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A Proportional Risk Model for Time-to-event Analysis in Randomized Controlled Trials

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Abstract

Regression models for continuous, binary, nominal, and ordinal outcomes almost completely rely on parametric models, whereas time-to-event outcomes are mainly analyzed by Cox's Proportional Hazards model, an essentially non-parametric method. This is done despite a long list of disadvantages that have been reported for the hazard ratio, and also for the odds ratio, another effect measure sometimes used for time-to-event modelling. In this paper, we propose a parametric proportional risk model for time-to-event outcomes in a two-group situation. Modelling explicitly a risk instead of a hazard or an odds solves the current interpretational and technical problems of the latter two effect measures. The model further allows for computing absolute effect measures like risk differences or numbers needed to treat. As an additional benefit, results from the model can also be communicated on the original time scale, as an accelerated or an prolongated failure time thus facilitating interpretation for a non-technical audience. Parameter estimation by maximum likelihood, while properly accounting for censoring, is straightforward and can be implemented in each statistical package that allows coding and maximizing a univariate likelihood function. We illustrate the model with an example from a randomized controlled trial which assesses the efficacy of a new glucose-lowering drug for the treatment of type 2 diabetes mellitus.

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Introduction

It is one of the phenomenons in medical statistics that regression models for continuous, binary, nominal, and ordinal outcomes almost completely rely on parametric modelling, whereas time-to-event outcomes are mainly analyzed by the Proportional Hazards (PH) model of Cox [1], an essentially non-parametric method [2]. This is even more astonishing as the list of disadvantages of the hazard ratio (HR), which is the primary result of a Cox PH model, is long and still growing. For example, Sutradhar/Austin stated that researchers "should refrain from using the magnitude of the HR to describe the magnitude of the relative risk - this is incorrect", because the hazard ratio is a ratio of rates, and not one of risks [3]. Hernán [4] pointed to the fact that hazard ratios, even in randomized trials, "have a built-in selection bias", because they are conditional measures, conditioning at each time point on the set of observations which is still under risk. In the words of Aalen et al. [5], "for a randomized study of survival times the first contribution to the Cox partial likelihood is based on a randomized comparison, but subsequent partial likelihood contributions are based on biased comparisons. This bias arises when there are known or unknown factors influencing survival which are not controlled for in the analysis; we believe this is almost always the case." Following Stensrud, the Cox model here effectively operates on left truncated samples, and not on the original study population [6].

Ironically, even Cox himself would "normally want to tackle problems parametrically", and therefore "take the underlying hazard to be a Weibull or something", because the answers from these models are "very insensitive to the parametric formulation of the underlying distribution" [7]. The skepticism towards the Cox model culminated in the provocative question of Bendix Carstensen, who over the years gave several talks asking "Who needs the Cox model anyway?" [8]

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Finally, the hazard ratio has been criticized for being non-collapsible[9]. That is, adjusting for a covariate that is associated with the event will in general change the HR, even if this covariate is not associated with the exposure, that is, is no confounder. This limits the usefulness of the Cox model for confounder adjustment (its primary task!) considerably. As a further consequence, hazard ratios from models with different sets of covariates in the same data set will be different, although the underlying causal HR is identical[3].

Interestingly, the hazard ratio shares this unfortunate property of non-collapsibility with the odds ratio[10;11], which is the typical result from a logistic regression model, but is also used in time-to-event analysis, e.g., in the proportional odds model[12]. And in a further analogy to the hazard ratio, the odds ratio has also been criticized for being interpreted as a relative risk, although this approximation is only valid for very low prevalences of the event of interest[13].

In response to the various disadvantages of the hazard and the odds ratio we show how a "real" proportional risk model (which is not just an approximated proportional hazard or proportional odds model) for time-to-event outcomes can be defined and estimated in a two-group situation. We illustrate the model with a data set from a large randomized controlled trial (RCT) which assesses the efficacy of a new glucose-lowering drug, empagliflozin, for the treatment of type 2 diabetes mellitus[14].

