Supplementary Material for "A frailty model for semi-competing risk data with applications to colon cancer"

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A: Conditional survival functions

Using these conditional transition rates, we can now derive the conditional survival function $S(t|Z)$, the probability of staying in state 0 until time t:

$$S(t|Z) = P[T > t|Z] = P[\text{Still in state 0 at } t|Z] = e^{-Z(\Delta_{01}(t)+\Delta_{02}(t))}. \tag{A-1}$$

If there is a transition to state 1 at time t_1, the conditional probability of staying in state 1 until time t_2 is given by

$$\begin{aligned} S_{12}(t_2|t_1, Z) &= e^{-Z\int_{t_1}^{t_2}\lambda_{03}(s)ds} \\ &= e^{-Z(\int_0^{t_2}\lambda_{03}(s)ds - \int_0^{t_1}\lambda_{03}(s)ds)} \\ &= e^{-Z\Delta_{03}(t_1,t_2)}, \end{aligned} \tag{A-2}$$

where $\Delta_{0i}(t) = \int_0^t \lambda_{0i}(u)du$ for $i = 1, 2, 3$, are the cumulative baseline hazard functions, and $\Delta_{03}(u, t) = \Delta_{03}(t) - \Delta_{03}(u)$.

B: Proof of Theorem 1

Proof of (a). From (3), we have

$$
\begin{aligned}
\lambda_1(t_1) &= \lim_{\Delta\to 0} \frac{\mathbb{P}[T_1 \in [t_1, t_1+\Delta)|T_1 \geq t_1, T_2 \geq t_1]}{\Delta} \\
&= \lim_{\Delta\to 0} \frac{\mathbb{P}[T_1 \in [t_1, t_1+\Delta), T_1 \geq t_1, T_2 \geq t_1]}{\Delta \mathbb{P}[T_1 \geq t_1, T_2 \geq t_1]} \\
&= \lim_{\Delta\to 0} \int_0^\infty \frac{\mathbb{P}[T_1 \in [t_1, t_1+\Delta), T_1 \geq t_1, T_2 \geq t_1, z]}{\Delta \mathbb{P}[T_1 \geq t_1, T_2 \geq t_1]} dz \\
&= \int_0^\infty \left(\lim_{\Delta\to 0} \frac{\mathbb{P}[T_1 \in [t_1, t_1+\Delta)|T_1 \geq t_1, T_2 \geq t_1, z]}{\Delta} \right) \frac{\mathbb{P}[T_1 \geq t_1, T_2 \geq t_1|z] g(z)}{\mathbb{P}[T_1 \geq t_1, T_2 \geq t_1]} dz
\end{aligned}
$$

where, the first term is $\lambda_1(t_1|Z)$, the denominator of the second term is $S(t_1)$, the total survival function in t_1, and $g(z)$ is the density function of Z. Thus,

$$
\lambda_1(t_1) = \frac{1}{S(t_1)} \int_0^\infty \lambda_1(t_1|z) \mathbb{P}[T_1 \geq t_1, T_2 \geq t_1|z] g(z) dz, \tag{B-1}
$$

Since T_1 and T_2 are conditionally independent (given Z), we have

$$
\mathbb{P}[T_1 \geq t_1, T_2 \geq t_1|z] = \mathbb{P}[T_1 \geq t_1|z]\mathbb{P}[T_2 \geq t_1|z] = e^{-Z(\Delta_{01}(t_1)+\Delta_{02}(t_1))}, \tag{B-2}
$$

Now, using this result, we have

$$
\begin{aligned}
S(t_1) &= \int_0^\infty \mathbb{P}[T_1 \geq t_1, T_2 \geq t_1|z] g(z) dz = \int_0^\infty e^{-Z(\Delta_{01}(t_1)+\Delta_{02}(t_1))} g(z) dz \\
&= \mathcal{L}_Z(\Delta_{01}(t_1) + \Delta_{02}(t_1)),
\end{aligned} \tag{B-3}
$$

where, $\mathcal{L}_Z(\cdot)$ is the Laplacian function of Z. Therefore, using (B-2) and (B-3) in (B-1) we have:

$$
\lambda_1(t_1) = \frac{\lambda_{01}(t_1)}{\mathcal{L}_Z(s)} \int_0^\infty z e^{-zs} g(z) dz = -\frac{\lambda_{01}(t_1)}{\mathcal{L}_Z(s)} \frac{d}{ds} \mathcal{L}_Z(s), \tag{B-4}
$$

where, $s = \Delta_{01}(t_1) + \Delta_{02}(t_1))$. The result for $\lambda_2(t_2)$ follows analogously. $\square$

Proof of (b). Following the same idea as the previous proof, we have

$$
\begin{aligned}
\lambda_{12}(t_2|t_1) &= \lim_{\Delta\to 0} \frac{\mathbb{P}[T_2 \in [t_2, t_2+\Delta)|T_1 = t_1, T_2 \geq t_2]}{\Delta} \\
&= \frac{1}{\mathbb{P}[T_1 = t_1, T_2 \geq t_2]} \int_0^\infty \lambda_{12}(t_2|t_1, z) \mathbb{P}[T_1 = t_1, T_2 \geq t_2|z] g(z) dz
\end{aligned} \tag{B-5}
$$

