



A repeated time-to-event model for epileptic seizures in patients undergoing antiepileptic drug withdrawal during video-electroencephalography monitoring



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Objectives

When the primary event of interest is a clinical outcome statistical models for time-to-event (TTE) are recognized as a useful tool. Video-electroencephalographic monitoring (Video-EEG) is the gold standard neurodiagnostic technique to characterize the epileptic focus of patients with seizure-related disorders, it is useful in the diagnosis and pre-surgical evaluation of these patients.

The aims of this study were: a) to develop a repeated TTE (RTTE) model for the occurrence of seizures during a Video-EEG using a Population Analysis; b) to explore clinical information as predictors of the occurrence of seizures.

Methods

Data
Data were collected retrospectively from Caucasian patients with seizures submitted to a Video-EEG at the Hospitals of the University of Coimbra, Portugal (October 1998 - June 2005).

After the admission in the hospital, patients followed a previously established drug discontinuation protocol to precipitate the occurrence of seizures during the Video-EEG. One antiepileptic drug was withdrawn from inpatients' drug treatment every 48 hours and the time at which each seizure took place was recorded.

The time to occurrence of seizures from admission at the hospital and censoring time were included in the analysis.

Model Development

Parametric survival models defined in terms of hazard were evaluated by nonlinear mixed-effects modelling using NONMEM 7.3.1¹ PsN (<http://psn.sourceforge.net/>) and Xpose (<http://xpose.sourceforge.net/>) were used to facilitate model execution and graphical evaluation.

Initially, the distribution of the RTTE data was explored and different types of baseline hazards, $h_0(t)$, were tested in the survival function parameterized over time (t) as:

$$\text{Constant hazard} \quad h_0(t) = \lambda \quad (1)$$

$$\text{Weibull hazard} \quad h_0(t) = \lambda \cdot \gamma \cdot (\lambda \cdot t)^{\gamma-1} \quad (2)$$

$$\text{Gompertz hazard} \quad h_0(t) = \lambda \cdot e^{\gamma \cdot t} \quad (3)$$

where λ and γ are the scale and shape parameters. Inter-individual variability (IIV) was tested in $h_0(t)$, λ and γ , using an exponential model.

Using the hazard, the predicted fraction of patients without an event (up until time T) was calculated as

$$\text{Survival function} \quad S(t) = e^{-\int_0^t h(t) dt} \quad (4)$$

The predicted probability of having an event (up until time T), was derived by the cumulative distribution function as

$$F(t=T) = p(\text{event} \leq T) = 1 - S(t) \quad (5)$$

Thereafter, the influence of the number of anti-epileptic drugs each patient was taking throughout the study was explored on $h_0(t)$, λ and γ by means of a discrete or continuous time-varying covariate as an absolute number (NOAD), as an absolute change from baseline treatment (DNOAD) or as a relative change from baseline (RCNOAD), exemplified for $h_0(t)$:

For both continuous and categorical covariates

$$h(t) = h_0(t) \cdot e^{\theta_{cov} \cdot COV} \quad (6)$$

For categorical NOAD, DNOAD and RCNOAD with n categories

$$h(t) = \begin{cases} h_0(t), & \text{category} = 1 \\ h_0(t) \cdot (1 + \theta_2), & \text{category} = 2 \\ \vdots \\ h_0(t) \cdot (1 + \theta_n), & \text{category} = n \end{cases} \quad (7)$$

where θ represents the estimated covariate effect.

Finally, other covariates were explored as predictors of the occurrence of seizures (using eq. 6): age; sex; body weight and a combined covariate (CLASS) including the type of epilepsy (generalized vs. partial) and location of the epileptogenic focus in case of partial epilepsy (temporal vs. extra-temporal vs. both).

Model Selection and Qualification

The assessment of statistical significance of included covariates in a nested model was based on the likelihood ratio test ($\alpha = 0.05$) and the predictive performance of key-models was evaluated with Visual Predictive Checks (VPCs) of the Kaplan Meier (KM) curves.²

References

1. Beal, S., Sheiner, L.B., Boeckmann, A., & Bauer, R.J. NONMEM User's Guides 1989-2009; Icon Development Solutions, Ellicott City, MD, USA, 2009.
2. Holford N, Lavielle M. A tutorial on time to event analysis for mixed effects modellers. PAGE 20 (2011) Abstr 2281 [www.page-meeting.org/?abstract=2281].

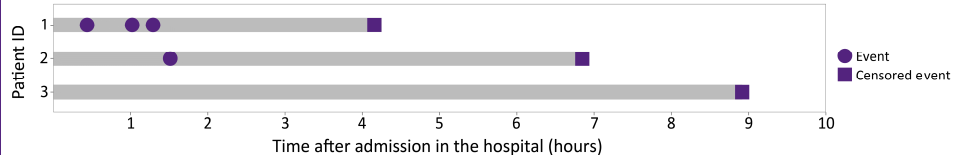
Results

During the evaluative period of 111 patients, 81 patients experienced at least one epileptic seizure (table 1). The typical patient was a 31-year-old woman that experienced 2 seizures during a mean stay at the hospital around 7 days. Patients whose time to seizure was greater than the monitoring end time ($n=30$) were right censored.

