Threshold Regression and Connections with the PH Model

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Outline

- The Cox model is widely used in analyzing time-to-event data. It requires, however, the proportional hazards (PH) assumption.
- Threshold regression (TR) is an alternative model without the PH assumption.
- Brief introduction of the TR model.
- Extensions
- Connections between TR and PH models

A non-proportional hazard example:

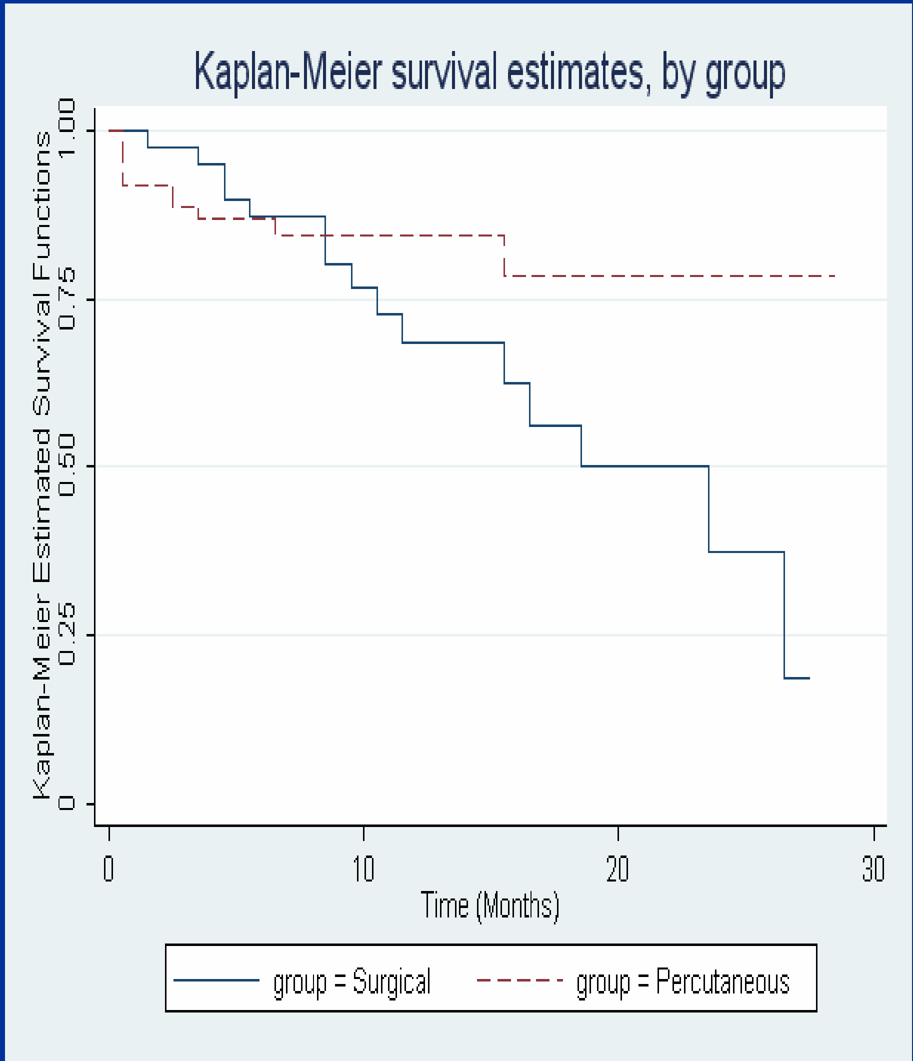
Time to infection of kidney dialysis patients with different catheterization procedures

