Statistical Analysis of Competing Risks: Overall Survival in a Group of Chronic Myeloid Leukemia Patients

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Abstract

Background: Survival analysis is a collection of statistical methods for inference on time-to-event data. If several causes of failure occur and the occurrence of one event precludes the occurrence of the other events, the situation is known as competing risks. Since the competing risks violate the fundamental assumption of independent censoring, specific methods for inference are needed.
Objectives: The aim of this paper is to recall the competing risks model and statistical methods for nonparametric analysis, and to illustrate the competing risks methods on a real data set of 118 Chronic Myeloid Leukemia (CML) patients from the Clinic of Haemato-oncology of the University Hospital in Olomouc.
Methods: The overall survival probability and risk factors of two types of failure (death due to CML and death from other causes) are assessed. Predicted probabilities of the two types of failure with stratification based on the risk factors (Sokal score, haematological response to treatment) are shown.
Results: Outcomes of the specific methods designed for the competing risks analysis are compared with the outcomes of the standard survival analysis methods. The effect of the Sokal score classification is found ambiguous. While the score should identify high- and low-risk CML patients, it seems to be predictive only for the failure due to other causes than CML.

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Conclusions: The importance of careful censoring and the need of using proper methods of analyses of competing risks data is shown. The use of the Sokal score for classification of the CML patients should be considered more thoroughly.

Keywords

Competing risks, chronic myeloid leukemia (CML), overall survival, cause-specific hazard, cumulative incidence function

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1 Introduction

Methods of survival analysis have become widely used in medical research in the past few decades. Standard survival data (also called time-to-event data) arise in studies where time from some origin to an end-point is measured. The end-point is defined by occurrence of a certain event of interest. The time until the specified event occurs can be characterized by several functions. The most widely used are the survival function, representing the probability of an individual surviving up to time t (i.e. the probability that the event has not occurred before t), and the hazard function, representing the rate of occurrence of the event at a given time. Under the assumption of in-

dependent censoring, these functions are estimated by the Kaplan-Meier estimator of the survival function and the Nelson-Aalen estimator of the hazard function (for more information, see e.g. [1] or [2]).

In some cases, several causes of failure are possible but the occurrence of one event precludes the occurrence of the other events (e.g. when failures are different causes of death, only the first one can be observed). This situation is known as competing risks. Often, only one event is chosen for analysis, the competing causes of failure are ignored and treated as right-censored observations, and classical survival methods are used for inference [3]. However, this approach leads to a bias in the Kaplan-Meier estimate [4]. The bias is caused by violating one of the fundamental assumptions underlying the Kaplan-Meier estimator – the assumption of independence of distribution of the time to the event and the censoring distribution. Furthermore, independence between distinct causes of failure cannot be verified on the basis of the observed competing risks data [5]. Specific methods are thus needed for the estimation of survival probabilities. The Cox proportional hazards model may be used for regression analysis, but the interpretation of the results becomes different [4].

This paper presents the competing risks model and statistical methods for nonparametric analysis. The methods are then illustrated on real Chronic Myeloid Leukemia (CML) data from the Clinic of Haemato-oncology of the University Hospital in Olomouc, Czech Republic. All statistical methods are implemented with the R software, using the *survival*, *cmprsk* and *mstate* packages [6].

2 Methods

Competing risks are used to model a situation where subjects under investigation are exposed to several causes of failure. If failures represent different causes of death, only the first event to occur is observed. In other settings, second and subsequent failures may be observable, but not of interest. The violation of the assumption of independent censoring, leading to a biased Kaplan-Meier estimator, is an important issue in competing risks models. If the competing event time distributions were independent of the distribution of time to the event of interest, this would imply that at each time the risk of this event is the same for subjects that have not yet failed and are still under follow-up as for subjects that have experienced a competing event by that time [4]. However, a subject that is censored due to failure from a competing risk will certainly not experience the event of interest. Since subjects that will never fail (by the failure of interest) are treated as if they could fail (they are censored), the standard Kaplan-Meier estimator overestimates the probability of failure and underestimates the corresponding survival probability [4], [7].

The competing risks data are represented by the failure time T, the failure cause D and a vector of covariates $\mathbf{Z}$ (T is assumed to be a continuous and positive random variable, D takes values in the finite set $\{1,\ldots,m\}$). Former approach to competing risks used multivariate failure time models. In such models each subject was assumed to have a potential failure time for each type of event. The earliest event was actually observed and the others were latent. This approach focused on the joint distribution of the times $T_1,\ldots,T_m$ of the m different failure types, described by the joint survival function

$$S(t_1,\ldots,t_m) = P(T_1 > t_1,\ldots,T_m > t_m).$$

The marginal hazard function

$$h_j(t) = \lim_{\Delta t\to 0^+} \frac{P(t \le T_j < t+\Delta t | T_j \ge t)}{\Delta t}$$

is defined by the marginal survival

$$S_j(t) = P(T_j > t) = S(0,\ldots,0,t,0,\ldots,0).$$

However, without additional assumptions, neither the joint survival function is identifiable from the observed data, nor are the marginal distributions [2], [8], [5]. This "latent failure time" approach has thus little practical use.

