}(t_{2j}^{\alpha}-\tau^{\alpha})}{1+e^{-\alpha\beta_0-\alpha\beta_1 x_1}\tau^{\alpha} + e^{-\alpha\beta_0-\alpha\beta_1 x_2}(t_{2j}^{\alpha}-\tau^{\alpha})}\right] = 0$$

$$\frac{\partial \log L}{\partial \beta_1} = -\alpha (n_1 x_1 + n_2 x_2) + 2\alpha \sum_{j=1}^{n_1}\left[\frac{e^{-\alpha\beta_0-\alpha\beta_1 x_1} t_{1j}^{\alpha} x_1}{1+e^{-\alpha\beta_0-\alpha\beta_1 x_1} t_{1j}^{\alpha}}\right] + 2\alpha \sum_{j=1}^{n_2}\left[\frac{x_1 e^{-\alpha\beta_0-\alpha\beta_1 x_1}\tau^{\alpha} + x_2 e^{-\alpha\beta_0-\alpha\beta_1 x_2}(t_{2j}^{\alpha}-\tau^{\alpha})}{1+e^{-\alpha\beta_0-\alpha\beta_1 x_1}\tau^{\alpha} + e^{-\alpha\beta_0-\alpha\beta_1 x_2}(t_{2j}^{\alpha}-\tau^{\alpha})}\right] = 0$$

The Fisher information matrix is obtained by taking the expected values of the second partial, and mixed partial derivatives of $\log L(\beta_0, \beta_1)$ with respect to , β_0, β_1. We have obtained

$$F = \frac{2}{6} n\alpha^2 \begin{bmatrix} 1 & x_1 A_1 + x_2 A_2 \\ x_1 A_1 + x_2 A_2 & x_1^2 A_1 + x_2^2 A_2 + (x_1 - x_2)^2 A_3 \end{bmatrix} \tag{5}$$

where

$$A_1 = \frac{\left(2+\frac{\tau^{\alpha}}{\lambda_1^{\alpha}}\right)\frac{\tau^{\alpha}}{\lambda_1^{\alpha}}}{\left(1+\frac{\tau^{\alpha}}{\lambda_1^{\alpha}}\right)^2}, \qquad A_2 = 1 - A_1 \quad \text{and} \quad A_3 = \frac{\frac{\tau^{\alpha}}{\lambda_1^{\alpha}}}{\left(1+\frac{\tau^{\alpha}}{\lambda_1^{\alpha}}\right)^2}.$$

4. APPLICATION

When plasma cortisol levels in subjects with PTSD + MDD were compared to PTSD – MDD and healthy controls, there is a significant diagnosis by time interaction and a significant time main effect. The PTSD – MDD group did not differ from the PTSD + MDD group, nor did the PTSD – MDD group differ from the control group in plasma cortisol at any time point. The largest group difference was between PTSD + MDD patients and healthy controls at 1:30 a.m. The largest effects for PTSD – MDD compared to controls and for

PTSD + MDD compared to PTSD – MDD were of moderate size, and occurred at 2:00 a.m. and 6:30 a.m., respectively. This is the continuous sampling study to report lower early a.m. plasma cortisol levels ratio in a subgroup of individuals with PTSD + MDD compared to non-traumatized healthy controls. Subjects with PTSD – MDD had similar plasma cortisol levels compared to healthy subjects.

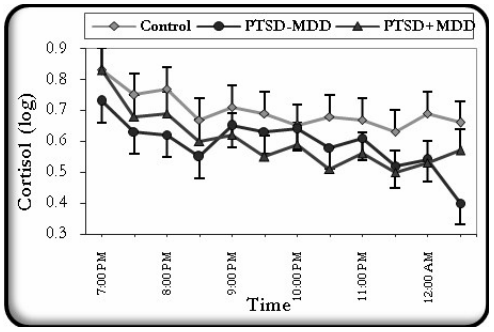

Figure 1

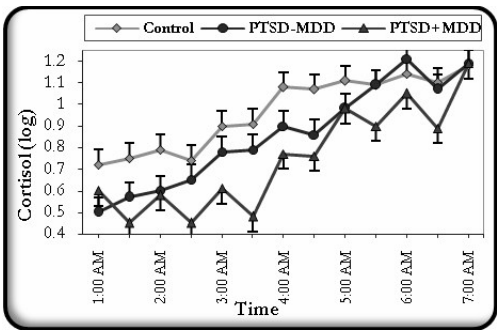

Figure 2

Figure 1 & 2: Plasma Cortisol Levels Compared to Healthy Controls and Patients with PTSD + MDD, PTSD – MDD

