Survival Analysis with Applications in Medicine: Take-home examination

2025-03-27

A. Weibull regression models

Q1. For a proportional hazards model with $S_0(t)$ that is a Weibull distribution, show that survival $S(t)$ is also from a Weibull distribution.

Given a proportional hazards model with survival function $S(t|x) = S_0(t)^{\exp(\beta x)}$

for time t and a given covariate x, $S_0(t)$ is the baseline survival function, and β is the log hazard ratio.

We have the Weibull survival function $S_0(t) = \exp(-\lambda t^k)$ for a scale parameter λ and a shape parameter k.

Substituting $S_0(t)$ in the proportional hazards model, we get the survival function as

$S(t|x) = \left[\exp(-\lambda t^k)\right]^{\exp(\beta x)}$

$\Rightarrow S(t|x) = \exp(-\lambda t^k \exp(\beta x))$

which is in form $S(t|x) = \exp(-\tilde{\lambda}_a t^k)$ where $\tilde{\lambda}_a = \lambda \exp(\beta x)$ is the new scale parameter for the same shape parameter k.

Hence, the survival function $S(t|x)$ for a proportional hazards model is also from a Weibull distribution.

Q2. For an accelerated failure time model with $S_0(t)$ that is a Weibull distribution, show that survival $S(t)$ is also from a Weibull distribution.

Given an accelerated failure time model with survival function $S(t|x) = S_0(t\exp(-\tilde{\beta}x))$

for time t and a given covariate x, $S_0(t)$ is the baseline survival function, and $\tilde{\beta}$ is the log time ratio.

Substituting $S_0(t)$ in the accelerated failure time model, we get the survival function as

$S(t|x) = \exp(-\lambda\big(t\exp(-\tilde{\beta}x)\big)^k)$

$\Rightarrow S(t|x) = \exp(-\lambda t^k \exp(-k\tilde{\beta}x))$

which is in form $S(t|x) = \exp(-\tilde{\lambda}_b t^k)$ where $\tilde{\lambda}_b = \lambda \exp(-k\tilde{\beta}x)$ is the new scale parameter for the same shape parameter k.

Hence, the survival function $S(t|x)$ for an accelerated failure time model is also from a Weibull distribution.

Q3. What is the relationship between β and $\tilde{\beta}$ if both models have a Weibull baseline survival function?

For the proportional hazards model, we have $S(t|x) = \exp(-\lambda t^k \exp(\beta x))$.

For the accelerated failure time model, we have $S(t|x) = \exp(-\lambda t^k \exp(-k\tilde{\beta}x))$.

Equating the two models, we get $\exp(\beta x) = \exp(-k\tilde{\beta}x)$.

Taking the natural logarithm of both sides, we get $\beta x = -k\tilde{\beta}x$.

Therefore, the relationship between β and $\tilde{\beta}$ is $\beta = -k\tilde{\beta}$ if both models have a Weibull baseline survival function.

B: Interval-censored likelihood

For a data tuple (t_i, u_i, v_i) where t_i is the (left truncated) delayed entry time, and the event is observed in the interval $(u_i, v_i]$ for an individual i.

Q1a. Express the log-likelihood in terms of Survival function $S(t)$ at time t:

The Likelihood for the interval-censored data: $u_i < T \leq v_i$ for an entry time t_i is given by:

$L_i = \frac{S(u_i)-S(v_i)}{S(t_i)}$

where $S(t)$ is the Survival function.

This represents the probability that the event occurs in the interval $(u_i, v_i]$ given that the event has not occurred before u_i and the individual survives up to t_i and is at risk at time t_i.

Hence, the log-likelihood in terms of Survival function $S(t)$ at time t for this data tuple is given by $\log(S(u_i) - S(v_i)) - \log(S(t_i))$.

Q1b. Express the log-likelihood in terms of the hazard function $h(t)$ at time t:

Now, for the derivation of the log-likelihood in terms of the hazard function $h(t)$ at time t, we need to express the Survival function $S(t)$ in terms of the hazard function $h(t)$.

We know that, the survival function $S(t)$ is given by $-log(S(t)) = H(t)$,

where $H(t)$ is the cumulative hazard function, and $H(t) = \int_0^t h(u)du$ for the hazard function $h(t)$.

Therefore, the log-likelihood in terms of the hazard function $h(t)$ at time t is:

$\log L_i = \log(S(u_i) - S(v_i)) - \log(S(t_i))$

$\Rightarrow \log L_i = \log(exp(-H(u_i)) - exp(-H(v_i))) - \log(exp(-H(t_i)))$

$\Rightarrow \log L_i = \log(exp(-H(v_i)) * (exp(H(v_i) - H(u_i)) - 1)) + H(t_i)$

$\Rightarrow \log L_i = \log(exp(-H(v_i))) + \log(exp(H(v_i) - H(u_i)) - 1) + H(t_i)$

$\Rightarrow \log L_i = H(t_i) - H(v_i) + \log(exp(H(v_i) - H(u_i)) - 1)$

$\Rightarrow \log L_i = \int_0^{t_i} h(t)dt - \int_0^{v_i} h(t)dt + \log(exp(\int_{u_i}^{v_i} h(t)dt) - 1)$

$\Rightarrow \log L_i = -\int_{t_i}^{v_i} h(t)dt + \log(exp(\int_{u_i}^{v_i} h(t)dt) - 1)$

Hence, the log-likelihood in terms of the hazard function $h(t)$ at time t is given by $-\int_{t_i}^{v_i} h(t)dt + \log(exp(\int_{u_i}^{v_i} h(t)dt) - 1)$.

Q2. Can you express these data using the Surv function from the survival package? If so, show an example; if not, explain why.

The `Surv` function is used to create a survival object that represents the survival time of an individual. It takes the form `Surv(time, event)` where `time` is the survival time and `event` is the event indicator.

For interval-censored data, we can use the `Surv` function as `Surv(time, time2, type = "interval2")` where `time` is the start of the interval, `time2` is the end of the interval and type `interval2` is used to indicate interval-censored data effectively.

Although, the `Surv` function doesn't support left truncation directly, we can filter out the left truncated data by taking the maximum of the entry time and the left truncation time.

In conclusion, we cannot directly use the `Surv` function to directly express left truncated interval censored data, but we can indirectly use it to express by filtering beforehand.

Here is an example of how to express left-truncated interval-censored data indirectly using the `Surv` function:

```r
library(survival)

# sample data for the given data tuple structure (t_i, u_i, v_i)
d = data.frame(left_truncation_time = c(1,1,3,3,3),
               entry_time = c(0,0,2,2,2),
               exit_time = 1:5,
               event = c(1,0,1,0,1))

# filter out left truncated data
d$entry_time = pmax(d$entry_time, d$left_truncation_time)

# interval-censored data
with(d, Surv(entry_time, exit_time, type="interval2"))
```

```
## [1] 1      [1, 2] 3      [3, 4] [3, 5]
```

C: Truncated distributions

For a continuous random variable T, we have the survival function $S(t) = P(T > t)$.

Let the quantile function $Q(p)$ such that $Q(p) = S^{-1}(1-p) \Rightarrow 1 - p = S(Q(p)) = P(T > Q(p))$.