A recent concept in competing risks models is *the cause-specific hazard function* and *the cumulative incidence function.* These two functions completely specify the joint distribution of (T, D), the failure time and the failure cause [9]. The cause-specific hazard function for the $j-$th cause is defined by

$$\lambda_j(t) = \lim_{\Delta t\to 0^+} \frac{P(t \le T < t+\Delta t, D = j | T \ge t)}{\Delta t},$$

for $j = 1,\ldots,m$. It represents the hazard of failing from cause j in the presence of the competing events. The cumulative cause-specific hazard is then defined by

$$\Lambda_j(t) = \int_0^t \lambda_j(u)du.$$

A function $S_j(t) = \exp(-\Lambda_j(t))$ should not be interpreted as a marginal survival function unless the competing event time distributions and the censoring distribution are independent (in case of independent censoring, the marginal distribution models the situation when competing events do not occur) [9]. The total hazard $\lambda(t)$ and the overall survival function $S(t)$ are defined in terms of the cause-specific hazards:

$$\lambda(t) = \lim_{\Delta t\to 0^+} \frac{P(t \le T < t+\Delta t | T \ge t)}{\Delta t} = \sum_{j=1}^{m} \lambda_j(t),$$

$$\begin{aligned} S(t) &= P(T > t) = \exp\left(-\int_0^t \lambda(u)du\right) = \\ &= \exp\left(-\sum_{j=1}^{m}\int_0^t \lambda_j(u)du\right) = \end{aligned}$$

$$= \exp\left(-\sum_{j=1}^{m}\Lambda_j(t)\right).$$

This overall survival function does have an interpretation: It is the probability of not having failed from any cause at time t [3].

The cumulative incidence function of cause j, $I_j(t)$, is defined by

$$I_j(t) = P(T \le t, D = j), \qquad j = 1, \ldots, m,$$

and represents the probability of a subject failing due to cause j in the presence of all the competing risks. It can be expressed in terms of the cause-specific hazard and the overall survival function as

$$I_j(t) = \int_0^t \lambda_j(u)S(u)du, \qquad j = 1, \ldots, m. \qquad (1)$$

This function is sometimes called "crude cumulative incidence function" or "subdistribution function". It is not a proper distribution function because the cumulative probability to fail from cause j remains less than unity, as $I_j(\infty) = P(D = j)$ [1]. The standard Kaplan-Meier estimator of the probability of failing due to cause j before or at time t satisfies

$$1 - S_j(t) = \int_0^t \lambda_j(u)S_j(u)du, \qquad (2)$$

which is similar to the expression of cumulative incidence function $I_j(t)$. Equations (1) and (2) differ by replacing $S(t)$ by $S_j(t)$. Since

$$S(t) \le S_j(t),$$

then

$$I_j(t) \le 1 - S_j(t),$$

with equality at t if there is no competition, i.e. if

$$\sum_{k=1,k\neq j}^{m}\Lambda_k(t) = 0.$$

This shows the bias of the Kaplan-Meier estimator if it is used to estimate $I_j(t)$ [4].

The cumulative incidence function can be estimated using the Kaplan-Meier methodology restricted to specific failures for each cause: Let $0 < t_1 < t_2 < \cdots < t_n$ be the ordered distinct times at which failures of any cause occur. Let d_{jk} denote the number of patients failing from cause j at t_k, and let $d_k = \sum_{j=1}^{m} d_{jk}$ denote the total number of failures (from any cause) at t_k. Let n_k be the number of patients at risk (i.e. patients still in follow-up who have not failed from any cause) at time t_k. Then the cumulative incidence function of cause j at time t is estimated by

$$\hat{I}_j(t) = \sum_{k:t_k\le t}\hat{\lambda}_j(t_k)\hat{S}(t_{k-1}),$$

where the discretized version of the cause-specific hazard $\lambda_j(t_k) = P(T = t_k, D = j|T > t_{k-1})$ is estimated by

$$\hat{\lambda}_j(t_k) = \frac{d_{jk}}{n_k}$$

and

$$\hat{S}(t) = \prod_{k:t_k\le t}\left(1 - \sum_{j=1}^{m}\hat{\lambda}_j(t_k)\right).$$

More detailed derivation of this estimator of $I_j(t)$ can be found in [1] and [4].

In addition to estimating the cumulative incidence functions of the events, it is often of interest to compare the cause-specific cumulative incidence functions among different groups of patients. In standard survival analysis this is done using the nonparametric tests comparing curves generated with the Kaplan-Meier method (e.g. the log-rank test, the Gehan-Wilcoxon test, etc.). In the presence of competing risks, however, these tests are inappropriate. Instead, Gray [10] proposed a class of generalized linear rank statistics for testing equality of the cumulative incidence functions. The tests are based on comparing weighted averages of the hazards of the cumulative incidence function for the failure type of interest.

