Biost 517
Applied Biostatistics I

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Lecture 6:
(Right) Censored Data Descriptives

October 15, 2010

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Lecture Outline

- Graphical Depiction of the Entire Distn
- Methods for Right Censored Data
  - Setting
  - Motivating example
  - Estimation of survivor functions
    - Life table methods
    - Kaplan-Meier estimates

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Graphical Characterizations of an Entire Distribution

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Probability Distribution Function

- For ordered variables, we define
  - Cumulative distribution function (cdf):
    - $F(x) = Pr(X \leq x)$
  - Survivor function:
    - $S(x) = Pr(X > x) = 1 - F(x)$

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Empirical Distribution Function

- Sample cumulative distribution function or survivor function can be used as an estimate
  - (Just treat the sample as if it were the population)
- These functions can sometimes be estimated for censored data (unlike histograms, densities, etc.)

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Empirical CDF: No Censoring

- Definition:

For uncensored data $\{X_1, X_2, \ldots, X_n\}$

Empirical cumulative distribution function

$$\hat{F}(x) = \frac{1}{n}\sum_{i=1}^{n} 1_{[X_i \le x]} = \frac{\#\text{observations} \le \text{x}}{\text{n}}$$

Empirical survivor function

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

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Empirical CDF: Properties

- The empirical cdf assigns probability mass of 1/n at each observation
  - Step function:
    - jumps at each observation
    - level between observations
- The empirical cdf can be graphed for an ordered variable
    - Because we draw conclusions from the spacing of the x-axis, this makes most sense when the measurements are on an interval or ratio scale

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Stata: Empirical CDF

- "`cumul` *var*`, gen(`*Fvar*`) equal`"
  - Generates a new variable named *Fvar* with empirical CDF
  - (Note the need to use the "equal" option to handle ties)
- "`line` *Fvar* `var, sort connect(stairstep)`"
  - Produces empirical CDF (as a step function)
  - (Note the need to use the "sort" option)

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Stata Ex: Age CDF (FEV data)

- `cumul age, gen(Fage) equal`
- `line Fage age, connect(stairstp) sort xtitle("Age (years)") ytitle("Empirical CDF") t1("Empirical CDF for Age in FEV Data")`

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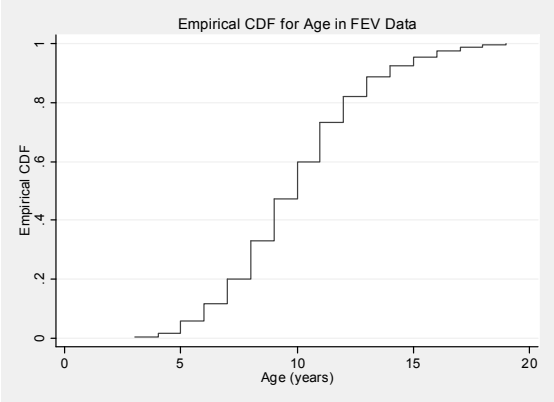
Stata Ex: Age CDF (FEV data)



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Setting for Right Censored Data

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Missing Data

- Ideal:

"Just say no."

- Nancy Reagan

- Real life:

"Missing data happens."

- Bumper sticker (rough translation)

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Missing Data Classifications

- Mechanistic classification
  - Missing completely at random (MCAR)
  - Missing at random (MAR)
    - Missingness can depend on other observed data
  - Missing not at random (MNAR)
- Functional classification
  - Ignorable (MCAR and sometimes MAR)
    - Discarding cases with missing data does not bias results
  - Nonignorable (MNAR and most times MAR)
    - Omitting cases with missing data leads to erroneous conclusions

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Sad Facts of Life

"Bloodsuckers hide beneath my bed"

- *Eyepennies*, Mark Linkous (Sparklehorse)

- Typically, nothing in your data can tell you whether missing data is ignorable or nonignorable
  - You just have to deal with what you worry about

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Censored Data

- Special type of nonignorable missing data
  - The value is known to be in some interval, but the exact value is not always known
  - Commonly arises when measuring time to some event
  - Can also arise when measuring laboratory values due to nondetectable levels or saturation of the device

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Types of Censored Data

- Right censoring:
  - For some observations it is only known that the true value exceeds some threshold
- Left censoring:
  - For some observations it is only known that the true value is below some threshold
- Interval censoring:
  - For some observations it is only known that the true value is between some thresholds

