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

Stat Methods Med Res (2015)

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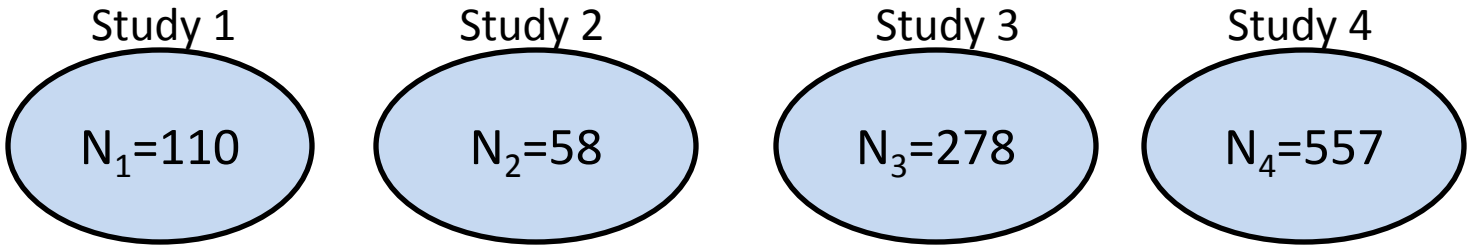
Outline

- Review -- meta-analysis
- Review -- joint model
- Proposed method
- Simulation
- Data analysis
- Extension to recurrent events data

Meta-Analysis

- Combine multiple independent studies



$$\text{Combined sample size} : \sum_{i=1}^{4} N_i = 1003$$

- Useful to estimate small effect size:
  - Treatment effect of chemotherapy on survival
    : Head & neck cancer (Pignon et al. 2009)
  - The effect of *CXCL12* gene on survival
    : Ovarian cancer (Ganzfried et al. 2013)
  - The effect of *ECRG4* gene on survival
    : Breast cancer (Sabatier et al. 2011)

Typical endpoints in cancer studies

- **Time-to-progression (TTP)**

  (e.g., recurrence, metastasis)

- **Overall survival (OS)**

  (Death from any cause)

Event times of interest (bivariate)

- **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
See the book Hougaard (2000)

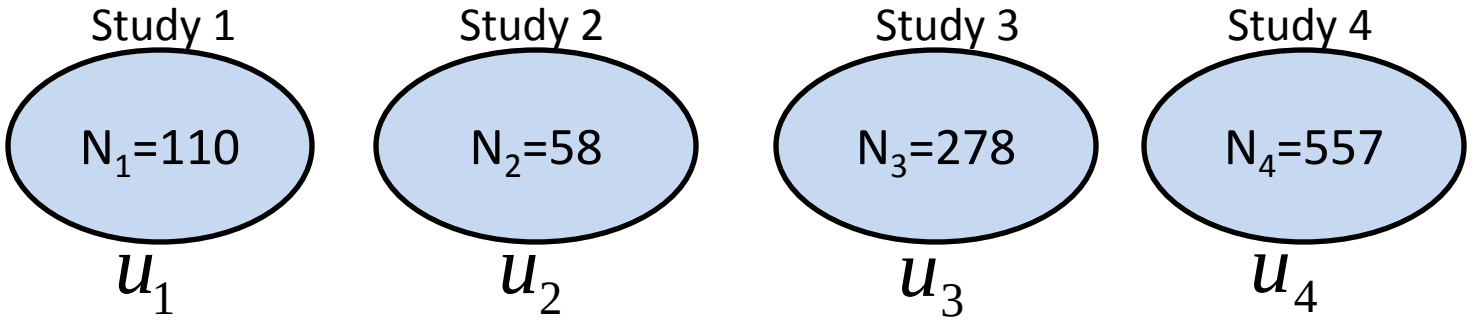
Meta-analysis requires random effect to
model the heterogeneity between studies

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

ii) Semi-competing risks analysis (Rondeau et al. 2011) :
TTP is observed only if TTP < OS
(semicompeting risks)

- Unobserved random effect (called frailty)

  capture the heterogeneity of risks between studies



$$\text{Gamma frailty}: \; u_i \sim f_\eta(u) = \frac{1}{\Gamma(1/\eta)\eta^{1/\eta}} u^{\frac{1}{\eta}-1} \exp\left(-\frac{u}{\eta}\right), \quad \begin{cases} E[u_i] = 1 \\ Var[u_i] = \eta \end{cases}$$

- Clustered data structure:

G independent studies ($i = 1, 2, ..., G$); e.g., G=4

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

Ref:(Burzykowski et al. 2001; Rondeau et al. 2011)

Motivation: Meta-analysis for ovarian cancer (Ganzfried et al. 2013)

A meta-analytic data of ovarian cancer patients.