From (3) and conditioning via frailty Z, we have

$$\mathbb{P}[T_1 = t_1, T_2 \geq t_2|z] = \frac{\mathbb{P}[T_1 = t_1, T_2 = t_2|Z]}{\lambda_{12}(t_2|t_1, Z)}, \;\; 0 < t_1 < t_2.$$

In (D-4), we present the proof of

$$\mathbb{P}[T_1 = t_1, T_2 = t_2|Z] = \lambda_1(t_1|Z)\lambda_{12}(t_2|t_1, Z)S(t_1|Z)S_{12}(t_2|t_1, Z)$$

where $S_{12}(t_2|t_1, Z) = e^{-Z(\Delta_{03}(t_2)-\Delta_{03}(t_1))}$, and $S(t_1|Z) = e^{-Z(\Delta_{01}(t_1)+\Delta_{02}(t_1))}$

Thus,

$$\mathbb{P}[T_1 = t_1, T_2 \geq t_2|z] = Z\lambda_{01}(t_1)e^{-Z(\Delta_{01}(t_1)+\Delta_{02}(t_1)+\Delta_{03}(t_2)-\Delta_{03}(t_1))}. \tag{B-6}$$

Using this result, we get

$$\begin{aligned}
\mathbb{P}[T_1 = t_1, T_2 \geq t_2] &= \int_0^\infty \mathbb{P}[T_1 = t_1, T_2 \geq t_2|z]g(z)dz \\
&= \int_0^\infty Z\lambda_{01}(t_1)e^{-Z(\Delta_{01}(t_1)+\Delta_{02}(t_1)+\Delta_{03}(t_2)-\Delta_{03}(t_1))}g(z)dz \\
&= -\lambda_{01}(t_1)\frac{d}{ds}\mathcal{L}_Z(s) \qquad \text{(B-7)}
\end{aligned}$$

where, $s = \Delta_{01}(t_1) + \Delta_{02}(t_1) + \Delta_{03}(t_2) - \Delta_{03}(t_1)$. Finally, substituting (B-6) and (B-7) in (B-5), we get

$$\begin{aligned}
\lambda_{12}(t_2|t_1) &= -\frac{\lambda_{03}(t_2)}{\frac{d}{ds}\mathcal{L}_Z(s)}\int_0^\infty Z^2 e^{-Z(\Delta_{01}(t_1)+\Delta_{02}(t_1)+\Delta_{03}(t_2)-\Delta_{03}(t_1))}g(z)dz \\
&= -\frac{\lambda_{03}(t_2)}{\frac{d}{ds}\mathcal{L}_Z(s)}\frac{d^2}{ds}\mathcal{L}_Z(s) \\
&= -\lambda_{03}(t_2)\frac{d}{ds}\log\left(\frac{1}{ds}\mathcal{L}_Z(s)\right). \qquad \text{(B-8)}
\end{aligned}$$

where, $s = \Delta_{01}(t_1) + \Delta_{02}(t_1) + \Delta_{03}(t_2) - \Delta_{03}(t_1)$.

□

C: Derivation of some important results

Local measure of association

Following Clayton (1978) and Oakes (1982), we can compute a local measure of association between T_1 and T_1, $\vartheta^\star(t_1, t_2)$, defined in (7). First, for the general model, from (5) and considering the PVF frailty model, we can write the joint survival function $S(t_1, t_2)$ as:

$$S(t_1,t_2)=\exp\left\{\frac{1-\gamma}{\theta\gamma}\left[1-\left(1+\frac{\theta(\Delta_{01}(t_1)+\Delta_{02}(t_2)+\Delta_{03}(t_2)-\Delta_{03}(t_1))}{1-\gamma}\right)^{\gamma}\right]\right\} \tag{C-1}$$

We also have

$$\begin{aligned}
\frac{\partial S(t_1,t_2)}{\partial t_1} &= -S(t_1,t_2)(\lambda_{01}(t_1)+\lambda_{02}(t_1)-\lambda_{03}(t_1)) \qquad \text{(C-2)}\\
&\times\left(1+\frac{\theta(\Delta_{01}(t_1)+\Delta_{02}(t_2)+\Delta_{03}(t_2)-\Delta_{03}(t_1))}{1-\gamma}\right)^{\gamma-1},\\
\frac{\partial S(t_1,t_2)}{\partial t_2} &= -S(t_1,t_2)\lambda_{03}(t_2)\left(1+\frac{\theta(\Delta_{01}(t_1)+\Delta_{02}(t_2)+\Delta_{03}(t_2)-\Delta_{03}(t_1))}{1-\gamma}\right)^{\gamma-1}, \qquad \text{(C-3)}\\
\frac{\partial S(t_1,t_2)}{\partial t_1\partial t_2} &= S(t_1,t_2)(\lambda_{01}(t_1)+\lambda_{02}(t_1)-\lambda_{03}(t_1))\lambda_{03}(t_2)\\
&\times\left(1+\frac{\theta(\Delta_{01}(t_1)+\Delta_{02}(t_2)+\Delta_{03}(t_2)-\Delta_{03}(t_1))}{1-\gamma}\right)^{\gamma-2}\\
&\times\left[\theta+\left(1+\frac{\theta(\Delta_{01}(t_1)+\Delta_{02}(t_2)+\Delta_{03}(t_2)-\Delta_{03}(t_1))}{1-\gamma}\right)^{\gamma}\right] \qquad \text{(C-4)}
\end{aligned}$$

