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A Mathematical Log-Logistic distribution to PH model for the effects of an acute serotonergic challenge on brain-gut responses in irrirable bowel syndrome

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Abstract: *In this paper, we have introduced a simple extension of the log-logistic distribution to a PH model to analyze the ACTH profiles. Serotonin, a key denominator of the brain–gut axis is involved in the regulation of gastro-intestinal function as well as cognition, mood and hypothalamic pituitary adrenal axis mediated neuroendocrine responses. All the plots reveal that the ACTH suppression levels are high in the control placebo when injecting patient placebo dose as compare with the citalopram dose and control. It is concluded that the log-logistic distribution to a PH model is well fitted to analyze medical data mathematically. It is useful for medical professionals.*

Keywords: *ACTH, Cox PH, Hazard rate function, Log-logistic distribution*

Mathematical subject classification: $62H_{xx}$; $62NO_5$; $90B25$.

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I. Introduction

Proportional hazard (PH) models play a vital role in analyzing time-to-event data. A key assumption in the PH model is that the hazard ratio comparing any two specifications of covariates is constant over time (commonly known as PH assumption). Although the PH assumption may not hold for one or more covariates over the entire study period, it may hold in shorter time intervals. Therefore, violation of the PH assumption may be handled using time-dependent covariates **[9].** One of the appealing features of PH models is that the regression coefficients have relative risk interpretation, which is preferred by many clinicians.

The Cox PH model **[2]** is the most popular in survival analysis mainly because of two reasons: (a) no assumption is required about the probability distribution of survival times (i.e., a semi-parametric model), and (b) it usually fits the data well no matter which parametric model is appropriate. In contrast, distributional assumption is required for a fully parametric PH model**[8][11].**

This also leads to the added requirement of checking the appropriateness of the chosen distribution. Nevertheless, as demonstrated parametric models lead to more efficient estimates than Cox's model **[3]** under certain conditions. More specifically, if the distributional assumption is valid, a parametric model leads to smaller standard errors of the estimates than would be in the absence of a distributional assumption **[3].** Moreover, the use of Cox PH in joint modeling of time-to-event and longitudinal data usually leads to an under estimation of the standard errors of the parameter estimates **[6]** and therefore most methods for joint modeling are based on parametric response distributions. Regarding the choice between a parametric and Cox's PH model, suggested using a richer parametric model or simply the Cox's model[**3]** in case of an unsatisfactory fit of the chosen probability distribution.

The most commonly used parametric time-to-event models are the Weibull, log-logistic and log-normal distributions. The log-logistic and log-normal distributions belong to the accelerated failure time (AFT) family, and are useful in modeling non monotone hazard rates **[17].** Note that the log-logistic also accommodates decreasing hazard functions. Only a few parametric models are closed under PH assumption, the most common of which is the Weibull that accommodates only monotone hazard func tions. In fact, Weibull is the only distribution that is closed under both AFT and PH families **[8]. [12]** Proposed a generalization of the Weibull distribution which permits parametric PH regression modeling. It is a three parameter distribution and is capable of modeling both monotone and non- monotone hazard functions. One difficulty with this model is that it is nonregular (the support depends on some parameters) in the case of increasing hazard functions, and therefore the standard maximum likelihood asymptotics do not hold. In this paper, we propose a simple

extension of the log-logistic model which is closed under the PH relationship. The proposed generalized log-logistic model is a three-parameter distribution, and has characteristics similar to those of the log-logistic model. Moreover, it approaches the Weibull in the limit. These features enable it to satisfactorily handle both monotone (increasing and decreasing) and nonmonotone (unimodal) hazard functions.

And we introduce the generalized log-logistic model and discuss estimation and testing of the parameters using the maximum likelihood method. The proposed method is then illustrated with applications to four data sets, one of which involves joint modeling of time-to-event and longitudinal data. A simulation study is presented to evaluate the performance of generalized log-logistic in comparison with other commonly used PH models to describe different types of time-to-event data. We conclude by summarizing our findings.

