MET 2 - Lecture 7:

Survival analysis

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Coming up: BSPH Jahresabschlussfeier- all invited!

BSPH-Jahresabschlussfeier

Friday, 14.6.19 at 17:00

CVK, Lehrgebäude / Forum 3

Introduction

Common clinical and epidemiological research goal:

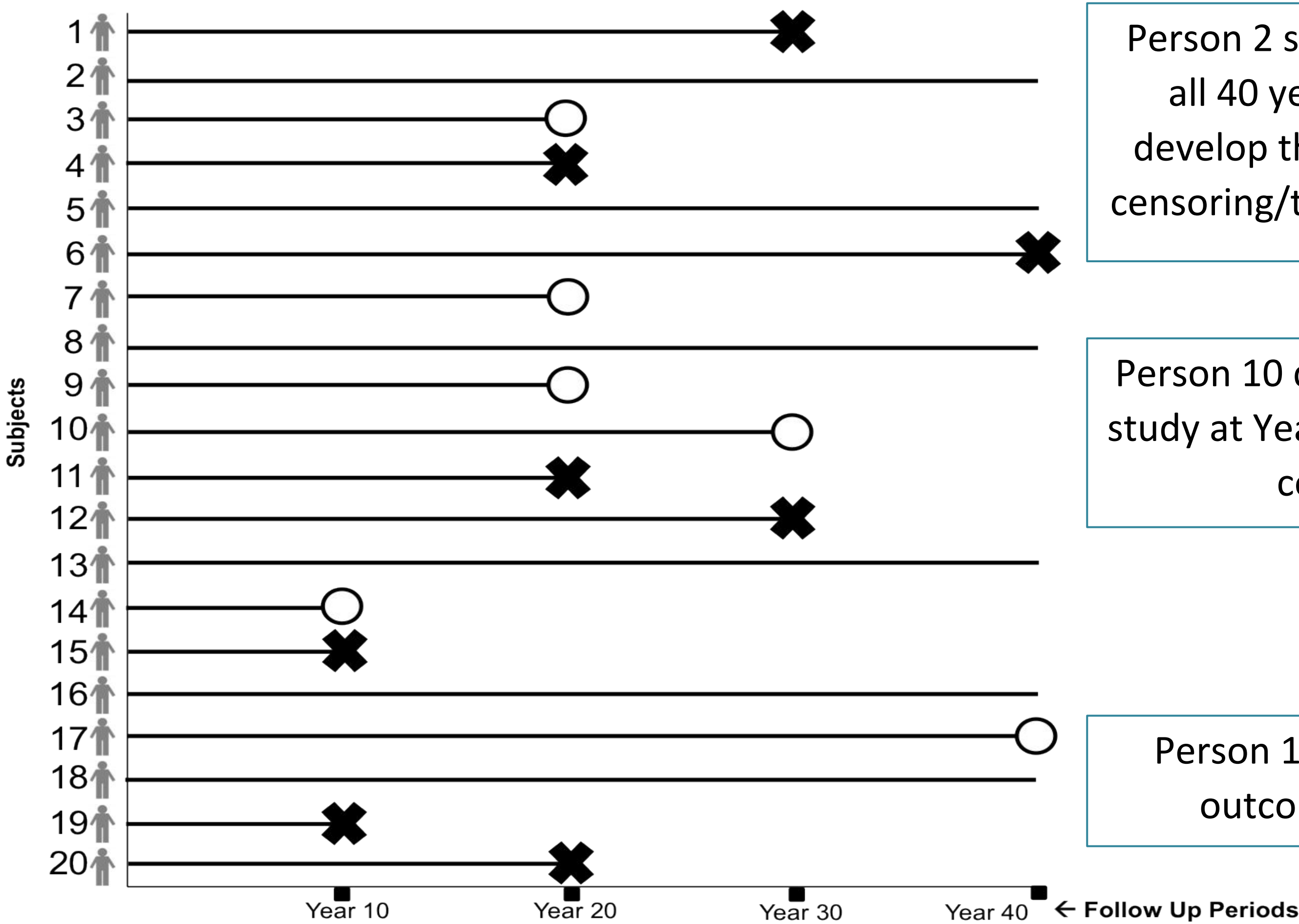
Develop/improve treatments/outcomes and/or

identify possible risk factors

Methods encountered:

