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Comparison of the marginal hazard & sub-distribution hazard for competing risks with an assumed copula

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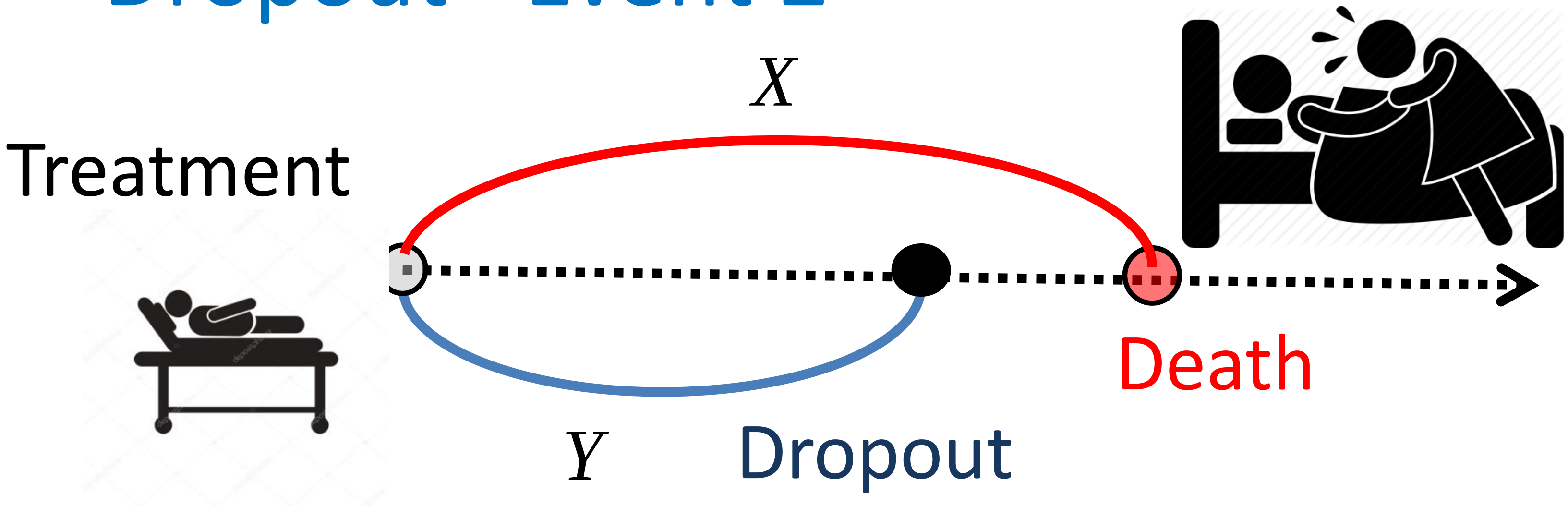
Joint work with Ha ID, Shih JH, Wilke RA

What is competing risk ?

Death=Event 1

Dropout =Event 2



Death time is ***unobserved*** due to dropout

➔ Dropout is a ***competing risk*** for death

Competing risks

- X : time to "Event 1"
- Y : time to "Event 2"
- $T = \min(X, Y)$: observed event time
- $\delta = \mathbf{I}(T = X)$: observed event type

