Estimating the Effect of a Time-Dependent Factor on Pre-Treatment Survival

Qi Gong   Douglas E. Schaubel

Department of Biostatistics
University of Michigan

Symposium in Honor of Anastasios (Butch) Tsiatis
North Carolina State University
July 13, 2013

Outline

- Motivating example: liver transplantation
- Existing methods
- Proposed methods:
  - parameter estimation
  - asymptotic properties
  - simulation study
- Application: comparing acute and chronic liver failure patients
- Discussion

Data Structure: General Description

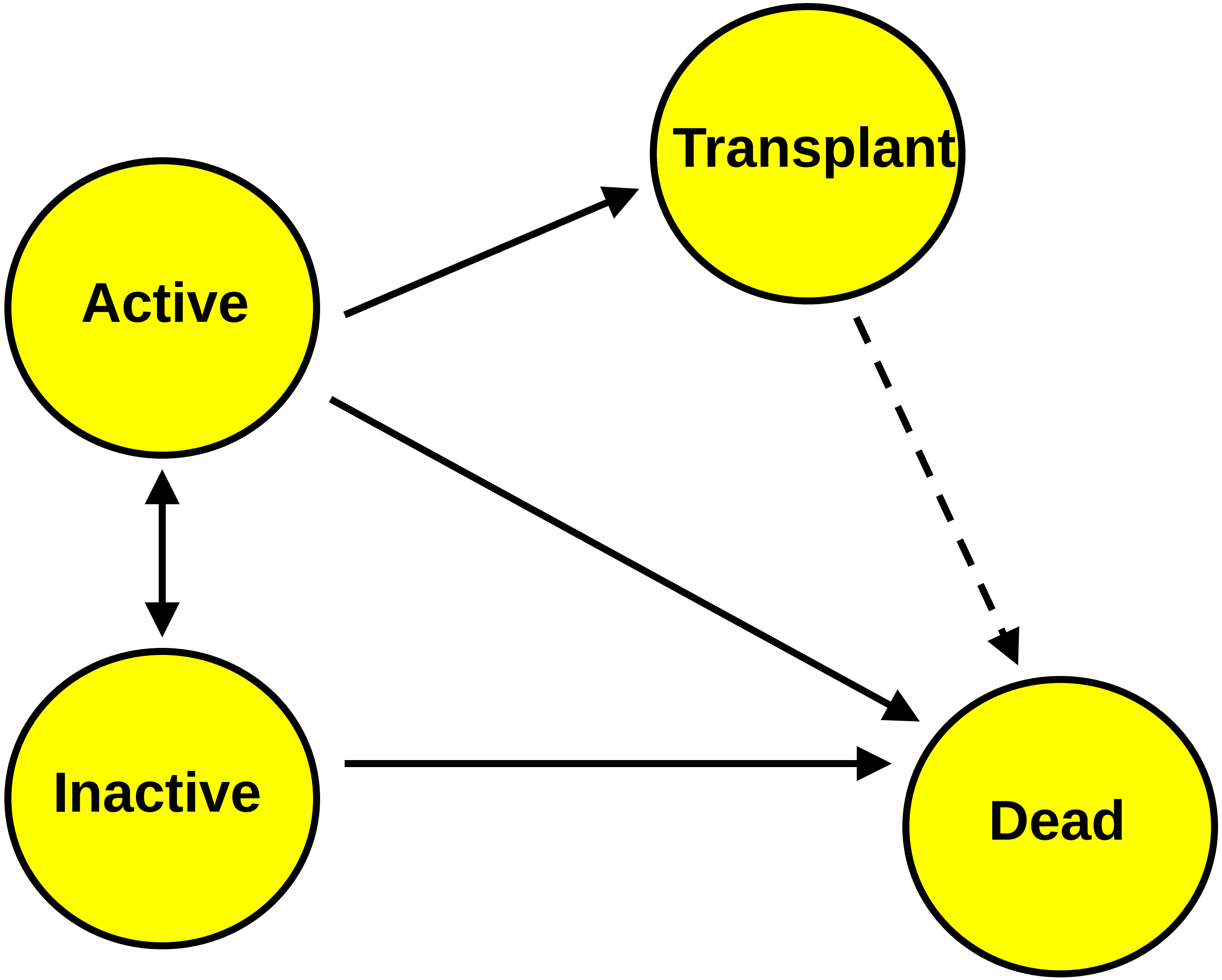
- *Pre-treatment* survival is of interest
  - treatment is time-dependent
  - treatment assignment depends on time-dependent factors
  - subjects can experience periods of treatment ineligibility
- Treatment is assigned in calendar time
- Database is very large

Motivating Example: Liver Failure

- Treatment: liver transplantation
  - medically suitable patients are wait listed; Why?
  - more patients (000's more) in need of transplantation than there are donor livers
- Liver allocation is *urgency-based*
  - each available liver should be allocated to the (eligible) patient who would die fastest in the absence of transplantation

Liver Failure Data (continued)

- Patients are prioritized by their pre-transplant death rates
  - *acute* liver failure (*Status 1*) patients are given first priority
  - *chronic* end-stage liver disease patients are ordered by MELD score
  - patients may be inactivated
- Liver transplantation dependently censors pre-transplant death