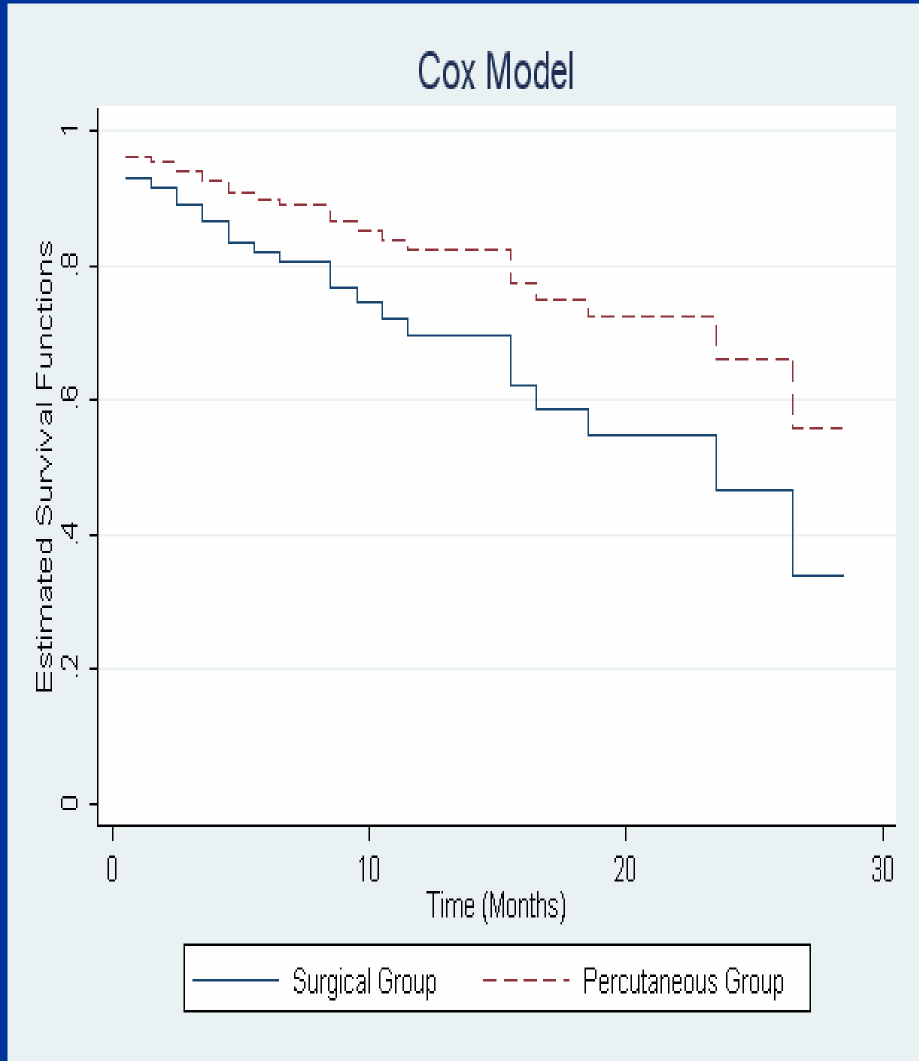
(Nahman *et al* 1992, Klein & Moesberger 2003)

- Surgical group: 43 patients utilized a surgically placed catheter
- Percutaneous group: 76 patients utilized a percutaneous placement of their catheter

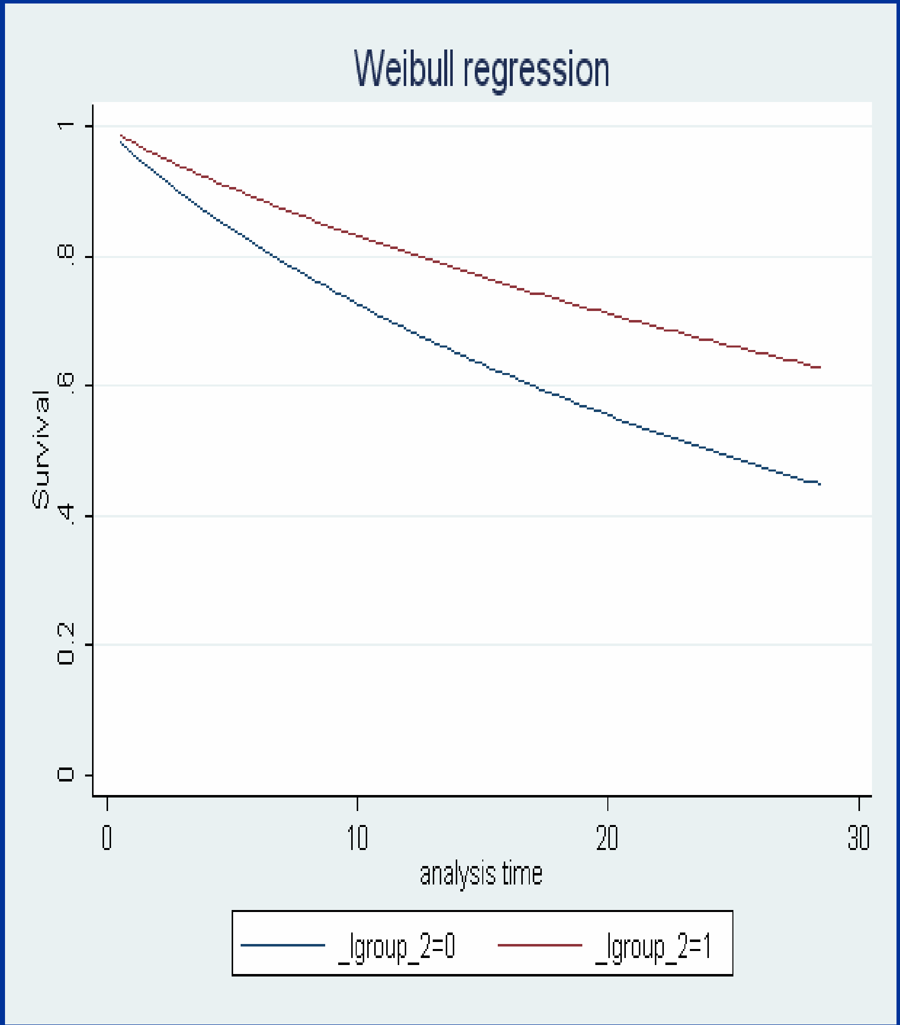
The event time is defined by the time to cutaneous exit-site infection.

