Survival Exam

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1 Theoretical part

1.1 Marginal models

1) The marginal survival distribution of W_1 given X can be written as

$$\begin{aligned} P(W_1 > w \mid X) &= \int_0^\infty P(W_1 > w, \mid \rho, X) P(\mathrm{d}\rho \mid X) \\ &= \int_0^\infty P(W_1 > w \mid \rho, X) P(\mathrm{d}\rho) \\ &= \int_0^\infty \exp(-\Lambda_1(w)\rho e^{X^T\beta_1}) P(\mathrm{d}\rho), \end{aligned}$$

where we have used the independence between X and ρ for the second step and the assumption about the conditional survival of W_1 given X, and ρ. We can recognize the last expression as the Laplace transform of (the density) of the random variable ρ. For a Gamma distributed random variable with shape $k > 0$ and scale $\eta > 0$, the Laplace transform is given as

$$\mathcal{L}_{k,\eta}(s) = (1 + \eta s)^{-k}. \tag{1}$$

For a Gamma distributed random variable with mean 1 and variance θ the shape and scale parameters become $k = \theta^{-1}$ and $\eta = \theta$, so

$$P(W_1 > w \mid X) = \mathcal{L}_{1/\theta,\theta}(\Lambda_1(w)e^{X^T\beta_1}) = (1 + \theta\Lambda_1(w)e^{X^T\beta_1})^{-1/\theta}.$$

The marginal hazard of W_1 given X can be calculated directly from this using that $\log(\mathcal{L}_{1/\theta,\theta}(s))' = -(1 + \theta s)^{-1}$, which then gives that

$$\frac{\partial}{\partial w}\left\{-\log(P(W_1 > w \mid X))\right\} = \frac{\lambda_1(w)e^{X^T\beta_1}}{1 + \theta\Lambda_1(w)e^{X^T\beta_1}}.$$

2) We can write

$$\begin{aligned}
&P(W_1 \in [t, t+h] \mid W_1 > t, C > t, X, \rho) \\
&= \frac{P(W_1 \in [t, t+h], C > t, X, \rho)}{P(W_1 > t, C > t, X, \rho)} \\
&= \frac{P(C > t \mid W_1 \in [t, t+h], X, \rho) P(W_1 \in [t, t+h], X, \rho)}{P(C > t \mid W_1 > t, X, \rho) P(W_1 > t, X, \rho)} \\
&= \frac{P(C > t \mid X, \rho) P(W_1 \in [t, t+h], X, \rho)}{P(C > t \mid X, \rho) P(W_1 > t, X, \rho)} \\
&= \frac{P(W_1 \in [t, t+h], X, \rho)}{P(W_1 > t, X, \rho)} \\
&= P(W_1 \in [t, t+h] \mid W_1 > t, X, \rho),
\end{aligned}$$

where we have used $C \perp\!\!\!\perp W_1 \mid (X, \rho)$ for the third equality. Taking the limit for $h \to 0$ in the expression above shows that the observed hazard of W_1 given X and ρ is equal to the hazard of W_1 given X and ρ when there is no censoring, which is immediately derived to be $\lambda_1(t)\rho e^{X^T \beta_1}$.

a) Using similar arguments as above, we can write

$$\begin{aligned}
&P(W_1 \in [t, t+h] \mid W_1 > t, C > t, X) \\
&= \frac{\int_0^\infty P(C > t \mid X, \rho) P(W_1 \in [t, t+h], X, \rho) \, \mathrm{d}\rho}{\int_0^\infty P(C > t \mid X, \rho) P(W_1 > t, X, \rho) \, \mathrm{d}\rho},
\end{aligned}$$

and then using that $C \perp\!\!\!\perp \rho \mid X$ we get

$$\begin{aligned}
P(W_1 \in [t, t+h] \mid W_1 > t, C > t, X) &= \frac{\int_0^\infty P(W_1 \in [t, t+h], X, \rho) \, \mathrm{d}\rho}{\int_0^\infty P(W_1 > t, X, \rho) \, \mathrm{d}\rho} \\
&= \frac{P(W_1 \in [t, t+h], X)}{P(W_1 > t, X)} \\
&= P(W_1 \in [t, t+h] \mid W_1 > t, X).
\end{aligned}$$

Taking the limit $h \to 0$ shows that the observed marginal hazard is equal to the marginal hazard when there is no censoring, which we derived in question 1).

b) Because the hazard for the observed process is the same as the hazard for the uncensored process, the parameters of hazard of the uncensored process can be estimated based on the observed data. So, the short answer is "yes". A longer explanation is as follows.

We know that inference for marginal models with an unobserved frailty can be achieved in a two-stage method (Martinussen/Scheike book and Frank's lecture notes): 1) Estimate the marginal parameters (ignoring the frailty). 2) Plug the marginal estimates into the likelihood for θ and maximize this.

This can be done by noting that with a cox marginal model and gamma distributed frailty, the observed likelihood for cluster i is proportional to:

$$\sum_j \int_0^\tau \log(1+\theta \sum_j N_{ij}(t-)) dN_{ij}(\tau) H_{ij} - (1/\theta + \sum_j N_{ij}(\tau)) \log(1+\sum_j \exp(\theta H_{ij}) - 1)),$$

where $H_{ij} = \exp(\beta^T X_{ij}) \Lambda_{01}(T_{ij})$. So, replacing β and Λ_{01} by the marginal estimates, we can obtain a pdseudolikelihood, for which consistency and asymptotic normality have been shown. Another approach is the one-step approach, where an estimator can be obtained by maximizing over both the marginal parameters and frailty parameter in one step.

3) With similar arguments as above and using that $W_2 \perp\!\!\!\perp (W_1, C) \mid (X, \rho)$ we have that

$$\begin{aligned}
&P(W_2 \in [t, t+h] \mid W_2 > t, C > W_1 + t, X, \rho) \\
&= \frac{P(W_2 \in [t, t+h], C > W_1 + t, X, \rho)}{P(W_2 > t, C > W_1 + t, X, \rho)} \\
&= \frac{P(C > W_1 + t \mid W_2 \in [t, t+h], X, \rho) P(W_2 \in [t, t+h], X, \rho)}{P(C > W_1 + t \mid W_2 > t, X, \rho) P(W_2 > t, X, \rho)} \\
&= \frac{P(C > W_1 + t \mid X, \rho) P(W_2 \in [t, t+h], X, \rho)}{P(C > W_1 + t \mid X, \rho) P(W_2 > t, X, \rho)} \\
&= \frac{P(W_2 \in [t, t+h], X, \rho)}{P(W_2 > t, X, \rho)} \\
&= P(W_2 \in [t, t+h] \mid W_2 > t, X, \rho) \\
&\xrightarrow{h \to 0} \frac{\lambda_2(w) e^{X^T \beta_2}}{1 + \theta \Lambda_2(w) e^{X^T \beta_2}},
\end{aligned}$$

where the last result follows by the same arguments as in question 1).

a) We can use $W_1 \perp\!\!\!\perp W_2 \mid (X, \rho)$ and $\rho \perp\!\!\!\perp X$ to write

$$\begin{aligned}
H(w_1, w_2 \mid X) &= P(W_1 \leq w_1, W_2 > w_2 \mid X) \\
&= \int_0^\infty P(W_1 \leq w_1, W_2 > w_2 \mid X, \rho) P(\mathrm{d}\rho \mid X) \\
&= \int_0^\infty P(W_1 \leq w_1 \mid X, \rho) P(W_2 > w_2 \mid X, \rho) P(\mathrm{d}\rho).
\end{aligned}$$

Using the assumptions about $P(W_j > w_j \mid X, \rho)$, for $j \in \{1, 2\}$, we get that

$$\begin{aligned}
H(w_1, w_2 \mid X) &= \int_0^\infty \left(1 - \exp\left\{-\Lambda_1(w_1) \rho e^{X^T \beta_1}\right\}\right) \exp\left\{-\Lambda_2(w_2) \rho e^{X^T \beta_2}\right\} P(\mathrm{d}\rho) \\
&= \int_0^\infty \exp\left\{-\Lambda_2(w_2) \rho e^{X^T \beta_2}\right\} P(\mathrm{d}\rho) \\
&\quad - \int_o^\infty \exp\left\{-\rho \left(\Lambda_1(w_1) e^{X^T \beta_1} + \Lambda_2(w_2) e^{X^T \beta_2}\right)\right\}
\end{aligned}$$

which we again can recognize as Laplace transformations, i.e.,

$$H(w_1, w_2 \mid X) = \mathcal{L}_{1/\theta, \theta}\left(\Lambda_2(w_2) e^{X^T \beta_2}\right) - \mathcal{L}_{1/\theta, \theta}\left(\Lambda_1(w_1) e^{X^T \beta_1} + \Lambda_2(w_2) e^{X^T \beta_2}\right)$$

with $\mathcal{L}_{k,\eta}$ defined in (1).

b) To find the marginal observed hazard of W_2 given only X, first define

$$F(t, h \mid X) := P(W_2 > t + h, C > W_1 + t \mid X),$$

and note that the hazard of interest can be written as

$$-\frac{\partial}{\partial h}\bigg|_{h=0} \frac{F(t, h \mid X)}{F(t, 0 \mid X)}.$$

Next, using again that $\rho \perp\!\!\!\perp X$, $(W_1, W_2) \perp\!\!\!\perp C \mid (X, \rho)$, and $C \perp\!\!\!\perp \rho \mid X$ we can

write

$$\begin{aligned}
F(t,h \mid X) &= \int_0^\infty P(W_2 > t+h, C > W_1 + t \mid X, \rho) P(\mathrm{d}\rho) \\
&= \int_0^\infty \int_t^\infty P(W_2 > t+h, C > W_1 + t \mid X, \rho, C = s) P(\mathrm{d}s \mid X, \rho) P(\mathrm{d}\rho) \\
&= \int_0^\infty \int_t^\infty P(W_2 > t+h, s > W_1 + t \mid X, \rho, C = s) P(\mathrm{d}s \mid X, \rho) P(\mathrm{d}\rho) \\
&= \int_0^\infty \int_t^\infty P(W_2 > t+h, s > W_1 + t \mid X, \rho) P(\mathrm{d}s \mid X) P(\mathrm{d}\rho) \\
&= \int_t^\infty \int_0^\infty P(W_2 > t+h, s > W_1 + t \mid X, \rho) P(\mathrm{d}\rho) P(\mathrm{d}s \mid X).
\end{aligned}$$

Defining $\bar{G}_c(s \mid X) := 1 - G_c(s \mid X) = P(C \leq s \mid X)$ and using the definition of H from question 3) a) we can write

$$F(t,h \mid X) = \int_t^\infty H(s-t, t+h \mid X) \bar{G}_c(\mathrm{d}s \mid X).$$

