# Proportional Hazards

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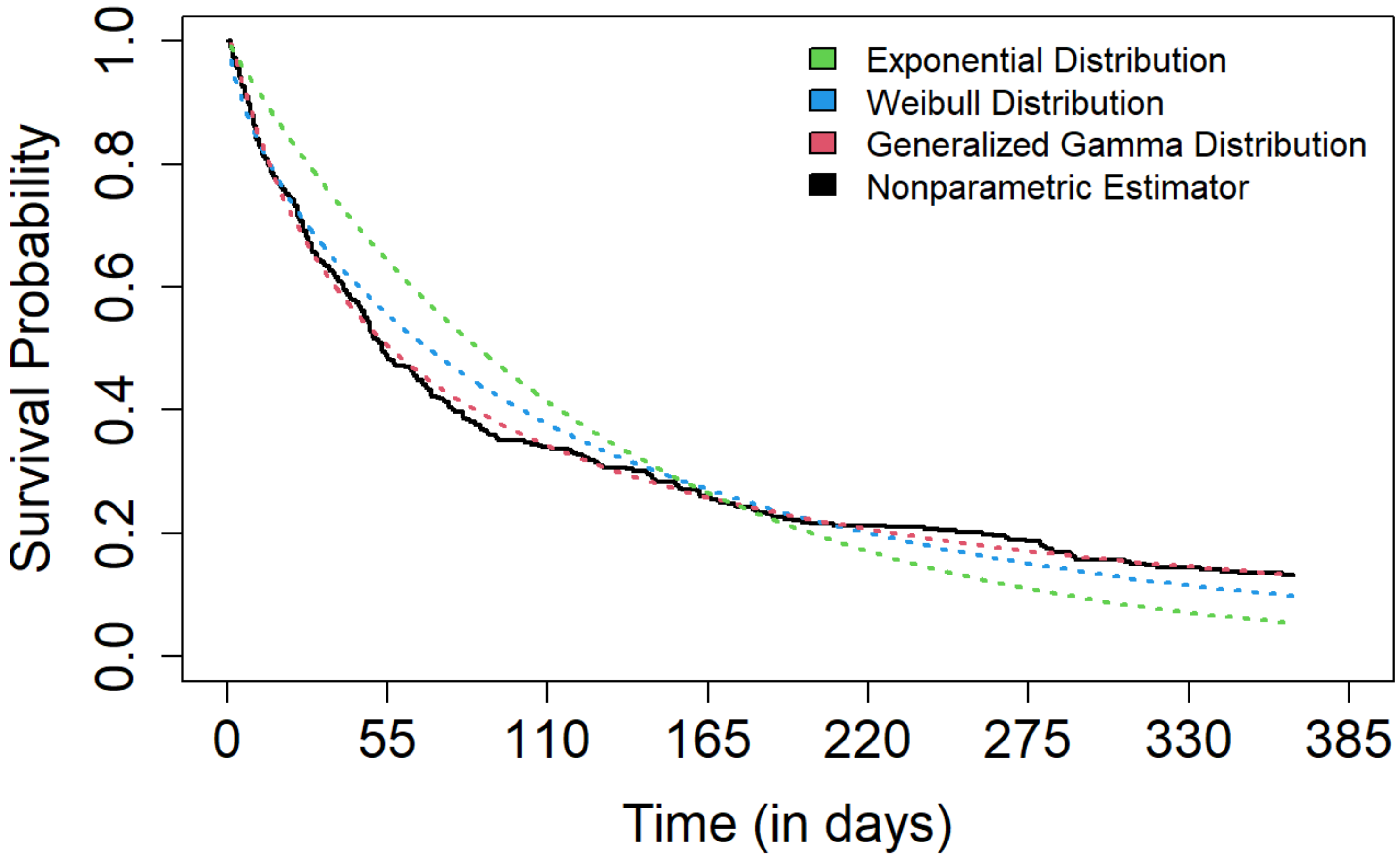
# What is Survival Analysis?