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Example: Setting

- A clinical trial of aspirin in prevention of cardiovascular mortality
  - 10,000 subjects are randomized equally to receive either aspirin or placebo
  - Subjects are randomized over a three year period
  - Subjects are followed for fatal events for an additional three year period following accrual of the last subject

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Example: Right Censoring

- Problem:
  - At the end of the clinical trial, some subjects have been observed to die
    - True time to death is known for these subjects
  - At the end of the clinical trial, most subjects are likely to be still alive
    - Death times of these subjects are only known to be longer than the observation time
    - "(Right) Censored observations"

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Example: Wrong Approach

- Cannot ignore censored data
  - These are our treatment successes
  - If we throw these cases out of the dataset, we will underestimate the probability of longer survival

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Example: Bad Solution #1

- Cannot just treat as binary (live/die) data
  - Potential time of follow-up (censoring time) differs across subjects
    - Administrative censoring (alive at time of analysis)
    - Loss to follow-up due to adverse events
  - Confounding vs loss of precision
    - Confounding if pattern of censoring differs across groups

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Example: Bad Solution #2

- Should not just treat as binary (live/die) data at time of earliest censoring
  - May not answer the scientific question
    - Detecting short term versus long term effects
  - Statistically less efficient

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Right Censored Data

- Notation:

Unobserved:

True times to event: $\{T_1^0, T_2^0, \ldots, T_n^0\}$

Censoring Times: $\{C_1, C_2, \ldots, C_n\}$

Observed data:

Observation Times: $T_i = \min(T_i^0, C_i)$

Event indicators: $D_i = \begin{cases} 1 & \text{if } T_i = T_i^0 \\ 0 & \text{otherwise} \end{cases}$

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Motivating Example

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Motivating Example

- Hypothetical study of subject survival
  - Subjects accrued to study and followed until time of analysis
    - Study done at three centers, which started the studies in three successive years
    - Censoring time thus differs across centers

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Data by Date (Real Time)

Staggered study entry by site

Year		Accrual Group A	B	C
1990	On study	100	--	--
	Died	43		
	Surviving	57		
1991	On study	57	100	--
	Died	27	53	
	Surviving	30	47	
1992	On study	30	47	100
	Died	13	22	55
	Surviving	17	25	45

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Data by Study Time

Realign data according to time on study

Year		Accrual Group A	B	C
1	On study	100	100	100
	Died	43	53	55
	Surviving	57	47	45
2	On study	57	47	--
	Died	27	22	
	Surviving	30	25	
3	On study	30	--	--
	Died	13		
	Surviving	17		

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Combined Data

Year		Accrual Group A	B	C	Combined
1	On study	100	100	100	300
	Died	43	53	55	151
	Surviving	57	47	45	149
2	On study	57	47	--	104
	Died	27	22		49
	Surviving	30	25		55
3	On study	30	--	--	30
	Died	13			13
	Surviving	17			17

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Problem Posed by Missing Data

- Sampling scheme causes (informative) missing data
  - Potentially, we might want to estimate three year survival probabilities
  - Different centers contribute information for varying amounts of time
    - One year survival can be estimated at A, B, C
    - Two year survival can be estimated at A, B
    - Three year survival can be estimated at A

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Possible Remedies

- WRONG: Ignore missing
  - E.g., 17 of 300 subjects alive at three years
- RIGHT BUT WRONG QUESTION: Use data only up to earliest censoring time
  - E.g., 149 of 300 subjects alive at one year
- RIGHT BUT INEFFICIENT: Use only center A
  - E.g., 17 of 100 subjects alive at three years

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Best Approach

- RIGHT AND EFFICIENT
  - Use all available data to estimate that portion of survival for which it is informative
    - Use Centers A, B, and C to estimate one year survival
    - Use Centers A and B to estimate proportion of one-year survivors who survive to two years
    - Use Center A to estimate proportion of two-year survivors who survive to three years

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Theoretical Basis for Approach

- Properties of probabilities
  - Probability of event A and B occurring is product of
    - Probability that A occurs when B has occurred
    - Probability that B has occurred

$$\Pr(A \cap B) = \Pr(A \mid B) \times \Pr(B)$$

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Application of Theory to Survival

- For times $T_1 < T_2$, probability of surviving beyond time T_2 is the product of
  - Probability of surviving beyond time T_2 given survival beyond time T_1, and
  - Probability of surviving beyond time T_1

$$\text{For } t_0 \le t_1 \le t_2 \le \cdots \le t_k$$
$$\Pr(T^0 \ge t_j) = \Pr(T^0 \ge t_j \cap T^0 \ge t_{j-1})$$
$$= \Pr(T^0 \ge t_j \mid T^0 \ge t_{j-1}) \Pr(T^0 \ge t_{j-1})$$