If we define

$$H_{k,\eta}(w_1, w_2 \mid X) := \mathcal{L}_{k,\eta}\left(\Lambda_2(w_2) e^{X^T \beta_2}\right) - \mathcal{L}_{k,\eta}\left(\Lambda_1(w_1) e^{X^T \beta_1} + \Lambda_2(w_2) e^{X^T \beta_2}\right),$$

and use that $\mathcal{L}_{1/\theta,\theta}(s)' = -\mathcal{L}_{1/\theta+1,\theta}(s)$ we can write

$$\left.\frac{\partial}{\partial h}\right|_{h=0} F(t,h \mid X) = -\lambda_2(w_2) e^{X^T \beta_2} \int_t^\infty H_{1/\theta+1,\theta}(s-t, t \mid X) \bar{G}_c(\mathrm{d}s \mid X).$$

Thus the hazard of interest is

$$\lambda_2(w_2) e^{X^T \beta_2} \frac{\int_t^\infty H_{1/\theta+1,\theta}(s-t, t \mid X) \bar{G}_c(\mathrm{d}s \mid X)}{\int_t^\infty H_{1/\theta,\theta}(s-t, t \mid X) \bar{G}_c(\mathrm{d}s \mid X)}.$$

4) Using the tower property we have that

$$\begin{aligned}
L(w_1, w_2) &= \mathbb{E}\left[\frac{\mathbb{1}\{W_1 \leq w_1, W_2 > w_2\} \mathbb{1}\{C > W_1 + w_2\}}{G_c(W_1 + w_2 \mid X)}\right] \\
&= \mathbb{E}\left[\mathbb{E}\left[\mathbb{1}\{C > W_1 + w_2\} \mid W_1, W_2, X, \rho\right] \frac{\mathbb{1}\{W_1 \leq w_1, W_2 > w_2\}}{G_c(W_1 + w_2 \mid X)}\right].
\end{aligned}$$

As $C \perp\!\!\!\perp (W_1, W_2) \mid (X, \rho)$ and $C \perp\!\!\!\perp \rho \mid W$ we have that

$$\begin{aligned}
\mathbb{E}\left[\mathbb{1}\{C > W_1 + w_2\} \mid W_1, W_2, X, \rho\right] &= \mathbb{E}\left[\mathbb{1}\{C > W_1 + w_2\} \mid W_1, X\right] \\
&= G_c(W_1 + w_2 \mid X),
\end{aligned}$$

and so

$$L(w_1, w_2) = \mathbb{E}\left[G_c(W_1 + w_2 \mid X) \frac{\mathbb{1}\{W_1 \leq w_1, W_2 > w_2\}}{G_c(W_1 + w_2 \mid X)}\right] = P\left(W_1 \leq w_1, W_2 > w_2\right).$$

a) When G_c is known, the estimator

$$\hat{L}_n(w_1, w_2) = \frac{1}{n} \sum_{i=1}^n \frac{\mathbb{1}\{W_{1,i} \leq w_1, W_{2,i} > w_2\} \mathbb{1}\{C_i > W_{1,i} + w_2\}}{G_c(W_{1,i} + w_2 \mid X_i)}$$

is an unbiased estimator of $L(w_1, w_2)$. In particular, as $W_2 > 0$ a.s. we have that $P(W_1 \leq w_1) = P(W_1 \leq w_1, W_2 > 0)$, so we can estimate $P(W_1 \leq w_1)$ with $\hat{L}_n(w_1, 0)$.

b) Using the results from 4) we can estimate $P(W_2 > w_2 \mid W_1 \leq w_1)$ with

$$\frac{\hat{L}_n(w_1, w_2)}{\hat{L}_n(w_1, 0)}.$$

1.2 Marginal Models for recurrent events

1) We have that

$$N(t) = \int_0^t \mathbb{1}(s \leq T)\, \mathrm{d}N^*(s),$$

and thus we can write

$$\begin{aligned}
\int_0^t r(s)\mathbb{1}(s \leq D)\, \mathrm{d}N(s) &= \int_0^t r(s)\mathbb{1}(s \leq D)\mathbb{1}(s \leq T)\, \mathrm{d}N^*(s) \\
&= \int_0^t \frac{\mathbb{1}(C \geq s \wedge D)\mathbb{1}(s \leq D)\mathbb{1}(s \leq T)}{G_c(s \wedge D)}\, \mathrm{d}N^*(s) \\
&= \int_0^t \frac{\mathbb{1}(C \geq s \wedge D, s \leq D, s \leq C)}{G_c(s \wedge D)}\, \mathrm{d}N^*(s).
\end{aligned}$$

Now, it holds that

$$(C \geq s \wedge D, s \leq D, s \leq C) = (C \geq s \wedge D, s \leq D), \tag{2}$$

and so

$$\int_0^t \frac{\mathbb{1}(C \geq s \wedge D, s \leq D, s \leq C)}{G_c(s \wedge D)}\, \mathrm{d}N^*(s) = \int_0^t \frac{\mathbb{1}(C \geq s \wedge D)}{G_c(s \wedge D)} \mathbb{1}(s \leq D)\, \mathrm{d}N^*(s).$$

Using that $C \perp\!\!\!\perp (D, N^*)$ we then have that

$$\begin{aligned}
\mathbb{E}\left[\int_0^t r(s)\mathbb{1}(s \leq D)\, \mathrm{d}N(s)\right] &= \mathbb{E}\left[\int_0^t \frac{\mathbb{1}(C \geq s \wedge D)}{G_c(s \wedge D)} \mathbb{1}(s \leq D)\, \mathrm{d}N^*(s)\right] \\
&= \mathbb{E}\left[\mathbb{E}\left[\int_0^t \frac{\mathbb{1}(C \geq s \wedge D)}{G_c(s \wedge D)} \mathbb{1}(s \leq D)\, \mathrm{d}N^*(s) \;\middle|\; N^*, D\right]\right] \\
&= \mathbb{E}\left[\int_0^t \frac{\mathbb{E}\left[\mathbb{1}(C \geq s \wedge D) \mid N^*, D\right]}{G_c(s \wedge D)} \mathbb{1}(s \leq D)\, \mathrm{d}N^*(s)\right] \\
&= \mathbb{E}\left[\int_0^t \frac{\mathbb{E}\left[\mathbb{1}(C \geq s \wedge D)\right]}{G_c(s \wedge D)} \mathbb{1}(s \leq D)\, \mathrm{d}N^*(s)\right] \\
&= \mathbb{E}\left[\int_0^t \frac{G_c(s \wedge D)}{G_c(s \wedge D)} \mathbb{1}(s \leq D)\, \mathrm{d}N^*(s)\right] \\
&= \mathbb{E}\left[\int_0^{t \wedge D} \mathrm{d}N^*(s)\right] \\
&= \mathbb{E}\left[N^*(t \wedge D)\right] \\
&= \mu(t).
\end{aligned}$$

2) The censoring martingale is

$$\begin{aligned}
\int_0^s \frac{1}{G_c(u)}\, \mathrm{d}M^C(u) &= \int_0^s \frac{1}{G_c(u)}\, \mathrm{d}N^C(u) - \int_0^s \frac{Y(s)}{G_c(u)}\, \mathrm{d}\Lambda^C(u) \\
&= \frac{(1-\delta)\mathbb{1}(T \leq s)}{G_c(T)} - \int_0^{s \wedge T} \frac{1}{G_c(u)}\, \mathrm{d}\Lambda^C(u).
\end{aligned}$$

Assuming that C has density with respect to Lebesgue measure, it holds that the survival function of C can be written as $G_c(u) = e^{-\Lambda^C(u)}$ from which it follows that

$$\frac{\partial}{\partial u}\frac{1}{G_c(u)} = \frac{\partial}{\partial u} e^{\Lambda^C(u)} = \lambda^C(u) e^{\Lambda^C(u)} = \frac{\lambda^C(u)}{G_c(u)}$$

and thus

$$\int_0^{s\wedge T} \frac{1}{G_c(u)}\,\mathrm{d}\Lambda^C(u) = \left[\frac{1}{G_c(u)}\right]_0^{s\wedge T} = \frac{1}{G_c(s\wedge T)} - 1.$$

From this we obtain

$$1 - \int_0^s \frac{1}{G_c(u)}\,\mathrm{d}M^C(u) = \frac{1}{G_c(s\wedge T)} - \frac{(1-\delta)\mathbb{1}(T\le s)}{G_c(T)}.$$

When $C < s\wedge D$ the above expression equals 0 and otherwise equals $G_c(s\wedge T)$, which shows that it is identical to $r(s) = \mathbb{1}(C \ge s\wedge D)/G_c(s\wedge D)$.

3) Using again the identity in (2) and the previous result, we can write

$$\begin{aligned}
\int_0^t r(s)\mathbb{1}(s\le D)\,\mathrm{d}N(s) &= \int_0^t r(s)\mathbb{1}(s\le D)\,\mathrm{d}N^*(s)\\
&= \int_0^t \mathbb{1}(s\le D)\,\mathrm{d}N^*(s) - \int_0^t\int_0^s \frac{\mathrm{d}M^C(u)}{G_c(u)}\mathbb{1}(s\le D)\,\mathrm{d}N^*(s)\\
&= \int_0^t \mathbb{1}(s\le D)\,\mathrm{d}N^*(s) - \int_0^t\int_u^t \mathbb{1}(s\le D)\,\mathrm{d}N^*(s)\frac{\mathrm{d}M^C(u)}{G_c(u)}\\
&= \int_0^t \mathbb{1}(s\le D)\,\mathrm{d}N^*(s) - \int_0^t H(u,t)\frac{\mathrm{d}M^C(u)}{G_c(u)}.
\end{aligned}$$

4) By 1) and 3) we have that $\mathbb{E}\left[\rho(t)\right] = 0$ and thus

$$\begin{aligned}
\mathrm{Var}\left[\rho(t)\right] = \mathbb{E}\left[\rho(t)^2\right] =& \mathbb{E}\left[(H(0,t)-\mu(t))^2\right] + \mathbb{E}\left[\left(\int_0^t \frac{H(s,t)}{G_c(s)}\,\mathrm{d}M^C(s)\right)^2\right]\\
&- 2\,\mathbb{E}\left[(H(0,t)-\mu(t))\int_0^t \frac{H(s,t)}{G_c(s)}\,\mathrm{d}M^C(s)\right].
\end{aligned} \tag{3}$$

