Progression and Death as Competing Risks in Ovarian Cancer

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Abstract: *Background*: Progression of a cancer disease and dying without progression can be understood as competing risks. The Cause-Specific Hazards Model and the Fine and Gray model on cumulative incidences are common statistical models to handle this problem. The pseudo value approach by Andersen and Klein is also able to cope with competing risks. It is still unclear which model suits best in which situation.

Methods: For a simulated dataset and a real data example of ovarian cancer patients who are exposed to progression and death the three models are examined. We compare the three models with regards to interpretation and modeling requirements.

Results: In this study, the parameter estimates for the competing risks are similar from the Cause-Specific Hazards Model and the Fine and Gray model. The pseudo value approach yields divergent results which are heavily dependent on modeling details.

Conclusions: The investigated approaches do not exclude each other but moreover complement one another. The pseudo value approach is an alternative that circumvents proportionality assumptions. As in all survival analyses, situations with low event rates should be interpreted carefully.

Keywords: Multistate Models, pseudo values, cause-specific hazards, cumulative incidence, Fine and Gray model.

1. BACKGROUND

A situation with multiple time-to-event endpoints, where one endpoint could be prevented by the occurrence of another endpoint but not vice versa, is called a semi-competing risks situation [1-4]. Classically, the three-state illness-death model without recovery [5, 6] represents such a disease process. Observations starting in the healthy state are exposed to two risks: experiencing a disease progression and dying. While censoring prevents observation of both events independently, death may censor disease progresses, depending on individual characteristics which also influence the progression likelihood.

This problem could easily be dealt with by analyzing a combined endpoint. However, this technique induces a loss of information and is unsatisfactory, especially when differentiation of those two events is reasonable. Particular techniques have been previously developed to cope with competing risks in a three-state illness-death model [3, 7-11]. There are basically two different approaches: The Cause-Specific Hazards Model accounts for competing events by analyzing unconditional hazards of the particular events. In contrast, the cumulative incidence models relate to cumulative event probabilities.

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This article is organized as follows: In section two, a simulated example and a real data example will be introduced. In section three, the Cause-Specific Hazards Model (which we will call CSHM) as well as the two cumulative incidence models, namely the Fine and Gray Model and the pseudo value approach by Andersen and Klein [12-14], will be reviewed. Results will be presented in section four. In section five, the results will be opposed and specific characteristics of the investigated models will be discussed. Section six closes with concluding remarks.

2. EXAMPLES

The first data example is a simulated collective of 1000 subjects which are exposed to two competing risks A and B. A binary covariable *cov1* has a cause-specific risk parameter $\beta_A = -0.5$ for risk A ($\exp^{\beta_A} = 0.61$) and the parameter for risk B is $\beta_B = 0.5$ ($\exp^{\beta_B} = 1.65$). If an event occurs, the probability that the subject failed from A is 0.5. For simplicity, we assume no censoring. Details of the simulation technique can be reviewed at [15].

The second example is about real clinical data of 215 ovarian cancer patients, undergoing primary surgery between 1996 and 2004 at the University Medical Center in Hamburg-Eppendorf [16, 17]. Ovarian cancer is the ninth most common cancer among woman and accounts for the highest disease-related mortality among all gynecologic malignancies [18]. Most of the patients experience a disease

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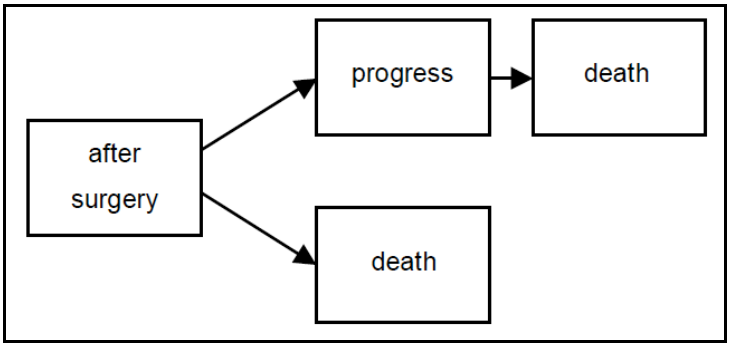

Figure 1: A modified illness-death model. Progression and death before progression as competing events.

progress within few years during the eventually fatal course of the disease. Yet, there are also cases where patients die without experiencing a progress or, in other words, a progress is circumvented by an early death. It is unclear whether these patients die from other causes, or on the opposite, if their deaths are highly related to the disease. In this work, we define and analyze progression and dying before progression as competing events, see Figure **1**. We considered the three most important covariables, which are the patients' age in years, presence of a residual tumor after surgery, and a binary tumor staging indicator, derived from the Fédération Internationale de Gynécologie et d' Obstétrique (FIGO) tumor staging classification [19].