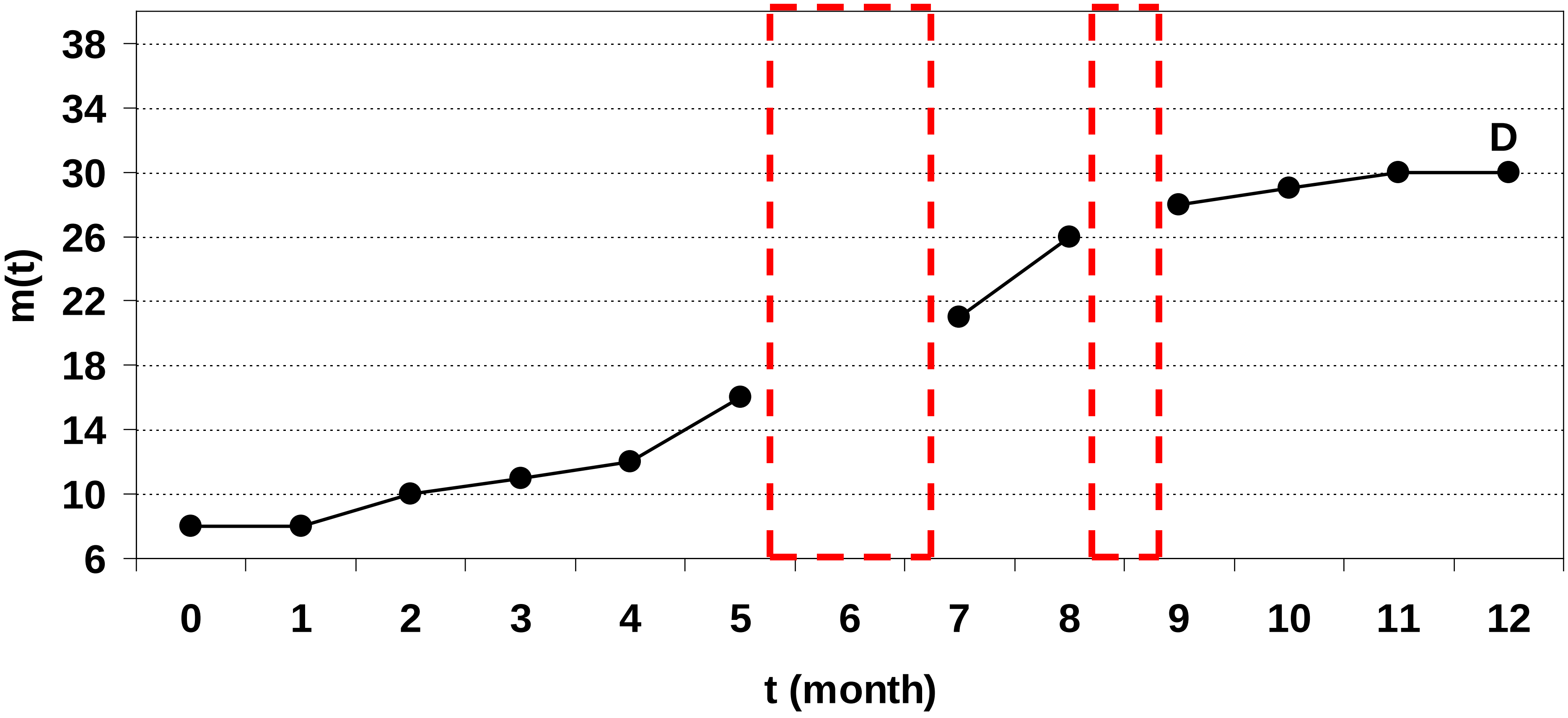

Transplant
Active
Inactive
Dead

Acute vs Chronic Liver Disease

- Very little research comparing *acute* versus *chronic* pre-transplant death rates
  - assumed that *acute* patients die the quickest
- *Status 1* designation: somewhat subjective
- MELD score is based on lab measures
  - must be updated at regular intervals
  - intended to be objective, and not subject to manipulation

- Question: In the absence of liver transplantation, are there MELD scores at which mortality is higher than Status 1?

e.g., MELD trajectory



Notation

i : subject

D_i: time of death, subject i

C_i: censoring time

T_i: time of transplant

$X_i = D_i \wedge C_i \wedge T_i$

$\boldsymbol{Z}_i(t)$: covariate vector

Notation: Counting Processes

$Y_i(t) = I(X_i \geq t)$

$N_i^D(t) = I(D_i \leq t,\ D_i < C_i \wedge T_i)$

$N_i^T(t) = I(T_i \leq t,\ T_i < X_i)$

$A_i(t) = I\{i \text{ active at time } t\}$

Note: *active* = *transplant-eligible*

Traditional Methods: Time-Dependent Covariates

Time-Dependent Covariates

- Time-dependent proportional hazards model:

$$\lambda_i(t) \quad = \quad \lambda_0(t) \exp\left\{ \boldsymbol{\beta}_0' \boldsymbol{Z}_i(t) \right\}$$

- In context of liver disease data:
    - MELD categories represented by time-dependent categories reference = Status 1
- Issues:
    - time scale, t
    - updating of covariate vector
    - handling of transplant-ineligibility (INACTIVE state)

Related Literature

- Estimating treatment effect, in presence of time-dependent covariates:
  - SNFTM: e.g., Robins (1986, 1987, ...)
  - MSM: e.g., Robins, Hernan, Brumback (2000)
  - HA-MSM: e.g., Petersen et al. (2007)
  - Schaubel et al. (2009)
  - Zhang & Schaubel (2012)
  - Taylor et al (2013)
- In our setting, the time-dependent covariate is of chief interest (treatment is a nuisance)

ACTIVE Status

- Arguments for and against censoring at INACTIVE
  - for: results of analysis will only be applied to ACTIVE patients
  - against: patients often made INACTIVE when their health declines

Time Scale

- Traditional analysis: time scale t represents *follow-up time*
- However, transplants are allocated in *calendar time*
- e.g., a deceased-donor liver is recovered on 13-JUL-2013
  - 3 patients are on the wait list

Order	MELD	ACTIVE
1	Status 1	yes
2	38	no
3	34	yes

- Pertinent time scale: *time from 13-JUL-2013*

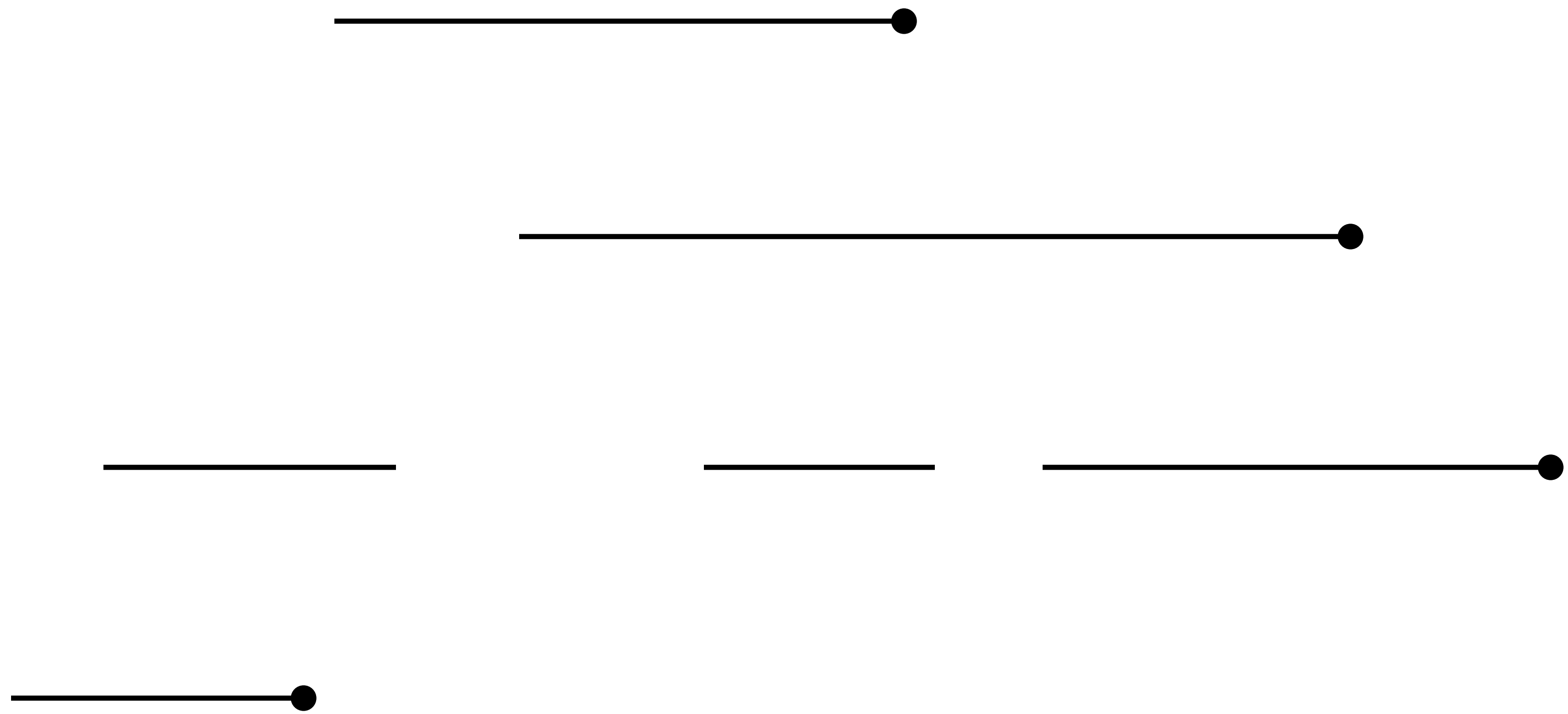
Proposed Methods: Partly Conditional Model