Next, if we define the "true" (unobserved) censoring process $M^{C*}(t) = \mathbb{1}(C\le t) - \int_0^t \mathbb{1}(C>s)\,\mathrm{d}\Lambda^C(s)$ we have that

$$M^C(t) = \int_0^t \mathbb{1}(D>u)\,\mathrm{d}M^{C*}(u).$$

Given (N^*, D), the process $s\mapsto H(s,t)\mathbb{1}(D>s)/G_c(s)$ is deterministic and hence predictable, and because C is independent of (N^*, D) the process $M^{C*}(s)$ is a martingale, also when conditioning on (N^*, D). This implies that

$$\begin{aligned}
&\mathbb{E}\left[(H(0,t)-\mu(t))\int_0^t \frac{H(s,t)}{G_c(s)}\,\mathrm{d}M^C(s)\right]\\
&\mathbb{E}\left[(H(0,t)-\mu(t))\int_0^t \frac{H(s,t)\mathbb{1}(D>s)}{G_c(s)}\,\mathrm{d}M^{C*}(s)\right]\\
&= \mathbb{E}\left[(H(0,t)-\mu(t))\,\mathbb{E}\left[\int_0^t \frac{H(s,t)\mathbb{1}(D>s)}{G_c(s)}\,\mathrm{d}M^{C*}(s)\;\middle|\; N^*, D\right]\right]\\
&= 0,
\end{aligned}$$

showing that the third term on the right-hand-side of (3) disappears. By similar

arguments we have that

$$\begin{aligned}
\mathbb{E}\left[\left\langle \int_0^t \frac{H(s,t)}{G_c(s)}\,\mathrm{d}M^C(s)\right\rangle\right] &= \mathbb{E}\left[\left\langle \int_0^t \frac{H(s,t)\mathbb{1}(D>s)}{G_c(s)}\,\mathrm{d}M^{C*}(s)\right\rangle\right] \\
&= \mathbb{E}\left[\mathbb{E}\left[\left\langle \int_0^t \frac{H(s,t)\mathbb{1}(D>s)}{G_c(s)}\,\mathrm{d}M^{C*}(s)\right\rangle \,\middle|\, N^*, D\right]\right] \\
&= \mathbb{E}\left[\mathbb{E}\left[\int_0^t \frac{\{H(s,t)\mathbb{1}(D>s)\}^2}{G_c(s)^2}\,\mathrm{d}\left\langle M^{C*}\right\rangle(s) \,\middle|\, N^*, D\right]\right] \\
&= \mathbb{E}\left[\mathbb{E}\left[\int_0^t \frac{\{H(s,t)\mathbb{1}(D>s)\}^2}{G_c(s)^2}\mathbb{1}(C>s)\,\mathrm{d}\Lambda^C(s) \,\middle|\, N^*, D\right]\right] \\
&= \mathbb{E}\left[\int_0^t \frac{\{H(s,t)\mathbb{1}(D>s)\}^2}{G_c(s)^2}\,\mathbb{E}\left[\mathbb{1}(C>s) \mid N^*, D\right]\mathrm{d}\Lambda^C(s)\right] \\
&= \mathbb{E}\left[\int_0^t \frac{\{H(s,t)\mathbb{1}(D>s)\}^2}{G_c(s)^2}\,\mathbb{E}\left[\mathbb{1}(C>s)\right]\mathrm{d}\Lambda^C(s)\right] \\
&= \mathbb{E}\left[\int_0^t \frac{\{H(s,t)\mathbb{1}(D>s)\}^2}{G_c(s)}\,\mathrm{d}\Lambda^C(s)\right] \\
&= \int_0^t \mathbb{E}\left[\{H(s,t)\mathbb{1}(D>s)\}^2\right]\frac{\mathrm{d}\Lambda^C(s)}{G_c(s)}.
\end{aligned}$$

By definition of the predictable variation process

$$\mathbb{E}\left[\left(\int_0^t \frac{H(s,t)}{G_c(s)}\,\mathrm{d}M^C(s)\right)^2\right] = \mathbb{E}\left[\left\langle \int_0^t \frac{H(s,t)}{G_c(s)}\,\mathrm{d}M^C(s)\right\rangle\right],$$

and thus the second term of the right-hand-side of (3) equals

$$\int_0^t \mathbb{E}\left[\{H(s,t)\mathbb{1}(D>s)\}^2\right]\frac{\mathrm{d}\Lambda^C(s)}{G_c(s)},$$

which gives the wanted result.

5) Let $\mathcal{F}_t$ be the observed filtration. By the construction of the conditional expectation it holds for any s that

$$\mathbb{E}\left[\mathbb{1}(D>s)\left\{H(s,t)-\alpha(s)\right\}^2\right]$$

is minimized over all $\mathcal{F}_{s-}$ measurable functions α by $\alpha_0(s) = \mathbb{E}\left[H(s,t) \mid \mathcal{F}_{s-}\right]$. Hence subtracting $\int_0^t \frac{\alpha(s)}{G_c(s)}\,\mathrm{d}M^C(s)$ from $\rho(t)$ will minimize the variance among all correction term on that form by the previous result.

a) When the function is not allowed to depend on data, it will be minimized by $\alpha_0(s) = \mathbb{E}\left[H(s,t) \mid \mathcal{F}_0\right]$, which, using that $\mathbb{E}\left[H(0,t)\right] = \mu(t)$, we can write as

$$\alpha_0(s) = \mathbb{E}\left[H(0,t) - H(0,s)\right] = \mu(t) - \mu(s).$$

b) From the previous result and question 1) we can estimate $\alpha_0(s)$ by $\hat{\mu}(t) - \hat{\mu}(s)$, with $\hat{\mu}(t)$ defined in 1). Using question 3) this suggests the estimator

$$\hat{\mu}(t) - \int_0^t \frac{\hat{\mu}(t) - \hat{\mu}(s)}{G_c(s)}\,\mathrm{d}M^C(s).$$

2 Practial

2.1 Colrectal Cancer

We consider the colorectal cancer data from the `frailtypack` `R` package. This data set contains the new lesions prior to death during follow-up of metastatic colorectal cancer patients. The data consist of 150 patients from the follow-up of the FFCD 2000-05 multicenter phase III clinical trial originally including 410 patients with metastatic colorectal cancer randomized into two therapeutic strategies: combination and sequential. The dataset contains times of observed appearances of new lesions censored by a terminal event (death or right-censoring) with baseline characteristics (treatment arm `treatment`, age group `age`, WHO performance status `who.ps`).

We have used the following `R` libraries for this practical assignment and the `colorectal` data set from the `frailtypack` package.

```
library(frailtypack)
library(mets)
library(knitr)
library(data.table)
library(survminer)
library(ggfortify)
library(riskRegression)
library(gridExtra)
library(prodlim)
data("colorectal")
colorectal <- setDT(copy(colorectal))
```

We shall be interested in the covariate effects of treatment, age, and who.ps effect on the recurrent event of getting new lesions. We use follow up time as the main time-scale. Part of this exercise is to figure out how to answer the posed question, and draw relevant conclusions and also consider and state important assumptions.

2.1.1. Covariates important for death using Cox modelling

To model the risk of death, we will limit the attention to the three baseline covariates mentioned in the exercise. When using Cox modelling and not entering the covariates as strata, we are assuming proportional hazard functions on covariate level. This assumption will be tested by the end of this sub-exercise.

Modelling death, with death being a terminal event, we can fit a model with only the death/censoring times using `time1` and the event of death variable `state == 1`. Hence we can consider only the last observation per patient. As we will later be interested in modelling the recurrent event of new lesions together while considering death as a terminal event, we decide to not reduce the data to only look at the last time interval, when modelling death. But then, we would have to take into account that patients can be observed more than once. Using only the last observed time per individual will also return identical parameter coefficients, only the standard errors of the parameter coefficients will be slighty different.

Each participant in the study can appear in the data set multiple times. Their first initial start time is at the time of randomization and a new time is collected for each new lesion, the terminal event of death or end of follow-up (censoring). Using the provided data set, we can account for multiple observations per patient by calculating robust standard errors (using `cluster(id)`) or using a frailty model on the id (`frailty(id)`). We decide to use the former rather than the latter, to make no assumptions about the frailty distribution.

We then fit a Cox regression model:

```
cox_death <- coxph(Surv(time0, time1, state == 1) ~ treatment + age +
                     who.PS + cluster(id), data = colorectal)
summary(cox_death)
```

```
## Call:
## coxph(formula = Surv(time0, time1, state == 1) ~ treatment +
##     age + who.PS, data = colorectal, cluster = id)
##
##   n= 289, number of events= 121
##
##                    coef exp(coef) se(coef) robust se      z Pr(>|z|)
## treatmentC     -0.1167    0.8899   0.1906    0.1930 -0.605 0.545492
## age60-69 years -0.1829    0.8329   0.2347    0.2372 -0.771 0.440653
## age>69 years   -0.2206    0.8021   0.2184    0.2130 -1.035 0.300495
## who.PS1        -0.0739    0.9288   0.2084    0.2088 -0.354 0.723435
## who.PS2         0.8718    2.3911   0.2450    0.2328  3.744 0.000181 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                exp(coef) exp(-coef) lower .95 upper .95
## treatmentC        0.8898     1.1238    0.6095     1.299
## age60-69 years    0.8329     1.2007    0.5233     1.326
## age>69 years      0.8021     1.2468    0.5283     1.218
## who.PS1           0.9288     1.0767    0.6168     1.398
## who.PS2           2.3911     0.4182    1.5150     3.774
##
## Concordance= 0.585  (se = 0.03 )
## Likelihood ratio test= 14.76  on 5 df,   p=0.01
## Wald test            = 17.91  on 5 df,   p=0.003
## Score (logrank) test = 18.05  on 5 df,   p=0.003,   Robust = 16.97  p=0.005
##
##   (Note: the likelihood ratio and score tests assume independence of
##      observations within a cluster, the Wald and robust score tests do not).
```

From the model output, we find no effect of the treatment or age group of patients at baseline on the risk of death on a 0.05 significance level. Having a WHO performance score of 2 compared to 0 results in a significant larger hazard, with a hazard ratio of 2.39 (95% CI: 1.48; 3.87, p-value: 0.0002). The effect of treatment, age group and WHO performance status at

baseline on the hazard of death was also investigated using univariate Cox models with the same conclusions.

