Introduction to Survival Analysis

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Educational objectives

- Identify problems falling in survival analysis framework
- Understand the basic properties of time-to-event data
- Learn summary measures for the main quantities used in survival analysis
- Become familiar with regression models used in survival analysis and their interpretation

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Name:	Role in Meeting:
Kwang Woo Ahn, PhD	Activity Director
Haley Montsma, BBA	Planning Committee
Ruta Brazauskas, PhD	Presenter

Evaluation forms

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Help us plan future meetings, by completing and submitting your evaluation forms.

Thank you.

Outline

- Time-to-event data
- Univariate analysis
  - Survival
  - Competing risks
- Multivariable analysis: Regression
  - Cox proportional hazards models
  - Fine-Gray model for competing risks

Time-to-event data

- Quantity of interest: time to event
- Examples:
  - time from cancer diagnosis to death
  - time to disease recurrence
  - time to infection after severe burns
- Questions of interest:
  - quantify risk of an event over time
  - compare risk of experiencing the event of interest between groups of patients
  - identify risk factors which affect the outcome
  - predict survival at some point in time

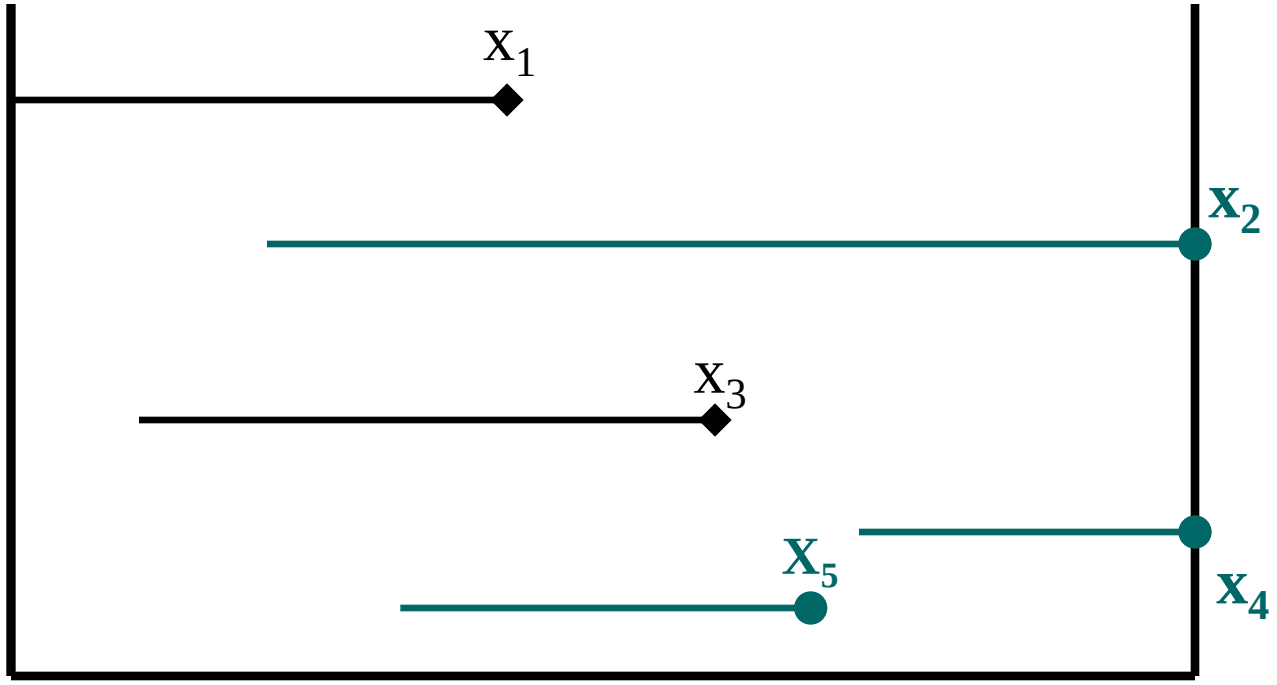
Censored data

- Complications: patients lost to follow up and only partial information available (right censoring).
- Example:
- Patients enter the study at different time points and the study ends at a fixed time:
  - Patients who are alive may have different follow-up times.
  - For patients alive at last visit, it is unknown what will happen later (called censored individuals/observations):