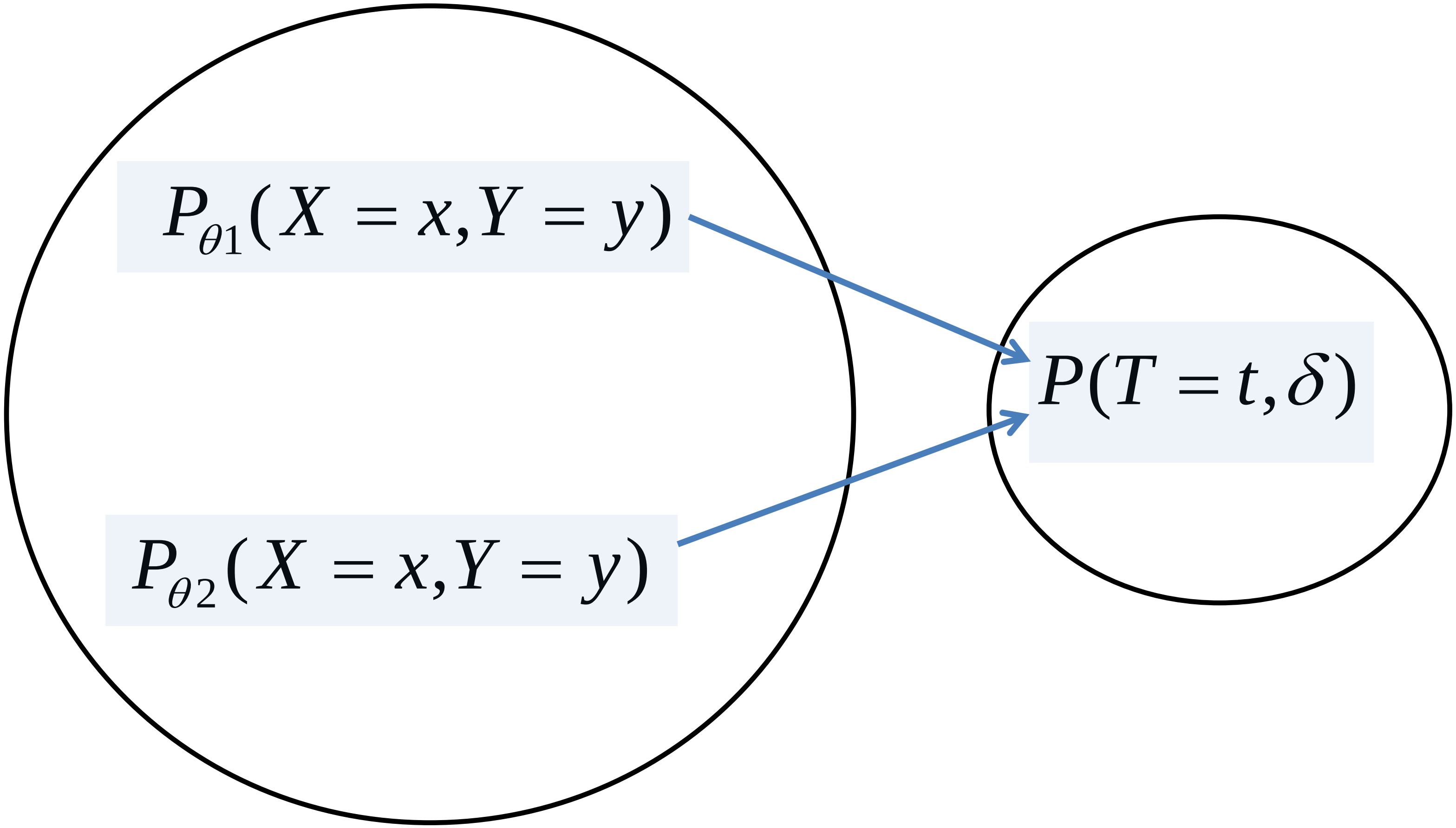
Marginal hazard functions

$$\begin{cases} \lambda_1(t) = \Pr(t \le X \le t + dt \mid X \ge t) / dt, \\ \lambda_2(t) = \Pr(t \le Y \le t + dt \mid Y \ge t) / dt, \end{cases}$$

*Marginal distributions are **non-identifiable** from observed quantities (T, δ) (Tsiatis 1975)

Non-identifiability

- Different models ➔ Same dist. for observations



- Sensitivity analysis (e.g., Chen 2010; Lo and Wilke 2010):
  - try several values of θ

To avoid nonidentifiability…

- Cause-specific hazard (Kalbfleish & Prentice 2002 Book)

$$\lambda_1^{CS}(t) = \Pr(t \le T < t + dt, \delta = 1 \mid T \ge t) / dt$$

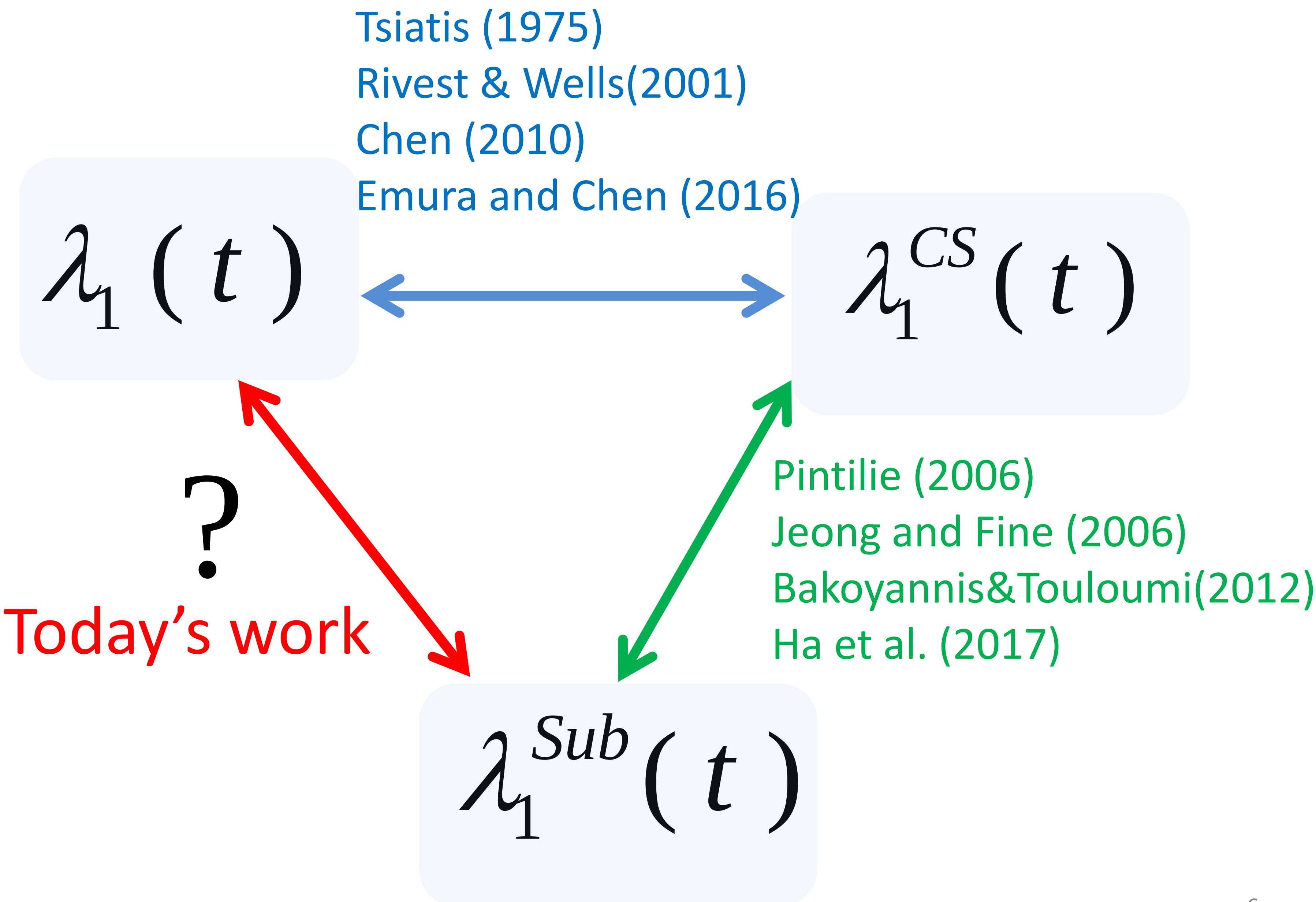
- Sub-distribution hazard (Fine & Gray 1999 JASA)

$$\lambda_1^{Sub}(t) = \Pr(t \le T < t + dt, \delta = 1 \mid \{T \ge t\} \cup \{T < t, \delta = 0\}) / dt$$

Problem:

How they are related to the marginal hazard ?

$$\lambda_1(t) = \Pr(t \le X \le t + dt \mid X \ge t) / dt$$


Tsiatis (1975)
Rivest & Wells(2001)
Chen (2010)
Emura and Chen (2016)
$\lambda_1(t)$
$\lambda_1^{CS}(t)$
?
Today's work
Pintilie (2006)
Jeong and Fine (2006)
Bakoyannis&Touloumi(2012)
Ha et al. (2017)
$\lambda_1^{Sub}(t)$