We can estimate the survival distribution from the fitted hazard (Cox) model or model the survival distribution directly using Kaplan-Meier. We start with using the fitted Cox regression model. As the WHO performance status was the only prognostic variable for death, we decide to fix all other covariates at their reference level, hence `age <60 years` and `treatment S`. The survival distribution for the WHO performance levels are shown below for `age<60 years` and sequential treatment.

```
preddata <- data.frame(who.PS =factor(c(0,1,2)), age = "<60 years",
                       treatment = "S")
pred <- survfit(cox_death, newdata = preddata)
ggsurvplot(pred, data = colorectal,
           conf.int = TRUE)
```

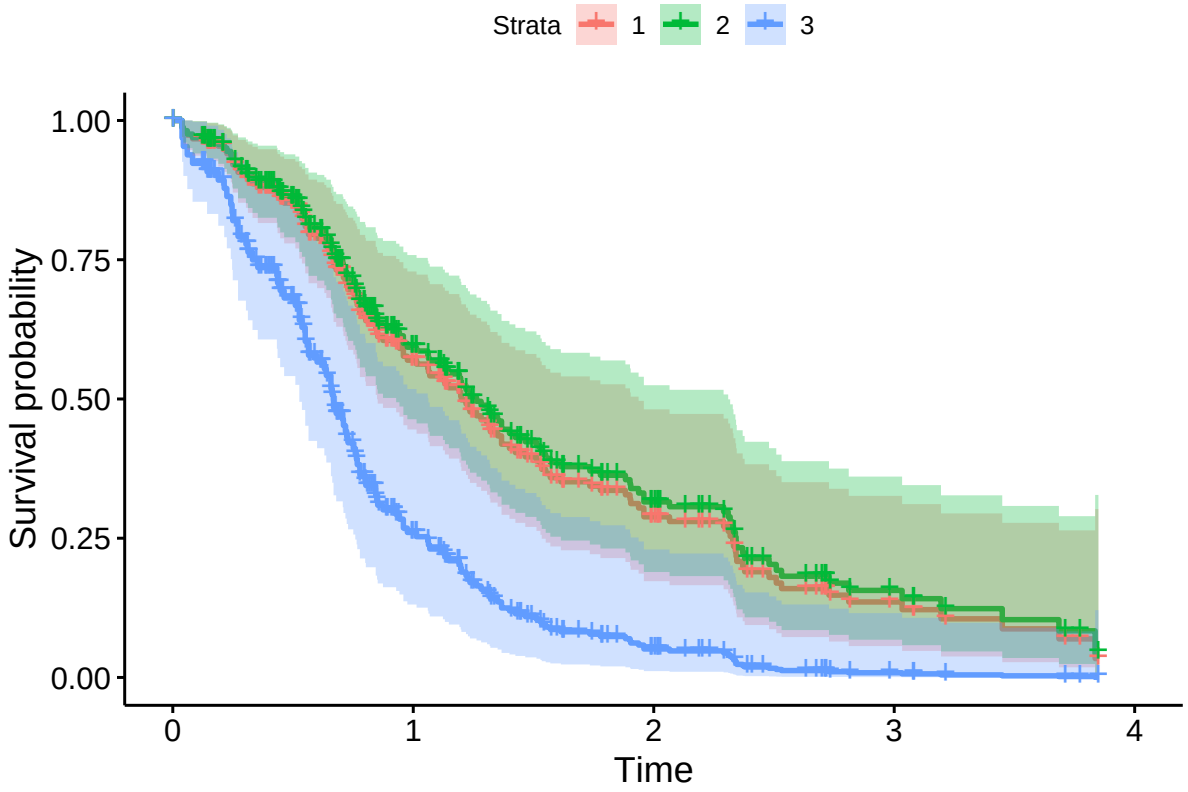
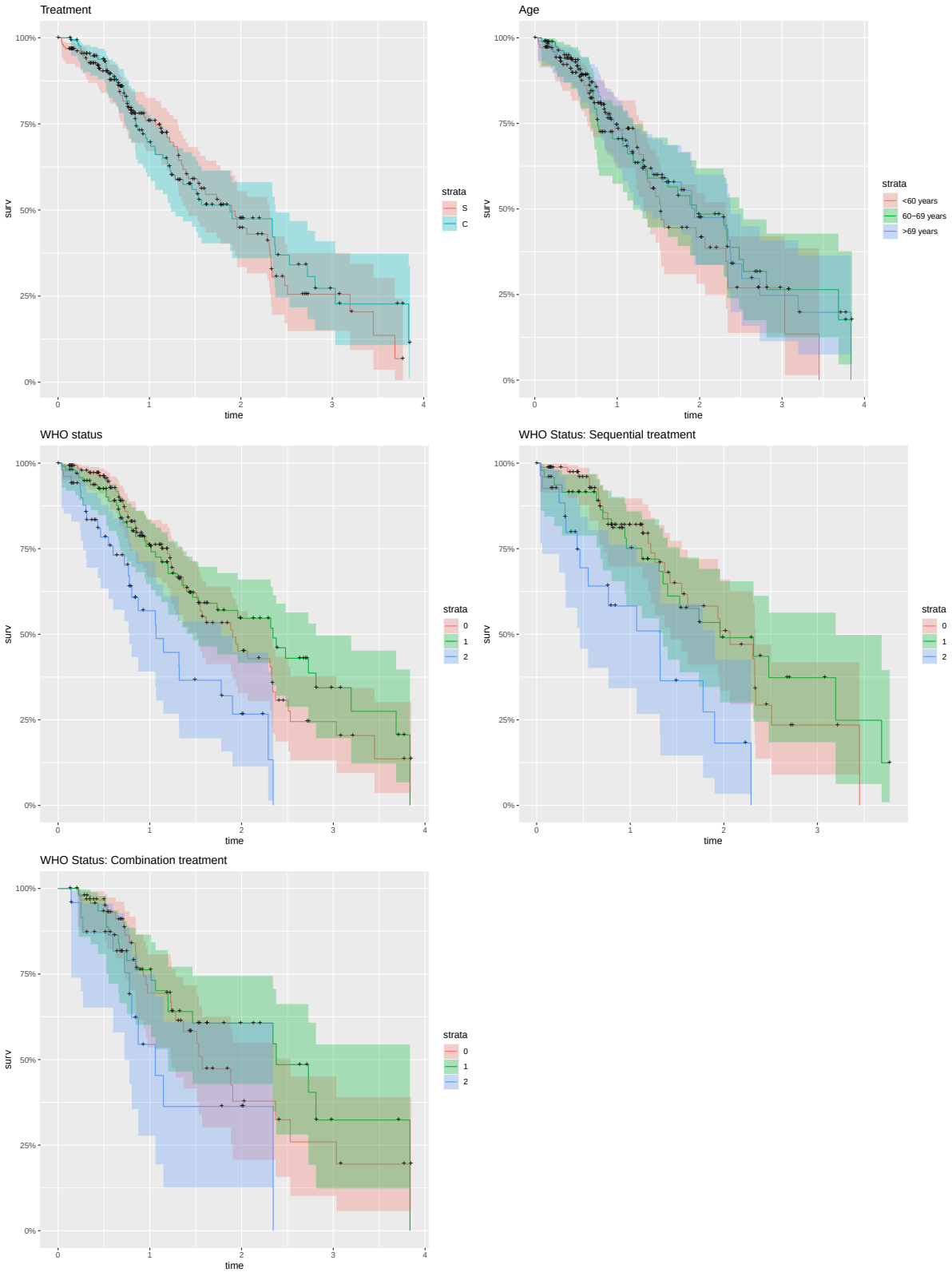
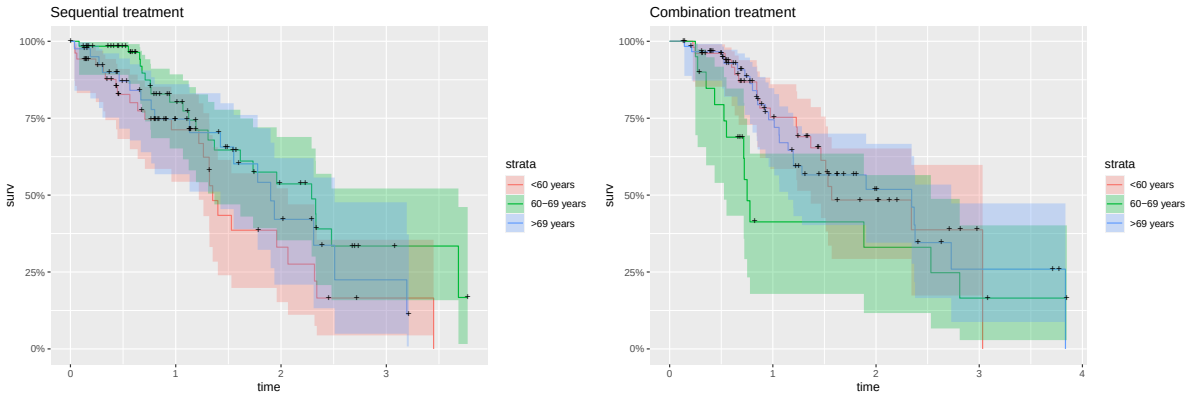


Figure 1: Survival curves (death as outcome) for who.PS score strata.

We can also compute survival curves using Kaplan-Meier. Plotting the survival curves for the three covariates and the who.PS score stratified by treatment, we find that the who performance score still looks like the only covariate associated with time to death.



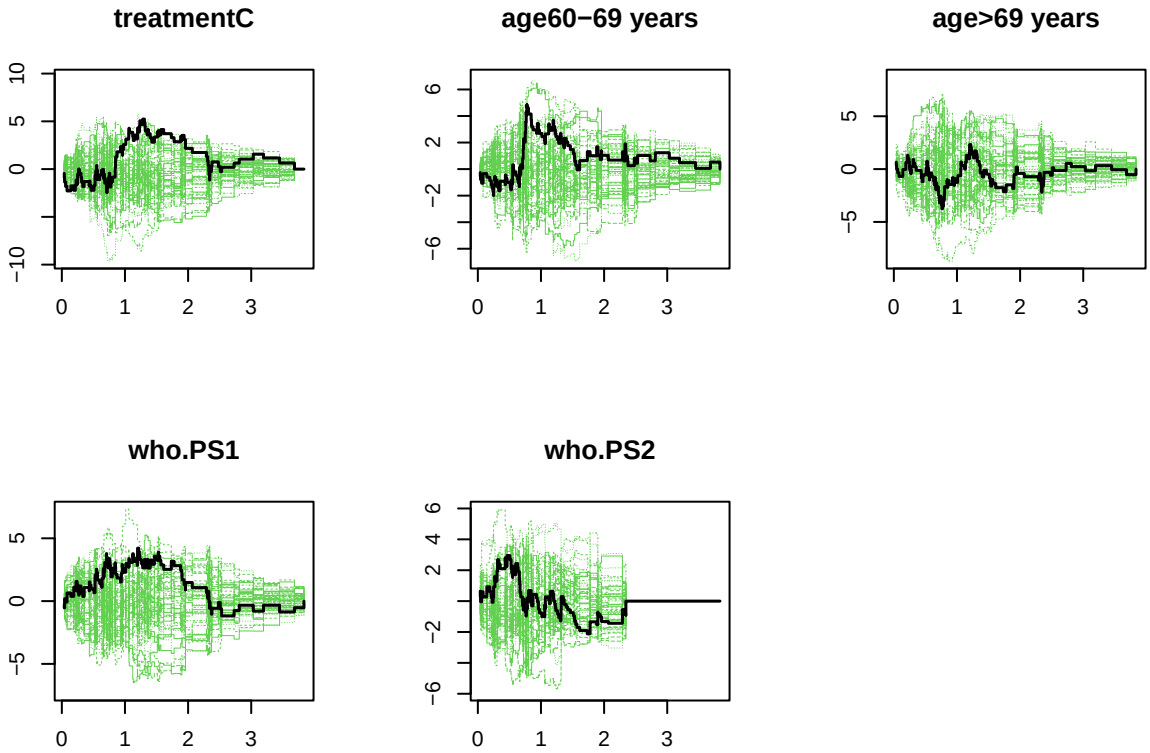
We can also consider a combination of treatment and age:



For the sequential treatment, the survival curves are overlapping, however, the combination treatment seems to be working more poorly for people aged 60-69, especially during the first 10 months. Note however, that there is only 15 subjects in this subgroup.

