Biostatistics (MATH11230)

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Proportional hazards model

General context

- ↪ We end the course discussing regression models for time to event/survival data.
- ↪ There are various ways for modelling the dependency between the event time and the factors that might affect it.
- ↪ The two most common approaches are known as the **proportional hazards model** and the **accelerated failure time model**.
- ↪ Due to time constraints, here we will only cover the first class of methods: proportional hazards models.

Proportional hazards model

Comparing two groups

- Let us start with the simplest example: suppose that two groups of (male) patients receive either a a standard treatment or a new treatment for prostate cancer.

- The primary goal is to identify whether patients in the two treatment groups have a different survival experience.

- Let $h_S(t)$ and $h_N(t)$ be the hazards of death at time t for patients in the standard and new treatment groups, respectively.

- A convenient model is to assume that the hazard at time t for a patient in the new treatment group is proportional to the hazard at the same time in the standard treatment.

- This proportional hazards model can be expressed as

$$h_N(t) = \psi h_S(t), \qquad t \geq 0, \tag{1}$$

where ψ is a constant.

Proportional hazards model

Comparing two groups

- An implication of the proportional hazards model is that the corresponding true survival functions for individuals in the new and in the standard treatments do not cross.

- To see why, recall that by assumption $h_N(t) = \psi h_S(t)$. Integrating both sides of this expression, multiplying by (-1) and exponentiating gives

$$\exp\left\{-\int_0^t h_N(u)\mathrm{d}u\right\} = \exp\left\{-\int_0^t \psi h_S(u)\mathrm{d}u\right\}.$$

- Further note that

$$\exp\left\{-\int_0^t \psi h_S(u)\mathrm{d}u\right\} = \left[\exp\left\{-\int_0^t h_S(u)\mathrm{d}u\right\}\right]^{\psi},$$

and remember that

$$S(t) = \exp\left\{-\int_0^t h(u)\mathrm{d}u\right\}.$$

Proportional hazards model

Comparing two groups

- Therefore, if $S_N(t)$ and $S_S(t)$ are the survival functions for the two groups, then

$$S_N(t) = [S_S(t)]^{\psi} .$$

- The parameter ψ is called the hazard ratio: it is the ratio of the hazard of death at any time for an individual in the standard treatment.

- If $0 < \psi < 1$, the hazard of death at time t is smaller for an individual on the new drug relative to an individual on the standard treatment.

- The new treatment is then an improvement on the standard treatment.

- On the other hand, if $\psi > 1$, the hazard of death at time t is greater for an individual in the new drug, and the standard treatment is superior.

Proportional hazards model

Comparing two groups

- An alternative way of expressing the model in (1) leads to a model that can be more easily generalised.
- Suppose that survival times are available on n individuals and denote the hazard function for the ith of these by $h_i(t)$, for $i = 1, \ldots, n$.
- Also, let $h_0(t)$ be the hazard function for an individual in the standard treatment group.
- The hazard function for an individual on the new treatment is then $\psi h_0(t)$.
- The relative hazard cannot be negative and so it convenient to set $\psi = \exp(\beta)$.
- Any value of $\beta \in (-\infty, +\infty)$ will lead to a positive value of ψ.

Proportional hazards model

Comparing two groups

- Now let X be an indicator variable, which takes the value zero if an individual is on the standard treatment and one if the individual is on the new drug.

- The hazard function for individual i is then written as

$$
\begin{aligned}
h_i(t) = h(t \mid X = x_i) &= h_0(t)e^{\beta x_i} \\
&= \begin{cases} h_0(t), & \text{if } x_i = 0 \\ h_0(t)e^{\beta}, & \text{if } x_i = 1 \end{cases}
\end{aligned}
$$

- This is the proportional hazards model for the comparison of two treatment groups.

- Here $\psi = e^{\beta}$ represents the ratio of the hazard of death for an individual on the new treatment relative to one on the standard treatment at any time t.

Proportional hazards model

General model

- The model we have considered just now can be generalised to the situation where the hazard of death (or, more generally, the hazard of the event of interest occurring) at a particular time point depends on the values of $x_1, \ldots, x_p$ of p explanatory variables/risk factors/covariates $X_1, \ldots, X_p$.

- The values of these variables will be assumed to have been recorded at the time origin of the study.

- We will not cover them but there are extensions of the model to cover the situation where the values of one or more explanatory variables change over time.

- Let $\mathbf{x}_i = (x_{i1}, \ldots, x_{ip})'$ be the explanatory variables for individual i.

Proportional hazards model

General model

$\hookrightarrow$ The proportional hazards model is given by

$$h_i(t) = h(t \mid \mathbf{x}_i) = h_0(t) \exp(x_{i1}\beta_1 + x_{i2}\beta_2 + \ldots + x_{ip}\beta_p) = h_0(t) \exp(x_i'\boldsymbol{\beta}), \tag{2}$$

where $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_p)'$.

$\hookrightarrow$ Note that there is no intercept β_0 in model (2).