Example: Independent risks

$$X \perp Y$$

- Marginal hazard = Cause-specific hazard

$$\lambda_1(t) = \lambda_1^{CS}(t)$$

- Subhazard < Marginal hazard

$$\lambda_1^{Sub}(t) = \lambda_1(t) \frac{\exp\{-\Lambda_1(t) - \Lambda_2(t)\}}{1 - \int_0^t \lambda_1(s) \exp\{-\Lambda_1(s) - \Lambda_2(s)\} dx}$$

$$\lambda_1^{Sub}(t) = \frac{f_1^{Sub}(t)}{1 - F_1^{Sub}(t)} \leq \frac{f_1(t)}{S_1(t)} = \lambda_1(t)$$

3 goals of this paper

1. **Establish a mathematical relationship**:

   Marginal vs. Subhazard

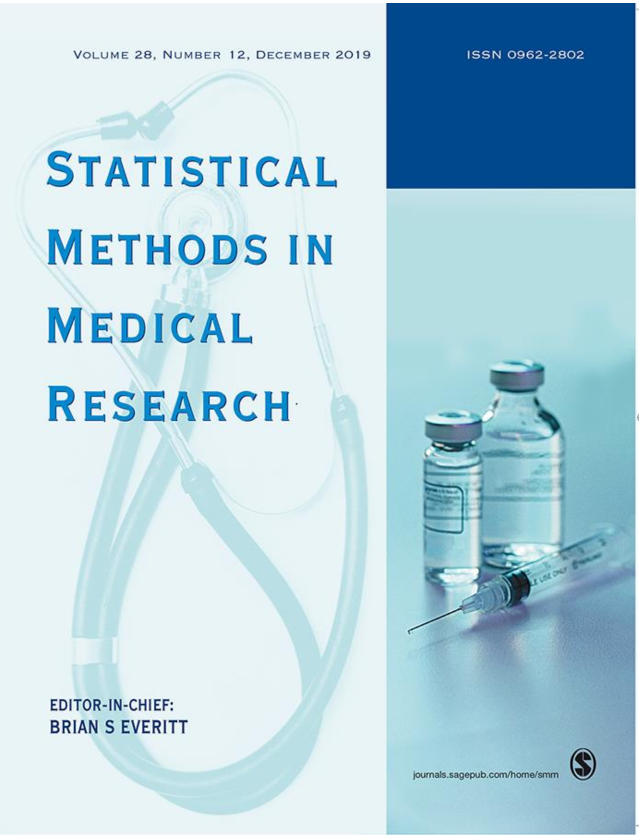
2. **Compare Cox-type models**

   Marginal vs. Subhazard

Comparative studies ***were*** not possible previously (non-indentifiability)

To appear within a few weeks…

Emura T, Shih JH, Ha ID, Wilke RA (2019) Comparison of the marginal hazard model and the sub-distribution hazard model for competing risks under an assumed copula,*



Survival copula model

$$\Pr(X > x, Y > y) = C_\theta\{ S_1(x), S_2(y) \}$$

The Clayton copula:

$$C_\theta(u, v) = (u^{-\theta} + v^{-\theta} - 1)^{-1/\theta}, \qquad \theta > 0,$$

The Gumbel copula:

$$C_\theta(u, v) = \exp\left[-\{ (-\log u)^{\theta+1} + (-\log v)^{\theta+1} \}^{\frac{1}{\theta+1}} \right], \qquad \theta \geq 0,$$

The Farlie-Gumbel-Morgenstern (FGM) copula:

$$C_\theta(u, v) = uv\{ 1 + \theta(1-u)(1-v) \}, \qquad -1 \leq \theta \leq 1.$$

Main results (1)

Theorem 1: *Under the model*

$$\Pr(X > x, Y > y) = C_\theta\{ S_1(x), S_2(y) \},$$

the marginal hazard and subhazard are connected through

$$\lambda_1^{Sub}(t) = \lambda_1(t) \frac{D_\theta^{[1,0]}\{ \Lambda_1(t), \Lambda_2(t) \}}{1 - \int_0^t \lambda_1(s) D_\theta^{[1,0]}\{ \Lambda_1(s), \Lambda_2(s) \} ds}.$$

where

$$D_\theta(s, t) = C_\theta\{ \exp(-s), \exp(-t) \}, \quad D_\theta^{[1,0]}(s, t) = -\frac{\partial}{\partial s} D_\theta(s, t)$$

Proof of Theorem 1

The sub-distribution function for Event 1 is

$$F_1^{Sub}(t) = \Pr(X \le t, Y \ge X) = \int_0^t -\frac{\partial}{\partial x}\Pr(X > x, Y \ge y)\Big|_{x=y} dy \,.$$

$$\Rightarrow F_1^{Sub}(t) = \int_0^t -\frac{\partial}{\partial x} D_\theta\{\Lambda_1(x), \Lambda_2(s)\}\Big|_{x=s} ds = \int_0^t \lambda_1(s) D_\theta^{[1,0]}\{\Lambda_1(s), \Lambda_2(s)\} ds.$$

$$\Rightarrow \lambda_1^{Sub}(t) = -d\log[1 - F_1^{Sub}(t)]/dt \,,$$

$$\Rightarrow \lambda_1^{Sub}(t) = \lambda_1(t)\frac{D_\theta^{[1,0]}\{\Lambda_1(t), \Lambda_2(t)\}}{1 - \int_0^t \lambda_1(s) D_\theta^{[1,0]}\{\Lambda_1(s), \Lambda_2(s)\} ds}$$

Example 1 (Clayton copula)

By Theorem 1,

$$\lambda_1^{Sub}(t) = \lambda(t)\frac{2\exp\{\theta\Lambda(t)\}[2\exp\{\theta\Lambda(t)\}-1]^{-1/\theta-1}}{1+[2\exp\{\theta\Lambda(t)\}-1]^{-1/\theta}}.$$

Under the Weibull model of $\Lambda(t) = \lambda t^{\nu}$,

$$\lambda_1^{Sub}(t) = \lambda\nu t^{\nu-1}\frac{2\exp(\lambda\theta t^{\nu})\{2\exp(\lambda\theta t^{\nu})-1\}^{-1/\theta-1}}{1+\{2\exp(\lambda\theta t^{\nu})-1\}^{-1/\theta}}.$$

Under the log-logistic (or Pareto type II) model of $\Lambda(t) = \gamma\log(1+\lambda t)$,

$$\lambda_1^{Sub}(t) = \frac{\gamma\lambda}{1+\lambda t}\frac{2(1+\lambda t)^{\theta\gamma}[2(1+\lambda t)^{\theta\gamma}-1\}^{-1/\theta-1}}{1+[2(1+\lambda t)^{\theta\gamma}-1\}^{-1/\theta}}.$$