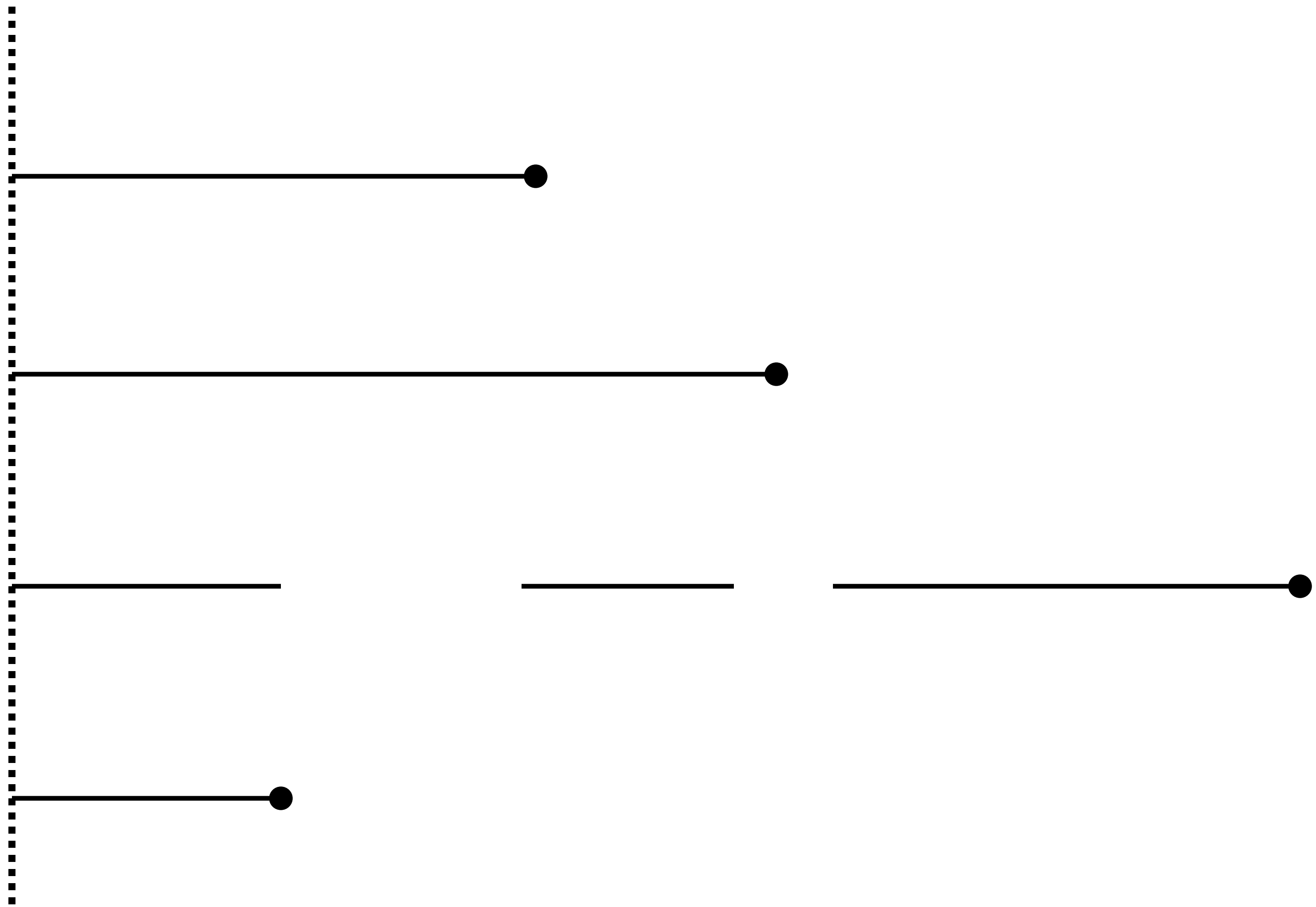
Related Literature

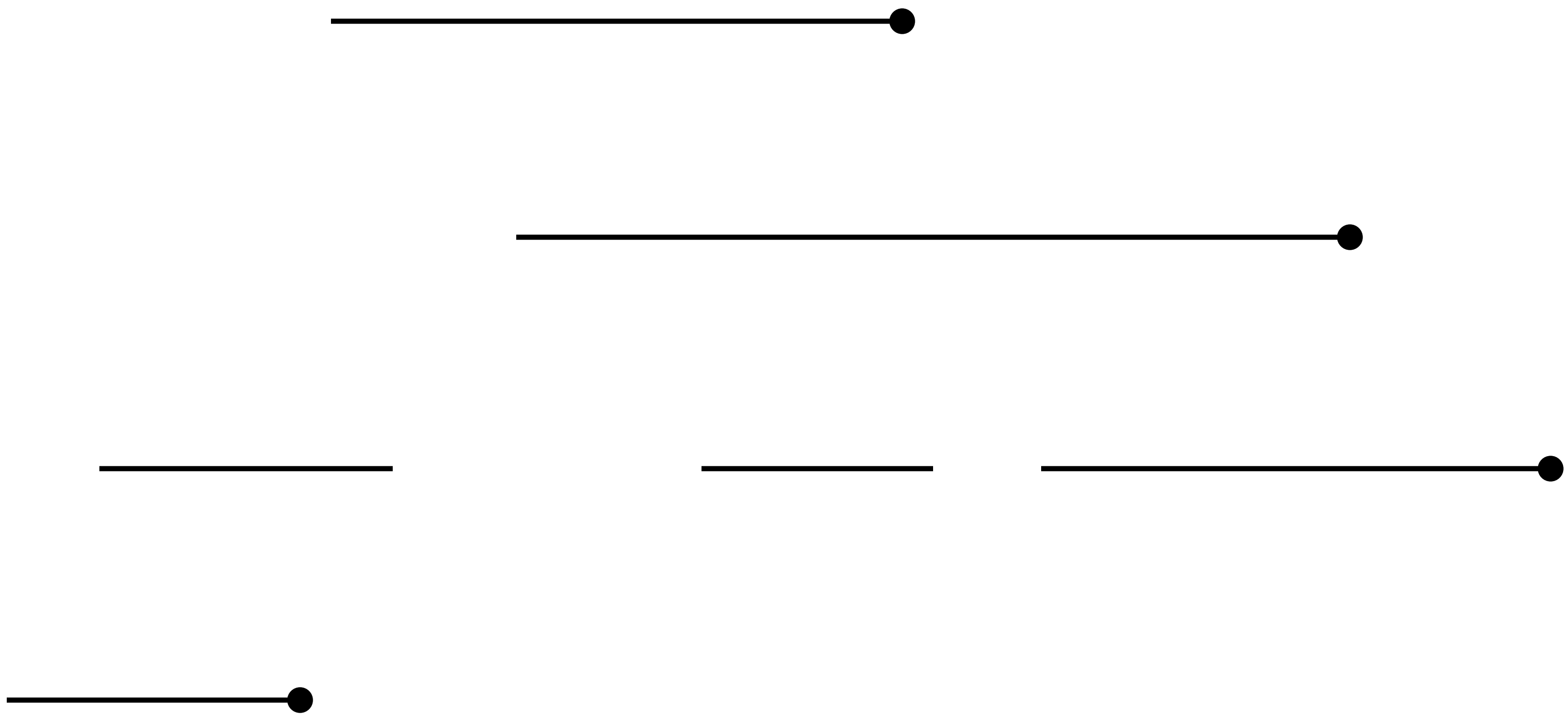
- Landmark analysis:
  - Feuer et al (1992)
  - Van Houwelingen (2007)
  - Van Houwelingen & Putter (2008)
- Marginal hazard models:
  - Wei, Lin & Weissfeld (1989)
- Partly conditional survival models:
  - Zheng & Heagerty (2005)
- Inverse Probability of Censoring Weighting (IPCW):
  - Robins & Rotnitzky (1992)

