# Association between Bilirubin and Survival in Primary Biliary Cirrhosis

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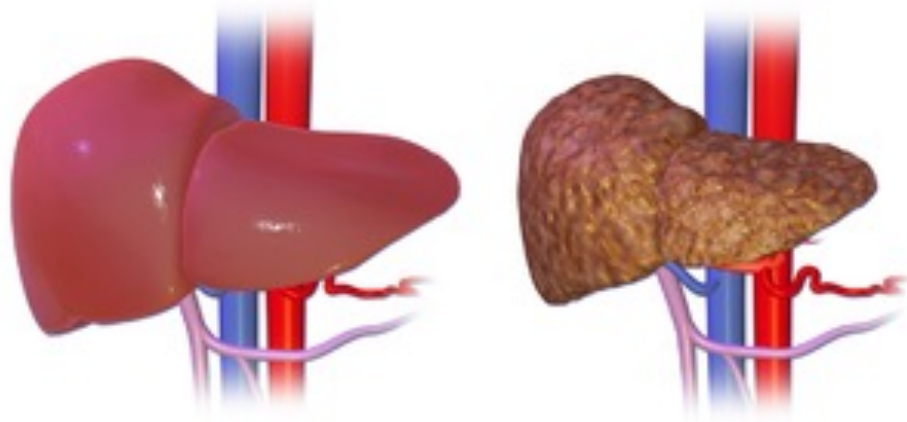
Mount Holyoke College

Memorial Sloan Kettering
Cancer Center

# Primary Biliary Cirrhosis (PBC)



Normal Liver       Liver Cirrhosis

(Source: Bruce Blaus, Wikimedia Commons)

- Immune system attacks liver
- Damage bile ducts
- Lead to liver fibrosis and cirrhosis
- Possibly lead to liver cancer

- Relatively rare disease (1/3000)
- Common in women

Symptoms:
- Jaundice
- Fatigue
- Loss of appetite
- No symptoms

Treatment:
- Medications
- Liver transplantation

# Study data - PBC Clinical Trial

- Follow-up for 10 years

- 312 patients: 154 in placebo group

    158 in treatment group

- Clinical factors: age, drug, sex

- Longitudinal biomarkers: Repeatedly measured

at 6 months, one year, and annually thereafter

e.g: **serum bilirubin**, albumin, prothrombin, platelets, etc.

- Outcome: alive/transplanted vs died

# Research objectives

1. Measure the association between bilirubin and overall survival among PBC patients

Motivation:
- High level of bilirubin causes yellowing of the skin
- Help personalize patient care
- Better adjust medication for patients
- Allocate healthcare resources efficiently

# Research objectives

1. Measure the association between bilirubin and overall survival among PBC patients

2. Use three different statistical approaches in survival analysis

3. Compare the results from three models

# Survival Analysis

- Study of **time-to-event/censored data**

- Outcome variables:

  - Time: $y_i = min(T_i, C_i)$

  Event: death, tumor recurrence, etc.

  - Event indicator: $\delta_i$

  1 if event observed; 0 otherwise

| id | years | status |
|----|-------|--------|
| 1 | 1.09 | dead |
| 2 | 14.15 | alive |
| 3 | 2.78 | dead |
| 4 | 5.27 | dead |
| 5 | 4.12 | transplanted |
| 6 | 6.85 | dead |
| 7 | 6.84 | alive |
| 8 | 6.75 | dead |
| 9 | 6.57 | dead |
| 10 | 0.14 | dead |

# Survival Analysis

- Censoring:
  - Loss to follow-up
  - Withdrawal from study
  - Event not observed

- Motivation for Cox PH Model
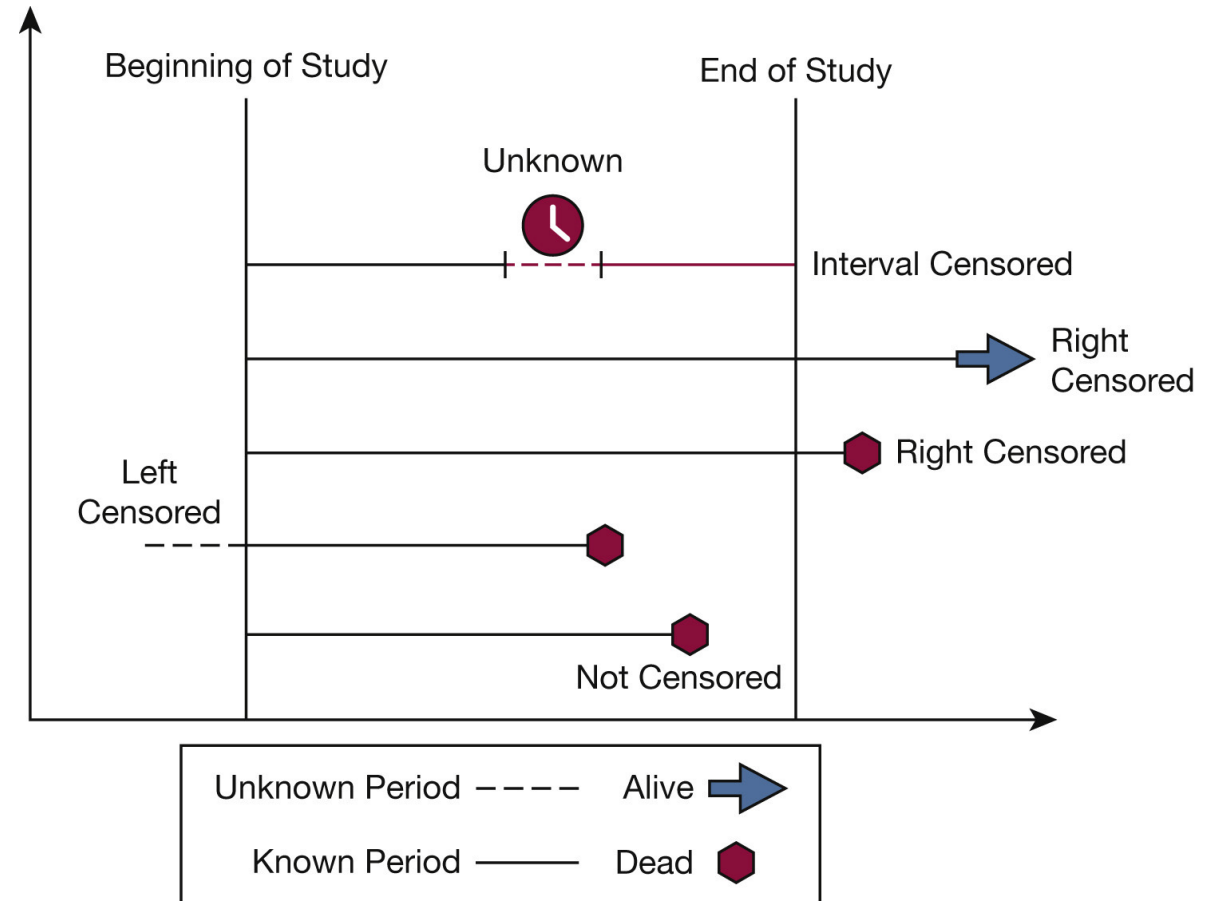


Source: Dey, Tanujit, Anish Mukherjee, and Sounak Chakraborty. *Chest* 158.1 (2020).

# Hazard Function

- Formula: $h(t) = \lim\limits_{dt \to 0} \dfrac{\Pr(t \le T^* \le t+dt \mid T^* \ge t)}{dt}$

  Instantaneous risk for event occurrence in time interval $[t, t + dt)$

- Cumulative hazard function: $H(t) = \int_0^t h(s)\,ds$

  Accumulated risk up to time $t$

# Survival Function

- Formula:  $S(t) = \Pr(T^* > t) = \int_t^\infty f(s)ds$

  $S(t) = \exp\{-H(t)\} = \exp\{-\int_0^t h(s)ds\}$

- Kaplan-Meier Approach:

  $\hat{S}(t) = \hat{S}(t-1) \times \Pr(T^* > t \mid T^* > t - 1)$

  $= \prod_{i:\, t_i \leq t}(T^* > t \mid T^* > t - 1)$

  $= \prod_{i:\, t_i \leq t} \dfrac{r_i - d_i}{r_i}$

  $d_i$: number of events at $t_i$
  $r_i$: number of subjects at risk at time $t_i$

# Cox Proportional Hazards Model

- Formula: $h_i(t \mid w_i) = h_0(t) \exp\{\gamma^T w_i\}$

- Baseline function $h_0(t)$ unspecified

- Hazard Ratio (HR): $\dfrac{h_i(t \mid w_i)}{h_k(t \mid w_k)} = \exp\{\gamma^T(w_i - w_k)\}$