Assume that we have a truncated distribution with survival function $P(T > t | T > t_0)$ for left truncation time t_0.

Q1. Express the survival function for the truncated distribution in terms of the survival function for T.

The survival function for the truncated distribution is given by:

$P(T > t | T > t_0)$

$\Rightarrow \frac{P(T>t, T>t_0)}{P(T>t_0)}$ by definition of conditional probability.

$\Rightarrow \frac{P(T>t)}{P(T>t_0)}$ because $(T > t, T > t_0)$ implies $(T > t)$ as t_0 is the left truncation time.

Since, $P(T > t) = S(t)$ and $P(T > t_0) = S(t_0)$ by the survival function for T,

the survival function for the truncated distribution is given by $\frac{S(t)}{S(t_0)}$.

Q2. For the truncated distribution, what is the quantile function $Q(p|t_0)$ that solves $P(T > t|T > t_0) = 1 - p$ for t in terms of the survival and quantile functions for T at quantile (probability) p?

Given $P(T > t|T > t_0) = 1 - p$,

we know that $P(T > t|T > t_0) = \frac{S(t)}{S(t_0)} = 1 - p$.

Therefore, the quantile function $Q(p|t_0) = t$ that solves $P(T > t|T > t_0) = 1 - p$:

$S(t) = (1 - p)S(t_0)$

$\Rightarrow t = S^{-1}((1-p)S(t_0))$

$\Rightarrow Q(p|t_0) = S^{-1}((1-p)S(t_0))$.

To solve for $S^{-1}((1-p)S(t_0))$, we know that $Q(p) = S^{-1}(1-p) \rightarrow Q(1-p) = S^{-1}(p)$.

$\Rightarrow Q(p|t_0) = S^{-1}((1-p)S(t_0)) = Q(1-(1-p)S(t_0))$.

i.e., the p-th quantile of left truncated distribution is the $(1-(1-p)S(t_0))$-th quantile of the original distribution.

Q3. Using this algorithm, write, run and report on R code to calculate the 0.4 quantile from a truncated log-normal distribution where $T \sim LogNormal(\mu = 1, \sigma^2 = 1.2^2)$ for a log-normal distribution with mean μ and standard deviation σ on the log scale for $t_0 = 2$.

We can derive the quantile function $Q(p = 0.4|t_0 = 2)$ as follows:

$Q(p|t_0) = Q(1-(1-p)S(t_0))$.

To derive $S(t_0)$, we know that $S(t_0) = P(T > t_0) = 1 - P(T \leq t_0) = 1 - F(t_0)$,

where $F(t)$ is the cumulative distribution function for T.

For a log-normal distribution of T, we can compute $S(t_0)$ using `plnorm` function in R.

Then, we can substitute the $S(t_0)$ value back to $Q(1-(1-p)S(t_0))$ and compute the quantile using `qlnorm` function in R for the probability $p = 0.4$.

```r
#' @param p is the probability
#' @param meanlog mean on the log scale
#' @param sdlog standard deviation on the log scale
#' #' @param t0 left truncation time
#' @return the quantile from a truncated log-normal distribution

f = function(p, meanlog, sdlog, t0) {
  S2 = 1 - plnorm(t0, meanlog, sdlog)
  Q = qlnorm(1 - (1-p)*S2, meanlog, sdlog)
  return(Q)
}

# function call
f(p = 0.4, meanlog = 1, sdlog = 1.2, t0 = 2)
```

```
## [1] 4.171994
```

Hence, the 0.4 quantile from a truncated log-normal distribution with $T \sim LogNormal(\mu = 1, \sigma^2 = 1.2^2)$ for $t_0 = 2$ is approximately 4.172.

Q4. Check your value of the 0.4 quantile from the truncated log-normal distribution in question C3 by given random sampling code.

Given `R` code to return a vector of random numbers t sampled from a truncated log-normal distribution:

```r
#' @param n the number of random numbers
#' @param meanlog mean on the log scale
#' @param sdlog sd on the log scale
#' @param t0 left truncation time(s)
#' @return vector of random numbers drawn from a truncated log-normal distribution
rtrunc_lnorm = function(n, meanlog, sdlog, t0) {
    y = rlnorm(n, meanlog, sdlog)
    while (any(y<t0))
```

```
        y[y<t0] = rlnorm(n, meanlog, sdlog)[y<t0]
    y
}
```

Now, let's try to compute the 0.4 quantile for the above random numbers using the `quantile` function in R for large sample sizes of $n = 100,000$ and $n = 1,000,000$.

```
# set seed for reproducibility
set.seed(123)

# generate 100,000 random numbers from truncated log-normal distribution
y = rtrunc_lnorm(n = 100000, meanlog = 1, sdlog = 1.2, t0 = 2)

# calculate the 0.4 quantile
quantile(y, 0.4)
```

```
##      40%
## 4.179444
```

```
# generate 1,000,000 random numbers from truncated log-normal distribution
y = rtrunc_lnorm(n = 1000000, meanlog = 1, sdlog = 1.2, t0 = 2)

# calculate the 0.4 quantile
quantile(y, 0.4)
```

```
##      40%
## 4.177875
```

This is very close to the value of 4.172 obtained from the algorithm in question C3.

D: Cox's partial likelihood with a time-varying effects

Q1. Let the right censored data tuple $(t_i, \delta_i, x_i(.))$ for individual $i \in \{1, 2, ..., n\}$, with follow-up from time 0 to time t_i, event indicator δ_i (with value 1 if the event is observed at time t_i, otherwise censored with value 0), and time-varying effects $x_i(t)$. Let the time-varying hazard ratio be $exp(x_i(t)^T\beta)$ for regression coefficients β. Let the risk set $R(t_i)$ be the set of individuals $\{j : t_j \geq t_i\}$. Assume that there are no tied event times. Write out the partial likelihood $L(\beta)$.

The cox proportional hazards model has the hazard at time t given time-varying covariates $x(t)$ as

$h(t|x) = exp(x(t)^T\beta)h_0(t)$, where $h_0(t)$ is the baseline hazard function.

The partial likelihood function $L(\beta)$ is the product over all individuals who experience an event $(\delta_i = 1)$ of the conditional probability that that particular individual experiences the event at time t_i, given that the event occurs at that time within the risk set $R(t_i)$.

For an individual i who experiences an event at time t_i, the conditional probability is given by the ratio of their hazard to the sum of the hazards of all individuals in the risk set at time t_i:

$$\frac{h_i(t_i|x_i)}{\sum_{j\in R(t_i)} h_j(t_i|x_i)}$$

$$\Rightarrow \frac{exp(x_i(t_i)^T\beta)h_0(t_i)}{\sum_{j\in R(t_i)} exp(x_j(t_i)^T\beta)h_0(t_i)}$$

$$\Rightarrow \frac{exp(x_i(t_i)^T\beta)}{\sum_{j\in R(t_i)} exp(x_j(t_i)^T\beta)}.$$

Hence, the partial likelihood function $L(\beta)$ is the product of these conditional probabilities over all n individuals for whom an event is observed:

$L(\beta) = \prod_{i=1}^{n} \left(\frac{exp(x_i(t_i)^T\beta)}{\sum_{j\in R(t_i)} exp(x_j(t_i)^T\beta)} \right)^{\delta_i}$

where δ_i is the event indicator for individual i, $x_i(t_i)$ is the time-varying effects vector for individual i at observed time t_i, $R(t_i)$ is the risk set at time t_i, β is the vector of regression coefficients.