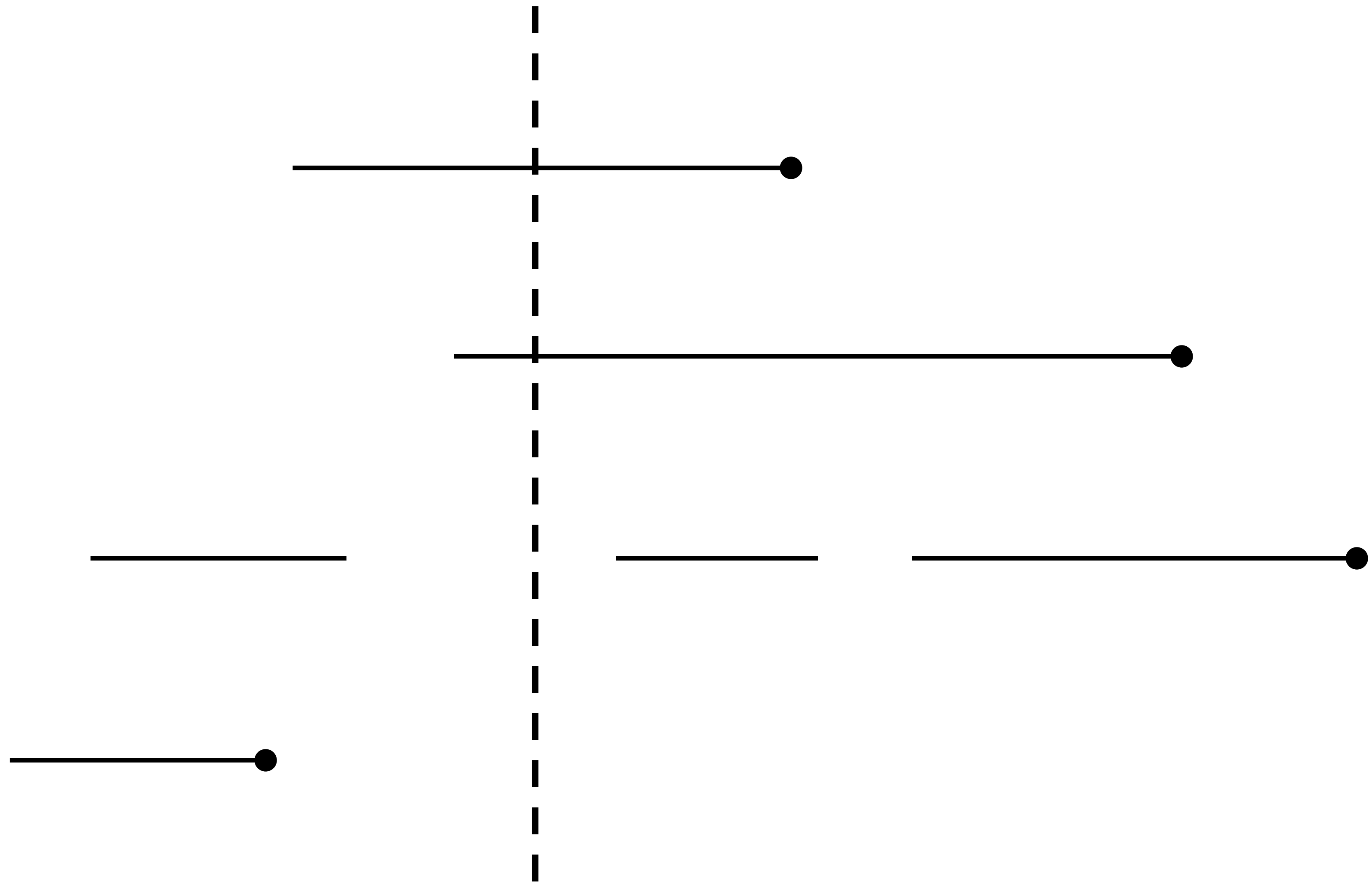
Proposed Methods: Overview

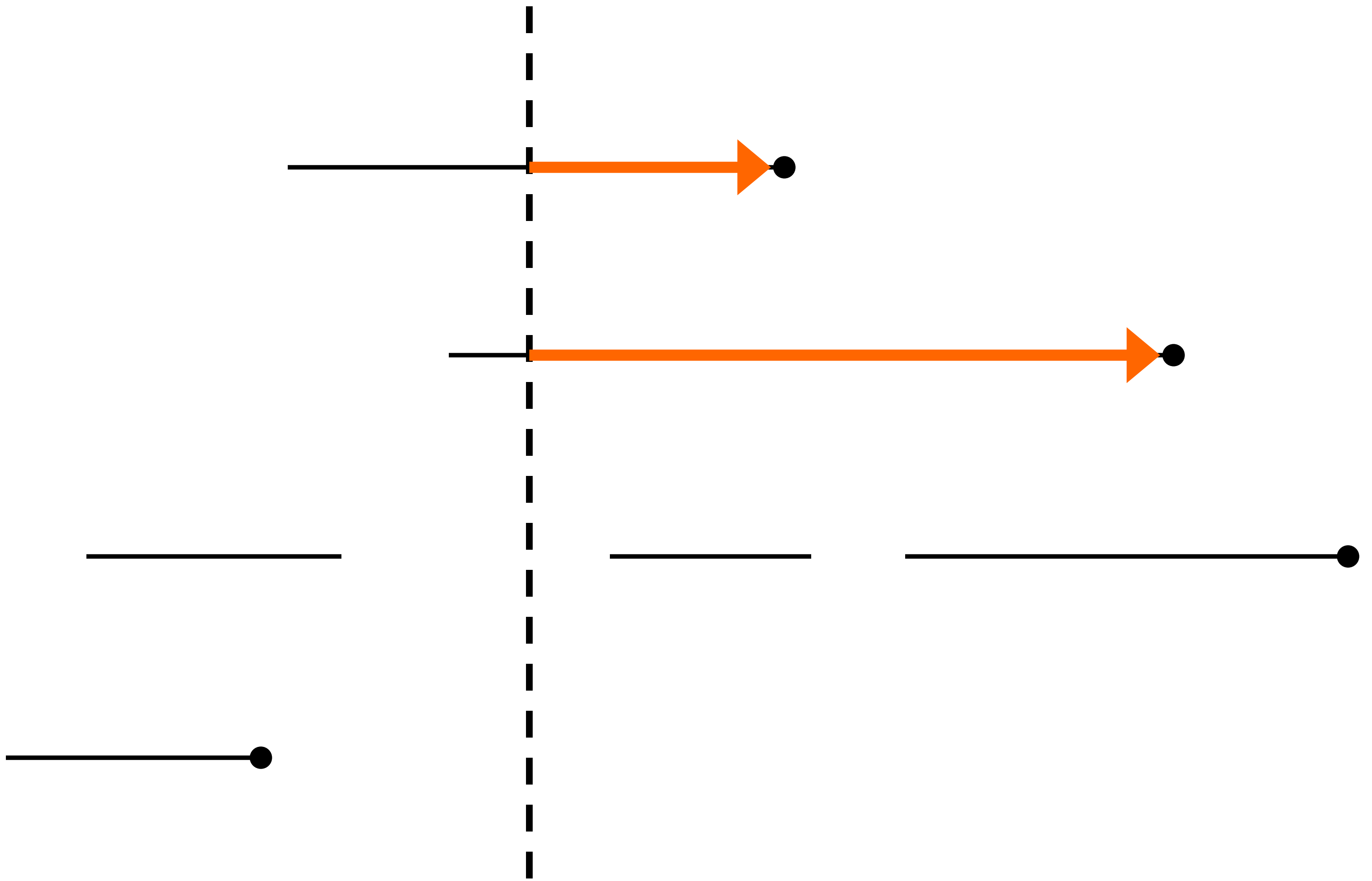
- Select a random set of cross-section (calendar) times
- For each cross-section, include patients who are:
  - alive, uncensored
  - transplant-free, active
- "Freeze" covariate at time of cross-section
- ACTIVE is an *entry* criterion
  INACTIVE is not a *censoring* event
- Use IPCW: dependent censoring (receipt of treatment)











Proposed Method: Additional Notation

- Random set of K cross-section times,

$$CS_1,\ CS_2,\ \ldots,\ CS_K$$

  each of which is a calendar date

- Let S_{ik} = follow-up time, patient i, at cross-section k
- At each cross-section, k, include patients with

$$A_i(S_{ik}) \times Y_i(S_{ik}) = 1$$

- Freeze covariate at cross-section date: $\boldsymbol{Z}_i(S_{ik})$
- Time scale = time since cross section

Partly Conditional Model

- Restructure observed data:

$$
\begin{aligned}
Y_{ik}(t) &\equiv A_i(S_{ik})\, Y_i(S_{ik}+t) \\
N_{ik}^D(t) &\equiv A_i(S_{ik}) \int_{S_{ik}}^{S_{ik}+t} dN_i^D(s)
\end{aligned}
$$

- Pre-treatment death:

$$
\lambda_{ik}^D(t) = \lambda_{0k}^D(t) \exp\{\boldsymbol{\beta}_0' \boldsymbol{Z}_i(S_{ik})\}, \quad t > S_{ik}
$$

  - $t =$ time from cross-section
  - conditional on $[A_i(S_{ik}) = 1]$

Dependent Censoring

- Model conditions on $\boldsymbol{Z}_i(S_{ik})$
