Delfini Pearls

Analyzing Results: Time-To-Event Analysis—Kaplan Meier Survival Curves & Hazard Ratios

Healthcare Information & Decision Equation: <u>Information➔Decision ➔Action➔Outcome</u>
Is it true➔Is it useful ➔Is it usable?

Survival Curves measure the length of time to an outcome of interest, (e.g., time-to-pregnancy, time-to-cancer progression). **Synonyms**: Life table analysis and survival analysis which refers to the method regardless of whether survival is the outcome. Kaplan-Meier methodology is the most commonly used survival analysis in healthcare.

- Because a bias could result from subjects spending different amounts of time in the study (e.g., a subject being enrolled near the end of the study), "censoring" is almost always utilized in time-to-event analysis.

Censoring is the practice of removing the patient from the curve at a specific point in time. Examples of censoring:
1) Patients who don't experience the event (administrative censoring or right censoring and which is considered acceptable); and , 2) Other reasons determined by the investigators and called "censoring rules" (non-administrative censoring such as lost to follow-up or dying before a non-mortality outcome of interest is reached). These latter censoring rules should be evaluated for potential bias.

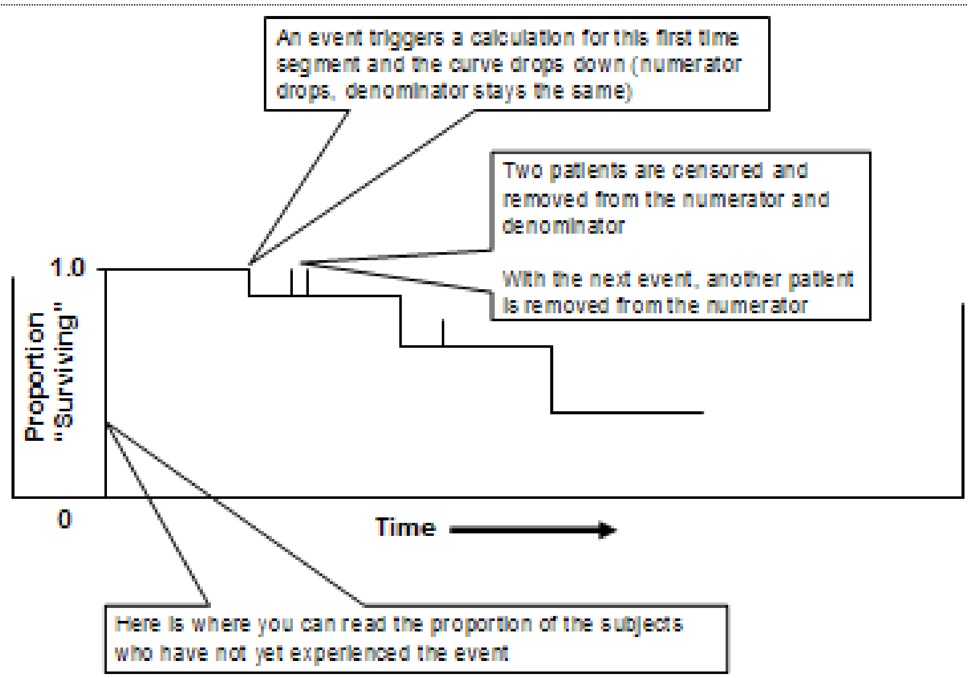
- Censored data is assumed to occur randomly (may not be a valid assumption).
- Censoring reduces sample size which may reduce reliability of results.
- Censored subjects may differ from subjects remaining in the study and may create bias.

Creation of the curve involves computing the number of people who experience the outcome at a certain time point, divided by the number of people who were still in the study at that time taking into account the censored patients.

- When a patient's data are censored, the number of patients "at risk" (numerator and denominator decrease) is reduced by one when the calculation for that time segment is performed. When a patient experiences the outcome, the "survival" for the interval is calculated (numerator decreases) according to the number remaining at risk at the time of event. (Denominator is decreased for the next interval.)