No. of patients	Female/male (n)	Age (yr)	Body weight (kg)	Length of hospitalisation (h)	No. of antiepileptic drugs at t_0	Seizures per patient	Number of patients		
							Single event only	2+ events	No event
111	58/53	31.1±11.6 (12-64)	68.1±15.0 (36-108)	161±43.5 (45-335)	2 (1-4)	2 (0-16)	16	65	30

Table 1 – Summary of demographic and clinical characteristics of patients. Results expressed as mean ± standard deviation (range) or median (range); t_0 : time of admittance in the hospital.

The distribution of events in 3 typical subjects are shown below (grey bar represents evaluative period). The first patient (ID 1) had 3 seizures during the study; the second patient (ID 2) only had 1 seizure; the third patient (ID 3) was right censored.



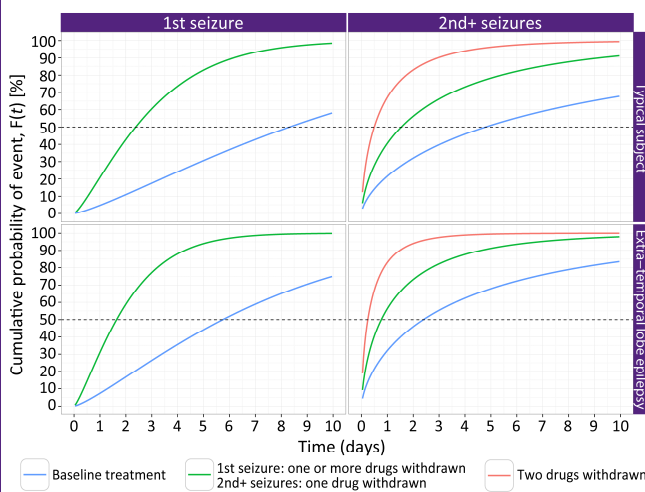
The use of the same distribution to fit model parameters for all events in simultaneous did not lead to reasonable VPCs of the KM curves. Therefore, hazard parameters were estimated independently for the 1st and subsequent (2nd+) events. The RTTE model that best described the data was based on a combination of a Weibull hazard rate that increases and decreases with time for the 1st and 2nd+ events, respectively; furthermore, the scale parameter λ was also allowed to differ. Inter-individual variability was estimated for all events simultaneously on λ .

The inclusion of an effect of DNOAD on $h_0(t)$ was found to best describe the data and was statistically significant ($p<0.001$). Patients with extra-temporal lobe epilepsy were found to have a higher risk for having a seizure ($p<0.05$) compared with patients with temporal lobe or generalized epilepsy (typical subjects). The results of the final model are presented in Table 2.

Table 2 – Final parameter estimates

	1st event ^a	2 nd + events ^a
λ [h^{-1}]	0.00374 (6.97)	0.00504 (3.93)
γ	1.26 (8.65)	0.670 (14.9)
Fractional change in $h_0(t)$ for DNOAD -2 and -1	3.83 (3.28)	—
Slope for DNOAD 2 nd + events	—	-0.761 (17.6)
Effect of CLASS on $h_0(t)$	0.4652	
IIV on λ (%CV)	104 (5.19) ^b	

The instantaneous risk of having a seizure increased with a decrease in the number of anti-epileptic drugs with respect to the baseline: for the first event, DNOAD was treated as categorical while for 2nd+ events it was treated as continuous. The effects of the covariates on the cumulative probability of an event, $F(t)$, are represented in figure 1.

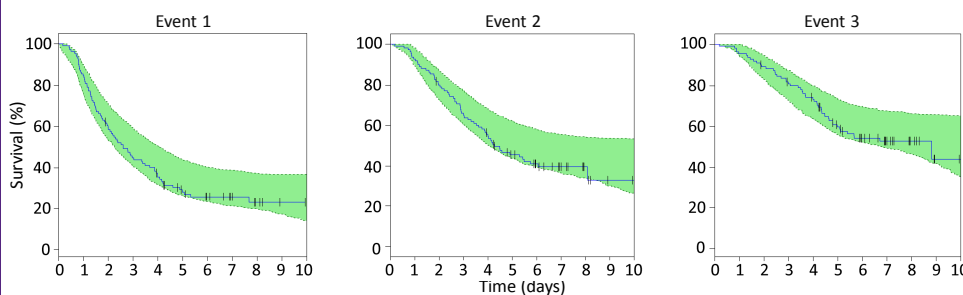


^aValues expressed as mean (%RSE), unless specified otherwise; ^bThe %RSE for the corresponding variance term; CV: coefficient of variation; IIV: Interindividual variability; RSE: relative standard error

Figure 1 (left) – Estimated cumulative probability of having a first or subsequent epileptic seizure in a typical patient (with generalized or temporal lobe epilepsy) and in a patient with extra-temporal lobe epilepsy. Colored lines represent the effect of the number of drugs withdrawn from the baseline treatment.

The descriptive properties of the model are shown below by VPCs of the KM curves, i.e. percentage of seizure-free patients vs. time, for the 1st, 2nd and 3rd events.

Figure 2 (below) – KM plots with vertical lines showing censored observations and shaded area representing 95% confidence intervals for the simulated data.



Conclusions

A parametric repeated time-to-event model comprising a combination of different hazard rates for the first and for the subsequent seizures and including the drug effect as a time-varying covariate described the data well.

Patients with extra-temporal lobe epilepsy were found to have a higher risk for having a seizure compared with patients with temporal lobe epilepsy or generalized epilepsy.

Acknowledgments

Leonardo da Vinci programme T4CD by the University of Coimbra.



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