Healthcare Information & Decision Equation: Information➜Decision ➜Action➜Outcome
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 and related terms**: 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 rules: 1) Patients who don't experience the event (administrative censoring or right censoring and which is necessary); and, 2) Other reasons developed by the investigators (non-administrative censoring such as lost-to-follow-up or protocol violations). These latter censoring rules should be evaluated for potential 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 the **incidence rate**, i.e., the probability of an event rate for an individual who has neither been censored nor experienced an event.
- The **hazard rate** is the slope of a survival curve in each group—a measure of **how rapidly subjects are experiencing the outcome of interest (taking into account that censoring affects the slope).**
- A **hazard ratio** (calculated using Cox proportional hazards model) approximates the **relative risk** of events in groups being studied, based on the event rates in the groups, based on the event rates in the groups, plus accounting for censoring.
- **HR Interpretation**
    - For example, an HR of 2 is usually explained as "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."
    - As the hazard ratio is akin to relative risk: a hazard ratio of .63 would be a 37% relative risk reduction (1-.63), meaning that subjects in the intervention group have a 37% reduced risk of dying compared to the control group within the study time period.
- **…and caveats**
    - However, remember that **censoring is part of HR calculation** which can affect the results.
    - Furthermore, the HR is an average, but distribution of events may be affected by time (i.e., **proportional hazards assumption**.
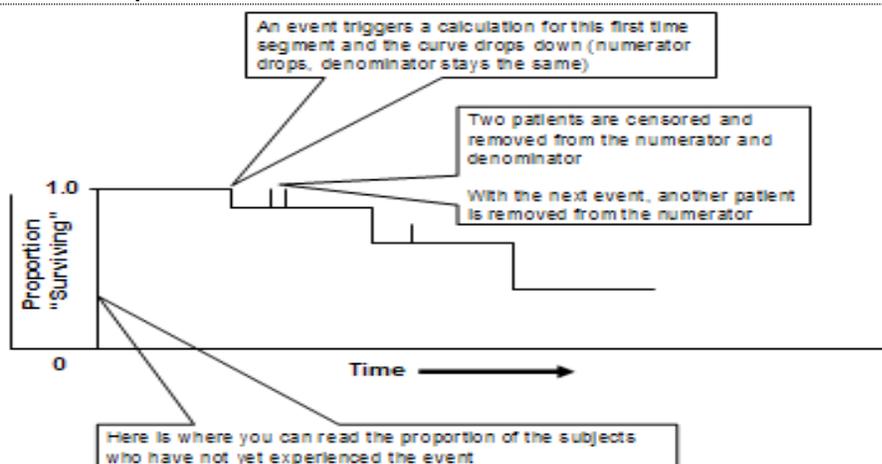
Assumptions & Considerations

The methodology—

· Is prone to certain biases, so the analysis must be critically appraised.
· At best, can be rather confusing and, at best, should probably be taken "impressionistically."

KM Models result in certain assumptions being made about similarities in patients. As examples—

· The likelihood of experiencing an endpoint is the same for subjects (such as early enrolled subjects and those enrolled later or, censored vs not censored), i.e., "proportional hazards assumption" (may not be valid)
· The likelihood of experiencing an endpoint is the same for censored and non-censored patients (may not be valid).
· Censored data is assumed to occur randomly (may not be a valid assumption).
· Censored subjects may differ from subjects remaining in the study and may create bias.
· 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.

Other issues—

1. Censoring reduces sample size which may reduce reliability of results.
2. The average HR (usual way of reporting HRs) ignores the distribution of events over time.
3. 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." Readers should be aware that this is technically not ITT analysis as final values are not imputed for the missing, and censoring other than right censoring otherwise removes data from analysis. However, this implies patients are analyzed as randomized.
4. 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)

Critical Appraisal Issues

· See assumptions and considerations above.
· Non-administrative censoring rules should be evaluated for bias (e.g., censoring subjects who stop taking Rx, are lost to f/u, etc.) may introduce significant bias in completers which may have been different without data loss.
· 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).

Advice. In an otherwise valid study, if randomization and concealment of allocation appear to have been done effectively, and if the only censoring rule is right censoring or non-administrative censoring that you feel fairly confident will not introduce an imbalance between the groups, then you can probably trust the direction of the results. Keep in mind the above, including the HR probably cannot be thought of as exact.

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

Survival 0.87
Survival 0.7
Survival 0.47

Proportion Surviving — 1.0 — 0

Time