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The proportional odds cumulative incidence model for competing risks

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Summary

We suggest an estimator for the proportional odds cumulative incidence model for competing risks data. The key advantage of this model is that the regression parameters have the simple and useful odds ratio interpretation. The model has been considered by many authors, but it is rarely used in practice due to the lack of reliable estimation procedures. We suggest such procedures and show that their performance improve considerably on existing methods. We also suggest a goodness-of-fit test for the proportional odds assumption. We derive the large sample properties and provide estimators of the asymptotic variance. The method is illustrated by an application in a bone marrow transplant study and the finite-sample properties are assessed by simulations.

Keywords

Competing risks; Estimating equations; Flexible modelling; Linear transformation model; Proportional odds model; Odds ratio; Semiparametric; Survival

1. Introduction

Competing risks failure times, where subjects may fail from any of K different causes, are inherent in many applications in medical research. For each subject we observe a follow-up time and an indicator that tells us which of the competing risks that caused the failure. In bone marrow transplant studies it is common to consider treatment-related mortality and cancer relapse as competing risks (causes), and for these there is often an interest in quantifying how risk covariates influence the event probabilities as a function of follow-up time. For this quantification to be useful it is crucial to use a link function that gives a simple and easy interpretation. We return to this in a small worked example below.

Supplementary Materials

The Web Appendix referenced in Section 2 and 6 is available with this paper at the Biometrics website on Wiley Online Library. The supplementary web material also includes an R script that illustrates how we use the `prop.odds.subdist` function from the `timereg` package to analyze the bone marrow transplant data in Section 5. The BMT data set is available as a part of the `timereg` package.

Considering the first cause, the cumulative incidence function is defined as the probability of dying of cause one before time t , in the presence of all the competing risks, $F_1(t) = P(T^* \leq t, \varepsilon = 1)$, where T^* is the failure time and ε indicates the type of failure. It is the proper summary curve in analyzing competing risks data. We wish to assess the effect of covariates Z on the cumulative incidence function.

Consider the proportional odds model for the cumulative incidence function

$$\text{logit}(F_1(t; Z)) = \text{logit}(F_1(t; \beta, H, Z)) = \log(H(t)) + Z^T \beta, \quad (1)$$

where $H(t)$ is an increasing positive function with $H(0) = 0$. The cumulative incidence is thus linear on the logit scale with an intercept increasing over time and time-constant log-odds ratio for failure from cause one. The model implies that the cumulative incidence function is

$$F_1(t; Z) = \frac{H(t) \exp(Z^T \beta)}{1 + H(t) \exp(Z^T \beta)}, \quad (2)$$

and the subdistribution hazard of failure from cause one is

$$-\frac{\partial}{\partial t} \log(1 - F_1(t; Z)) = \frac{1}{e^{-Z^T \beta} + H(t-)} h(t) \quad (3)$$

where $h(t)$ is the derivative of $H(t)$. Proportional odds models have been rigorously studied for univariate survival data (Bennett, 1983; Murphy et al., 1997; Chen et al., 2002).

The proportional odds model is a special case of the general class of semiparametric transformation models

$$g(F_1(t; Z)) = \log(H(t)) + Z^T \beta \quad (4)$$

where $H(\cdot)$ is an unspecified positive monotone increasing function and where $g(\cdot)$ is a known increasing link function.

Several authors have proposed inference procedures for F_1 in (4) without simultaneously estimating models for F_k , $k = 2, \dots, K$. Fine and Gray (1999) proposed a Cox type regression model for the subdistribution hazard. This gives a model where the complementary log-log transformed cumulative incidence function is linear in the covariates, i.e. $g(x) = \log(-\log(1-x))$ in (4). They used inverse probability of censoring weighting of the ordinary proportional hazards estimating equations with modified risk sets for inference from right-censored data. Sun et al. (2006) considered a more flexible and general model for the subdistribution hazard proposed for survival data by Martinussen and Scheike (2002).

Fine (2001) pointed out that the proportional subdistribution model has parameters that are quite difficult to interpret. We get back to this in the data example. As a more attractive

alternative he suggested direct estimation of F_1 within transformation models of the type (4), with the proportional odds model (1) as a special case (Fine, 1999, 2001).

Another direct regression approach for the cumulative incidence function is the pseudo-observation technique by Andersen et al. (2003) and Klein and Andersen (2005). The inference is based on pseudo-values from a jackknife statistic constructed from the estimated cumulative incidence curve. Still another procedure for direct estimation of F_1 is the binomial regression method of Scheike et al. (2008). This approach is based on binomial modelling of inverse probability of censoring weighted event indicators.

When considering the Fine and Gray (1999) model, the estimation approaches above are not as efficient as the subdistribution approach. They also have implementation issues. In particular, the direct approaches mentioned above require that one selects a time-window in which to do the estimation, and the Fine (2001) method considers all pairs and is therefore quadratic in the data, and has not been implemented in available software.