Substituting (C-1), (C-2), (C-3) and (C-4) in (7), we obtain the local measure association $\vartheta^*(t_1,t_2)$ for the general model, given in (8). Analogously, we can get $\vartheta^*(t_1,t_2)$ for the restricted model ($\lambda_{02}(\cdot)=\lambda_{03}(\cdot)$).

Marginal transition probabilities

(a) **Transition probability to recurrence state:**

$$\begin{aligned}
\mathbb{P}_{01}(t) &= \mathbb{P}[\text{still in state 1 at } t|\text{the state 0 was entered at time } t=0]\\
&= \mathbb{P}[\text{not having had a transition out of state 0 before the transition of interest}]\\
&\times(\text{transition to state 1 before } t)\\
&\times\mathbb{P}[\text{staying at state 1 until time } t]
\end{aligned}$$

Using conditioning arguments (on Z), this can be written as:

$$\begin{aligned}
\mathbb{P}_{01}(t) = \int_0^\infty\int_0^t &\mathbb{P}[\text{not having had a transition out of state 0 before time s}|z]\\
&\times(\text{transition to state 1 at time } s \text{ given } z)\\
&\times\mathbb{P}[\text{staying at state 1 until time } t|z]g(z)dsdz,
\end{aligned}$$

where $g(z)$ represents the probability density function of the frailty Z. This is equivalent to

$$\mathbb{P}_{01}(t) = \int_0^\infty \int_0^t S(s|z)\lambda_1(s|z)S_{12}(t|s,z)g(z)dsdz$$

where $S(s|Z)$, $\lambda_1(s|Z)$ and $S_{12}(t|s,Z)$ are given in (A-1), (4) and (A-2), respectively. Thus

$$\mathbb{P}_{01}(t) = \int_0^\infty \int_0^t e^{-z(\Delta_{01}(s)+\Delta_{02}(s))} z\lambda_{01}(s)e^{-z\Delta_{03}(s,t)}g(z)dsdz$$

where $\Delta_{0i}(t) = \int_0^t \lambda_{0i}(s)ds$ for $i = 1, 2, 3$, are the cumulative baseline hazard functions and $\Delta_{03}(u,t) = \Delta_{03}(t) - \Delta_{03}(u)$. Thus,

$$\mathbb{P}_{01}(t) = \int_0^t \lambda_{01}(s) \int_0^\infty e^{-z(\Delta_{01}(s)+\Delta_{02}(s)+\Delta_{03}(s,t))} zg(z)dsdz$$

Now, using the Laplace transform of the frailty Z with PVF distribution given in (2) with median 1 and variance $\theta > 0$, we have:

$$\mathbb{P}_{01}(t) = \int_0^t \lambda_{01}(s)\left(1 + \frac{\theta s_1(s,t)}{1-\gamma}\right)^{\gamma-1} \exp\left\{\frac{1-\gamma}{\theta\gamma}\left[1 - \left(1 + \frac{\theta s_1(s,t)}{1-\gamma}\right)^{\gamma}\right]\right\} ds.$$

where $s_1(t, t_1) = \Delta_{01}(s) + \Delta_{02}(s) + \Delta_{03}(s,t)$.

(b) **Transition probability to death state:**

The derivation of $\mathbb{P}_0 2(t)$ follows similarly, and we have

$$\mathbb{P}_{02}(t) = \int_0^t \lambda_{02}(s)\left(1 + \frac{\theta s_2(s)}{1-\gamma}\right)^{\gamma-1} \exp\left\{\frac{1-\gamma}{\theta\gamma}\left[1 - \left(1 + \frac{\theta s_2(s)}{1-\gamma}\right)^{\gamma}\right]\right\} ds.$$

where $s_2(s) = \Delta_{01}(ts) + \Delta_{02}(s)$. Since state 2 is absorbing in this function, we do not have a contribution from staying in state 2 until time t.