- Time-to-event
- Time from beginning of treatment to death
- Time until remission
- Time to a certain stage of disease
- …

Recall… person-time



Person 2 stayed in the study all 40 years and did not develop the outcome (right censoring/terminal censoring)

Person 10 dropped out of the study at Year 30 (intermediate censoring)

Person 19 developed the outcome at Year 10

From Keyes/Galea - Chapter 5

Person-time: needed to calculate incidence rates

- In the K & G book example, everyone started the study at the same time.
- Participants can also enroll in a study at different times
  - Often a combination of both (many at start, additional partic. join later)
- Either way, person-time is calculated by subtracting the start time of the study from the stop time
  - Day 10 - Day 0 = 10 Days or… Day 20-Day 10 = 10 days
  - Can be measured in person-days, person-seconds, person-minutes, etc.
  - Be careful when combining different units (e.g. months + days)!

Kaplan Meier Theatre

This exercise is adapted from a workshop with Thomas A. Gerds and Gerds T. The Kaplan Meier Theatre. *Teaching Statistics*. 2016.

Goals:

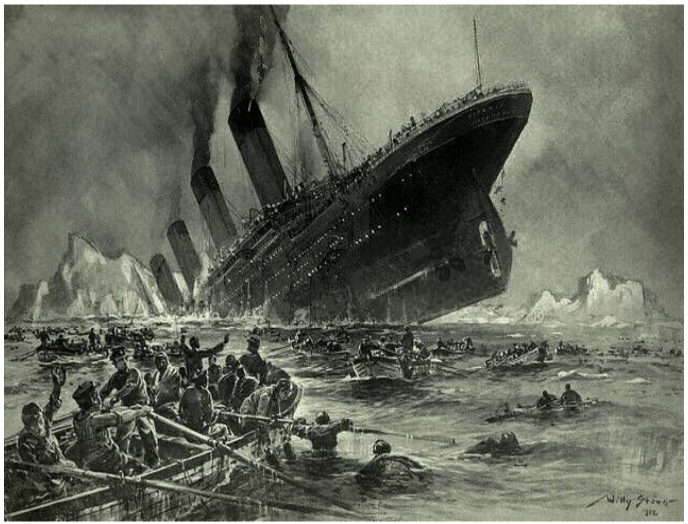
- To gain an intuitive understanding of how the Kaplan-Meier method deals with censored data
- To understand how censoring factors into survival probability
- Understand the limits & interpretation of Kaplan-Meier curves

I need 9 volunteers...

.... Step right up!

Then: https://www.youtube.com/watch?v=BxquiHIALjo

We are passengers aboard the Titanic…
….and it just started to sink!



“Untergang der Titanic” Illustration by Willy Stöwer in “Die Gartenlaube”

- The lifeboats are gone and the water is rising!
- We’ll have to hold our breath and stay afloat; if we can’t, we’ll drown! (=event)
- I decide to conduct one final epidemiological study in my last minutes… (the results were found in a bottle washed up on shore years later...)
- Since the ship is sinking on a slant; passengers hit water at different times

Rules for the theater

- Start of the study: Participants line up on step; tap on shoulder = fall into water (start swimming, record start time)
- Study ends when I call ‘stop’ (i.e. I fall into the water and can’t observe anymore)

Rules for the theater

- Start of the study: Participants line up on step; tap on shoulder = fall into water (start swimming, record down start time)
- Study ends when I call ‘stop’ (i.e. I fall into the water and can’t observe anymore)
- Participants who **cannot** swim to the end, drown (have an event= drowned) and will **raise their hand** at that time
- Participants who **can** swim until ‘stop’ survive
  - (=censoring; we don’t know when they drowned)
- Important: start & stop time (of each individual) must be recorded!

Stopwatch

- http://www.online-stopwatch.com/full-screen-stopwatch/

Did you survive? For how long?

How long could you stay afloat once you hit the water? We will write down the total number of seconds on a…

BLUE sheet if you drowned

=had an event

or a…

WHITE sheet if you survived

=censored

Summary of what we saw

Participant Number	Start time	Stop time	Elapsed time	Censored?
1	0	42	42	0
2	5	80	75	1
3	10	80	70	1
4	13	80	67	1
5	20	71	51	0
6	25	64	39	0
7	30	57	27	0
8	38	80	42	1
9	45	80	35	1

First organize, then analyze!