Consider now a regression model for the competing risks. As in any other regression analysis, it is used to identify potential prognostic factors for a particular failure in the presence of competing risks, or to assess a prognostic factor of interest after adjusting for other potential risk factors in the model. First, consider a regression model for the cause-specific hazard functions. Since the cause-specific hazard functions are identifiable, regression on these functions is possible and a competing risks analogue of the Cox proportional hazards model becomes a logical choice [2]. It models the cause-specific hazard of cause j for a subject with a covariate vector $\mathbf{Z}$ by

$$\lambda_j(t, \mathbf{Z}) = \lambda_{0j}(t)\exp(\beta_j^T\mathbf{Z}),$$

where $\lambda_{0j}(t)$ is the baseline cause-specific hazard of cause j and β_j is a vector of the regression coefficients related to cause j. Both the baseline hazards and the regression coefficients are permitted to vary arbitrarily over the j failure types. Again, let $t_{j1} < t_{j2} < \cdots < t_{jk_j}$ denote the k_j times of type j failures, $j = 1, \ldots, m$, and let $\mathbf{Z}_{ji}$ be the covariates for the individual that fails at t_{ji}. Partial likelihood is constructed with conditioning at each failure time: (1) on the previous history of failures and censoring, (2) that at time t_{ji}, a single type j failure occurs [4]. The partial likelihood function then reads [2]:

$$L(\beta_1, \ldots, \beta_m) = \prod_{j=1}^{m}\prod_{i=1}^{k_j}\frac{\exp\left(\beta_j^T\mathbf{Z}_{ji}(t_{ji})\right)}{\sum_{\gamma\in R(t_{ji})}\exp\left(\beta_j^T\mathbf{Z}_{\gamma}(t_{ji})\right)},$$

where $R(t_{ji})$ is the risk set at time t_{ji}. Estimation and comparison of the regression coefficients β_j can be con-

structed by applying asymptotic likelihood techniques individually to the m factors.

Unfortunately, the cause-specific hazard function does not have a direct interpretation in terms of survival probabilities for the particular failure type. Moreover, the effect of a covariate on the cause-specific hazard function may be very different from the effect of the covariate on the corresponding cumulative incidence function [10]. Therefore, Fine and Gray [11] proposed a method for direct regression modeling on the cumulative incidence functions for the competing risks data. The Fine and Gray model is a semiparametric proportional hazards model using the partial likelihood principle and weighting techniques. It uses a $\log(-\log)$ transformation such that it is reasonable to assume a constant difference between the cumulative incidence functions independent of the time point t. For events of type j, the model reads

$$g_j\left(I_j(t,\mathbf{Z})\right) = h_{0j}(t) + \beta_j^T\mathbf{Z}, \qquad j = 1,\ldots,m,$$

where g_j is some known increasing function, $h_{0j}(t)$ is an invertible and monotone increasing function, $\mathbf{Z}$ is a covariate vector and β_j is a vector of regression coefficients related to cause j. The procedure is based on the transformation

$$g = \log\left(-\log(1-u)\right)$$

corresponding to the proportional hazards model, and it utilizes the subdistribution hazards (hazards related to the cumulative incidence functions) constructed by Gray in [10]. After the transformation, the model reads

$$I_j(t,\mathbf{Z}) = 1 - \exp\left(-\exp(\beta_j^T\mathbf{Z})h_{0j}(t)\right),$$

which allows to assess the effects of the covariates on the cumulative incidence function directly. The partial likelihood constructed by Fine and Gray differs from the traditional cause-specific hazard analysis: in the Fine-Gray model, the risk set for type j events is constructed so that subjects having already experienced events other than type j are always at future risk of a type j event, while in the traditional model the occurrence of an event other than type j removes an individual from future risk sets [11]. A comprehensive discussion may be found in [11] and [12].

3 Data

For illustration of the competing-risks techniques, data from the Clinic of Haemato-oncology of the University Hospital in Olomouc are used. The data contain 118 patients suffering from Chronic Myeloid Leukemia (CML). CML is a cancer of the white blood cells. It is a form of leukemia characterized by the increased and unregulated growth of predominantly myeloid cells in the bone marrow and the accumulation of these cells in the blood. The median age at time of the diagnosis of the disease is 53 years [in 1999], but all age groups, including children, are affected [13]. The natural history of CML is progression from a benign chronic phase to a blast crisis within three to five years [14]. Blast crisis is the final phase in the evolution of CML, and behaves like an acute leukemia, with rapid progression and short survival. The blast crisis is often preceded by an accelerated phase, which signals that the disease is progressing and transformation to blast crisis is imminent. Drug treatment can usually stop this progression if started early [13], [14], [15]. In the Czech Republic, there are about 200 newly diagnosed CML patients per year [16].

