CSA-KSS-JSS Special Invited Sessions

2014 / 12 / 6

A joint frailty-copula model between disease progression and death for meta-analysis

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Part I (Review)

- Meta-analysis
- Survival analysis
- Joint model & motivating example

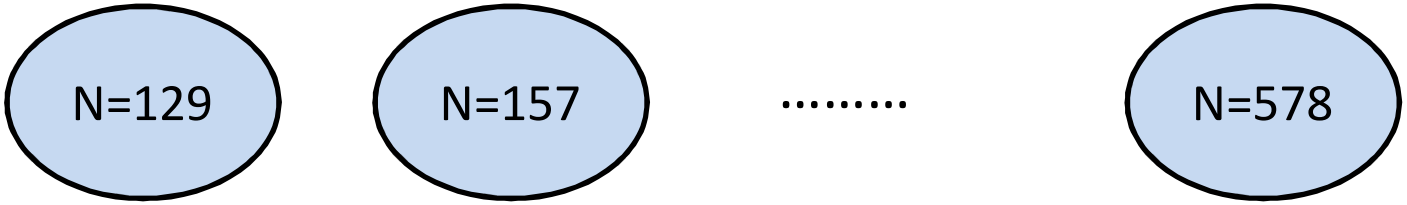
Part II (Proposed)

- Proposed method -- Copula approach
- Simulation
- Data analysis:

  -- Meta-analysis of ovarian cancer data

Meta-Analysis

- Synthesize multiple independent studies



- Useful to detect small (but consistent) effect
  - Treatment effect of chemotherapy on survival in head & neck cancer (Pignon et al. 2009)
  - The effect of CXCL12 gene on survival in ovarian cancer (Ganzfried et al. 2013)
  - The effect of ECRG 4 gene on survival in breast cancer (Sabatier et al. 2011)

Choice of endpoints

- Time-to-progression (TTP)

  (e.g., recurrence, metastasis)
- Death (OS)

  (Death from any cause)

} Two events of interest

- **Progression-free survival [PFS = min(TTP, OS)]**

Meta-analysis on event times

1) Head & neck cancer data (Pignon et al., 2000; 2009)

➔ Fit *separate* Cox models on PSF and OS, respectively

2) Ovarian cancer data (Ganzfried et al. 2013)

➔ Fit a Cox model on OS

3) Breast cancer data (Sabatier et al. 2011)

➔ Fit *separate* Cox models on PFS and OS, respectively

- Joint model = a bivariate model for TTP and OS

Time-to-progression (TTP)
Death (OS)
} Bivariate survival models (Large literature)

In meta-analysis:

➔Study specific (random) effect to explain the heterogeneity

i) Bivariate survival analysis (Burzykowski et al. 2001) :
(TTP, OS) is jointly observed

ii) Semi-competing risks analysis (Rondeau et al. 2011) :
TTP can be dependently censored by OS
: TTP is observed if TTP < OS

- Combining heterogeneous studies

  using unobserved random effect (called frailty)

$$u_i \sim f_\eta(u) = \frac{1}{\Gamma(1/\eta)\eta^{1/\eta}} u^{\frac{1}{\eta}-1} \exp\left(-\frac{u}{\eta}\right)$$

- Data structure:

G independent studies ($i = 1, 2, ..., G$)

each study contain N_i subjects ($j = 1, 2, ..., N_i$)

Share the same u_i

Data structure

$X_{ij} = \text{TTP}\ (\text{Recurrence},\ \text{Relapse},\ \text{etc.}\ )$

$D_{ij} = \text{OS}\ (\text{Death}\ \text{from}\ \text{any}\ \text{cause}\ )$

$C_{ij} = \text{Administrative}\ \text{censoring}\ (\text{e.g., study end})$

Joint frailty model (Rondeau et al., 2011)

$$\begin{cases} r_{ij}(t \mid u_i) = u_i r_0(t) \exp(\boldsymbol{\beta}_1' \mathbf{Z}_{ij}) & (\ \text{hazard for}\ \ X_{ij}\ ) \\ \lambda_{ij}(t \mid u_i) = u_i^{\alpha} \lambda_0(t) \exp(\boldsymbol{\beta}_2' \mathbf{Z}_{ij}) & (\ \text{hazard for}\ \ D_{ij}\ ) \end{cases}$$

$u_i = \text{Study}\ \text{specific}\ \text{random}\ \text{effect}\ (\text{frailty})$

$\boldsymbol{\beta}_1' = \text{Effect}\ \text{on}\ \text{time-to-progression}\ X_{ij}$

$\boldsymbol{\beta}_1' = \text{Effect}\ \text{on}\ \text{time-to-death}\ D_{ij}$

Data structure

$X_{ij} = \text{TTP}\ (\text{Recurrence},\ \text{Relapse},\ \text{etc.}\ )$

$D_{ij} = \text{OS}\,(\text{Death from any cause}\ )$

$C_{ij} = \text{Administrative censoring}\ (\text{e.g., study end}\ )$

Observation :

$(T_{ij}, T_{ij}^*, \delta_{ij}, \delta_{ij}^*, \mathbf{Z}_{ij}), \quad i = 1, 2, ..., G, \quad j = 1, 2, ..., N_i$

Semi-competing risks setting :

* First occuring event time

Indicator of progression

$$T_{ij} = \min(X_{ij}, D_{ij}, C_{ij}), \qquad \delta_{ij} = \mathbf{I}(T_{ij} = X_{ij})$$

* Terminal event time

Indicator of death

$$T_{ij}^* = \min(D_{ij}, C_{ij}), \qquad \delta_{ij}^* = \mathbf{I}(T_{ij}^* = D_{ij})$$