(c) **Transition probability from recurrence state to death state:**

The transition probability $\mathbb{P}_{12}(t|t_1)$ is conditional on the state 1 reached at time t_1. Using similar conditioning arguments as above, this can be expressed as:

$$\mathbb{P}_{12}(t|t_1) = \int_0^\infty \int_0^t S_{12}(s|t_1,z)\lambda_{12}(s|t_1,z)g(z)dsdz$$

where $S_{12}(t|s, Z)$ and $\lambda_{12}(s|t_1, z)$ are given in (A-2) and (4), respectively. Thus

$$\mathbb{P}_{01}(t) = \int_0^t \lambda_{03}(s) \int_0^\infty e^{-z\Delta_{03}(s,t)} zg(z) ds dz$$

Finally, using the Laplacian of Z, and for $s_3(s, t_1) = \Delta_{03}(t_1, s)$, we get,

$$\mathbb{P}_{12}(t|t_1) = \int_0^t \lambda_{02}(s) \left(1 + \frac{\theta s_3(s,t)}{1-\gamma}\right)^{\gamma-1} \exp\left\{\frac{1-\gamma}{\theta\gamma}\left[1 - \left(1 + \frac{\theta s_3(s,t)}{1-\gamma}\right)^{\gamma}\right]\right\} ds.$$

D: Likelihood

First, we derive the expressions of marginal transition rates, and the joint probability density function. This leads to the construction of the likelihood function.

Marginal transition rates

(a) **Marginal transition rate to recurrence and death:**

Using the definition of transition rate to recurrence given in (3), for $t_1 > 0$, we have

$$\begin{aligned}\lambda_1(t_1) &= \lim_{\Delta\to 0} \frac{\mathbb{P}[T_1 \in [t_1, t_1 + \Delta)|T_1 \geq t_1, T_2 \geq t_1]}{\Delta} \\ &= \lim_{\Delta\to 0} \frac{\mathbb{P}[T_1 \in [t_1, t_1 + \Delta), T_1 \geq t_1, T_2 \geq t_1]}{\Delta \mathbb{P}[T_1 \geq t_1, T_2 \geq t_1]}\end{aligned}$$

Since $\{T_1 \in [t_1, t_1 + \Delta), T_2 \geq t_1\} \subset \{T_1 \in [t_1, t_1 + \Delta), T_1 \geq t_1, T_2 \geq t_1\}$, we get

$$\begin{aligned}\lambda_1(t_1) &= \lim_{\Delta\to 0} \frac{\mathbb{P}[T_1 \in [t_1, t_1 + \Delta), T_2 \geq t_1]}{\Delta} \frac{1}{\mathbb{P}[T_1 \geq t_1, T_2 \geq t_1]} \\ &= \frac{\mathbb{P}[T_1 = t_1, T_2 \geq t_1]}{\mathbb{P}[T_1 \geq t_1, T_2 \geq t_1]}\end{aligned} \tag{D-1}$$

Similarly, for $t_2 > 0$, we have

$$\lambda_2(t_2) = \frac{\mathbb{P}[T_2 = t_2, T_1 \geq t_2]}{\mathbb{P}[T_1 \geq t_2, T_2 \geq t_2]}. \tag{D-2}$$

(b) **Marginal transition rate from recurrence to death:** Similarly, from the definition of transition rates to death after recurrence given in (3), for $0 < t_1 < t_2$, we have

$$\begin{aligned}\lambda_{12}(t_2|t_1) &= \lim_{\Delta\to 0} \frac{\mathbb{P}[T_2 \in [t_2, t_2 + \Delta)|T_1 = t_1, T_2 \geq t_2]}{\Delta} \\ &= \lim_{\Delta\to 0} \frac{\mathbb{P}[T_2 \in [t_2, t_2 + \Delta), T_1 = t_1, T_2 \geq t_2]}{\Delta} \frac{1}{\mathbb{P}[T_1 = t_1, T_2 \geq t_2]}\end{aligned}$$

Since $\{T_2 \in [t_2, t_2+\Delta), T_1 = t_1,\} \subset \{T_2 \in [t_2, t_2+\Delta), T_1 = t_1, T_2 \geq t_2\}$, we have

$$\begin{aligned}
\lambda_{12}(t_2|t_1) &= \lim_{\Delta \to 0} \frac{\mathbb{P}[T_2 \in [t_2, t_2+\Delta), T_1 = t_1]}{\Delta} \frac{1}{\mathbb{P}[T_1 = t_1, T_2 \geq t_2]} \\
&= \frac{\mathbb{P}[T_2 = t_2, T_1 = t_1]}{\mathbb{P}[T_1 = t_1, T_2 \geq t_2]} \qquad \text{(D-3)}
\end{aligned}$$

Joint probability density function

We now derive the expression of the joint density function, denoted by $f(t_1, t_2)$, in the upper quadrant $0 < t_1 < t_2$. This is given as

$$f(t_1, t_2) = \mathbb{P}[T_1 = t_1, T_2 = t_2 > t_1] = \mathbb{P}[T_1 = t_1, T_2 = t_2, T_2 > t_1],$$