Dataset[a]	Sample size	The number of observed events (event rates %)		
		Relapse ($\delta_{ij}=1$)	Death ($\delta_{ij}^*=1$)	Censoring ($\delta_{ij}^*=0$)
GSE17260	$N_1=110$	76 (69%)	46 (42%)	64 (58%)
GSE30161	$N_2=58$	48 (83%)	36 (62%)	22 (38%)
GSE9891	$N_3=278$	185 (67%)	113 (41%)	165 (59%)
TCGA	$N_4=557$	266 (48%)	290 (52%)	267 (48%)
Total	$\sum_{i=1}^{4} N_i=1003$	575 (57%)	485 (48%)	518 (52%)

Risks of relapse are heterogeneous

- Goal of Gantzfried et al.: Survival analysis on death (OS).
- Our goal: Joint survival analysis of relapse (TTP) and death (OS)

$X_{ij} = \text{TTP}$ (Time to progression due to recurrence, Relapse, etc.)

$D_{ij} = \text{OS}$ (Overall survival = time to death from any cause)

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

Joint frailty model (Rondeau et al., 2011)

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

$u_i =$ random effect with $\text{E}[u_i] = 1$ and $\text{Var}[u_i] = \eta$ (frailty)

$u_i < 1$: Low risk; $u_i > 1$: High risk;

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

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

$\mathbf{Z}_{ij}$ = Covariates measured at time 0

$\alpha = 0 \Rightarrow$ No random effect for D_{ij},

$\alpha = 1 \Rightarrow$ Same random effect for X_{ij} and D_{ij}

Data structure

$X_{ij} = \text{TTP}$ (Time to progression due to recurrence, Relapse, etc.)

$D_{ij} = \text{OS}$ (Overall survival = time to death from any cause)

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

Observations are in semicompeting risks form (Fine et al., 2001):

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

* First occuring event time

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

Indicator of progression

* Terminal event time

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

Indicator of death

Data structure

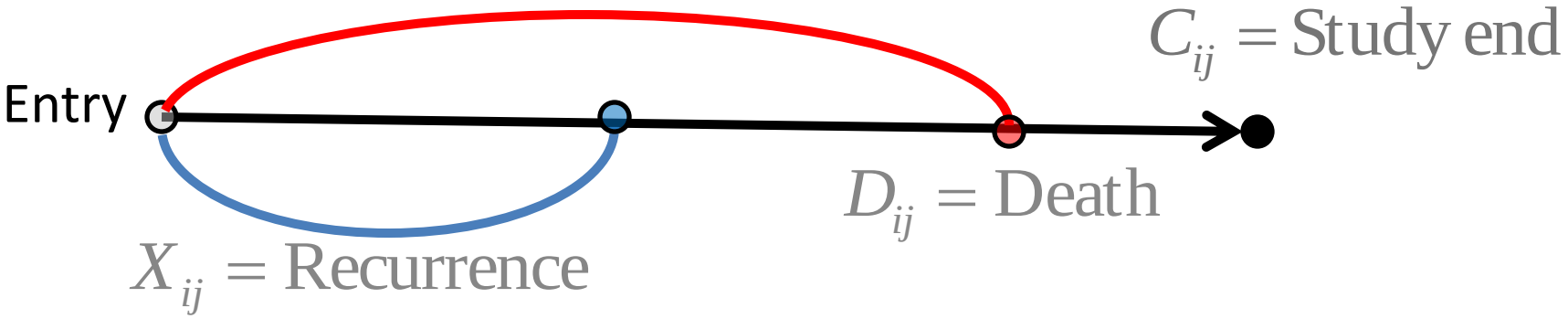


Fig. Case of $\delta_{ij} = 1, \quad \delta_{ij}^{*} = 1$

* 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 :

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

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

4 patterns

	Likelihood contribution
• Relapse → Death T_{ij} T_{ij}^*	$\Pr(X_{ij} = T_{ij}, D_{ij} = T_{ij}^* \mid u_i)$
• Relapse → Censoring T_{ij} T_{ij}^*	$\Pr(X_{ij} = T_{ij}, D_{ij} > T_{ij}^* \mid u_i)$
• Death (without relapse) $T_{ij} = T_{ij}^*$	$\Pr(X_{ij} > T_{ij}, D_{ij} = T_{ij}^* \mid u_i)$
• Censoring (neither relapse nor death) $T_{ij} = T_{ij}^*$	$\Pr(X_{ij} > T_{ij}, D_{ij} > T_{ij}^* \mid u_i)$

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)

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

Proposed Idea

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

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

Joint frailty model (Rondeau et al., 2011)

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

- They assume Independence within a subject *j* :

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

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

Joint frailty-copula model (Proposed)

Joint frailty model (Rondeau et al., 2011)

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

+

Copula model (new):

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

C_θ : Copula (Nelsen, 2006), $R_{ij}(x \mid u_i) = \int_0^x r_{ij}(v \mid u_i) dv$ $\Lambda_{ij}(y \mid u_i) = \int_0^y \lambda_{ij}(v \mid u_i) dv$