The aim of this work is to develop an estimator of the proportional odds model based on its underlying subdistribution hazard that has improved efficiency and good large and small sample properties for estimating β . Our approach represents an extension of the approach of Chen et al. (2002) for survival data to estimation of the cumulative incidence through the subdistribution hazard by inverse probability of censoring weighting. We also provide a detailed description of the asymptotics of the baseline $H(\cdot)$ through a Volterra equation. This is useful for prediction of the cumulative incidence function and the related confidence bands. Dealing with the inverse probability of censoring weighting in the score equations is no trivial extension due to a complicated recursive structure of the baseline estimator. The procedures can be extended to handle a wider class of link functions g in (4), but we will restrict the discussion to the logit-link because of its simple and useful odds ratio interpretation.

The paper is organized as follows. In Section 2 we specify the model, establish estimating equations and outline the large sample properties. Section 3 presents a goodness-of-fit test and a resampling technique for constructing confidence bands. In a simulation study presented in Section 4 we show how our subdistribution based estimation procedure improves on the existing binomial regression approach in terms of numerical properties and smaller standard errors. This is similar to what is experienced for the Fine and Gray (1999) model, where the original subdistribution based estimator has superior properties. Section 5 contains a worked example and Section 6 some discussion. All technical details, including derivations of the large sample properties of the estimators can be found in the Web Appendix.

2. Odds ratio inference for competing risks data

Under right-censoring we cannot observe the failure time T^* , but only the follow-up time $T = T^* \wedge C$, where C denotes the censoring time, and the indicator $\delta = I(T^* \leq C)$ that takes value one if the failure time is uncensored. For censored individuals the cause of failure ε is not observed. We assume that the censoring times are independently distributed with $P(C >$

$t) = G_0(t)$, and that the observations $(T_i = T_i^* \wedge C_i, \varepsilon_i, Z_i)$ are independent and identically distributed replications of (T, ε, Z) , for $i = 1, \dots, n$. Let τ denote a finite maximum follow-up time.

Define the counting process $N_i^1(t) = I\{T_i^* \leq t, \varepsilon_i = 1\}$ indicating if individual i has experienced a cause one event prior to time t , and the modified at-risk indicator $Y_i^1(t) = 1 - N_i^1(t-)$. Note that any individuals who have not yet failed from cause one at time t , are "at risk" at this time, including those who are known to have failed from a competing cause. When $\varepsilon_i = 0$ individual i is observed until time C_i , thereafter the status, including the values of N_i^1 and Y_i^1 , is uncertain.

If there was no censoring we could estimate F_1 , without modelling the competing causes, by writing up estimating equations for the subdistribution hazard of cause one based on the compensated counting processes

$$M_i^1(t) = N_i^1(t) - \int_0^t Y_i^1(u) \alpha(H_0(u-), \beta_0, Z_i) dH_0(u), \quad (5)$$

where $\alpha(H, \beta, Z) = (e^{-Z^T \beta} + H)^{-1}$. Chen et al. (2002) used such estimating equations for transformation models in the single cause survival setting. True values of unknown parameters are marked with subscript 0.

To estimate the parameters of the model with right-censoring we proceed as Fine and Gray (1999) and write up estimating equations for the subdistribution based on inverse probability of censoring weighting (IPCW). Following them, we denote knowledge of vital status of individual i at time t by $r_i(t) = I(C_i \geq T_i^* \wedge t)$. Although the counting processes $Y_i^1(t)$ and $N_i^1(t)$ are not observable when $r_i(t) = 0$, $r_i(t)Y_i^1(t)$ and $r_i(t)N_i^1(t)$ are always computable. Define the time dependent weight $w_i(t, G) = r_i(t)G(t-)/G[(T_i \wedge t)-]$, where G is a survival function for the censoring distribution. The quantity $r_i(t)/G_0[(T_i \wedge t)-]$ has expectation 1 conditional on T_i^*, ε_i . We will estimate the unknown censoring survival function G_0 with the Kaplan-Meier estimator, that we denote G_n .

Consider the following estimating equations for β_0 and $H_0(\cdot)$

$$n^{-1} \sum_{i=1}^n \int_0^\tau Z_i w_i(t, G_n) (dN_i^1(t) - Y_i^1(t) \alpha(H(t-), \beta, Z_i) dH(t)) = 0 \quad (6)$$

$$n^{-1} \sum_{i=1}^n w_i(t, G_n) (dN_i^1(t) - Y_i^1(t) \alpha(H(t-), \beta, Z_i) dH(t)) = 0, \quad \forall t \in [0, \tau]. \quad (7)$$

The estimating equations are similar to those of Chen et al. (2002), but weighted with the inverse probability of censoring as in Fine and Gray (1999). Following Gorfine et al. (2006); Martinussen et al. (2011) among others, we will solve these equations by recursively profiling out the baseline function. Define

$$S_j(t, H(t-), \beta, G) = n^{-1} \sum_{i=1}^n Y_i^1(t) w_i(t, G) Z_i^{\otimes j} \alpha(H(t-), \beta, Z_i), \quad j=0, 1, 2.$$