- Both pre-treatment death and treatment rates depend on $\boldsymbol{Z}_i(t)$, $t > S_{ik}$
    - given only $\boldsymbol{Z}_i(S_{ik})$, pre-treatment death is dependently censored by treatment
- Inverse weight the observed pre-treatment experience

Model: Treatment Assignment

- Treatment assignment:

$$\lambda_i^T(t) \quad = \quad A_i(t)\lambda_0^T(t)\exp\{\boldsymbol{\theta}_0'\boldsymbol{Z}_i(t)\}$$

  - here, t = follow-up time (unshifted)
  - treatment hazard defined as 0 during INACTIVE sub-intervals
  - INACTIVE experience excluded from model fitting

Inverse Weighting

- Type A weight:

$$W_{ik}^{A}(t) \quad = \quad Y_{ik}(t)\exp\{\Lambda_i^T(S_{ik}+t)-\Lambda_i^T(S_{ik})\}$$

- Type B:

$$W_{ik}^{B}(t) \quad = \quad Y_{ik}(t)\frac{\exp\{\Lambda_i^T(S_{ik}+t)-\Lambda_i^T(S_{ik})\}}{\exp\{\Lambda_{ik}^{\dagger}(t)\}}$$

- Type C:

$$W_{ik}^{C}(t) \quad = \quad Y_{ik}(t)\exp\{\Lambda_i^T(S_{ik}+t)\}$$

Parameter Estimation

- Estimate $\boldsymbol{\beta}_0$ through stratified, inverse-weighted Cox score function
- It can be shown that $n^{1/2}(\widehat{\boldsymbol{\beta}} - \boldsymbol{\beta}_0)$ converges in distribution to a Normal with mean $\mathbf{0}$ and a variance that can be consistently estimated
- Weighted Breslow-Aalen estimator for $\Lambda_{0k}(t)$
  - could combine $\widehat{\Lambda}_{0k}(t)$ $(k = 1, \ldots, K)$ to estimate $\Lambda_0(t)$, for prediction purposes

