Semiparametric inference for lifetime data with competing risks, additive risks and different mechanisms of missingness

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Competing Risks

Let denote by T the lifetime of a patient (or a device) and suppose that its death (or failure) can be due to p ($p \geq 2$) different causes, denoted by $d = 1, \ldots, p$..

Recall that the Cumulative Incidence Function (CIF) is defined by

$$F_j(t) = P(T \leq t, d = j),\ j = 1, \ldots, p; 0 < t < +\infty$$

and the cause specific hazard rate function by

$$\lambda_j(t) = \lim_{h \longrightarrow 0^+} \frac{P(T \in [t, t+h[, d = j | T \geq t)}{h},\ j = 1, \ldots, p.$$

In presence of a random censoring mechanism one can only observe:

$$\begin{cases} X & = & \min(T, C) \\ \delta & = & I(T \leq C) \\ d & & \text{if } \delta \neq 0 \end{cases},$$

where censoring r.v. C is supposed to be independent from (T, d).

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Let $Z = (Z(s))$ be a vector of time dependent covariates (with values in $\mathbb{R}^k$).

Let us assume an Aalen's additive risks model on the cause specific hazard rate functions, i.e. :

$$\lambda_j(t|Z) = \lambda_{0j}(t) + \beta_j^T Z(t), \quad t \geq 0,$$

where $\lambda_{0j}(\cdot)$ is an unknown baseline cause specific hazard rate function associated to the jth cause and $\beta_j \in \mathbb{R}^k$ is a vector of regression parameter (under the constraint that $\lambda_j(t|Z) \geq 0$).

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It may happen that the cause of death (or failure) d is some times missing (even if T is uncensored). Write

$$M = \begin{cases} 1 & \text{if cause } d \text{ is observed} \\ 0 & \text{if not.} \end{cases}$$

We will consider two different missingness mechanisms:

- MCAR (Missing Completly At Random);
- MAR (Missing At Random).

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1^{st} Model: MCAR mechanism

Let us assume that:

$$P(M = 1|X, Z, d, \delta = 1) = P(M = 1|\delta = 1) = \alpha \in [0, 1]$$

and

$$P(M = 0|X, Z, d, \delta = 0) = P(M = 0|\delta = 0) = 1.$$

In this case one can only observe (X, δ, D, Z) where

$$D = \delta M d.$$

One can see (X, δ, D), conditionally to Z, as an inhomogeneous Markov process with an initial state and (p+2) absorbing states.

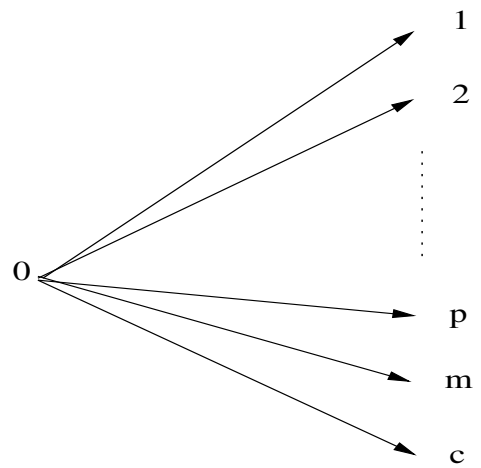

Figure: Markov graph associated to (X, M, D)

Denoting, for $x \in \{1, \ldots, p, m, c\}$, $\lambda'_x(\cdot|Z)$ the transition rate $0 \to x$, conditionally to Z, we get:

$$\begin{cases} \lambda'_j(t|Z)(t) &= \alpha\lambda_j(t|Z) = \alpha(\lambda_{0j}(t) + \beta_j^T Z) \text{ for } j \in \{1, \ldots, p\}, \\ \lambda'_m(t|Z)(t) &= (1-\alpha)\sum_{j=1}^p \lambda_j(t|Z) = (1-\alpha)\left(\lambda_m(t) + \beta_m^T Z\right), \\ \lambda'_c(t|Z)(t) &= \lambda_C(t), \end{cases}$$

where $\lambda_m(\cdot) = \sum_{j=1}^p \lambda_{0j}(\cdot)$ and $\beta_m = \sum_{j=1}^p \beta_j$.