Data structure

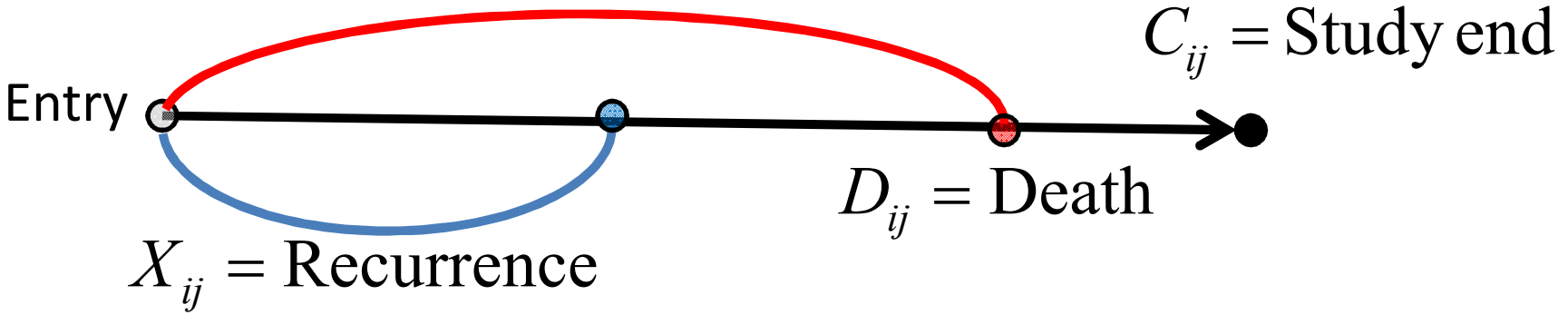


Fig. Case of $\delta_{ij} = 1, \quad \delta_{ij}^* = 1$

* First occuring event time :

$$T_{ij} = \min(X_{ij}, D_{ij}, C_{ij}) = X_{ij}$$

$$\delta_{ij} = \mathbf{I}(T_{ij} = X_{ij}) = 1$$

* Terminal event time :

$$T_{ij}^* = \min(D_{ij}, C_{ij}) = D_{ij}$$

$$\delta_{ij}^* = \mathbf{I}(T_{ij}^* = D_{ij}) = 1$$

Meta-analysis for ovarian cancer

Table 2. Data sets in the $G = 4$ independent studies of ovarian cancer from Ganzfried et al. (2013).

Data set (GEO accession number)	Sample size	The number of observed events		
		Relapse $\delta_{ij} = 1$	Death $\delta_{ij}^* = 1$	Censoring $\delta_{ij}^* = 0$
GSE17260	$N_1 = 110$	76	46	64
GSE30161	$N_2 = 58$	48	36	22
GSE9891	$N_3 = 278$	185	113	165
TCGA	$N_4 = 557$	266	290	267
Total	$\sum_{i=1}^{4} N_i = 1003$	575	485	314

4 patterns of event process

- Relapse → Death (before censoring)
- Relapse → Censoring (without die)
- Death (without relapse, before censoring)
- Censoring (neither relapse nor death)

Table 1. Four mutually exclusive cases.

First occurring event	T_{ij}	T_{ij}^*	δ_{ij}	δ_{ij}^*	Likelihood contribution
Progression	X_{ij}	D_{ij}	1	1	$\Pr(X_{ij} = T_{ij}, D_{ij} = T_{ij}^* \mid u_i)$
Progression	X_{ij}	C_{ij}	1	0	$\Pr(X_{ij} = T_{ij}, D_{ij} > T_{ij}^* \mid u_i)$
Death	D_{ij}	D_{ij}	0	1	$\Pr(X_{ij} > T_{ij}, D_{ij} = T_{ij}^* \mid u_i)$
Censoring	C_{ij}	C_{ij}	0	0	$\Pr(X_{ij} > T_{ij}, D_{ij} > T_{ij}^* \mid u_i)$

log-likelihood of Rondeau et al. (2011):

$$\ell(\alpha, \eta, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2, r_0, \lambda_0)$$

$$= \sum_{i=1}^{G} \left[\sum_{j=1}^{N_i} \{ \delta_{ij} \log r_{ij}(T_{ij}) + \delta_{ij}^* \log \lambda_{ij}(T_{ij}^*) \} \right.$$

$$\left. + \log \int_0^\infty \left\{ u_i^{m_i + \alpha m_i^*} \exp\left(-u_i \sum_{j=1}^{N_i} R_{ij}(T_{ij}) - u_i^\alpha \sum_{j=1}^{N_i} \Lambda_{ij}(T_{ij}^*) \right) \right\} f_\eta(u_i) du_i \right],$$

where $m_i = \sum_{j=1}^{N_i} \delta_{ij}$ and $m_i^* = \sum_{j=1}^{N_i} \delta_{ij}^*$.

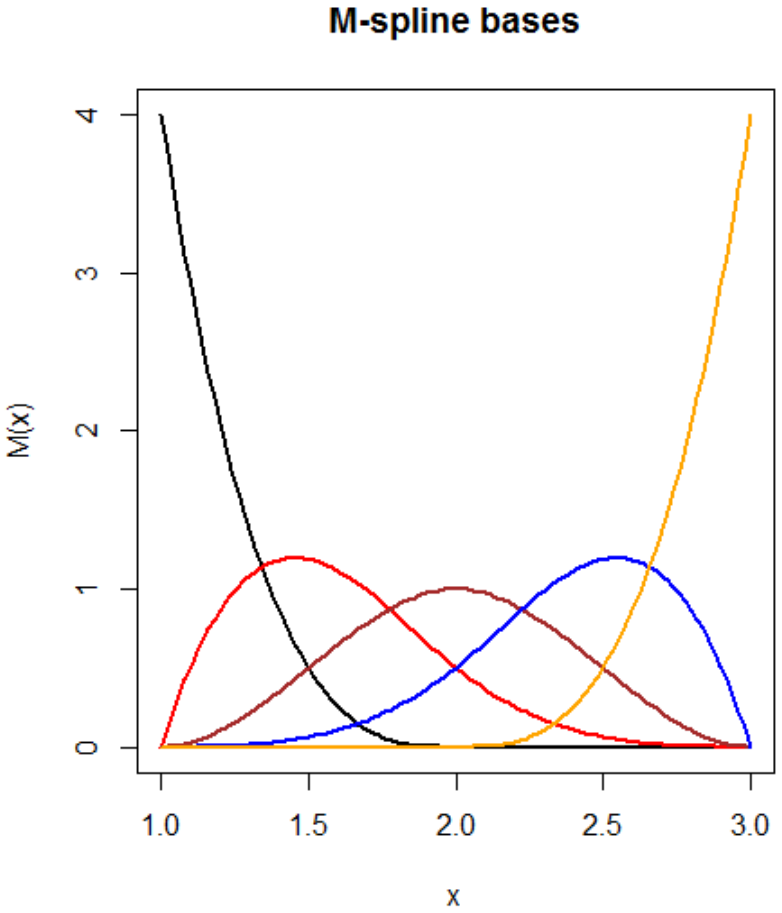
- Nonparametric hazard approximation via **Cubic M-Spline** (O' Sullivan 1988; Joly, Commenges and Letenneur 1998)