Note that the x_j in the denominator are evaluated at time t_i .

Q2. Analytically derive the gradient (or score) $\frac{d\log(L)}{d\beta_k}$.

The log partial likelihood function is given by:

$\log(L(\beta)) = \sum_{i=1}^{n} \delta_i \left(x_i(t_i)^T\beta - \log\left(\sum_{j\in R(t_i)} exp(x_j(t_i)^T\beta) \right) \right).$

The gradient of the log partial likelihood function with respect to the k-th element of β is:

$\frac{d\log(L)}{d\beta_k} = \sum_{i=1}^{n} \delta_i \left(x_{ik}(t_i) - \frac{\sum_{j\in R(t_i)} x_{jk}(t_i) exp(x_j(t_i)^T\beta)}{\sum_{j\in R(t_i)} exp(x_j(t_i)^T\beta)} \right).$

where $x_{ik}(t_i)$ is the k-th element of the time-varying effects vector $x_i(t_i)$ for individual i and

$x_{jk}(t_i)$ is the k-th element of the time-varying effects vector $x_j(t_i)$ for individual j in the risk set $R(t_i)$ at time t_i.

Q3. Let a binary exposure be defined by z_i for individual i and let $x_i(t) = (z_i, z_i t)^T$. Write out a formula for the hazard ratio as a function of time t for those exposed compared with those not exposed.

Considering an exposure z_i, the hazard function for an individual i is given by:

$h_i(t|x_i) = exp(x_i(t)^T\beta)h_0(t).$

$\Rightarrow exp(z_i\beta_1 + z_i t\beta_2)h_0(t).$

The hazard ratio at time t for those exposed $(z_i = 1)$ compared with those not exposed $(z_i = 0)$ is given by:

$\frac{h_i(t|x_i=(1,t)^T)}{h_i(t|x_i=(0,0)^T)} = \frac{exp(\beta_1+t\beta_2)h_0(t)}{exp(0)h_0(t)} = exp(\beta_1 + t\beta_2).$

Q4. The following code is used to investigate whether the hazard ratio between distant and localised cancer varies by time. Write out the regression model and carefully interpret the four parameters.

Given the following code:

```r
library(survival)
library(biostat3)
transform(biostat3::colon, stage=relevel(stage,"Localised")) |>
    coxph(Surv(surv_mm,status=="Dead: cancer")~stage+tt(stage), data=_,
          tt=function(x,t,...) (x=="Distant")*t/12) |>
    summary()
```

```
## Call:
## coxph(formula = Surv(surv_mm, status == "Dead: cancer") ~ stage +
##     tt(stage), data = transform(biostat3::colon, stage = relevel(stage,
##     "Localised")), tt = function(x, t, ...) (x == "Distant") *
##     t/12)
##
##   n= 15564, number of events= 8369
```

```
##
##                   coef exp(coef) se(coef)      z Pr(>|z|)
## stageUnknown   0.93904   2.55753  0.03777 24.865  < 2e-16 ***
## stageRegional  0.80311   2.23248  0.04105 19.566  < 2e-16 ***
## stageDistant   2.21903   9.19837  0.03561 62.321  < 2e-16 ***
## tt(stage)     -0.12347   0.88385  0.01551 -7.959 1.73e-15 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##               exp(coef) exp(-coef) lower .95 upper .95
## stageUnknown     2.5575     0.3910    2.3751    2.7540
## stageRegional    2.2325     0.4479    2.0599    2.4195
## stageDistant     9.1984     0.1087    8.5783    9.8632
## tt(stage)        0.8839     1.1314    0.8574    0.9111
##
## Concordance= 0.727  (se = 0.003 )
## Likelihood ratio test= 5849  on 4 df,   p=<2e-16
## Wald test            = 5310  on 4 df,   p=<2e-16
## Score (logrank) test = 6821  on 4 df,   p=<2e-16
```

From the above code, the cox regression model being fitted can be written as:

$$\mathbf{h(t|stage)} = \mathbf{h_0(t)exp(}\boldsymbol{\beta_1} \times \mathbf{stageUnknown} + \boldsymbol{\beta_2} \times \mathbf{stageRegional} + \boldsymbol{\beta_3} \times \mathbf{stageDistant} + \boldsymbol{\beta_4} \times \mathbf{tt(stage)}).$$

where $h(t|stage)$ is the hazard function at time t given the stage of cancer, $h_0(t)$ is the baseline hazard function, $\beta_1, \beta_2, \beta_3, \beta_4$ are the regression coefficients for the stage of cancer, $tt(stage)$ is the time-varying effect for the Distant stage and $stageUnknown, stageRegional, stageDistant$ are indicator variables for the Unknown, Regional, and Distant stages of cancer respectively.

Here, $tt(stage)$ is defined as $(x == Distant) \times t/12$ and Localised is the reference level for the stage of cancer.

The four parameters in question are:

- β_1: The log hazard ratio between the Unknown stage and the Localised stage of cancer.
- β_2: The log hazard ratio between the Regional stage and the Localised stage of cancer.
- β_3: The log hazard ratio between the Distant stage and the Localised stage of cancer at $t = 0$.
- β_4: The time-dependent change in the log hazard ratio between the Distant stage and the Localised stage of cancer per year.

The p-value of each parameter is a very small value ($\ll 0.05$), indicating that the parameters are all statistically significant. This means that all stages of cancer have a significant impact on the hazard of death from cancer compared to the Localised stage and the hazard ratio between Distant and Localised cancer varies over time.

Interpretation of the parameters:

- Patients with Unknown stage cancer have $exp(\beta_1) \sim$ **2.56** times higher risk of death from cancer compared to patients with Localised stage cancer.
- Patients with Regional stage cancer have $exp(\beta_2) \sim$ **2.23** times higher risk of death from cancer compared to patients with Localised stage cancer.
- Patients with Distant stage cancer have $exp(\beta_3) \sim$ **9.20** times higher risk of death from cancer compared to patients with Localised stage cancer.
- The hazard for Distant stage cancer decreases over time at a rate of $1 - exp(\beta_4) \sim 1 - 0.88 = 0.12$, meaning approximately a **12%** reduction in hazard per year.

The 95% confidence interval for the hazard ratio of time varying effect is (0.86, 0.91), which indicates that the hazard for Distant stage cancer decreases by approximately 9% to 14% per year compared to Localised stage cancer with 95% confidence.