The additive property is almost conserved.

- Let $(X_i, \delta_i, D_i, Z_i(X_i))_{1 \leq i \leq n}$ be the n i.i.d replications of $(X, \delta, D, Z(X))$.
- For $j \in \{1, \ldots, p, m\}$, let us define the elementary counting processes:

$$\begin{aligned} N_{ij}(t) &= 1(X_i \leq t, D_i = j) \text{ for } j \neq m, \\ N_{im}(t) &= 1(X_i \leq t, \delta_i = 1, D_i = 0). \end{aligned}$$

- Let Y_i be the at risk process defined by $Y_i(t) = 1(X_i \geq t)$.
- For $1 \leq i \leq n$ and $j \in \{1, \ldots, p, m\}$ the the processes M_{ij} defined by:

$$M_{ij}(t) = N_{ij}(t) - \int_0^t Y_i(s) \lambda'_j(s|Z) ds, \quad t \geq 0,$$

are $\mathbb{F}$-martingales with respect to the filtration $\mathbb{F} = (\mathcal{F}_t)_{t \geq 0}$ where:

$$\mathcal{F}_t = \sigma\{N_{ij}(s), Y_i(s); s \leq t; 1 \leq i \leq n, j \in \{1, \ldots, p, m\}\}.$$

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Let $\tau < +\infty$ be the upper bound of the interval of study. An estimator of α is:

$$\hat{\alpha} = \hat{\alpha}(\tau) = \frac{\sum_{i=1}^{n} 1(D_i > 0)}{\sum_{i=1}^{n} 1(\delta_i = 1)} = \frac{\sum_{j=1}^{p} N_{.j}(\tau)}{N_{..}(\tau)},$$

where

$$N_{.j}(t) = \sum_{i=1}^{n} N_{ij}(t) \text{ and } N_{..}(t) = \sum_{j=1}^{p} N_{.j}(t) + \sum_{i=1}^{n} N_{im}(t), \text{ for all } t.$$

Extending an approach proposed by Lin and Ying (1994) in case of a single cause of death, one can estimate β_j, for $j = 1, \ldots, p$, by the solution $\hat{\beta}_j$ of the estimating equation $\mathcal{U}_j(\beta, \hat{\alpha}, \tau) = 0$ where

$$\mathcal{U}_j(\beta, \hat{\alpha}, \tau) = \sum_{i=1}^{n} \int_0^{\tau} \left[Z_i(s) - \bar{Z}(s) \right] \left[dN_{ij}(s) - \hat{\alpha}\beta^T Z_i(s) Y_i(s) ds \right],$$

and

$$\bar{Z}(s) = \frac{\sum_{i=1}^{n} Y_i(s) Z_i(s)}{\sum_{i=1}^{n} Y_i(s)}.$$

Closed-form expressions of these estimators are available.

In the sequel we write

$$\hat{\beta}_{WMC} = \begin{pmatrix} \hat{\beta}_1 \\ \vdots \\ \hat{\beta}_p \end{pmatrix}$$

the estimator of the regression parameters which only takes into account the lifetimes with known cause of death (WMC abbreviates "Without taking into account the Missing Causes").

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We have obtained estimators $\hat{\beta}_j$ of β_j, for $j = 1, \ldots, p$.

But one can also estimate $\beta_m = \beta_1 + \cdots + \beta_p$ by the solution $\hat{\beta}_m$ of the estimating equation $\mathcal{U}_m(\beta, \hat{\alpha}, \tau) = 0$ where

$$\mathcal{U}_m(\beta, \hat{\alpha}, \tau) = \sum_{i=1}^{n} \int_0^{\tau} \left[Z_i(s) - \bar{Z}(s) \right] \left[dN_{im}(s) - (1 - \hat{\alpha}) \beta^T Z_i(s) Y_i(s) ds \right.$$

We will use $\hat{\beta}_m$ in order to improve the estimation of the first parameters β_j, for $j = 1, \ldots, p$.