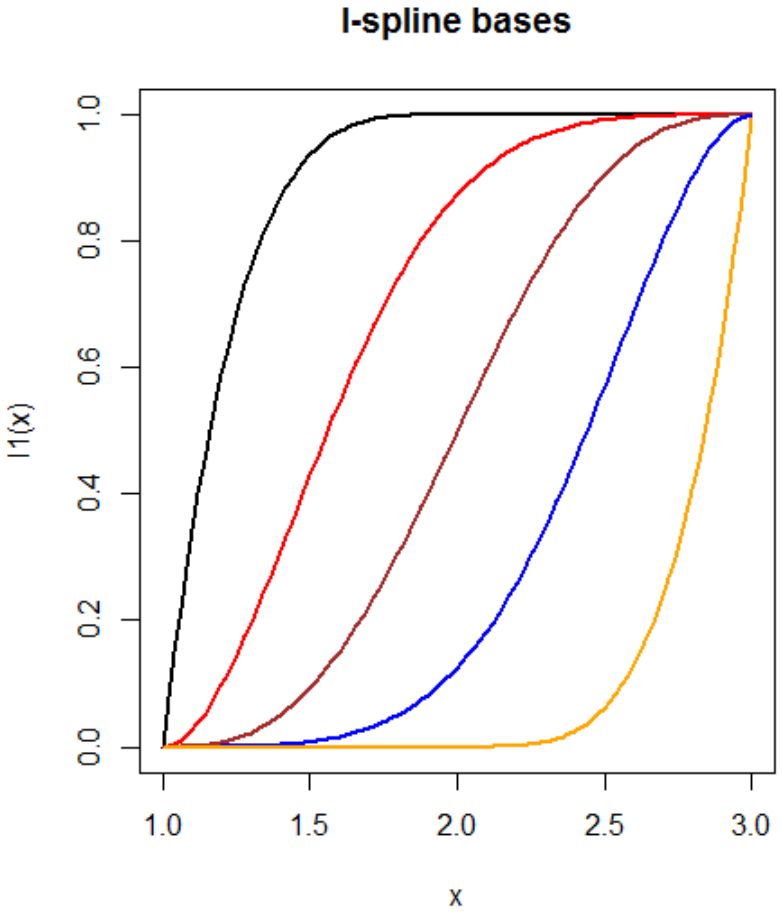
$$r_0(t) = \sum_{\ell=1}^{L_r} g_\ell M_\ell(t), \qquad \lambda_0(t) = \sum_{\ell=1}^{L_\lambda} h_\ell M_\ell(t)$$

Cubic M-spline bases:

Equally spaced knots $\xi_1 = 1, \quad \xi_2 = 2, \quad \xi_3 = 3$

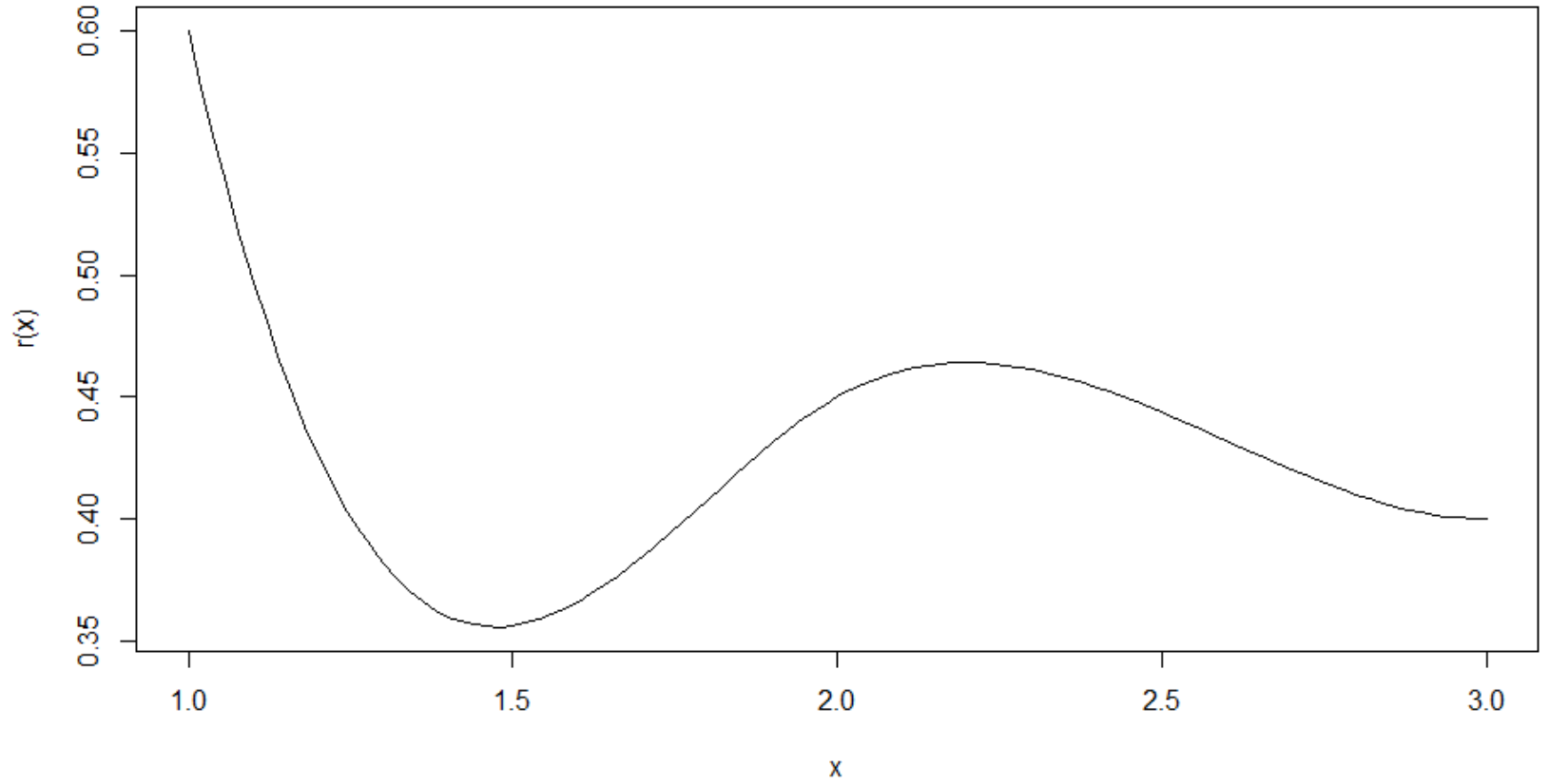
➔ **5 bases** : $M_1(t), M_2(t), M_3(t), M_4(t), M_5(t)$