To check the proportional hazards assumption of the cox model, we can use either a graphical or a more formal testing approach. Starting with the graphical, we use the martingale residuals to check the proportional hazards assumption. As the black line is well within the simulated cumulative martingale residuals, we do not find evidence for rejecting the hypothesis of proportional hazards. See Figure **??**.

```
cox_death <- phreg(Surv(time0, time1, state)~treatment + age + who.PS,
                   data = colorectal)
gof1 <- gof(cox_death)
par(mfrow=c(2,3))
plot(gof1)
```



We can also do a more formal test, as done below using the cumulative score process test for proportionality. With all p-values > 0.05, we reject the hypothesis of the hazards being non-proportional.

```
gof1
```

```
## Cumulative score process test for Proportionality:
##                 Sup|U(t)|  pval
## treatmentC       5.240899 0.232
## age60-69 years   4.844747 0.229
## age>69 years     3.763129 0.578
## who.PS1          4.217036 0.404
## who.PS2          2.949119 0.657
```

2.1.2. Is death and the number new lesions related?

To answer this question, we construct a variable, stating the number of new lesions per person (id), as a cumulated sum per time point. This is included in the cox model as a factor. Note that in order not to condition on the future (the end of the time interval when we are at the beginning of the time interval), we shift the sum of lesions to the next time interval. This is done in the following way:

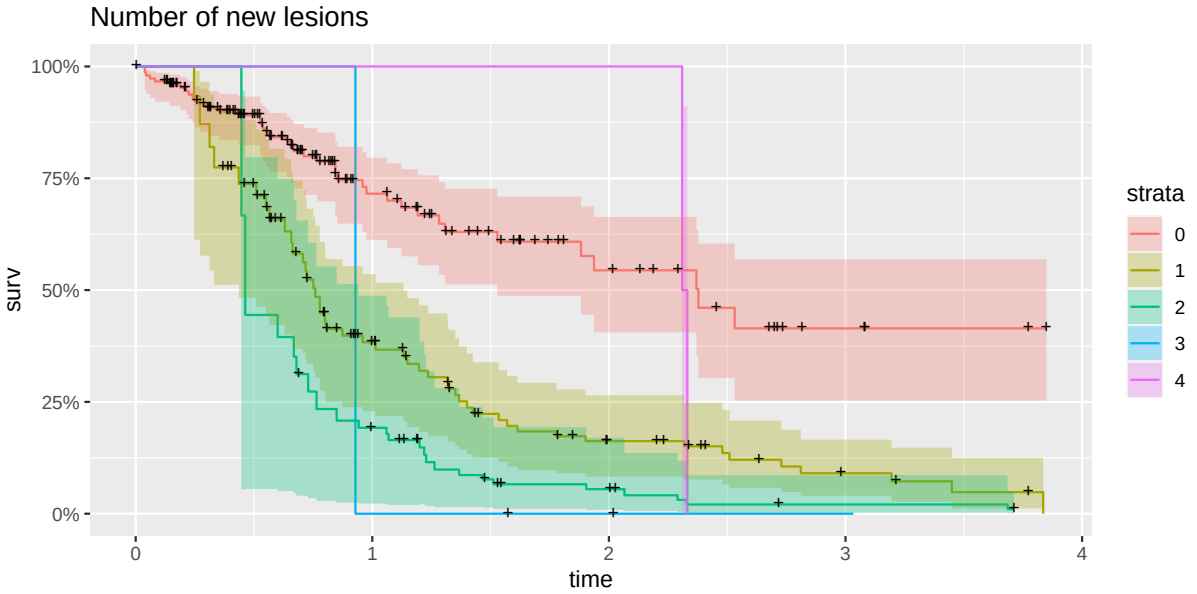
```
colorectal <- colorectal[order(id, time1)]
colorectal[, cum.lesions:=head(c(0,cumsum(new.lesions)),n=-1),
           by=id] #Shift number of lesions
colorectal[, cum.lesions2:=cumsum(new.lesions),
           by=id] # will be used later
```

We fit a cox model using `cum.lesions` as a covariate, including `cluster(id)`, as we have repeated measurements per id. We could also have modelled the repeated measurements per subject with a frailty model, adding `frailty(id)`, but we choose use the `cluster(id)`, where a robust estimate of the standard errors is used. Thereby, possible dependence between the subjects is modelled. As mentioned, this could also have been done with a frailty model, where the dependence between subjects is modelled usually as gamma or log-normal random effects. Furthermore, we now include both time1 as before, as well as time0, which is the start of the time interval (0 or the previous recurrence time). This is done as we now have a time-dependent covariate (number of previous lesions).

```
m.cox.1 <- coxph(Surv(time0, time1, state) ~ treatment + age + who.PS +
                   factor(cum.lesions) + cluster(id), data = colorectal)
summary(m.cox.1)$coef[,c(1:3, 6)]
```

```
##                              coef  exp(coef)  se(coef)     Pr(>|z|)
## treatmentC            0.13175098  1.1408242 0.2012790 4.897415e-01
## age60-69 years       -0.07633202  0.9265085 0.2395540 7.417388e-01
## age>69 years         -0.12641235  0.8812514 0.2233971 5.332424e-01
## who.PS1               0.06875890  1.0711779 0.2174739 7.336111e-01
## who.PS2               0.80734586  2.2419496 0.2549191 6.294231e-04
## factor(cum.lesions)1  1.04277158  2.8370693 0.2427949 2.054560e-05
## factor(cum.lesions)2  1.74228679  5.7103870 0.2941123 3.212235e-10
## factor(cum.lesions)3  1.65396340  5.2276581 0.4161305 2.610566e-08
## factor(cum.lesions)4  2.81120637 16.6299680 0.8137467 1.905439e-06
```

From the summary, we can see that the hazard of dying (as compared to no new lesions) is increasing with the number of new lesions (significant increase for all lesion groups). The same picture is seen in the survival curve below. Note that in the four lesion group, there are only two subjects that both die after around 27 months, which gives this sudden fall in the survival curve. So, it could seem that subjects with four lesions have a longer lifespan, but after a certain time threshold, they die. All the 9 subjects in the three lesion group also die eventually. From the figure, we can also see that having one and two lesions affects the hazard of death similarly over time.



As we have so few subjects in the four and three lesion group, we try to model the number of lesions as continuous covariate instead. We fit a cox model using this continuous covariate, again with a `time0` and `cluster(id)`, as we have repeated measurements per id:

```
m.cox.2 <- coxph(Surv(time0, time1, state) ~ treatment + age + who.PS +
                   cum.lesions + cluster(id), data = colorectal)
round(summary(m.cox.2)$coef[,c(1:3, 6)],4)
```

```
##                    coef exp(coef) se(coef) Pr(>|z|)
## treatmentC       0.0802    1.0836   0.2001   0.6762
## age60-69 years -0.0595    0.9423   0.2360   0.7973
## age>69 years   -0.1108    0.8951   0.2219   0.5931
## who.PS1          0.1063    1.1121   0.2148   0.6026
## who.PS2          0.8951    2.4475   0.2470   0.0001
## cum.lesions      0.6655    1.9455   0.1041   0.0000
```

We can see that the hazard of dying increases significantly with number of lesions which we also expected from the graphical interpretation.

To do model validation about the proportionality assumption, we do a formal test where we look at the time dependent variable (number of lesions) as a discrete variable. We will do a cumulative score process test for the proportionality assumption:

```
m.cox.1 <- phreg(Surv(time0, time1, state) ~ treatment + age + who.PS +
                   factor(cum.lesions) + cluster(id), data = colorectal)
gof(m.cox.1)
```

```
## Cumulative score process test for Proportionality:
##                         Sup|U(t)|  pval
## treatmentC               4.273149 0.415
## age60-69 years           3.998409 0.415
## age>69 years             3.663895 0.604
```

```
## who.PS1                4.801055 0.242
## who.PS2                2.964060 0.565
## factor(cum.lesions)1   2.263136 0.961
## factor(cum.lesions)2   2.891205 0.633
## factor(cum.lesions)3   2.623224 0.134
## factor(cum.lesions)4   1.354326 0.131
```

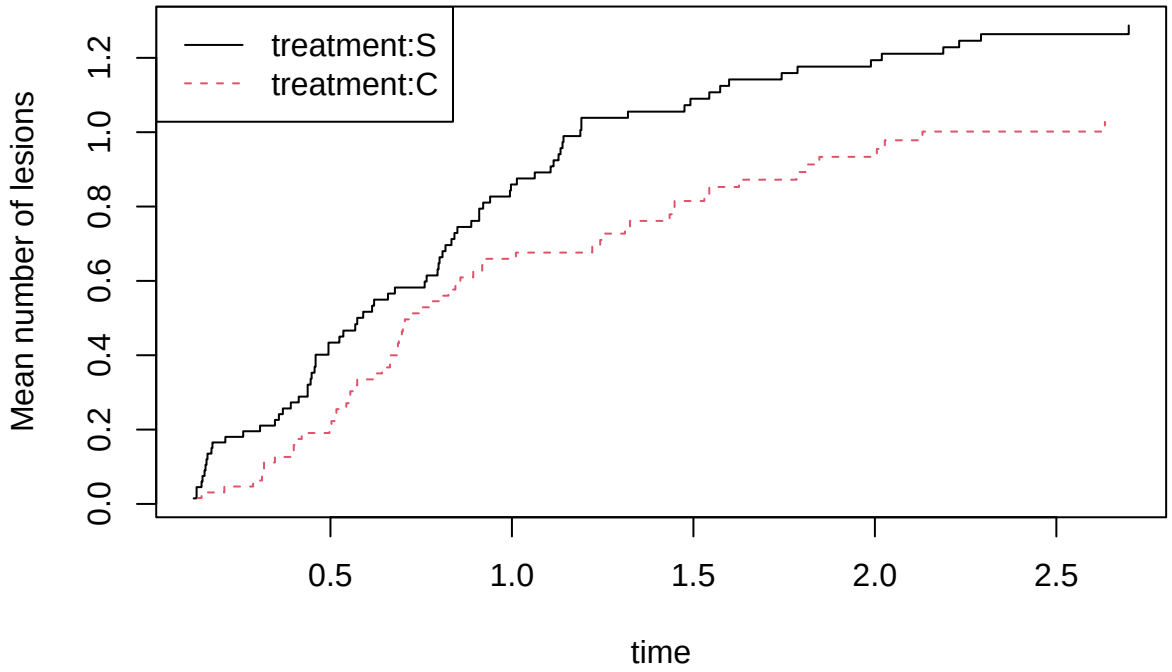
We find that the tests for non-proportionality are rejected on a 0.05 level.