We estimate H_0 by a non-decreasing function $\hat{H}_n$ with jumps only at observed cause one event times. Solving (7) for a fixed β we get that the jump size at time t , i.e. $\hat{H}_n(t, \beta) - \hat{H}_n(t-, \beta)$ can be estimated by the recursive estimator

$$\Delta \hat{H}_n(t, \beta) = n^{-1} \sum_{i=1}^n \frac{w_i(t, G_n) dN_i^1(t)}{S_0(t, \hat{H}_n(t-, \beta), \beta, G_n)}.$$

Inserting $\hat{H}_n$ into (6), the estimating equation for β reads

$$U_n(\beta) = U_n(\beta, \tau) = 0, \quad (8)$$

where

$$U_n(\beta, t) = n^{-1} \sum_{i=1}^n \int_0^t w_i(s, G_n) \left(Z_i - \frac{S_1(s, \hat{H}_n(s-, \beta), \beta, G_n)}{S_0(s, \hat{H}_n(s-, \beta), \beta, G_n)} \right) dN_i^1(s).$$

Note that the estimating equation (8) is a function of β only. We solve this estimating equation by a Fisher scoring algorithm. Given the solution $\hat{\beta}$ to (8) we estimate $H_0(t)$ by $\hat{H}_n(t, \hat{\beta})$.

We establish the asymptotic properties of the proposed estimators under the following regularity conditions.

- (C1) There is a maximum follow-up time $\tau < \infty$ such that $P(T = \tau) > K_C > 0$, where K_C is a constant.
- (C2) The censoring time C is independent of T , ε and Z , and the censoring variables are independently distributed with $P(C > t) = G_0(t)$.
- (C3) H_0 is differentiable with derivative $h_0(t) = H_0'(t)$, such that $\sup_{t \in [0, \tau]} h_0(t) < h_{\max}$ for a constant $h_{\max} < \infty$, and $\beta \in \mathcal{B}$ where $\mathcal{B}$ is known and compact.
- (C4) The covariates Z are bounded, almost surely.
- (C5) $A_n(\beta_0, t) = \lim_{\beta \rightarrow \beta_0} U_n(\beta, t)$ is asymptotically positive semi-definite with probability one.

Remark 1

We assume (C2) for simplicity. The IPCW technique can be generalized to allow for dependence between C and Z , for example by assuming that a proportional hazards model holds for the conditional distribution of C given Z .

Remark 2

The derivative A_n in (C5) can be calculated recursively by

$$\begin{aligned} \frac{\partial}{\partial \beta} U_n(\beta, t) &= -n^{-1} \sum_{i=1}^n \int_0^t w_i(s, G_n) \left(\frac{\frac{\partial}{\partial \beta} S_1(s, \hat{H}_n(s-, \beta), \beta, G_n)}{S_0(s, \hat{H}_n(s-, \beta), \beta, G_n)} \right. \\ &\quad \left. - \frac{S_1(s, \hat{H}_n(s-, \beta), \beta, G_n) \frac{\partial}{\partial \beta} S_0(s, \hat{H}_n(s-, \beta), \beta, G_n)}{S_0^2(s, \hat{H}_n(s-, \beta), \beta, G_n)} \right) dN_i^1(s) \end{aligned}$$

where

$$\begin{aligned} \frac{\partial}{\partial \beta} S_j(t, \hat{H}_n(t-, \beta), \beta, G_n) &= -n^{-1} \sum_{i=1}^n Y_i^1(t) w_i(t, G_n) Z_i^{\otimes j} \alpha^j(H(t-), \beta, Z_i) \times \left(\frac{\partial}{\partial \beta} \hat{H}_n(t-, \beta) + Z_i \exp(-Z_i \beta) \right), \\ \frac{\partial}{\partial \beta} \hat{H}_n(t, \beta) &= n^{-1} \sum_{i=1}^n \int_0^t \frac{w_i(s, G_n) \frac{\partial}{\partial \beta} S_0(s, \hat{H}_n(s-, \beta), \beta, G_n)}{S_0^2(s, \hat{H}_n(s-, \beta), \beta, G_n)} dN_i^1(s). \end{aligned}$$

In Web Appendix B we prove the following consistency theorem.

Theorem 1 (Consistency)

Under assumptions (C1)–(C5), $\hat{\beta} \xrightarrow{a.s.} \beta_0$ and $\hat{H}_n(t, \hat{\beta}) \xrightarrow{a.s.} H_0(t)$ uniformly in t .

When the estimating function U_n is evaluated in the true parameter values β_0 , H_0 and G_0 , it is a sum of mean zero i.i.d. variables. However, the asymptotic analysis is complicated by the fact that H_0 is estimated by a recursively constructed estimator and the fact that we have to estimate the censoring distribution. Still, in Web Appendix C we establish that

$$n^{1/2} U_n(\beta_0, t) = n^{-1/2} \sum_{i=1}^n (\zeta_i(t) + \eta_i(t)) + o_p(1), \quad (9)$$

where the $\zeta_i(t)$ and $\eta_i(t)$'s are mean zero i.i.d. random processes. Let $\hat{\zeta}_i(t)$ and $\hat{\eta}_i(t)$ denote empirical expressions for these terms, where all unknown quantities are replaced by their estimates. Explicit expressions are given in Web Appendix C.