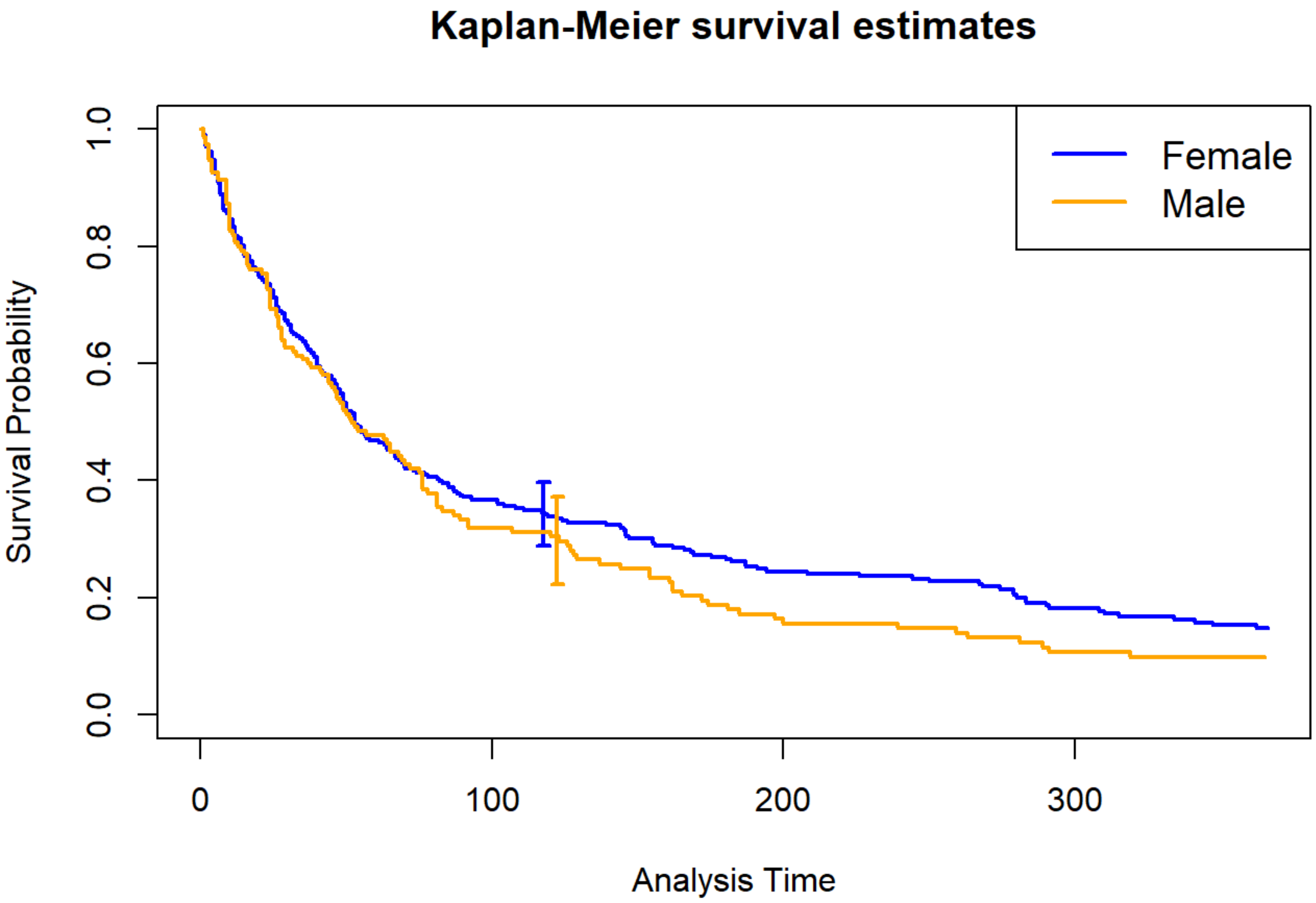
Linear Regression on a time scale.

Observations followed up with until the response (terminating event) occurs.

Linear Regression with the ability to deal with censoring (dropouts).