Example: Clayton copula

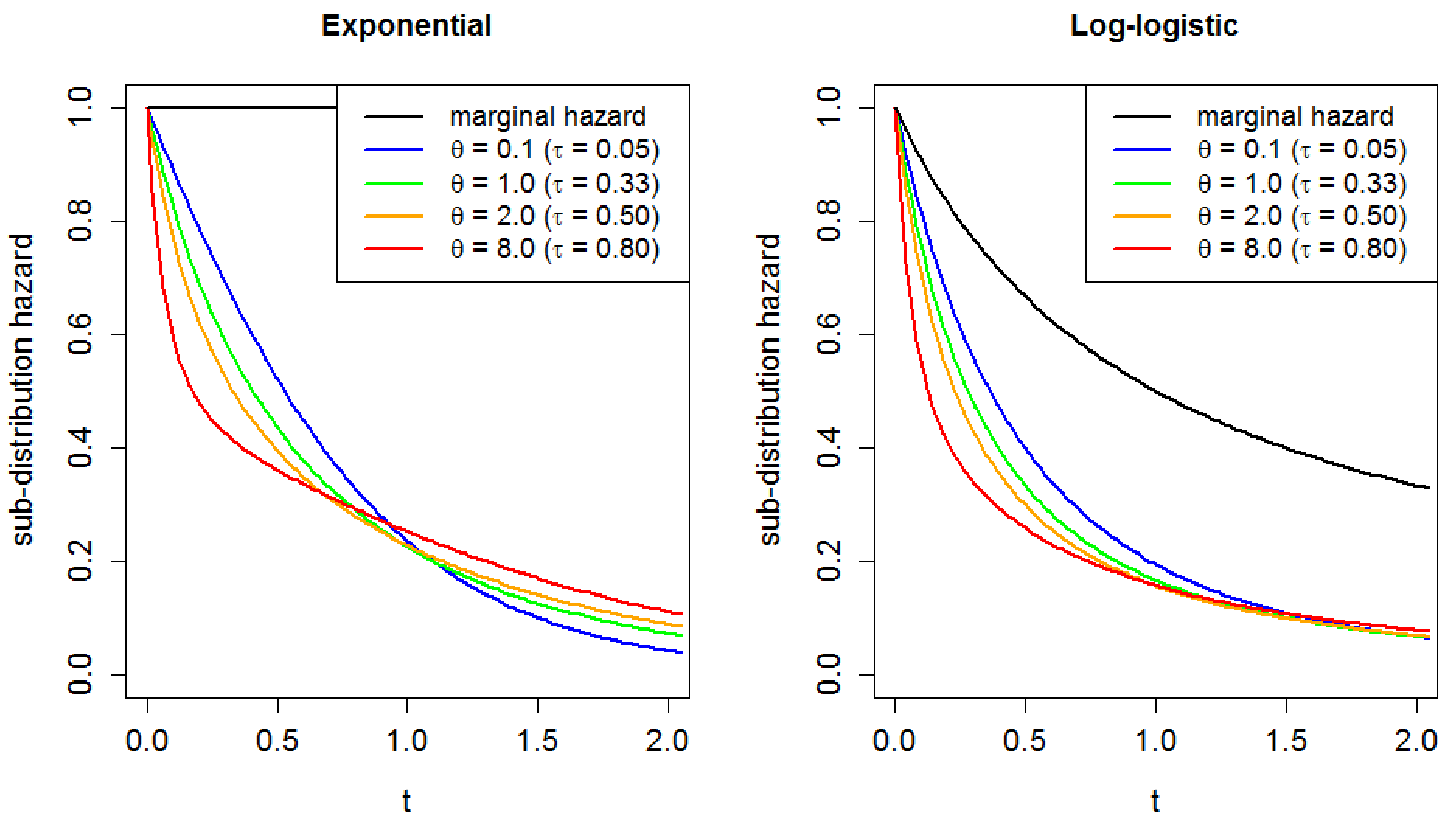


Figure 1. The marginal hazard and sub hazard under the Clayton copula.

The exponential model ($\nu = 1$) for the left, and log-logistic model ($\gamma = 1$) for the right.

Main results (2)

- When $\lambda_1^{Sub}(t) = \lambda_1(t)$ hold?

Theorem 2:

$$\lambda_1^{Sub}(t) = \lambda_1(t) \;\; \forall t \geq 0 \qquad \textit{if and only if} \qquad \Pr(X \leq Y) = 1$$

Y is never observed

- **Conclusion**: $\lambda_1^{Sub}(t) = \lambda_1(t)$ does not hold for any real competing risks model

Proof of Theorem 2

We first rewrite the condition $\lambda_1^{Sub}(t)=\lambda_1(t)\ \ \forall t\geq 0$ as $f_1^{Sub}(t)S_1(t)=f_1(t)\{1-F_1^{Sub}(t)\}\ \forall t\geq 0$.

The right-hand-side of this equation can be written as

$$
\begin{aligned}
f_1(t)\{1-F_1^{Sub}(t)\} &= f_1(t)\{\,S_1(t)+\Pr(\,X\leq t,\,X>Y\,)\}\\
&= f_1^{Sub}(t)S_1(t)+\{\,f_1(t)-f_1^{Sub}(t)\,\}S_1(t)+f_1(t)\Pr(\,X\leq t,\,X>Y\,).
\end{aligned}
$$

Hence, $\lambda_1^{Sub}(t)=\lambda_1(t)\ \ \forall t\geq 0$ is equivalent to

$$\{\,f_1(t)-f_1^{Sub}(t)\,\}S_1(t)+f_1(t)\Pr(\,X\leq t,\,X>Y\,)=0\quad \forall t. \tag{9}$$

Since $S_1(t)$ is non-increasing in t, $\exists t^*\in[0,\infty]$ such that $S_1(t)=0$ for $\forall t\geq t^*$. Note that $S_1(t)=0$ implies $f_1(t)=0$. Hence Equation (9) holds for $\forall t\geq t^*$. On the other hand, for $\forall t<t^*$, we have a positive value $S_1(t)>0$. Thus, a necessary condition for Equation (9) is $\{\,f_1(t)-f_1^{Sub}(t)\,\}=0\ \forall t<t^*$.