II. The Generalized Log-Logistic Model

The generalized log-logistic distribution for a nonnegative random variable *T* can be conveniently specified in terms of the hazard function as follows:

$$h(t;\alpha) = \frac{k\rho(\rho t)^{k-1}}{1+(\gamma t)^k}\ , t > 0 \quad ----------(1)$$

where $\rho > 0$, $k>0$ and $\gamma > 0$ are parameters and $\alpha = (k, \gamma, \rho)'$ If γ depends on ρ via $\gamma = \rho$ and $\gamma = \rho\eta^{\frac{-1}{k}}$ with $\eta > 0$, then (1) reduces to the hazard function of the log logistic **[11]** distributions. Taking γ not dependent on ρ, it is easy to verify that (1) is closed under PH relationship .The hazard function is monotone decreasing when $k \leq 1$, and unimodal when k > 1 (i.e., $h(t; \alpha) = 0$ at $t = 0$, increases to a maximum at $t = [(k - 1)/\gamma \ \ k\ ]1/k$, and then approaches zero monotonically as $t \to \infty$). Note that (1) approaches the Weibull hazard function as $\gamma k \to 0$.

This particular feature of the generalized log logistic model enables it to handle monotone increasing hazard satisfactorily via k > 1 and γ small (close to zero).

The survival function, probability density function and cumulative hazard function of the generalized log-logistic distribution are, respectively,

$$S(t;\alpha) = (1+(\gamma t)^k)^{\frac{-\rho^k}{\gamma^k}}\ , t > 0 \quad ----------(2)$$

$$f(t;\alpha) = \frac{k\rho(\rho t)^{k-1}}{(1+(\gamma t)^k)^{\frac{\rho^k}{\gamma^k}+1}}\ , t > 0 \quad ----------(3)$$

$$H(t;\alpha) = \frac{\rho^k}{\gamma^k}\log\left[1+(\gamma t)^k\right], t > 0 \quad ----------(4)$$

III. Applications

Absolute ACTH levels did not significantly differ between groups at baseline (patients 22.6 ± 2.6, 27.6 ± 3.3; controls 23.0 ± 2.3, 23.1 ± 2.3 ng/L in the citalopram and placebo condition respectively). The ACTH concentrations increased significantly in the citalopram condition compared with

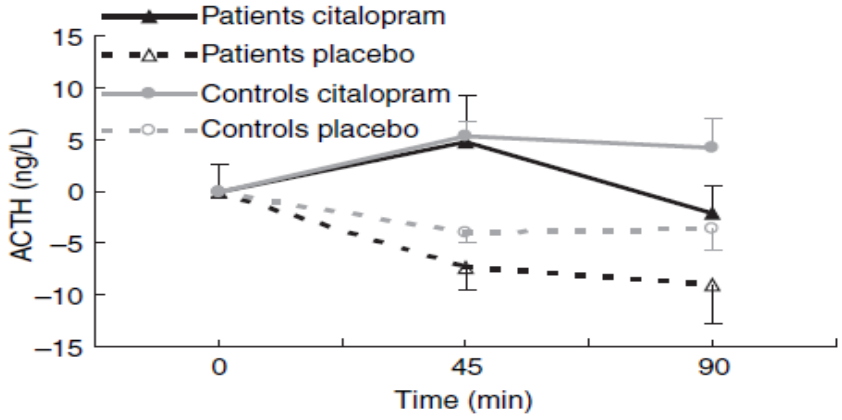


Fig 3.1. *Mean ± S.E.M. plasma adrenocorticotropic hormone (ACTH; measured as change from baseline) responses as a function of time in diarrhoea-predominant irritable bowel syn-drome (d-IBS) patients and control subjects respectively, receiving citalopram 20 mg and placebo, respectively, infused intraven-ously over 15 min starting at time '0'. Citalopram significantly increased ACTH levels compared with placebo [F(2,52) ¼ 16.5, P < 0.001].*

Placebo [F(2,52) ¼ 16.5, P < 0.001].This effect did not significantly differ between the two subject groups (p> 0.6 ; Fig 3.1)

Post hoc correlations.