Please line up at the front of the room according to:

Fewest seconds -------------⟶ Most seconds

(paper color **doesn't** matter!)

We care about **person-time!** How much did you contribute?

Check… did we do it right?

27	35 (C)	39	42	42 (C)	51	67 (C)	70 (C)	75 (C)

Q1: Total amount of person-time contributed by all participants?

Q2: What are the units?

Q3: Does censoring (ie. whether or not a person was censored) have an impact on this calculation?

Check… did we do it right?

27	35 (C)	39	42	42 (C)	51	67 (C)	70 (C)	75 (C)

Total amount of person-time contributed by all participants

=27+35+39+42+42+51+67+70+75 seconds

= 448 person-seconds

- Note: whether the participant had an event or was censored has **no** impact on this calculation!

Create simple risk table with Efron's 'Redistribution to the Right' algorithm (modified life table)

- Each participant is holding a piece of paper indicating their "probability mass"
    - Since there are 9 participants, each piece of paper "weighs" 1/9 (= probability mass)

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive :)

Time contributed to the study

at risk for the event at specified time point

Kaplan-Meier estimator, S(t)

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9				

What happened at 27 seconds?

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1			

Participant #7 (on the farthest left): drowned after 27 seconds

- When participant #7 drowned, all other 8 participants were still in alive and in the study
- What does this mean for the survival probability?...

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1			

Participant #7 (on the farthest left): drowned after 27 seconds

- When participant #7 drowned, all other 8 participants were still in alive and in the study
- What does this mean for the survival probability?

- To visualize, Participant #7, please take your piece of paper (1/9 weight) with you and sit down.

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9

- What does this mean for the survival probability? ….
- Kaplan-Meier estimate of survival at 27 seconds drops from 100% (=1) by 1/9 to 88.9%

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9

When was the next time “something” happened?
How many participants were still in the study up until this time?
What “something” happened?

(let’s add this info to the table)

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8				

Participant #9 was censored (lost to follow up) after 35 seconds

- We assume P#9 drowned later, but we don't know ***when***
- Kaplan-Meier method assumes P#9's survival chances after 35 seconds **are the same** as the remaining 7 participants
  - How to complete the table?

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change

Participant #9 was censored (lost to follow up) after 35 seconds

- We assume P#9 drowned later, but we don't know ***when***
- Kaplan-Meier method assumes P#9's survival chances after 35 seconds **are the same** as the remaining 7 participants

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change

Participant #9 was censored (lost to follow up) after 35 seconds

- We assume P#9 drowned later, but we don't know ***when***
- Kaplan-Meier method assumes P#9's survival chances after 35 seconds **are the same** as the remaining 7 participants
- P#9: Tear your paper into 7 pieces and give a piece to each of the remaining participants (***= redistribution to the right***) and then sit down

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
39	7				

What happened at 39 seconds?

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
39	7	1	0	76.2	0.889–1/9–1/7*1/9

Participant #6: drowned after 39 seconds

- P#6: Please take your papers with you and sit down
- Survival probability drops again by:
  1/9 = own contribution to probability mass (full sheet)
  AND
  1/7 * 1/9 = contribution from participant #9 (one-seventh of P#9's probability mass)

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
39	7	1	0	76.2	0.889–1/9–1/7*1/9
42	6				

What happened at 42 seconds?

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
39	7	1	0	76.2	0.889–1/9–1/7*1/9
42	6	1	1	63.5	0.762–1/9–1/7*1/9

Two things happened at 42s (= a 'tie')!

first, let's handle the event (Breslow method)

First, Participant #1: drowned after 42 seconds

- Survival probability drops by:
  1/9 = own contribution
  AND 1/7 * 1/9 = contribution from participant #9

P#1: Please take your papers with you and sit down

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
39	7	1	0	76.2	0.889–1/9–1/7*1/9
42	6	1	1	63.5	0.762–1/9–1/7*1/9

Also, Participant #8 was censored at 42 seconds

- Again, we assume P#8 drowned later, but we don't know ***when***
- Kaplan-Meier method assumes P#8's survival chances after 42s **are the same** as the remaining 4 participants

P#8: Tear your papers into 4 pieces and give to each of the remaining participants ***(= redistribution to the right)*** & sit down

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
39	7	1	0	76.2	0.889–1/9–1/7*1/9
42	6	1	1	63.5	0.762–1/9–1/7*1/9
51	4				

What happened at 51 seconds?