This is also a sufficient condition for Equation (9) since

$$\frac{d}{dt}\Pr(\,X\leq t,\,X>Y\,)=f_1(t)-f_1^{Sub}(t)=0\ \ \forall t<t^*\ \ \textit{iff}\ \ \Pr(\,X\leq t,\,X>Y\,)=0\ \ \forall t<t^*.$$

Hence, $\lambda_1^{Sub}(t)=\lambda_1(t)\ \ \forall t\geq 0$ is equivalent to $\Pr(\,X\leq t,\,X>Y\,)=0\ \ \forall t<t^*$. The proof complete since

$$\Pr(\,X\leq t,\,X>Y\,)=0\ \ \forall t<t^*\quad \textit{iff}\quad \Pr(\,X>Y\,)=0\quad \textit{iff}\quad \Pr(\,X\leq Y\,)=1. \quad \square$$

Example of Theorem 2

$\lambda_1^{Sub}(t) = \lambda_1(t)$ hold if

(i) Fréchet-Hoeffding upper bound copula

$$\Pr(X > x, Y > y) = C_{\infty}\{S_1(x), S_2(y)\}$$
$$= \min\{S_1(x), S_2(y)\}$$

(ii) Stochastic ordering:

$$S_1(t) < S_2(t) \ \forall t \geq 0$$

↑ *Y* is never observed

By Theorem 2, $\Pr(X \leq Y) = 1$

How covariates affect hazards ?

Assume a marginal Cox model for Cause 1:

$$\lambda_1(t \mid \mathbf{Z}) = \lambda_{10}(t)\exp(\boldsymbol{\beta}_1'\mathbf{Z})$$

By Theorem 1,

$$\lambda_1^{Sub}(t \mid \mathbf{Z}) = \lambda_{10}(t)\exp(\boldsymbol{\beta}_1'\mathbf{Z})\frac{D_\theta^{[1,0]}\{\Lambda_{10}(t)\exp(\boldsymbol{\beta}_1'\mathbf{Z}), \Lambda_2(t)\}}{1-\int_0^t \lambda_{10}(s)\exp(\boldsymbol{\beta}_1'\mathbf{Z})D_\theta^{[1,0]}\{\Lambda_{10}(s)\exp(\boldsymbol{\beta}_1'\mathbf{Z}), \Lambda_2(s)\}ds}$$

A non-proportional sub-distribution hazard in **Z**

⇨ The proportional sub-distribution model (Fine and Gray 1999)

$$\lambda_1^{Sub}(t \mid \mathbf{Z}) = \lambda_{10}^{Sub}(t)\exp(\boldsymbol{\beta}_1^{Sub}\mathbf{Z})$$ does not hold !.

Indirect influence of covariates

The case of $\boldsymbol{\beta}_1 = \mathbf{0}$; i.e., no marginal effect on Event 1.

$$\rightarrow \quad \lambda_1^{Sub}(t\,|\,\mathbf{Z}) = \lambda_{10}(t)\frac{D_\theta^{[1,0]}\{\Lambda_{10}(t), \Lambda_2(t\,|\,\mathbf{Z})\}}{1-\int_0^t \lambda_{10}(s) D_\theta^{[1,0]}\{\Lambda_{10}(s), \Lambda_2(s\,|\,\mathbf{Z})\}ds}.$$

“Indirect influence” of covariates on Even 1

Possibility of

“Non-sinificant for marginal, but significant for subhazard”

Statistical Inference

- X_i : time to Event 1
- Y_j : time to Event 2
- C_j : independent censoring time
- $\mathbf{Z}_j$: covariates

Observed data: $(T_j, \delta_{1j}, \delta_{2j}, \mathbf{Z}_j)$, $j = 1, 2, ..., n$.

$$T_j = \min(X_j, Y_j, C_j), \quad \delta_{1j} = \mathbf{I}(T_j = X_j), \quad \delta_{2j} = \mathbf{I}(T_j = Y_j)$$

Semiparametric Regression

The Cox model on the sub hazards (Fine and Gray 1999)

$$\lambda_{1j}^{Sub}(t \mid \mathbf{Z}_j) = \lambda_{10}^{Sub}(t)\exp(\,\boldsymbol{\beta}_1^{Sub}\mathbf{Z}_j\,)$$

$\hat{\boldsymbol{\beta}}_1^{Sub}$ = the *cmprsk* R package (Gray 2014)

The Cox model on the marginal hazards (Chen 2010)

$$\lambda_{1j}(t \mid \mathbf{Z}_j) = \lambda_{10}(t)\exp(\,\boldsymbol{\beta}_1'\mathbf{Z}_j\,), \qquad \lambda_{2j}(t \mid \mathbf{Z}_j) = \lambda_{20}(t)\exp(\,\boldsymbol{\beta}_2'\mathbf{Z}_j\,).$$

$$\Pr(\,X_j > x\,, Y_j > y \mid \mathbf{Z}_j\,) = C_\theta[\,\exp\{-\Lambda_{1j}(x \mid \mathbf{Z}_j)\},\exp\{-\Lambda_{2j}(y \mid \mathbf{Z}_j)\}\,],$$

$(\hat{\boldsymbol{\beta}}_1, \hat{\boldsymbol{\beta}}_2, \hat{\Lambda}_{10}, \hat{\Lambda}_{20})$ = a semi-parametric MLE (Chen 2010).