Since $\{T_1 = t_1, T_2 = t_2\} \subset \{T_1 = t_1, T_2 = t_2, T_2 > t_1\}$, we have

$$\begin{aligned}
f(t_1, t_2) &= \mathbb{P}[T_1 = t_1, T_2 = t_2] \\
&= \mathbb{P}[T_1 = t_1, T_2 = t_2] \left(\frac{\mathbb{P}[T_1 = t_1, T_2 > t_1]}{\mathbb{P}[T_1 = t_1, T_2 > t_1]}\right) \left(\frac{\mathbb{P}[T_1 > t_1, T_2 > t_1]}{\mathbb{P}[T_1 > t_1, T_2 > t_1]}\right) \left(\frac{\mathbb{P}[T_1 = t_1, T_2 \geq t_2]}{\mathbb{P}[T_1 = t_1, T_2 \geq t_2]}\right) \\
&= \mathbb{P}[T_1 > t_1, T_2 > t_1] \left(\frac{\mathbb{P}[T_1 = t_1, T_2 > t_1]}{\mathbb{P}[T_1 > t_1, T_2 > t_1]}\right) \left(\frac{\mathbb{P}[T_1 = t_1, T_2 = t_2]}{\mathbb{P}[T_1 = t_1, T_2 \geq t_2]}\right) \left(\frac{\mathbb{P}[T_1 = t_1, T_2 \geq t_2]}{\mathbb{P}[T_1 = t_1, T_2 > t_1]}\right)
\end{aligned}$$

Then, from (D-1) and (D-3), we have

$$f(t_1, t_2) = \lambda_1(t_1)\lambda_{12}(t_2|t_1)\mathbb{P}[T_1 > t_1, T_2 > t_1] \left(\frac{\mathbb{P}[T_2 \geq t_2 | T_1 = t_1]}{\mathbb{P}[T_2 > t_1 | T_1 = t_1]}\right),$$

Now, using $S(t_1) = \mathbb{P}[T_1 > t_1, T_2 > t_1]$, $S_{12}(t_2|t_1) = \mathbb{P}[T_2 \geq t_2 | T_1 = t_1]$ and $\mathbb{P}[T_2 > t_1 | T_1 = t_1] = 1$, we obtain the joint probability density function as

$$\begin{aligned}
f(t_1, t_2) &= \lambda_1(t_1)\lambda_{12}(t_2|t_1)S(t_1)S_{12}(t_2|t_1) \\
&= \lambda_1(t_1)\lambda_{12}(t_2|t_1) \exp\left\{-\int_0^{t_1} (\lambda_1(s) + \lambda_2(s))ds\right\} \exp\left\{-\int_{t_1}^{t_2} \lambda_{12}(s|t_1)ds\right\} \qquad \text{(D-4)}
\end{aligned}$$

where, $S(t)$ is the general survival function.

Probability density function on line $T_1 = \infty$

Note

$$\begin{aligned}
f_\infty(t_2) &= \mathbb{P}[T_1 = \infty, T_2 = t_2] \\
&= \mathbb{P}[T_1 > t_2, T_2 = t_2] \\
&= \frac{\mathbb{P}[T_1 > t_2, T_2 = t_2]}{\mathbb{P}[T_1 > t_2, T_2 > t_2]} \mathbb{P}[T_1 > t_2, T_2 > t_2],
\end{aligned}$$

Using (D-2), and the fact $S(t_2) = \mathbb{P}[T_1 > t_2, T_2 > t_2]$, we obtain

$$f_\infty(t_2) = \lambda_2(t_2)S(t_2) = \lambda_2(t_2)\exp\left\{-\int_0^{t_2}(\lambda_1(s) + \lambda_2(s))ds\right\} \tag{D-5}$$

Likelihood construction

Let $\boldsymbol{\vartheta} = (\theta, \boldsymbol{\eta}_1, \boldsymbol{\eta}_2, \boldsymbol{\eta}_3, \boldsymbol{\varphi}_1, \boldsymbol{\varphi}_2, \boldsymbol{\varphi}_3)$ be the vector of estimable parameters, and $(Y_1, Y_2, \delta_1, \delta_2)$ the observation for each individual where $Y_2 = \min\{T_2, C\}$, $\delta_2 = I_{\{T_2 \le C\}}$, $Y_1 = \min\{T_1, Y_2\}$ and $\delta_1 = I_{\{T_1 \le Y_2\}}$. We construct the likelihood function for each of the possible observable cases shown in Table 1.

Table 1: Possible $(Y_1, Y_2, \delta_1, \delta_2)$ combinations under semi-competing risks.