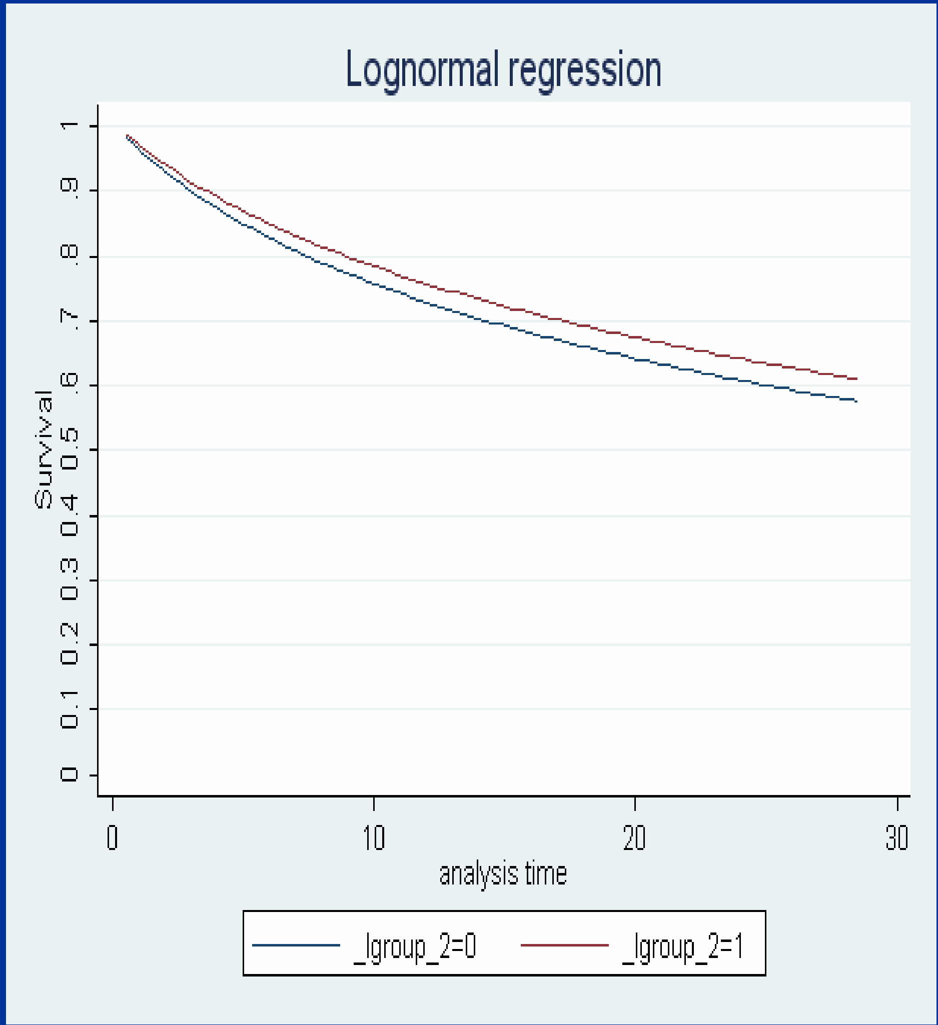
Kaplan-Meier Estimate versus PH Cox Model