θ must be pre-specified (assumed) to avoid nonidentifiability

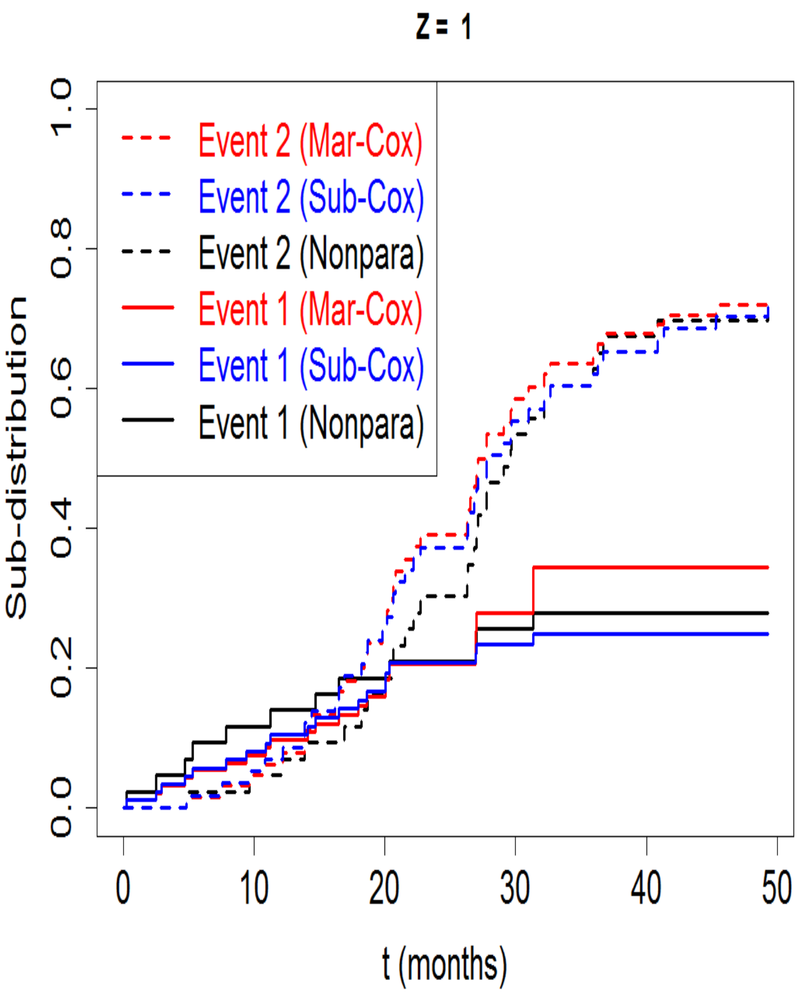
Graphical model diagnostic tools

Estimate under marginal Cox model

Sub-distribution function:

$$F_1^{Sub}(t \mid \mathbf{Z}) = \Pr(T \le t, \delta = 1 \mid \mathbf{Z})$$

Estimate under Subhazard Cox model



Estimators of $F_1^{Sub}(t \mid \mathbf{Z}) = \Pr(T \le t, \delta = 1 \mid \mathbf{Z})$

- *Under the marginal Cox model* (New estimator)

$$F_{1,\hat{\xi}}^{Sub}(t \mid \mathbf{Z}) = \sum_{j: T_j \le t} \delta_{1j} \hat{\lambda}_1(T_j \mid \mathbf{Z}) D_{\theta}^{[1,0]}\{\hat{\Lambda}_1(T_j \mid \mathbf{Z}), \hat{\Lambda}_2(T_j \mid \mathbf{Z})\},$$

- *Under the subhazard Cox model*

$$\hat{F}_1^{Sub}(t \mid \mathbf{Z}) = 1 - \exp[-\hat{\Lambda}_1^{Sub}(t \mid \mathbf{Z})], \qquad \hat{\Lambda}_1^{Sub}(t \mid \mathbf{Z}) = \hat{\Lambda}_{10}^{Sub}(t)\exp(\hat{\boldsymbol{\beta}}_1^{Sub}\mathbf{Z}).$$

- *The nonparametric (model-free) estimator*

$$\hat{F}_1^{NP}(t \mid \mathbf{Z}) = \sum_{j: T_j \le t, \mathbf{Z}_j = \mathbf{Z}} \hat{S}(T_j \mid \mathbf{Z}) \frac{\delta_{1j}}{n_{j,\mathbf{Z}}},$$

where $\hat{S}(t \mid \mathbf{Z}) = \prod_{j: T_j \le t, \mathbf{Z}_j = \mathbf{Z}} \{1 - (\delta_{1j} + \delta_{2j}) / n_{j,\mathbf{Z}}\}$ and $n_{j,\mathbf{Z}} = \sum_{i: \mathbf{Z}_i = \mathbf{Z}} \mathbf{I}(T_i \ge T_j)$.

Choice of copula parameter θ

- Cramér-von Mises (CvM) distance:

$$\mathrm{CvM} = \sum_{\mathbf{Z} \in I} \left[\sum_{k=1}^{2} \frac{1}{n_{k,\mathbf{Z}}^{\delta}} \sum_{j:\mathbf{Z}_j = \mathbf{Z}} \delta_{kj} \{ F_{k,\hat{\xi}}^{Sub}(T_j \mid \mathbf{Z}) - \hat{F}_k^{NP}(T_j \mid \mathbf{Z}) \}^2 \right]$$