Baseline hazard via cubic M-spline:

$$r_0(x) = 0.15 \times M_1(t) + 1 \times M_2(t) + 0.3 \times M_3(t) + 0.2 \times M_4(t) + 0.1 \times M_5(t)$$



Part II: Proposed Methods

- We generalize the approach of Rondeau (2011) to account for the intra-subject dependence between TTP and OS

- Copula (Nelsen 2006) is used as a modeling tool (a flexible model for dependence)

Proposed Idea

$$X_{ij} = \text{TTP}\ (\text{Recurrence},\ \text{Relapse},\ \text{etc.}\ )$$

$$D_{ij} = \text{OS}\ (\text{Death}\ \ \text{from}\ \ \text{any}\ \ \text{cause}\ )$$

Joint frailty model (Rondeau et al., 2011)

$$\begin{cases} r_{ij}(t \mid u_i) = u_i r_0(t) \exp(\boldsymbol{\beta}_1' \mathbf{Z}_{ij}) & (\ \text{time-to-progression}\ \ X_{ij}\ ) \\ \lambda_{ij}(t \mid u_i) = u_i^{\alpha} \lambda_0(t) \exp(\boldsymbol{\beta}_2' \mathbf{Z}_{ij}) & (\ \text{time-to-death}\ \ D_{ij}\ ) \end{cases}$$

- Still Independent censoring within a cluster

$$X_{ij} \perp D_{ij} \mid u_i$$

➔ **Our proposed idea:**
Relax this intra-cluster independence assumption via Copulas

Copula approach (Proposed)

- A Copula

$$C:\ [0,1]\times[0,1]\mapsto[0,1]$$

uniquely characterizes the dependence between two continuous random variables (Sklar's Theorem 1959):

Example 1: Independence copula: $C[v, w] = vw$

Example 2: Clayton copula (Clayton, 1978)

$$C_\theta(v,w) = (v^{-\theta} + w^{-\theta} - 1)^{-1/\theta}, \quad \begin{cases} \theta = 0 & \text{independence} \\ \theta > 0 & \text{positively dependece} \end{cases}$$

Joint frailty-copula model (Proposed)

Frailty model (Rondeau et al., 2011)

$$\begin{cases} r_{ij}(t \mid u_i) = u_i r_0(t) \exp(\boldsymbol{\beta}_1' \mathbf{Z}_{ij}) & (\text{ time - to - progression } X_{ij}) \\ \lambda_{ij}(t \mid u_i) = u_i^{\alpha} \lambda_0(t) \exp(\boldsymbol{\beta}_2' \mathbf{Z}_{ij}) & (\text{ time - to - death } D_{ij}) \end{cases}$$

+

Copula model:

$$\Pr(X_{ij} > x, D_{ij} > y \mid u_i) = C_\theta[\exp\{-R_{ij}(x \mid u_i)\}, \exp\{-\Lambda_{ij}(y \mid u_i)\}]$$

where C_θ is a copula (Nelsen, 2006), and

$$R_{ij}(x \mid u_i) = \int_0^x r_{ij}(v \mid u_i) dv, \qquad \Lambda_{ij}(y \mid u_i) = \int_0^y \lambda_{ij}(v \mid u_i) dv$$

Dependence parameter

Copula parameter θ

➔ Related to intra-class Kendall's tau

$$\tau_\theta(X_{ij}, D_{ij} \mid u_i)$$

e.g., Clayton copula:

$$\tau(X_{ij}, D_{ij} \mid u_i) = \theta/(\theta + 2)$$

Why such an elaborate copula model is necessary?

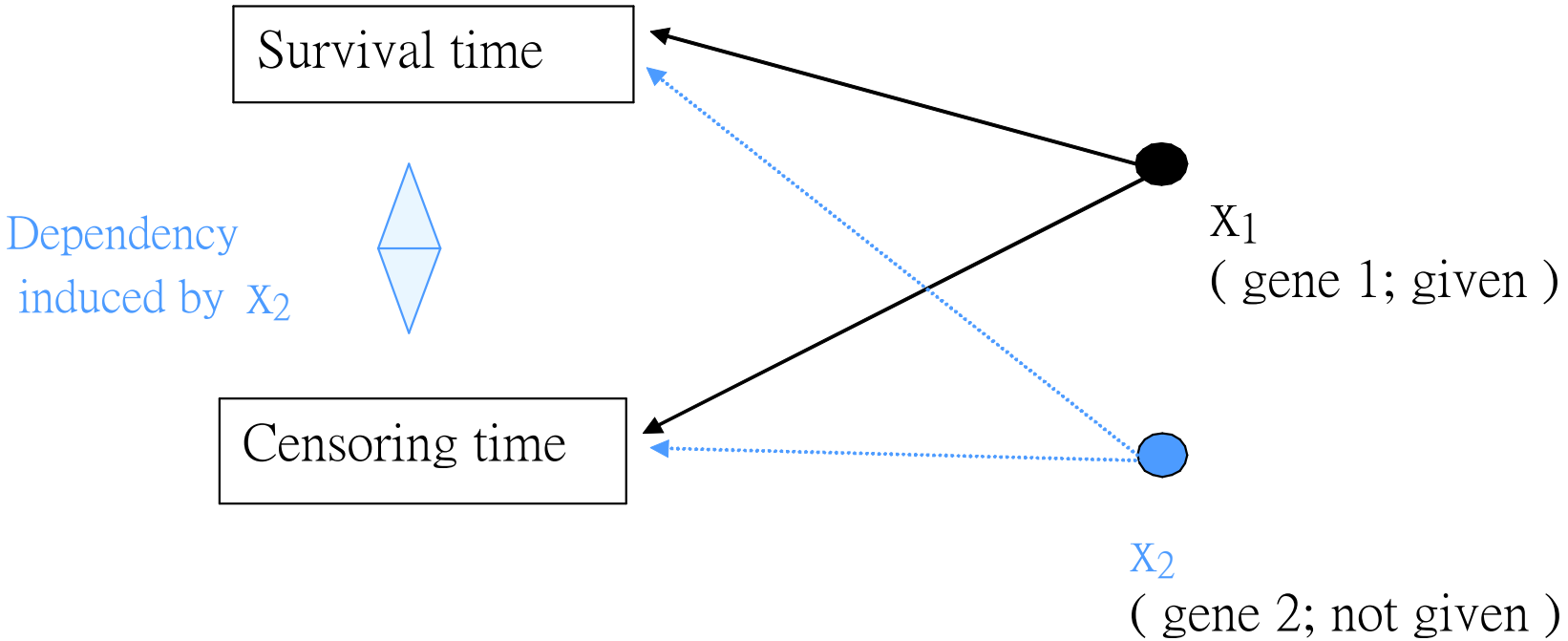
- Death immediately after progression.