The first term in the i.i.d. decomposition (9) corresponds to the influence function we would get with known censoring weights, i.e. if the censoring distribution had been known and not estimated from data. The second term in the decomposition stems from the fact that we estimate the censoring weights by the Kaplan-Meier estimator. The key argument in establishing (9) is the product integration theory also used by Dabrowska (2005), Gorfine et al. (2006) and Martinussen et al. (2011), among others.

From the fact that $U_n(\hat{\beta}) = 0$, (9), and a first-order expansion around β_0 ,

$$n^{1/2} (\hat{\beta} - \beta_0) = -A_n^{-1}(\beta_0, \tau) n^{1/2} U_n(\beta_0) + o_P(1). \quad (10)$$

Combining (9) and (10) with the central limit theorem we have the following result.

Theorem 2 (Weak convergence of $\hat{\beta}$)

Under assumptions (C1)–(C5), $n^{1/2} (\hat{\beta} - \beta_0)$ is asymptotically normally distributed with variance that can be consistently estimated by

$$A_n(\hat{\beta}, \tau)^{-1} \sum_n A_n(\hat{\beta}, \tau)^{-1},$$

$$\text{where } \sum_n = n^{-1} \sum_{i=1}^n \left(\hat{\zeta}_i(\tau) + \hat{\eta}_i(\tau) \right)^{\otimes 2}.$$

Similarly, the limit of $n^{1/2} (\hat{H}_n(t, \beta) - H_0(t))$ can be written as a sum of mean zero i.i.d. processes $v_i(t)$, with empirical version $\hat{v}_i(t)$. The terms $v_i(t)$ can again be decomposed into a term corresponding to known censoring weights and a contribution that adjusts for the estimation of the censoring weights. The estimated influence functions can be used for resampling to construct confidence bands. In Web Appendix D we give an expression for v_i and establish the following result.

Theorem 3 (Weak convergence of $\hat{H}_n$)

Under assumptions (C1)–(C5), $n^{1/2} (\hat{H}_n(t, \beta) - H_0(t))$ converges weakly to a tight Gaussian process with variance at time t that can be consistently estimated by $n^{-1} \sum_{i=1}^n \hat{v}_i^{\otimes 2}(t)$.

We stress that the extension to deal with the uncertainty from the estimated censoring weights is complicated by the recursive structure of the estimator for the non-parametric component, and therefore is not just a simple extension along the standard arguments for dealing with inverse probability of censoring weights. All details can be found in the Web Appendix.

3. Prediction of cumulative incidence functions and goodness-of-fit

We briefly outline how to construct confidence bands and how to make a goodness-of-fit test for the constant proportional odds assumption. The techniques are based on the influence functions and approximation of the asymptotic distribution by resampling of the residual processes.

To predict $F_1(t; \beta_0, H_0, z)$ we plug-in the estimates and use $F_1(t; \hat{\beta}, \hat{H}_n, z)$. The consistency of $\hat{\beta}$ and $\hat{H}_n(\cdot, \hat{\beta})$ ensure that $F_1(t; \hat{\beta}, \hat{H}_n, z)$ converges almost surely to $F_1(t; \beta_0, H_0, z)$ uniformly in t . By the weak convergence of $n^{1/2}(\hat{\beta} - \beta_0, \hat{H}_n(\cdot, \hat{\beta}) - H_0(\cdot))$, and the functional delta method (van der Vaart, 1998, Theorem 20.8) applied to F_1 , $n^{1/2}(F_1(t; \hat{\beta}, \hat{H}_n(\cdot, \hat{\beta}), z) - F_1(t; \beta_0, H_0(\cdot), z))$ converges weakly to a mean-zero Gaussian process with the same asymptotic distribution as

$$= \frac{\exp(z^T \beta_0)}{1 + H_0(t) \exp(z^T \beta_0)} (1 - F_1(t, \beta_0, H_0, z)) \left(n^{1/2} (\hat{H}(t, \hat{\beta}) - H_0(t)) + H_0(t) z^T \sqrt{n} (\hat{\beta} - \beta_0) \right) \\ = \frac{\exp(z^T \beta_0)}{1 + H_0(t) \exp(z^T \beta_0)} (1 - F_1(t, \beta_0, H_0, z)) \times n^{-1/2} \sum_{i=1}^n (v_i(t) - H_0(t) z^T A_n^{-1}(\beta_0, \tau) (\zeta_i(\tau) + \eta_i(\tau))) + o_p(1).$$

Confidence bands for the predictions can be calculated using conditional multiplier resampling based on this expansion, along the lines of Martinussen and Scheike (2006, p. 147) or Lin et al. (1994).