In post hoc analyses, correlations between level of affective dysregulation and citalopram induced ACTH responses was investigated. Significant negative correlations between HAM-D17, SCL-90 and HADS scores with ACTH responses were found (Pearson's r ¼)0.36,
P < 0.05; r ¼)0.53, P < 0.01 and r ¼)0.60, P < 0.001 respectively).

IV. Discussion

We have demonstrated that acutely increasing the serotonergic activity by selective serotonin reuptake inhibition does not significantly influence visceral urge or pain perception. However, the citalopram challenge was significantly associated with increased ACTH and enhanced affective memory performance because of a bias towards positive material in d-IBS patients and healthy matched controls.Data concerning the role of SSRIs on visceral perception are conflicting. Reduced oesophageal sensitivity to distension has been described, but these drugs seem to lack this effect at gastric level**.[15]** This is the first investigating the acute effects of an SSRI on brain and gut responses simultaneously. Two preliminary studies indicated that acute i.v. administration of 20 mg citalopram did not alter the sensitivity to descending colonic pressure distension**.[1][16]**

A single oral dose of another SSRI fluoxetine, did not modify rectal perception in healthy controls**.[14]** In addition, 6-week treatment with fluoxetine 20 mg b.d. in 40 non-depressed IBS patients did not significantly change rectal sensitivity or compliance**.[10]** .Citalopram significantly enhanced memory performance. These results are in line with a study of Harmer et al., which demonstrated that 10 mg i.v. citalopram administration increased memory consolidation**.[4].** In addition to enhanced memory performance, citalopram induced an affective memory bias towards positive material without significantly influencing the subjective mood status, using the POMS. These results are in line with data which demonstrated that citalopram administration reduces the processing of negative relative to positive emotional material without notable mood differences**.[4][5].**

This seems to be confirmed by our current findings as well as by the findings of Kemp et al., which demonstrated that acute citalopram administration enhances pleasant, and suppresses unpleasant cortical electrophysiological responses to emotional images without altering patient's subjective responses. The memory performance was significantly impaired in d-IBS compared with controls.Consistent with other studies citalopram significantly increased ACTH level. However, we did not demonstrate a significant effect of citalopram on plasma prolactin levels. Failure of oral citalopram administration to increase prolactin levels has been reported. Neuroendocrine responses were however, not significantly attenuated in d-IBS patients compared with controls which may be explained by the fact that(i) we excluded patients with a previous psychiatric diagnosis or first-degree family history of affective disorders and (ii) the level of affective dysregulation in our IBS patients was less pronounced compared with patients primarily presenting with affective disorders or (iii) a type II error.