- HR: Constant over time $\rightarrow$ Proportionality Assumption

  Assessing Technique: Goodness-of-fit test

# Methods

Cox Proportional Hazard Model

Time-Dependent Cox Model

Joint Model

# Cox PH Model

- Measure the association between <u>baseline</u> level of biomarker and survival

! Problem: Can only handle baseline bilirubin

$$h(t \mid w_i) = h_0(\text{t}) \exp\{\textcolor{red}{\boldsymbol{\gamma}^T \boldsymbol{w_i}}\}$$

| Cox PH Model | Time-Dependent Cox Model |
|---|---|
| • Measure the association between <u>baseline</u> level of biomarker and survival | • Measure the association between <u>current</u> level of biomarker and survival <br> • Account for progression of biomarker over time |
| ! Problem: Can only handle baseline bilirubin | ! Problem: Assume bilirubin is exogenous |
| $h(t \mid w_i) = h_0(t) \exp\{\boldsymbol{\gamma^T w_i}\}$ | $h(t \mid Y_i(t), w_i)$ <br><br> $= h_0(t) \exp\{\boldsymbol{\gamma^T w_i} + \alpha \boldsymbol{y_i}(t)\}$ |

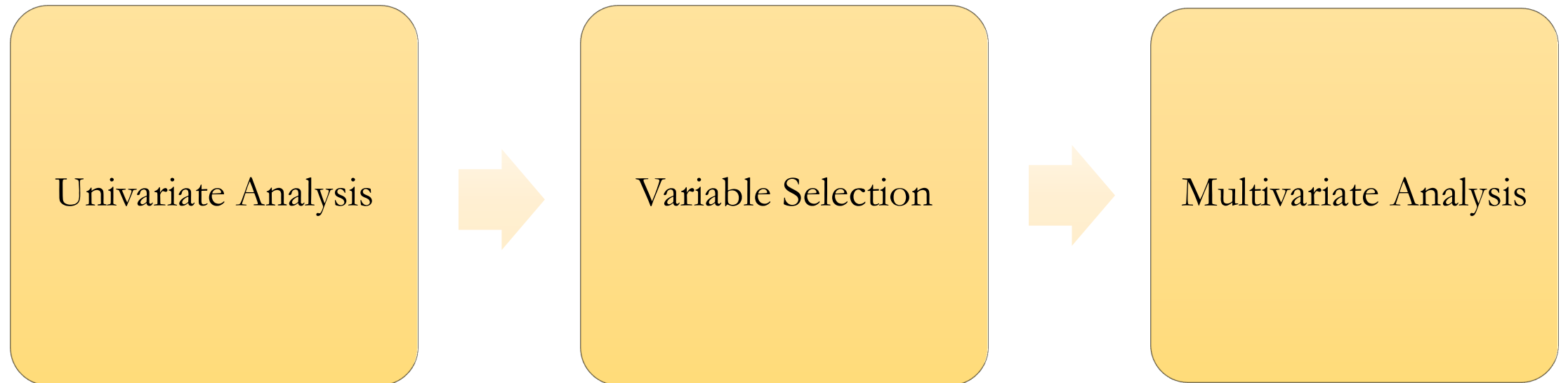| Cox PH Model | Time-Dependent Cox Model | Joint Model |
|---|---|---|
| • Measure the association between <u>baseline</u> level of biomarker and survival | • Measure the association between <u>current</u> level of biomarker and survival<br>• Account for progression of biomarker over time | • Measure the association between <u>current</u> level of biomarker and survival<br>• Account for progression of biomarker over time<br>• Account for measurement error |
| ! Problem: Can only handle baseline bilirubin | ! Problem: Assume bilirubin is exogenous | Longitudinal sub-model:<br>$y_i(t) = \color{blue}{m_i(t)} + \varepsilon_i(t)$<br>$\varepsilon_i(t) \sim \mathcal{N}(0, \sigma^2 I_{n_i})$<br><br>Survival sub-model: |
| $h(t \mid w_i) = h_0(t) \exp\{\color{red}{\gamma^T w_i}\}$ | $h(t \mid Y_i(t), w_i)$<br><br>$= h_0(t) \exp\{\color{red}{\gamma^T w_i} + \alpha \color{green}{y_i(t)}\}$ | $h(t \mid M_i(t), w_i)$<br><br>$= h_0(t) \exp\{\color{red}{\gamma^T w_i} + \alpha \color{blue}{m_i(t)}\}$ |

# Methodology

Each model follows this procedure:

| Univariate Analysis | → | Variable Selection | → | Multivariate Analysis |

# Summary Statistics

- 51% in treatment group

- Median age: 50 (IQR: 42 – 57)

- Sex: 88.5% females

- Median baseline bilirubin: 1.4 (IQR: 0.8 – 3.4)