Simulation Study

$(n = 1000)$

Simulation Results: Version B Weight

$C\%$	β_1	BIAS	ESD	ASE	CP
10%	-0.64	0.004	0.130	0.121	0.94
20%		0.008	0.121	0.116	0.94
40%		-0.008	0.113	0.112	0.94
10%	-0.32	-0.005	0.136	0.130	0.94
20%		-0.005	0.122	0.117	0.94
40%		0.003	0.112	0.109	0.93
10%	0	0.005	0.135	0.126	0.93
20%		-0.005	0.123	0.118	0.94
40%		0.004	0.109	0.109	0.95

Simulation Results: Relative Efficiency

$C\%$	β_1	Type A	Type B	Type C
10%	-0.64	1	1.03	0.86
20%		1	1.40	0.99
40%		1	1.64	0.83
10%	-0.32	1	1.15	1.00
20%		1	1.32	0.83
40%		1	1.65	0.84
10%	0	1	1.08	0.84
20%		1	1.22	0.87
40%		1	1.72	0.85

Application to Liver Failure Data

Application: Liver Wait List Mortality

- Data were obtained from the Scientific Registry of Transplant Recipients (SRTR)
- Included patients added to the liver wait list from 01-MAR-2002 to 31-DEC-2009
- Cross-sections drawn weekly
  - $K = 409$ cross-sections
  - total of $n = 23,657$ patients
- Objective: compare MELD (> 20) categories with Status 1 (reference)

Analysis of Liver Data: Death Model

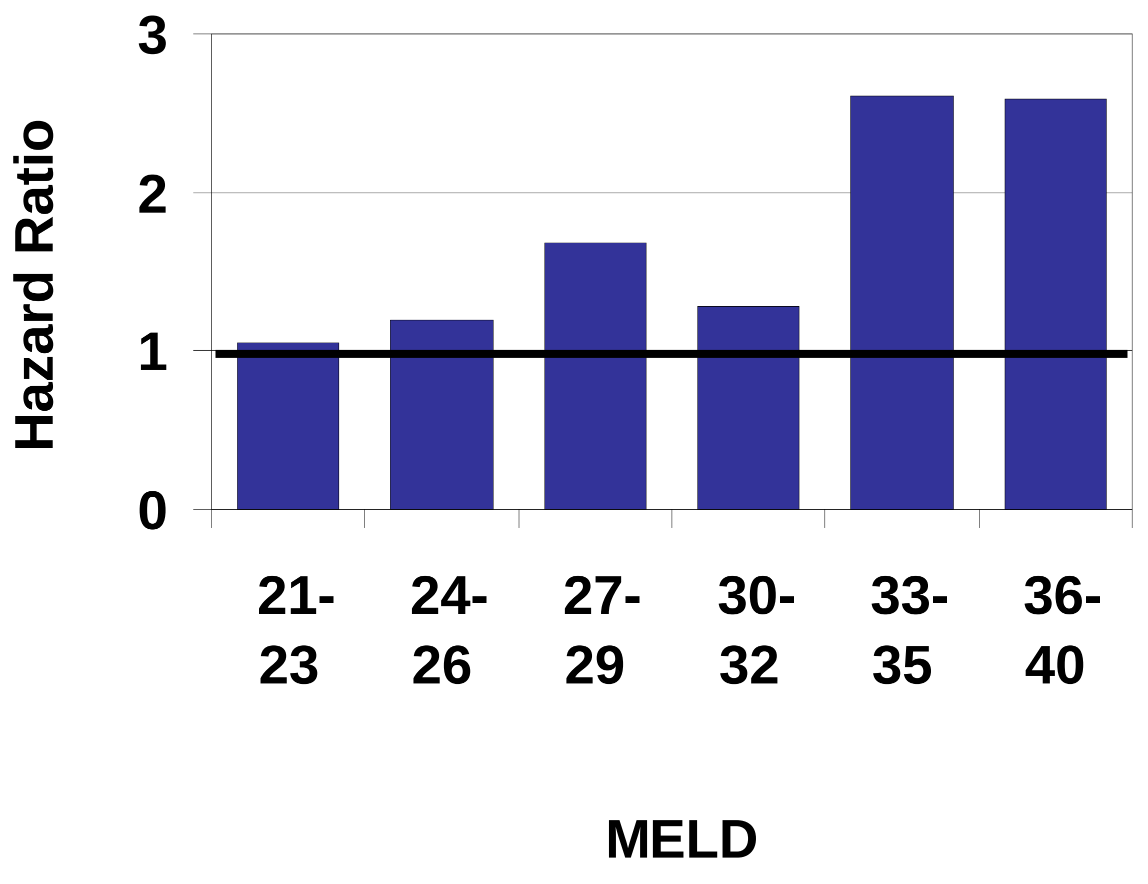
- <u>Death model</u>: Adjustment covariates
  - age, gender, race, UNOS region (stratified)
  - blood type, diabetes, diagnosis, Hep C, ICU
  - albumin, dialysis, ascites, encephalopathy, BMI
  - at time of cross-section:

    albumin slope
    % time on dialysis
    % time INACTIVE

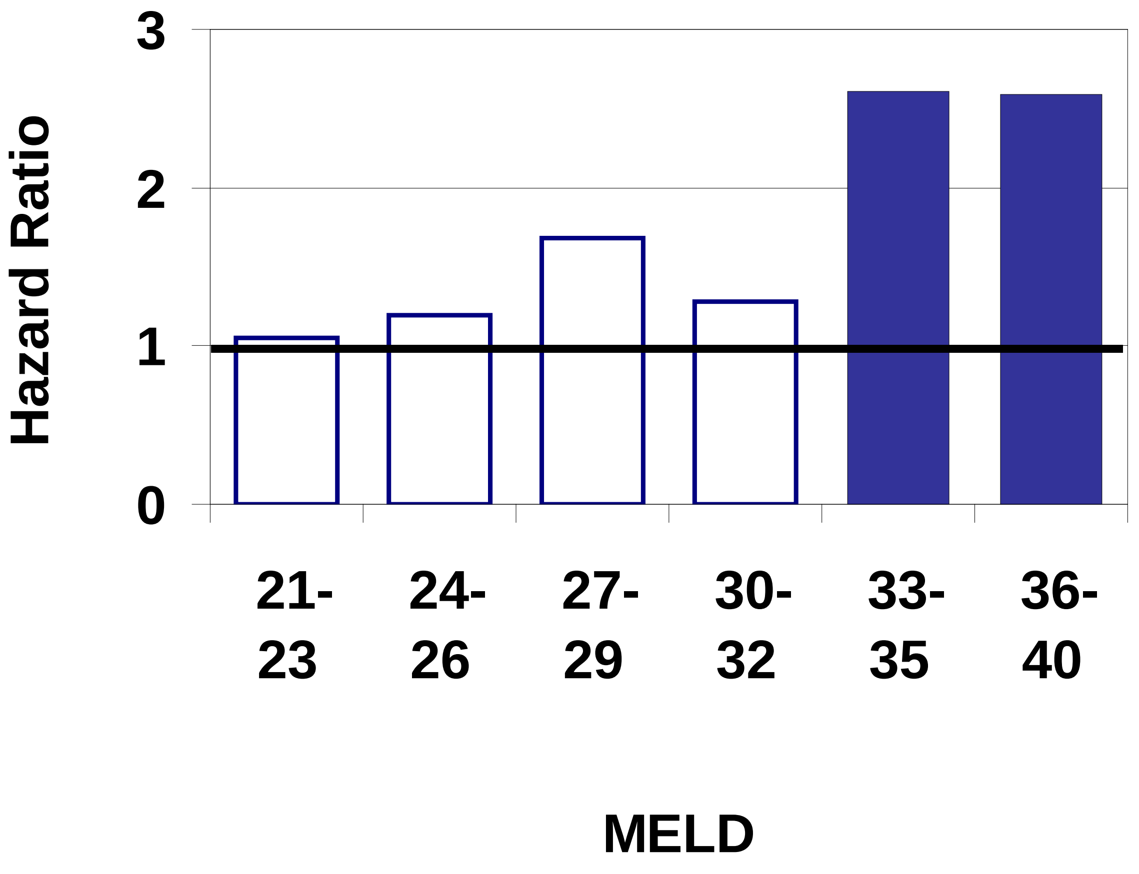
Analysis of Liver Data: Transplant Model