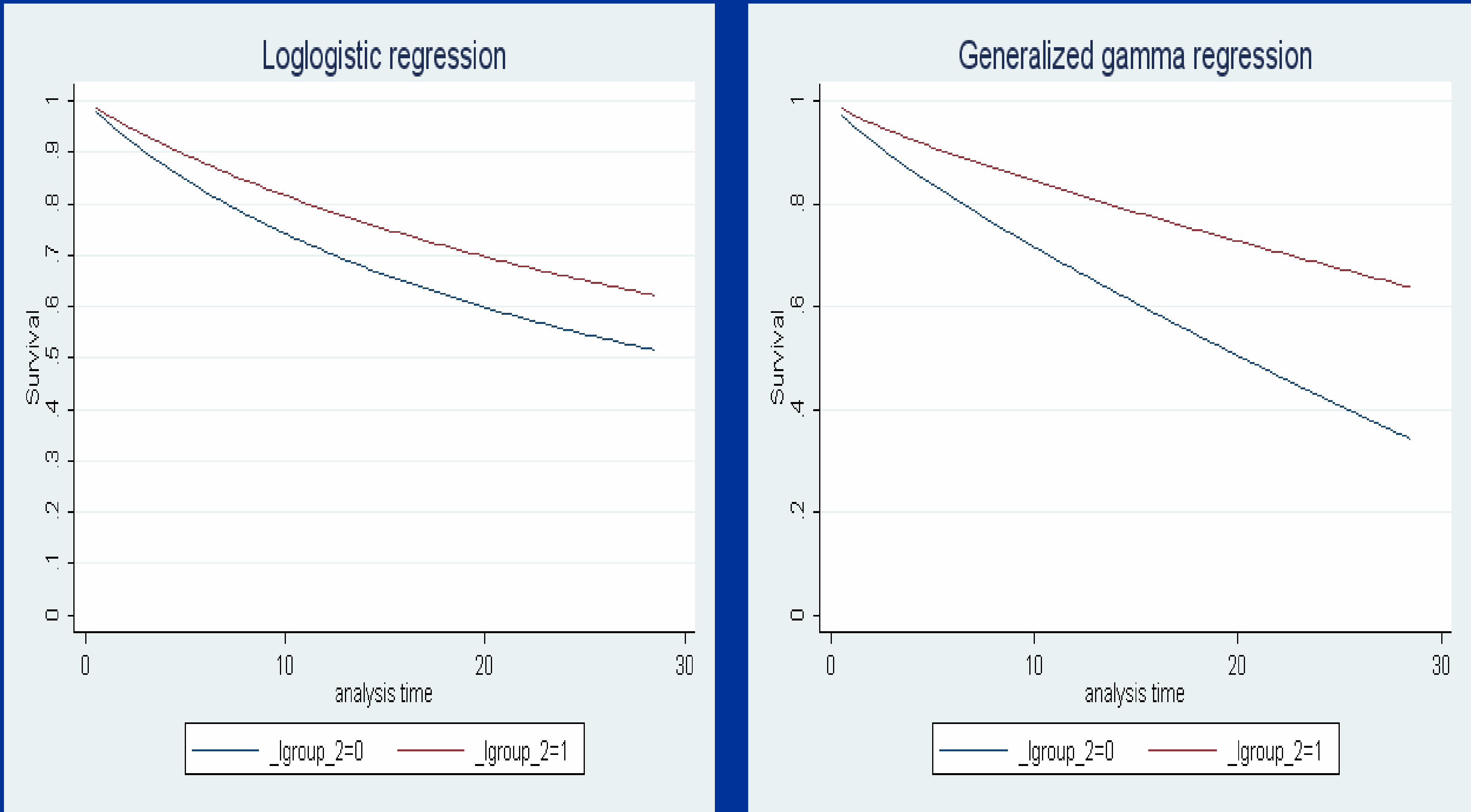


Weibull versus Lognormal

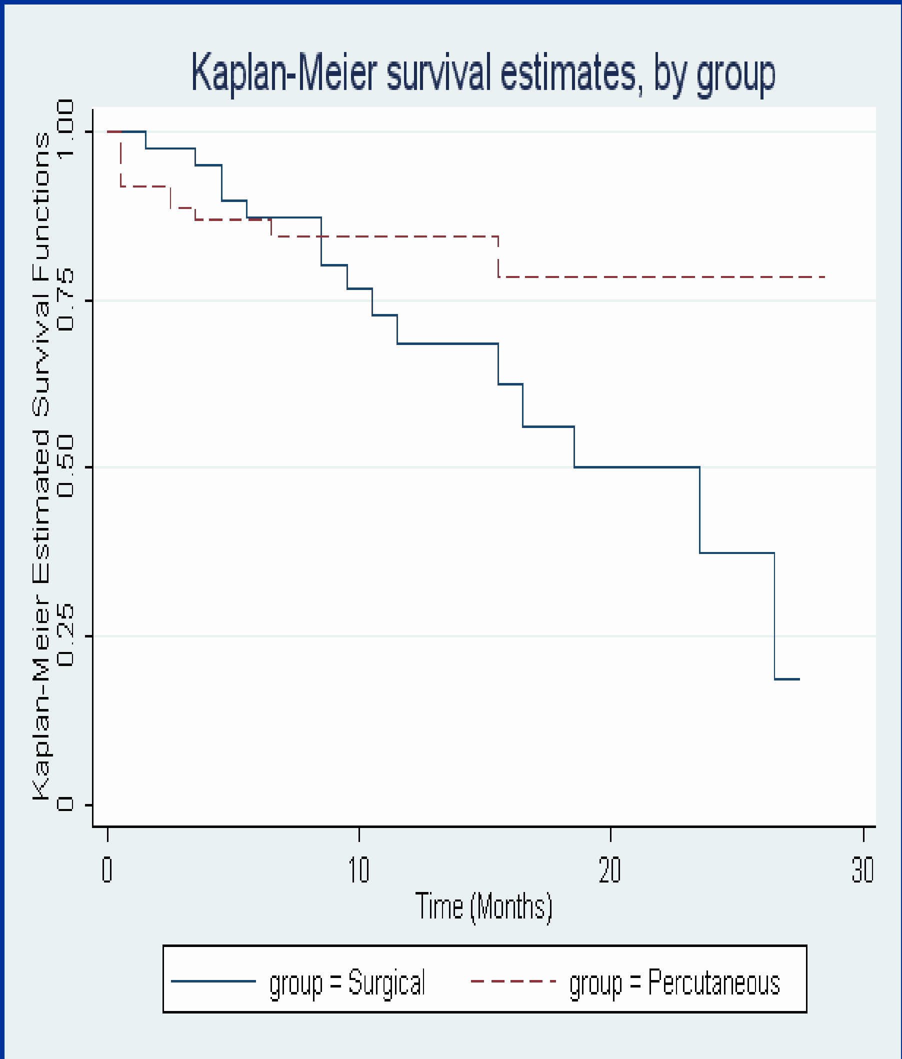


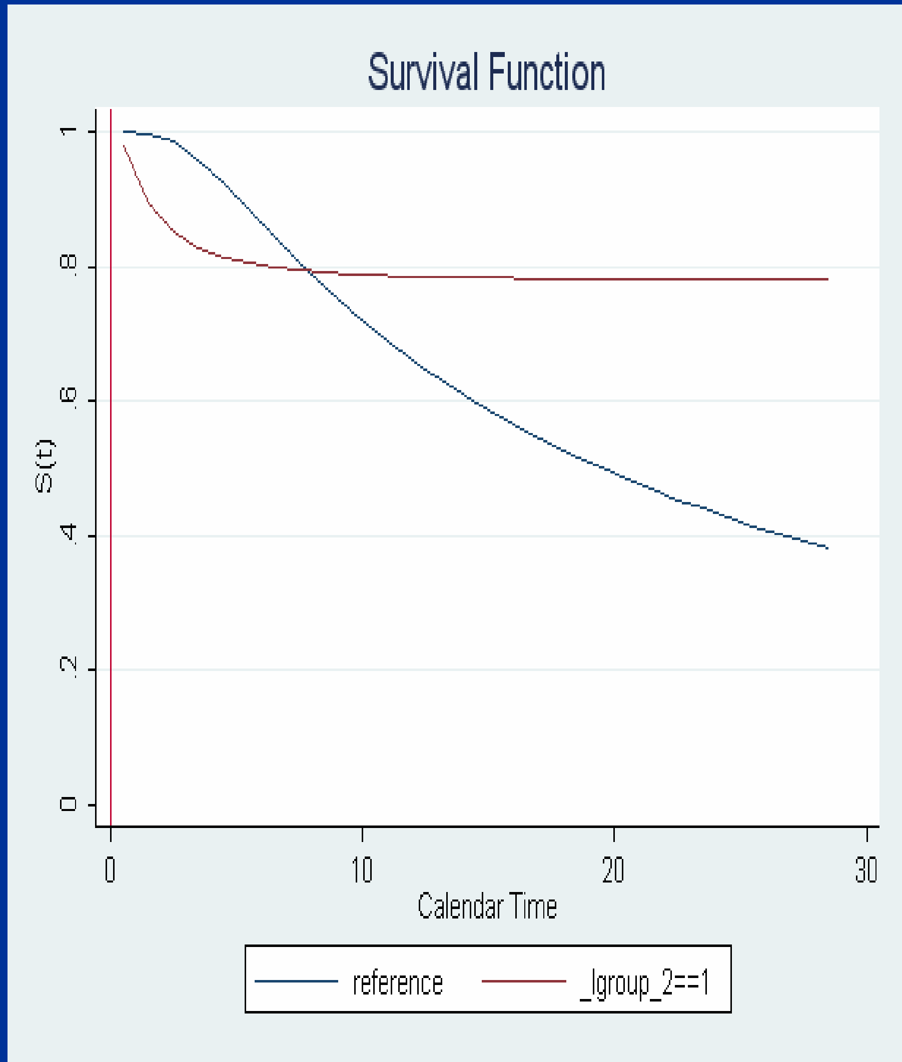


Loglogistic versus Gamma



Kaplan-Meier Estimate versus Threshold Regression Model





Threshold Regression is based on **First-hitting-time Methodology :**

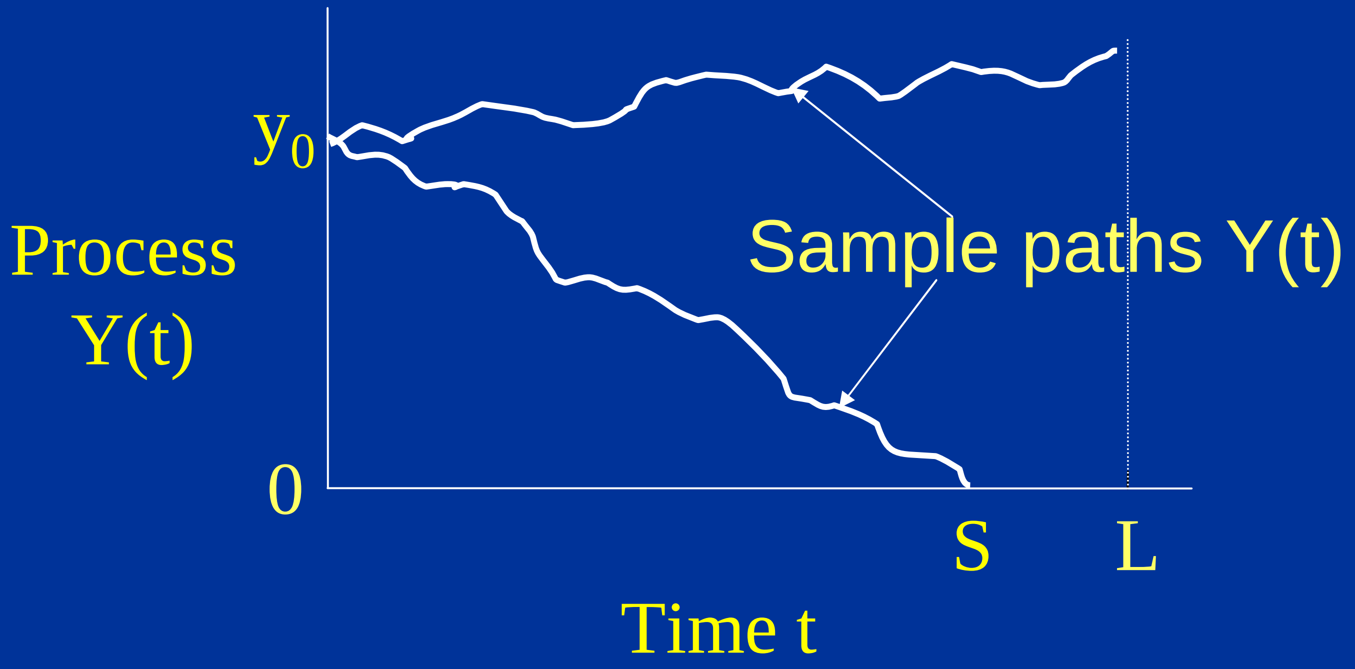
- Example: Engineering
  Equipment fails when its cumulative wear first reaches a failure threshold.

- Example: Health and Medicine
  A patient dies of heart disease when condition of the heart deteriorates to a critical state.

- Example: Social Sciences
  Divorce occurs when tensions in a marriage reach a breaking point.

A review article:

Modeling Event Times by Stochastic Process Reaching a Boundary (Lee & Whitmore 2006, *Statistical Sciences*)



Two sample paths of a stochastic process of interest:

(1) One path experiences 'failure' at first hitting time S

(2) One path is 'surviving' at end of follow up at time L

First Hitting Time (FHT) Models

{Y(t)} : **the stochastic process of interest**

B **:** the threshold or boundary set

First hitting time S defined by

$$S = \inf \{ t : Y(t) \in B \}$$

Parameters for the FHT Model

Model parameters for a latent process $Y(t)$:

- Process parameters: $\theta = (\mu, \sigma^2)$, where μ is the mean drift and σ^2 is the variance

- Baseline level of process: $Y(0) = y_0$

- Because Y(t) is latent, we set $\sigma^2 = 1$.

Likelihood Inference for the FHT Model

The likelihood contribution of each sample subject is as follows.

- If the subject fails at S=s:

$$f\ (s \mid y_0, \mu) = \ \ \Pr\ [\text{ first-hitting-time in } (s, s+ds)\ ]$$

- If the subject survives beyond time *L*:

$$1- F\ (L \mid y_0\ , \mu)\ \ =\ \ \Pr\ [\text{ no first-hitting-time before } L\ ]$$

$$\ln L(\theta, x_0) = \sum_{i=1}^{n} \left\{ d_i \ln f\left(t_i \middle| \theta, x_0\right) + (1 - d_i) \ln \overline{F}\left(t_i \middle| \theta, x_0\right) \right\}.$$

where

d_i is the failure indicator for subject i

t_i is a censored survival time $(t_i = s_i$ if subject i fails$)$

f and $\overline{F}$ denote the FHT p.d.f and complementary c.d.f.