All 118 patients in the data set were treated in the Olomouc University Hospital in the years 1989–2010. The last admissible date of diagnosis for the analysis was in 2006 in order to have sufficient follow-up time for all the patients. There is one limitation of the data concerning its consistency: the treatment protocol was changed in 2001 because a new drug – Glivec – had been approved for treatment of the chronic phase of CML. Until 2001, patients were treated by Interferon.

For first-line treatment, Interferon was used for all patients in the Olomouc data set (even those diagnosed after 2001) and most of the patients surviving after 2001 were then treated by Glivec. Out of the 118 patients, 67 are males (57%). The age of the patients at the date of diagnosis ranges from 18 to 71, with the mean of 48 years and median of 50 years. At the date of diagnosis, the Sokal score [17] is evaluated for patients with CML. It identifies low- and high-risk patients according to their age, spleen size and blood cell count.

The high risk group (Sokal score 3) contains 21% of the Olomouc patients ($n = 25$), the low risk group (Sokal score 1) covers 39% ($n = 46$). All other patients were classified with the Sokal score 2. Complete blood count was recorded at the date of diagnosis and haematological response to the treatment was assessed. Overall, 73 patients (62%) achieved complete haematological response (CHR) to the Interferon treatment. The CHR is assessed by improvement of all parameters of the blood cell count of a patient. Median time of CHR is 3 months after the Interferon treatment. Although other types of failure could be considered as well (e.g. progression-free survival, after-treatment survival, etc.), the focus of this paper is the overall survival with initial point being the date of diagnosis of CML and terminal point being death.

The events of interest (competing risks) are two types of failure: death due to CML (includes accelerating disease, progressive disease and blast crisis), and death from other causes (different types of cancer, graft-versus-host disease after stem cell transplantation, suicide, other). By January 2010, 39 patients (33%) have died, 23 patients died due to CML (20%) and 16 due to other causes (14%). Seventy nine patients (67%) did not experience any of these events and were censored in January 2010. All the competing risks estimations are made in terms of the overall survival, i.e. time from the diagnosis of CML to death is considered.

4 Results and Discussion

Figure 1 shows the estimates of the probabilities of "CML-related death" and "death from other causes" for all patients. The CML curves are represented as survival curves, while the other event curves are represented as probability distribution functions (one minus survival) for greater clarity. Estimates based on the Kaplan-Meier method are grey, whereas the estimates of the cumulative incidence functions are black.

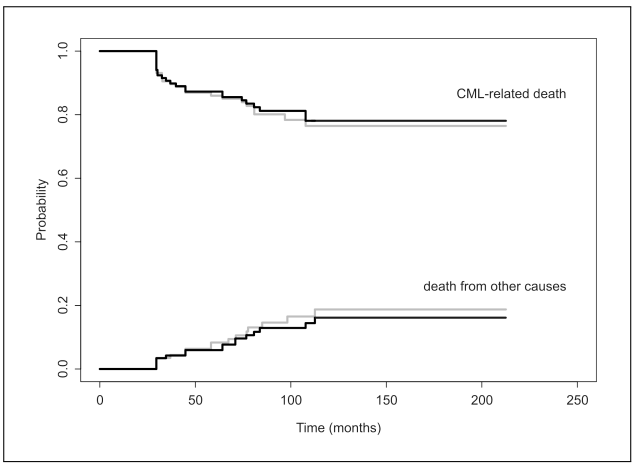

Figure 1: Estimates of probabilities of CML-related death (represented as survival curves) and death from other causes (represented as probability distribution functions), based on Kaplan-Meier (grey) and on cumulative incidence functions (black).

For this data, the two estimates are relatively close to each other, however, the difference between the curves is obvious. The estimates of probability of failure based on Kaplan-Meier after 10 years (120 months) of follow-up are $P = 0.24$ for CML-related event resp. $P = 0.19$ for other type of event, while cumulative incidence estimates are $P = 0.22$ and $P = 0.16$ for CML and other type of event, respectively. This illustrates the formerly mentioned claim that the Kaplan-Meier estimator overestimates the probability of failure and underestimates the corresponding survival probability.

Table 1: Basic characteristics of the continuous covariate variables: age, leukocyte count and haemoglobin level at the date of diagnosis.

	Mean	Median	Min	Max
Age (years)	48	50	18	71
Leu ($\times 10^9/l$)	131	86	2	777
Hgb (g/l)	125	126	70	161

Figure 2 shows the estimated cumulative incidence curves again, displayed in a different way – they are stacked. The bottom curve represents the estimate of the cumulative incidence function of CML ($\hat{I}_{CML}(t)$), the top curve represents the sum of estimates of the cumulative incidence functions of CML and other types of death ($\hat{I}_{CML}(t) + \hat{I}_{other}(t)$). This representation allows an easy comparison of the respective probabilities at any time t.