E: Data analysis of a randomised controlled trial for hormonal treatment of breast cancer patients in Germany

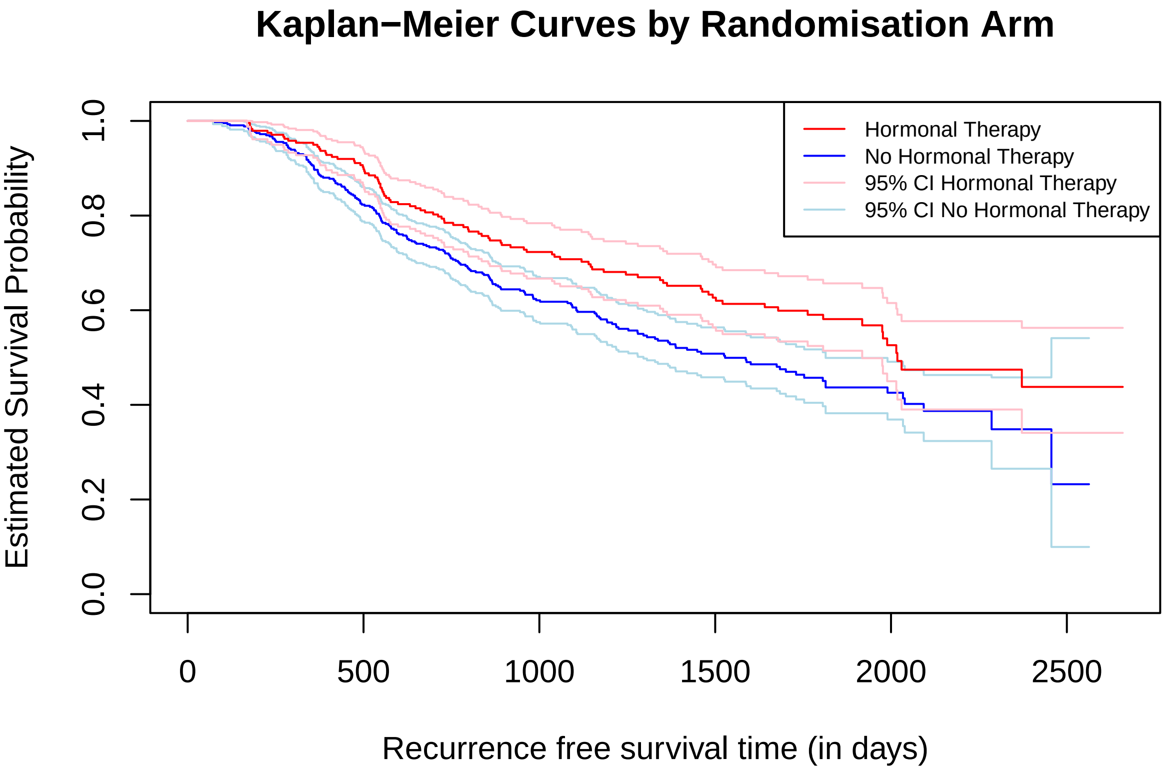
Q1. Plot the Kaplan-Meier curves by randomisation arm, including a legend and appropriate axis labels. Carefully describe the pattern.

To focus on the effect of recurrence in the hormonal therapy with follow-up time rectime and recurrence status indicated by censrec (1 = recurrence, 0 = censored), first we plot the kaplan-meier curves with solely the binary variable hormon (1 = hormonal therapy, 0 = no hormonal therapy) by randomisation arm.

```
# Load the data
library(survival)
library(rstpm2)

data(brcancer)

# Fit the kaplan-meier curves
fit <- survfit(Surv(rectime, censrec) ~ hormon, data = brcancer)

# Preview the summary of the fit for first 5 time points
summary(fit, times = 1:5)
```

```
## Call: survfit(formula = Surv(rectime, censrec) ~ hormon, data = brcancer)
##
##                 hormon=0
##  time n.risk n.event survival std.err lower 95% CI upper 95% CI
##     1    440       0        1       0            1            1
##     2    440       0        1       0            1            1
##     3    440       0        1       0            1            1
##     4    440       0        1       0            1            1
##     5    440       0        1       0            1            1
##
##                 hormon=1
##  time n.risk n.event survival std.err lower 95% CI upper 95% CI
##     1    246       0        1       0            1            1
##     2    246       0        1       0            1            1
##     3    246       0        1       0            1            1
##     4    246       0        1       0            1            1
##     5    246       0        1       0            1            1
```

```
# Plot the kaplan-meier curves
plot(fit,
     col = c("blue","lightblue", "lightblue", "red", "pink", "pink" ),
     lty = c(1,1),
     conf.int = TRUE, # display confidence intervals
     xlab = "Recurrence free survival time (in days)",
     ylab = "Estimated Survival Probability",
     main = "Kaplan-Meier Curves by Randomisation Arm")

# Add a legend
legend("topright",
       legend = c( "Hormonal Therapy", "No Hormonal Therapy",
                   "95% CI Hormonal Therapy", "95% CI No Hormonal Therapy"),
       col = c("red", "blue", "pink", "lightblue"),
       lty = c(1,1),
       cex = 0.7)
```



We see the following pattern in the Kaplan-Meier curves:

- **Initial Survival Probability:** At time zero, both curves start at survival probability 1.0 as no patients have experienced recurrence yet.
- **Separation of Curves:** The survival probability for patients receiving hormonal therapy remains higher than those not receiving hormonal therapy throughout the follow-up period. This indicates that hormonal therapy is associated with a lower risk of recurrence.
- **Nature of the Curves:** The Kaplan Meier estimate remains constant between events and drops only at observed recurrence times, leading to stepwise changes in the curves. The curves show a decreasing trend in survival probability over time as more patients experience recurrence.
- **Confidence Intervals:** The lighter lines around the Kaplan-Meier curves represent the 95% confidence intervals for the survival probabilities. The confidence intervals are wider at later time points due to fewer patients being at risk. The upper bound of no hormonal therapy arm and the lower bound of hormonal therapy arm jump above and below each other throughout the follow-up period.
- **Drop in Survival Probability:** The survival probability drops sharply at 2500 days for the no hormonal therapy arm to 0.2 survival probability, indicating fewer patients surviving without recurrence after 7 years. Whereas, the hormonal therapy arm shows a more gradual decrease in survival probability at around 500 and 2000 days.

The hormonal therapy arm shows a consistently higher survival probability compared to the no hormonal therapy arm, indicating a beneficial effect of hormonal therapy in reducing the risk of recurrence in breast cancer patients.

Q2. Fit a Cox regression model, adjusting for hormonal treatment. Write out the regression model, defining any notation. Describe your findings, including the estimand of choice to compare those on hormonal treatment compared with those not.

To fit a Cox regression model adjusting for hormonal treatment, we consider the following regression model:

$$h(t|hormon, X) = h_0(t)exp(\beta \times hormon + \gamma \times X)$$

where $h(t|hormon, X)$ is the hazard function at time t given hormonal treatment and list of covariates, such as, age, menopausal status, tumour information, $h_0(t)$ is the baseline hazard function, *hormon* is the indicator variable for hormonal therapy, β is the regression coefficient for hormonal treatment, X is the vector of covariates and γ is the vector of regression coefficients for covariates.

We will compare the model performance with all covariates and a reduced model with only the hormonal treatment variable.