Let us look for an estimator $\tilde{\beta}_{Topt}$ such that:

$$\tilde{\beta}_{Topt} = \begin{pmatrix} \tilde{\beta}_1 \\ \vdots \\ \tilde{\beta}_p \end{pmatrix} = \hat{H} \begin{pmatrix} \hat{\beta}_1 \\ \vdots \\ \hat{\beta}_p \\ \hat{\beta}_m \end{pmatrix}$$

where

$$\hat{H} = \underset{H \in \mathcal{H}}{\operatorname{argmin}} \ \operatorname{trace}(H \hat{\Sigma}_{\hat{\beta},\infty} H^T)$$

and $\hat{\Sigma}_{\hat{\beta},\infty}$ is an estimator of the asymptotic variance-covariance matrix of $(\hat{\beta}_1^T, \ldots, \hat{\beta}_p^T, \hat{\beta}_m^T)^T$.

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Theorem

Under some hypotheses, the random vector $\sqrt{n}(\hat{\beta}_{WMC} - \beta)$ *is asymptotically mean zero gaussian distributed with covariance matrix* Σ *that we can estimate by plug-in.*

Theorem

Under the same hypotheses, $\sqrt{n}(\tilde{\beta}_{Topt} - \beta)$ *is asymptotically mean zero gaussian gaussien with covariance matrix whose trace minimizes* $q(H) = trace(H\Sigma_{\hat{\beta},\infty}H^T)$ *over* $H \in \mathcal{H}$.

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Estimation of the functional parameters

Write: $S_l(\cdot)$, for $l = 0, 1, 2$, the processes defined by

$$S_l(s) = \frac{1}{n} \sum_{i=1}^{n} Y_i(s) Z_i^{\otimes l}(s).$$

We have, for $j = 1, \ldots, p+1$:

$$dN_{\cdot j}(s) = dM_{\cdot j}(s) + \alpha_j Y(s) d\Lambda_{0j}(s) + \alpha_j n S_1^T(s) \beta_j ds$$

where the $\alpha_j = \alpha$, for $j = 1, \ldots, p$, and $\alpha_{p+1} = 1 - \alpha$.
Thus, an estimator of $\Lambda_{0j}(t)$ is given, for all $t \in [0, \tau]$, by

$$\hat{\Lambda}_{0j}(t) = \frac{1}{\hat{\alpha}_j} \int_0^t \frac{dN_{\cdot j}(s)}{Y(s)} - \hat{\beta}_j^T \int_0^t \frac{S_1(s)}{S_0(s)} ds.$$

Then we propose to estimate $\Lambda_j(\cdot|\mathbb{Z})$, for $j = 1, \ldots, p+1$, by $\hat{\Lambda}_j(\cdot|\mathbb{Z})$ defined, for $t \geq 0$, by

$$\begin{aligned}\hat{\Lambda}_j(t|\mathbb{Z}) &= \hat{\Lambda}_{0j}(t) + \hat{\beta}_j^T \int_0^t Z(s)ds \\ &= \frac{1}{\hat{\alpha}_j} \int_0^t \frac{dN_{\cdot j}(s)}{Y(s)} + \hat{\beta}_j^T \left(\int_0^t Z(s)ds - \int_0^t \frac{S_1(s)}{S_0(s)} ds \right).\end{aligned}$$

We are able to derive the large sample behavior of these functional parameters as well as of their improved version obtained thanks to an adaptation of the idea used for the regression parameters.