Common reasons for censoring:

- Loss to follow-up
- End of study

Censored data example



Beginning of Study

Calendar Time

End of Study

Observed survival data

- Each observation consists of two quantities:
  - Event time or follow-up time
  - Event indicator: 1 = dead; 0= alive
- Additional information on each patient may be available (age, gender, disease status, etc.)
- Example:

ID	Time	Dead	Gender	Age
1	40.3	1	Male	22
2	2.7	0	Male	58
3	10.4	0	Female	39
4	60.0	1	Female	20

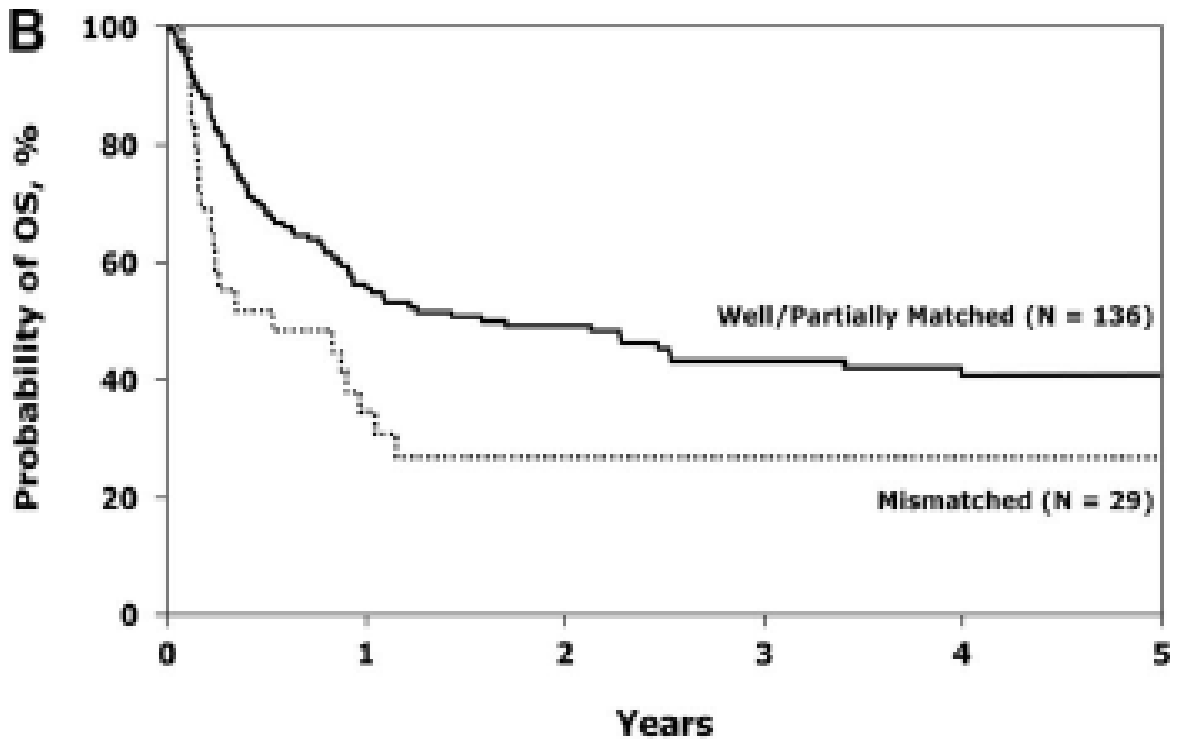
Quantifying the risk

- Kaplan-Meier (KM) curve:
  - estimates probability of survival, i.e. being event free, at any point in time t:

    $$S(t)=\text{Prob}(\text{alive by time } t)$$

  - it is designed to accommodate censoring
  - may be used to estimate the median survival time of a study cohort
  - usually presented as a graph
- Note: the mean survival time is difficult to estimate when the largest observation is censored

Example: Kaplan-Meier curves



Marks et al. Blood **112** (2), 2008.