$\hookrightarrow$ Obviously,

$$h(t \mid \mathbf{x}_i = \mathbf{0}) = h_0(t),$$

and, therefore, $h_0(t)$ is often called the baseline hazard function.

$\hookrightarrow$ It can be interpreted as the hazard function for a standard subject, which is a subject with $\mathbf{x} = \mathbf{0}$.

Proportional hazards model

General model

- Any parametric hazard function can be used for $h_0(t)$ and as we will see next week, $h_0(t)$ can be left completely unspecified without sacrificing the ability to estimate β, by the use of Cox's semiparametric proportional hazards model.

- The hazard function for the ith subject always has the same general shape as $h_0(t)$, but can be, say, doubled or halved, depending in the individual's risk factors.

- The term $\exp(x_i'\beta)$ is in many cases the function of primary interest as it describes the (relative) effects of the risk factors.

- Note that the model separates clearly the effect of time from the effect of the risk factors.

Proportional hazards model

General model

↪ The proportional hazards model can also be written in terms of the survival function:

$$
\begin{aligned}
S_i(t) = S(t \mid \mathbf{x}_i) &= \exp\left(-\int_0^t h_i(u)\mathrm{d}u\right) \\
&= \exp\left(-\int_0^t h_0(u)\exp(x_i'\boldsymbol{\beta})\mathrm{d}u\right) \\
&= \left[\exp\left(-\int_0^t h_0(u)\mathrm{d}u\right)\right]^{\exp(x_i'\boldsymbol{\beta})} \\
&= S_0(t)^{\exp(x_i'\boldsymbol{\beta})},
\end{aligned}
$$

where $S_0(t)$ is the baseline survival function.

Proportional hazards model

General model

- On the log-hazard scale this model can be written as

$$\log h_i(t) = \log h_0(t) + x_i' \boldsymbol{\beta}.$$

- The coefficient β_j associated with the risk factor X_j represents the change in the log hazard when X_j is increased by one unit, all the other risk factors being constant, that is,

$$\beta_j = \log h(t \mid X_1, X_2, \ldots, X_j + 1, \ldots, X_p) - \log h(t \mid X_1, X_2, \ldots, X_j, \ldots, X_p),$$

  which is equivalent to the log of the ratio of the hazards at time t.

- Equivalently,

$$\frac{h(t \mid X_1, X_2, \ldots, X_j + 1, \ldots, X_p)}{h(t \mid X_1, X_2, \ldots, X_j, \ldots, X_p)} = e^{\beta_j}.$$

- Therefore, e^{β_j} represents the ratio of the hazards for a one unit change in X_j at any time t while keeping all the other risk factors constant.

Proportional hazards model

General model

- The main assumption of this model is the **proportional hazards assumption**, that is, the fact that the ratio of the hazard functions for two subjects with covariates $\mathbf{x}_i$ and $\mathbf{x}_l$ is constant over time, that is,

$$\frac{h(t \mid \mathbf{x}_i)}{h(t \mid \mathbf{x}_l)} = \frac{\exp(x_i'\beta)}{\exp(x_l'\beta)} = \exp\{(\mathbf{x}_i - \mathbf{x}_l)'\beta\}.$$

- In other words, all the time dependency is captured by the baseline hazard function which is common to all observations.

- The proportional hazards model also further assumes that the relationship between the risk factors and the log hazard function is linear.

Proportional hazards model

Toy example (from Klein and Moeschberger, 2003, p248)

- Let us consider for the sake of simplicity/illustration that the only risk factor that needs to be considered is race.
- Let us consider that race is a three level factor, whose levels are: black, white, hispanic.
- Define

$$X_1 = \begin{cases} 1, & \text{if the subject is black,} \\ 0, & \text{otherwise,} \end{cases} \qquad X_2 = \begin{cases} 1, & \text{if the subject is white,} \\ 0, & \text{otherwise.} \end{cases}$$

- Hispanic is therefore the reference category.

Proportional hazards model

Toy example (from Klein and Moeschberger, 2003, p248)

↪ The proportional hazards model is

$$\begin{aligned} h(t \mid X_1, X_2) &= h_0(t)\exp(X_1\beta_1 + X_2\beta_2) \\ &= \begin{cases} h_0(t), & \text{if } X_1 = X_2 = 0 \text{ (hispanic subject)}, \\ h_0(t)\exp(\beta_1), & \text{if } X_1 = 1, X_2 = 0 \text{ (black subject)}, \\ h_0(t)\exp(\beta_2), & \text{if } X_1 = 0, X_2 = 1 \text{ (white subject)}. \end{cases} \end{aligned}$$

↪ The risk of the event occurring among black subjects relative to the risk of the event occurring among hispanic subjects is e^{β_1}.

↪ The risk of the event occurring among white subjects relative to the risk of the event occurring among hispanic subjects is e^{β_2}.

↪ The risk of the event occurring among black subjects relative to the risk of the event occurring among white subjects is $e^{\beta_1 - \beta_2}$.