2.1.3. Estimate the mean number of new lessions as a function of time, i.e., the marginal mean of the recurrent events ($\mu(t)$ in the previous exercise).

We now wish to take the re-occurence of new lesions into account, and estimate the mean number of new lesions as a function of time. Following Per's slides, we assume that there is no "gap" times, ie. a wait time where a new lesion was not possible does not exist. It is also a plausible assumption that a subject is at risk for getting a lesion again immediately after experiencing a lesion. As we saw in the previous exercise, a large number of the subjects experience the terminal event death, so we have presence of a non-negligible mortality rate that we need to take into account in the modelling.

When mortality plays a role, the Nelson-Aalen estimator for $\mu(t)$ will be upwards biased, as events can only happen as long as the subject is still alive. We will use a simple estimator for $\mu(t)$ that accounts for mortality, which is given by the "Ghosh-Lin" estimator. To do this in `R`, we use the `phreg` function from the `mets` package. First, we estimate the mean number of new lesions non-parametrically in the following way (inlcuding the same covariates as in the previous exercises, stratifying by treatment as using the `cluster(id)` option as argued earlier):

```
library(mets)
survobj <- phreg(Surv(time0, time1, state == 1) ~ strata(treatment) + age +
                   who.PS + cluster(id), data = colorectal, km = TRUE)
recevobj <- phreg(Surv(time0, time1, new.lesions == 1) ~ strata(treatment) +
                  age + who.PS + cluster(id), data = colorectal, km = TRUE)
obj <- recmarg(recevobj, survobj)
bplot(obj, ylab = "Mean number of lesions")
```



This shows, that over time, the mean number of lesions is larger for sequential than combination treatment. The effect seems roughly constant over time (one might argue that the effect is more pronounced after around 12 months, but the effect is not noticeable from the plot). We now estimate the treatment effect on the mean function in a Ghosh-Lin regression model using the `recreg` function in the `mets` package. Note that to do this, we need to construct a censoring variable, and we also construct the variable "status", which contains information about both death and lesions, such that:

- status=0 means alive and no lesion
- status=1 means dead
- status=2 means alive and new lesion.

```
colorectal[,status:=state]
colorectal[new.lesions==1,status:=2]
colorectal$cens <-ifelse(colorectal$state==0,1,0) #Censoring variable
m.goshlin <- recreg(EventCens(time0, time1, status, cens) ~ treatment + age +
                      who.PS + cluster(id), data = colorectal,
                    cause = 2, death.code = 1,
                    cens.code = 1, cens.model ~ 1)
summary(m.goshlin)$coef
```

```
##                    Estimate      S.E.   dU^-1/2   P-value
## treatmentC     -0.25053314 0.1592898 0.1758116 0.1157620
## age60-69 years -0.12319697 0.1902138 0.2126833 0.5171944
## age>69 years   -0.13647908 0.1863036 0.2025636 0.4638252
## who.PS1        -0.23099135 0.1792848 0.1929288 0.1976052
## who.PS2        -0.04935763 0.2019346 0.2369963 0.8069026
```

The model is fitted using the same covariates as in the previous exercises. As expected from the plot above, the mean number of lesions is lower over time for combination treatment, with an estimated mean ratio of $\exp(-0.25053314) = 0.78$. This means that, constant over time, we have 22% less lesions for combination as compared to sequential treatment. Note, however, that the treatment effect is non-significant, with a p-value of $0.11 > 0.05$.

2.1.4 Probability of having more than one new lesion

In the previous exercise, we considered the mean number of new lesions, however, now we wish to investigate another summary measure, namely the probability of a patient having more than one new lesion.

To investigate if covariates are important for this probability we can fit a cause specific cox model. To fit this model, we need to coerce the data to the wanted format. This means to stop observing patients after more than one new lesion (cause 1) has been observed or to stop observing them at time of death (cause 2) or to stop at censoring if none of the events (causes) has occurred during the study time. We can then fit a cause specific Cox model:

```
colorectal[,cum.lesions1 := 1*(cum.lesions2 > 1)]
last <- colorectal[,.SD[.N],by = id]
prob.colo <- rbind(colorectal[cum.lesions1 == 1 | state == 1, .SD[1], by=id],
                   last[cum.lesions1 == 0 & state == 0,])
prob.colo[,status := ifelse(cum.lesions1 == 1, cum.lesions1, state*2)]
CSC(Hist(time1, status) ~ treatment + age + who.PS,
    data = prob.colo)
```

```
## CSC(formula = Hist(time1, status) ~ treatment + age + who.PS,
##     data = prob.colo)
##
## Right-censored response of a competing.risks model
##
## No.Observations: 150
##
## Pattern:
##
## Cause     event right.censored
##   1          36              0
##   2          87              0
##   unknown     0             27
##
##
## ----------> Cause:  1
##
## Call:
## coxph(formula = survival::Surv(time, status) ~ treatment + age +
##     who.PS, x = TRUE, y = TRUE)
##
```

```
##   n= 150, number of events= 36
##
##                    coef exp(coef) se(coef)      z Pr(>|z|)
## treatmentC     -0.3949    0.6737   0.3480 -1.135    0.256
## age60-69 years -0.2701    0.7633   0.4081 -0.662    0.508
## age>69 years   -0.6199    0.5380   0.4102 -1.511    0.131
## who.PS1        -0.5789    0.5605   0.3900 -1.484    0.138
## who.PS2         0.2157    1.2407   0.4690  0.460    0.646
##
##                exp(coef) exp(-coef) lower .95 upper .95
## treatmentC        0.6737      1.484    0.3406     1.333
## age60-69 years    0.7633      1.310    0.3430     1.699
## age>69 years      0.5380      1.859    0.2408     1.202
## who.PS1           0.5605      1.784    0.2610     1.204
## who.PS2           1.2407      0.806    0.4948     3.111
##
## Concordance= 0.627  (se = 0.052 )
## Likelihood ratio test= 6.77  on 5 df,   p=0.2
## Wald test            = 6.43  on 5 df,   p=0.3
## Score (logrank) test = 6.56  on 5 df,   p=0.3
##
##
##
## ----------> Cause:  2
##
## Call:
## coxph(formula = survival::Surv(time, status) ~ treatment + age +
##     who.PS, x = TRUE, y = TRUE)
##
##   n= 150, number of events= 87
##
##                     coef exp(coef) se(coef)      z Pr(>|z|)
## treatmentC     -0.11434   0.89196  0.22263 -0.514  0.60754
## age60-69 years -0.14001   0.86935  0.28359 -0.494  0.62152
## age>69 years   -0.10846   0.89721  0.25520 -0.425  0.67084
## who.PS1         0.05392   1.05540  0.24607  0.219  0.82656
## who.PS2         0.84591   2.33009  0.28691  2.948  0.00319 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                exp(coef) exp(-coef) lower .95 upper .95
## treatmentC        0.8920     1.1211    0.5766     1.380
## age60-69 years    0.8694     1.1503    0.4987     1.516
## age>69 years      0.8972     1.1146    0.5441     1.480
## who.PS1           1.0554     0.9475    0.6516     1.709
## who.PS2           2.3301     0.4292    1.3279     4.089
```

```
##
## Concordance= 0.57  (se = 0.036 )
## Likelihood ratio test= 9.31  on 5 df,   p=0.1
## Wald test            = 10.64  on 5 df,   p=0.06
## Score (logrank) test = 11.23  on 5 df,   p=0.05
```

We see that none of covariates seems to significally affect the hazard of having more than one new lesion (two or more), but the WHO score affects the risk of death. We will do a model checking on the model by evaluating the two cause specific hazards. We can fit two cox models, one for each cause, where we treat the other cause as censoring. These models can be used to evaluate the hazard functions and make model control based on the hazards. We make two cox models:

```
coxcheck1 <- phreg(Surv(time1, status == 1) ~ treatment + age + who.PS,
                   data = prob.colo)
coxcheck2 <- phreg(Surv(time1, status == 2) ~ treatment + age + who.PS,
                   data = prob.colo)
```

We can start by doing the formal test:

```
gof(coxcheck1)
```

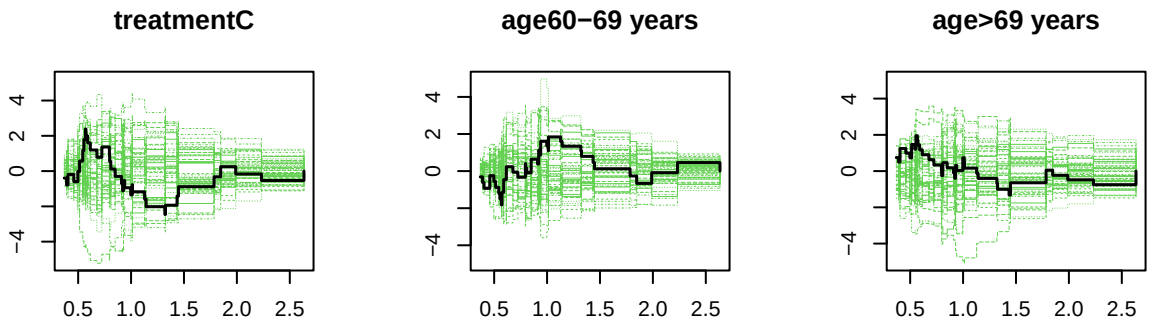
```
## Cumulative score process test for Proportionality:
##                 Sup|U(t)|  pval
## treatmentC       2.458437 0.361
## age60-69 years   1.841867 0.592
## age>69 years     1.950049 0.515
## who.PS1          1.392845 0.803
## who.PS2          1.509776 0.558
```

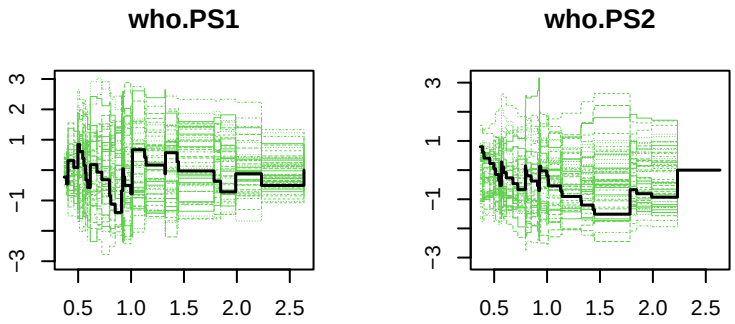
```
gof(coxcheck2)
```

```
## Cumulative score process test for Proportionality:
##                 Sup|U(t)|  pval
## treatmentC       3.715092 0.429
## age60-69 years   4.815250 0.102
## age>69 years     3.966101 0.339
## who.PS1          2.523182 0.780
## who.PS2          3.112589 0.396
```