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
39	7	1	0	76.2	0.889–1/9 – 1/7*1/9
42	6	1	1	63.5	0.762–1/9 – 1/7*1/9
51	4	1	0	47.6	0.635–1/9 – 1/7*1/9 – 1/4*1/9 – 1/4*1/7*1/9

Participant #5: drowned after 51 seconds (take papers and sit down)

- Survival probability drops by:

$$\underbrace{1/9}_{\text{Own contribution}} + \underbrace{1/7\times 1/9}_{\text{from P\#9}} + \underbrace{1/4\times 1/9}_{\text{from P\#8}} + \underbrace{1/4\times 1/7\times 1/9}_{\text{from P\#9 via P\#8}}$$

=15.9%

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
39	7	1	0	76.2	0.889–1/9–1/7*1/9
42	6	1	1	63.5	0.762–1/9–1/7*1/9
51	4	1	0	47.6	0.635–1/9 – 1/7*1/9 – 1/4*1/9 – 1/4*1/7*1/9
67	3				

What happened at 67 seconds?

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
39	7	1	0	76.2	0.889–1/9–1/7*1/9
42	6	1	1	63.5	0.762–1/9–1/7*1/9
51	4	1	0	47.6	0.635–1/9 – 1/7*1/9 – 1/4*1/9 – 1/4*1/7*1/9
67	3	0	1	47.6	no change

Participant #4 is censored at 67 seconds

- Kaplan-Meier method assumes P#4's survival chances after 67s **are the same** as the remaining 2 participants

P#4: Tear all your papers into half and ***redistribute to the right*** & sit down

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
39	7	1	0	76.2	0.889–1/9–1/7*1/9
42	6	1	1	63.5	0.762–1/9–1/7*1/9
51	4	1	0	47.6	0.635–1/9 – 1/7*1/9 – 1/4*1/9 – 1/4*1/7*1/9
67	3	0	1	47.6	no change
70	2				

What happened at 70 seconds?

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
39	7	1	0	76.2	0.889–1/9–1/7*1/9
42	6	1	1	63.5	0.762–1/9–1/7*1/9
51	4	1	0	47.6	0.635–1/9 – 1/7*1/9 – 1/4*1/9 – 1/4*1/7*1/9
67	3	0	1	47.6	no change
70	2	0	1	47.6	no change

Participant #3 is censored at 70 seconds

- Kaplan-Meier method assumes P#3's survival chances after 70 seconds **are the same** as the remaining 1 participant

P#3: Redistribute all your papers to the person on your right & sit down

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
39	7	1	0	76.2	0.889–1/9–1/7*1/9
42	6	1	1	63.5	0.762–1/9–1/7*1/9
51	4	1	0	47.6	0.635–1/9 – 1/7*1/9 – 1/4*1/9 – 1/4*1/7*1/9
67	3	0	1	47.6	no change
70	2	0	1	47.6	no change
75	1				

What happened at 75 seconds?

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
39	7	1	0	76.2	0.889–1/9–1/7*1/9
42	6	1	1	63.5	0.762–1/9–1/7*1/9
51	4	1	0	47.6	0.635–1/9 – 1/7*1/9 – 1/4*1/9 – 1/4*1/7*1/9
67	3	0	1	47.6	no change
70	2	0	1	47.6	no change
75	1	0	1	47.6	no change

Participant #2 is censored at 75 seconds

- Beyond 75s, the Kaplan-Meier estimate is *no longer defined*
- Question: What would have happened to the survival probability if P#2 would have drowned?

Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
39	7	1	0	76.2	0.889–1/9–1/7*1/9
42	6	1	1	63.5	0.762–1/9–1/7*1/9
51	4	1	0	47.6	0.635–1/9 – 1/7*1/9 – 1/4*1/9 – 1/4*1/7*1/9
67	3	0	1	47.6	no change
70	2	0	1	47.6	no change
75	1	0	1	47.6	no change

- Question: What would have happened to the survival probability if P#2 would have drowned?
- A: If P#9 had drowned, the survival probability would have dropped all the way to zero!