Hazards, Hazard Rates and Hazard Ratios

- A hazard is an incidence rate. A hazard rate (slope of the survival curve) is a measure of how rapidly subjects are experiencing the endpoint. A hazard ratio (calculated using Cox proportional hazards model) approximates the relative risk in the intervention group compared to the control group and is assumed to remain constant (may be an invalid assumption). Median survival is usually presented with hazard ratios. Example: With an HR of 2, a patient who has not yet experienced the outcome at a certain time has twice the chance of experiencing the outcome at the next point in time compared to a subject in the control group.

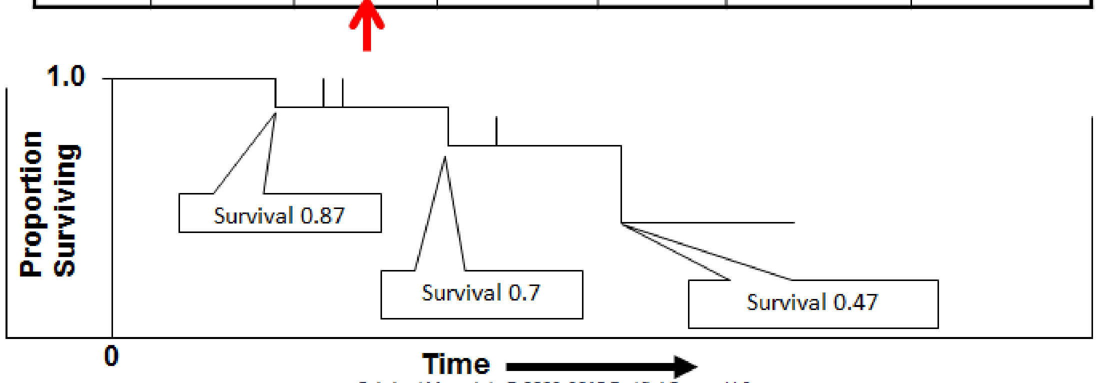


Considerations & Critical Appraisal Issues

- KM models assume on average the likelihood of experiencing an endpoint is the same for early enrolled subjects and subjects enrolled later (may not be valid).
- KM models assume that the likelihood of experiencing an endpoint is the same for censored and non-censored patients (may not be valid).
- The average HR (usual way of reporting HRs) ignores the distribution of events over time.
- Period-specific HRs are also biased in that susceptible subjects are removed over time resulting in a study population that may have different prognostic variables.
- Appraisers need details of censoring—how many subjects censored in each time segment and why; without this information appraisers cannot evaluate the possible impact of censoring or perform sensitivity analyses
- Survival analysis should not be applied to reoccurring rates so need to ensure double-counting does not occur (e.g., composite endpoint of mortality and MI).
- If any data are available at all for each patient in a study, the investigators frequently state that they analyzed the data according to "the Intention-to-Treat (ITT) principle." However, because the patient's future information is effectively removed at the point at which they have been censored, this is technically not ITT analysis, plus there is no imputation of missing values.
- Censoring reduces sample size which reduces reliability.
- Censoring may not occur at random.
- Censoring assumes that subjects lost to follow-up are similar to those who are not lost — they may not be, so amount of loss and loss difference between groups matters.
- Outcomes in completers may be different from what outcomes would have been without data loss (i.e., censoring may result in attrition bias).
- Even without differential loss between the groups overall, a differential loss could occur in prognostic variables.
- Assessing outcomes through models (e.g., Kaplan Meier estimates) has been reported to potentially erroneously misrepresent outcomes by a relative 50% or higher (Lachin: PMID 11018568)

Kaplan Meier Curve

Time Interval	# Subjects Start	Censored	# Died (or other event); always = 1	Subjects in Denom	Subjects Surviving Interval	Cumulative Survival
0-1	8	0	1	8	7/8=0.87	0.87
1-2	7	2	1	5	4/5=0.8	0.87*0.8=0.7
2-3	4	1	1	3	2/3=0.67	0.7*.67 =.47



 14