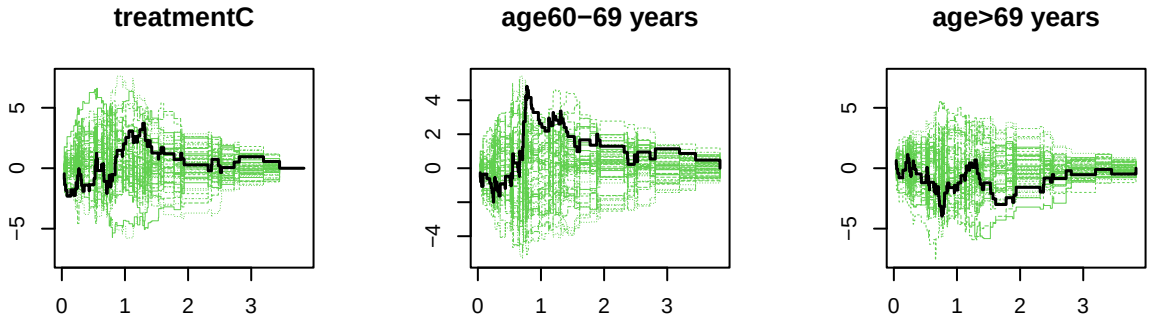
The martingale residuals can also be plotted for both cause specific cox models:

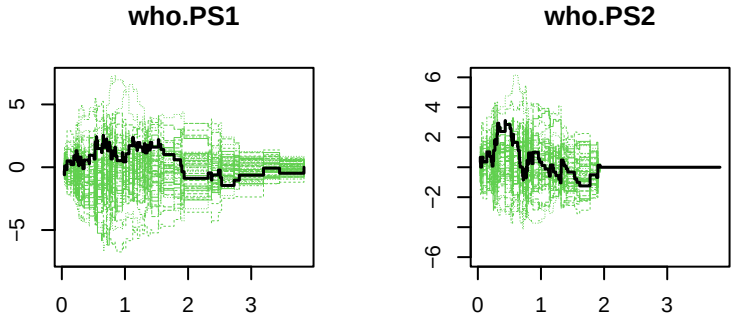
```
gof1 <- gof(coxcheck1)
par(mfrow=c(2,3))
plot(gof1)
```






```
gof2 <- gof(coxcheck2)
par(mfrow=c(2,3))
plot(gof2)
```

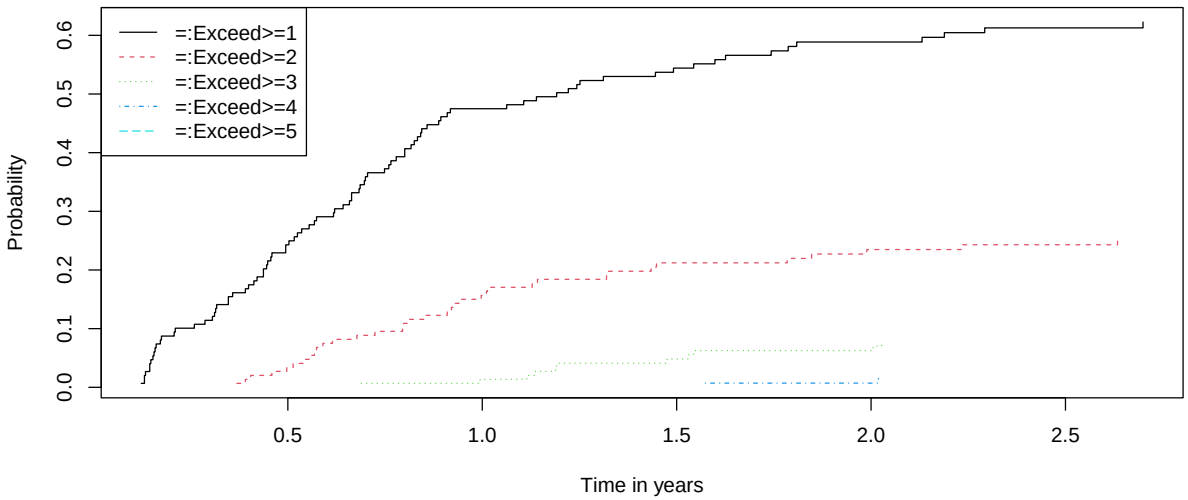




We find no evidence of any of the covariates affecting non-proportional on the hazard by the graphical and more formal tests.

Fitting then the marginal probability of observing more than one new lesion can be done non-parametrically using marginals. For this purpose, we use the function `prob.exceedRecurrent` from the `mets` package (https://cran.r-project.org/web/packages/mets/vignettes/recurrent-events.html):

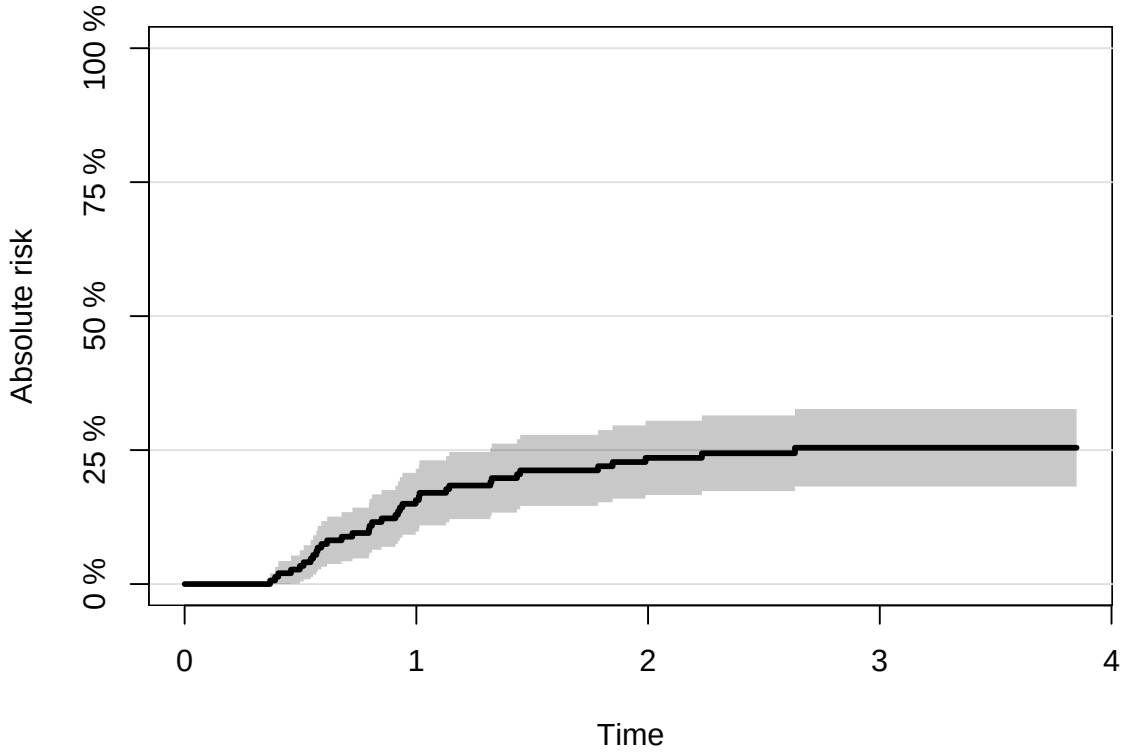
```
prob.obj <- count.history(colorectal, status="new.lesions") #Set up data
prob.exceed <- prob.exceedRecurrent(prob.obj, 1, status = "new.lesions",
                                    death="state", start="time0",
                                    stop="time1", id="id")
bplot(prob.exceed, ylab = "Probability", xlab = "Time in years")
```

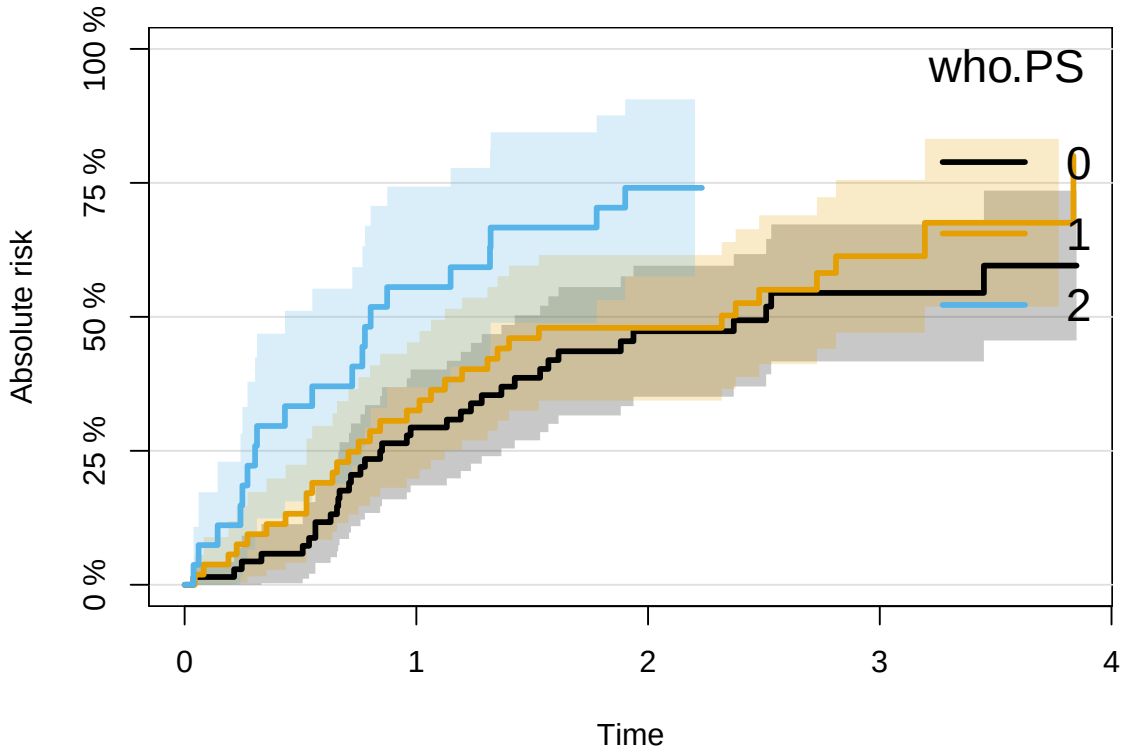


So, the probability we are interested in is getting more than one lesion (> 1), which is the red curve (two or above). So, not including any covariates, the probability of getting more than one lesion is increasing with time (as expected), with a steeper increase in the first months. For example, after 10 months, the probability of getting more than one lesion is around 10%, and after 25 months, it is approximately 23%.