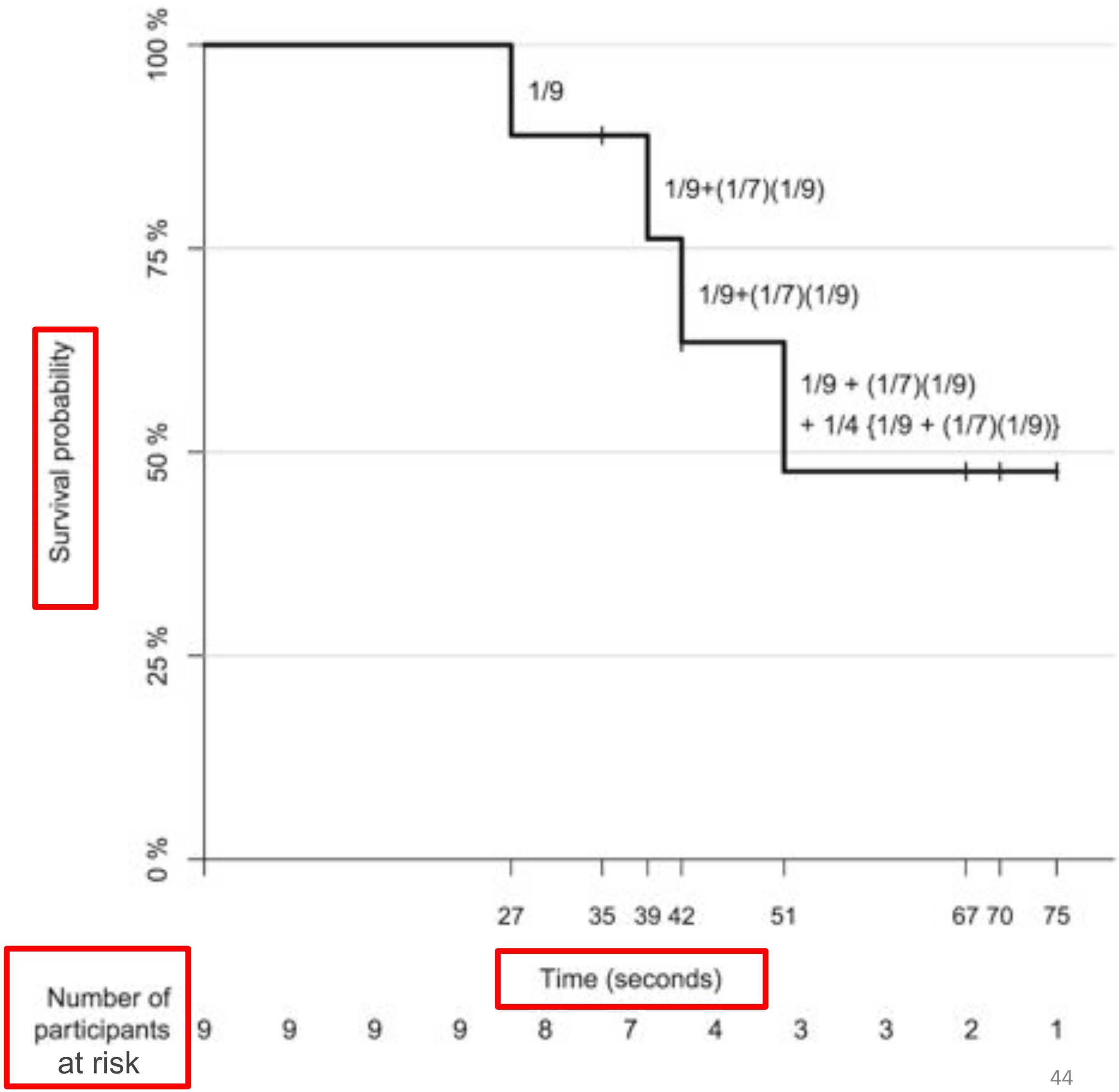
Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
39	7	1	0	76.2	0.889–1/9–1/7*1/9
42	6	1	1	63.5	0.762–1/9–1/7*1/9
51	4	1	0	47.6	0.635–1/9–1/7*1/9–1/4 (1/9–1/7*1/9)
67	3	0	1	47.6	no change
70	2	0	1	47.6	no change
75	1	0	1	47.6	no change

Any questions on the table?