The Cox regression model with all the given variables in the dataset is as follows:

```
# Fit the Cox regression model with all covariates
cox_model_all <- coxph(Surv(rectime, censrec) ~ hormon + x1 + x2 + x3 + x4
                       + x4a + x4b + x5 + x5e + x6 + x7, data = brcancer)
summary(cox_model_all)
```

```
## Call:
## coxph(formula = Surv(rectime, censrec) ~ hormon + x1 + x2 + x3 +
##     x4 + x4a + x4b + x5 + x5e + x6 + x7, data = brcancer)
##
##   n= 686, number of events= 299
##
##              coef  exp(coef)   se(coef)      z Pr(>|z|)
## hormon -0.3915461  0.6760109  0.1290423 -3.034  0.00241 **
## x1     -0.0076306  0.9923984  0.0092399 -0.826  0.40890
## x2      0.1953784  1.2157709  0.1823888  1.071  0.28407
## x3      0.0050364  1.0050491  0.0039393  1.278  0.20108
## x4      0.1186359  1.1259598  0.1360418  0.872  0.38318
## x4a     0.4968241  1.6434934  0.2982030  1.666  0.09570 .
## x4b            NA         NA  0.0000000     NA       NA
## x5     -0.0211165  0.9791049  0.0199231 -1.060  0.28919
## x5e    -2.3671988  0.0937430  0.4949707 -4.783 1.73e-06 ***
## x6     -0.0023312  0.9976715  0.0005684 -4.101 4.11e-05 ***
## x7      0.0004454  1.0004455  0.0004767  0.934  0.35007
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##        exp(coef) exp(-coef) lower .95 upper .95
## hormon   0.67601     1.4793   0.52494    0.8706
## x1       0.99240     1.0077   0.97459    1.0105
## x2       1.21577     0.8225   0.85036    1.7382
## x3       1.00505     0.9950   0.99732    1.0128
## x4       1.12596     0.8881   0.86243    1.4700
## x4a      1.64349     0.6085   0.91609    2.9485
## x4b           NA         NA        NA        NA
## x5       0.97910     1.0213   0.94161    1.0181
## x5e      0.09374    10.6675   0.03553    0.2473
## x6       0.99767     1.0023   0.99656    0.9988
## x7       1.00045     0.9996   0.99951    1.0014
##
## Concordance= 0.698  (se = 0.015 )
## Likelihood ratio test= 132.6  on 10 df,   p=<2e-16
## Wald test            = 125.7  on 10 df,   p=<2e-16
## Score (logrank) test = 132.4  on 10 df,   p=<2e-16
```

The Cox regression model with all covariates suggests that hormonal treatment, the decaying exponential function of number of positive nodes and progesterone receptor level are significantly associated with the risk of breast cancer recurrence from their p-values. The concordance index is 0.698, indicating that the model has moderate predictive accuracy. The likelihood ratio test, Wald test, and Score test all have p-values much less than 0.05, indicating that the model is statistically significant.

Now, let's look at the Cox regression model with only hormonal treatment:

```
# Fit the Cox regression model with only hormonal treatment
cox_model_basic <- coxph(Surv(rectime, censrec) ~ hormon, data = brcancer)
summary(cox_model_basic)
```

```
## Call:
## coxph(formula = Surv(rectime, censrec) ~ hormon, data = brcancer)
##
##   n= 686, number of events= 299
##
##           coef exp(coef) se(coef)      z Pr(>|z|)
## hormon -0.3640    0.6949   0.1250 -2.911   0.0036 **
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##        exp(coef) exp(-coef) lower .95 upper .95
## hormon    0.6949      1.439    0.5438    0.8879
##
## Concordance= 0.543  (se = 0.014 )
## Likelihood ratio test= 8.82  on 1 df,   p=0.003
## Wald test            = 8.47  on 1 df,   p=0.004
## Score (logrank) test = 8.57  on 1 df,   p=0.003
```

The concordance index is 0.543, indicating that the model has poor predictive accuracy, almost as the same as random guessing. The likelihood ratio test, Wald test, and Score test all have p-values less than 0.05, indicating that the model is statistically significant. These values are not as good as the model with all covariates.

Now, let's fit an optimized Cox regression model with hormonal treatment and the statistically significant covariates $x5e$, $x6$ from the all covariates model:

```
cox_model_optm <- coxph(Surv(rectime, censrec) ~ hormon + x5e + x6, data = brcancer)
summary(cox_model_optm)
```

```
## Call:
## coxph(formula = Surv(rectime, censrec) ~ hormon + x5e + x6, data = brcancer)
##
##   n= 686, number of events= 299
##
##              coef  exp(coef)   se(coef)      z Pr(>|z|)
## hormon -0.3831264  0.6817267  0.1250651 -3.063  0.00219 **
## x5e    -2.0532114  0.1283221  0.2256488 -9.099  < 2e-16 ***
## x6     -0.0025404  0.9974629  0.0005533 -4.591 4.41e-06 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##        exp(coef) exp(-coef) lower .95 upper .95
## hormon    0.6817      1.467   0.53352    0.8711
## x5e       0.1283      7.793   0.08246    0.1997
## x6        0.9975      1.003   0.99638    0.9985
##
## Concordance= 0.685  (se = 0.015 )
## Likelihood ratio test= 119  on 3 df,   p=<2e-16
## Wald test            = 116.3  on 3 df,   p=<2e-16
## Score (logrank) test = 119.1  on 3 df,   p=<2e-16
```

Here, the concordance index is 0.685, which is better than the basic model with only hormonal treatment and pretty close to the model with all covariates. This indicates that this model has moderate predictive accuracy.

The likelihood ratio test, Wald test, and Score test all have p-values much less than 0.05, indicating that the model is statistically significant, and the model fits the data well. The p-value of the model is better than the basic model with only hormonal treatment, suggesting that the model with hormonal treatment, $x5e$ and $x6$ is a better fit. The individual p-values for hormonal treatment, $x5e$ and $x6$ indicate that they are all statistically significant.

Hence, our optimized Cox regression model with hormonal treatment, $x5e$ and $x6$ as covariates is the best fit for the data.

$h(t|hormon, x5e, x6) = h_0(t)exp(\beta_1 \times hormon + \beta_2 \times x5e + \beta_3 \times x6)$

where $h(t|hormon, x5e, x6)$ is the hazard function at time t given hormonal treatment, the decaying exponential function of number of positive nodes and the progesterone receptor level, $h_0(t)$ is the baseline hazard function, $hormon$ is the indicator variable for hormonal therapy, $x5e$ is the decaying exponential function of number of positive nodes, $x6$ is the progesterone receptor level in fmol/mg, and β_1, β_2, β_3 are the regression coefficients for hormonal treatment, $x5e$ and $x6$ respectively.

The Cox regression model estimates the hazard ratio (ψ) for hormonal treatment compared to no hormonal treatment. The estimand of choice is the hazard ratio, which represents the relative risk of recurrence for patients receiving hormonal treatment compared to those not receiving hormonal treatment after adjusting for covariates $x5e$ and $x6$. This is equivalent to the exponential of the regression coefficient β_1 in the Cox regression model.

The Cox regression model assumes that the hazard of breast cancer recurrence is proportional between the two treatment arms i.e., hazard ratio between groups is constant over time.