Our observation of lower early morning plasma cortisol levels in subjects with PTSD + MDD, but not in PTSD – MDD subjects resembles the hypocortisolemia reported in prior studies of PTSD subjects with co-morbid depression [5]. Lower plasma cortisol levels in the combined sample of subjects with PTSD with and without MDD in this study is similar to only one serial sampling study in Vietnam veterans with PTSD which reported lower plasma cortisol levels between 7 p.m. and 9 p.m.[12], however, did not distinguish between participants with PTSD + MDD and PTSD – MDD, is neither reported nor controlled for. In contrast to the only report of hypocortisolemia in serial sampling of PTSD subjects [9], other continuous plasma studies in PTSD subjects [11] did not replicate this finding. Taken together, the data from this study adds to the nascent literature suggesting that plasma cortisol levels are lower only in PTSD patients with co-morbid depression.

5. RESULT

The co-morbid MDD could explain lower early morning plasma cortisol levels observed in PTSD subjects, that is PTSD + MDD may be a distinct or a more severe condition with a unique biological profile from that of PTSD – MDD, and these differences need to be taken into account in future studies in PTSD that evaluate neurobiology and treatment response to low-dose glucocorticoids.

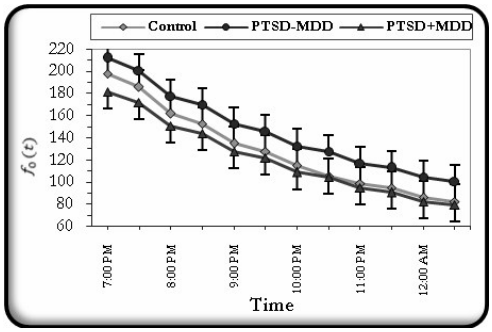

Figure 3

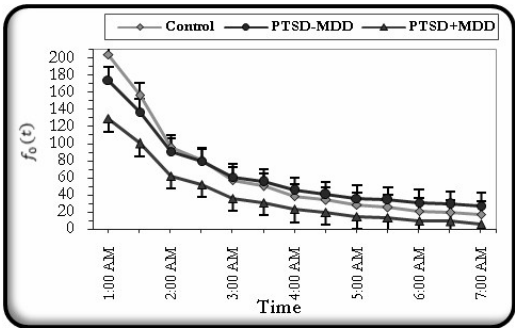

Figure 4

Figure 3 & 4: The Functional Value of $f_0(t)$, Corresponding to Control, PTSD + MDD and PTSD – MDD

The plasma cortisol levels in PTSD + MDD and PTSD – MDD is due to differences in glucocorticoid feedback sensitivity evaluated by a low-dose dexamethasone suppression test. The application part is fitted with the mathematical part and the conclusion obtained is the functional value of $f_0(t)$, corresponding to PTSD + MDD decreases rapidly than the value of the Control and PTSD – MDD. The Fisher information matrix for the application part is given by

$$F = 0.4591418 \begin{bmatrix} 1 & 0.670821591 \\ 0.670821591 & 0.756032678 \end{bmatrix}$$

6. CONCLUSION

As expected, the participants with PTSD + MDD were significantly more depressed than those with PTSD – MDD despite comparable severity of PTSD symptoms. The results are consistent and the log-logistic step stress model conclude that the functional value of $f_0(t)$, corresponding to PTSD + MDD decreases rapidly than the value of the PTSD – MDD. PTSD + MDD may be a distinct or a more severe condition with a unique biological profile from that of PTSD – MDD, and these differences need to be taken into account in future studies in PTSD that evaluate neurobiology and treatment response to low-dose glucocorticoids.

This model can be extended to the estimation of optimal stress change of time by using the variable of stress management.

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