3. COMPETING RISKS MODELS

One special challenge is that there are two logical ways of understanding hazard ratios for competing events. Assume for example the following situation: A factor favors progression and death at the same time, but the impact on mortality is much stronger. Then the absolute number of progressions would decrease with increasing factor, because individuals failing to death can not experience a progression. More theoretically, an increased cause-specific hazard for one risk is not equivalent with the increase of the marginal event probability, when competing risks are present. The cumulative incidence approach refers to marginal event probabilities, whereas the cause-specific hazard rate models the instantaneous potential of the specific event to occur, given that neither the event of interest nor any other competing event has occurred yet.

3.1. Inference from the Cause-Specific Hazards Model

Let *T* be a random variable representing failure times with a survivor function *S(t)* and a density function *F(t)*. Let D={1,…,K} denote *K* different causes of events which are competing. In the CSHM, we concentrate on hazards for specific events [11, 20],

$$\alpha_k(t) = \frac{f(t)}{S(t)} = \lim_{\Delta t \to 0} \frac{P(t \le T < t + \Delta t, D = k \mid T \ge t)}{\Delta t} \quad (1)$$

Events other than the one of interest are understood as censorings. As in the classical Cox model [21, 22], the cause-specific hazards follow the proportional hazards assumption, expressed in the general formulation

$$\alpha_k(t, Z) = \alpha_{k,0}(t)\exp(\beta_k^T Z) \quad (2)$$

with baseline hazard function $\alpha_{k,0}(t)$ for events of type *k* and vectors *Z* for covariates and β_k for regression coefficients. The cause-specific hazard ratios from the regression model in (2) can be understood as the instantaneous risk of experiencing the specific event *k*, which could of course be circumvented by a competing event or by independent censoring.

In the one-risk case, there is a one-to-one relation between the hazard rate and survival function, $S(t) = \exp(-\int_0^t \alpha(u)du)$, denoting the probability of not experiencing the event until *t*. In case of competing risks, the naive derived function

$$S_k(t) = \exp(-\int_0^t \alpha_k(s)ds) \quad (3)$$

may not be understood as a cause-specific marginal survival function, giving the probability of no event *k* until *t*. For the probability of staying event-free, the competing events $j \neq k$ also have to be considered. Formula (3) underestimates the cumulative incidence in case of competing events.

A survival function describing the probability of no event until *k* is given by

$$S(t) = \exp\left(-\sum_{k=1}^{K} \int_0^t \alpha_k(s)ds \right) \quad (4)$$

Another important function describing an equivalent to the distribution function $F(t) = 1 - S(t)$ in the one-risk-case is the cumulative incidence function $C_k(t) = P(T \le t, D = k)$, which gives the probability of failure from cause *k* before time *t*. The cumulative incidence function (CIF) is a function of the cause-specific hazards from all causes of failure,

$$C_k(t) = S(u-)\alpha_k(u)du \, . \quad (5)$$

Putter *et al*. [11] propose the following interpretation for the CIF: If the time interval [0,t] is decomposed into many small intervals of length Δ, then the events reaching state *k* in $[u, u+\Delta]$ are disjunct. The probability of surviving just prior to *u*, denoted by *u-,* times the conditional probability of reaching state *k* in the interval $[u, u+\Delta]$ is the event probability in every time interval. Of course, $C_k(t)$ also depends on every competing risk through *S(u-)*, because being at risk for *k* at time *u* requires no competing event until *u-*.

3.2. Inference from Cumulative Incidence Models

The cumulative incidence models focus on the marginal probability of having failed from one event prior to a specific time point.

The Model by Fine and Gray

The key concept of the model proposed by JP Fine and RJ Gray [3] is to regress on a subdistributional hazard rate that is derived directly from the cumulative incidence function,

$$\tilde{\alpha}_k(t) := \frac{\partial \log(1 - C_k(t))}{\partial t} \quad (6)$$

Then, a regression step analogue to the Cox partial likelihood in (2) will be performed, assuming the subdistribution hazard rates $\tilde{\alpha}_k(t)$ to be proportional. The difference between the hazard rates $\tilde{\alpha}_k(t)$ in (6) and $\alpha_k(t)$ in (2) is that individuals stay in the risk set after experiencing a competing event in the Fine and Gray model, whereas these individuals are treated as censored in the cause-specific hazard framework.

The Pseudo Value Approach

The pseudo value approach on cumulative incidences proposed by PK Andersen and JP Klein [14] circumvents the proportional hazards assumption. Pseudo values for the cumulative incidence function will be generated by the leave-one-out system known from the jackknife approach from the cumulative incidence function in a generalized linear model.