# What Does Survival Analysis Look Like?

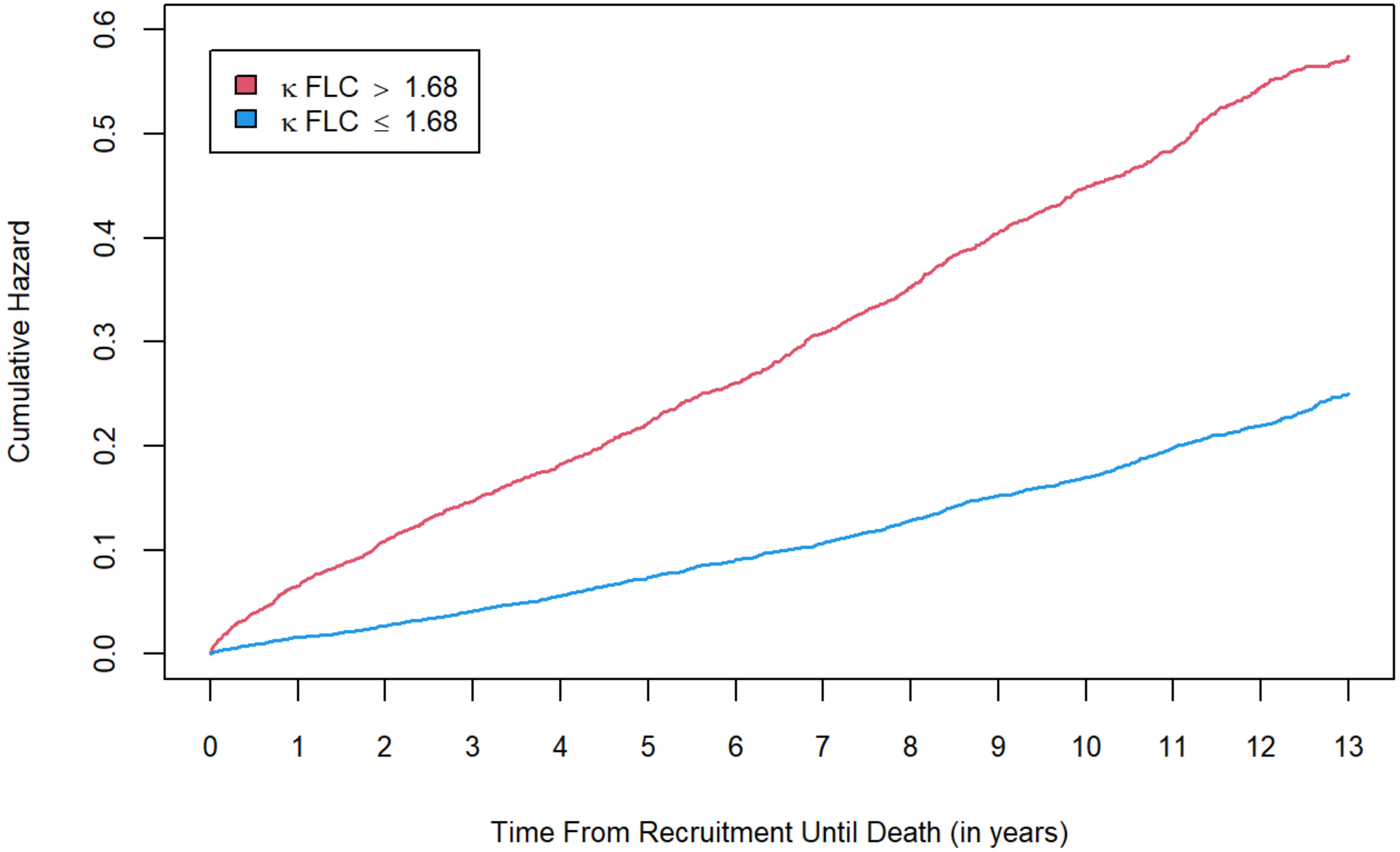





# Limits of Basic Survival Analysis Estimators?

It would be nice to know how multiple covariates impact the **hazard** of time to event, not just one.