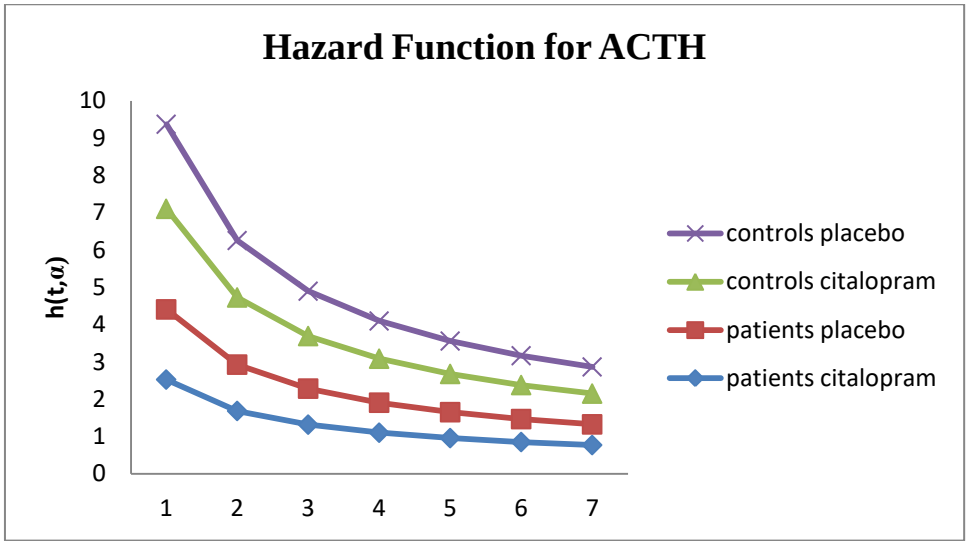
Our findings of increased plasma serotonergic and hormonal parameters and presence of an affective memory bias favour a peripheral as well as central influence of citalopram. Regarding citalopram pharmacokinetics, reported that plasma citalopram metabolite concentrations were constant from the end of 20 mg i.v. administration until 160 min afterwards. Although we lack biochemical evidence of an increased serotonergic activity in the brain, the citalopram induced alteration of affective memory performance indicate that central effects are apparent. Acute citalopram administration did not significantly decrease visceral perception. Although the pharmacokinetic and pharmacodynamic effect window do not need to be identical it is unlikely that during the assessment of visceral perception the pharmacodynamic effect was not yet present. Induced a memory bias towards a loss of positive material and we hypothesized that this response bias maybe responsible for the induced enhanced visceral perception by affecting afferent visceral processing. However, in this paper increasing the serotonergic synthesis induced a response bias towards positive material without an effect on visceral perception.

The antidepressant effect of SSRIs in patients with major depression is known to occur after about 6 weeks of treatment. However, 6-week treatment with fluoxetine did not change rectal sensitivity in non-psychiatric IBS patients. The present results concern the change in brain–gut interaction due to an acute increase of serotonergic activity. Whether these findings are also valid in a prolonged change of serotonergic activity by pharmacological or nutritional means and whether there is a differential effect in IBS with and without psychiatric comorbidity needs to be investigated.

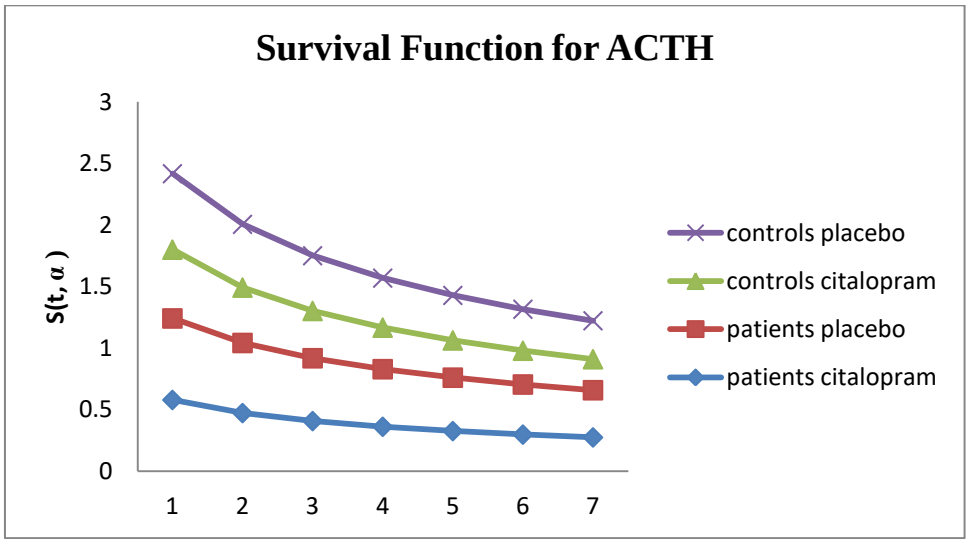
The SERT polymorphism has been associated with vulnerability to stress induced depressive symptoms and with the speed and rate of response to antidepressant treatment. In addition, SERT polymorphism has been associated with altered neuroendocrine and neuromodulatory responses following citalopram administration. Also in IBS there is some evidence that genetic polymorphisms at the SERT promoter are associated with d-IBS and treatment response. Whether functional responses of the serotonin system, may

represent a neurobiological substrate for the differential response to antidepressant treatment in IBS needs to be elucidated. We have provided evidence that acute serotonergic modulation by selective serotonin reuptake inhibitionInfluences neuroendocrine responses and cognition in d-IBS and controls without a significant effect on visceral perception.