We could also fit the absolute risk using `prodlim` where we can adjust for who.PS on the absolute risk on the event of death.

```
par(mfrow=c(2,1))
plot(prodlim(Hist(time1, status)~1 , data=prob.colo), cause = 1,
     atrisk = FALSE)
plot(prodlim(Hist(time1, status)~who.PS , data=prob.colo), cause = 2,
     atrisk = FALSE)
```


Absolute risk
0 %
25 %
50 %
75 %
100 %
0
1
2
3
4
Time


Absolute risk
0 %
25 %
50 %
75 %
100 %
who.PS
0
1
2
0
1
2
3
4
Time

2.1.5. Estimate the probability of a patient having more than two new lessions before dying as a function of time.

Same procedure as in question 4. We create a data set that fits the question at hand:

```
colorectal[,cum.lesions1 := 1*(cum.lesions2 > 2)]
last <- colorectal[,.SD[.N],by = id]
prob.colo <- rbind(colorectal[cum.lesions1 == 1 | state == 1, .SD[1], by=id],
                   last[cum.lesions1 == 0 & state == 0,])
prob.colo[,status := ifelse(cum.lesions1 == 1, cum.lesions1, state*2)]
CSC(Hist(time = time1, status) ~ treatment + age + who.PS,
    data = prob.colo)
```

```
## CSC(formula = Hist(time = time1, status) ~ treatment + age +
##     who.PS, data = prob.colo)
##
## Right-censored response of a competing.risks model
##
## No.Observations: 150
##
## Pattern:
##
## Cause     event right.censored
##   1          11              0
##   2         110              0
##   unknown     0             29
##
##
## ----------> Cause:  1
##
## Call:
## coxph(formula = survival::Surv(time, status) ~ treatment + age +
##     who.PS, x = TRUE, y = TRUE)
##
##   n= 150, number of events= 11
##
##                     coef exp(coef) se(coef)      z Pr(>|z|)
## treatmentC     -0.60810   0.54439  0.64601 -0.941    0.347
## age60-69 years -0.33936   0.71223  0.77574 -0.437    0.662
## age>69 years   -0.06618   0.93596  0.71334 -0.093    0.926
## who.PS1        -0.61449   0.54091  0.69360 -0.886    0.376
## who.PS2        -0.37517   0.68717  1.07688 -0.348    0.728
##
##                exp(coef) exp(-coef) lower .95 upper .95
## treatmentC        0.5444      1.837   0.15347     1.931
## age60-69 years    0.7122      1.404   0.15571     3.258
## age>69 years      0.9360      1.068   0.23124     3.788
```

```
## who.PS1           0.5409      1.849   0.13891     2.106
## who.PS2           0.6872      1.455   0.08326     5.672
##
## Concordance= 0.653  (se = 0.073 )
## Likelihood ratio test= 1.96  on 5 df,   p=0.9
## Wald test            = 1.93  on 5 df,   p=0.9
## Score (logrank) test = 1.99  on 5 df,   p=0.8
##
##
##
## ----------> Cause:  2
##
## Call:
## coxph(formula = survival::Surv(time, status) ~ treatment + age +
##     who.PS, x = TRUE, y = TRUE)
##
##   n= 150, number of events= 110
##
##                     coef exp(coef) se(coef)      z Pr(>|z|)
## treatmentC     -0.08639   0.91723  0.19979 -0.432 0.665447
## age60-69 years -0.16550   0.84747  0.24672 -0.671 0.502332
## age>69 years   -0.23580   0.78994  0.22923 -1.029 0.303641
## who.PS1        -0.03507   0.96554  0.21972 -0.160 0.873202
## who.PS2         0.88833   2.43106  0.25328  3.507 0.000453 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##                exp(coef) exp(-coef) lower .95 upper .95
## treatmentC        0.9172     1.0902    0.6200     1.357
## age60-69 years    0.8475     1.1800    0.5225     1.374
## age>69 years      0.7899     1.2659    0.5041     1.238
## who.PS1           0.9655     1.0357    0.6277     1.485
## who.PS2           2.4311     0.4113    1.4798     3.994
##
## Concordance= 0.588  (se = 0.03 )
## Likelihood ratio test= 13.87  on 5 df,   p=0.02
## Wald test            = 15.99  on 5 df,   p=0.007
## Score (logrank) test = 16.98  on 5 df,   p=0.005
```

We do model control on cause specific cox models by a formal test and looking at the martingale residual plots:

```
coxcheck1 <- phreg(Surv(time1, status == 1) ~ treatment + age + who.PS,
                   data = prob.colo)
coxcheck2 <- phreg(Surv(time1, status == 2) ~ treatment + age + who.PS,
                   data = prob.colo)
gof(coxcheck1)
```

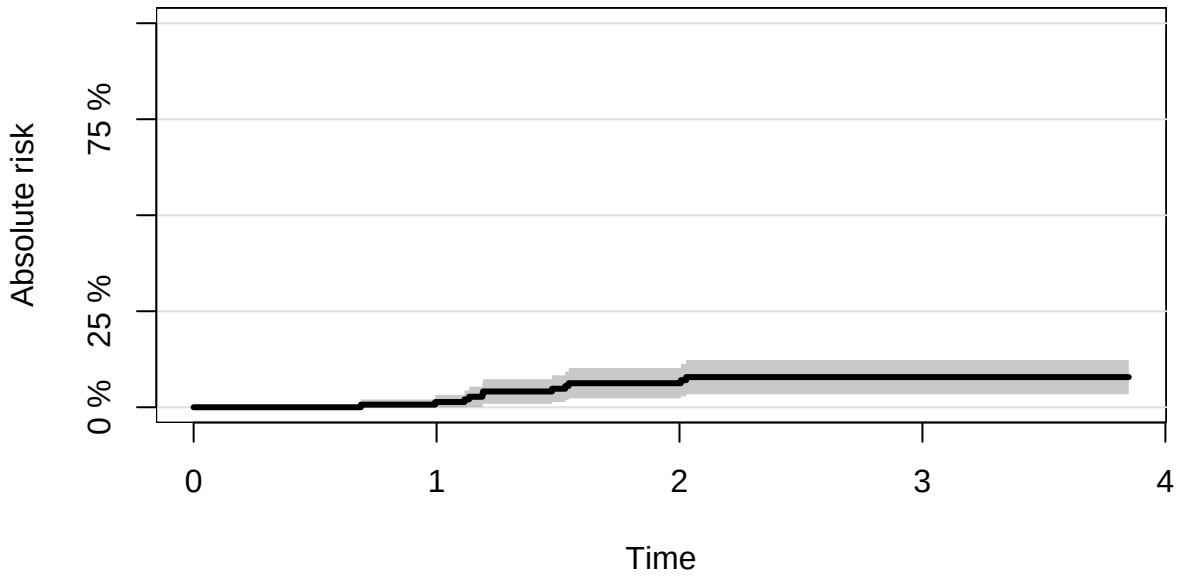
```
## Cumulative score process test for Proportionality:
##                 Sup|U(t)|  pval
## treatmentC      1.5419587 0.176
## age60-69 years 0.6562226 0.781
## age>69 years    1.2443609 0.365
## who.PS1         0.9856665 0.426
## who.PS2         0.9064968 0.294
```

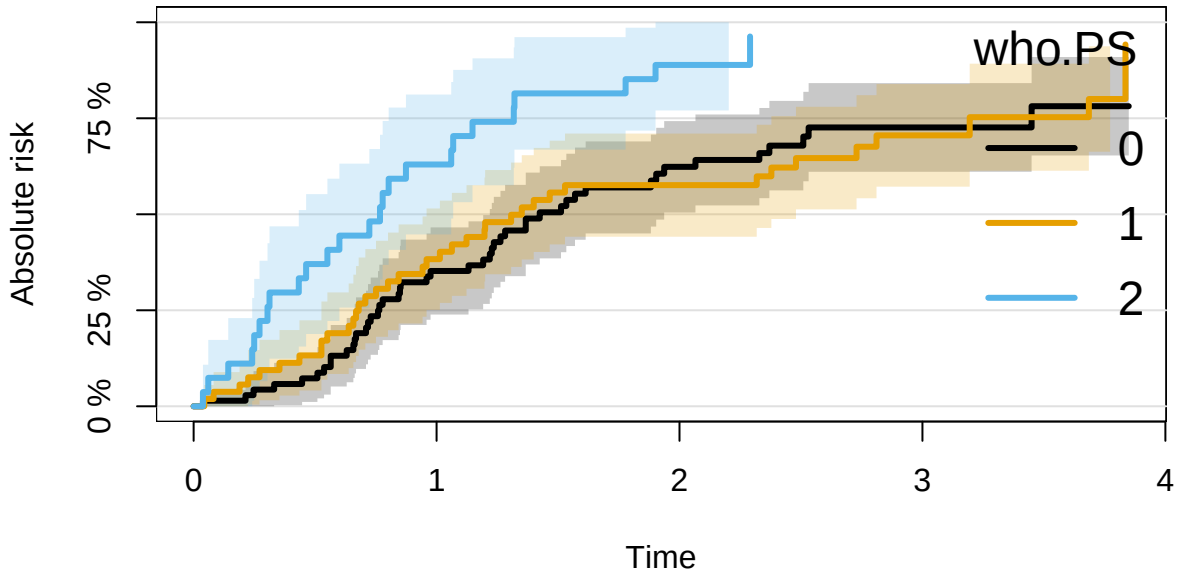
```
gof(coxcheck2)
```

```
## Cumulative score process test for Proportionality:
##                 Sup|U(t)|  pval
## treatmentC       4.028732 0.520
## age60-69 years  4.664973 0.203
## age>69 years     3.546400 0.609
## who.PS1          3.913823 0.443
## who.PS2          2.966006 0.611
```

We find no evidence of the proportionality assumption being violated. The marginal probability is plotted in question 4, but again we can plot the absolute risk of having more than 2 new lesions using prodlim. Again we adjust the event of death by WHO status.

```
par(mfrow=c(2,1))
plot(prodlim(Hist(time1, status)~1 , data=prob.colo), cause = 1,
     atrisk = FALSE)
plot(prodlim(Hist(time1, status)~who.PS , data=prob.colo), cause = 2,
     atrisk = FALSE)
```


Absolute risk
0 %
25 %
75 %
0
1
2
3
4
Time


Absolute risk
0 %
25 %
75 %
0
1
2
3
4
Time
who.PS
0
1
2