To evaluate the goodness-of-fit of the model we consider the estimating function evaluated in $\hat{\beta}$ as a process of time, $U_n(\hat{\beta}, t)$. This process is asymptotically equivalent to

$$U_n(\beta_0, t) - A_n(\beta_0, t) A_n^{-1}(\beta_0, \tau) U_n(\beta_0, \tau).$$

Thus $n^{-1/2} U_n(\hat{\beta}, t)$ is asymptotically equivalent to a process that can be written as

$$n^{-1/2} \sum_{i=1}^n \left\{ \zeta_i(t) + \eta_i(t) - A_n(\beta_0, t) A_n^{-1}(\beta_0, \tau) (\zeta_i(\tau) + \eta_i(\tau)) \right\}.$$

This can be used for resampling of this process as in Lin et al. (1993), see also Martinussen and Scheike (2006, p. 197).

4. Simulation study

We evaluate the finite-sample performance of the proposed estimator on simulated data and compare the performance to the binomial direct modelling (BM) approach proposed by Scheike and Zhang (2007) and Scheike et al. (2008). For the BM we consider the proportional odds model using the `comp.risk` function of the `timereg` package for R. These estimates are directly comparable to those from our new estimator. We also compare the performance of our method with that of Fine (2001).

Comparison with BM

Table 1 and Table 2 report the summary of a simulation study of a model with two covariates; one Bernoulli distributed covariate Z_1 with success probability 0.5, and one standard normal covariate Z_2 .

The cause one failure times are generated from the proportional odds model (1) with $H(t) = \int_0^t e^{-\lambda u} du = \lambda^{-1} (1 - e^{-\lambda t})$, $\lambda > 0$. From the form of the cumulative incidence function (2), $F_1(\infty | Z_1, Z_2) = \{1 + \lambda \exp(-\beta_1 Z_1 - \beta_2 Z_2)\}^{-1}$. The failure times of the other cause are generated from $F_2(t | Z_1, Z_2) = (1 - F_1(\infty | Z_1, Z_2)) [1 - \exp(-t \exp(\beta_1 Z_1 + \beta_2 Z_2))]$. The parameter λ controls the total cumulative incidence rate of cause one. The covariate effects are $\beta_1 = \beta_2 = 0.5$ in all scenarios. Censoring times are generated from a uniform distribution, $U(0, \tau]$, where τ is used to control the censoring rate. We consider all settings with total sample sizes

of 50, 100 and 300 and censoring rates 15%, 30% and 50%. A total of 5000 replication samples are generated in all simulation settings.

Table 1 and Table 2 show the simulation results with a high, 0.72 ($\lambda = 0.5$), and a low, 0.30 ($\lambda = 3$), average cause one event rate, respectively. Both approaches provide satisfactory results in estimating the covariate effects, and provide reasonable consistent variance estimators. The biases are small even for small sample sizes such as $n=50$ with 50% censoring. Our new proposed approach appears to be more efficient than the binomial approach; Table 1 shows an average efficiency gain in the range 18% – 43% for the binary covariate, and 11% – 58% for the continuous covariate, for a high cause one rate. Table 2 shows a gain from 11% – 46% for the binary covariate, and 17% – 59% for the continuous covariate, for a low cause one rate. We note that the coverage of the 95% confidence intervals are close the nominal level in all cases.

Comparison with Fine (2001)

Table 3 shows the results of a simulation study which uses our estimation method on data generated under the setting reported in Table 2 in Fine (2001). The proportional odds model considered here contains two independent standard normal covariates with regression coefficients, $\beta_{11} = 0.5$ and $\beta_{12} = 0.5$. We refer to Fine (2001) for further details on how the data was generated.

Table 2 in Fine (2001) reports the performance of the estimator for the regression coefficient β_{11} based on his estimation procedure. In Table 3 we report Table 2 of Fine (2001) together with the performance of our procedure. Our new estimator seems to perform quite a bit better than Fine's suggestion. We have less bias and a considerably smaller variance, roughly speaking by a factor of one half.

Numerical stability

Again we consider the simulation set-up reported in Table 1, but now with ten independent standard normal covariates, where five covariates have effect 0.3 and the other five effect -0.3 . Based on 70 observations and 2000 replications, we compute the averages and standard deviations of the estimates using the BM approach and the new procedure. These are -1.35 (38.06), and 1.24 (27.15) for the first two covariates from the BM method (mean (SD)), respectively. For the new procedure we get -0.32 (0.27) and 0.32 (0.28), respectively. Due to symmetry, results are similar for the remaining eight covariates. All replications lead to estimates with both procedures, but the estimates from the BM approach are highly volatile due to what is probably lacking convergence in some of the replications. In contrast our new proposal is highly stable and converges in all replications to estimates that appear almost unbiased.

Baseline finite sample properties

We now turn to the estimates of the baseline and the related asymptotic description of it. In a simulation study similar to that producing Table 1 we investigate the relative bias of the estimates (mean of estimates relative to true baseline) and the coverage of the 95% confidence intervals for the sample sizes 100, 200 and 400, respectively. The result is

depicted in Figure 1 where we see that the coverage is very close to the nominal 95% level for the larger sample sizes, and that the baseline is generally almost unbiased.

Computation time

We consider the simulation set-up reported in Table 1 to compare the computing times of the new estimator and the BM approach. For a sample size of $n=1000$, the new estimator uses 0.9 seconds to estimate the parameters and compute the standard errors, in contrast the BM uses 0.3. When increasing the sample size to $n=2000$, the new estimator uses 4.4 seconds and the BM approach uses 0.5. This shows that in the current implementation, the new approach is computationally quite demanding. For very large data sets the BM approach may thus be preferable when efficiency is not quite so important.