Copula parameter θ

➔ Intra-subject Kendall's tau $\tau_\theta(X_{ij}, D_{ij} \mid u_i)$

e.g., Clayton copula: $\tau(X_{ij}, D_{ij} \mid u_i) = \theta/(\theta+2)$

Data structure: Clustered semicompeting risks data

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

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

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

$$+ \log \int_0^\infty \left\{ u_i^{m_i + \alpha m_i^*} \prod_{j=1}^{N_i} \psi_\theta[\, u_i R_{ij}(T_{ij}), u^\alpha \Lambda_{ij}(T_{ij}^*)\,]^{\delta_{ij}} \psi_\theta^*[\, u_i R_{ij}(T_{ij}), u_i^\alpha \Lambda_{ij}(T_{ij}^*)\,]^{\delta_{ij}^*} \right.$$

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

where $r_{ij}(t) = r_0(t)\exp(\boldsymbol{\beta}_1' \mathbf{Z}_{ij})$, $\lambda_{ij}(t) = \lambda_0(t)\exp(\boldsymbol{\beta}_2' \mathbf{Z}_{ij})$,

$r_0(t) = \sum_{\ell=1}^{L_r} g_\ell M_\ell(t)$, $\lambda_0(t) = \sum_{\ell=1}^{L_\lambda} h_\ell M_\ell(t)$, ⇦ Cubic M-spline

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

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

⇧ Derivatives of copula

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)

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

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

- κ_1 = Smoothing parameter for the hazard of TTP
- κ_2 = Smoothing parameter for the hazard of OS

The values $(\hat{\kappa}_1, \hat{\kappa}_2)$ chosen by LCV (Joly, et al. 1998)

$$(\hat{\alpha}, \hat{\eta}, \hat{\theta}, \hat{\boldsymbol{\beta}}_1, \hat{\boldsymbol{\beta}}_2, \hat{r}_0, \hat{\lambda}_0)$$
$$= \underset{(\alpha, \eta, \theta, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2, r_0, \lambda_0)}{\arg\max} \left[\ell(\alpha, \eta, \theta, \boldsymbol{\beta}_1, \boldsymbol{\beta}_2, r_0, \lambda_0) - \hat{\kappa}_1 \int \ddot{\gamma}_0(t)^2 dt - \hat{\kappa}_2 \int \ddot{\lambda}_0(t)^2 dt\right]$$

- Automatic computing implemented in our R *joint.Cox* package

  Accuracy of the package checked by simulations (in our paper)

Simulation setting: G=5, N_i=100 or 200

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

$$R_{ij}(x \mid u_i) = u_i r_0 x \exp(\beta_1 Z_{ij}), \quad \Lambda_{ij}(y \mid u_i) = u_i \lambda_0 y \exp(\beta_2 Z_{ij})$$

where $r_0 = 1$ and $\lambda_0 = 1$ (Exponential distribution)

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

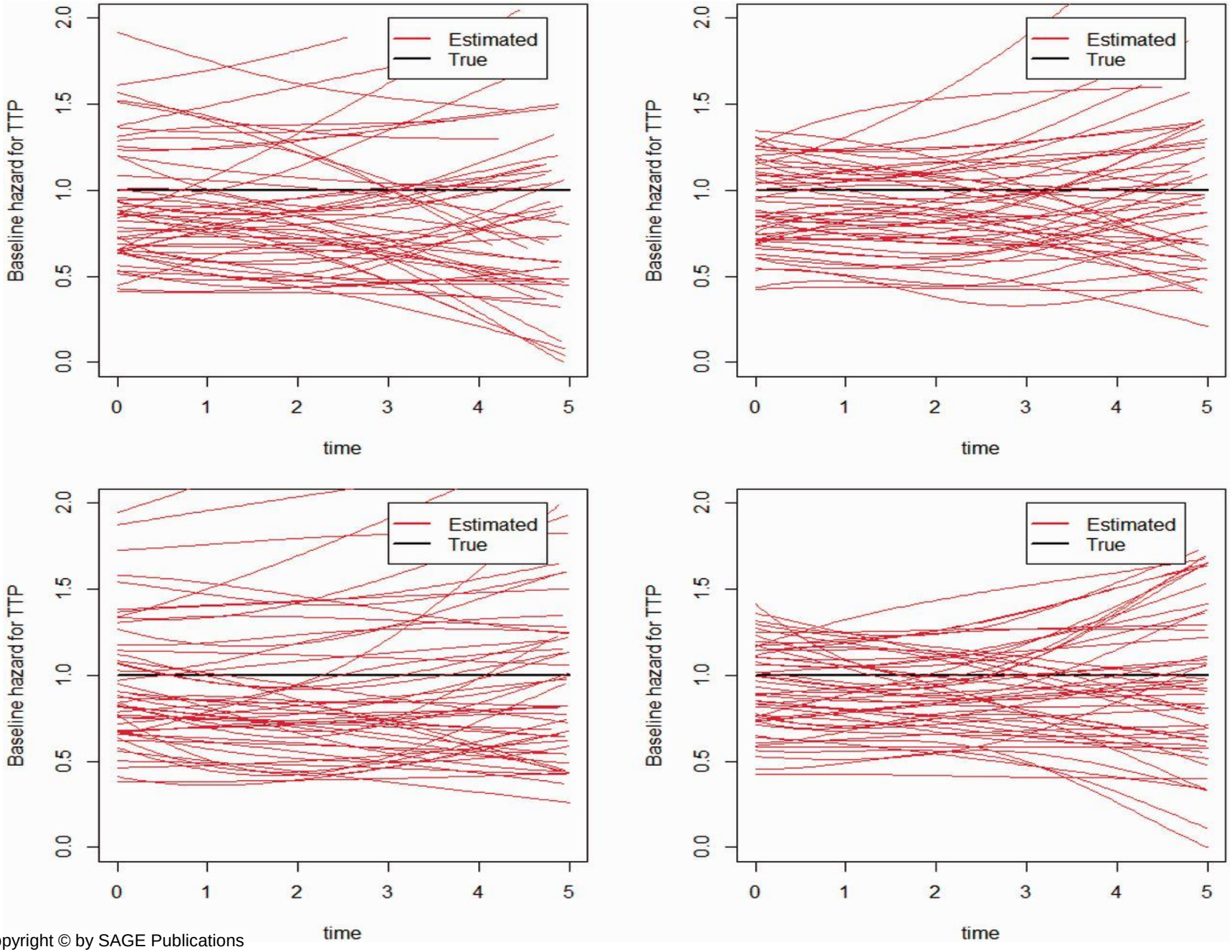
- Censoring, $C_{ij} \sim \text{Unif}(0, 5)$ ➔ 16~37% censored subjects