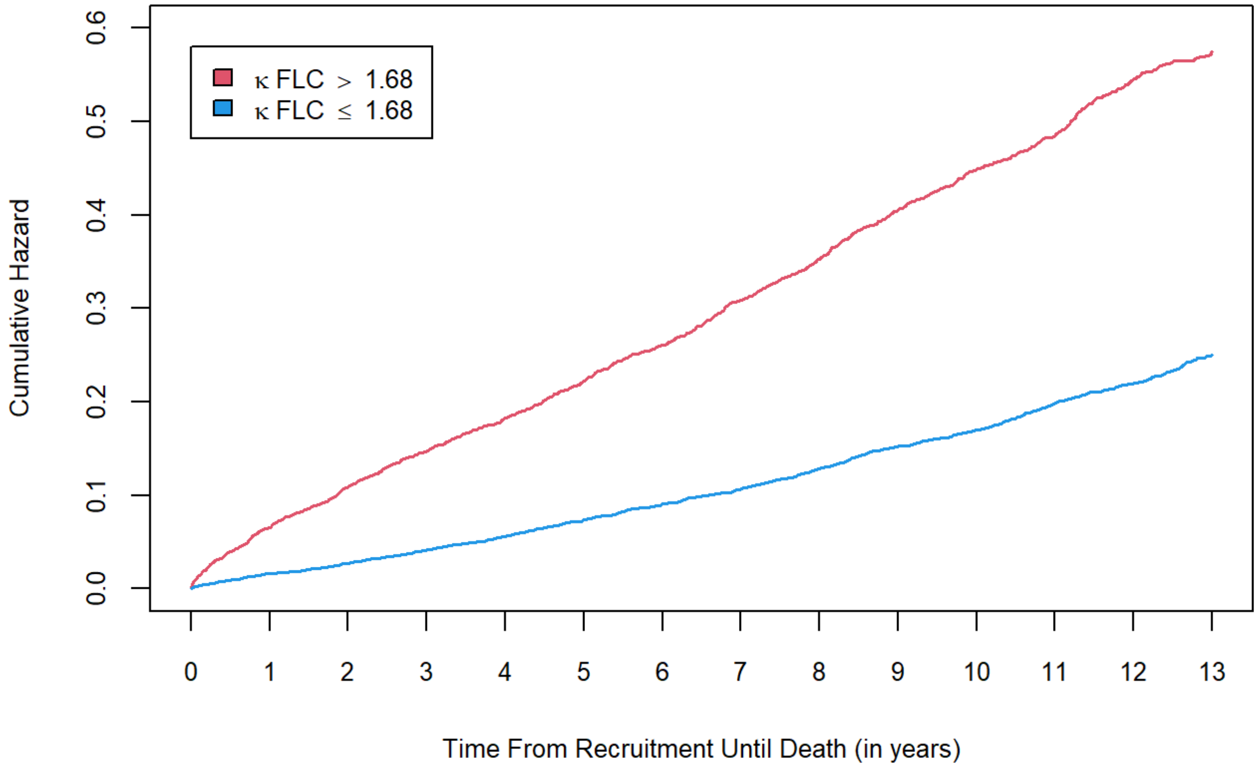
How useful is linear regression when we only use a single predictor?




# Estimating Hazards?

How do we measure the simultaneous impact of many covariates on the hazard of each subgroup?

# Sir David Cox




# Cox's Proportional Hazards Model

Consider the same cumulative hazard example.

$$h_1(t) = c \times h_0(t)$$

$$\frac{h_1(t)}{h_0(t)} = \mathrm{c}$$

If c < 1, subgroup 1 has a lower hazard than subgroup 2

If c > 1, subgroup 1 has a greater hazard than subgroup 2

# Cox's Proportional Hazards Model

Consider **two** sets of covariates for two different subgroups.

$(\boldsymbol{z_1}, \boldsymbol{z_2}, \boldsymbol{z_3} \ldots \boldsymbol{z_n})$ & $(\widetilde{\boldsymbol{z_1}}, \widetilde{\boldsymbol{z_2}}, \widetilde{\boldsymbol{z_3}} \ldots \widetilde{\boldsymbol{z_n}})$ for things like (age, received treatment, sex, censored, etc.)

Then we can write the hazard ratio as…

$$\frac{h_1(t)}{h_0(t)} = \frac{h(t|\widetilde{z_1},\widetilde{z_2},\widetilde{z_3},\ldots,\widetilde{z_n})}{h(t|z_1,z_2,z_3,\ldots,z_n)} = \frac{h(t)e^{\beta_1\widetilde{z_1}+\beta_2\widetilde{z_2}+\beta_3\widetilde{z_3}+\ldots+\beta_n\widetilde{z_n}}}{h(t)e^{\beta_1 z_1+\beta_2 z_2+\beta_3 z_3+\ldots+\beta_n z_n}}$$

$$= e^{\beta_1(\widetilde{z_1}-z_1)+\beta_2(\widetilde{z_2}-z_2)+\beta_3(\widetilde{z_3}-z_3)+\ldots+\beta_n(\widetilde{z_n}-z_n)}$$

# Algebraic Example

Let's say group one consists of treated males with a treatment dosage of 50 mg/day, while group two consists of treated females with a treatment dosage of 30 mg/day. Then the hazard ratio can be written…

$$e^{\beta_{Sex}(1-0)+\beta_{Treated}(1-1)+\beta_{Dosage}(50-30)} = e^{\beta_{Sex}+\beta_{Dosage}(20)}$$