Our conclusion is that the new estimator based on our recursive estimating equations provides a good efficiency gain compared the binomial regression estimator and the proposal by Fine (2001). The proposed estimator performs well for even very small sample sizes and is numerically more stable than the BM approach. Also the asymptotic description of the baseline appears to have good finite sample properties.

We now turn to evaluating the goodness-of-fit test based on looking at the score process to see if the effects are proportional over time (see Section 3). To construct a non-proportional effect we consider two strata of size $n/2$, one with baseline given by $\lambda = 0.2$ and covariate $X = 0$, and one with $\lambda = 0.7$ and covariate $X = 1$. This generates a relatively weak departure from proportionality in X , where the effect of X is essentially equivalent to a linearly decreasing effect that decreases -0.15 per time unit. In addition we include a covariate Z with proportional effect $\beta = 0.5$. We simulate data with both discrete and continuous Z , but report only the simulations where Z is standard normal. The binary covariate gives similar results. In a second set of simulations we construct samples with only proportional covariate effects by letting the entire sample of size n have baseline $\lambda = 0.2$. For both the proportional and non-proportional generating models we consider the time interval $[0, 6]$, leading to around 20% censoring.

We calculate p-values from the supremum test of proportionality (with 1000 resamples) in 2000 simulated samples of size n . Table 4 reports the proportion of tests where the hypothesis of proportionality was rejected at the 5% significance level. For both covariates in the proportional generating model and the Z covariate in the non-proportional model, the hypothesis of proportionality is true and the table gives the observed size of the test. We note that for all sample sizes the size of the test is close the nominal 5% significance level. In contrast, for X in the non-proportional model, the hypothesis is false and the table gives the power of the test. We note that the power is increasing as we increase the sample size.

5. Bone marrow transplant example

To illustrate the proposed inference procedure we consider data on myelodysplasia patients treated with HLA-identical sibling bone marrow transplantation (BMT) from the Center for International Blood and Marrow Transplant Research (CIBMTR) (Sierra et al., 2002). The CIBMTR Data Collection Center located at the Medical College of Wisconsin has a

repository of information regarding the results of transplants shared by clinical and basic scientists at more than 450 transplant centers worldwide.

In this study we consider two competing events; treatment-related mortality (TRM), defined as death without relapse, and cancer relapse. In total 408 patients with complete information are included in the study. We model the cumulative incidence for treatment-related mortality. Three covariates are considered; platelet level (PLT), a binary covariate with levels $100 \times 10^9/L$ ($n=128$) and $< 100 \times 10^9/L$ ($n=280$); AGE, a continuous variable standardized and centered at age 35 and scaled by 15; and graft-versus-host disease prophylaxis (T-DEPL), a binary covariate with levels T-cell depletion ($n=54$) or no T-cell depletion ($n=354$).

We fit the data using the proportional odds model (1) with our proposed inference procedure. The estimates for PLT, AGE, T-DEPL are $\hat{\beta}_{PLT} = -0.526$ ($\hat{\sigma}_{PLT} = 0.220$; $p = 0.018$), $\hat{\beta}_{age} = 0.429$ ($\hat{\sigma}_{age} = 0.099$; $p < 0.001$), and $\hat{\beta}_{T-depl} = -0.735$ ($\hat{\sigma}_{T-depl} = 0.324$; $p = 0.023$), respectively. This indicates that all three variables significantly affect the treatment-related mortality. The coefficients can be interpreted as the log of the odds ratio for treatment-related mortality. For example, the odds for the high platelet level patient is $\exp(-0.526) = 0.591$ times the low platelet level patient. The goodness-of-fit test based on the score process did not reject the model. Based on 1000 resamples the p-values of the tests for PLT, AGE, T-DEPL were 0.25, 0.46 and 0.33, respectively.

The BM estimates for PLT, AGE, T-DEPL are $\hat{\beta}_{PLT} = -0.675$ ($\hat{\sigma}_{PLT} = 0.240$; $p = 0.005$), $\hat{\beta}_{age} = 0.404$ ($\hat{\sigma}_{age} = 0.111$; $p < 0.001$), and $\hat{\beta}_{T-depl} = -0.831$ ($\hat{\sigma}_{T-depl} = 0.349$; $p = 0.017$), respectively. These are quite similar to those from the proposed subdistribution estimator.

On the same data set, the Fine and Gray model gives the coefficients $\hat{\beta}_{PLT} = -0.519$ ($\hat{\sigma}_{PLT} = 0.181$; $p = 0.004$), $\hat{\beta}_{age} = 0.408$ ($\hat{\sigma}_{age} = 0.084$; $p < 0.001$), and $\hat{\beta}_{T-depl} = -0.651$ ($\hat{\sigma}_{T-depl} = 0.2734$; $p = 0.017$). The conclusion about the importance of the covariates is exactly the same as for the proportional odds model. However, the interpretation of the Fine and Gray estimates is different. In the Fine and Gray model the adjusted platelet level effect is the log of the ratio of $-\log(1 - F_{TRM}(t))$ between high and low platelet patients. In other words, the log of the probability of experiencing relapse or surviving have the ratio $\exp(-0.519)$ between a high level platelet patient and a low level platelet patient.