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2^{nd} Model: MAR mechanism

Let us assume that:

$$P(M = 1|d, \delta = 1, X, Z) = P(M = 1|\delta = 1, X, Z) = \pi(X, Z) = \pi(\mathbb{O}),$$

where $\mathbb{O}$ denotes (X, Z) to shorten notation. Thus, given $\delta = 1$ and $\mathbb{O}$, the probability that the cause is missing depends only on $\mathbb{O}$ and not on the cause of death. It is also assumed that

$$P(M = 0|d, \delta = 0, \mathbb{O}) = 1.$$

The above assumption of independence between M and d, given $\delta = 1$ and $\mathbb{O}$, allows us to write, for $j = 1, \ldots, p$:

$$\begin{aligned} P(d = j | \delta = 1, M = 0, \mathbb{O}) &= P(d = j | \delta = 1, M = 1, \mathbb{O}) \\ &= P(d = j | \delta = 1, \mathbb{O}) = h_j(\mathbb{O}). \end{aligned}$$

In the following, we will assume that we observe a sample

$$(X_i, \delta_i, D_i, Z_i(X_i))_{1 \leq i \leq n}$$

of $(X, \delta, D, Z(X))$, where we still write $D = \delta M d$.

Following Lu and Liang (2008), one can introduce parametric models $\pi(\mathbb{O}, \gamma)$ (resp. $h_j(\mathbb{Q}, \zeta)$, for $j = 1, \ldots, p$) on the unknown probability $\pi(\mathbb{O})$ (resp. probabilities $h_j(\mathbb{Q})$, for $j = 1, \ldots, p$).

Due to the MAR assumption, one can get estimators $\hat{\gamma}$ and $\hat{\zeta}$ of γ and ζ respectively by maximization of the likelihoods

$$\prod_{i=1}^{n} \left(\pi(\mathbb{O}_i, \gamma)\right)^{M_i \delta_i} \left(1 - \pi(\mathbb{O}_i, \gamma)\right)^{(1-M_i)\delta_i},$$

and

$$\prod_{i=1}^{n} \left[\prod_{j=1}^{p-1} \left(h_j(\mathbb{Q}_j, \zeta)\right)^{I\{D_i=j\}} \right] \times \left(1 - h_1(\mathbb{Q}_i, \zeta) - \cdots - h_{p-1}(\mathbb{Q}_i, \zeta)\right)^{I\{D_i=p\}}.$$

Let us introduce two new families of counting processes:

$$\tilde{N}_{ij}(t) = I\{X_i \leq t, d_i = j\} \text{ and } N_i^*(t) = I\{X_i \leq t, \delta_i = 1\},$$

for $i = 1, \ldots, n$, $j = 1, \ldots, p$ and all $t > 0$.

Estimators of the β_j and the $\Lambda_{0j}(\cdot)$, for $j = 1, \ldots, p$, will be obtained as solutions of the following estimating equations:

$$\sum_{i=1}^{n} \left\{ \frac{M_i}{\pi(\mathbb{O}_i, \hat{\gamma})} d\tilde{N}_{ij}(t) - \frac{M_i - \pi(\mathbb{O}_i, \hat{\gamma})}{\pi(\mathbb{O}_i, \hat{\gamma})} h_j(\mathbb{Q}_i, \hat{\zeta}) dN_i^*(t) \right.$$
$$\left. - Y_i(t)\beta_j^T Z_i(t)dt - Y_i(t)d\Lambda_{0j}(t) \right\} = 0, \text{ for all } t > 0$$

$$\sum_{i=1}^{n} \int_0^\tau Z_i(t) \left\{ \frac{M_i}{\pi(\mathbb{O}_i, \hat{\gamma})} d\tilde{N}_{ij}(t) - \frac{M_i - \pi(\mathbb{O}_i, \hat{\gamma})}{\pi(\mathbb{O}_i, \hat{\gamma})} h_j(\mathbb{Q}_i, \hat{\zeta}) dN_i^*(t) \right.$$
$$\left. - Y_i(t)\beta_j^T Z_i(t)dt - Y_i(t)d\Lambda_{0j}(t) \right\} = 0.$$