Time (sec)	Number su	Number of	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0				100	everyone alive
27					1–1/9
35					ge
39					7 1/9
42					7 1/9
51					/9–1/4
67	3				
70	2	0			
75	1	0	1		e

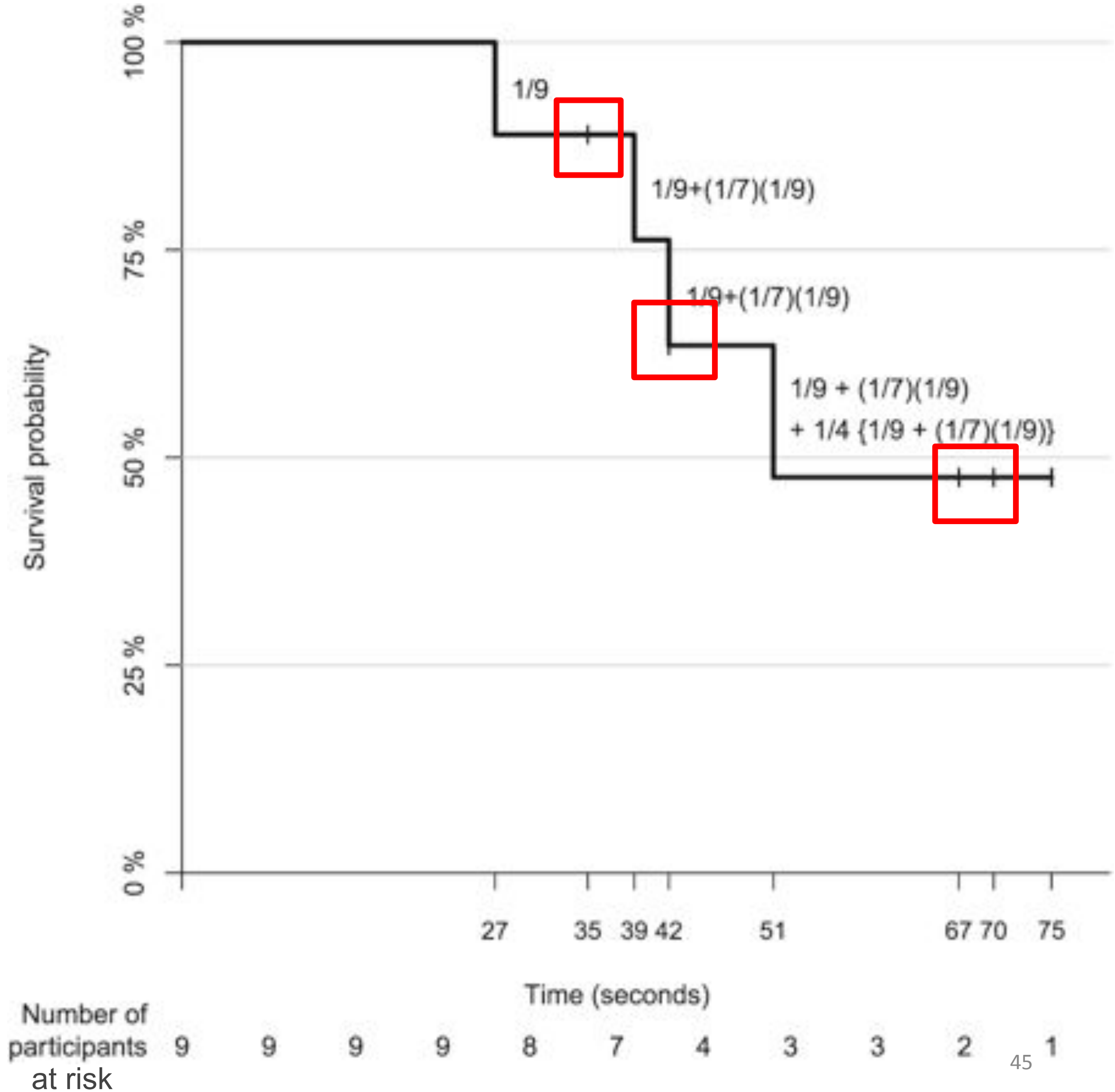
Not so easy to visualize this way, so let's create a plot instead!