  ➔ Strong dependence between TTP and OS (Kendall's tau > 0.5)

- Only a few covariates consistently measured across studies in meta-analysis

  ➔ Residual dependence between TTP and OS (unadjusted by covariates)

How independent censoring violate?



(Figure, Emura and Chen, 2014 SMMR)

- Survival (TTP) and censoring (OS) times usually cannot be conditionally independent given only x_1 regarding x_2 as unobserved covariate

The data observed

$(T_{ij} , T_{ij}^{*}, \delta_{ij} , \delta_{ij}^{*})$ for

$i = 1, 2, ..., G$ and $j = 1, 2, ..., N_i$.

First occurring event	T_{ij}	T_{ij}^{*}	δ_{ij}	δ_{ij}^{*}	Likelihood contribution
Progression	X_{ij}	D_{ij}	1	1	$\Pr(X_{ij} = T_{ij}, D_{ij} = T_{ij}^{*} \mid u_i)$
Progression	X_{ij}	C_{ij}	1	0	$\Pr(X_{ij} = T_{ij}, D_{ij} > T_{ij}^{*} \mid u_i)$
Death	D_{ij}	D_{ij}	0	1	$\Pr(X_{ij} > T_{ij}, D_{ij} = T_{ij}^{*} \mid u_i)$
Censoring	C_{ij}	C_{ij}	0	0	$\Pr(X_{ij} > T_{ij}, D_{ij} > T_{ij}^{*} \mid u_i)$

Log-likelihood (proposed)

$$\ell(\alpha, \eta, \theta, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2, r_0, \lambda_0)$$

$$= \sum_{i=1}^{G} \Bigg[\sum_{j=1}^{N_i} \{ \delta_{ij} \log r_{ij}(T_{ij}) + \delta_{ij}^* \log \lambda_{ij}(T_{ij}^*) \}$$

Intra-class dependence structure

$$+ \log \int_0^{\infty} \Bigg\{ \prod_{j=1}^{N_i} \eta_{\theta,\alpha}[\, R_{ij}(T_{ij}), \Lambda_{ij}(T_{ij}^*) \,|\, u_i \,]^{\delta_{ij}} \eta_{\theta,\alpha}^*[\, R_{ij}(T_{ij}), \Lambda_{ij}(T_{ij}^*) \,|\, u_i \,]^{\delta_{ij}^*}$$

$$\times \Theta_{\theta,\alpha}[\, R_{ij}(T_{ij}), \Lambda_{ij}(T_{ij}^*) \,|\, u_i \,]^{\delta_{ij}\delta_{ij}^*} D_{\theta,\alpha}[\, R_{ij}(T_{ij}), \Lambda_{ij}(T_{ij}^*) \,|\, u_i \,] \Bigg\} f_{\eta}(u_i) du_i \Bigg],$$

Heterogeneity

where $R_{ij}(t) = R_0(t)\exp(\boldsymbol{\beta}_1' \mathbf{Z}_{ij})$, $\Lambda_{ij}(t) = \Lambda_0(t)\exp(\boldsymbol{\beta}_2' \mathbf{Z}_{ij})$

$$D_{\theta,\alpha}(\, s, t \,|\, u \,) = C_{\theta}[\, \exp(-us), \exp(-u^{\alpha} t) \,],$$

$$\eta_{\theta,\alpha} = D_{\theta,\alpha}^{[1,0]} / D_{\theta,\alpha}, \quad \eta_{\theta,\alpha}^* = D_{\theta,\alpha}^{[0,1]} / D_{\theta,\alpha}, \quad \Theta_{\theta,\alpha} = D_{\theta,\alpha}^{[1,1]} D_{\theta,\alpha} / D_{\theta,\alpha}^{[1,0]} D_{\theta,\alpha}^{[0,1]},$$

where $D_{\theta,\alpha}^{[1,0]} = -\partial D_{\theta,\alpha} / \partial s$, $D_{\theta,\alpha}^{[0,1]} = -\partial D_{\theta,\alpha} / \partial t$, and $D_{\theta,\alpha}^{[1,1]} = \partial^2 D_{\theta,\alpha} / \partial s \partial t$.

Log-likelihood (proposed)

- Independent copula $C_\theta(v, w) = vw$

➔ reduces to the log-likelihood of Rondeau et al. (2011):

$$\ell(\alpha, \eta, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2, r_0, \lambda_0)$$
$$= \sum_{i=1}^{G} \left[\sum_{j=1}^{N_i} \{ \delta_{ij} \log r_{ij}(T_{ij}) + \delta_{ij}^* \log \lambda_{ij}(T_{ij}^*) \} \right.$$
$$\left. + \log \int_0^\infty \left\{ u_i^{m_i + \alpha m_i^*} \exp\left(-u_i \sum_{j=1}^{N_i} R_{ij}(T_{ij}) - u_i^\alpha \sum_{j=1}^{N_i} \Lambda_{ij}(T_{ij}^*) \right) \right\} f_\eta(u_i) du_i \right],$$

where $m_i = \sum_{j=1}^{N_i} \delta_{ij}$ and $m_i^* = \sum_{j=1}^{N_i} \delta_{ij}^*$.