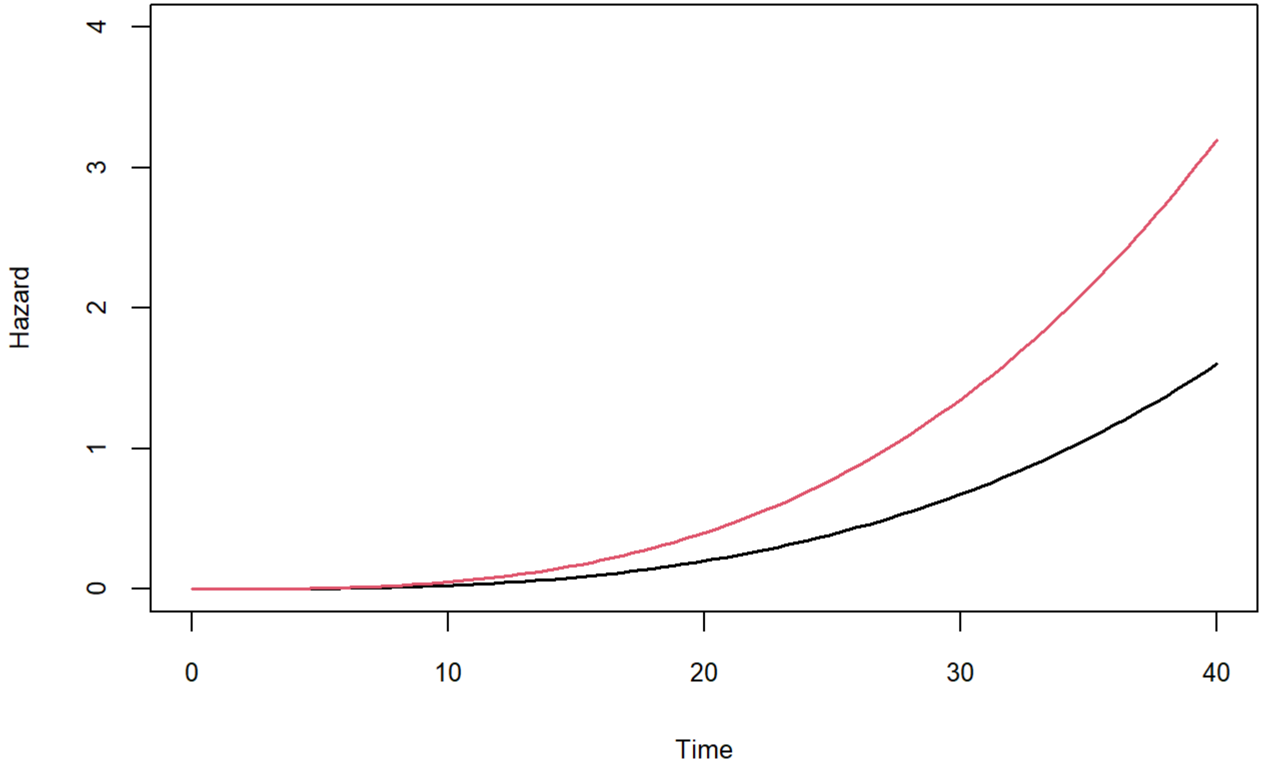
The above can be interpreted as: *The hazard ratio comparing subgroups of males against females with a dosage difference of 20 mg/day, while adjusting for all other covariates.*