This is a Kaplan-Meier curve for survival probability



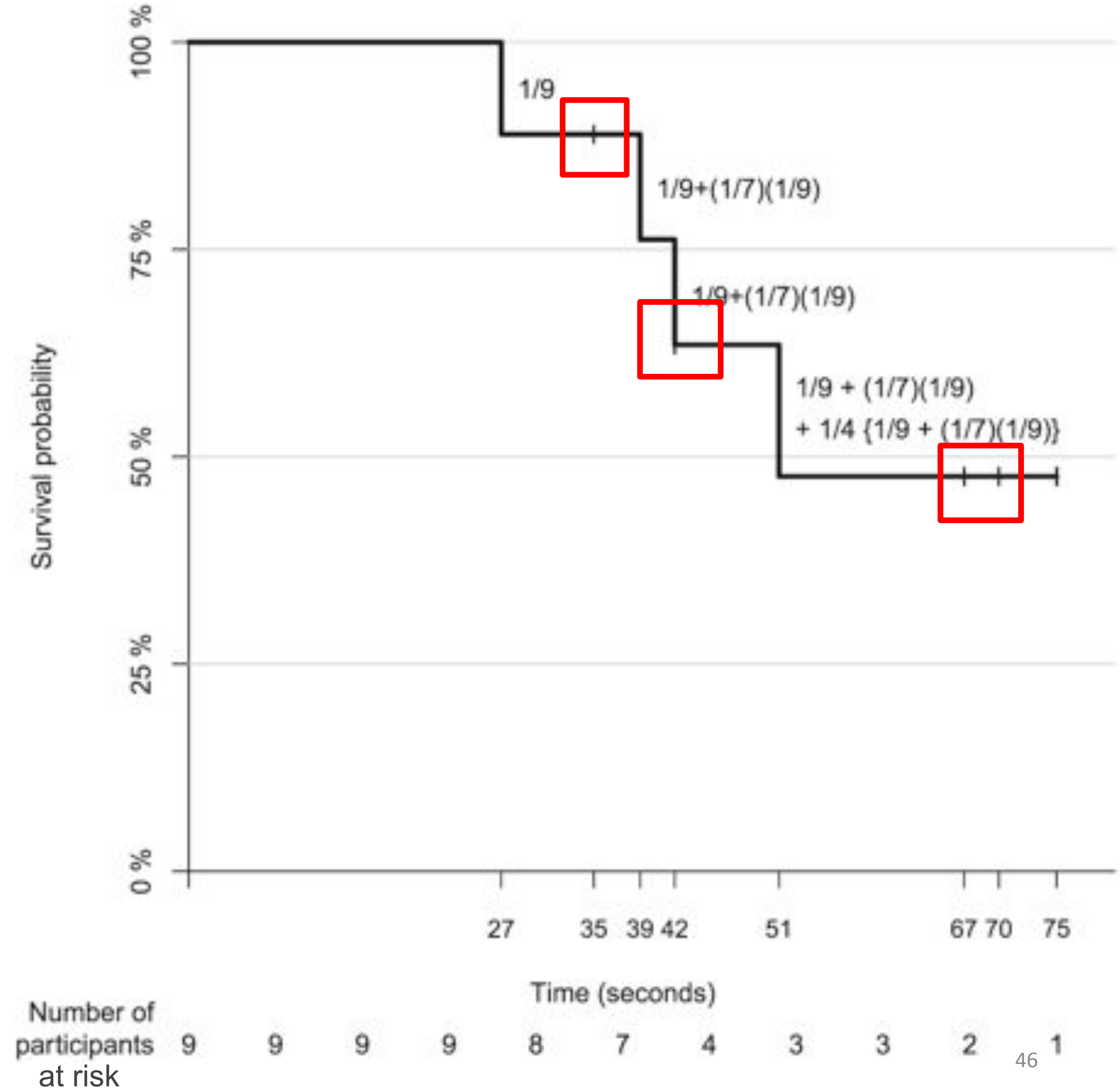
Questions:

Q1. What might the small vertical tick marks on the plot represent?