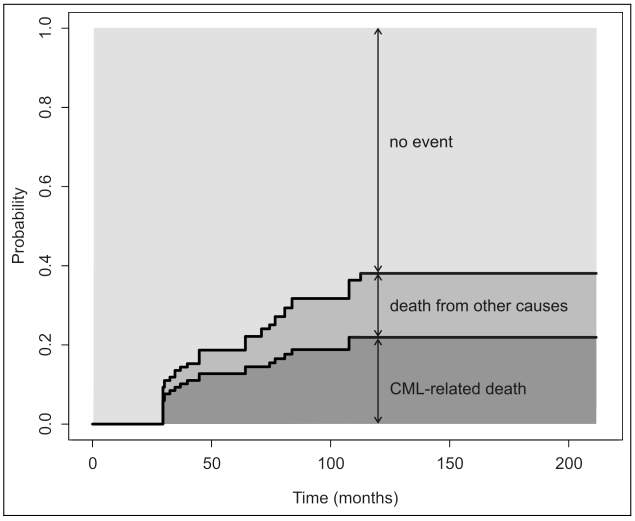

Figure 2: Cumulative incidence curves of CML-related death and death from other causes. Differences between the curves represent probabilities of the particular events.

For the regression analysis on cause-specific hazards, several covariates are used. Basic characteristics of the covariates are shown in Tables 1 and 2. Sex, Sokal score and complete haematological response to treatment (CHR) are categorical variables, whereas age at diagnosis, leukocyte count (Leu) and haemoglobin level (Hgb) at diagnosis are continuous. For purposes of the analyses, in order to make interpretation of results easier, these continuous variables were converted into dichotomous. The cut-off levels were set (by the medical staff) to 45 years of age, $50 \times 10^9/l$ of leukocytes and $110 g/l$ of haemoglobin.

Table 2: Basic characteristics of the categorical covariate variables. One value is missing in the Sokal score and the complete haematological response to treatment (CHR) variable.

		N	%
Sex	male	67	57
	female	51	43
Sokal score	1	46	39
	2	46	39
	3	25	21
CHR	yes	73	62
	no	44	37

Table 3 reports the results of the univariate Cox regression analysis with single covariates sex, age, Leu, Hgb, Sokal score and CHR. It is evident that the blood count has strong effect on the rate of occurrence of CML-related death. The leukocyte level above 50 negatively affects overall survival of the CML patients (hazard ratio (HR)

Table 3: Relative risk estimation for the CML-related death and death from other causes with single covariates, based on the Cox regression model on the cause-specific hazard functions.

	CML		other	
	$\exp(\hat{\beta}_{CML})$	$p-$value	$\exp(\hat{\beta}_{other})$	$p-$value
Sex (male)	1.30	0.55	0.52	0.20
Age (≥ 45)	1.40	0.46	1.43	0.51
Leu (≥ 50)	2.52	0.09	2.31	0.19
Hgb (≥ 110)	0.42	0.04	0.40	0.08
Sokal score	1.43	0.19	2.74	0.004
CHR (yes)	0.33	0.01	0.81	0.70

Table 4: Relative risk estimation for the CML-related death and death from other causes for the Sokal score represented as a pair of dummy variables. Based on the Cox regression model on the cause-specific hazard functions.

	CML		other	
	$\exp(\hat{\beta}_{CML})$	$p-$value	$\exp(\hat{\beta}_{other})$	$p-$value
Sokal score 2 versus 1	1.59	0.35	4.10	0.08
Sokal score 3 versus 1	2.05	0.20	8.92	0.007
Sokal score 3 versus 2	1.29		2.17	

= 2.52, $p = 0.09$), while the effect of haemoglobin level above 110 is protective (HR = 0.42, $p = 0.04$). Patients who achieve complete haematological response to treatment, are in a lower risk of death due to CML (HR = 0.33, $p = 0.01$). There is no evidence of any dependence of CML-related death rates on sex, age or the Sokal score.

On the other hand, the strongest effect on the rate of occurrence of other causes of death is achieved by the Sokal score. The hazard ratio for each extra point in the Sokal score is 2.74 ($p = 0.004$). Thus, an individual having Sokal score 3 has 7.54−times higher risk of death due to other causes compared to the individual having Sokal score 1 (the estimated coefficient $\hat{\beta}_{other} = 1.01$). In case of the Sokal score, it is not important whether the variable is coded as a single covariate (with three categories) or as a pair of dummy variables when modeling. The results are similar (see Table 4).

The effect of haemoglobin level above 110 is the same for other causes of death as for the CML-related death: haemoglobin level above 110 lowers the risk (HR = 0.40, $p = 0.08$). There seems to be no effect of sex, age, leukocyte count and the achievement of complete haematological response to treatment on the risk of death from other causes than CML. However, the results for the sex covariate are interesting. Although the effects are not statistically significant ($p = 0.55$ and $p = 0.20$ for CML and other type of death, respectively), they are opposite for the two types of failure.