The findings from the Cox regression model are as follows:

- **Hazard Ratio of Hormonal Treatment:** The hazard ratio for hormonal treatment compared to no hormonal treatment is estimated to be $exp(\beta_1) = 0.6817$. This indicates that the hazard of breast cancer recurrence for patients receiving hormonal therapy is 31.83% lower than for those not receiving hormonal therapy, after adjusting for the decaying exponential function of number of positive nodes and progesterone receptor level in the model. The 95% confidence interval suggests that the true hazard ratio lies between 0.533 and 0.871 with 95% confidence. This is further supported by the Kaplan-Meier curves where the hormonal therapy arm shows a consistently higher survival probability compared to the no hormonal therapy arm.

- **Hazard Ratio of x5e:** The hazard ratio for $x5e$ is estimated to be $exp(\beta_2) = 0.1283$. This indicates that the hazard of breast cancer recurrence is 87.17% lower for each unit increase in the decaying exponential function of number of positive nodes ($x5e$), after adjusting for hormonal treatment and progesterone receptor level in the model. The 95% confidence interval suggests that the true hazard ratio lies between 0.082 and 0.1997 with 95% confidence. This suggests that number of positive nodes has incremental effect on the hazard of breast cancer recurrence in the form of decaying exponential function.

- **Hazard Ratio of x6:** The hazard ratio for progesterone receptor level $x6$ is estimated to be $exp(\beta_3) = 0.9975$. This indicates that the hazard of breast cancer recurrence is almost constant for each fmol unit increase in the progesterone receptor level ($x6$), after adjusting for hormonal treatment and decaying exponential function of number of positive nodes in the model. The 95% confidence interval suggests that the true hazard ratio lies between 0.9964 and 0.9985 with 95% confidence. This suggests that progesterone receptor level has a minimal effect on the hazard of breast cancer recurrence.

Q3. Provide a formal test for proportional hazards by treatment arm. Clearly describe which test, motivate why you chose that test, and describe what the test found.

To test for the proportional hazards assumption by treatment arm, we can use the Schoenfeld residuals test. The Schoenfeld residuals test is a widely used and straightforward method for assessing the proportional hazards assumption in Cox regression models. It tests whether the covariates have time-varying effects on the hazard of the event of interest.

Null Hypothesis H_0: The effect of hormonal treatment on the hazard of recurrence is constant over time (proportional hazards assumption holds).

Alternate Hypothesis H_1: The hormonal treatment has time-varying effects on the hazard of recurrence (proportional hazards assumption is violated).

For p-value < 0.05, we reject the null hypothesis and conclude that the proportional hazards assumption is violated.

We use the `cox.zph` function in R to perform the Schoenfeld residuals test, which calculates the scaled Schoenfeld residuals and tests for independence of these residuals with time.

```r
# Test for proportional hazards using Schoenfeld residuals
schoenfeld_test <- cox.zph(cox_model_optm)

# Display the results of the Schoenfeld residuals test
schoenfeld_test
```

```
##        chisq df     p
## hormon 0.222  1 0.638
## x5e    0.952  1 0.329
## x6     4.258  1 0.039
## GLOBAL 5.227  3 0.156
```

The Schoenfeld residuals test results are as follows:

- **Hormonal Treatment:** The p-value for the test of proportional hazards for hormonal treatment is 0.64, we do not reject the null hypothesis. This suggests that the hazard ratio for hormonal treatment is constant over time, supporting the validity of the Cox regression model.
- **x5e:** The p-value for the test of proportional hazards for $x5e$ is 0.33, we do not reject the null hypothesis. This suggests that the hazard ratio for the decaying exponential function of number of positive nodes is constant over time, which says that time-varying effect of $x5e$ is not significant.
- **x6:** The p-value for the test of proportional hazards for $x6$ is 0.039, we reject the null hypothesis. This suggests that the hazard ratio for the progesterone receptor level is not constant over time, violating the proportional hazards assumption.
- **Global Test:** The global test for the proportional hazards assumption has a p-value of 0.156. This suggests that the proportional hazards assumption holds for the model as a whole.

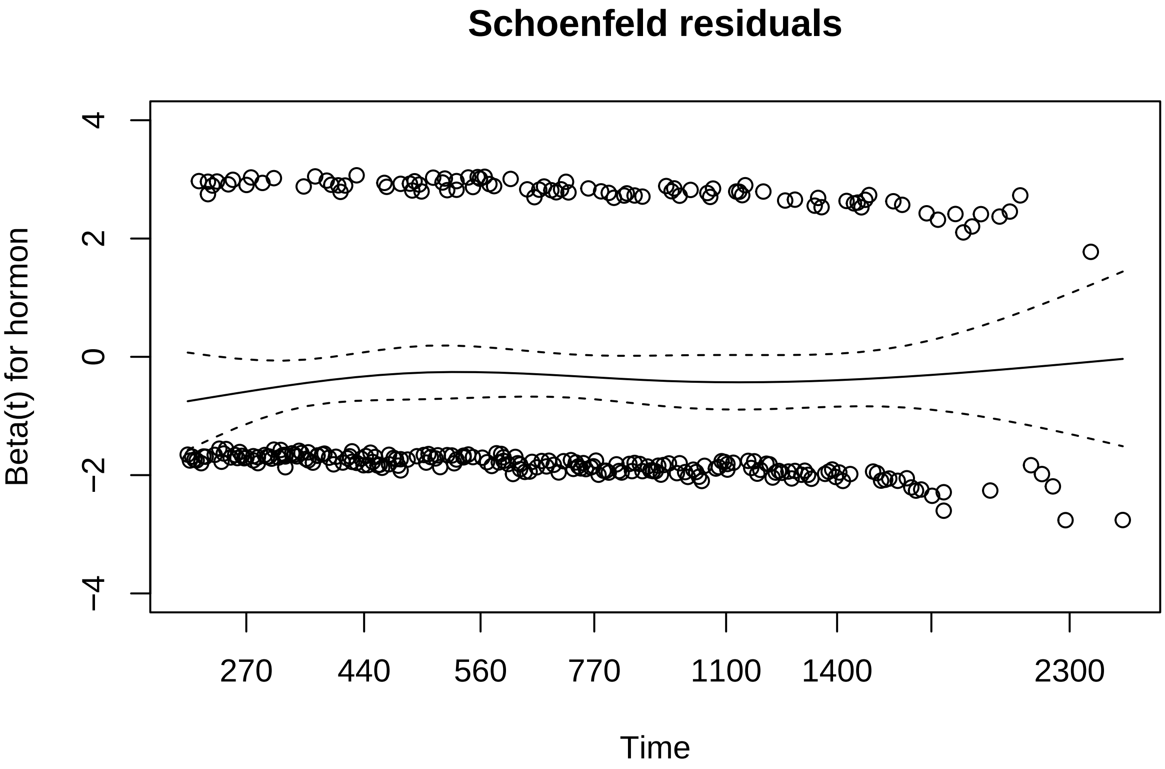
Since the variable $x6$ violates the proportional hazards assumption and has minimal effect on the hazard ratio, we can further check whether the cox model with only hormonal treatment and x5e is a better fit for the data using graphical evaluation of proportional hazards.