Cases	Scenario	(Y_1, Y_2)	(δ_1, δ_2)
1	recurrence and censoring before death	(T_1, C)	$(1, 0)$
2	Death after recurrence	(T_1, T_2)	$(1, 1)$
3	Death without recurrence	(T_2, T_2)	$(0, 1)$
4	Censoring before recurrence and death	(C, C)	$(0, 0)$

Case 1: When the first observation is recurrence with the censoring indicator $(\delta_1, \delta_2) = (1, 0)$, and $(Y_1, Y_2) = (T_1, C)$, then

$$\begin{aligned} L_1(\boldsymbol{\vartheta}, Z) &= \mathbb{P}[T_1 = Y_1, T_2 > Y_2|\boldsymbol{\vartheta}, Z] \\ &= \int_{Y_2}^{\infty} \mathbb{P}[T_1 = Y_1, T_2 = v|\boldsymbol{\vartheta}, Z]dv \\ &= \int_{Y_2}^{\infty} f(Y_1, v|\boldsymbol{\vartheta}, Z)dv \end{aligned}$$

Using (D-4), we have

$$\begin{aligned} L_1(\boldsymbol{\vartheta}, Z) = \lambda_1(Y_1|\boldsymbol{\vartheta}, Z)&\exp\left\{-\int_0^{Y_1}(\lambda_1(s|\boldsymbol{\vartheta}, Z) + \lambda_2(s|\boldsymbol{\vartheta}, Z))ds\right\} \\ \times &\int_{Y_2}^{\infty} \lambda_{12}(v|Y_1, \boldsymbol{\vartheta}, Z)\exp\left\{-\int_{Y_1}^{v}\lambda_{12}(s|Y_1, \boldsymbol{\vartheta}, Z)ds\right\}dv \end{aligned}$$

Furthermore, from (D-3) and the fact that $S_{12}(v|Y_1, \boldsymbol{\vartheta}, Z) = \exp\left\{-\int_{Y_1}^{v}\lambda_{12}(s|Y_1, \boldsymbol{\vartheta}, Z)ds\right\}$, we can show that

$$S_{12}(Y_2|Y_1, \boldsymbol{\vartheta}, Z) = \int_{Y_2}^{\infty} \lambda_{12}(v|Y_1, \boldsymbol{\vartheta}, Z)\exp\left\{-\int_{Y_1}^{v}\lambda_{12}(s|Y_1, \boldsymbol{\vartheta}, Z)ds\right\}dv$$

With this, and from the conditional model given in (4), we have

$$
\begin{aligned}
L_1(\boldsymbol{\vartheta}, Z) &= Z\lambda_{01}(Y_1|\boldsymbol{\vartheta}) \\
&\quad \times \exp\left\{-Z\left(\int_0^{Y_1} \lambda_{01}(s|\boldsymbol{\vartheta})ds + \int_0^{Y_1} \lambda_{02}(s|\boldsymbol{\vartheta})ds + \int_0^{Y_2} \lambda_{03}(s|\boldsymbol{\vartheta})ds - \int_0^{Y_1} \lambda_{03}(s|\boldsymbol{\vartheta})ds\right)\right\} \\
&= Z\lambda_{01}(Y_1|\boldsymbol{\vartheta}) \exp\left\{-Z\left(\Delta_{01}(Y_1|\boldsymbol{\vartheta}) + \Delta_{02}(Y_1|\boldsymbol{\vartheta}) + \Delta_{03}(Y_2|\boldsymbol{\vartheta}) - \Delta_{03}(Y_1|\boldsymbol{\vartheta})\right)\right\}
\end{aligned}
$$

where $\Delta_{0i}(t|\boldsymbol{\vartheta}) = \int_0^t \lambda_{0i}(s|\boldsymbol{\vartheta})ds$ is the cumulative baseline hazard function, $i = 1, 2, 3$. Therefore, the marginal likelihood function is given by

$$
L_1(\boldsymbol{\vartheta}) = \lambda_{01}(Y_1|\boldsymbol{\vartheta}) \int_0^{\infty} Z \exp\left\{-Z\left(\Delta_{01}(Y_1|\boldsymbol{\vartheta}) + \Delta_{02}(Y_1|\boldsymbol{\vartheta}) + \Delta_{03}(Y_2|\boldsymbol{\vartheta}) - \Delta_{03}(Y_1|\boldsymbol{\vartheta})\right)\right\} g(z)dz
$$

where $g(z)$ is the density function of frailty Z with PVF distribution given in (1). Then, using the Laplacian $\mathcal{L}_Z^{(r)}(s) = (-1)^r \mathbb{E}[Z^r e^{-Zs}]$, we obtain

$$
\begin{aligned}
L_1(\boldsymbol{\vartheta}) &= \lambda_{01}(Y_1|\boldsymbol{\vartheta}) \left(1 + \frac{\theta(\Delta_{01}(Y_1|\boldsymbol{\vartheta}) + \Delta_{02}(Y_1|\boldsymbol{\vartheta}) + \Delta_{03}(Y_2|\boldsymbol{\vartheta}) - \Delta_{03}(Y_1|\boldsymbol{\vartheta}))}{1-\gamma}\right)^{\gamma-1} \\
&\quad \times \exp\left\{\frac{1-\gamma}{\gamma\theta}\left[1 - \left(1 + \frac{\theta(\Delta_{01}(Y_1|\boldsymbol{\vartheta}) + \Delta_{02}(Y_1|\boldsymbol{\vartheta}) + \Delta_{03}(Y_2|\boldsymbol{\vartheta}) - \Delta_{03}(Y_1|\boldsymbol{\vartheta}))}{1-\gamma}\right)^{\gamma}\right]\right\}
\end{aligned}
\tag{D-6}
$$