Threshold Regression

Users may choose different link functions for

- **baseline parameter ln Y(0) = g_1 (X1,…, Xp)**
- **drift parameter μ = g_2 (X1,…, Xp)**

Current research includes the following link functions:

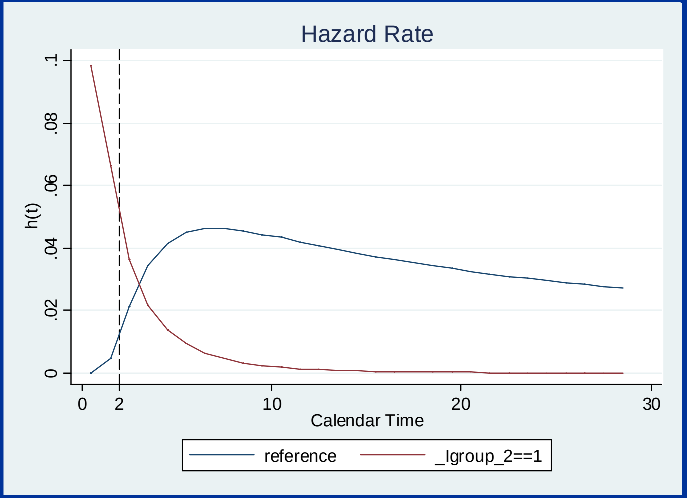
- **Linear combinations of covariates $X_1,\ldots, X_p$**
- **Polynomial combinations of $X_1, \ldots, X_p$**
- **Regression splines**
- **Penalized regression splines**
- **Random effects**

```
. xi: threg,lny0(i.group) mu(i.group) failure(infection) time(time) hr(group) timevalue(20) graph(hz)
i.group           _Igroup_1-2         (naturally coded; _Igroup_1 omitted)

initial:       log likelihood =  -195.3771
alternative:   log likelihood = -148.13505
rescale:       log likelihood = -145.85663
rescale eq:    log likelihood = -136.64417
Iteration 0:   log likelihood = -136.64417
Iteration 1:   log likelihood = -124.66982
Iteration 2:   log likelihood = -116.90825
Iteration 3:   log likelihood = -116.49296
Iteration 4:   log likelihood = -116.49094
Iteration 5:   log likelihood = -116.49094
ml model estimated; type -ml display- to display results

Threshold Regression Estimates                   Number of obs   =        119
                                                 Wald chi2(1)    =      32.20
Log likelihood = -116.49094                      Prob > chi2     =     0.0000

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
lny0         |
   _Igroup_2 |  -1.073099    .189111    -5.67   0.000     -1.44375   -.7024485
       _cons |   1.411294   .1434661     9.84   0.000     1.130106    1.692482
-------------+----------------------------------------------------------------
mu           |
   _Igroup_2 |   .6377025   .1279852     4.98   0.000      .386856    .8885489
       _cons |  -.0959271   .0764877    -1.25   0.210    -.2458402    .0539861
------------------------------------------------------------------------------
Hazard Ratio for Scenario , at Calendar Time  =  20
-----------------------------
         var | Hazard Ratio
-------------+---------------
   _Igroup_2 | .00572720033
-----------------------------
```

Threshold Regression Model can estimate hazard ratios at different time points

timevalue=2

xi: threg,lny0(i.group) mu(i.group) failure(infection) /*
*/ time(time) hr(group) timevalue(2) graph(hz)

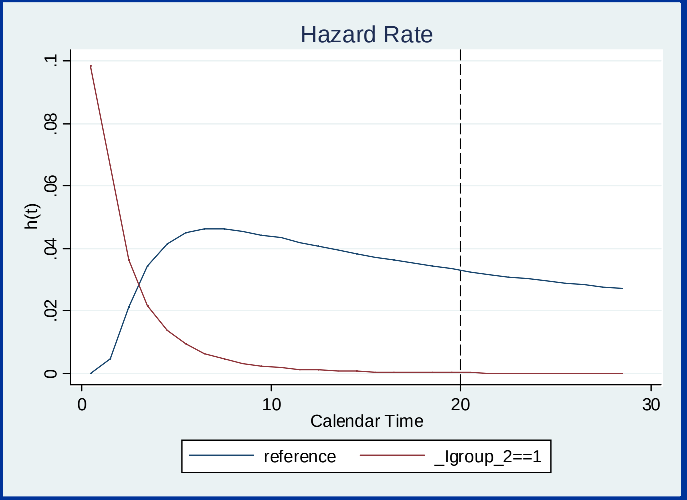


Hazard Ratio for Scenario , at Calendar Time = 2

var	Hazard Ratio
_Igroup_2	3.8025843664

timevalue=20

xi: threg,lny0(i.group) mu(i.group) failure(infection) /*
*/ time(time) hr(group) timevalue(20) graph(hz)



Hazard Ratio for Scenario , at Calendar Time = 20

var	Hazard Ratio
_Igroup_2	.00572720033

Proportional Hazard Cox Model can only estimate a constant hazard ratio

stset time, failure(infection)
xi: stcox i.group

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
_Igroup_2	.5389281	.2145616	-1.55	0.120	.2469704	1.176026