In case of CML-related death, males may be in higher risk than females (HR = 1.30), while in case of other types of death, the hazard ratio for males relative to females is 0.52. Sex is the only covariate with such opposite effects on the two types of failure. In the multivariate Cox regression model, no combinations of the above mentioned six covariates prove to have statistically significant effects on the risk of failure due to any of the competing risks.

Table 5: Contingency table with counts of patients according to the Sokal score classification and the cause of death.

	cause		
Sokal score	CML	other	alive
1	7	2	37
2	10	7	29
3	6	7	12

Based on the results of the Cox regression, predicted cumulative incidence curves can be obtained. Figures 3 and 4 show the predicted occurrence of CML-related death and death from other causes for the groups of patients with and without complete haematological response to treatment and for the Sokal score classification. For the CML-related death, the CHR achievement has a strong protective effect: The predicted probabilities of failure due to CML after ten years (120 months) are $P = 0.15$ and $P = 0.38$ for the "CHR yes" and the "CHR no" groups, respectively. On the other hand, there seems to be no relationship between the CHR outcome and failure due to other causes than CML, which is to be expected. For both CHR groups, the predicted probability of death from other causes after ten years from the diagnosis is relatively low ($P = 0.15$). The CHR achievement after the Interferon treatment thus may be used as a reliable predictor of lower

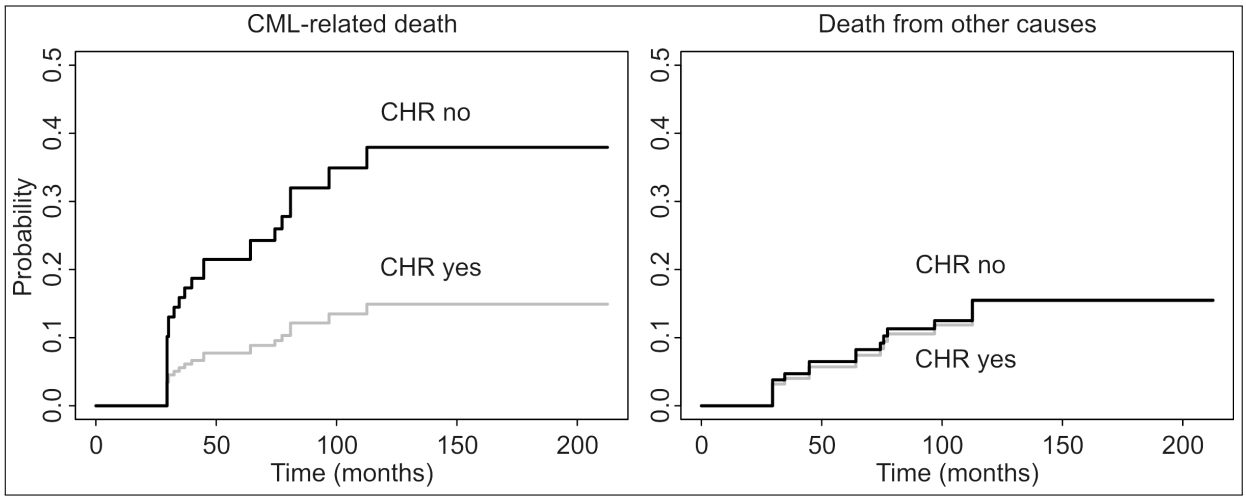

Figure 3: Predicted cumulative incidence functions for CML-related death (left) and death from other causes (right), for patients with and without complete haematological response to treatment, based on the proportional hazards model for the cause-specific hazards.