Simulation results for the proposed method (G = 5 studies) based on 500 replications.

		$N_i = 100$				$N_i = 200$			
	Parameter	Mean	SD	SE	CP%	Mean	SD	SE	CP%
CEN=16%	$\beta_1 = 1$	1.003	0.189	0.194	0.96	1.004	0.135	0.135	0.95
	$\beta_2 = 1$	1.010	0.154	0.163	0.96	1.004	0.114	0.114	0.95
	$\eta = 0.5$	0.408	0.264	0.248	0.88	0.399	0.289	0.238	0.82
	$\theta = 2$	2.023	0.247	0.242	0.95	2.015	0.178	0.169	0.94
	κ_1	58.8	176.1	–	–	26.9	100.8	–	–
	κ_2	268.5	418.0	–	–	191.9	363.4	–	–
CEN=32%	$\beta_1 = -1$	−1.001	0.236	0.230	0.95	−1.001	0.157	0.160	0.95
	$\beta_2 = -1$	−1.000	0.194	0.192	0.95	−1.001	0.136	0.134	0.95
	$\eta = 0.5$	0.404	0.263	0.246	0.88	0.395	0.281	0.237	0.82
	$\theta = 2$	2.038	0.296	0.294	0.96	2.019	0.209	0.203	0.94
	κ_1	256.2	389.9	–	–	124.4	276.4	–	–
	κ_2	555.4	470.3	–	–	521.7	469.9	–	–
CEN=18%	$\beta_1 = 1$	1.006	0.154	0.161	0.95	1.004	0.114	0.112	0.95
	$\beta_2 = 1$	1.011	0.143	0.151	0.95	1.004	0.107	0.105	0.95
	$\eta = 0.5$	0.411	0.268	0.249	0.87	0.397	0.279	0.237	0.82
	$\theta = 6$	6.089	0.567	0.561	0.94	6.036	0.396	0.390	0.94
	κ_1	114.1	273.9	–	–	56.7	181.6	–	–
	κ_2	279.9	423.4	–	–	213.5	380.4	–	–
CEN=37%	$\beta_1 = -1$	−1.002	0.197	0.194	0.94	−1.000	0.134	0.135	0.95
	$\beta_2 = -1$	−1.001	0.177	0.179	0.95	−1.001	0.124	0.124	0.96
	$\eta = 0.5$	0.407	0.268	0.248	0.88	0.394	0.274	0.236	0.83
	$\theta = 6$	6.129	0.690	0.672	0.95	6.056	0.462	0.463	0.95
	κ_1	301.5	414.4	–	–	123.5	275.6	–	–
	κ_2	551.8	468.6	–	–	517.8	464.7	–	–

CEN = the percentage that both death and progression are censored; $100 \times \Pr(X_{ij} > C_{ij}, D_{ij} > C_{ij})$. SD = the sample standard deviation of the estimates. SE = the average of the standard errors. CP% = the coverage ratio for the 95% confidence intervals.

Simulation results for estimating the baseline hazard based on 50 replications.