Comparing survival experience between two groups

- Hypothesis of interest:

  Ho: $S_1(t) = S_2(t)$ for all time points t

  Ha: survival probabilities $S_1(t)$ and $S_2(t)$ differ at some time t

  Here, $S_1(t)$ and $S_2(t)$ are survival probabilities at time t in group 1 and 2, respectively.

- Log-rank test:
  - compare observed number of events in each group to the number expected if the survival experiences were the same. Large differences provide evidence against Ho.
  - small p-values ($p<0.05$) indicate that there is statistically significant difference between the two survival curves.

Competing risks data

- Data
  - Each subject may fail due to one of several causes
  - Failure from one cause precludes the occurrence of other events
- Examples:
  - Cause-specific mortality in cancer research
  - Bone marrow transplant (BMT) failure due to relapse or treatment related toxicity

Observed competing risks data

- Each observation consists of two quantities:
  - Event time or follow-up time
  - Event indicator: 1 = death from the cause of interest; 2=failure from other cause; 0= censored observation
- Additional information on each patient may be available (age, gender, disease status, etc.)
- Example:

ID	Time	Event	Gender	Age
1	40.3	2	Male	22
2	2.7	0	Male	58
3	10.4	0	Female	39
4	60.0	1	Female	20

Quantifying the risk: competing risks data

- Cumulative incidence (CI) curve:
  - estimates the probability of failure from the cause of interest by time t:

    CI_1 (t)=Prob(failure from cause 1 by time t)

    Example: $CI_{relapse}$ (t)=Prob(relapse by time t)

    Here, death is competing risk
  - With complete follow-up on all patients to time t, CI at time t would be calculated as the proportion of the total study group who experienced the event of interest by time t
  - Calculation of CI takes into account failures of both types
  - Usually presented as a graph
  - Statistical tests to compare two cumulative incidence curves exist