Let us denote these estimators

$$\hat{\beta}_{DR} = \begin{pmatrix} \hat{\beta}_1 \\ \vdots \\ \hat{\beta}_p \end{pmatrix} \text{ and } \hat{\Lambda}_0^{DR}(\cdot) = \begin{pmatrix} \hat{\Lambda}_{01}(\cdot) \\ \vdots \\ \hat{\Lambda}_{0p}(\cdot) \end{pmatrix}.$$

Theorem

Under some Assumptions and if at least one of the two parametric models assumed on the MAR mechanism is well specified, then the r.v.

$$\sqrt{n}\left(\hat{\beta}_{DR} - \beta\right)$$

converges in distribution in $\mathbb{R}^{pk}$ to a mean zero Gaussian r.v. with covariance that we can estimate.

Theorem

Under some assumptions and if at least one of the two parametric models assumed on the MAR mechanism is well specified, then the multivariate process

$$\sqrt{n}\left(\hat{\Lambda}_0^{DR}(\cdot) - \Lambda_0(\cdot)\right)$$

converges weakly in $D^p[0,\tau]$*, when* $n \to +\infty$*, to a zero mean Gaussian process with covariance matrix functions that we can estimate.*

Remark: an estimator of the conditional cumulative hazard rate function is given by:

$$\hat{\Lambda}_j(t|\mathbb{Z}) = \hat{\Lambda}_{0j}(t) + \int_0^t \hat{\beta}_j^T Z(u) du,$$

for $j = 1, \ldots, p$ and $t \in [0, \tau]$.

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We carried out Monte Carlo simulations with only two causes of death and a time-independent covariate Z of dimension 1 with continuous distribution.

More precisely, let T_1 (resp. T_2) denote the continuous latent, or potential, survival time associated with risk/cause 1 (resp. 2). Hence, the individual lifetime T is given by $T = \min(T_1, T_2)$ and $d = 1$ (resp. $d = 2$) if $T = T_1$ (resp. $T = T_2$).

We assumed that the bivariate survival function of (T_1, T_2), conditionally on $Z = z$, is given by

$$S_{T_1,T_2}(t_1, t_2|z) = \exp\left(-(\lambda_1 + \beta_1 z)t_1 - (\lambda_2 + \beta_2 z)t_2 - \lambda_3 t_1 t_2\right),$$

where λ_3 is such that $0 \leq \lambda_3 < \min(\lambda_1, \lambda_2)$.

One can see that, conditionally on $Z = z$, the r.v. T_1 and T_2 are dependent if $\lambda_3 > 0$ and that the distribution of T_j is exponential with rate $\lambda_j + \beta_j z$ for $j = 1, 2$.

The assumption of an additive hazard rate model is fulfilled in this case, since

$$\lambda_j(t|z) = \lambda_j + \lambda_3 t + \beta_j z, \qquad \text{for } t \geq 0,$$

for $j = 1, 2$.

Finally, we assumed that the covariate Z is uniformly distributed on $(0, \tau_Z)$ and that the censoring time has an exponential distribution with rate λ_C.

We chose the following set of parameters:
$(\lambda_1, \lambda_2, \lambda_3) = (1, 1, 0.5)$, $(\beta_1, \beta_2) = (1, 2)$, $\tau_Z = 2$ and $\lambda_C = 3$.

These parameters yield empirically (based on 100 000 replications of the above simulation scenario): 38.2% of censoring, 25.4% of failure from cause 1, and 36.4% of failure from cause 2.