Ovarian cancer meta-analysis

(Ganzfried et al. 2013)

Dataset[a]	Sample size	The number of observed events (event rates %)		
		Relapse ($\delta_{ij}=1$)	Death ($\delta^*_{ij}=1$)	Censoring ($\delta^*_{ij}=0$)
GSE17260	$N_1=110$	76 (69%)	46 (42%)	64 (58%)
GSE30161	$N_2=58$	48 (83%)	36 (62%)	22 (38%)
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TCGA	$N_4=557$	266 (48%)	290 (52%)	267 (48%)
Total	$\sum_{i=1}^{4} N_i=1003$	575 (57%)	485 (48%)	518 (52%)

- Goal 1: Marginal analysis of relapse (TTP) and death (OS)

$$\begin{cases} r_{ij}(t\,|\,u_i)=u_i r_0(t)\exp(\ \beta_1\times \mathrm{CXCL12}\ ) & (\ \text{hazard for TTP}\ ) \\ \lambda_{ij}(t\,|\,u_i)=u_i^{\alpha}\lambda_0(t)\exp(\ \beta_2\times \mathrm{CXCL12}\ ) & (\ \text{hazard for OS}\ ) \end{cases}$$

- Goal 2: Association analysis of TTP and death

Copula model:

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

Table 5. The joint analysis of recurrence (TTP) and death (OS) for the meta-analytic data (four studies, 1003 patients) for ovarian cancer patients of Ganzfried et al.[19].

	Proposed method: Estimate (95% CI)	Method of Rondeau et al.[6]: Estimate (95% CI)
RR[a] for relapse (TTP) : $\exp(\beta_1)$	1.22 (1.13-1.32)	1.24 (1.14-1.35)
RR[a] for death (OS) : $\exp(\beta_2)$	1.18 (1.08-1.29)	1.17 (1.07-1.29)
Heterogeneity: $\eta = Var_\eta(u_i)$	0.033 (0.006-0.186)	0.028 (0.004-0.180)
Copula parameter: θ	2.35 (1.90-2.90)	0.00 (assumed fixed)
RR for death after relapse: $\theta+1$	3.35 (2.90-3.90)	1.00 (assumed fixed)
Kendall's tau: $\tau = \theta/(\theta+2)$	0.54 (0.49-0.59)	0.00 (assumed fixed)
Maximum penalized log-likelihood	-8604.093	-8744.023

Notes: [a]RR (Relative Risk) of *CXCL12* expression on the hazards are examined.