- Median follow-up duration: 6.3 years

- Patients: 172 alive/transplanted

        140 died
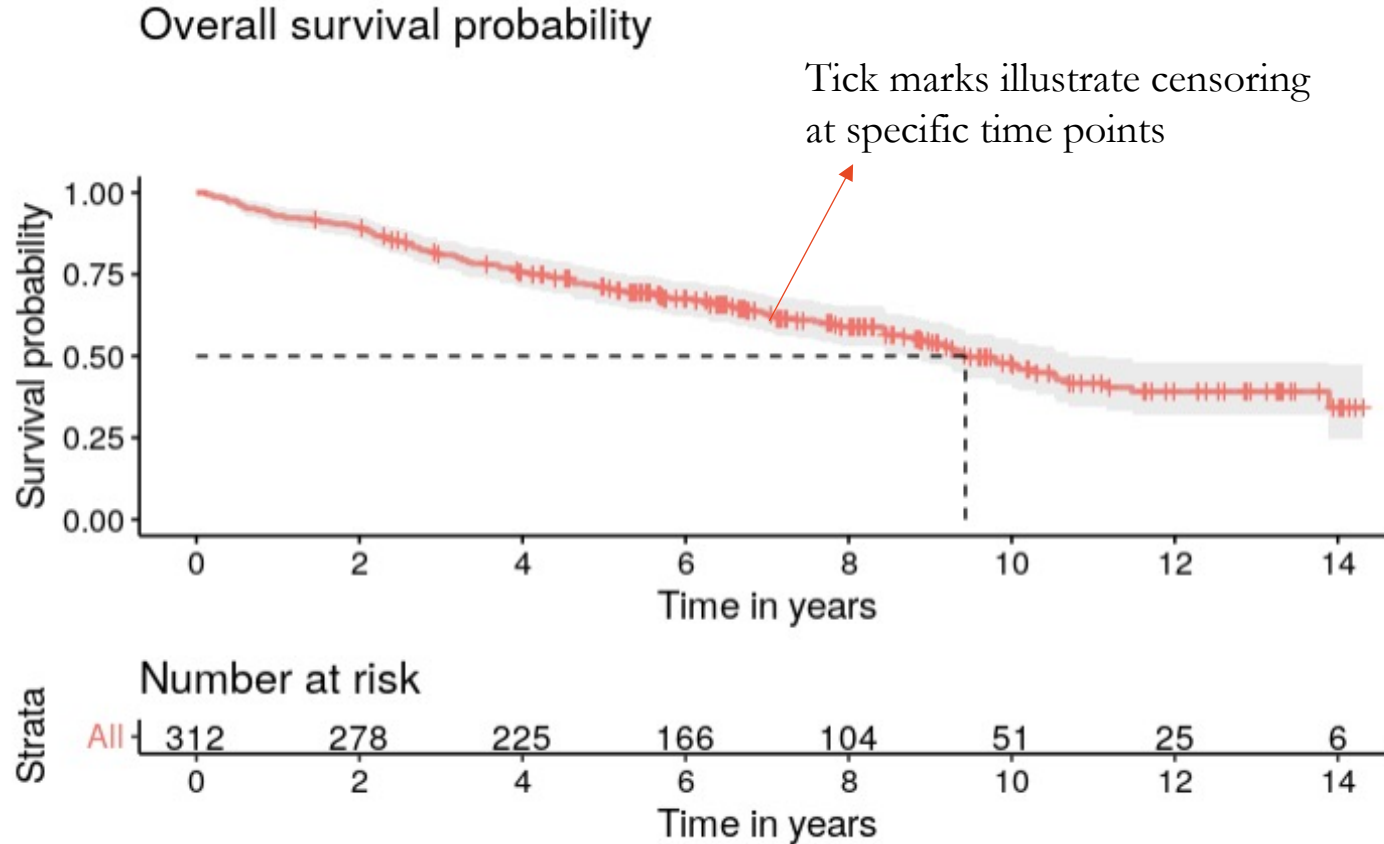
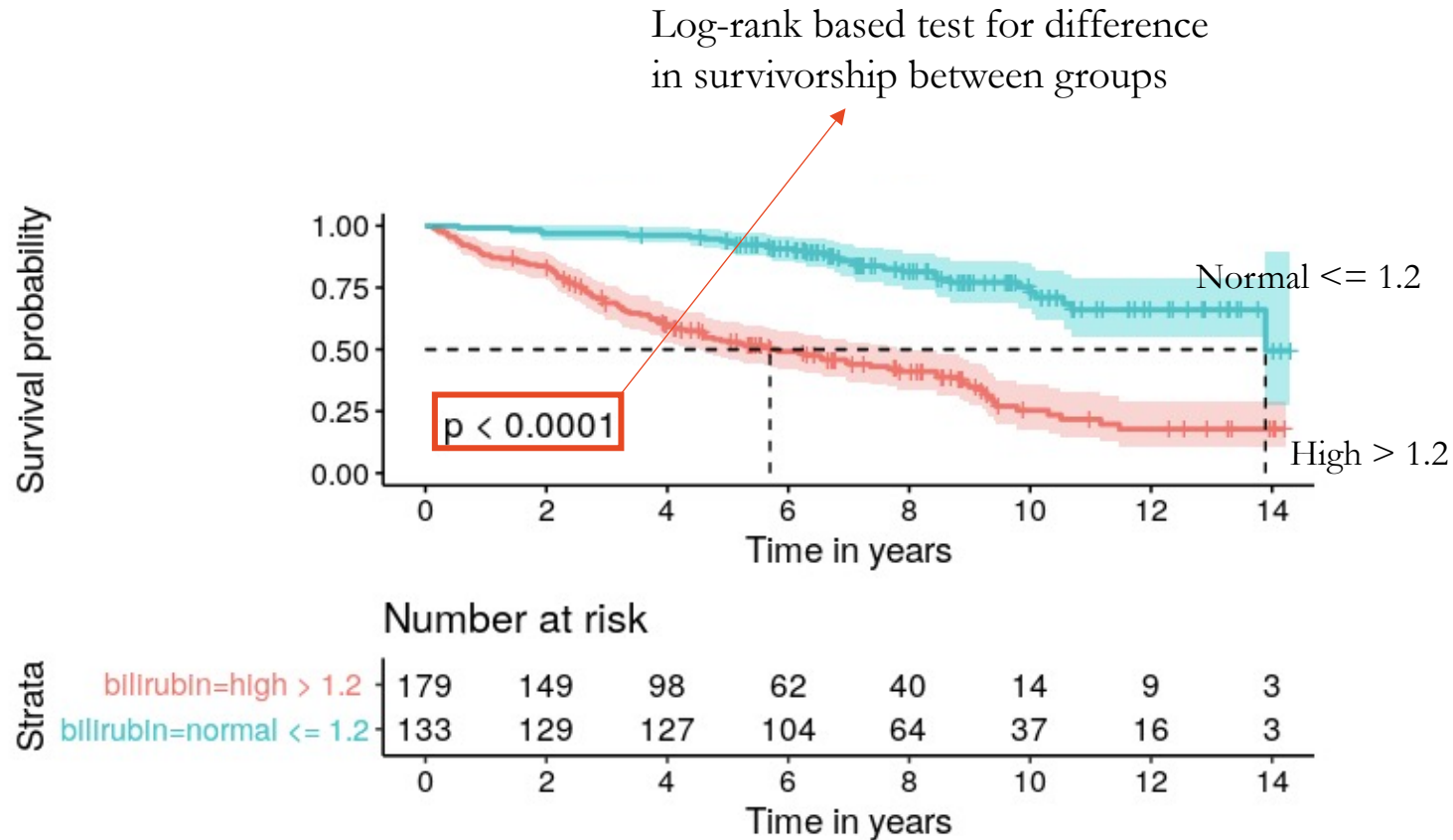Histogram of Baseline Bilirubin
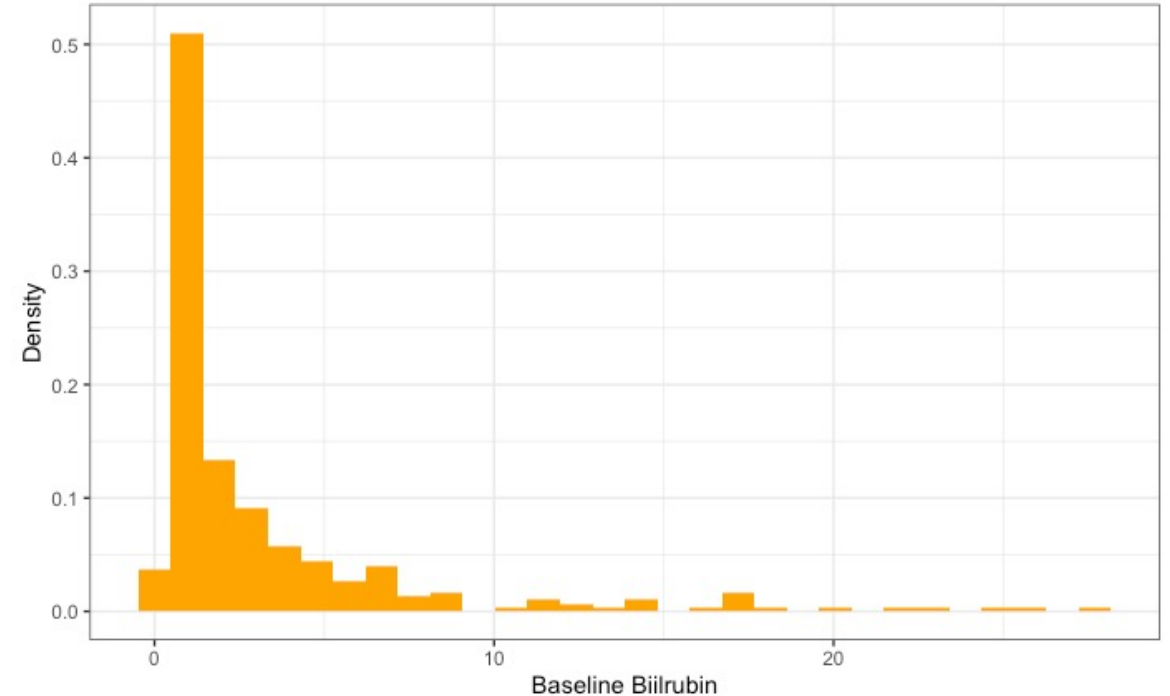
# Spaghetti plot of longitudinal bilirubin
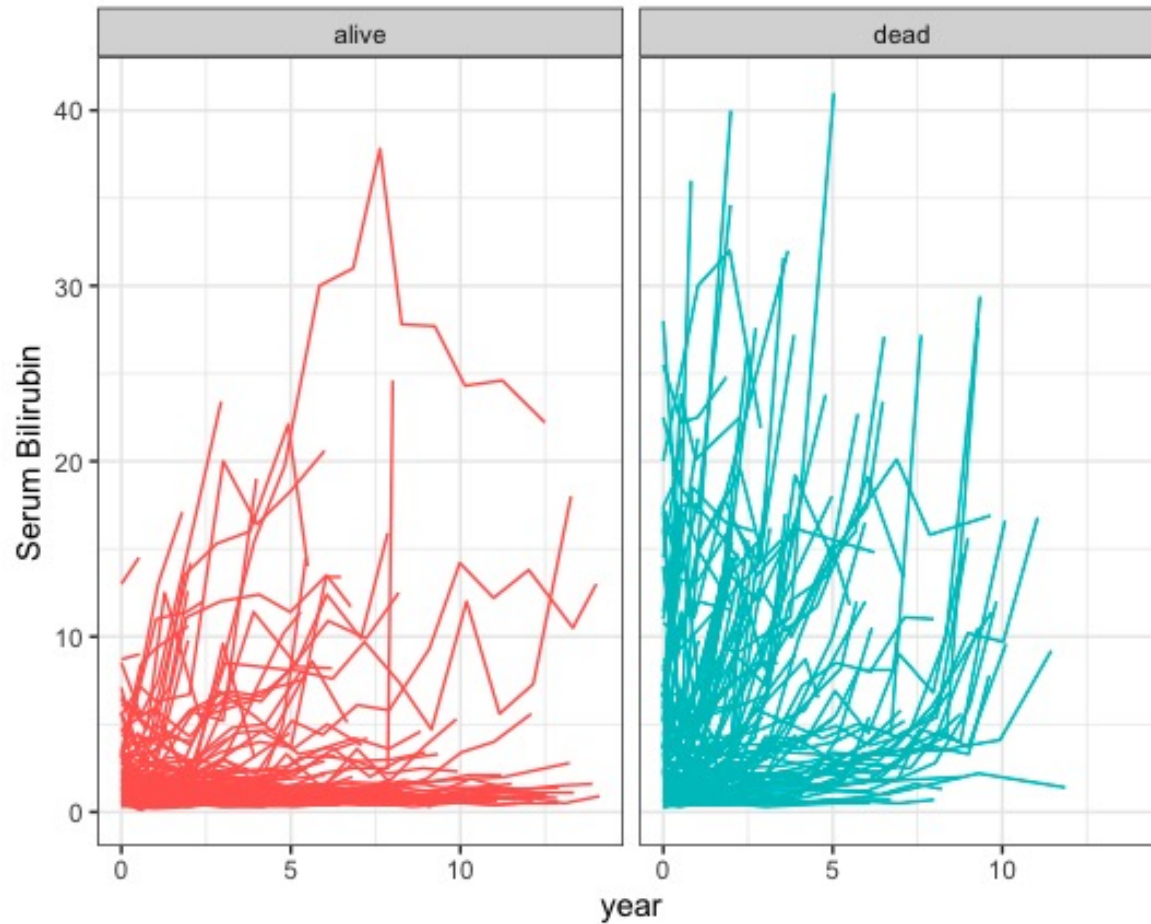