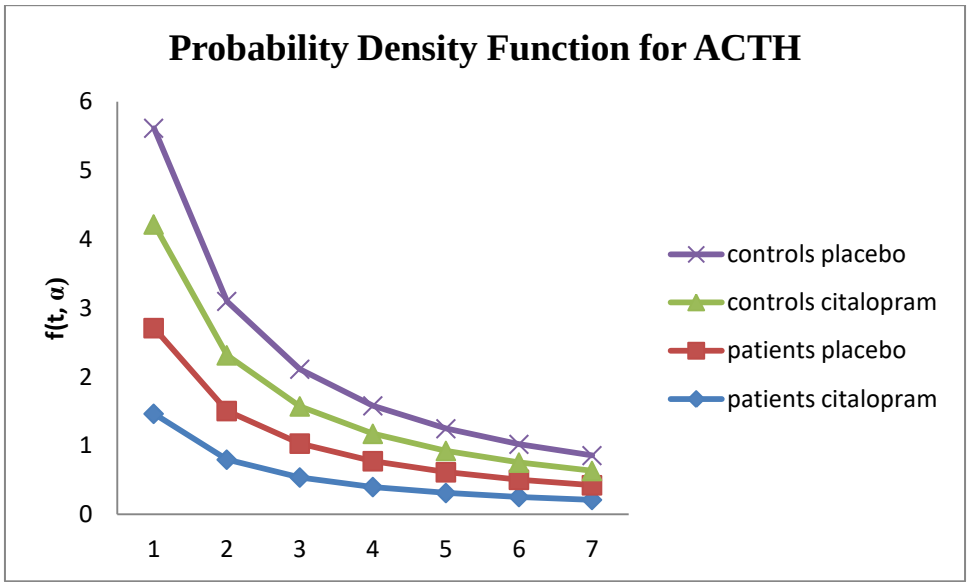
V. Mathematical Results



The hazard rate of ACTH dose function is extremely good than the hazard rates of placebo and control functions. According to plots the hazard rate functions, the hazard rates of patients Placebo, Patients citalopram and control functions are 6.9, 4.2, and 2.9 respectively. The hazard rate is also known as failure rate. The failure rate of development of ACTH levels is high when injecting patients placebo dose comparing with the injecting patients citalopram dose and control.



The plot of probability survival function of ACTH patients' placebo dominates the patients citalopram dose and control survival functions in the specified range. The probability survival function of ACTH Placebo dose decreases rapidly than citalopram dose and control functions. The probability of suppression of ACTH levels when injected patients placebo dose beyond any given specified time is higher than the other two cases of patients citalopram dose and control.



The plot of probability density function of ACTH patients Placebo dose shows its superiority than the functions ACTH patients citalopram and ACTH control. The plot of ACTH patients Placebo dose function initially monotonically increasing up to t=6 h and then decreasing monotonically. The rate of decreasing is comparatively good than ACTH patients Placebo and control functions. ACTH levels are suppressed as time goes on.

VI. Conclusion

In this paper, we used a simple extension of the log-logistic distribution to a PH model by appending an additional parameter to analyze the ACTH profiles of placebo and citalopram Here we have plotted probability density function, probability survival function, hazard rate functions for the selected medical data. The suppression levels of ACTH profiles of Placebo when injecting the control, patient's placebo dose and patient's citalopram dose has been observed. All the plots reveal that the ACTH suppression levels are high in the control placebo when injecting patient placebo dose as compare with the citalopram dose and control. It is concluded that the log-logistic distribution to a PH model is well fitted to analyze medical data mathematically. It is useful for medical professionals.

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