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

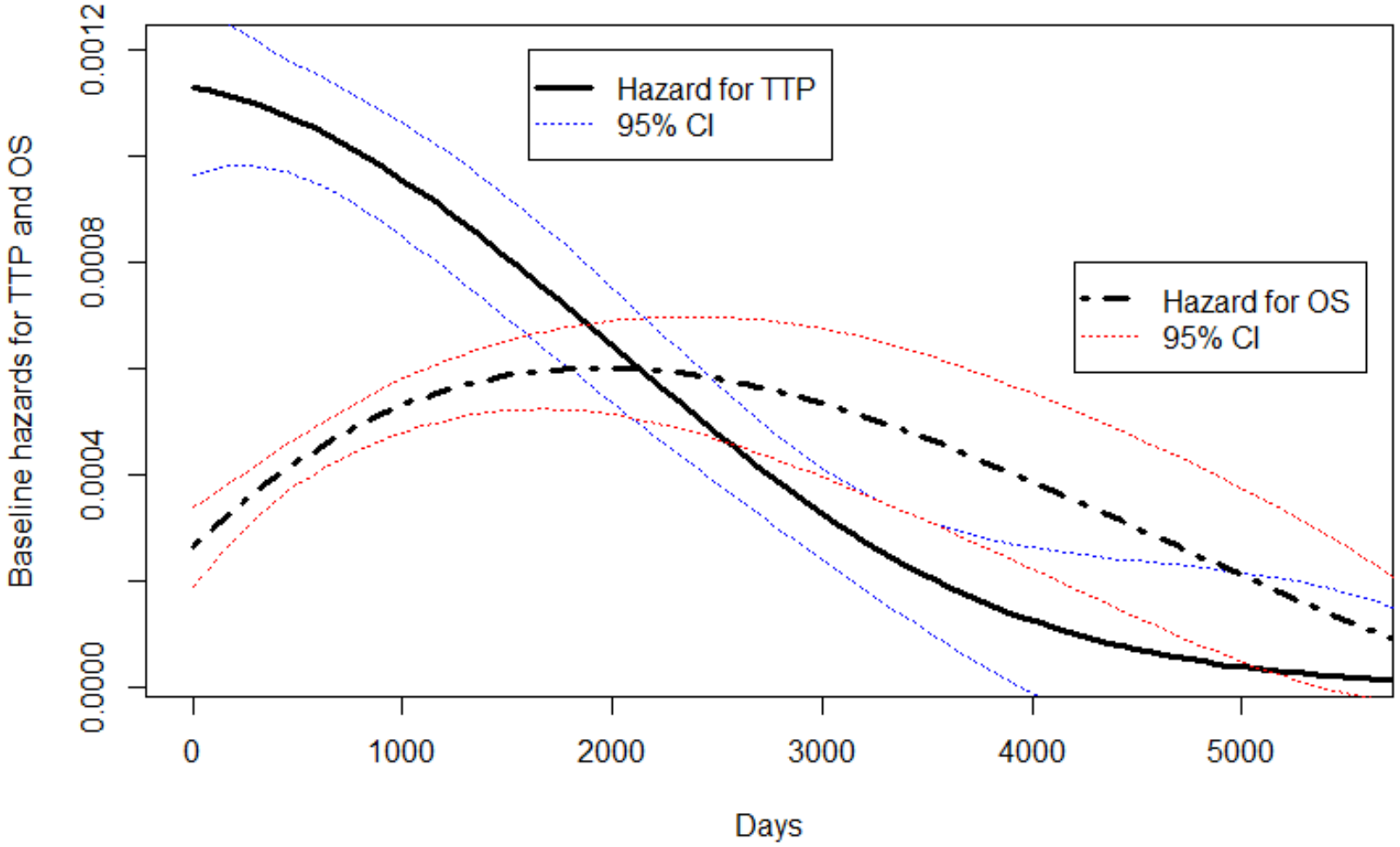


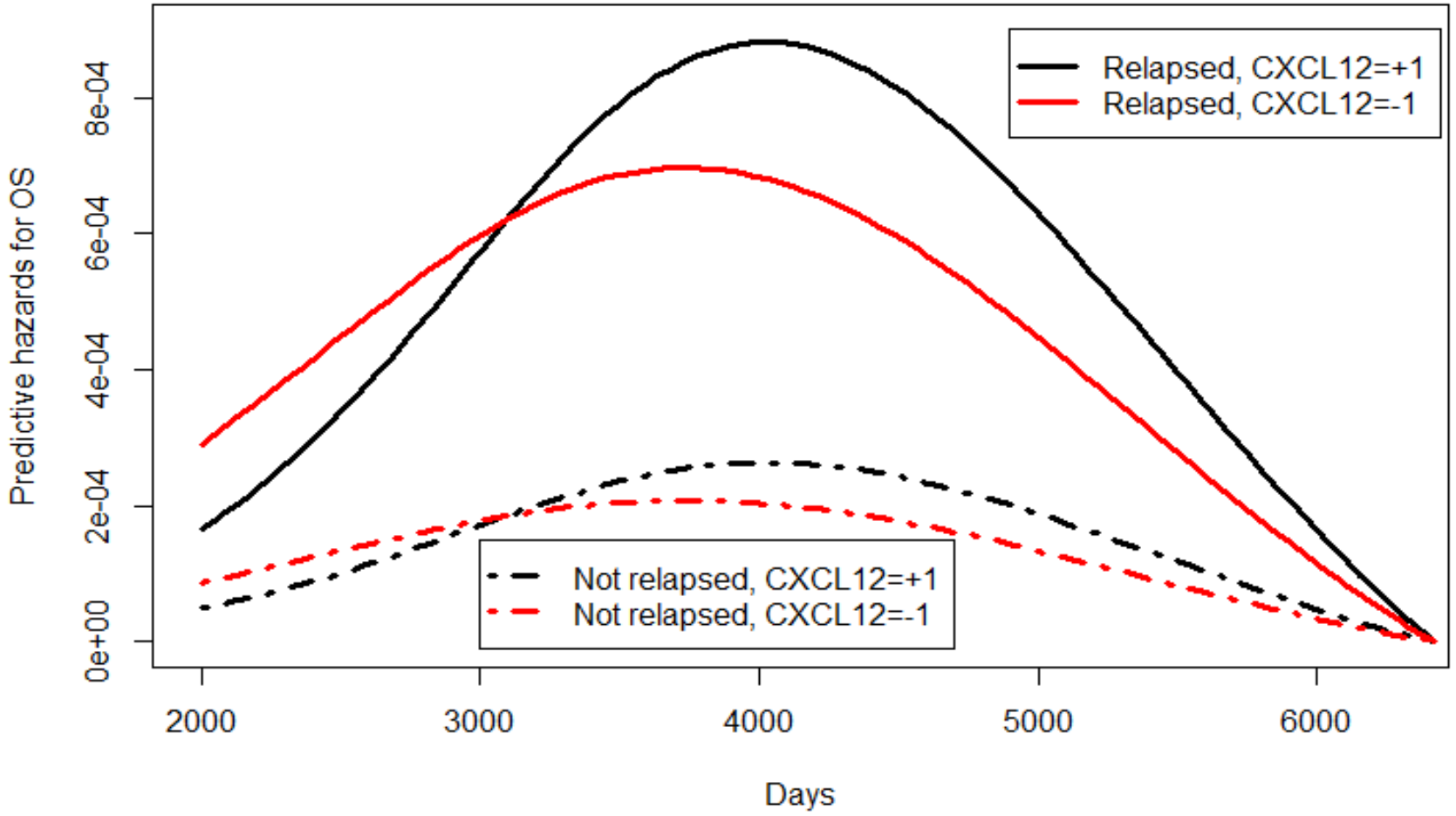
Figure 2. Baseline hazard functions for TTP (recurrence) and OS (death) based on the meta-analytic data of ovarian cancer patients. The dotted lines (red or blue color) show the 95% confidence intervals.