Extensions of Threshold Regression (TR)

1. Process Y(t): **Wiener process, gamma process, etc**

2. Boundary: **straight lines or curves**

3. Time scale: **calendar time, running or analytical time**

Connection of the TR model with the PH model

Most survival distributions are hitting time distributions for stochastic processes (the basic TR model)

Families of PH functions can be generated by varying time scales or boundaries of a TR model

The same family of PH functions can be produced by different TR mode

Benefits of the TR Model

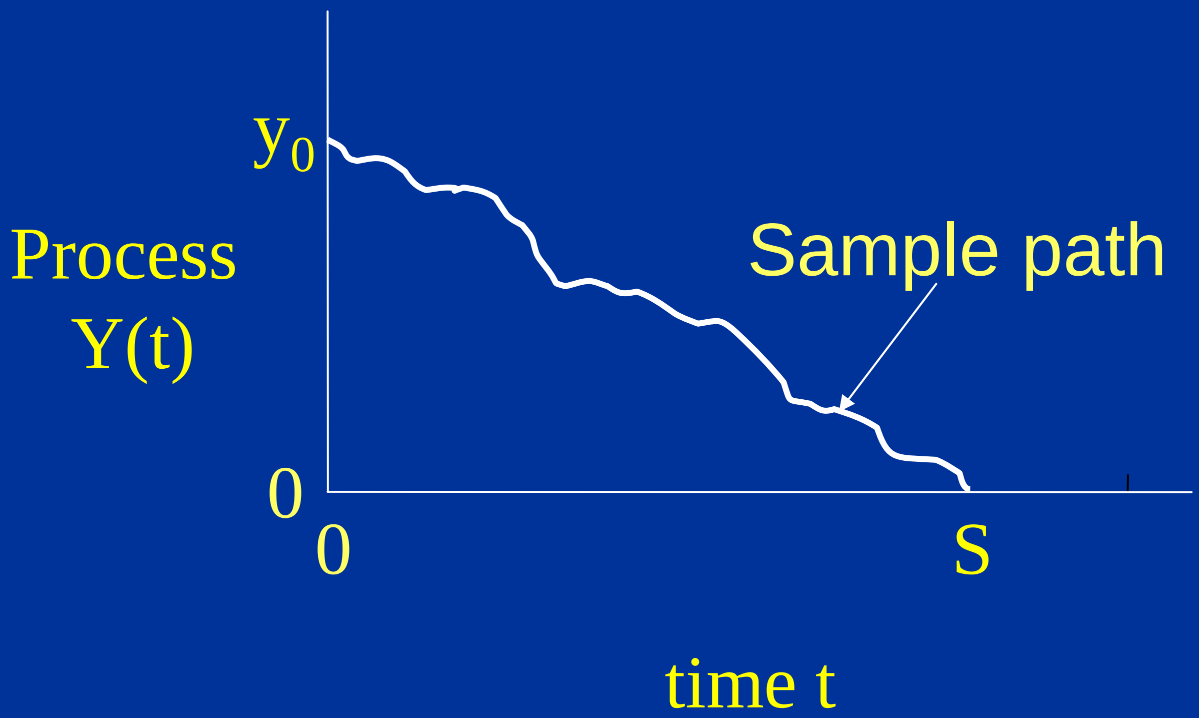
Probing the causal forces behind a hazard function is always a worthwhile endeavor.

A TR model represents more fundamental knowledge about the underlying science than its corresponding PH model.

These insights would deepen the investigator's understanding of the case application.

References

- **Aalen O.O. and Gjessing H.K. (2001). Understanding the shape of the hazard rate: a process point of view. *Statistical Science*, 16: 1-22.**
- **Lawless, J. F. (2003). *Statistical Models and Methods for Lifetime Data*, Second Edition, Wiley.**
- **Lee, M.-L. T. and G. A. Whitmore (2006). Threshold regression for survival analysis: modeling event times by a stochastic process reaching a boundary. *Statistical Sciences.***
- **Aalen O.O., Borgon O, and Gjessing H.K (2008). *Survival and Event History Analysis: A process Point of View*. Springer.**
- **Yu Z, Tu W, Lee M-LT (2009). A Semiparametric Threshold Regression Analysis of Sexually Transmitted Infections in Adolescent Women, *Statistics in Medicine* (in press).**



First hitting time S of a fixed boundary at level zero for a stochastic process of interest Y(t)

First Hitting Time (FHT) Models

- The first hitting time (FHT) model describes many time-to-event applications
- The stochastic process of interest {Y(t)} may represent the latent (unobservable) health status of a subject.
- The threshold constitutes the critical level of the process that triggers the failure event (e.g., symptomatic cancer, death). The event occurs when health status {Y(t)} first decreases to the zero threshold.