Even though the interpretation of the regression coefficients in the Fine and Gray model is different from, and somewhat unappealing compared to, the proposed proportional odds model, both can be used to estimate the cumulative incidence function. We compare the estimated cumulative incidence functions from the two models for given values of patient characteristics and graft-versus-host disease prophylaxis used. Figure 2 shows the cumulative incidence curves for a low platelet level 35 years old patient for who no T-cell depletion was used for graft-versus-host disease prophylaxis. The black curve corresponds to the proposed proportional odds estimator (PO), the red curve to the Fine and Gray estimator, and the green curve to the proportional odds BM estimator. From the plot we can see that the two models provide almost the same prediction of the cumulative incidence functions. The BM provides slightly different predictions in the early time-period where this

estimator has a difficult task due to the few number of events. The confidence intervals based on the proposed proportional odds estimator, reveal that the early difference between the BM and the PO estimator is somewhat problematic.

6. Discussion

Censored competing risks data is commonly encountered in biomedical studies. For this type of data the cumulative incidence curve of a particular cause of failure is a proper summary curve. The proportional odds cumulative incidence model is very useful in practice for its ease of interpretation.

In this paper, we suggest a new subdistribution based inference procedure for proportional odds modelling of the cumulative incidence function and establish its large sample properties. In a simulation study we show that the procedure has good numerical properties and work well for small sample problems. In the simulation study our method outperforms existing methods. Unfortunately, we have no theoretical justification for the improved efficiency but this is indeed a subject for further investigations that we will pursue. The fitting procedure is available in the R package `timereg` in the `prop.odds.subdist` function.

One difficulty with the suggested method is that the estimation is somewhat slow for large to very large data sets. A way around this is to consider a modified version of the score equations where the weights do not depend on time in the same way. Let $w_i(G_n) = I(T_i < C_i)/G_n(T_i)$. With this modified weight the score equations (6) and (7) become

$$\begin{aligned} n^{-1} \sum_{i=1}^n Z_i w_i(G_n) \left(N_i^1(\tau) + \log(1 - F_1(\tilde{T}_i; \beta, Z_i)) \right) &= 0 \\ n^{-1} \sum_{i=1}^n w_i(G_n) \left(dN_i^1(t) - Y_i^1(t) \alpha(H(t-), \beta, Z_i) dH(t) \right) &= 0, \forall t \in [0, \tau], \end{aligned}$$

where $\tilde{T}_i = \min(T_i I(\varepsilon_i = 1) + \mathcal{U}(\varepsilon_i - 1), C_i)$, which are easier to compute as there is one integral less. Asymptotics for this estimator can be developed along the lines of Section 2 and the Web Appendix. Alternatively, with large data sets one may also use the binomial regression that is computationally possible even with very large data sets.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Baseline finite sample properties. The upper part shows the relative bias of the baseline estimates (mean of estimates relative to true baseline) and the lower part the coverage of the 95% pointwise confidence intervals over time for sample sizes 100, 200 and 400.

Figure 2.

Predicted cumulative incidence probability of TRM for a 35 years old patient with low platelet level who received an HLA-identical sibling transplant and no T-deplete BMT for the Fine & Gray model (FG), the proportional odds model using either binomial modelling (BM) or the new approach (PO). 95% confidence intervals based on the PO approach (95% CI).

Table 1

Simulation results for $\beta_1 = \beta_2 = 0.5$ with average $F_1(\infty) = 0.72$, and with $Z_1 \sim B(0.5)$ and $Z_2 \sim N(0, 1)$. New denotes the newly proposed proportional odds estimator, BM denotes the direct binomial modelling approach, n is the sample size, c is censoring rate SD denotes the sample standard error of the estimate, $E(\hat{\sigma})$ denotes the sample mean of the estimated standard error, and MSEratio is the sample mean of the mean square error ratio between New and BM