Proportional Risk Model

Basic definition

We consider a situation with two treatment (or exposure) groups where 1 denotes the treatment (or exposed), and 0 the control (or non-exposed) group. We assume that event times in the two groups follow an exponentiated-uniform (EU) distribution with parameters θ_1 and θ_0 in treatment and control group, respectively, and a common parameter α, where $\theta_1, \theta_0, \alpha > 0$. The cumulative distribution functions $F_{EU,*}(t)$ in the groups are then given by

$$F_{EU,0}(t) = (\theta_0 t)^\alpha, \quad 0 < t < 1/\theta_0, \tag{1}$$

and

$$F_{EU,1}(t) = (\theta_1 t)^\alpha, \quad 0 < t < 1/\theta_1. \tag{2}$$

By definition, $F(t) = P(T < t)$, the probability of experiencing the event before an arbitrary time point t. Dividing $F_{EU,1}(t)$ by $F_{EU,0}(t)$ thus leads to a ratio of probabilities or a relative risk

$$\frac{F_{EU,1}(t)}{F_{EU,0}(t)} = \frac{(\theta_1 t)^\alpha}{(\theta_0 t)^\alpha} = \frac{\theta_1^\alpha t^\alpha}{\theta_0^\alpha t^\alpha} = \left(\frac{\theta_1}{\theta_0}\right)^\alpha = k^\alpha, \tag{3}$$

with $k = \frac{\theta_1}{\theta_0}$ or $\theta_1 = k\theta_0$. As this relative risk k^α is independent of t, the model fulfills a "proportional risk" property.

Using elementary relations between survival function, density, and hazard, the corresponding densities $f_{EU,*}$ and hazards $\lambda_{EU,*}$ are

$$f_{EU,0}(t) = \alpha(\theta_0 t)^{\alpha-1}, \;\; f_{EU,1}(t) = \alpha(k\theta_0 t)^{\alpha-1},$$

and

$$\lambda_{EU,0}(t) = \frac{\alpha(\theta_0 t)^{\alpha-1}}{1-(\theta_0 t)^\alpha}, \;\; \lambda_{EU,1}(t) = \frac{\alpha(k\theta_0 t)^{\alpha-1}}{1-(k\theta_0 t)^\alpha}.$$

This results in a hazard ratio $HR_{EU}(t)$ of

$$HR_{EU}(t) = \frac{\lambda_{EU,1}(t)}{\lambda_{EU,0}(t)} = \frac{\frac{\alpha(k\theta_0 t)^{\alpha-1}}{1-(k\theta_0 t)^\alpha}}{\frac{\alpha(\theta_0 t)^{\alpha-1}}{1-(\theta_0 t)^\alpha}} = k^{\alpha-1}\left(\frac{1-(\theta_0 t)^\alpha}{1-(k\theta_0 t)^\alpha}\right),$$

which depends on t. The model in (3) is therefore not a proportional hazard model, except in the trivial case of $k = 1$, where the event times in both groups are equal and $HR_{EU}(t) = 1$.

Finally, for the odds ratio $OR_{EU}(t)$ we get

$$OR_{EU}(t) = \frac{\frac{F_1(t)}{1-F_1(t)}}{\frac{F_0(t)}{1-F_0(t)}} = \frac{\frac{(k\theta_0 t)^\alpha}{1-(k\theta_0 t)^\alpha}}{\frac{(\theta_0 t)^\alpha}{1-(\theta_0 t)^\alpha}} = k^\alpha\left(\frac{1-(\theta_0 t)^\alpha}{1-(k\theta_0 t)^\alpha}\right) = k \times HR_{EU}(t),$$

which also depends on t. Therefore the model in (3) is also not a proportional odds model, except in the trivial case of $k = 1$.

The $l-th$ moment of a random variable Z with exponentiated-uniform distribution and parameters θ and α is [15]

$$E(Z^l) = \frac{\alpha}{\alpha + l}\left(\frac{1}{\theta}\right)^l.$$

As such, mean and variance of Z are

$$E(Z) = \frac{\alpha}{(\alpha+1)\theta}, \;\; Var(Z) = \frac{\alpha}{(\alpha+1)^2(\alpha+2)}\left(\frac{1}{\theta}\right)^2. \tag{4}$$

Absolute Risk Measures

It is a common understanding in clinical research that absolute risk measures should be always reported in addition to relative risk measures. This recommendation has been given at various places in the literature in recent years, as for example by The Academy of Medical Sciences that recommends, that "... absolute risk or absolute risk difference is always presented alongside any measure of relative risk or attributable risk so that the level of risk or size of intervention effects can be properly understood. This applies to the general and scientific media, regulatory agencies, and scientists."[16]