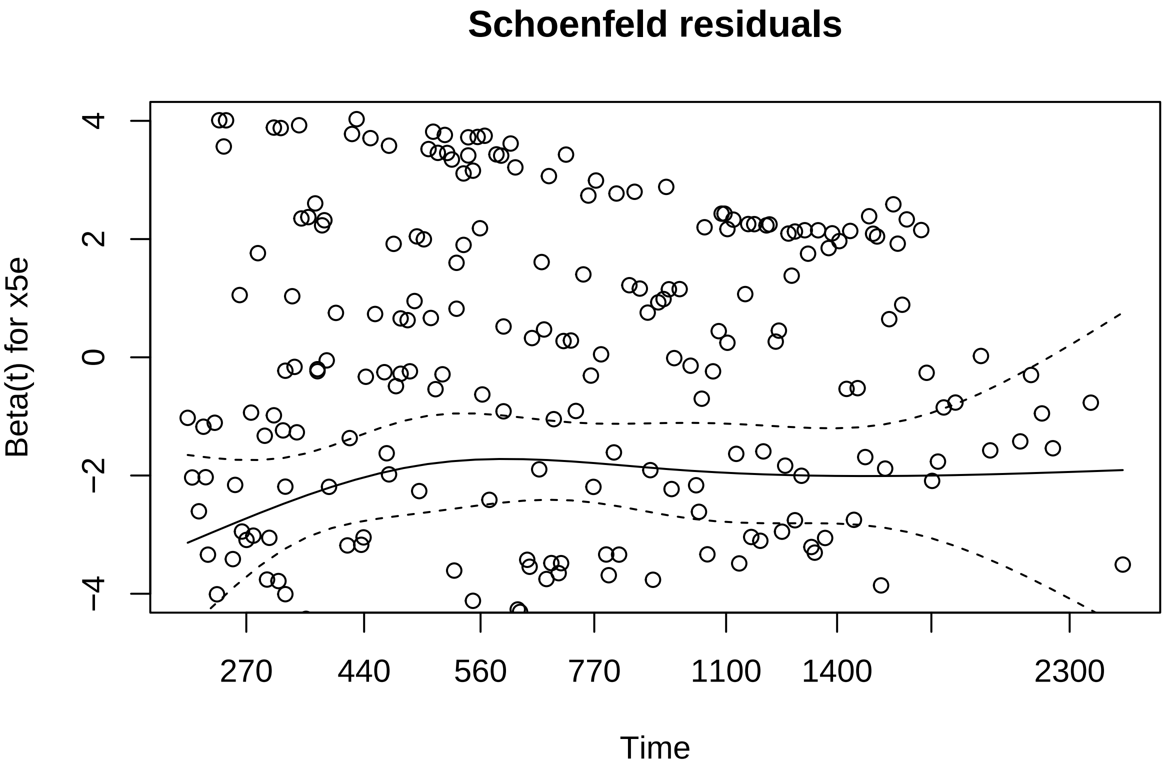
Q4. Provide a plot to graphically evaluation whether there is evidence for proportional hazards. Motivate your choice of method, and describe the method and the results of the evaluation.

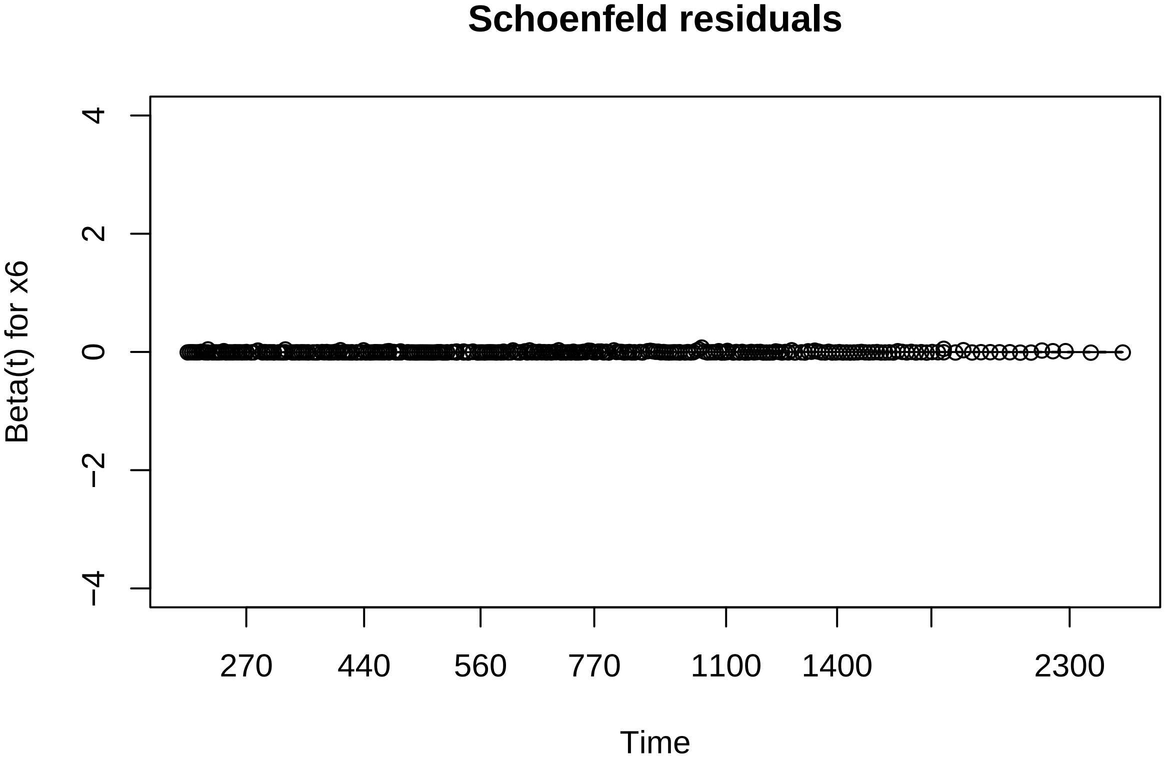
To graphically evaluate whether there is evidence for proportional hazards, we can plot the scaled Schoenfeld residuals against time. This plot can help us visually assess whether the residuals are independent of time, which is a key assumption for proportional hazards.

The plot shows the residuals as a function of time. If the line shows a systematic pattern or trend, it suggests that the proportional hazards assumption is violated, and the hazard ratio is not constant over time, else if the line is horizontal, it indicates that the proportional hazards assumption holds.

```
par(mfrow=c(1,1))
for (var in 1:3)
    plot(schoenfeld_test,var=var,resid=TRUE, se=TRUE, main="Schoenfeld residuals",
         ylim=c(-4,4))
```







- The curve for hormonal treatment is very close to horizontal and centered around zero, which supports the proportional hazards assumption. The residuals are randomly scattered around zero, indicating that the hazard ratio for hormonal treatment is constant over time. The confidence interval bands around the residuals are narrow and do not show any systematic pattern, further supporting the assumption of proportional hazards. This is supported by the p-value obtained from the Schoenfeld residuals test, which indicated that the proportional hazards assumption holds for hormonal treatment.