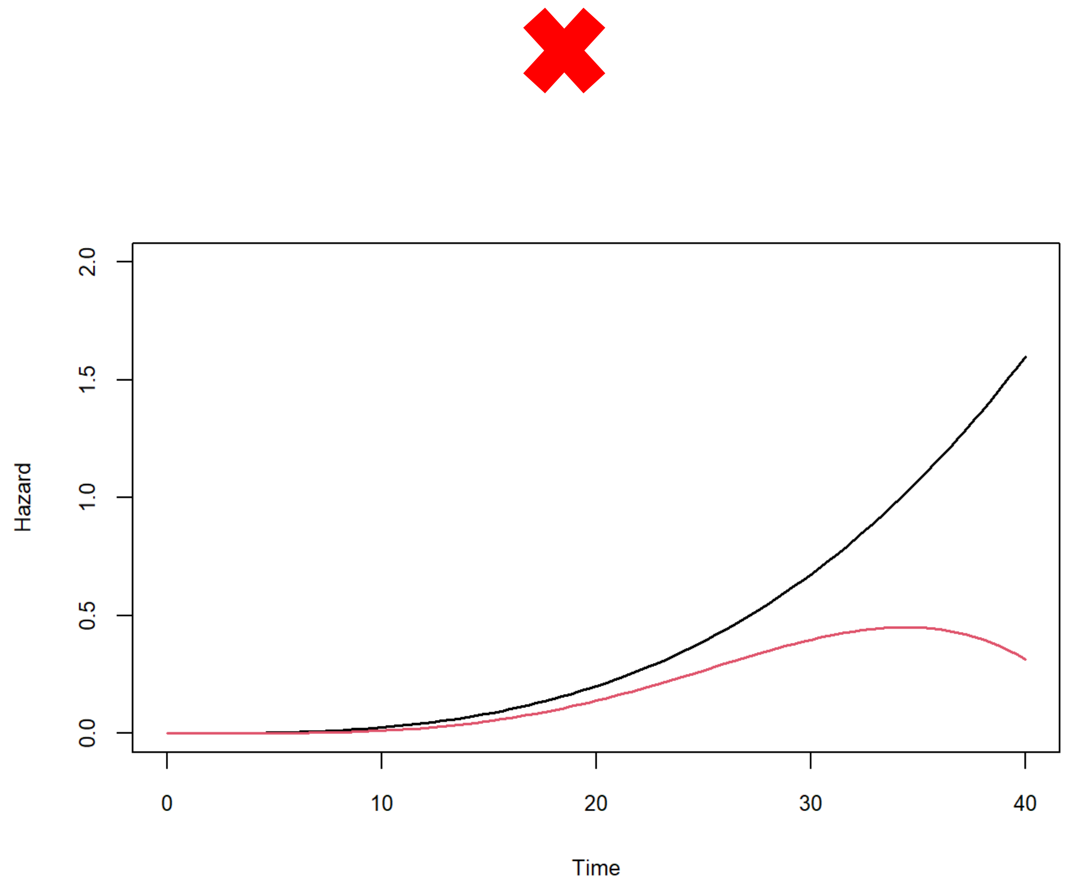
# Proportional Hazard Assumptions

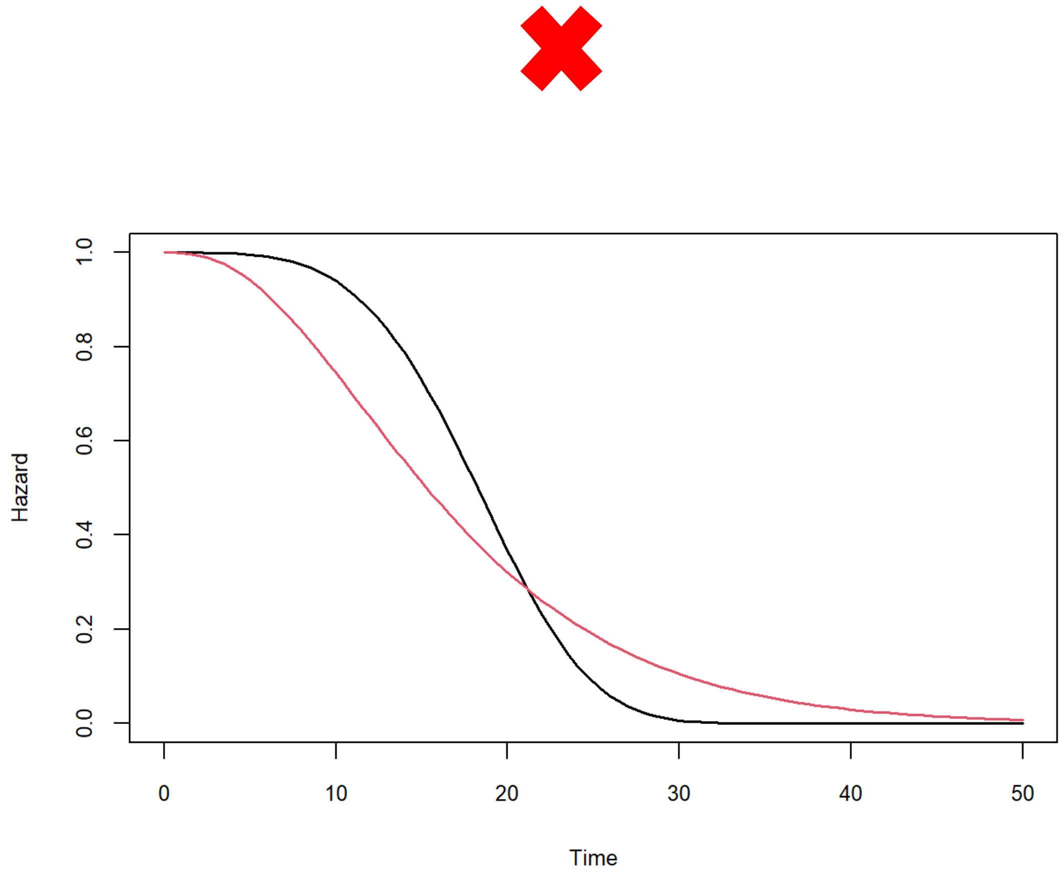
The hazards must be proportional .