- Penalized likelihood with cubic M-spline

  ➔ Directly follow Rondeau et al. (2011)

$$\ell(\alpha, \eta, \theta, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2, r_0, \lambda_0) - \kappa_1 \int \ddot{\gamma}_0(t)^2 dt - \kappa_2 \int \ddot{\lambda}_0(t)^2 dt$$

$$\int \ddot{r}_0(t)^2 dt = \sum_{k=1}^{L_r} \sum_{\ell=1}^{L_r} g_k g_\ell \int \ddot{M}_k(t) \ddot{M}_\ell(t) dt, \quad \int \ddot{\lambda}_0(t)^2 dt = \sum_{k=1}^{L_\lambda} \sum_{\ell=1}^{L_\lambda} h_k h_\ell \int \ddot{M}_k(t) \ddot{M}_\ell(t) dt$$

- Optimal smoothing parameters (routine)

Likelihood cross-validation (LCV) score

$$\text{LCV}(\kappa_1, \kappa_2) = \hat{\ell}(\kappa_1, \kappa_2) - \text{tr}\{\hat{H}_{PL}^{-1}(\kappa_1, \kappa_2)\hat{H}\},$$

- $\hat{\ell}(\kappa_1, \kappa_2)$ is the log-likelihood evaluated at the penalized MLE
- $\hat{H}_{PL}^{-1}(\kappa_1, \kappa_2)$ is the converged Hessian matrix of the penalized ML estimation
- $\hat{H}$ is the converged Hessian matrix of the un-penalized ML estimation

Standard error (SE)

- 95% confidence interval for β_1

$$\hat{\beta}_1 \pm 1.96 \times \mathrm{SE}(\beta_1) = \hat{\beta}_1 \pm 1.96 \times \sqrt{-\{\hat{H}_{PL}^{-1}(\kappa_1, \kappa_2)\}_{\beta_1}}$$

- 95% confidence interval for the baseline hazard $r_0(t)$ is

$$\hat{r}_0(x) \pm 1.96 \times \mathrm{SE}\{\hat{r}_0(x)\} = \mathbf{M}'(x)\hat{\mathbf{g}} \pm 1.96 \times \sqrt{-\mathbf{M}'(x)\{\hat{H}_{PL}^{-1}(\kappa_1, \kappa_2)\}_{\mathbf{g}}\mathbf{M}(x)},$$

where $\mathbf{M}(t) = (M_1(x), \ldots, M_{L_r}(x))'$.

Simulations: G=5, N=100 or 200

Simulation settings:

- Frailty: $u_i \sim$ Gamma $(1/\eta, \eta)$ where $\eta = 0.5$
- Covariate: $Z_{ij} \sim \text{Unif}(0,1)$
- Joint frailty-copula model

$$\Pr(X_{ij} > x, D_{ij} > y \mid u_i) = [\exp\{\theta R_{ij}(x \mid u_i)\} + \exp\{\theta \Lambda_{ij}(y \mid u_i)\} - 1]^{-1/\theta},$$

at $\theta = 2$ ➔ $\tau(X_{ij}, D_{ij} \mid u_i) = 0.5$.

- Marginals: $R_{ij}(x \mid u_i) = u_i r_0 x \exp(\beta_1 Z_{ij})$, $\Lambda_{ij}(y \mid u_i) = u_i^{\alpha} \lambda_0 y \exp(\beta_2 Z_{ij})$

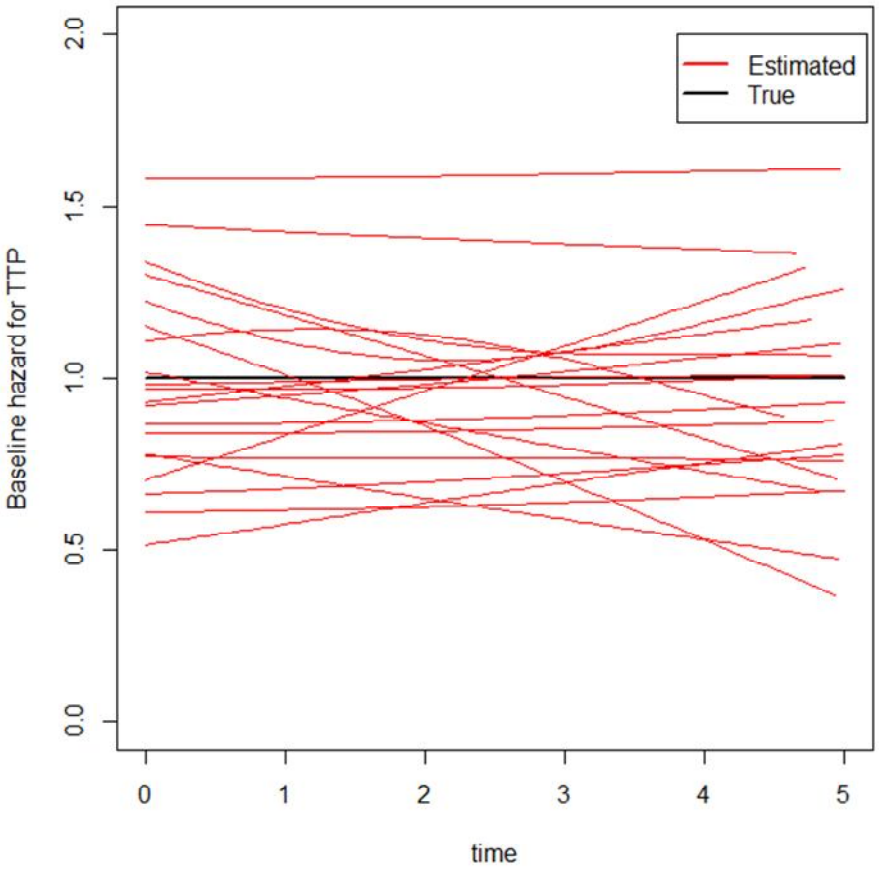
where $r_0 = 1$ and $\lambda_0 = 1$

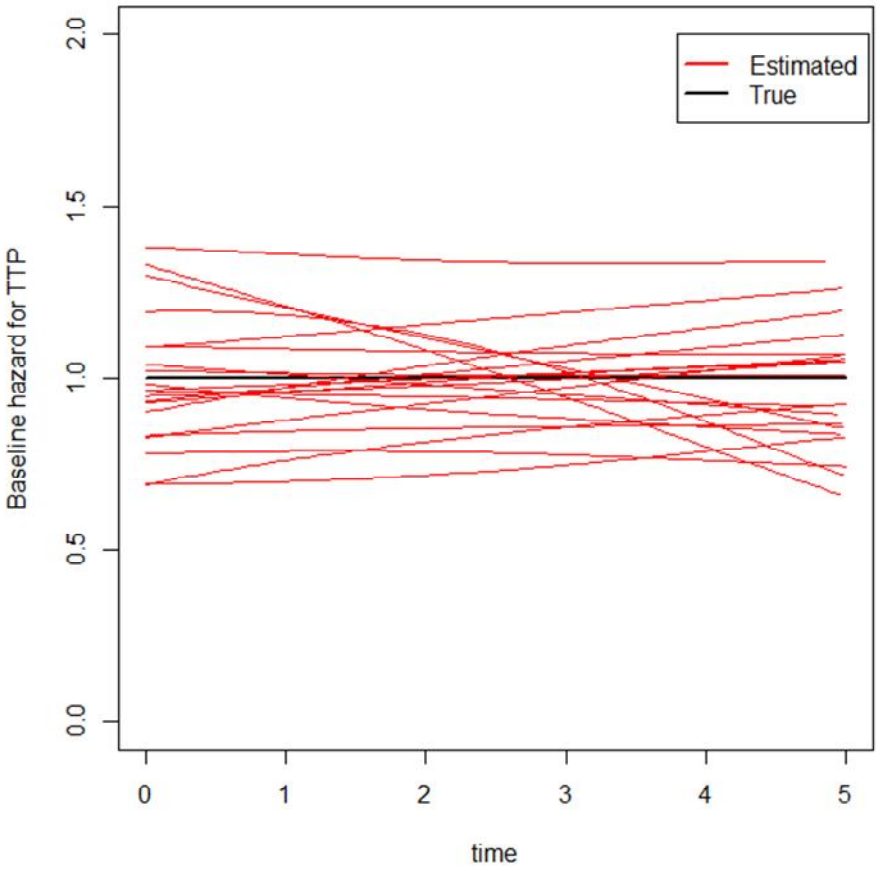
- $C_{ij} \sim \text{Unif}(0, 5)$ ➔ 15~31% censored subjects