Let $N_k(t)$ be a counting process representing the number of individuals who experienced an event of type *k* by time *t* and let *Y(t)* denote the number of individuals at risk at *t*. An estimator for the CIF in (5) is

$$C_k(t) = \int_0^t \prod_{T_i < u} \left(1 - \frac{\sum_{h=1}^{K} dN_h(T_i)}{Y(T_i)} \right) \frac{dN_k(u)}{Y(u)} \, . \quad (7)$$

If the censoring time is independent of *(T, k)*, $C_k(t)$ is an approximately unbiased estimator of $C_k(t)$ [14].

Presume some time points $t_1, \ldots, t_M$. It is recommended to choose M = 5 to 10, spaced equally across the event scale, or some specific time points predefined with special interest for the researcher [23]. At every time point, the cumulative incidence function will be estimated based on the complete data set $C_k(t_j)$ and on the reduced data set $C_k^{(i)}(t_j)$, which denotes the complete data set leaving the *i*th individual out. The pseudo value of the *i*th subject at time t_j is then defined as

$$\theta_{ij}(t_j) = nC_k(t_j) - (n-1)C_k^{(i)}(t_j) \quad (8)$$

and can be interpreted as the contribution of individual *I* to the estimated cumulative incidence function at time t_j.

The next step is to perform a regression analysis of θ_{ij} on Z_i, to link the pseudo values and the vector of covariates. This is done by a generalized linear model

$$g(\theta_{ij}) = \beta_0 + \sum \beta_j Z_j \quad (9)$$

with a link function *g(.)*. Andersen *et al*. (2003) propose several link functions, thereunder the logit link, $g(x) = \log(x/(1-x))$, the complementary log-log function on x, $g(x) = \log(-\log(x))$, or the complementary log-log function on (1-x), that is $g(x) = \log(-\log(1-x))$. The complementary log-log function relates to the cumulative incidence of event times and is therefore comparable to the subdistribution hazards model by Fine and Gray. The logit link is analogue to a proportional odds model [23]. Let furthermore μ_i be the inverse link function,

$$\theta_i = g^{-1}(\beta_0 + \sum \beta_j Z_j) = \mu(\beta_0 + \sum \beta_j Z_j)\,, \qquad (10)$$

The regression coefficients β_j in (9) will now be estimated by a generalized estimation equation approach (GEE) [24, 25],

$$U(\beta) = \sum_i \left(\frac{\partial \mu_i}{\partial \beta} \right) \cdot V_i^{-1}(\theta_i - \theta_i) = \sum_i U_i(\beta) = 0 \qquad (11)$$

with a working covariance matrix V_i for θ_i. Klein and Andersen (2005) suppose the identity matrix, the exact working covariance matrix or a common working covariance matrix estimated as a product-moment correlation matrix of the θ_{ij} as possible working covariance matrices.

4. RESULTS

From the 1000 simulated subjects, 383 failed by chance from risk A and 617 from risk B. The CSHM yields estimated hazard ratios HR=0.579 (95%CI:[0.469; 0.715]) for A and HR=1.778 (95%CI:[1.510; 2.093]) for B. The Fine and Gray model results estimated subdistributional hazard ratios of SHR=0.426 (95%CI:[0.344; 0.527]) for risk A and SHR=2.013 (95%CI:[1.708; 2.373]) for risk B. The pseudo value approach using nine grid time points estimates SHR=0.490 (95%CI:[0.386; 0.620]) for A and SHR=1.953 (95%CI:[1.625; 2.348]) for B.

From the 215 ovarian cancer patients from the second example, 111 experienced a progression and 19 deaths in remission were observed. The median follow up was 23 months. An overview of descriptive statistics is presented in Table **1**.

The results for the clinical example are opposed in Table **2**. We applied the pseudo value model twice, using five and ten time points, equally distributed across the event scale. For the progression intensity, all four models agree. Whereas age has no impact on progression, staging and residual tumor are prognostic markers for the progression intensity. All applied models reveal a significantly increased progression risk of approximately 50% for patients with residual disease, compared with patients who are tumor-free after surgery. The progression hazard is even tripled in the high stage group compared to the lower staged group. Results for the dying intensity differ among the models. The proportional hazards models, namely the CSHM and the Fine and Gray model show similar non-significant results, while the pseudo value method differs. Especially for the staging effect, the pseudo value models estimate strong and significant stage effects.

5. MODEL COMPARISON AND DISCUSSION

The Cause-Specific Hazards Model and the cumulative incidence approaches should not be compared directly, because they have a different meaning relating to different aspects of the process. However, similarity of cause-specific hazard ratios and subdistribution hazard ratios is informative and may be interpreted as absence of a strong interdependency between the competing events of interest.

For the simulated example, results from the CSHM are very close to the predetermined values. The estimates from the cumulative incidence models are again not directly comparable to the default values, as the simulation based on cause-specific hazards. The results from the Fine and Gray and the pseudo value estimates are quite similar with also comparably wide confidence intervals.