- Median follow-up duration: 6.3 years
- Patients who died seemed to have higher level of bilirubin

# Kaplan-Meier Curve



Overall survival probability

Tick marks illustrate censoring at specific time points

- Survival decreases over time
- Median survival time: 9.5 years
- After 6 years: 166 patients at risk

# Baseline bilirubin



Log-rank based test for difference in survivorship between groups

p < 0.0001

Normal <= 1.2

High > 1.2

- Clinical cutoff: 1.2 mg/dl

- Normal baseline bilirubin

- High baseline bilirubin

# Univariate Analysis for Cox Models

| Clinical Factor | Hazard Ratio | 95% Confidence Interval | p-value |
|---|:---:|:---:|:---:|
| **Drug** | 1.00 | (0.72 – 1.39) | >0.9 |
| **Age** | 1.05 | (1.03 – 1.06) | <0.001 |
| **Sex: male** | Ref | | |
| **female** | 0.52 | (0.34 – 0.80) | 0.005 |

Interpretation:

- There's no treatment effect on the survival
- One-year increase in the baseline age is associated with a 5% increase in the hazard of death
- Female patients have a 48% lower hazard of death than male patients

# Univariate Analysis for Cox Models

| Biomarker | Hazard Ratio | 95% Confidence Interval | p-value |
|---|---|---|---|
| **Albumin** | 0.19 | (0.13 – 0.28) | <0.001 |
| **Alkaline** | 1.00 | (1.00 – 1.00) | 0.094 |
| **SGOT** | 1.01 | (1.00 – 1.01) | <0.001 |
| **Platelets** | 1.00 | (0.99 – 1.00) | <0.001 |
| **Prothrombin** | 2.12 | (1.81 – 2.48) | <0.001 |
| **Ascites** *(No/Yes)* | 7.58 | (4.78 – 12.0) | <0.001 |
| **Hepatomegaly** *(No/Yes)* | 3.06 | (2.14 – 4.38) | <0.001 |
| **Spiders** *(No/Yes)* | 2.42 | (1.72 – 3.42) | <0.001 |
| **Edema**: *No edema* | ref | | <0.001 |
| *Edema no diuretics* | 1.63 | (1.04 – 2.55) | |
| *Edema diuretics* | 10.9 | (6.61 – 18.0) | |
| **Histologic:** *1* | ref | | <0.001 |
| *2* | 6.39 | (0.86 – 47.5) | |
| *3* | 9.66 | (1.33 – 70.1) | |
| *4* | 24.0 | (3.33 – 174) | |

# Univariate Analysis – Serum Bilirubin

**Univariate Analysis - Serum Bilirubin**

| Model | Hazard Ratio | 95% Confidence Interval | p-value |
|---|---|---|---|
| Model 1: Cox PH | 1.16 | (1.13 – 1.19) | <0.001 |
| Model 2: Time-Dependent Cox | 1.16 | (1.14 – 1.18) | <0.001 |
| Model 3: Joint Model | 1.83 | (1.66 - 2.02) | <0.0001 |

Interpretation:

- Model 1(**baseline bilirubin**): One unit increase in the baseline bilirubin is associated with 16% increase in the death risk
- Model 2 (**longitudinal bilirubin**): One unit increase in the longitudinal bilirubin is associated with 16% increase in the death risk
- Model 3 (**longitudinal bilirubin & measurement error**): One unit increase in the longitudinal bilirubin is associated with 83% increase in the death risk

# Multivariate Analysis – Serum Bilirubin

| Multivariate Analysis - Serum Bilirubin | | | |
|---|---|---|---|
| **Model** | **Hazard Ratio** | **95% Confidence Interval** | **p-value** |
| Model 1: Cox PH | 1.11 | (1.06 – 1.15) | <0.001 |
| Model 2: Time-Dependent Cox | 1.20 | (1.17 – 1.22) | <0.001 |
| Model 3: Joint Model | 1.82 | (1.64 - 2.03) | <0.0001 |

**High bilirubin worsens survival**

Model Adjustment:
- Model 1: bilirubin, albumin, age, edema, histologic, SGOT, prothrombin
- Model 2: bilirubin, albumin, age, edema, histologic
- Model 3: bilirubin, albumin, age, edema
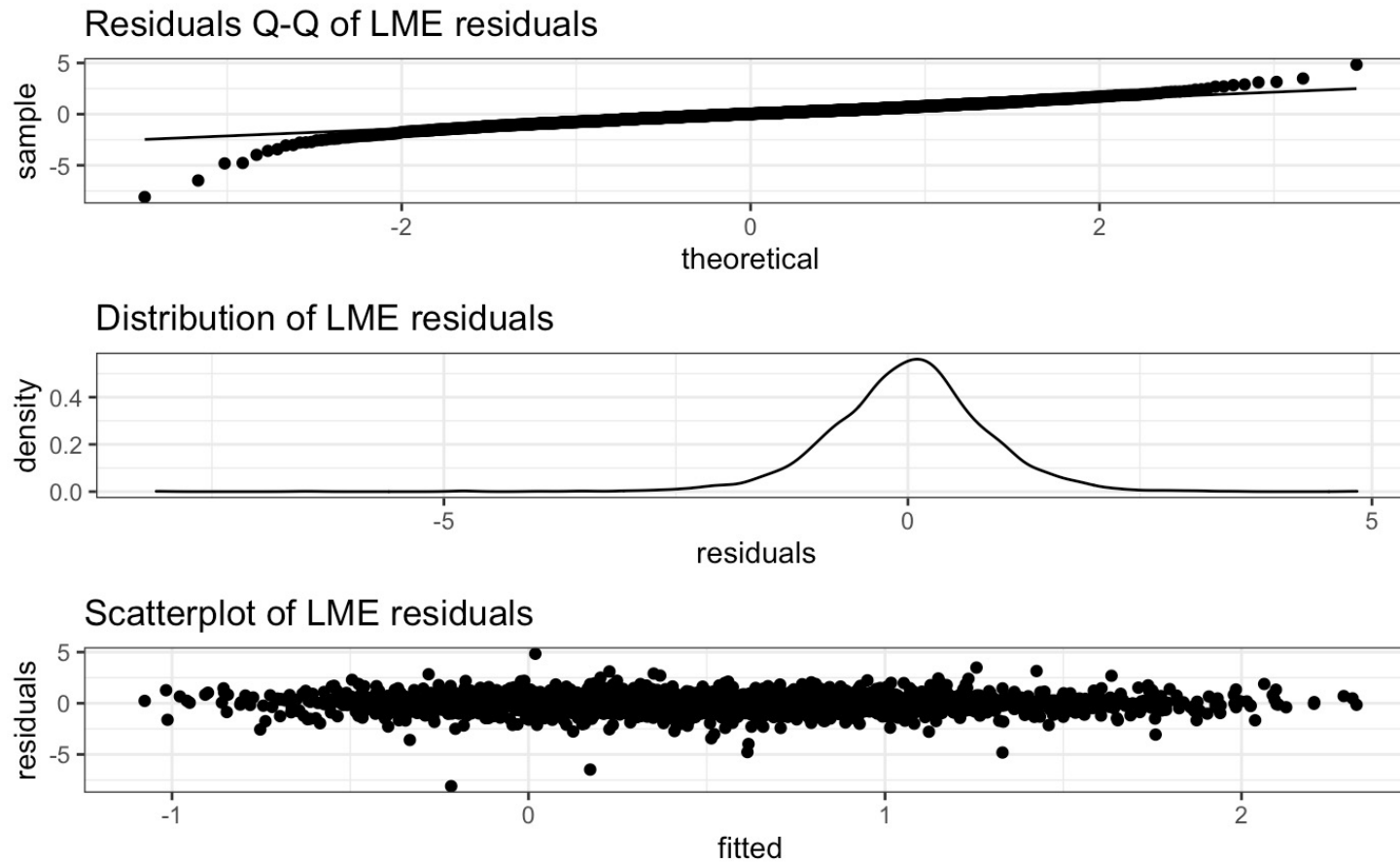
# Multivariate Analysis – Proportionality