Derivation of absolute risk measures is straightforward from the proportional risk model, albeit these are no longer independent of t. The risk difference becomes

$$\begin{aligned} RD_{EU}(t) &= F_{EU,0}(t) - F_{EU,1}(t) = (\theta_0 t)^\alpha - (\theta_1 t)^\alpha \\ &= \theta_0^\alpha t^\alpha - \theta_1^\alpha t^\alpha = t^\alpha(\theta_0^\alpha - \theta_1^\alpha), \end{aligned}$$

the number needed to treat as the reciprocal of the risk difference

$$NNT_{EU}(t) = \frac{1}{t^\alpha(\theta_0^\alpha - \theta_1^\alpha)}.$$

An absolute risk measure which is exclusively defined for time-to-event outcomes in an RCT situation is the difference Δ in restricted mean survival times as proposed by Royston/Parmar[17]:

$$\begin{aligned} \Delta &= RMST_1 - RMST_0 = \int_0^{t^*} (S_1(t) - S_0(t))dt = \\ &= \int_0^{t^*} (1 - F_1(t)) - (1 - F_0(t))dt = \\ &= \int_0^{t^*} (F_0(t) - F_1(t))dt, \end{aligned}$$

where t^* is the time point at which Δ is computed.

Here, we find Δ to be calculated as:

$$\Delta_{EU} = \int_0^{t^*} t^\alpha(\theta_0^\alpha - \theta_1^\alpha)dt = (\theta_0^\alpha - \theta_1^\alpha)\frac{t^{*\alpha+1}}{\alpha+1}$$

The simplicity of this formula even allows for a dynamic investigation of Δ_{EU} across varying time points t^* (then called a "Restricted Mean Survival Time *Curve*",[18]) with the proportional risk model.

The proportional risk model as an accelerated failure time (AFT) model

Parametric models for time-to-event modelling were available long before the Cox model, and they were reported to be simpler, more informative, more robust, and having the hazard function to be directly available[19]. Most parametric models are also accelerated failure time (AFT) models, whose parameters can be interpreted directly on the original time, and not on a hazard or odds scale. As such, AFT models describe de- or acceleration of event times (potentially visualized as slower or faster running "life clocks") as a function of covariates[20] and thus facilitate the communication of results from time-to-event models to laypersons considerably.

In technical terms this de- or acceleration is described by ratios of quantiles for fixed p with $0 < p < 1$[20]. For our two-group proportional risk model the two respective quantiles are

$$Q_{EU,0} = F^{-1}_{EU,0}(p) = t_0 = \sqrt[\alpha]{\frac{p}{\theta_0^\alpha}} = \frac{\sqrt[\alpha]{p}}{\theta_0},$$

$$Q_{EU,1} = F^{-1}_{EU,1}(p) = t_1 = \sqrt[\alpha]{\frac{p}{\theta_1^\alpha}} = \frac{\sqrt[\alpha]{p}}{\theta_1}.$$

Then, the ratio of quantiles, and thus the acceleration factor, is

$$\frac{F^{-1}_{EU,1}(p)}{F^{-1}_{EU,0}(p)} = \frac{t_1}{t_0} = \frac{\frac{\sqrt[\alpha]{p}}{\theta_1}}{\frac{\sqrt[\alpha]{p}}{\theta_0}} = \frac{\theta_0}{\theta_1} = \frac{1}{k}.$$

As this is independent of p, the proportional risk model is also an AFT model with the acceleration factor $1/k$. Interestingly, this acceleration factor is also independent of α.

The proportional risk model as a prolongated failure time (PFT) model

In the last subsection we commended AFT models for their easy interpretability on the time scale. However, AFT models are still multiplicative on the time scale, and communication with laypersons people would be even more easier when we could report absolute (instead of relative) time differences. Of course, the concept of residual life has already been developed and collected in a textbook[21], but the effect estimates from these approaches are conditional ones, which suffer again, similar to the hazard ratio, from the problem of selection bias.