- Transplant model: Adjustment covariates
  - $MELD(t)$, *Status.1(t)*
  - age, gender, race, UNOS region (stratified)
  - blood type, diabetes, diagnosis, Hep C, ICU, BMI
  - *albumin(t)*, $dialysis(t)$, $ascites(t)$, $encephalopathy(t)$
  - *albumin.slope(t)*, $\%.dialysis(t)$, $\%.INACTIVE(t)$

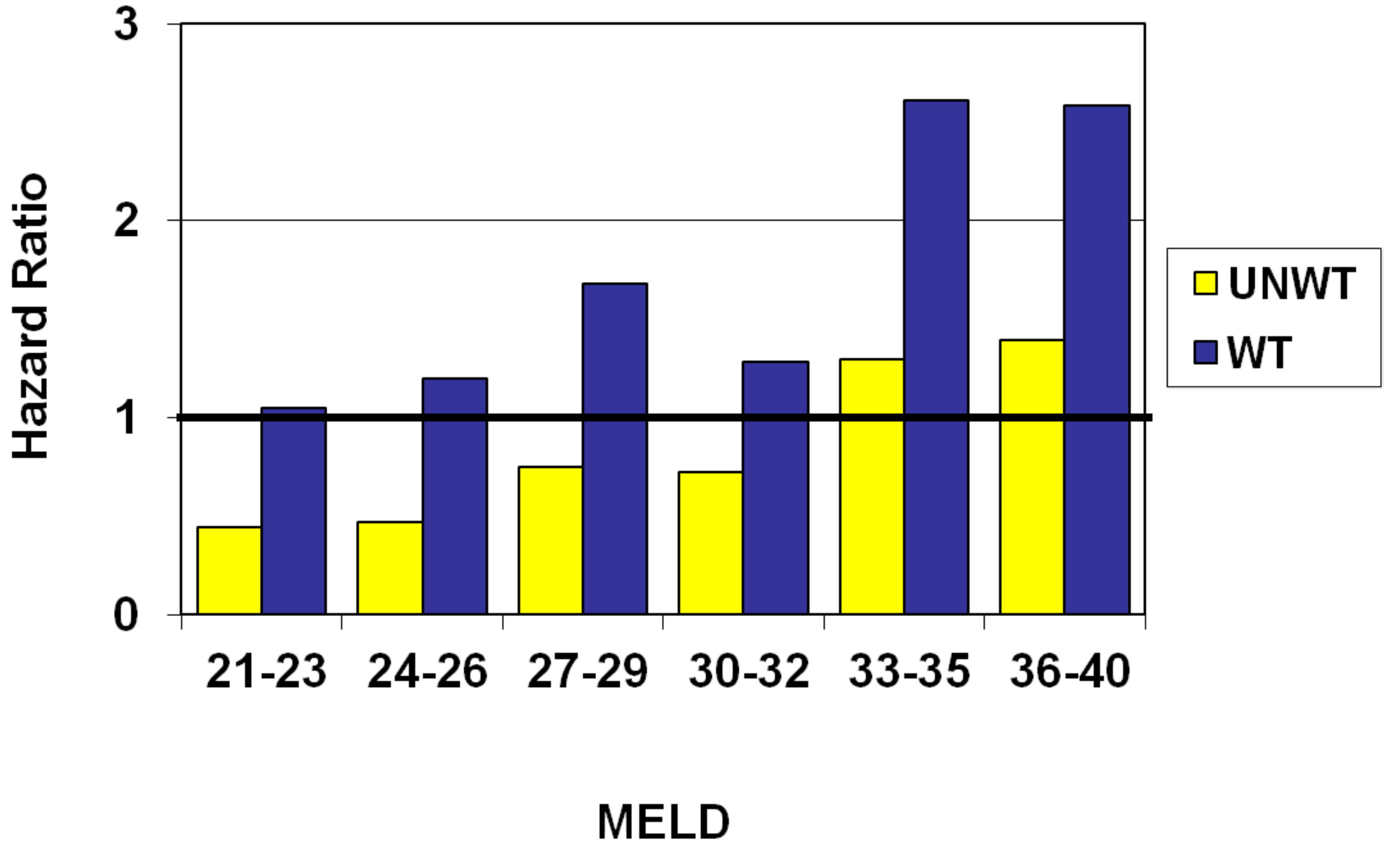
Partly Conditional Analysis



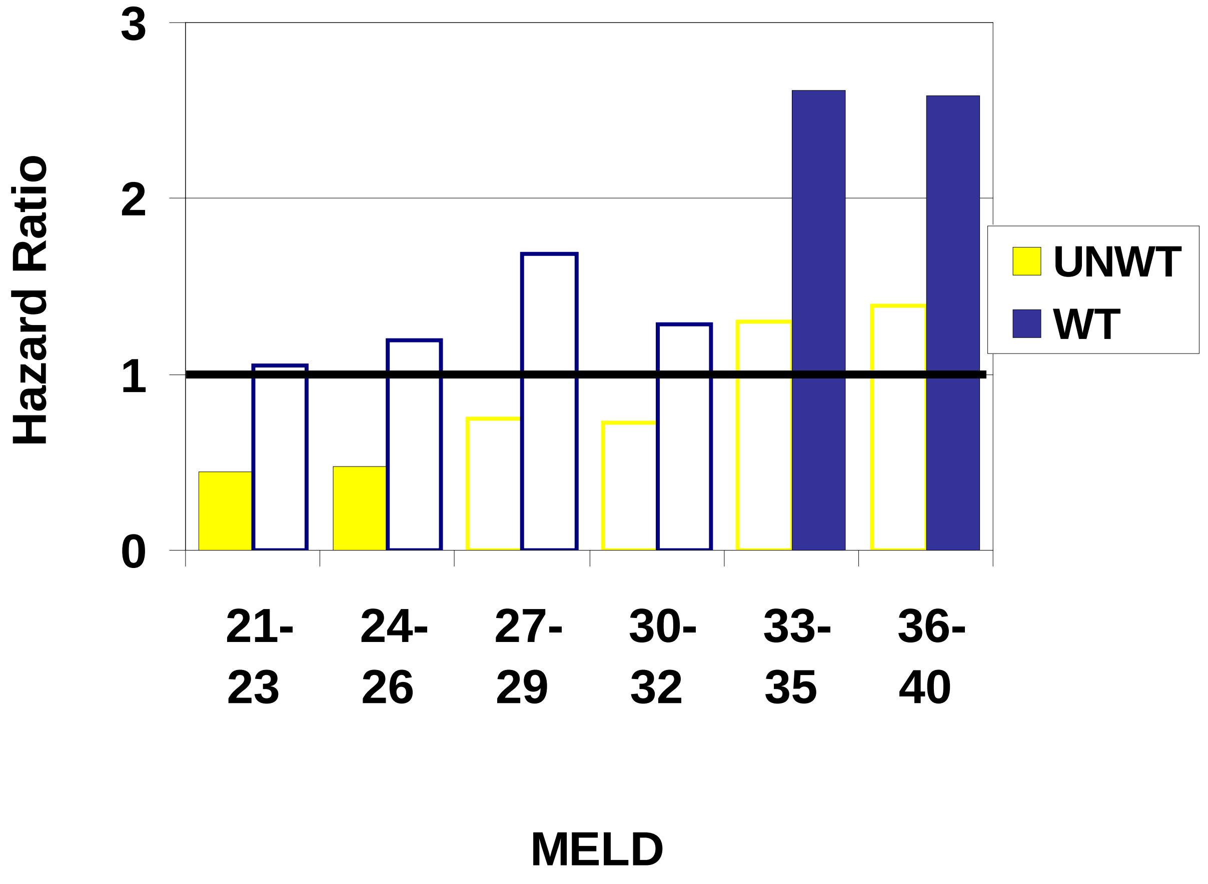
Partly Conditional Analysis



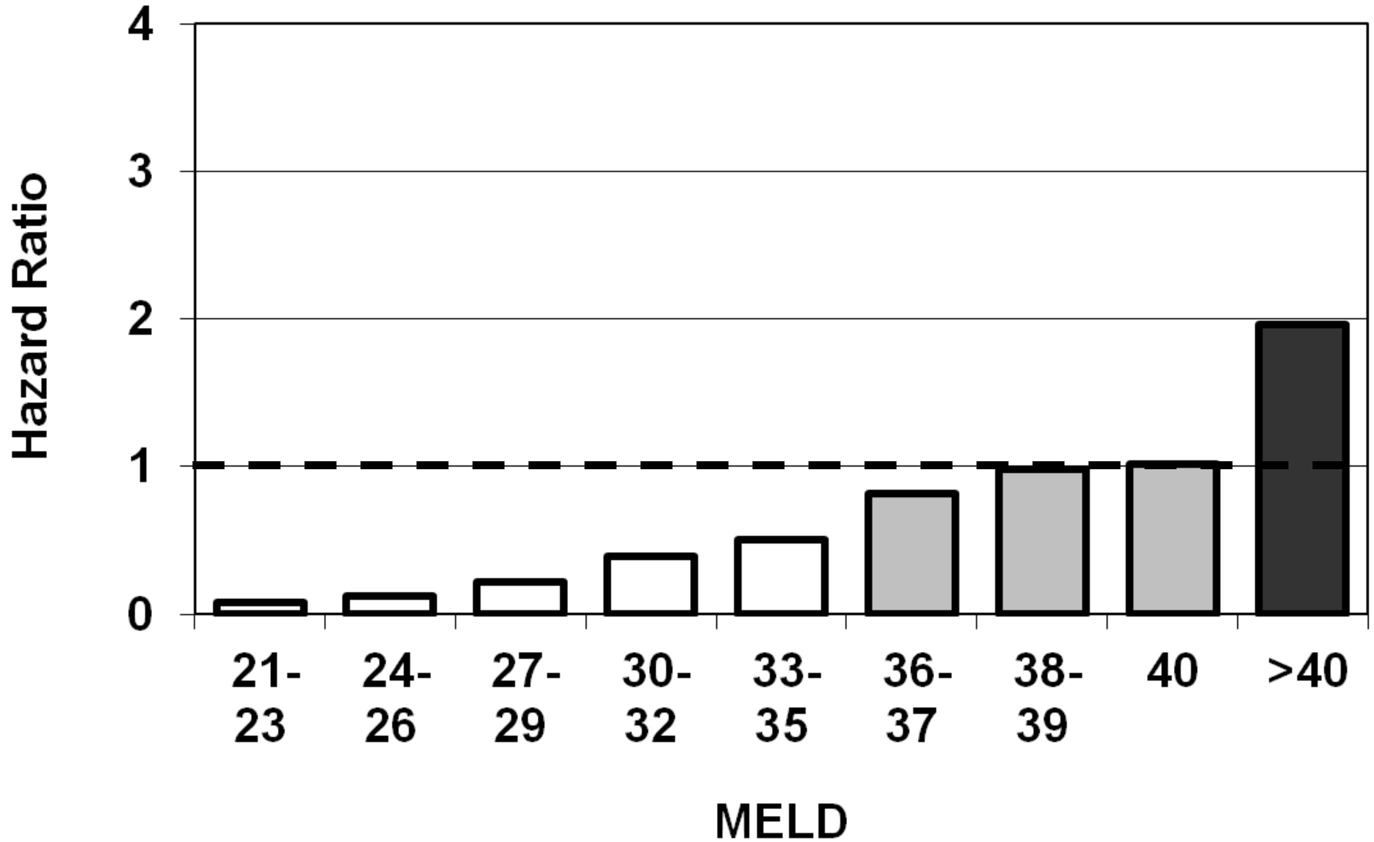
Partly Conditional Analysis



Partly Conditional Analysis



Time-Dependent Analysis



Conclusion

Summary

- Developed partly conditional methods
  - contrast time-dependent factors w.r.t. treatment-free death
  - cross-sections drawn in calendar time
  - accommodate dependent censoring
- Demonstrated that (in absence of liver transplantation) high-MELD is associated with higher mortality than Status-1
- Related work:
  - accommodating non-proportionality
  - treatment effect
  - measures other than hazard ratio

Acknowledgements

- National Institutes of Health (5R01 DK-70869)
- Jack Kalbfleisch; Min Zhang
- Scientific Registry of Transplant Recipients (SRTR)
- University of Michigan Kidney Epidemiology and Cost Center (KECC)
- Arbor Research Collaborative for Health

Reference

Gong, Q. and Schaubel, D.E. (2013). Partly conditional estimation of the effect of a time-dependent factor in the presence of dependent censoring. *Biometrics*, 69, 338-347.

Thank You!