## Cox PH Model

| Characteristics | Chisq | df | P-value |
|---|---|---|---|
| Bilirubin | 6.305 | 1 | 0.012 |
| Albumin | 3.043 | 1 | 0.081 |
| Age | 0.195 | 1 | 0.659 |
| Edema | 4.208 | 2 | 0.122 |
| Histologic | 6.603 | 3 | 0.086 |
| SGOT | 0.405 | 1 | 0.525 |
| Prothrombin | 1.482 | 1 | 0.223 |
| GLOBAL | 20.873 | 10 | 0.022 |

## Survival Sub-model of Joint Model

| Characteristics | Chisq | df | P-value |
|---|---|---|---|
| Albumin | 2.279 | 1 | 0.131 |
| Age | 0.204 | 1 | 0.651 |
| Edema | 4.848 | 2 | 0.089 |
| GLOBAL | 6.394 | 4 | 0.172 |

$H_0$: proportionality is met

$H_A$: proportionality is violated

# Diagnostic plots for LME

Residuals Q-Q of LME residuals

Distribution of LME residuals

Scatterplot of LME residuals

# Conclusions

1. Association between bilirubin and survival from Multivariate Analysis:

    Cox PH: HR = 1.11, Time-Dependent Cox: HR = 1.20, Joint Model: HR = 1.82

2. Difference in model outputs:

    - Cox PH: baseline values of bilirubin

    - Time-Dependent Cox: progression of bilirubin

    - Joint Model: progression of bilirubin & measurement error

# Conclusions

1. Association between bilirubin and survival from Multivariate Analysis:

    Cox PH: HR = 1.11, Time-Dependent Cox: HR = 1.20, Joint Model: HR = 1.82

2. Difference in model outputs:

   - Cox PH: baseline values of bilirubin

   - Time-Dependent Cox: progression of bilirubin

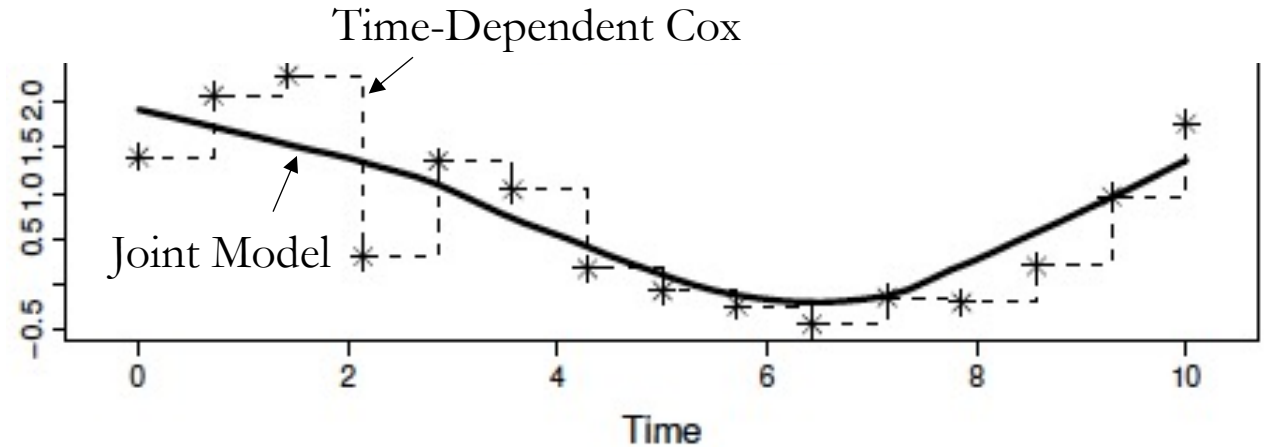   - **Joint Model: progression of bilirubin & measurement error**

# Discussion

Advantages of Joint Model:

- Smooth longitudinal trajectory
- Reduce potential bias

Disadvantages of Joint Model:

- Computational expense
- Large sample size
- → Time-Dependent Cox Model
    - Trade-off: Biased estimate of HR



Source: Joint Models (Rizopoulos, 2012)

# Discussion

<u>Model Adjustment:</u>

- Model 1: bilirubin, albumin, age, edema, histologic, SGOT, prothrombin
- Model 2: bilirubin, albumin, age, edema, histologic
- Model 3: bilirubin, albumin, age, edema

<u>Explanation:</u>

- Baseline SGOT and prothrombin not informative to the association in Model 2
- Baseline SGOT and prothrombin significant in the longitudinal generating process of bilirubin in Model 3

*Model 1: Cox PH; Model 2: Time-Dependent Cox; Model 3: Survival sub-model

# Limitations

- PBC Clinical Data: real dataset

    → Cannot evaluate model performances with the true HR

- Survival Sub-model of Joint Model:

    Baseline hazard is piecewise-constant with six knots

    More knots allow more flexibility

    ! Computational demand

# Future Work

- Simulation with predetermined censoring and hazard rate to estimate the bias

- Variable selection with BIC or AIC

- Multiple imputation method for missing data

- Competing Risk Analysis (alive vs transplanted)

- Joint Model for more than one longitudinal biomarker

# Acknowledgements

- Supervisor: Dr. Marie Ozanne

- Mentor: Dr. Audrey Mauguen

- QSURE faculties: Drs. Kay See Tan and Margaret Du

- Math/Stat Department, MHC

- Biostat/Epi Department, MSKCC
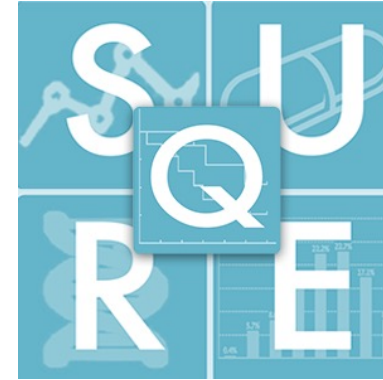
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- Rizopoulos, Dimitris. *Joint models for longitudinal and time-to-event data: With applications in R. CRC press, 2012.*
- Kleinbaum, D. G. and Klein, M. (2010), Survival analysis, Springer.
- Schober, Patrick, and Thomas R. Vetter. "Survival analysis and interpretation of time-to-event data: the tortoise and the hare." *Anesthesia and analgesia* 127.3 (2018): 792.
- Albert, Paul S. "Longitudinal data analysis (repeated measures) in clinical trials." *Statistics in medicine* 18.13 (1999): 1707-1732.
- Harrell Jr, Frank E., Kerry L. Lee, and Daniel B. Mark. "Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors." *Statistics in medicine* 15.4 (1996): 361-387.

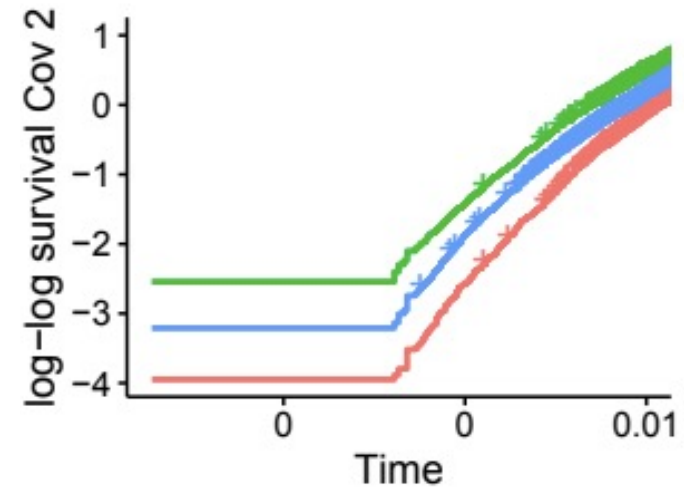# Thank you!

# Any question?

# Supplementary slides

# Assessing Proportionality

- Log-log survival curves

- Time-covariate interaction

- Goodness-of-fit test

# Graphics with survival curves

- Log-log transformation: $\ln\{-\ln(S(t))\}$

- If the assumption is met, the curves are equally spaced

- For continuous covariates, stratify them into groups depending on their distribution

# Time-covariate interaction

- $X_i$ is suspicious of having time-varying effect, the added term is $X_i f(t)$

- Function of time $f(t)$ can be linear, logarithmic, exponential, etc.