The simplicity of the proportional risk model also allows accessible inference here, and inspired by the term "accelerated" in the AFT model, we could use the term "prolongated" to describe this property of the proportional risk model. To be concrete, the expected absolute (unconditional) difference between event times is given by

$$PFT_{EU} = \int_0^1 (t_{EU,1}(p) - t_{EU,0}(p))dp = \int_0^1 (Q_{EU,1}(p) - Q_{EU,0}(p))dp =$$
$$\int_0^1 (F^{-1}_{EU,1}(p) - F^{-1}_{EU,0}(p))dp =$$
$$\int_0^1 \left(\frac{\sqrt[\alpha]{p}}{\theta_1} - \frac{\sqrt[\alpha]{p}}{\theta_0} \right) dp = \frac{(\theta_0 - \theta_1)}{\theta_0\theta_1} \int_0^1 p^{\frac{1}{\alpha}} dp =$$
$$\frac{(\theta_0 - \theta_1)}{\theta_0\theta_1} \frac{p^{\frac{1}{\alpha}+1}}{\frac{1}{\alpha}+1} \Bigg|_0^1 = \frac{(\theta_0 - \theta_1)}{\theta_0\theta_1} \frac{\alpha}{\alpha+1}.$$

As expected, PFT_{EU} is equal to the difference of means as given in (4) from two exponentiated-uniform distributions with parameters θ_0, θ_1, and a common parameter α.

Of course, in real data sets with not too many events, integrating from 0 to 1 would use extrapolated values for a wide range of p. As such, we might want to compute the expected mean difference in survival times only down to a certain fixed percentile p^*

with $0 < p^* < 1$. We then find

$$PFT_{EU,p^*} = \int_{p^*}^{1} (t_{EU,1}(p) - t_{EU,0}(p))dp = \frac{(\theta_0 - \theta_1)}{\theta_0\theta_1} \frac{p^{(\frac{1}{\alpha}+1)}}{\frac{1}{\alpha}+1} \Bigg|_{p^*}^{1} =$$

$$\frac{(\theta_0 - \theta_1)}{\theta_0\theta_1} \left(\frac{1 - p^{*(\frac{1}{\alpha}+1)}}{(\frac{1}{\alpha}+1)} \right). \tag{5}$$

Parameter Estimation

Parameter estimation (while properly accounting for censored observations) in the proportional risk model is straightforward by using maximum likelihood. As in all parametric survival models, observations with an event contribute the logarithm of the density, and censored observations contribute the logarithm of the survival function to the LogLikelihood function[22] p.159. Hence, each software that allows coding and maximizing a function with several parameters can be used. Corresponding SAS NLMIXED code for the example data set is given in the appendix.

Example: EMPAREG-Outcome study

In 2007, a meta-analysis questioned the cardiovascular safety of rosiglitazone[23], an approved glucose-lowering drug for the treatment of type 2 diabetes mellitus. In an immediate reaction to this, the U.S. Food and Drug Administration (FDA) issued a guidance for pharmaceutical industry which demands that trials submitted for approval for anti-diabetic drugs in the future should give solid evidence for cardiovascular safety. As a consequence, a number of large long-term cardiovascular safety trials were planned, conducted, or are still under way[24]. With respect to the striking linearity of the reported Kaplan-Meier estimates for death and other cardiovascular outcomes in many of these studies[14;25–27], these are predestinated for the models proposed here.

For illustration we use the EMPAREG-Outcome study[14] that evaluated empagliflozin, a sodium glucose cotransporter-2 (SGLT-2) inhibitor, for reducing severe cardiovascular outcomes in patients with type 2 diabetes at high cardiovascular risk. In this randomized, double-blind trial, 7020 patients were treated at 590 sites in 42 countries for a median observation time of 3.1 years. Patients in the treated group received 10 mg or 25 mg of empagliflozin, patients in the control group a placebo. For the analysis reported here

(and also for that in the original paper), the two treatment groups were collapsed. To avoid issues with competing risks, our outcome of interest is "Death from any cause", measured in months, which occurred in 462 patients, where 268 (of 4687 = 5.7 %) died in the treatment, and 194 (of 2333 = 8.3 %) in the placebo group. It should be noted that we had no access to the original data, but digitized the Kaplan-Meier estimates from the original paper by the open software tool WebPlotDigitizer, version 3.8[28], and extracted the data by using the algorithms and R tools of Guyot et al.[29]. To validate this extraction process we calculated a hazard ratio (with 95 % CI) from the proceeded data that amounted to 0.674 (0.560 - 0.811) which is essentially indistinguishable from the hazard ratio in the original paper ([14] Figure 1c), 0.68 (0.57 - 0.82).