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Estimate Conditional Survival

- Condition on surviving up until the start of the time interval
  - Denominator is number of subjects at start of interval
  - Numerator is deaths during the interval
- Requirement for validity
  - Subjects available at the start of each time interval are a random sample of the population surviving to that time
    - "Missing at Random" (MAR)
    - "Noninformative censoring"

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Estimate Survival Probability

- Estimate probability of survival at the endpoint of each time interval
  - Multiply the conditional probabilities for all intervals prior to the time point of interest

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Application to Example

- Within interval conditional probabilities
  - Use A, B, C to estimate $Pr\ (T^0 \geq 1)$
  - Use A, B to estimate $Pr\ (T^0 \geq 2 \mid T^0 \geq 1)$
  - Use A to estimate $Pr\ (T^0 \geq 3 \mid T^0 \geq 2)$
- Multiply to obtain unconditional cumulative survival
  - $Pr\ (T^0 \geq 1)$
  - $Pr\ (T^0 \geq 2) = Pr\ (T^0 \geq 2 \mid T^0 \geq 1)\ Pr\ (T^0 \geq 1)$
  - $Pr\ (T^0 \geq 3) = Pr\ (T^0 \geq 3 \mid T^0 \geq 2)\ Pr(T^0 \geq 2)$

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Motivating Example Results

Survival Probabilities

Yr	Combined	Each Year	Cumulative
1	On study 300		
	Died 151		
	Surviving 149	149/300 = 49.67%	49.67%
2	On study 104		
	Died 49		
	Surviving 55	55/104 = 52.88%	.4967*.5288 = 26.27%
3	On study 30		
	Died 13		
	Surviving 17	17/ 30 = 56.67%	.2627*.5667 = 14.88%

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Estimation of Survivor Functions

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Noninformative Censoring

- When estimating survivor functions using censored data:
  - Censoring must not be informative
    - Censored subjects neither more nor less likely to have an event in the immediate future
  - Censored individuals must be a random sample of those at risk at time of censoring: MAR
    - Missingness depends on time last observed
    - But random among all subjects at that time
  - Later: a random sample from all subjects at risk having similar modeled covariates: MAR
    - Missingness depends on time last observed and some other measured and modeled covariates

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Informative Censoring Examples

- Subjects in a RCT are withdrawn due to treatment failure
  - (likely they would die sooner than those remaining)
- Subjects in a RCT in a fatal condition are lost to follow up when they go on vacation
  - (likely they are healthier than those remaining)
- Leukemia patients in a RCT of bone marrow transplantation are censored if they die of infections rather than dying of cancer
  - (they might have had a more effective regimen to wipe out existing cancer)

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Detecting Informative Censoring

- As a general rule it is impossible to use the data to detect informative censoring
- The necessary data is almost certainly missing in the data set
- In some cases, it is impossible to ever observe the missing data: “Competing Risks”
  - Nonfelines can only die once
  - We cannot observe whether subjects dying of one cause are more or less likely to die of another if we cure them of the first cause

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Life Table Methods

- In the actuarial (e.g., insurance) setting
  - The time intervals are often chosen by years, decades, etc.
  - The data are presented for each year as
    - N_j: Number of subjects at risk at start of interval
    - C_j: Number censored during interval (these will contribute half a person)
    - D_j: Number of events in interval

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Life Table Methods: Notation

- Number at risk, censored, failed in each interval

$$\begin{aligned}&\text{Time interval:} && (t_{j-1}, t_j]\\ &\text{Number at risk:} && N_j\\ &\text{Number censored:} && C_j\\ &\text{Number of events:} && D_j\end{aligned}$$

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Life Table Methods: Formula

- Computation of probability of survival

$$\text{Conditional probability of survival in interval:}$$

$$\Pr\left(T^0 \geq t_j \mid T^0 \geq t_{j-1}\right) = 1 - \frac{D_j}{N_j - 0.5 \times C_j}$$

$$\text{Cumulative probability of survival:}$$

$$\Pr\left(T^0 \geq t_j\right) = \Pr\left(T^0 \geq t_j \mid T^0 \geq t_{j-1}\right)\Pr\left(T^0 \geq t_{j-1}\right)$$