Example: Cumulative incidence curves

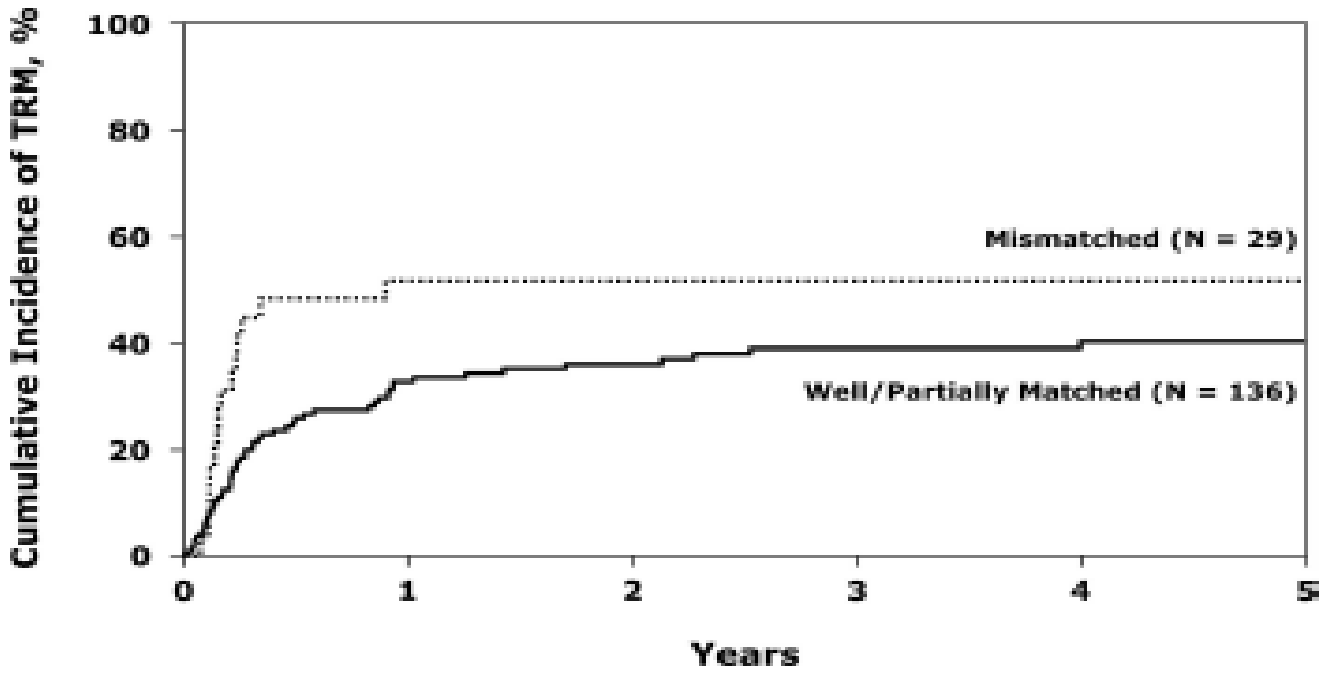


Figure 1. Cumulative incidence of TRM after unrelated donor transplantations for Philadelphia⁻ ALL in first CR, by donor-recipient HLA-match.

Marks et al. Blood **112** (2), 2008.

Why not to use 1-KM in competing risks problems?

- Disregarding competing events produces an incorrect estimate of the probability of the event of interest:
  - 1-KM overestimates the probability of a particular event by treating failures from other causes as censored observations;
- It is estimating probability of the event of interest if the other competing risks were removed
  - Example: For relapse, this would be an estimated probability of relapse in a hypothetical world where it is impossible to die from treatment related complications.

Multivariable analysis: Cox regression model

- Cox proportional hazards model for single endpoint studies:
  - Compares risk of death between groups over time
  - Focuses on comparing failure hazards which represent instantaneous rate of experiencing the event at every given point in time
- Uses:
  - Prognostic factor studies
  - Adjust for imbalances in treatment comparisons
  - Evaluate the effect of covariates

What does it model?

- Proportional hazards model:

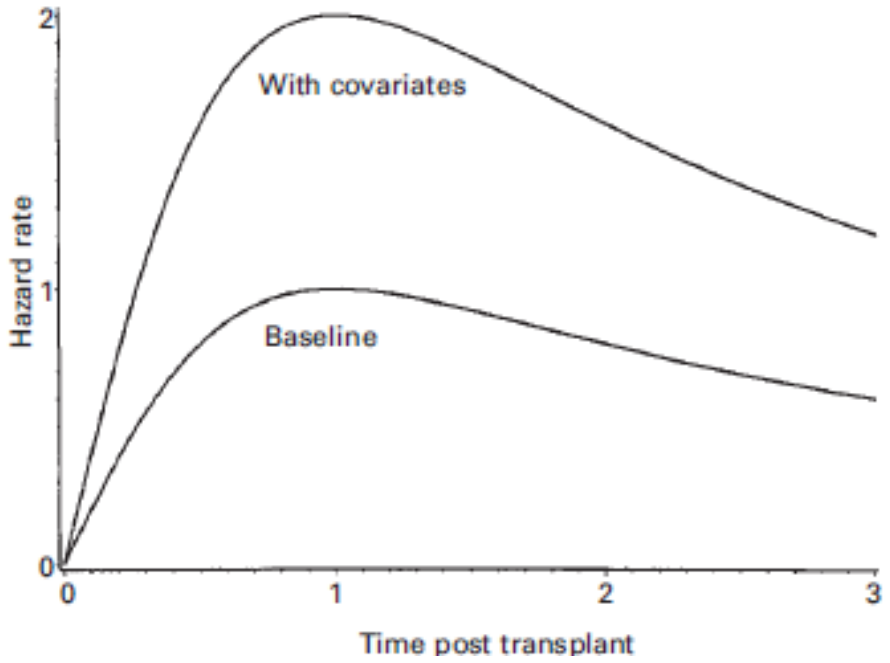
$$\log_e \frac{h(t|x_1,\ldots,x_p)}{h_0(t)} = \beta_1 x_1 + \ldots + \beta_p x_p$$

where

  - $h(t|x_1,\ldots x_p)$ is the hazard at time t for an individual with covariates $x_1,\ldots x_{p;}$
  - $h_0(t)$ is the baseline hazard rate.
- The ratio $h(t|x_1,\ldots x_p)/ h_0(t)$ is called the *hazard ratio* and quantifies how much more an individual with covariates $x_1,\ldots x_p$ is likely to die as compared to the "baseline" individual.