In Figure 1 the estimated CDFs from the EMPAREG-Outcome study are given. As already mentioned above, the CDFs look remarkably linear. In Table 1 we thus give the numerical results for the EU model together with those from its simpler special case with $\alpha = 1$ which assumes linear CDFs in both groups. Comparing the two models, the exponentiated-uniform is judged the better one, as can be seen from the smaller BIC as well as from the estimate of α, which clearly deviates from 1. The relative risk for death from any cause in the EMPAREG group is only 68.5 % of the risk in the placebo group. If interpreted as an accelerated time (or faster running life clock), patients in the placebo group move towards death from any cause by a 36.5 % higher speed. In terms of prolongated survival, we find an overall mean difference of 57.4 months favoring empagliflozin. However, as no patient was observed until mean survival in any of the groups was reached, it is clinically more sensible to report the difference in mean survival down to a fixed value of a percentile. Choosing the 90% percentile here corresponds roughly to four years of observation time in the placebo group. Using formula (5) to compute $PFT_{EU,90\%}$ we find a benefit for empagliflozin of 10.0 months in expected survival after about four years of treatment.

In figure 2 the fit from the exponentiated-uniform model is compared with the observed CDFs, and is found to be rather satisfactory. In figure 3 we additionally report on an absolute effect measure and give the number needed to treat together with pointwise 95 % confidence intervals. As expected in view of the small number of events in the EMPAREG data, the treatment effect looks much less impressive if reported as an absolute effect. For example, at $t = 24$ months, we would have to treat 65 (39 - 90) patients with empagliflozin to prevent one extra death, as compared to placebo.

We finally note that the reciprocals of the parameters θ, in line with the definitions in (1) and (2), could be interpreted as the maximum possible survival time in both groups. To

Figure 1. EMPAREG-Outcome study, Death from any cause, Empirical CDFs

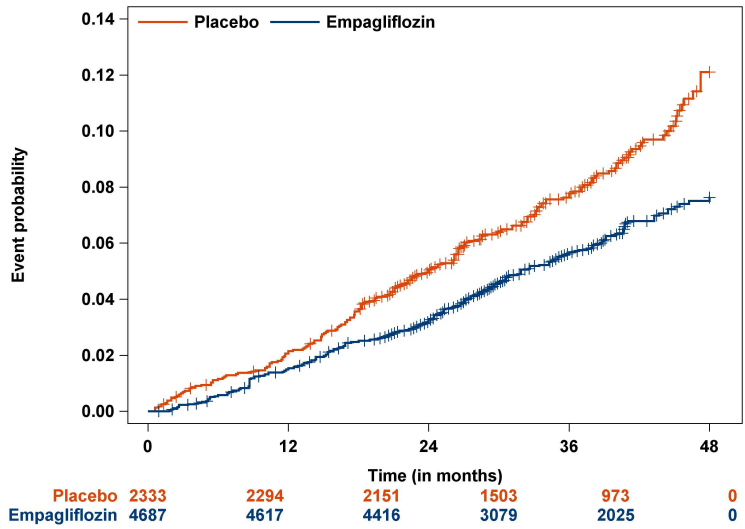


Table 1. Results for the EMPAREG-Outcome study for the exponentiated-uniform model and its linear special case with $\alpha = 1$. Parameters were estimated with SAS NLMIXED, 95% confidence intervals are Wald intervals. Abbreviations: RR, relative risk; AFT, accelerated failure time; PFT, prolongated failure time; BIC, Bayesian information criterion.