Then we considered separately two mechanisms of causes missingness:

- the MCAR model with $P(M = 1|X, Z, d, \delta = 1) = \alpha = 0.8$ which leads empirically to 12,6% of missing cause of failure, 20.2% of failure from cause 1, and 29.0% of failure from cause 2;
- the MAR model with a logistic regression model for the conditional probability $\pi(X, Z)$, i.e.

$$\pi(x, z) = P(M = 1|X = x, Z = z, d, \delta = 1) = \frac{e^{\gamma_0+\gamma_1 x+\gamma_2 z}}{1 + e^{\gamma_0+\gamma_1 x+\gamma_2 z}}.$$

We chose $\gamma_0 = -0.0855$ and $\gamma_1 = \gamma_2 = 1$ which leads empirically to 17,1% of missing cause of failure, 17.4% of failure from cause 1 and 26.1% of failure from cause 2.

This simulation design was replicated 10 000 times with different sample sizes: $n = 100, 400, 1000$

Table: Simulation results for the three regression parameter estimators under **MCAR** assumption. Monte Carlo estimates of the bias (Bias), the variance (Emp. Var.), the mean of estimated variance (Var. Mean) and the coverage percentage (Coverage %).

n	Estimator	WMC		T–optimal		DR	
		β_1	β_2	β_1	β_2	β_1	β_2
100	Bias	0.021	0.057	0.014	0.032	0.022	0.046
	Emp. Var.	0.699	1.051	0.638	0.951	0.649	0.937
	Var. Mean	0.701	1.037	0.638	0.908	0.794	0.970
	Coverage %	94.5	94.7	94.6	94.4	98.1	97.3
400	Bias	0.000	0.016	-0.001	0.011	-0.001	0.016
	Emp. Var.	0.161	0.231	0.148	0.207	0.150	0.208
	Var. Mean	0.162	0.239	0.150	0.213	0.164	0.198
	Coverage %	94.8	95.4	94.8	95.0	96.7	95.1

Table: Simulation results for the three regression parameter estimators under **MAR** assumption. Monte Carlo estimates of the bias (Bias), the variance (Emp. Var.), the mean of estimated variance (Var. Mean) and the coverage percentage (Coverage %).

	Estimator	WMC		T–optimal		DR	
n		β_1	β_2	β_1	β_2	β_1	β_2
100	Bias	0.541	0.805	-0.069	-0.133	0.017	0.059
	Emp. Var.	0.814	1.246	0.613	0.929	0.748	1.049
	Var. Mean	0.799	1.197	0.689	0.950	0.878	1.054
	Coverage %	93.4	91.6	95.0	93.8	98.0	97.3
400	Bias	0.516	0.745	-0.051	-0.118	0.001	0.014
	Emp. Var.	0.185	0.278	0.140	0.202	0.162	0.221
	Var. Mean	0.185	0.277	0.162	0.224	0.174	0.208
	Coverage %	79.8	72.6	96.0	94.7	96.5	95.3

Table: Simulation results for the regression parameter estimators under MCAR and MAR assumption. Monte Carlo estimates of the relative efficiency, defined as the ratio of the empirical Mean Square Error (MSE) of the estimator with the empirical MSE of the ML estimator.

Data	n	WMC vs. ML		T–optimal vs. ML		DR vs. ML	
		β_1	β_2	β_1	β_2	β_1	β_2
MCAR	100	1.493	1.450	1.363	1.309	1.387	1.292
	400	1.192	1.288	1.096	1.153	1.110	1.160
	1000	1.181	1.270	1.090	1.149	1.090	1.149
MAR	100	1.287	2.499	1.277	1.249	1.546	1.389
	400	3.088	4.283	0.976	1.110	1.109	1.137
	1000	5.370	7.958	0.927	1.230	1.022	1.121

We can use the criterion of the Mean Integrated Square Error (MISE) in order to compare the different estimators of the cause-specific baseline cumulative hazard rate functions.