*"…the hazard functions corresponding to every subgroup considered are proportional to one another"*

✓





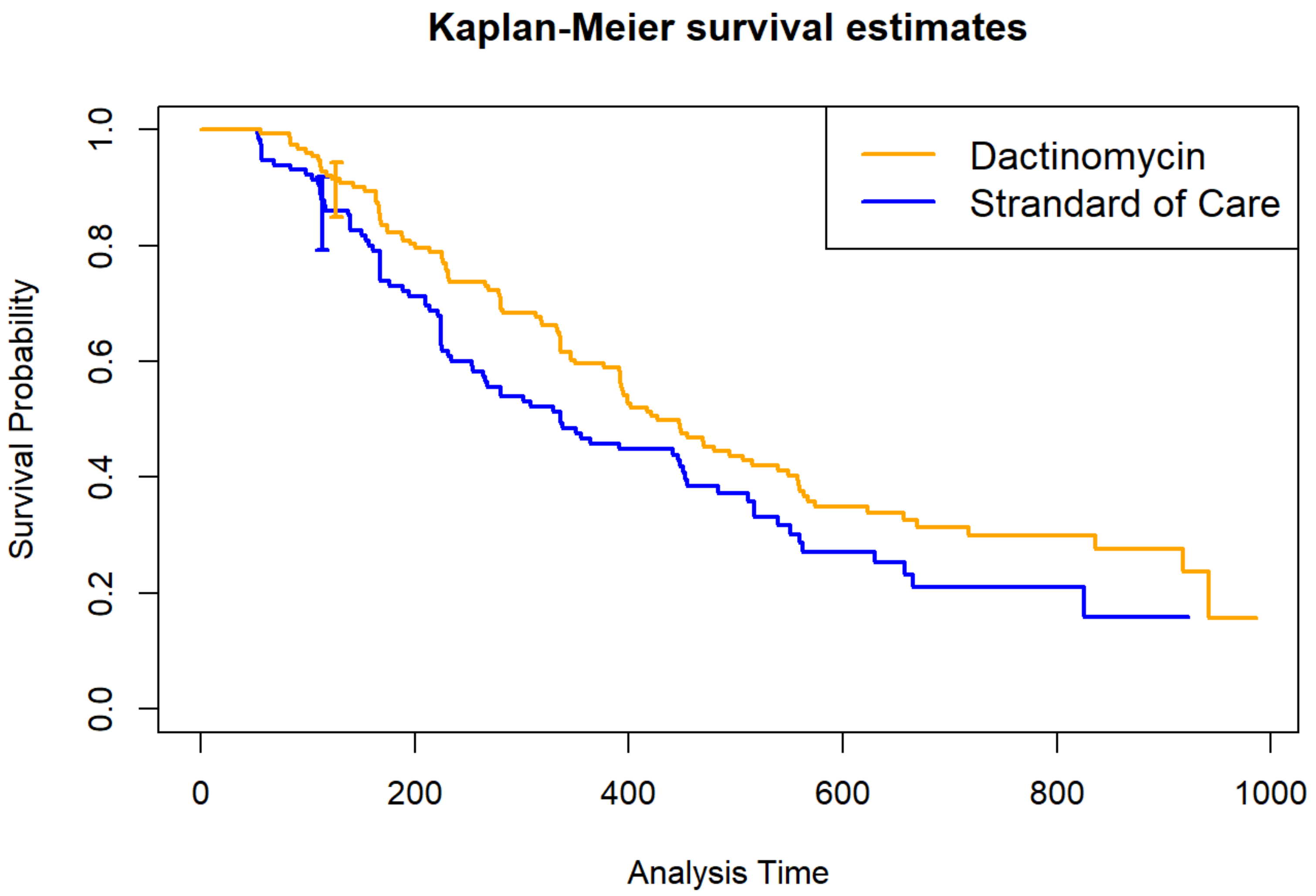




# Proportional Hazard Assumptions

# Acute Lymphoblastic Leukemia Clinical Trial Example

**Setup:** "In the CCG803 study, 268 children in remission of acute lymphoblastic leukemia were recruited from a number of clinical institutions and randomized to one of two maintenance regimes. Patients in the control group were assigned to the standard of care - chemotherapy with 6MP and methotrexate - while patients in the treatment group were also given dactinomycin."

**Scientific Question:** How is administration of Dactinomycin associated with the hazard of acute lymphoblastic leukemia relapse when accounting for white blood cell count and age?