Copula parameter: θ =2.35 (Kendall's tau=0.54)

Practical implication:

Relapse occurring before death can increase the risk of death by 3.35 times:

$$3.35 \approx \theta + 1 = \frac{\lambda_{ij}(y \mid X_{ij} = x, Z_{ij}, u_i)}{\lambda_{ij}(y \mid X_{ij} > x, Z_{ij}, u_i)}, \qquad y \geq x, \qquad Z_{ij} = \text{CXCL12}$$



Application to recurrent event data

- X_{ij} = Gap time between $(j-1)$-th and j-th recurrence times for $j = 1, 2, ..., N_i$ (e.g., rehospitalization, relapse)
- The terminal event = the induced gap times for death D_{ij} and censoring C_{ij}

Joint frailty model

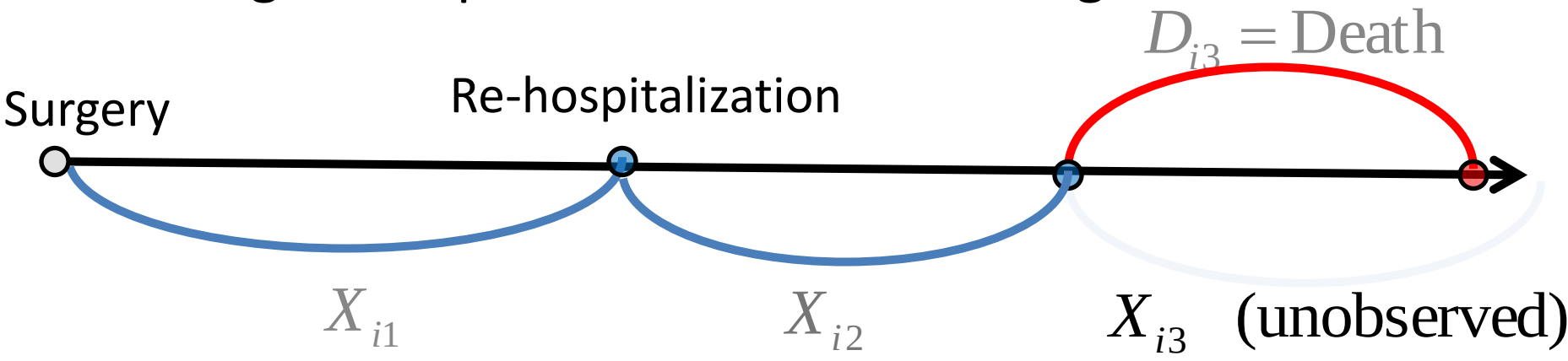
$$\begin{cases} r_{ij}(t \mid u_i) = u_i r_0(t) \exp(\boldsymbol{\beta}_1' \mathbf{Z}_{ij}) & (\text{time-to-recurrence } X_{ij}) \\ \lambda_{ij}(t \mid u_i) = u_i^{\alpha} \lambda_0(t) \exp(\boldsymbol{\beta}_2' \mathbf{Z}_{ij}) & (\text{time-to-death } D_{ij}) \end{cases}$$

Copula model

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

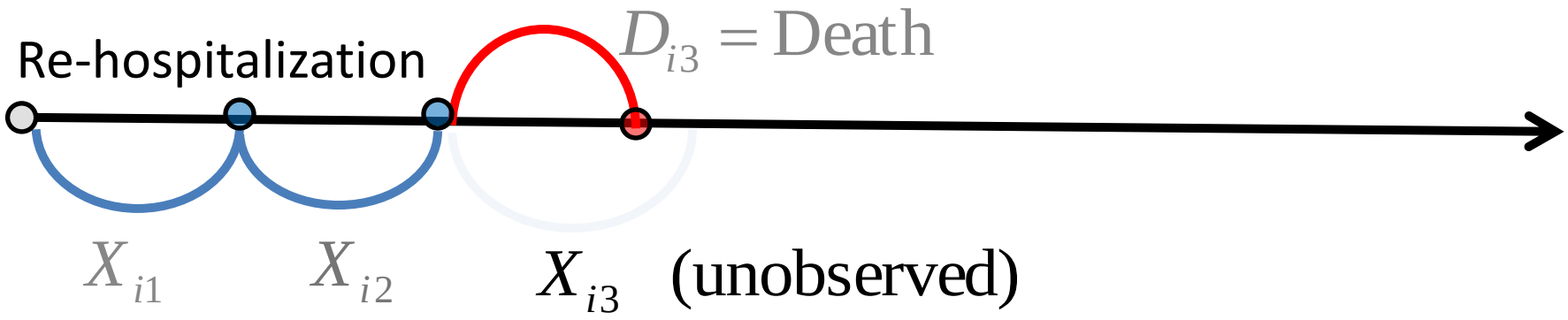
- **Patient 1**: (low risk; $u_i = 0.5$)