Parameter (95%-CI)	Exponentiated-uniform (EU) model	Linear (Uniform) model
	Estimate (95%-CI)	
θ_0	0.0035 (0.0032 - 0.0038)	0.0023 (0.0021 - 0.0024)
θ_1	0.0026 (0.0023 - 0.0028)	0.0016 (0.0012 - 0.0019)
α	1.215 (1.158 - 1.272)	1 (by definition)
$(\theta_1/\theta_0)^\alpha$ (=RR)	0.685 (0.589 - 0.781)	0.685 (0.529 - 0.840)
θ_0/θ_1 (=AFT)	1.365 (1.163 - 1.568)	1.460 (1.129 - 1.792)
Mean time to death (months), Group 0	157.1 (143.1 - 171.0)	220.6 (203.9 - 237.2)
Mean time to death (months), Group 1	214.4 (193.7 - 235.1)	322.1 (253.1 - 391.2)
Difference in mean times to death (months) (= PFT_{EU})	57.4 (34.9 - 79.9)	101.6 (30.5 - 172.6)
Difference in mean times to death (months) to the 90% percentile ((= $PFT_{EU,90\%}$))	10.0 (6.0 - 14.0)	19.3 (5.8 - 32.8)
BIC	6727.1	6736.5

be concrete, we find $\frac{1}{\theta_0} = 286\ (222 - 351)$ months, and $\frac{1}{\theta_1} = 391\ (306 - 476)$ months. We hesitate to interpret these values clinically, because they rely on massive out-of-sample predictions in our case. However, in cases with higher numbers of events values these estimates might give additional valuable information.

Figure 2. EMPAREG-Outcome study, Death from any cause, Empirical CDFs with predicted probabilities (with their pointwise 95 % confidence intervals) from the exponentiated-uniform fit.

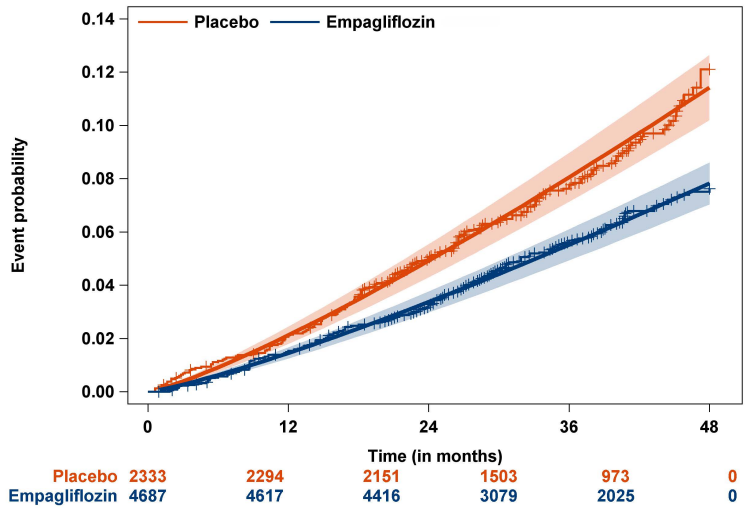
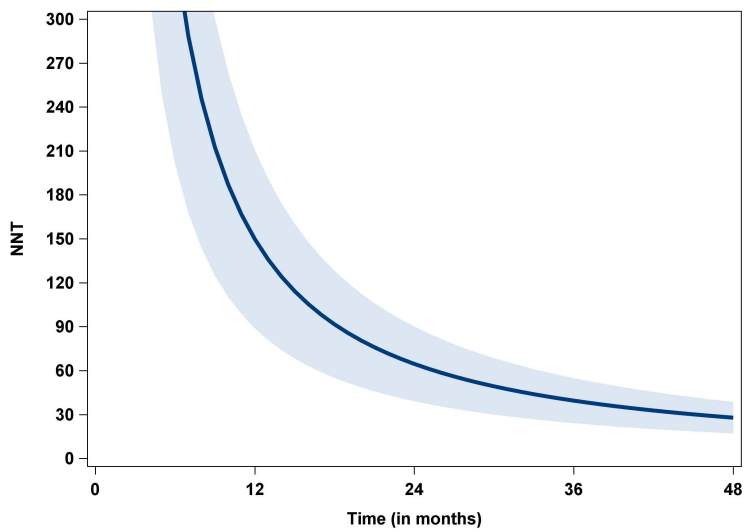


Figure 3. EMPAREG-Outcome study, Death from any cause, Estimated numbers needed to treat (with pointwise 95% confidence intervals) from the exponentiated-uniform fit