For cause $j = 1, 2$ and for each type of estimator (WMC, T–optimal and DR), based on N simulated samples, an empirical estimate of the MISE of this estimator is then given by:

$$\frac{1}{N} \sum_{k=1}^{N} \int_0^{\tau_k} \left(\hat{\Lambda}_{0j}^{(k)}(s) - \Lambda_{0j}(s) \right)^2 ds.$$

Table: Simulation results for the three estimators (WMC, T–optimal and DR) of the baseline cause-specific cumulative hazard rate functions $\Lambda_{01}(\cdot)$ and $\Lambda_{02}(\cdot)$ under MCAR and MAR assumptions. Monte Carlo estimates of MISE ($\times 10^3$).

	Estimator	WMC		T–optimal		DR	
Data	n	$\Lambda_{01}(\cdot)$	$\Lambda_{02}(\cdot)$	$\Lambda_{01}(\cdot)$	$\Lambda_{02}(\cdot)$	$\Lambda_{01}(\cdot)$	$\Lambda_{02}(\cdot)$
MCAR	100	11.69	15.89	11.31	15.19	10.85	14.59
	400	3.05	4.02	2.94	3.84	2.87	3.67
	1000	1.29	1.63	1.23	1.52	1.17	1.37
MAR	100	16.22	23.56	12.29	15.9	13.28	16.43
	400	7.30	12.35	4.17	5.61	3.52	4.18
	1000	5.35	8.69	2.39	2.97	1.39	1.44

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Pintilie (2006) dataset of 616 patients treated with radiation therapy for a Hodgkin's disease at the Princess Margaret Hospital between 1968 and 1986.

- Event of interest is the incidence of second malignancy, the death without malignancy is seen as a competing risk
- 84 patients with incidence of second malignancy and 195 without a second malignancy.
- The rate of censoring is about 54%.
- Only one covariate, age, with 308 young patients (30 years old or younger) and 308 older patients.
- Question of interest: does the younger subjects have the same risk of a new malignancy than the older ones ?

Let us call this dataset the "**Without Missing Cause (WMC) dataset**".

From this WMC dataset, we have artificially created two new datasets with some causes of death missing.

- One after the application of a MCAR mechanism with $\alpha = 0.4$ and called "**MCAR dataset**"
- The otehr one after the use of MAR mechanism with probability of missingness given by the logistic regression model $\text{logit}(\pi(X, Z)) = -1 + 0.01X + Z$ called "**MAR dataset**"

Table: WMC, MCAR and MAR datasets on Hodgkin's disease. Percentages of events.

Data	Censoring	Missing	Cause 1	Cause 2
WMC	54.7	0	13.6	31.7
MCAR	54.7	28.0	5.0	12.3
MAR	54.7	26.1	4.4	14.8

Table: WMC, MCAR and MAR datasets on Hodgkin's disease. WMC, T–optimal and DR estimates of the regression parameters, their estimated standard error (within parenthesis) and a 95% confidence interval.

Data	Method		β_1	β_2
WMC	WMC	Estim. (SE)	0.00558 (0.00198)	0.02435 (0.00305)
		95% CI	[0.00169, 0.00946]	[0.01837, 0.03034]
MCAR	WMC	Estim. (SE)	0.01064 (0.00325)	0.02681 (0.00463)
		95% CI	[0.00426, 0.01701]	[0.01773, 0.03588]
	T–optimal	Estim. (SE)	0.00827 (0.00300)	0.02166 (0.00376)
		95% CI	[0.00239, 0.01142]	[0.01430, 0.02902]
	DR	Estim. (SE)	0.00877 (0.00258)	0.02069 (0.00358)
		95% CI	[0.00370, 0.01383]	[0.01367, 0.02772]
MAR	WMC	Estim. (SE)	0.01083 (0.00287)	0.03882 (0.00427)
		95% CI	[0.00521, 0.01645]	[0.03044, 0.04720]
	T–optimal	Estim. (SE)	0.00576 (0.00272)	0.02601 (0.00360)
		95% CI	[0.00043, 0.01109]	[0.01894, 0.03307]
	DR	Estim. (SE)	0.00567 (0.00278)	0.02399 (0.00368)
		95% CI	[0.00022, 0.01111]	[0.01678, 0.03120]