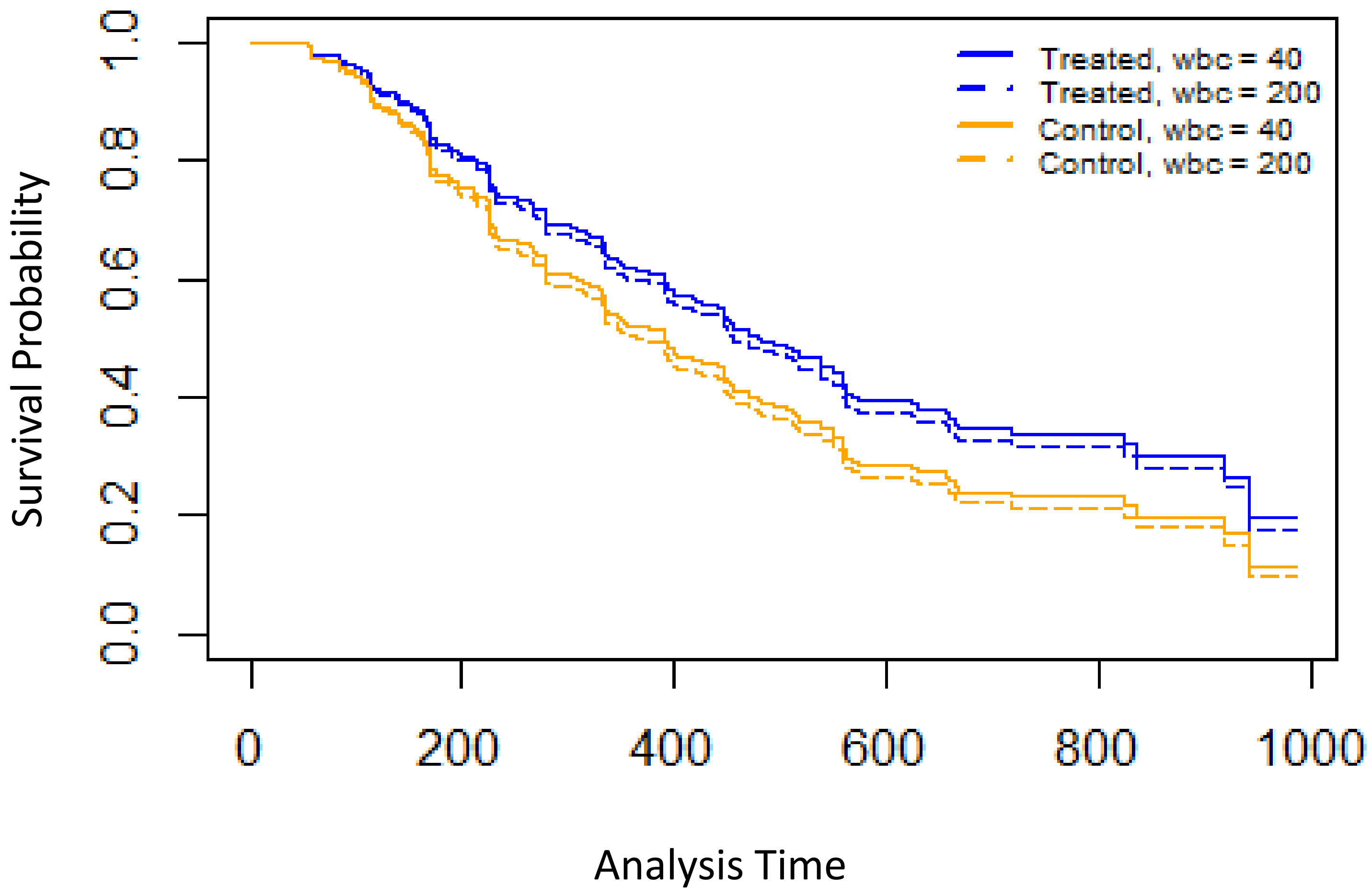

# Acute Lymphoblastic Leukemia Clinical Trial Example, **Assumptions**

# Acute Lymphoblastic Leukemia Clinical Trial Example, **Results**

```
ccg803_coxph_1b <- coxph(ccg803_surv ~ rx + wbc + age,
 data = ccg803_df)

tabcoxph(ccg803_coxph_1b)
```

| Variable | Beta (SE) | HR (95% CI) | P |
|---|---|---|---|
| rx | -0.30 (0.15) | 0.74 (0.55, 1.00) | 0.05 |
| wbc | 0.00 (0.00) | 1.00 (1.00, 1.00) | <0.001 |
| age | 0.00 (0.02) | 1.00 (0.96, 1.05) | 0.84 |




# Acute Lymphoblastic Leukemia Clinical Trial Example, **w/ Complex Hazard Ratios**

# Thank you!

Questions?