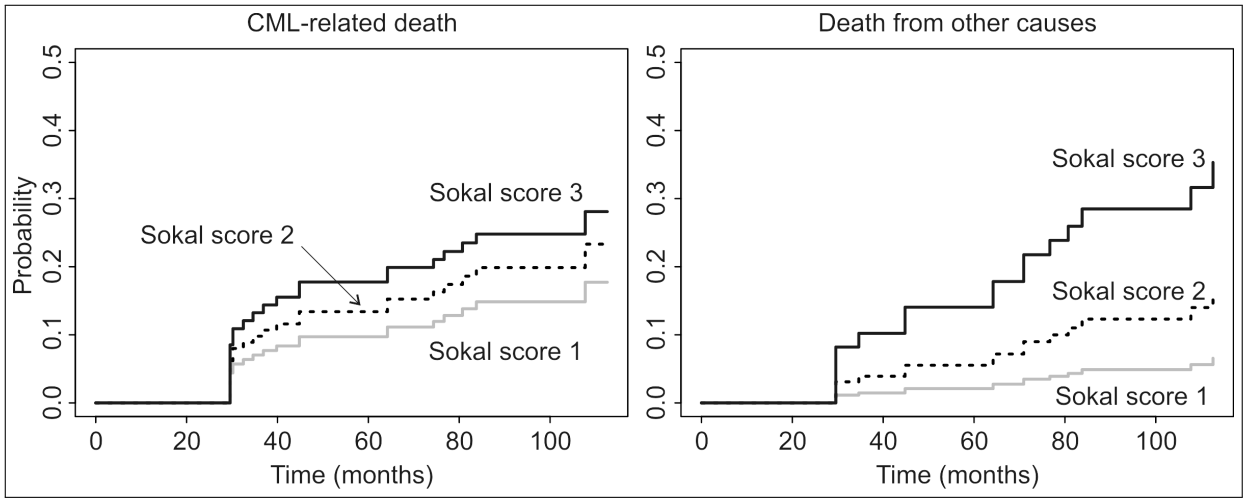

Figure 4: Predicted cumulative incidence functions for CML-related death (left) and death from other causes (right), for the Sokal score classification, based on the proportional hazards model for the cause-specific hazards.

risk of death due to CML. The effect of the Sokal score classification is ambiguous. While the score should identify high- and low-risk CML patients, it seems to be predictive only for the failure due to other causes than CML. The predicted probabilities of death from other causes after ten years are $P = 0.35$ and $P = 0.07$ for the Sokal score 3 group and the Sokal score 1 group, respectively. The predicted probabilities of death from CML after ten years are much closer one to another for all the groups – $P = 0.28$ for Sokal score 3 and $P = 0.18$ for Sokal score 1. For a better insight in the connection of Sokal classification to the different causes of death, contingency table with counts of patients is included (see Table 5). Other predicted cumulative incidence curves are not presented here, as they can easily be obtained from the results of the Cox regression (see Table 3).

To compare the results of the regression on the cause-specific hazards (shown in Table 3) and the regression on the cumulative incidence functions, the Fine and Gray model has been fitted to the data. The results of the Fine and Gray regression are reported in Table 6.

Both the regression models produce similar results for the CML data, thus the main difference between the two models is the interpretation of the results. Cause-specific hazards obtained from the Cox regression model may be translated into cumulative incidence curves, but the proportionality is lost by this process and the covariate effects on the cumulative incidence curves can no longer be expressed by a simple number [4]. Therefore, to determine the effect of a covariate on the cumulative incidence of an event of interest, the Fine and Gray approach using the proportionality of the subdistribution hazards is a better choice.

Table 7 reports the results of the Gray test of the cumulative incidence functions compared with the results of the log-rank test of the Kaplan-Meier estimates of the

Table 6: Relative risk estimation for the CML-related death and death from other causes with single covariates, based on the Fine and Gray regression model of the cumulative incidence functions.

	CML		other	
	$\exp(\hat{\beta}_{CML})$	$p-$value	$\exp(\hat{\beta}_{other})$	$p-$value
Sex (male)	1.42	0.41	0.51	0.17
Age (≥ 45)	1.32	0.55	1.39	0.52
Leu (≥ 50)	2.36	0.12	2.14	0.23
Hgb (≥ 110)	0.46	0.06	0.49	0.16
Sokal score	1.31	0.32	2.58	0.004
CHR (yes)	0.35	0.01	1.02	0.98

survival functions. The tests are computed for all the stratification groups used in the regression models.

The Gray test results are shown for both the competing events, the CML-related death and the death from other causes. For the log-rank test, two schemes of censoring are used: (1) the two types of death are considered separately, i.e. when focusing on the CML-related death, patients experiencing death from other causes are censored as well as patients experiencing no event (and vice versa when focusing on the death from other causes), (2) only event is considered – death from any cause, the differences in types of death are ignored, and censored are only those patients who have not died by January 2010. The censoring scheme (2) completely ignores not only the competing risks methods, but also the possibility of different causes of events.

Table 7: P-values resulting from the Gray test of the cumulative incidence functions (for competing risks) and the log-rank test of the Kaplan-Meier estimates of the survival functions (no competing risks). *Any = Death from any cause (censoring scheme (2)).

	Gray test		Log-rank test		
	CML	other	CML	other	any*
Sex	0.42	0.17	0.46	0.07	0.59
Age	0.53	0.52	0.76	0.33	0.40
Leu	0.11	0.22	0.16	0.14	0.04
Hgb	0.06	0.14	0.08	0.11	0.02
Sokal score	0.59	0.02	0.66	0.008	0.03
CHR	0.01	0.93	0.01	0.60	0.02

Unfortunately, this approach might be quite often in clinical studies where the information about the cause the patients' death are not available. While the results of the Gray test and the log-rank test of the scheme (1) censoring are similar, the results for the scheme (2) differ substantially. The scheme (2) finds statistically significant differences in overall survival between groups of patients stratified by Leu, Hgb, Sokal score and CHR.

However, these results are misleading, as the differences between the groups are limited to the "overall death" only and ignore the influence of the different causes of events. The results in Table 7 show the importance of careful censoring and the need of using proper methods of analyses.