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Kaplan-Meier Estimates

- Kaplan-Meier (Product Limit) Estimates
- With more precisely measured individual data
  - The time intervals are defined by unique observation times
  - The data are presented for each year as
    - N_j: Number of subjects at risk at start of interval
    - D_j: Number of events at end of interval
    - (Note no censoring or events during interval by definition)
    - (Note also that for ties, censoring occurs after deaths)

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Kaplan-Meier Notation

- Definition of intervals, number at risk, failures

Ordered distinct observation times :

$$t_1 \le t_2 \le \cdots \le t_k$$

Time interval : $(t_{j-1}, t_j]$

Number at risk at t_j : N_j

Number of events at t_j : D_j

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Kaplan-Meier Hazard Estimates

- Computation of hazard and conditional probability of survival in interval

Hazard for event in interval : $\frac{D_j}{N_j}$

Conditional probability of survival in interval :

$$\Pr\left(T^0 \ge t_j \mid T^0 \ge t_{j-1}\right) = 1 - \frac{D_j}{N_j}$$

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Kaplan-Meier Survival Estimate

- Estimating survival probability

S(t) = Pr (T^0 > t)

Cumulative probability of survival :

$$\Pr\left(T^0 > t_j\right) = \Pr\left(T^0 > t_j \mid T^0 > t_{j-1}\right)\Pr\left(T^0 > t_{j-1}\right)$$

$$\hat{S}\left(t_j\right) = \left(1 - \frac{D_j}{N_j}\right) \times \left(1 - \frac{D_{j-1}}{N_{j-1}}\right) \times \cdots \times \left(1 - \frac{D_1}{N_1}\right)$$

$$= \prod_{i=1}^{j}\left(1 - \frac{D_i}{N_i}\right)$$

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If Last Observation Censored

- For an interval which ends in a censored observation with no observed events, the conditional probability of surviving within the interval is 1.
- Note also that if the largest observation time is censored, the KM (PLE) survivor function never goes to zero
  - We generally regard the KM (PLE) survivor function to be undefined for times beyond the largest observation time in this situation

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Kaplan-Meier Properties

- The KM (PLE) survivor functions can be shown to be
  - Consistent: As sample sizes go to infinity, they estimate the true value
  - Nonparametric maximum likelihood estimates
    - But usual asymptotic (large sample) theory for regular, parametric MLE's does not apply
    - Asymptotic (large sample) normal distribution for estimates was established differently

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Other Derivations of KM

- The KM (PLE) survivor functions can also be derived as the
  - Self-consistent estimator
    - (see Miller, Survival Analysis)
  - "Redistribute to the right" estimator

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Redistribute to the Right

- Basic idea
  - Recall the empirical cdf assigns probability 1/n to each observation
  - A censored observation should be equally likely to have event time like any of the remaining uncensored observations
    - Recursively redistribute the mass of each censored observation among the subjects remaining at risk

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Ex: Redistribute to the Right

- Data: 1, 3, 4*, 5, 7*, 9, 10
  - (asterisk means censored)
- Initially: each point has mass 1/7
- Determine probability of events at earliest observed (uncensored) event times
  - Pr ($T^0 = 1$) = 1/7
  - Pr ($T^0 = 3$) = 1/7

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Ex: Redistribute to the Right

- Censored observation at 4
  - Divide the mass at 4 equally among the remaining subjects at risk
    - Now mass of 1/7 + 1/28 = 5/28 for each of 5, 7, 9, 10
- Determine probability of events at next observed (uncensored) event times
  - Pr ($T^0 = 5$) = 5/28

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Ex: Redistribute to the Right

- Censored observation at 7
  - Divide the mass at 7 equally among the remaining subjects at risk
    - Now mass of 5/28 + 5/56 = 15/56 for each of 9, 10
- Determine probability of events at next observed (uncensored) event times
  - Pr ($T^0 = 9$) = 15/56
  - Pr ($T^0 = 10$) = 15/56

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Ex: Redistribute to the Right

Kaplan-Meier estimate of Survival

t	Pr ($T^0 = t$)	Pr ($T^0 > t$)
0		1.000
1	1/ 7 = 0.143	.857
3	1/ 7 = 0.143	.714
4	0.000	.714
5	5/28 = 0.179	.536
7	0.000	.536
9	15/56 = 0.268	.268
10	15/56 = 0.268	.000

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Stata: Kaplan-Meier Commands