In contrast, the results from the clinical example show a very strong variation at one point. While the pseudo value model yields a very strong effect of tumor staging on mortality without progression, this effect is invisible using the Fine and Gray model or the CSHM. Furthermore, estimates from the pseudo value model

Table 1: Descriptive Statistics and Event Counts for the Clinical Example

	Patients	Progressions	Deaths before progression
Total	215 (100%)	111 (51.6%)	19 (8.8%)
No residual tumor	149 (69.3%)	64 (58.7%)	11 (57.9%)
Residual tumor	66 (30.7%)	47 (41.3%)	8 (42.1%)
Low stage	52 (24.2%)	13 (11.7%)	2 (10.5%)
High stage	163 (75.8%)	98 (88.3%)	17 (89.5%)
Age in years mean (sd)	57.4 (12.6)	58.1 (11.8)	61.4 (12.2)

Table 2: Results for the Clinical Example from the Cause-Specific Hazards Model (CSHM), the Fine and Gray Model (FG) and the Andersen an Klein Approach on Pseudo Values with 5 (AK5) and 10 (AK10) Grid Time Points

	Age			Stage			Residual tumor		
	HR	**95%-CI**	**p**	**HR**	**95%-CI**	**p**	**HR**	**95%-CI**	**p**
Progress									
CSHM	0.994	[0.976; 1.012]	0.520	3.372	[1.802; 6.308]	<0.001	1.646	[1.105; 2.451]	0.014
FG	0.995	[0.977; 1.012]	0.520	2.886	[1.531; 5.368]	0.001	1.459	[1.011; 2.211]	0.044
AK5	0.992	[0.975; 1.010]	0.353	3.168	[1.627; 6.169]	0.001	1.578	[1.037; 2.400]	0.033
AK10	0.994	[0.979; 1.010]	0.506	2.954	[1.511; 5.276]	0.001	1.571	[1.047; 2.358]	0.029
Death									
CSHM	1.025	[0.982; 1.071]	0.257	3.002	[0.647; 13.921]	0.160	1.356	[0.525; 3.502]	0.529
FG	1.024	[0.962; 1.074]	0.330	2.235	[0.492; 10.155]	0.300	1.206	[0.459; 3.167]	0.700
AK5	0.996	[0.942; 1.052]	0.877	11.649	[1.878; 72.223]	0.008	1.590	[0.554; 4.565]	0.388
AK10	0.998	[0.948; 1.050]	0.949	5.613	[1.390; 22.658]	0.015	1.464	[0.527; 4.064]	0.465

seem to depend heavily on the number and location of time points.

Until Fine and Gray developed their milestone model in 1999, competing risks problems were analyzed and interpreted mainly with the CSHM. Since then, both models were common tools for competing risk problems. Both approaches require a proportionality assumption, as they base on the Cox PH-Model. By construction, this assumption can only be met for one of both models. If the cause-specific hazard ratio is constant over time, the subdistributional hazard ratio has to change with time and vice versa. However, if the proportional hazards assumption holds, the subdistributional hazard ratio may still be interpreted as a time-averaged effect on the cumulative event probability, see also [26, 27]. The third approach by Andersen and Klein on pseudo values waives the proportional hazards assumption. But the variability of the results and the fact that there is no clear recommendation how to choose number and location of grid points yields unstable results from the pseudo value model, especially when low event counts are present.

With our work, we state that not one single approach is appropriate in a special situation. Moreover, the CSHM and the cumulative incidence approach complement one another. The CSHM allows a more clinical interpretation, as the results represent the effect of the instantaneous probability of each event. Etiological questions are better addressed to this model. The cumulative incidence approaches are more relevant for analyzing marginal probabilities. For example in requirements planning, cumulative incidence models can be preferred.

Regarding computational opportunities, The CSHM can be adapted using every statistical software that can handle the Cox model. In contrast, the Fine and Gray Model is not yet a standard procedure, but it is available for example in Stata 12.0 (*stcompet*) and in R (*cmprsk*). To adapt a pseudo value model, the software has to be firm with GEE models. Stata provides an .ado-file (*stpci*) that can handle competing risks models with the pseudo value approach [15].

6. CONCLUSIONS

We conclude that the CSHM and approaches on cumulative incidences do not exclude each other but moreover complement one another. Therefore, we recommend to compute both the Cause-Specific Hazards Model and the Fine and Gray model in competing risks situations. The pseudo value approach may be an alternative to the Fine and Gray model, when the proportional hazards assumption is not met. However, care has to be taken as the number and location of grid time points is arbitrary but of high relevance for the results. As in all survival analyses, situations with low event rates should be interpreted carefully.

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