- If $X_i f(t)$ is statistically significant, proportionality is violated

# Goodness-of-fit test

- Formula for Schoenfeld residuals of suspiciously time-varying covariate A:

$$Schoenfeld\ residual\ A = Observed\ A - Weighted\ Average\ A$$

- If Schoenfeld residuals are correlated with failure times, proportionality is violated

# Missingness mechanism

- Missing not at random (MNAR)

  Depend on both observed and unobserved data

- Missing completely at random (MCAR)

  Depend on unobserved data

- <span style="color:red">Missing at random (MAR)

  Not depend on observed or unobserved data</span>

## Short data format

| id <fctr> | years <dbl> | status <fctr> | drug <fctr> | age <dbl> |
|---|---|---|---|---|
| 1 | 1.0951703 | dead | D-penicil | 58.76684 |
| 2 | 14.1523382 | alive | D-penicil | 56.44782 |
| 3 | 2.7707809 | dead | D-penicil | 70.07447 |
| 4 | 5.2705071 | dead | D-penicil | 54.74209 |
| 5 | 4.1205782 | transplanted | placebo | 38.10645 |
| 6 | 6.8530281 | dead | placebo | 66.26054 |
| 7 | 6.8475523 | alive | placebo | 55.53609 |
| 8 | 6.7517249 | dead | placebo | 53.05826 |
| 9 | 6.5710218 | dead | D-penicil | 42.50904 |
| 10 | 0.1396342 | dead | placebo | 70.56182 |

## Counting Process format

| id <fctr> | years <dbl> | status <fctr> | drug <fctr> | age <dbl> |
|---|---|---|---|---|
| 1 | 1.0951703 | dead | D-penicil | 58.76684 |
| 1 | 1.0951703 | dead | D-penicil | 58.76684 |
| 2 | 14.1523382 | alive | D-penicil | 56.44782 |
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| 2 | 14.1523382 | alive | D-penicil | 56.44782 |

# Results from Multivariate Analysis

| Subsets of significant covariates from variable selection for Cox PH Model | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Multivariate Cox PH Model** | | | | **Multivariate Time-Dependent Cox Model** | | | | **Survival Submodel of Joint Model** | | | |
| **Characteristic** | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** |
| **bilirubin** | **1.11** | **(1.06-1.15)** | **<0.001** | **1.20** | **(1.17-1.23)** | **<0.001** | **1.81** | **(1.60-2.04)** | **<0.0001** |
| **albumin** | 0.52 | (0.32-0.85) | 0.008 | 0.59 | (0.36-0.97) | 0.036 | 0.67 | (0.41-1.08) | 0.1011 |
| **age** | 1.04 | (1.03-1.06) | <0.001 | 1.06 | (1.05-1.08) | <0.001 | 1.05 | (1.03-1.07) | <0.0001 |
| **edema** | | | 0.019 | | | 0.003 | | | 0.0003 |
| *no edema* | ref | | | ref | | | ref | | |
| *edema no diuretics* | 1.04 | (0.65-1.67) | | 1.18 | (0.72-1.93) | | 1.97 | (1.18-3.30) | |
| *edema diuretics* | 2.37 | (1.33-4.22) | | 3.09 | (1.66-5.72) | | 3.11 | (1.64-5.89) | |
| **histologic** | | | 0.014 | | | <0.001 | | | 0.3422 |
| *1* | ref | | | ref | | | ref | | |
| *2* | 4.49 | (0.60-33.8) | | 1.97 | (0.26-14.9) | | 1.72 | (0.26-11.26) | |
| *3* | 5.79 | (0.79-42.5) | | 4.48 | (0.61-33.0) | | 2.02 | (0.31-13.00) | |
| *4* | 8.04 | (1.09-59.5) | | 6.69 | (0.90-49.4) | | 2.58 | (0.40-16.70) | |
| **SGOT** | 1.00 | (1.00-1.01) | 0.012 | 1.00 | (0.99-1.00) | 0.4 | 1.00 | (0.99-1.00) | 0.9569 |
| **prothrombin** | 1.46 | (1.20-1.78) | <0.001 | 1.11 | (0.91-1.36) | 0.3 | 1.22 | (0.99-1.51) | 0.623 |

# Results from Multivariate Analysis

| Subsets of significant covariates from variable selection for Time-Dependent Cox Model | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Multivariate Cox PH Model** | | | | **Multivariate Time-Dependent Cox Model** | | | | **Survival Submodel of Joint Model** | | | |
| **Characteristic** | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** |
| **bilirubin** | **1.15** | **(1.11-1.18)** | **<0.001** | **1.20** | **(1.17-1.22)** | **<0.001** | **1.84** | **(1.65-2.06)** | **<0.0001** |
| **albumin** | 0.50 | (0.31-0.81) | 0.005 | 0.62 | (0.38-1.01) | 0.005 | 0.60 | (0.37-0.97) | 0.0364 |
| **age** | 1.04 | (1.02-1.06) | <0.001 | 1.07 | (1.05-1.09) | <0.001 | 1.05 | (1.03-1.07) | <0.0001 |
| **edema** | | | 0.002 | | | 0.001 | | | <0.0001 |
| *no edema* | ref | | | ref | | | ref | | |
| *edema no diuretics* | 0.97 | (0.60-1.55) | | 1.26 | (0.78-2.04) | | 2.16 | (1.30-3.59) | |
| *edema diuretics* | 2.92 | (1.62-5.27) | | 3.31 | (1.80-6.09) | | 3.63 | (1.96-6.70) | |
| **histologic** | | | <0.001 | | | <0.001 | | | 0.0878 |
| *1* | ref | | | ref | | | ref | | |
| *2* | 4.63 | (0.62-34.5) | | 1.85 | (0.24-14.0) | | 0.92 | (0.21-4.12) | |
| *3* | 6.39 | (0.88-46.7) | | 4.35 | (0.59-32.0) | | 1.23 | (0.28-5.29) | |
| *4* | 10.9 | (1.49-80.1) | | 7.09 | (0.96-52.3) | | 1.70 | (0.39-7.38) | |

# Results from Multivariate Analysis

| Subsets of significant covariates from variable selection for Joint Model | | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Multivariate Cox PH Model** | | | | **Multivariate Cox PH Model** | | | **Survival Submodel of Joint Model** | | |
| **Characteristic** | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** | **HR** | **95% CI** | **p-value** |
| **bilirubin** | **1.14** | **(1.11-1.17)** | **<0.001** | **1.19** | **(1.16-1.21)** | **<0.001** | **1.82** | **(1.64-2.03)** | **<0.0001** |
| **albumin** | 0.37 | (0.23-0.58) | <0.001 | 0.47 | (0.29-0.75) | 0.002 | 0.52 | (0.33-0.82) | 0.054 |
| **age** | 1.04 | (1.03-1.06) | <0.001 | 1.07 | (1.05-1.09) | <0.001 | 1.05 | (1.04-1.07) | <0.0001 |
| **edema** | | | <0.001 | | | <0.001 | | | <0.0001 |
| *no edema* | ref | | | ref | | | ref | | |
| *edema no diuretics* | 1.01 | (0.63-1.62) | | 1.32 | (0.83-2.10) | | 2.05 | (1.25-3.36) | |
| *edema diuretics* | 3.32 | (1.83-6.01) | | 4.16 | (2.25-7.70) | | 3.84 | (2.09-7.06) | |

# Results from Multivariable Analysis

| | Multivariable Cox PH Model | | | Multivariable Cox PH Model | | | Survival Submodel of Joint Model | | |
|---|---|---|---|---|---|---|---|---|---|
| Characteristic | HR | 95% CI | p-value | HR | 95% CI | p-value | HR | 95% CI | p-value |
| bilirubin | 1.11 | (1.06-1.15) | <0.001 | 1.20 | (1.17-1.23) | <0.001 | 1.81 | (1.60-2.04) | <0.0001 |
| bilirubin | 1.15 | (1.11-1.18) | <0.001 | 1.20 | (1.17-1.22) | <0.001 | 1.84 | (1.65-2.06) | <0.0001 |
| bilirubin | 1.14 | (1.11-1.17) | <0.001 | 1.19 | (1.16-1.21) | <0.001 | 1.82 | (1.64-2.03) | <0.0001 |

## Multivariable Analysis - Serum Bilirubin

| Model | Hazard Ratios | 95% Confidence Interval | p-value |
|---|---|---|---|
| Model 1: Cox PH | 1.11 | (1.06 – 1.15) | <0.001 |
| Model 2: Time-Dependent Cox | 1.20 | (1.17 – 1.22) | <0.001 |
| Model 3: Joint Model | 1.82 | (1.64 - 2.03) | <0.0001 |