- The curve for $x5e$ is almost horizontal with confidence interval bands including zero, which indicates that the proportional hazards assumption holds for the decaying exponential function of number of positive nodes. The residuals are randomly scattered around zero, suggesting that the hazard ratio for $x5e$ is constant over time. This is supported by the p-value obtained from the Schoenfeld residuals test, which indicated that the proportional hazards assumption holds for $x5e$.
- The curve for progesterone receptor level $x6$ is exactly horizontal with confidence interval bands coinciding with zero, which indicates that the proportional hazards assumption holds for the progesterone receptor level. The residuals are tightly clustered around zero, suggesting that the hazard ratio for $x6$ is constant over time. This is in contradiction with the p-value obtained from the Schoenfeld residuals test, which indicated that the proportional hazards assumption is violated for $x6$. Although, the coefficient of $x6$ is very close to zero, hence, the effect on the hazard ratio is minimal.

Hence, the proportional hazards assumption holds for the variables hormonal treatment and $x5e$. We can say that the model with hormonal treatment and $x5e$ is simpler than the model with hormonal treatment, $x5e$ and $x6$. The graphical evaluation of proportional hazards provides a visual confirmation of the results obtained from the Schoenfeld residuals test.

F: Analysis plan for a randomised controlled trial

Q1. Write an outline of how to analyse this study. The outline should include: the estimand of interest; the estimator for that estimand; how you will assess potential confounding; how you will model for potential confounding; whether and how to assess for proportional hazards; and a description of the tables and figures used for reporting. Your analysis plan should provide some motivation for your choices.

For the research question of *Does low-dose aspirin improve survival for patients diagnosed with colorectal cancer with a particular genetic signature?*, we are interested in estimating the causal effect of low-dose aspirin on the survival of patients with a particular genetic signature diagnosed with colorectal cancer over five years of follow-up.

Analysis Plan:

- **Estimand of Interest:** Causal effect of low-dose aspirin on the survival of patients can be measured by comparing the cause-specific death due to colorectal cancer between the experimental arm (low-dose aspirin) and the control arm (no low-dose aspirin) for patients with a particular genetic signature. This can be quantified using the Hazard Ratio, which is the ratio of the hazard of death due to colorectal cancer in the experimental arm to the hazard in the control arm. The hazard ratio is easy to interpret and provides a measure of the relative risk of death due to colorectal cancer between the two arms. Hazard ratio less than 1 indicates a beneficial effect of low-dose aspirin on survival.
- **Estimator:** The hazard ratio is primarily estimated using the Cox proportional hazards model. This model is mainly used for time-to-event data, and can adjust for potential confounders, handle censoring data, and assess the effect of low-dose aspirin on cause-specific death due to colorectal cancer. The Cox model is suitable for this study as it can model time-varying covariates, adjust for potential confounders, does not require assumption about underlying survival distribution and assess the effect of low-dose aspirin on survival.
- **Assessment of Potential Confounding:** Potential confounding can be modelled by adjusting for covariates that are associated with both the treatment and the outcome. Confounders may include age, sex, cancer stage, and other variables that can potentially influence the effect of low-dose aspirin on survival. We will assess potential confounding by examining the association between the covariates and the outcome and check the significance of the covariates in the model to include them as confounders.
- **Modeling for Potential Confounding:** We will adjust for potential confounders by including them as covariates in the Cox regression model. The regression model will look like:

$h(t|aspirin, X) = h_0(t)exp(\beta \times aspirin + \gamma \times X)$,

where $h(t|aspirin, X)$ is the hazard function at time t given aspirin treatment and covariates X, such as age, sex, etc. $h_0(t)$ is the baseline hazard function for no aspirin treatment and the reference levels of all the covariates, β is the regression coefficient for aspirin treatment, *aspirin* is the indicator variable for low-dose aspirin treatment, and γ are the regression coefficients for covariates X.

By adjusting for confounders, we want to estimate the total effect of low-dose aspirin on cause-specific death due to colorectal cancer, independent of other factors that may confound the relationship.

- **Assessment for Proportional Hazards:** We will assess the proportional hazards assumption using the Schoenfeld residuals test. We can test for proportional hazards by examining the scaled Schoenfeld residuals against time. A non-significant p-value indicates that the proportional hazards assumption holds. If the proportional hazards assumption is violated, we will consider time-varying effects as a part of the model.
- **Tables and Figures for Reporting:**
  - **Table 1:** Descriptive statistics of the study population, including baseline characteristics by treatment arm. This table will include the summary of patient demographics, cancer stage, and other relevant covariates, to help understand the characteristics of the study population.
  - **Table 2:** Results of the Cox regression model, including hazard ratio, 95% confidence interval, and p-value for the effect of low-dose aspirin on cause-specific death due to colorectal cancer. This summary will show us the individual hazard ratios of each of the potential confounders conditional on the other covariates and their significance level in the model.
  - **Figure 1:** Kaplan-Meier curves for the experimental and control arms, showing the survival probability over time. This will help us visualize the difference in survival between the two arms, and assess the effect of low-dose aspirin on survival on a high level.
  - **Figure 2:** Schoenfeld residuals plot to assess the proportional hazards assumption. This plot will help us evaluate whether the hazard ratio for low-dose aspirin is constant over time, and whether time varying effects need to be considered in the model.

Hence, with the help of the Cox proportional hazards model, we can estimate the causal effect of low-dose aspirin on cause-specific death due to colorectal cancer, while adjusting for potential confounders and assessing the proportional hazards assumption.

Q2. Finally, discuss whether non-collapsibility is an issue for the chosen estimator.

Yes, non-collapsibility can be an issue for the chosen estimator, the Cox proportional hazards model. Hazard ratio in Cox proportional hazards model is a non-collapsible measure of association. This means that the marginal hazard ratio, i.e., the hazard ratio seen when not conditioned on any other variables, can be different from the conditional hazard ratio, i.e., the hazard ratio seen when conditioned on other variables. This can be seen even when the other variables are not confounders.

We estimate the conditional hazard ratio in the Cox model, since hazard function is defined as:

$h(t|aspirin, X) = h_0(t)exp(\beta \times aspirin + \gamma \times X)$.

In the context of the study, non-collapsibility can be an issue if we are interested in the marginal effect of low-dose aspirin on cause-specific death due to colorectal cancer, independent of other covariates, such as the patient's age, sex and their stage of cancer, i.e., when estimating the causal effect of the treatment across a population. Whereas, the conditional hazard ratio estimated by the Cox model is estimating the effect within a specific subgroup, such as patients with a particular age group or cancer stage.

We can address the non-collapsibility by using regression standardisation to calculate the marginal effect, which can provide a better interpretative measure of the effect of low-dose aspirin from the conditional model. This method can help us estimate the average causal effect of low-dose aspirin on cause-specific death due to colorectal cancer, independent of other covariates.

We can also use Aalen's additive hazards model, which estimates the additive effect of low-dose aspirin on the cumulative hazard function, providing a collapsible measure of the marginal effect of the treatment. Although, in practice, the Cox model is widely used due to its flexibility and ease of interpretation, it is important to be aware of the non-collapsibility issue when interpreting the hazard ratios from the model.

I am declaring that I have used generative artificial intelligence (GAI) to assist me in completing this assignment in the form of Github co-pilot to improve my summarization and writing skills.

This assignment took me approximately 23 hours to complete.