Parameter	n	c	Bias		SD		$E(\hat{\sigma})$		Coverage		MSE ratio
			New	BM	New	BM	New	BM	New	BM	
β_1	50	15%	0.02	0.06	0.55	0.66	0.52	0.60	0.94	0.94	0.71
		30%	0.01	0.06	0.57	0.71	0.55	0.64	0.95	0.95	0.69
		50%	0.00	0.06	0.64	0.87	0.61	0.77	0.94	0.96	0.57
	100	15%	0.00	0.02	0.37	0.42	0.37	0.41	0.95	0.95	0.79
		30%	0.01	0.03	0.39	0.45	0.39	0.43	0.95	0.95	0.78
		50%	-0.00	0.02	0.44	0.52	0.43	0.50	0.95	0.96	0.71
β_2	300	15%	-0.00	0.00	0.21	0.24	0.21	0.23	0.95	0.95	0.82
		30%	-0.00	0.00	0.22	0.25	0.22	0.24	0.95	0.95	0.82
		50%	0.00	0.00	0.25	0.28	0.24	0.28	0.95	0.95	0.75
	50	15%	0.01	0.07	0.29	0.40	0.27	0.33	0.95	0.95	0.57
		30%	0.01	0.07	0.31	0.44	0.29	0.35	0.94	0.95	0.55
		50%	0.02	0.11	0.35	0.55	0.31	0.43	0.93	0.96	0.42
β_2	100	15%	0.01	0.03	0.20	0.24	0.19	0.22	0.95	0.95	0.71
		30%	0.00	0.03	0.21	0.25	0.20	0.23	0.94	0.95	0.71
		50%	0.01	0.03	0.22	0.29	0.22	0.27	0.95	0.96	0.61
	300	15%	0.00	0.01	0.11	0.12	0.11	0.12	0.95	0.95	0.79
		30%	0.00	0.01	0.11	0.13	0.12	0.13	0.95	0.95	0.78
		50%	0.00	0.01	0.13	0.15	0.13	0.15	0.95	0.96	0.69

Table 2

Simulation results for $\beta_1 = \beta_2 = 0.5$ with average $F_1(\infty) = 0.3$, and with $Z_1 \sim B(0.5)$ and $Z_2 \sim N(0, 1)$. New denotes the newly proposed proportional odds estimator, BM denotes the direct binomial modelling approach, n is the sample size, c is censoring rate, SD denotes the sample standard error of the estimate, $E(\hat{\sigma})$ denotes the sample mean of the estimated standard error, and MSEratio is the sample mean of the mean square error ratio between New and BM

Parameter	n	c	Bias		SD		$E(\hat{\sigma})$		Coverage		MSE ratio
			New	BM	New	BM	New	BM	New	BM	
β_1	50	15%	0.04	0.09	0.69	0.98	0.65	0.74	0.95	0.95	0.54
		30%	0.05	0.10	0.71	0.93	0.68	0.78	0.95	0.95	0.67
		50%	0.04	0.07	0.84	1.10	0.74	0.93	0.96	0.96	0.62
	100	15%	0.01	0.04	0.46	0.51	0.45	0.49	0.95	0.95	0.83
		30%	0.01	0.04	0.48	0.56	0.47	0.51	0.95	0.95	0.78
		50%	0.01	0.05	0.52	0.66	0.51	0.60	0.95	0.96	0.65
β_2	300	15%	0.00	0.01	0.26	0.27	0.26	0.27	0.95	0.95	0.89
		30%	0.00	0.01	0.27	0.29	0.27	0.28	0.95	0.95	0.86
		50%	0.01	0.02	0.29	0.34	0.29	0.33	0.95	0.95	0.74
	50	15%	0.03	0.12	0.36	0.61	0.33	0.41	0.93	0.95	0.42
		30%	0.03	0.12	0.39	0.63	0.34	0.43	0.92	0.95	0.43
		50%	0.04	0.12	0.43	0.67	0.37	0.52	0.92	0.97	0.41
β_2	100	15%	0.01	0.04	0.24	0.29	0.23	0.26	0.94	0.95	0.73
		30%	0.01	0.05	0.25	0.32	0.24	0.28	0.94	0.94	0.67
		50%	0.01	0.06	0.27	0.39	0.25	0.33	0.93	0.96	0.52
	300	15%	0.00	0.01	0.13	0.15	0.13	0.14	0.95	0.95	0.83
		30%	0.00	0.02	0.14	0.15	0.14	0.15	0.95	0.95	0.80
		50%	0.00	0.02	0.15	0.18	0.15	0.18	0.94	0.95	0.69

Simulation study comparing the proposed estimator Fine's 2001 procedure. $E(\hat{\beta}_{11})$ is the average of the $\hat{\beta}_{11}$ estimates and $\text{var}(\hat{\beta}_{11})$ the sample variance of the estimates. Column 4,5,6 correspond to our estimator, column 7,8 to Fine's Table 2. The table is based on 1000 replications.

Table 3

Size	[a,b]	% censored	$E(\hat{\beta}_{11})$	Coverage	$\text{var}(\hat{\beta}_{11})$	Fine: $E(\hat{\beta}_{11})$	Fine: $\text{var}(\hat{\beta}_{11})$
50	$[\infty, \infty]$	0	0.517	0.936	0.086	0.529	0.167
150	$[\infty, \infty]$	0	0.500	0.953	0.024	0.571	0.042
50	$[0.75, 1.5]$	30	0.525	0.939	0.095	0.593	0.321
150	$[0.75, 1.5]$	30	0.494	0.951	0.027	0.536	0.057

Table 4

Goodness-of-fit simulation study. Proportion of 2000 simulated samples where proportionality is rejected.

Generating model	n	Z	X
Proportional	50	0.049	0.057
Proportional	100	0.053	0.071
Proportional	200	0.048	0.063
Proportional	400	0.048	0.047
Non-proportional	50	0.047	0.099
Non-proportional	100	0.052	0.143
Non-proportional	200	0.053	0.223
Non-proportional	400	0.051	0.410