Case 2: When the first observation is recurrence followed by death with the censoring indicator $(\delta_1, \delta_2) = (1, 1)$, and $(Y_1, Y_2) = (T_1, T_2)$, we have

$$
L_2(\boldsymbol{\vartheta}, Z) = \mathbb{P}[T_1 = Y_1, T_2 = Y_2|\boldsymbol{\vartheta}, Z] = f(Y_1, Y_2|\boldsymbol{\vartheta}, Z)
$$

Using (D-4), we get

$$
\begin{aligned}
L_2(\boldsymbol{\vartheta}, Z) &= \lambda_1(Y_1|\boldsymbol{\vartheta}, Z)\lambda_{12}(Y_2|Y_1, \boldsymbol{\vartheta}, Z) \\
&\quad \times \exp\left\{-\left(\int_0^{Y_1} \lambda_1(s|\boldsymbol{\vartheta}, Z)ds + \int_0^{Y_1} \lambda_2(s|\boldsymbol{\vartheta}, Z)ds + \int_{Y_1}^{Y_2} \lambda_{12}(s|Y_1, \boldsymbol{\vartheta}, Z)ds\right)\right\} \\
&= Z^2\lambda_{01}(Y_1|\boldsymbol{\vartheta})\lambda_{03}(Y_2|\boldsymbol{\vartheta}) \\
&\quad \times \exp\left\{-Z\left(\int_0^{Y_1} \lambda_{01}(s|\boldsymbol{\vartheta})ds + \int_0^{Y_1} \lambda_{02}(s|\boldsymbol{\vartheta})ds + \int_0^{Y_2} \lambda_{03}(s|\boldsymbol{\vartheta})ds - \int_0^{Y_1} \lambda_{03}(s|\boldsymbol{\vartheta})ds\right)\right\}
\end{aligned}
$$

The marginal likelihood function is given by

$$\begin{aligned}L_2(\boldsymbol{\vartheta}) &= \lambda_{01}(Y_1|\boldsymbol{\vartheta})\lambda_{03}(Y_2|\boldsymbol{\vartheta}) \\ &\times \int_0^{\infty} Z^2 \exp\left\{-Z\left(\Delta_{01}(s|\boldsymbol{\vartheta}) + \Delta_{02}(s|\boldsymbol{\vartheta}) + \Delta_{03}(s|\boldsymbol{\vartheta}) - \Delta_{03}(s|\boldsymbol{\vartheta})\right)\right\} g(z)dz\end{aligned}$$

Once again, utilizing the Laplacian (as in Case 1), we have

$$\begin{aligned}L_2(\boldsymbol{\vartheta}) &= \lambda_{01}(Y_1|\boldsymbol{\vartheta})\lambda_{03}(Y_2|\boldsymbol{\vartheta}) \left(1 + \frac{\theta(\Delta_{01}(Y_1|\boldsymbol{\vartheta}) + \Delta_{02}(Y_1|\boldsymbol{\vartheta}) + \Delta_{03}(Y_2|\boldsymbol{\vartheta}) - \Delta_{03}(Y_1|\boldsymbol{\vartheta}))}{1-\gamma}\right)^{\gamma-2} \\ &= \times \left[\theta + \left(1 + \frac{\theta(\Delta_{01}(Y_1|\boldsymbol{\vartheta}) + \Delta_{02}(Y_1|\boldsymbol{\vartheta}) + \Delta_{03}(Y_2|\boldsymbol{\vartheta}) - \Delta_{03}(Y_1|\boldsymbol{\vartheta}))}{1-\gamma}\right)^{\gamma}\right] \\ &\times \exp\left\{\frac{1-\gamma}{\gamma\theta}\left[1 - \left(1 + \frac{\theta(\Delta_{01}(Y_1|\boldsymbol{\vartheta}) + \Delta_{02}(Y_1|\boldsymbol{\vartheta}) + \Delta_{03}(Y_2|\boldsymbol{\vartheta}) - \Delta_{03}(Y_1|\boldsymbol{\vartheta}))}{1-\gamma}\right)^{\gamma}\right]\right\}\end{aligned} \tag{D-7}$$

Case 3: When the recurrence time is censored by death with the censoring indicator $(\delta_1, \delta_2) = (0, 1)$ and $(Y_1, Y_2) = (T_2, T_2)$, we have

$$L_3(\boldsymbol{\vartheta}, Z) = \mathbb{P}[T_1 = \infty, T_2 = Y_2|\boldsymbol{\vartheta}, Z] = f_{\infty}(Y_2|\boldsymbol{\vartheta}, Z)$$