# Treatment effect
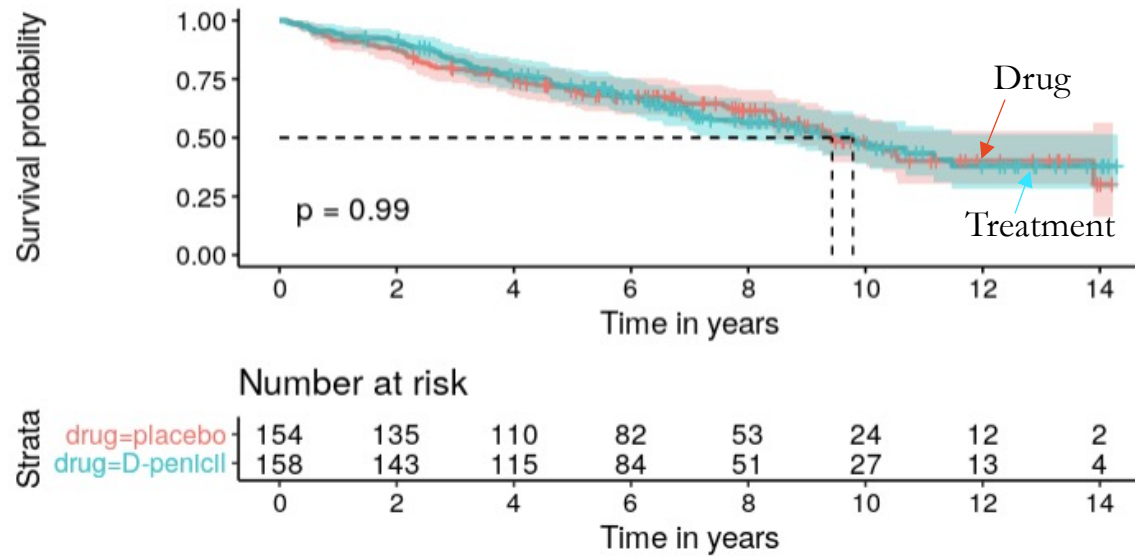
# Sex
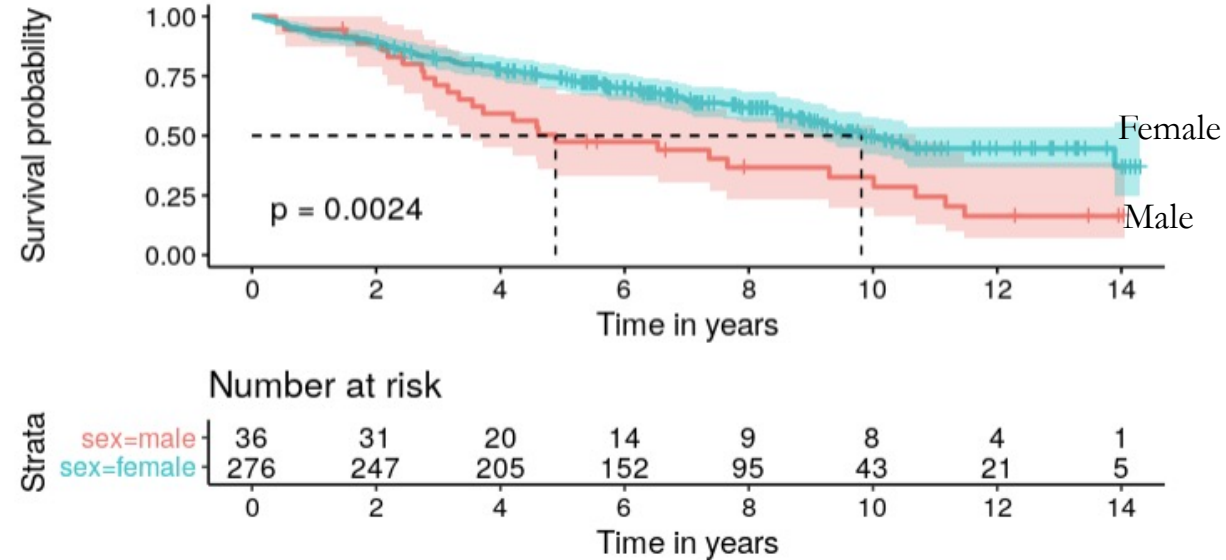
Log-rank based test for difference in survivorship between groups

Treatment effect

Sex
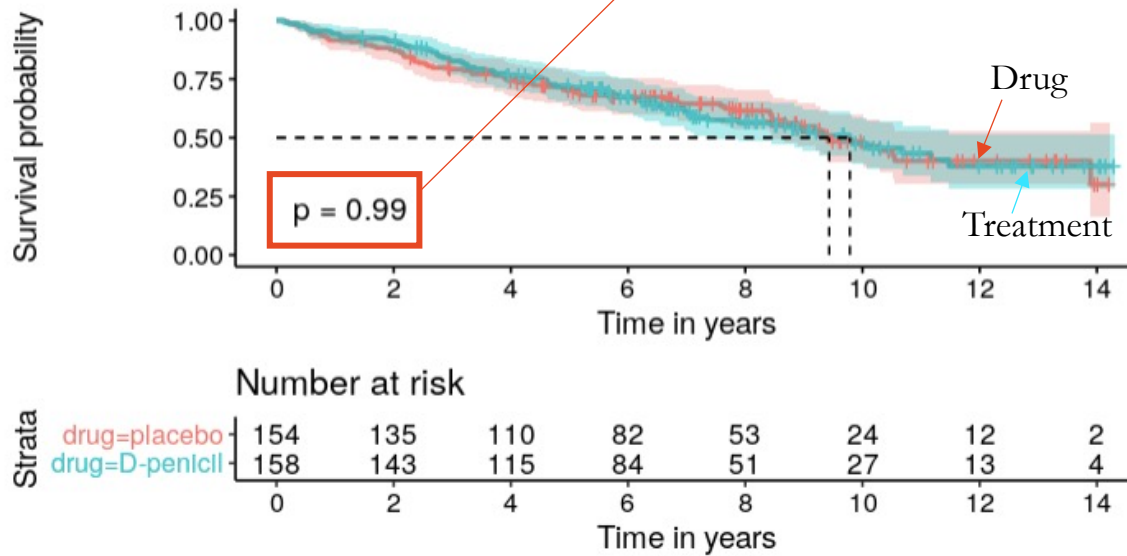
Drug is not statistically significant
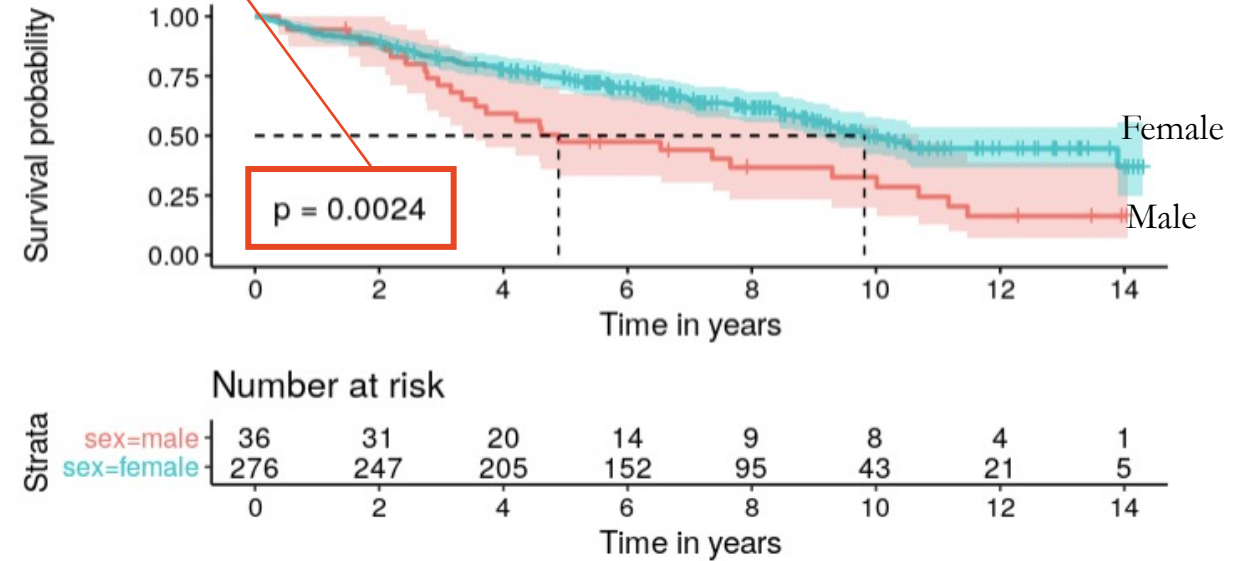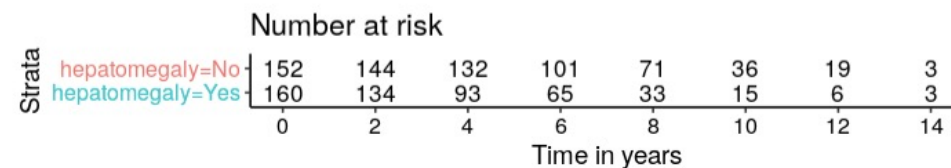
Sex is statistically significant