5 Conclusion

The competing risks model and statistical methods for nonparametric analysis are recalled in this paper. The bias in the standard Kaplan-Meier estimator and the need for specific methods for inference on competing risks data is explained. The data set of Chronic Myeloid Leukemia (CML) patients from the Clinic of Haemato-oncology of the University Hospital in Olomouc is analyzed. The overall survival probability and risk factors of two types of failure (death due to CML and death from other causes) are assessed. The interesting role of sex and the Sokal score classification on the overall survival of the CML patients is discussed. Predicted probabilities of the two types of failure with stratification based on the chosen risk factors are shown. Results of the specific methods designed for the competing risks analysis are compared with the results of the standard survival analysis methods. The effect of the Sokal score classification is found ambiguous. While the score should identify high- and low-risk CML patients, it seems to be predictive only for the failure due to other causes than CML. The use of the Sokal score should be considered more thoroughly.

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References

[1] J. P. Klein, M. L. Moeschberger: *Survival Analysis. Techniques for Censored and Truncated Data.* Springer, New York, 2003.

[2] J. D. Kalbfleisch, R. L. Prentice: *The Statistical Analysis of Failure Time Data.* John Wiley & Sons, New York, 2002.

[3] N. Porta, G. Gómez, M. Luz Calle: *The Role of Survival Functions in Competing Risks.* available at *http://www.eio.upc.es/nporta*, cited on June 20, 2011.

[4] H. Putter, M. Fiocco, R. B. Geskus: *Tutorial in Biostatistics: Competing Risks and Multi-State Events.* Statistics in Medicine 26 (2006), 2389–2430.

[5] A. Tsiatis: *A Nonidentifiability Aspect of the Problem of Competing Risks.* Proceedings of the National Academy of Sciences USA 72 (1975), 20–22.

[6] *http://www.R-project.org*

[7] T. A. Gooley, W. Leisenring, J. Crowley, B. E. Storer: *Estimation of Failure Probabilities in the Presence of Competing Risks: New Representations of Old Estimators.* Statistics in Medicine 18 (1999), 695–706.

[8] D. R. Cox: *The Analysis of Exponentially Distributed Lifetimes with 2 Types of Failure.* Journal of the Royal Statistical Society, Series B 21 (1959), 411–421.

[9] J. Lawless: *Statistical Models and Methods for Lifetime Data.* John Wiley & Sons, New York, 2003.

[10] R. J. Gray: *A Class of K−sample Tests for Comparing the Cumulative Incidence of a Competing Risk.* The Annals of Statistics 16 (1988), 1141–1154.

[11] J. P. Fine, R. J. Gray: *A Proportional Hazards Model for the Subdistribution of a Competing Risk.* Journal of the American Statistical Association 94 (1999), 496–509.

[12] J.-H. Jeong, J. P. Fine: *Parametric Regression on Cumulative Incidence Function.* Biostatistics 8 (2007), 184–196.

[13] C. L. Sawyers: *Chronic Myeloid Leukemia. Review Article.* The New England Journal of Medicine 340 (1999), 1330–1340.

[14] S. Faderl, M. Talpaz, Z. Estrov, H. M. Kantarjian: *Chronic Myelogenous Leukemia: Biology and Therapy.* Annals of Internal Medicine 131 (1999), 207–219.

[15] *http://en.wikipedia.org*, cited on July 13, 2011.

[16] *http://diagnoza-cml.cz*, cited on June 20, 2011.

[17] J. Sokal, M. Baccarani, D. Russo, S. Tura: *Staging and Prognosis in Chronic Myelogenous Leukemia.* Seminars in Hematology 25 (1988), 49–61.

[18] J. Fürstová: *Competing Risks of CML-related Death and Death from Other Causes.* Doktorandský den 2011, Matfyzpress, Praha, 2011.

[19] P. Hougaard: *Analysis of Multivariate Survival Data.* Springer, New York, 2000.

[20] H. T. Kim: *Cumulative incidence in Competing Risks Data and Competing Risks Regression Analysis.* American Association for Cancer Research 13 (2007), 559–565.

[21] R. L. Prentice, B. J. Williams, A. V. Peterson: *On the Regression Analysis of Multivariate Failure Time Data.* Biometrika 68 (1981), 373–379.

[22] H. Putter: *Tutorial in Biostatistics: Competing Risks and Multi-State Models. Analysis Using the mstate Package.* available at *http://cran.r-project.org/ web/ packages/ mstate/ vignettes/ Tutorial.pdf*, cited on June 1, 2011.

[23] L. Scrucca, A. Santucci, F. Aversa: *Competing Risk Analysis Using R: An Easy Guide for Clinicians.* Bone Marrow Transplantation 40 (2007), 381–387.

[24] T. M. Therneau, P. M. Grambsch: *Modeling Survival Data. Extending the Cox Model.* Springer, New York, 2000.

[25] P. R. Williamson, R. Kolamunnage-Dona, C. T. Smith: *The Influence of Competing-Risks Setting on the Choice of Hypothesis Test for Treatment Effect.* Biostatistics 8 (2007), 689–694.