Table 3. Simulations with 500 runs, $G = 5$

		$N_i = 100$				$N_i = 200$			
		Mean	SD	SE	CP%	Mean	SD	SE	CP%
CEN	β_1 =1	0.999	0.148	0.141	0.94	1.012	0.103	0.100	0.95
=15%	β_2 =1	1.009	0.115	0.115	0.95	1.006	0.082	0.081	0.95
	η =0.5	0.490	0.293	0.288	0.91	0.475	0.294	0.276	0.88
	α =2	2.027	0.244	0.234	0.95	2.014	0.172	0.164	0.94
		Mean	SD	SE	CP%	Mean	SD	SE	CP%
CEN	β_1 =-1	-1.014	0.183	0.184	0.94	-0.995	0.125	0.128	0.96
=31%	β_2 =-1	-1.001	0.147	0.148	0.95	-1.003	0.103	0.103	0.95
	η =0.5	0.483	0.298	0.288	0.88	0.493	0.301	0.285	0.88
	α =2	2.037	0.294	0.286	0.94	2.021	0.206	0.200	0.94
		Mean	SD	SE	CP%	Mean	SD	SE	CP%
CEN	β_1 =1	1.007	0.082	0.078	0.95	1.011	0.061	0.055	0.94
=16%	β_2 =1	1.012	0.071	0.070	0.93	1.008	0.053	0.049	0.94
	η =0.5	0.500	0.302	0.292	0.90	0.495	0.300	0.285	0.88
	α =6	6.097	0.565	0.538	0.94	6.030	0.401	0.375	0.94
		Mean	SD	SE	CP%	Mean	SD	SE	CP%
CEN	β_1 =-1	-1.009	0.112	0.110	0.95	-0.999	0.077	0.077	0.95
=34%	β_2 =-1	-1.003	0.101	0.094	0.94	-1.005	0.068	0.066	0.95
	η =0.5	0.497	0.309	0.297	0.89	0.516	0.306	0.299	0.90
	α =6	6.119	0.628	0.647	0.96	6.053	0.450	0.449	0.96

Simulations: 20 runs, G=5





Setting (b): $\beta_1 = -1$, $\beta_2 = -1$, $r_0(x) = 1$ and $\lambda_0(y) = 1$

Meta-analysis for ovarian cancer

Table 2. Data sets in the $G = 4$ independent studies of ovarian cancer from Ganzfried et al. (2013).

Data set (GEO accession number)	Sample size	The number of observed events		
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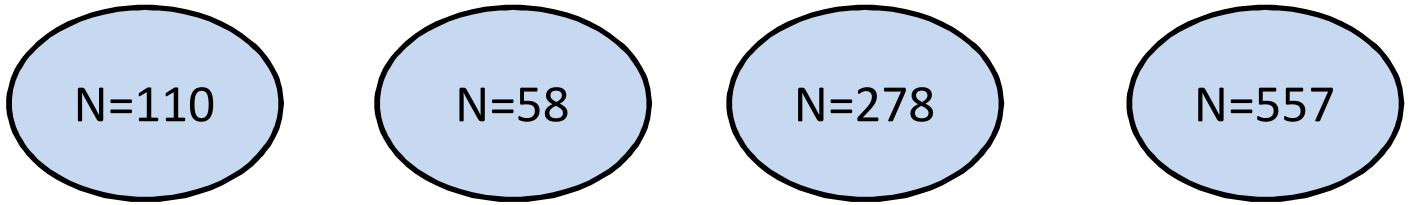
TCGA	$N_4 = 557$	266	290	267
Total	$\sum_{i=1}^{4} N_i = 1003$	575	485	314

- Synthesize 4 independent genomic studies of ovarian cancer



- A recently discovered CXCL12 gene expression
  ➔ Dignificant biomarker of OS in ovarian cancer
  (Popple et al., 2012; Ganzfried et al. 2013)

- **Our goal:** Confirm their finding by our proposed joint model on TTP and OS:

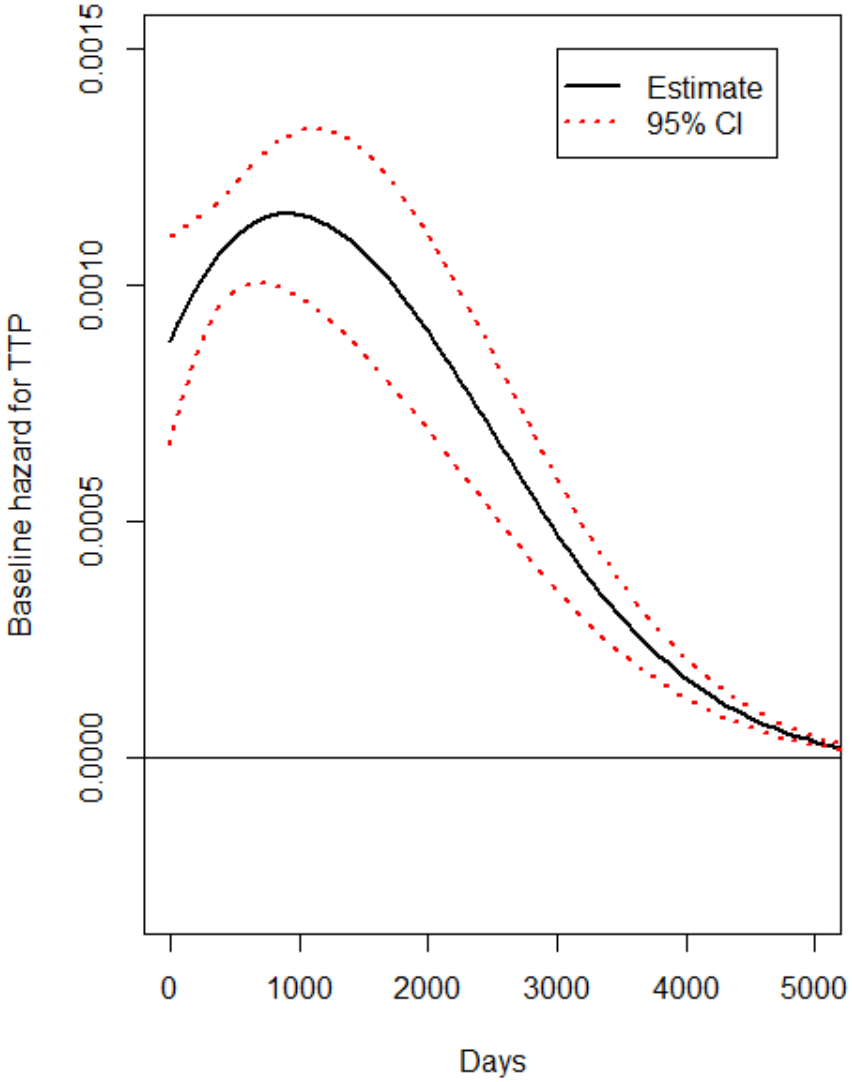
$$\begin{cases} r_{ij}(t \mid u_i) = u_i r_0(t) \exp(\ \beta_1 \times \text{CXCX12}\ ) & (\ \text{hazard for TTP}\ ) \\ \lambda_{ij}(t \mid u_i) = u_i^{\alpha} \lambda_0(t) \exp(\ \beta_2 \times \text{CXCX12}\ ) & (\ \text{hazard for OS}\ ) \end{cases}$$

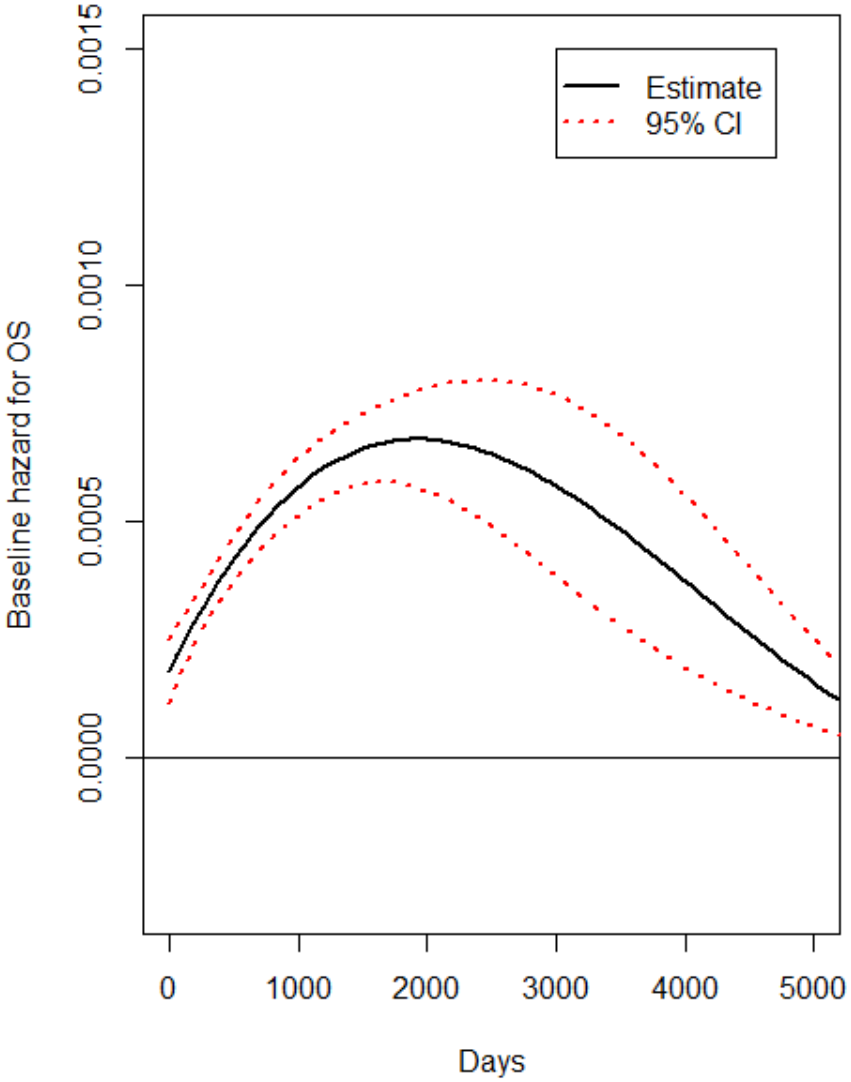
Result of fitting the joint model

		Proposed	Rondeau et al.
$\exp(\beta_1)$	RR for TTP (95%CI)	1.23 (1.14-1.33)	1.26 (1.16-1.36)
$\exp(\beta_2)$	RR for OS (95%CI)	1.18 (1.08-1.28)	1.17 (1.07-1.28)
	Heterogeneity $\eta = Var_\eta(u_i)$	0.035 (0.031)	0.025 (0.022)
	(SE)		
	Copula parameter θ (SE)	1.89 (0.24)	0.00 (fixed)
	Kendall's tau $\theta/(\theta+2)$	0.49 (0.03)	0.00 (fixed)
	Penalized log-likelihood	-8592.681	-8726.445

* Ganzfried et al. (2013) reported RR=1.15 (1.09-1.23) for OS based on 14 studies

Result of fitting the joint model





Summary

We proposed a **joint** frailty-copula model for dependence between **TTP** and **OS**

- Extend the joint frailty model of Rondeau et al. (2011)
  ➔ allow intra-cluster dependence via copulas
- Data analysis:
  Proposed method vs. method of Rondeau et al. produces similar result even for the significant intra-cluster dependence

Future work

- Is the method of Rondeau et al. robust against the amount of intra-cluster dependence ?
- We (with Dr. Nakatochi and Murotani) are searching the meta-analysis data of Sabatier et al. (2011 *PLoS ONE*)

Thank you !