Discussion

In this paper we proposed a parametric proportional risk model for time-to-event outcomes in a two-group situation. Modelling explicitly a relative risk instead of a hazard ratio or an odds ratio solves current interpretational and technical problems of the latter two effect measures. The model easily allows for computing absolute effect measures like risk differences or numbers needed to treat. As its most convincing advantage we conceive the fact that results can also be communicated on the original time scale, as an accelerated or an prolongated failure time which facilitates interpretation for a non-technical audience. Parameter estimation by maximum likelihood is straightforward and can be implemented using each statistical software that allows maximizing a univariate likelihood function. The underlying parametric exponentiated-uniform distribution is flexible enough to model survival functions with a convex or a concave shape, which we feel is sufficient for most actual applications in medical research. For $\alpha = 1$ the model reduces to a model with uniform densities, in which CDFs and survival functions are linear. In this case the probability of having an event is constant over time, which would mean especially that survival is independent of age. As such, the model might be also of interest for demography or bio-gerontology, with α as a simple measure for the dynamics of ageing in a population.

Limitations and future work

Of course, the model in its current state of development has some limitations. Up to now, including only a single binary covariate is allowed which might be enough for randomized trials, but which is a limitation for observational trials. One could use the model nevertheless in an observational setting, by, for example performing a propensity score matching and reducing the data set to the simple two-group situation as it is needed here. Of course, in future work we seek to generalize the model for more than one covariate.

Survival curves as seen in applied data sets might not necessarily obey to exponentiated-uniform distributions with the proportional risk assumption. As such, in future work we are seeking for other parametric distributions that are more flexible, but keep the proportional risk property. Another possibility for generalization would be to model piecewise linear CDFs that yield proportional risks within each time piece, but allow more general forms of CDFs overall.

In summary, we feel that our proportional risk model is a useful complement to the biostatistician's toolbox when analyzing time-to-event outcomes. It explicitly avoids the technical and interpretational difficulties of hazard and odds ratios, and additionally allows interpretations on the time scale.

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Appendix: SAS code for the EMPAREG-Outcome data

```
data empareg;
     input surv event treatment cens dummy;
     cards;
     0.60811      1          0          0       1
     0.60811      1          0          0       1
     0.60811      1          0          0       1
     0.89189      1          0          0       1
     0.91723      0          1          1       1
     1.15998      1          0          0       1
     1.15998      1          0          0       1
     1.32516      0          0          1       1
        .         .          .          .       .
        .         .          .          .       .
        .         .          .          .       .
;run;

proc nlmixed data=empareg df=10000;

   * Initialize parameters: Parameters are estimated on the log-scale to avoid a BOUNDS-Statement;
     parms logtheta0=-5 logtheta1=-5 logalpha=0.3;

   * Retransforming parameters;
     theta0=exp(logtheta0); theta1=exp(logtheta1); alpha=exp(logalpha);

   * Log-Likelihood for uncensored observations: log(f(t));
     if event = 1 then do;
        ll = log(alpha) + logpdf('UNIFORM',surv,0,1/((theta0+(theta1-theta0)*treatment))) +
```

```
                (alpha-1)*log(cdf('UNIFORM',surv,0,1/((theta0+(theta1-theta0)*treatment))));
      end;
    * Log-Likelihood for censored observations: log(S(t));
      if event = 0  then do;
         ll = log(1- cdf('UNIFORM',surv,0,1/((theta0+(theta1-theta0)*treatment)))**alpha);
      end;

      model dummy ~ general(ll);

      estimate "theta0" exp(logtheta0);
      estimate "theta1" exp(logtheta1);
      estimate "alpha" exp(logalpha);
      estimate "RR" (exp(logtheta1)/exp(logtheta0))**alpha;
      estimate "AFT" exp(logtheta0)/exp(logtheta1);
      estimate "Mean 0" exp(logalpha)/(exp(logalpha)+1)* 1/(theta0);
      estimate "Mean 1" exp(logalpha)/(exp(logalpha)+1)* 1/(theta1);
      estimate "PFT, Mean difference in survival times" (theta0-theta1)/(theta0*theta1)*(alpha/(alpha+1));
      estimate "PFT, Mean Difference in survival times, to the 90\% percentile"
                (theta0-theta1)/(theta0*theta1)*(1-0.9**(1/alpha+1))/(1/alpha+1);
      estimate "Maximum survival time 0" 1/theta0;
      estimate "Maximum survival time 1" 1/theta1;
run;
```