- First step is declaring data to be of censored survival type
- Potentially three variables may be used
  - Start of interval
    - Assumed to be at time 0 if nothing supplied
  - End of interval
  - Status at end of interval
    - 0 = censored
    - Nonzero = event occurred at end of interval

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Stata: Kaplan-Meier Commands

- Syntax for "setting survival data"
  - "`stset` *`endtime eventind`*`, t0(`*`entrytime`*`)`"
    - *endtime*: name of the variable measuring the time at the end of the interval
    - *eventind* : name of an indicator (0 or 1) variable indicating event status at the end of the interval
    - *entrytime*: name of the variable specifying the time at the start of the interval
      - (does not need to be supplied)
  - "`stset, clear`" resets the data set

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Stata: Kaplan-Meier Commands

- Syntax for getting estimates, plots
  - Plotting survival curves
    - "`sts graph`"
    - "`sts graph, atrisk`"
    - "`sts graph, cens(s)`"
  - Listing survival estimates
    - "`sts list`"
  - Saving survival estimates
    - "`sts gen` *`newvar`* `= s`"

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Example: PSA Data

- PSA data set
  - infile … obstime **str8 inrem** using psa.txt
  - g relapse = 0
  - replace relapse = 1 if inrem=="no"
  - stset obstime relapse
  - sts graph, xtitle("Time from Treatment (mos)")
  - sts list
  - sts gen estremt = s

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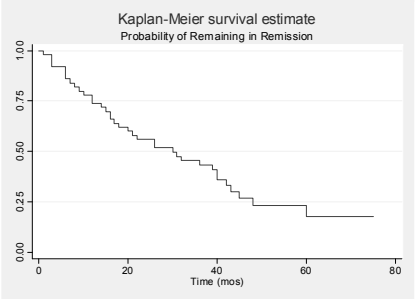
Example: KM Graph

- sts graph, xtitle("Time (mos)") t1("Probability of Remaining in Remission")



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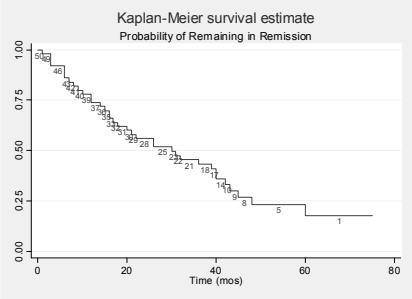
Example: KM Graph

- sts graph, atrisk xtitle("Time (mos)") t1("Probability of Remaining in Remission")



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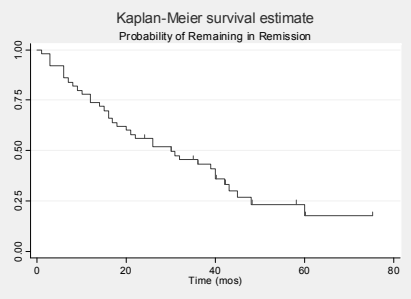
Example: KM Graph

- sts graph, cens(s) xtitle("Time (mos)") t1("Probability of Remaining in Remission")



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Example: KM Listing

- sts list

Time	Beg. Total	Net Fail	Net Lost	Survivor Function	Std. Error	[95% Conf.	Int.]
1	50	1	0	0.9800	0.0198	0.8664	0.9972
3	49	3	0	0.9200	0.0384	0.8007	0.9692
6	46	3	0	0.8600	0.0491	0.7286	0.9307
7	43	1	0	0.8400	0.0518	0.7054	0.9166
8	42	1	0	0.8200	0.0543	0.6826	0.9020
9	41	1	0	0.8000	0.0566	0.6602	0.8870
10	40	1	0	0.7800	0.0586	0.6381	0.8716
12	39	2	0	0.7400	0.0620	0.5947	0.8399
14	37	1	0	0.7200	0.0635	0.5735	0.8236
15	36	1	0	0.7000	0.0648	0.5525	0.8070
16	35	2	0	0.6600	0.0670	0.5114	0.7730
17	33	1	0	0.6400	0.0679	0.4911	0.7557

--more--

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Example: KM Listing

- sts list, at(24 27 30 33 36)

Time	Beg. Total	Fail	Survivor Function	Std. Error	[95% Conf.	Int.]
24	28	22	0.5600	0.0702	0.4124	0.6842
27	27	2	0.5185	0.0709	0.3725	0.6461
30	25	1	0.4978	0.0710	0.3529	0.6267
33	22	2	0.4545	0.0711	0.3124	0.5860
36	20	1	0.4318	0.0711	0.2913	0.5645

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