Using (D-5), we get

$$\begin{aligned}L_3(\boldsymbol{\vartheta}, Z) &= \lambda_2(Y_2|\boldsymbol{\vartheta}, Z) \exp\left\{-\left(\int_0^{Y_2} \lambda_1(s|\boldsymbol{\vartheta}, Z)ds + \int_0^{Y_2} \lambda_2(s|\boldsymbol{\vartheta}, Z)ds\right)\right\} \\ &= Z\lambda_{02}(Y_2|\boldsymbol{\vartheta}) \exp\left\{-Z\left(\Delta_{01}(Y_2|\boldsymbol{\vartheta}) + \Delta_{02}(Y_2|\boldsymbol{\vartheta})\right)\right\}\end{aligned}$$

Then, similar to (D-6), we get

$$\begin{aligned}L_3(\boldsymbol{\vartheta}) &= \lambda_{02}(Y_2|\boldsymbol{\vartheta}) \left(1 + \frac{\theta(\Delta_{01}(Y_2|\boldsymbol{\vartheta}) + \Delta_{02}(Y_2|\boldsymbol{\vartheta}))}{1-\gamma}\right)^{\gamma-1} \\ &\times \exp\left\{\frac{1-\gamma}{\gamma\theta}\left[1 - \left(1 + \frac{\theta(\Delta_{01}(Y_2|\boldsymbol{\vartheta}) + \Delta_{02}(Y_2|\boldsymbol{\vartheta}))}{1-\gamma}\right)^{\gamma}\right]\right\}\end{aligned} \tag{D-8}$$

Case 4: When the two failure times are censored with the censoring indicator $(\delta_1, \delta_2) = (0, 0)$ and $(Y_1, Y_2) = (C, C) = (Y_2, Y_2) = (Y_1, Y_1)$, we have

$$
\begin{aligned}
L_4(\boldsymbol{\vartheta}, Z) &= \mathbb{P}[T_1 > Y_2, T_2 > Y_2|\boldsymbol{\vartheta}, Z] \\
&= S(Y_2|\boldsymbol{\vartheta}, Z) \\
&= \exp\left\{-\left(\int_0^{Y_2} \lambda_1(s|\boldsymbol{\vartheta}, Z)ds + \int_0^{Y_2} \lambda_2(s|\boldsymbol{\vartheta}, Z)ds\right)\right\} \\
&= \exp\left\{-Z\left(\Delta_{01}(Y_2|\boldsymbol{\vartheta}) + \Delta_{02}(Y_2|\boldsymbol{\vartheta})\right)\right\}
\end{aligned}
$$

Using the Laplace transform of the frailty, we obtain that the marginal likelihood function is given by

$$
L_4(\boldsymbol{\vartheta}) = \exp\left\{\frac{1-\gamma}{\gamma\theta}\left[1 - \left(1 + \frac{\theta(\Delta_{01}(Y_2|\boldsymbol{\vartheta}) + \Delta_{02}(Y_2|\boldsymbol{\vartheta}))}{1-\gamma}\right)^{\gamma}\right]\right\} \tag{D-9}
$$

Finally, combining (D-6), (D-7), (D-8) and (D-9), and for a sample of size n, the likelihood function is given by

$$
\begin{aligned}
L(\boldsymbol{\vartheta}) = &\prod_{j=1}^{n} \lambda_{01}(Y_{j1}|\boldsymbol{\vartheta})^{\delta_{j1}} \lambda_{02}(Y_{j2}|\boldsymbol{\vartheta})^{\delta_{j2}(1-\delta_{j1})} \lambda_{03}(Y_{j2}|\boldsymbol{\vartheta})^{\delta_{j1}\delta_{j2}} \left\{\theta + \left(1 + \frac{\theta K_{j1}}{1-\gamma}\right)^{\gamma}\right\}^{\delta_{j1}\delta_{j2}} \\
&\times \left(1 + \frac{\theta K_{j1}}{1-\gamma}\right)^{\delta_{i1}(\gamma-1-\delta_{j2})} \left\{\exp\left(\frac{1-\gamma}{\theta\gamma}\left[1 - \left(1 + \frac{\theta K_{j1}}{1-\gamma}\right)^{\gamma}\right]\right)\right\}^{\delta_{j1}} \\
&\times \left(1 + \frac{\theta K_{j2}}{1-\gamma}\right)^{(\gamma-1)\delta_{j2}(1-\delta_{j1})} \left\{\exp\left(\frac{1-\gamma}{\theta\gamma}\left[1 - \left(1 + \frac{\theta K_{j2}}{1-\gamma}\right)^{\gamma}\right]\right)\right\}^{1-\delta_{j1}}
\end{aligned} \tag{D-10}
$$

where $K_{j1} = \Delta_{01}(Y_{j1}|\boldsymbol{\vartheta}) + \Delta_{02}(Y_{j1}|\boldsymbol{\vartheta}) + \Delta_{03}(Y_{j2}|\boldsymbol{\vartheta}) - \Delta_{03}(Y_{j1}|\boldsymbol{\vartheta})$, $K_{j2} = \Delta_{01}(Y_{j2}|\boldsymbol{\vartheta}) + \Delta_{02}(Y_{j2}|\boldsymbol{\vartheta})$ for $j = 1, \ldots, n$.

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