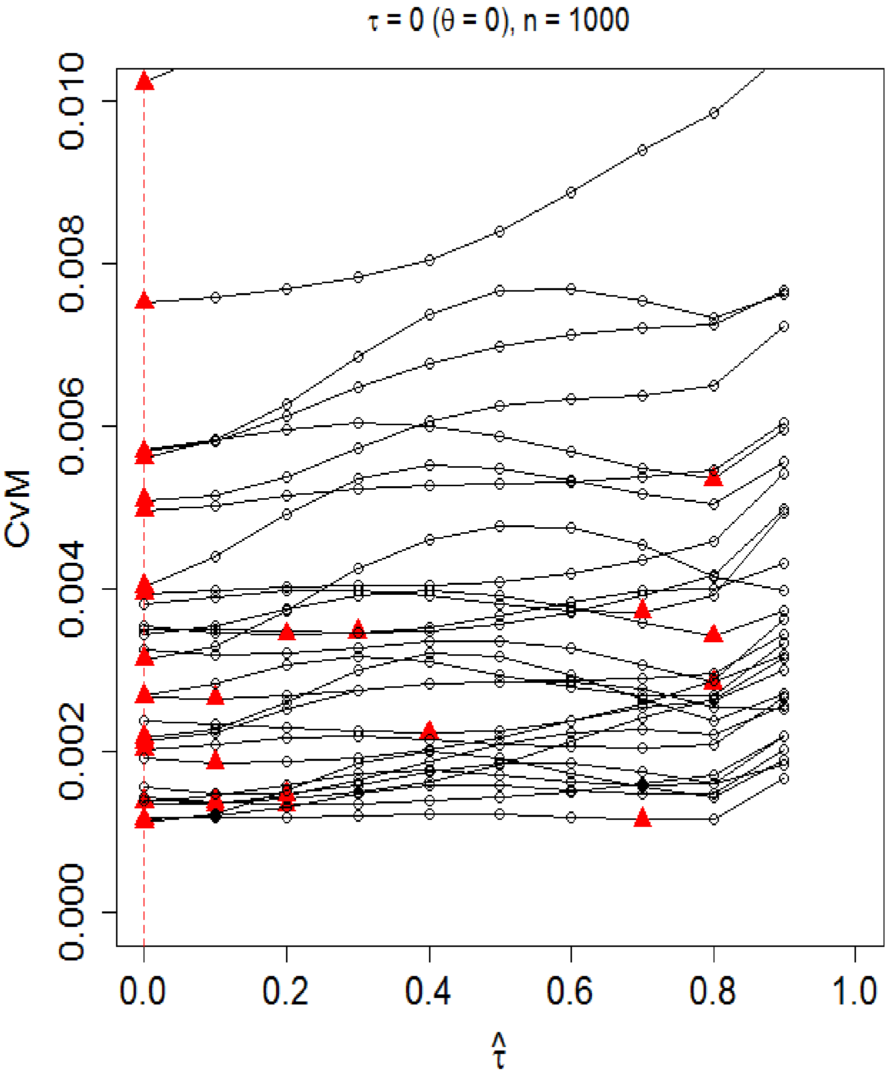
Estimator under marginal Cox model

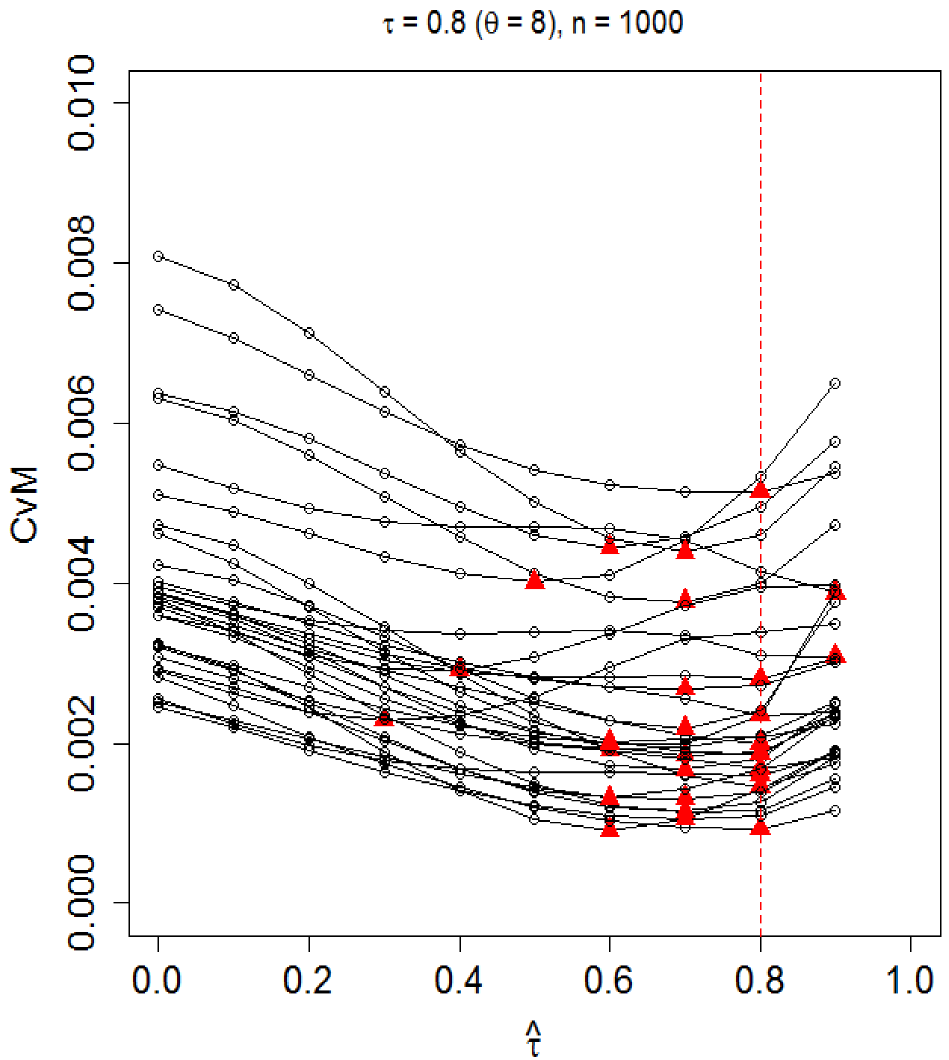
Nonparametric Estimator

- **Proposed estimator**: $\hat{\theta} = \arg\min_{\theta} \mathrm{CvM}$

  Very weakly consistent

Simulations for $\hat{\theta} = \arg\min_{\theta} \mathrm{CvM}$





Data: 125 lung cancer patients (Chen et al 2007)

- X_i = time-to-death (Cause 1)
- Y_j = time-to-dropout (Cause 2)
- Covariate = gene expression of *ZNF264*

The sub hazard model for Cause 1 (death)

$$\lambda_{1j}^{Sub}(t) = \lambda_{10}^{Sub}(t)\exp(\beta_1^{Sub} \times ZNF264_j),$$

The sub hazard model for Cause 2 (dropout)

$$\lambda_{2j}^{Sub}(t) = \lambda_{20}^{Sub}(t)\exp(\beta_2^{Sub} \times ZNF264_j).$$

Fitted by *cmprsk* (Gray 2017)

The Cox model on the marginal hazards for Cause 1 and Cause 2 are specified as

$$\begin{cases} \lambda_{1j}(t) = \lambda_{10}(t)\exp(\beta_1 \times ZNF264_j) \\ \lambda_{2j}(t) = \lambda_{20}(t)\exp(\beta_2 \times ZNF264_j) \\ \Pr(X_j > x, Y_j > y) = [\exp\{\theta\Lambda_{1j}(x)\} + \exp\{\theta\Lambda_{2j}(y)\} - 1]^{-1/\theta} \end{cases}$$

where we specified $\theta = 0$, 0.5, 2, or 8 ($\tau = 0$, 0.2, 0.5, or 0.8)

Fitted by *compound.Cox* (Emura et al. 2019)