Proportional hazards assumption

- It is assumed that the hazard ratio is constant over time:



Klein et al. (2001)

Covariates

- Fixed covariates: values known at time 0 and remain fixed throughout the study:
  - Examples: Age at diagnosis, gender, disease type;
- Time dependent covariates: explanatory variables whose values may change during the course of the study:
  - Examples: Developing an infection after surgery; occurrence of graft-versus-host disease after the bone marrow transplantation;
- Cox model is able to accommodate both types – fixed and time dependent - covariates

Model building

- Assumptions need to be checked prior to building any regression model
  - if proportionality is violated, stratification or time-dependent covariates may be used to correct the problem
- Standard model selection techniques (forward selection, backward elimination, stepwise model building) can be used to identify factors significant in predicting the outcome
- Most statistical packages have routines for Cox model implementation

Example: Cox model (1)

Table 4. Multivariate analysis of survival among patients 16 years of age and older who underwent URD transplants for Philadelphia-negative ALL in CR1

Variable	Event/no. evaluable	Relative risk of death (95% CI)	*P*
WBC at diagnosis			
100×10^9/L or less*	72/113	1.00§	
More than 100×10^9/L	25/38	1.73 (1.08-2.77)	$P_{12} = .023$
Unknown	11/14	2.32 (1.21-4.48)	$P_{13} = .012$
Time from diagnosis to CR1			
8 wk or less†	52/97	1.00§	
More than 8 wk	45/68	1.74 (1.16-2.62)	.008
Donor-recipient CMV status			
D^-/R^-	28/54	1.00§	
D^+ or R^+	69/111	1.62 (1.02-2.56)	.040
Donor-recipient HLA match			
Well or partially matched‡	75/136	1.00§	
Mismatched	22/29	1.88 (1.16-3.05)	.010
T-cell depletion			
No	84/149	1.00§	
Yes	13/16	2.62 (1.43-4.80)	.002

Marks et al. Blood **112** (2), 2008.

Example: Cox model (2)

- Cox regression analysis shows that the following factors are significantly associated with the higher risk of mortality (RR>1, p-value<0.05):
  - diagnostic WBC of more than 100×10^9/L,
  - HLA mismatch,
  - CMV seropositivity,
  - time to CR exceeding 8 weeks,
  - t-cell depletion.

Example: Cox model (3)

- Interpretation of the effect of HLA matching on the risk of death:
  - patients who had an HLA-mismatched unrelated donor were 1.88 times more likely to die as compared to those who had an HLA-matched donor (RR=1.88, 95%CI, 1.16-3.05);
  - the p-value of 0.010 implies that this difference in mortality rate is significant

Regression modeling of competing risks data

- Each of the competing risks is modeled separately
- Regression methods used for competing risks:
  - Cox model (treats failures from another cause as censored observations)
  - Fine-Gray regression model (models sub-distribution hazards arising in competing risks setting)
  - Pseudo-value regression (models the value of the cumulative incidence function at a particular point in time)

Software

- Singe endpoint studies: SAS, R, Stata, SPSS can be used to
  - produce the Kaplan-Meier estimates,
  - plot survival functions,
  - perform log-rank test for the equality of several survival functions
  - implement the Cox model
- Competing risks data:
  - SAS macros available estimating cumulative incidence probabilities
  - R package (*cmprsk*) is available to estimate the cumulative incidence function and fit the Fine-Gray regression model
  - Pseudo-value approach requires either a SAS macro or R function application in data preparation but the main analysis can be carried out with standard statistical packages

References

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Questions?