  ➔ long re-hospitalization time and long survival



- **Patient 2**: (high risk; $u_i = 2$)

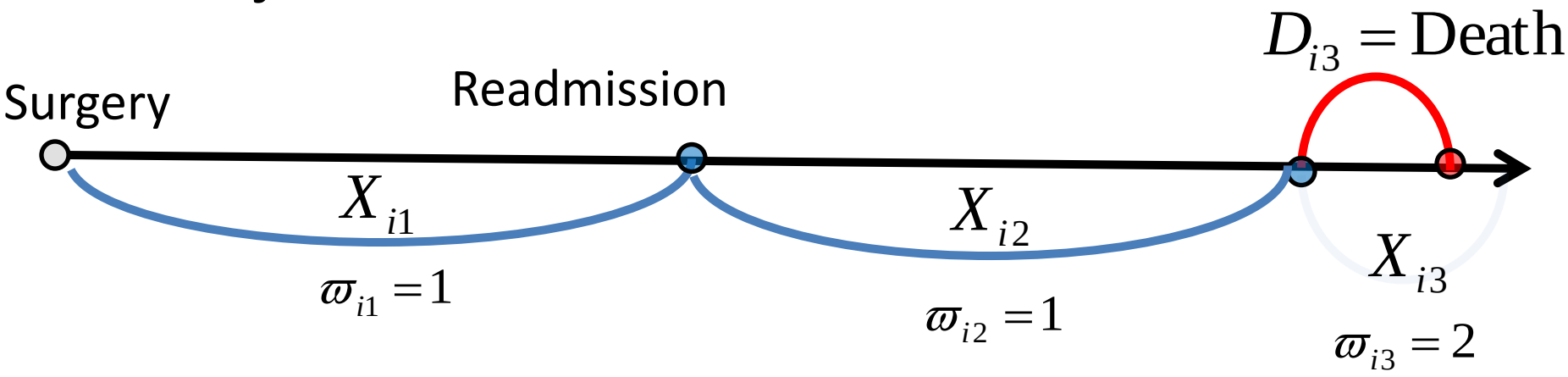
  ➔ short re-hospitalization time and short survival



How recurrence-specific (residual) dependenece arise?

- **Patient 3**: (low risk: $u_i = 0.5$)

  ➔ long re-hospitalization time and long survival **at j=1 and 2 recurrences**.



Short survival **at j=3**

Short re-hospitalization **at j=3**

➔ Strong dependence between D and X **at j=3**

This kind of temporal (recurrence-specific) dependence cannot be fully captured by the frailty only ➔ Need copula models

Joint analysis of re-hospitalization and death for the colorectal cancer data of González et al. (403 patients).

	Proposed method with the Clayton copula: Using *joint.Cox*	Method of Rondeau et al.[6]: Using *joint.Cox*	Method of Rondeau et al.[6]: Using *frailtypack*
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
RR[a] for readmission: $\exp(\beta_1)$	1.66 (1.26–2.20)	1.65 (1.24–2.19)	1.82 (1.36–2.42)
RR[a] for death: $\exp(\beta_2)$	1.88 (0.84–4.23)	1.79 (0.80–4.02)	1.45 (0.89–2.35)
Heterogeneity: $\eta = Var_\eta(u_i)$	1.16 (0.93–1.45)	1.14 (0.91–1.42)	1.01 (0.82–1.20)
α	3.5 (fixed)	3.5 (fixed)	1.35 (0.94–1.76)
Copula parameter: θ	0.57 (0.35–0.94)	0.00 (fixed)	0.00 (fixed)
RR for death after readmission: $\theta + 1$	1.57 (1.35–1.94)	1.00 (fixed)	1.00 (fixed)
Kendall's tau: $\tau = \theta/(\theta + 2)$	0.22 (0.14–0.31)	–	–
Maximum penalized log-likelihood	−5541.957	−5558.205	–

[a]RR (Relative Risk) of men (relative to women) on the hazards are examined. "RR>1" indicates that men have more readmissions or poor survival outcomes over women do. The smoothing parameters are estimated as $\kappa_1 = 3.4 \times 10^{13}$ and $\kappa_2 = 6.9 \times 10^{13}$ for both methods by using R *joint.Cox* package.

Conclusion

Propose a **joint** frailty-copula model for dependence between tumour progression and death

- Extend the joint frailty model of Rondeau et al. (2011)

➔ allow intra-subject dependence via copulas

➔ allow recurrence-specific dependence via copulas

Future extensions of our proposed model :

1) Dynamic prediction of death (OS) by prior relapse (TTP) as in Mauguen et al. (2013, 2015)
2) Validation of surrogate endpoints (e.g., PFS) in meta-analysis (with Virginie Rondeau, INSERM Institute, France)
3) Addition of high-dimensional genetic covariates (by using compound covariate approach)

Thank you !