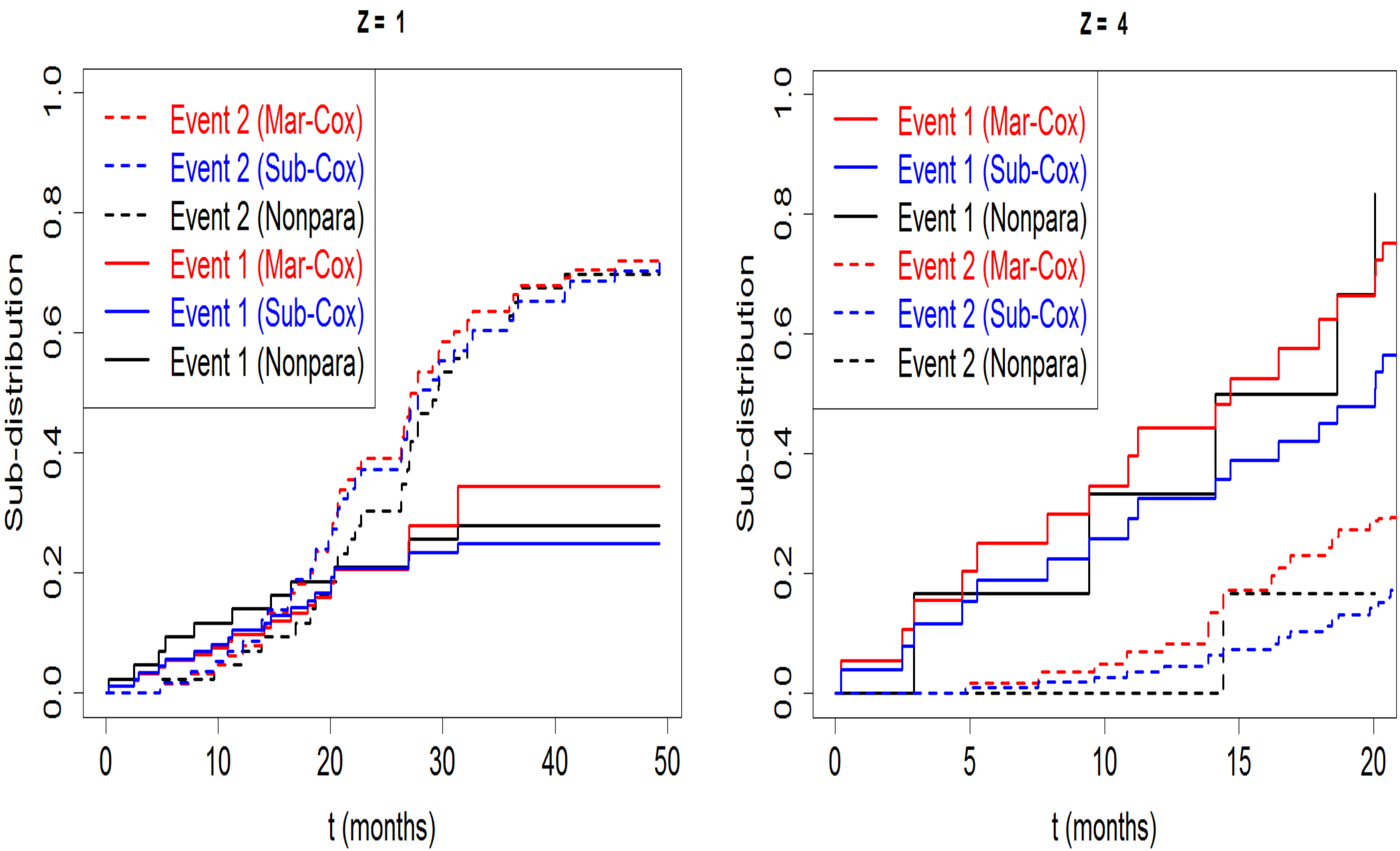
Table 1. Regression coefficients obtained by fitting the lung cancer data.

Model	Event 1 (death) $\hat{\beta}_1$ (95%CI)	Event 2 (censoring) $\hat{\beta}_2$ (95%CI)
Subhazard	0.425 (0.044, 0.807)	-0.222 (-0.586, 0.143)
Marginal ($\theta = 0.00$; $\tau = 0.0$)	0.548 (0.144, 0.952)	0.259 (-0.176, 0.694)
Marginal ($\theta = 0.22$; $\tau = 0.1$)	0.560 (0.154, 0.965)	0.272 (-0.158, 0.702)
Marginal ($\theta = 0.50$; $\tau = 0.2$)	0.570 (0.162, 0.979)	0.280 (-0.143, 0.704)
Marginal ($\theta = 0.86$; $\tau = 0.3$)	0.578 (0.169, 0.988)	0.290 (-0.129, 0.710)
Marginal ($\theta = 1.33$; $\tau = 0.4$)	0.585 (0.178, 0.991)	0.311 (-0.103, 0.725)
Marginal ($\theta = 2.00$; $\tau = 0.5$)	0.593 (0.198, 0.987)	0.349 (-0.051, 0.749)
Marginal ($\theta = 3.00$; $\tau = 0.6$)	0.599 (0.229, 0.969)	0.394 (0.026, 0.762)
Marginal ($\theta = 4.67$; $\tau = 0.7$)	0.591 (0.251, 0.932)	0.432 (0.101, 0.762)
Marginal ($\theta = 8.00$; $\tau = 0.8$)	0.561 (0.251, 0.872)	0.453 (0.156, 0.751)
Marginal ($\theta = 18.0$; $\tau = 0.9$)	0.508 (0.227, 0.788)	0.455 (0.187, 0.723)

Chosen by CvM

Fitted by compound.Cox (Emur

Model diagnostic : lung cancer data



Conclusions from data analysis

- Marginal and subhazard models **fit equally well**
- Regression **coefficients are different**

  (estimating different quantities)

$$\hat{\beta}_2 = 0.454 \qquad \hat{\beta}_2^{Sub} = -0.222$$

- CvM is smaller for the marginal model

  (but cannot be used for model selection)

Conclusions

- **Establish a mathematical relationship between sub-hazard and marginal hazard**
  (key: an assumed copula)
- **Two Cox models (sub-hazard & marginal hazard)**
  - The fitted values of β's are not similar
  - The interpretation of β's are qualitatively different
  - Non-significant for marginal, but significant for subhazard
- **Selection of θ is a concern in marginal hazard model**
  - CvM distance method (discrete covariate)
  - a sensitivity analysis (clustered data)

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