# Kaplan-Meier Curves
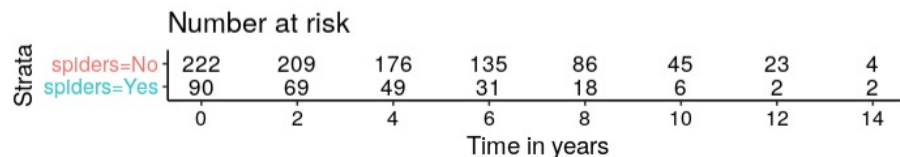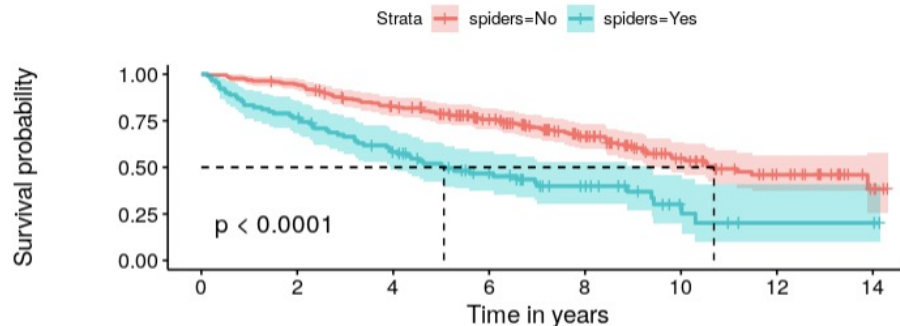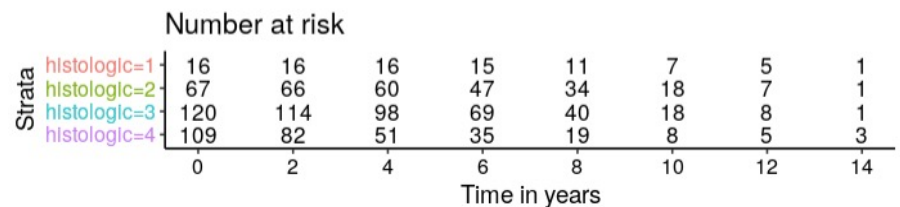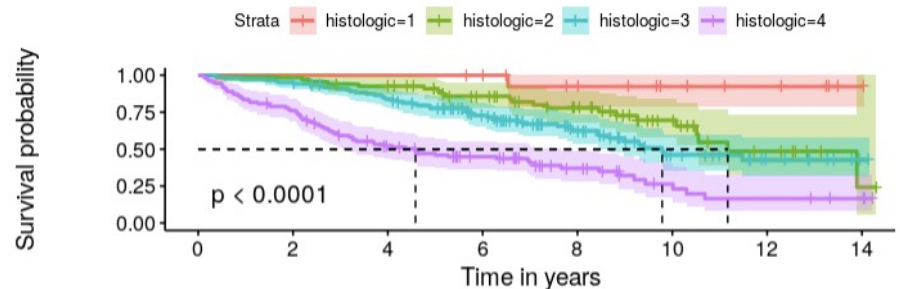
# Joint Model
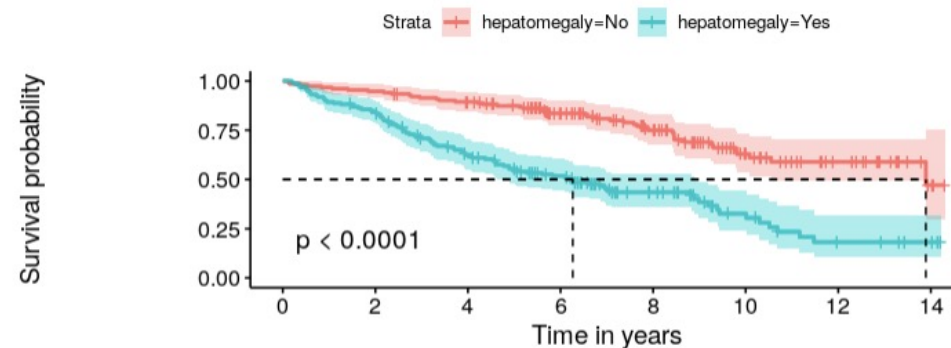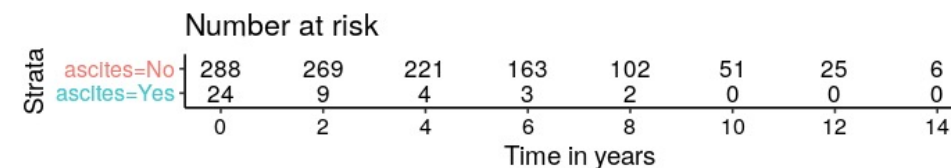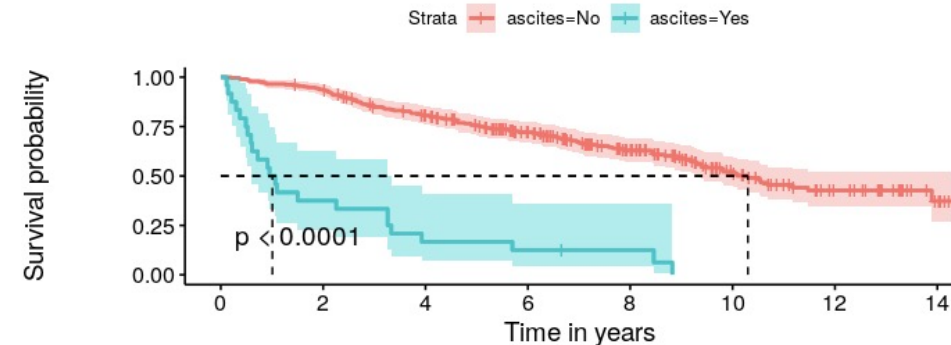
- **Longitudinal sub-model**: Linear Mixed-Effect model
  - Response: Longitudinal bilirubin
  - Predictors: sex and baseline covariates for ascites, hepatomegaly, spiders, albumin, alkaline, SGOT, and prothrombin
  - Random Effect: visit-time | id

  Bilirubin varies among patients and changes dynamically within individuals

- **Survival sub-model**: Cox PH model
  - Response: survival
  - Covariates: baseline values for albumin, edema, and age
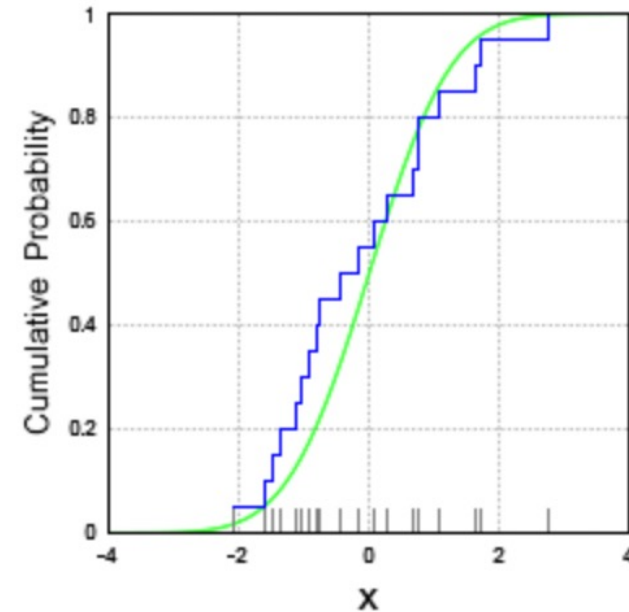
# Empirical CDF

- Formula:

  $$\hat{F}_n(t) = \frac{1}{n}\sum_{i=1}^{n} I(X_i \leq t)$$

- Indicator $I(X_i \leq t)$ is a

  Bernoulli R.V. with $p = F(t)$

- Without censoring:

  $$\hat{F}_n(t) = 1 - S(t)$$



Source: Wikipedia

# Competing Risks Framework

- Cause-Specific Hazards:

$$\lambda_{ik}^{\#}(t) = \lim_{dt \to 0} \frac{\Pr(t \leq T^* \leq t + dt, \; \Delta_i = k \mid T^* \geq t)}{dt}$$

- Sub-distribution Hazards:

$$\lambda_{ik}^{F}(t) = \lim_{dt \to 0} \frac{\Pr(t \leq T^* \leq t + dt, \Delta_i = k \mid T^* \geq t \cup T^* < t, \Delta_i \neq k)}{dt}$$

# Log-rank based test

- Nonparametric test for the difference in survival between two or more groups

- Formula:

$$\text{Log-rank statistic} = \sum_{i=1}^{G} \frac{(E_i - O_i)^2}{Var\ (E_i)}$$

- Note: $E_i, O_i$ are the expected and observed number of events

- Under null hypothesis, log-rank statistic approximately follows $\chi^2_{G-1}$ distribution