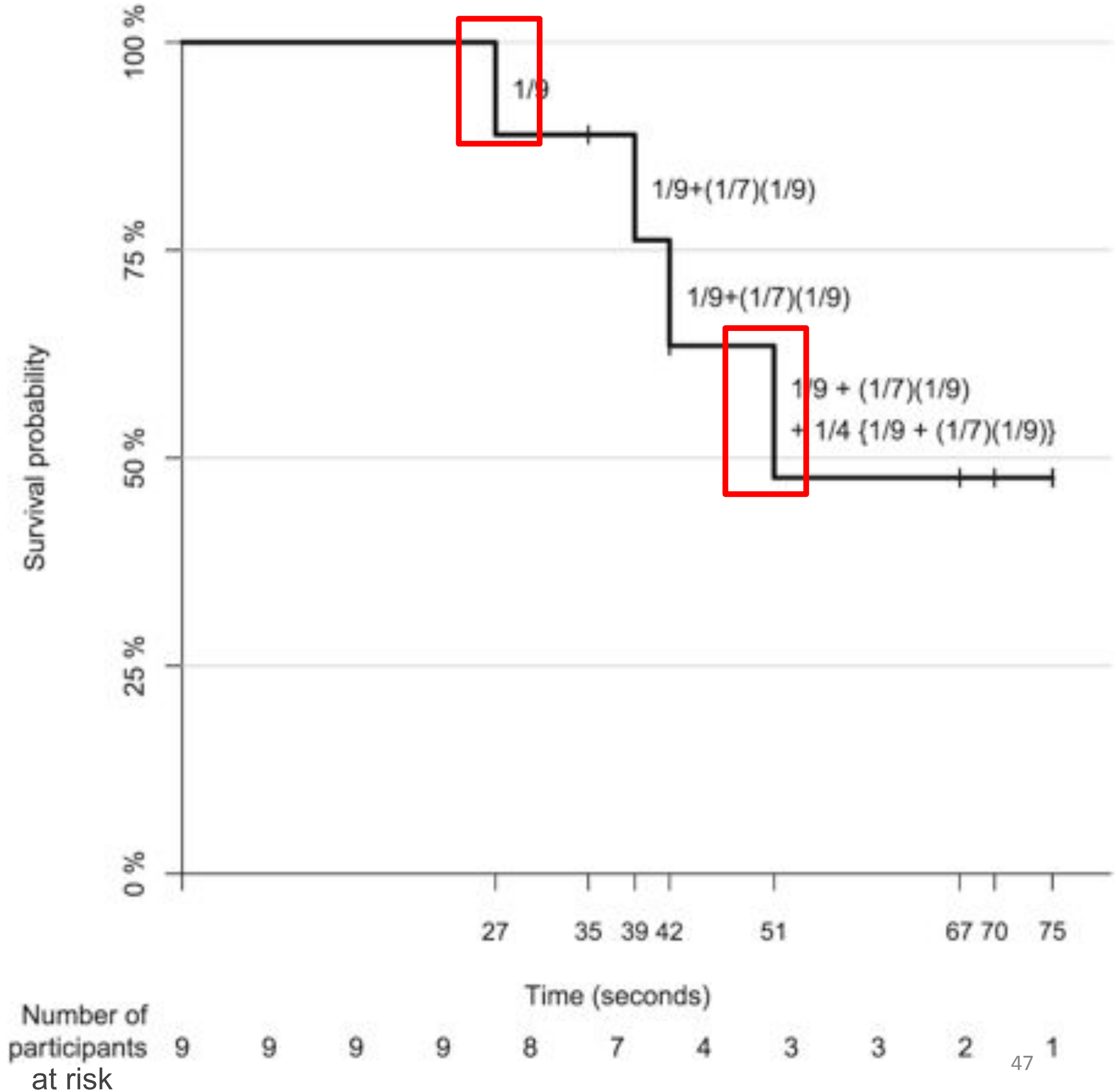


Q1. What might the small vertical tick marks on the plot represent?

A. Censored observations: “lost to follow up” at time point indicated

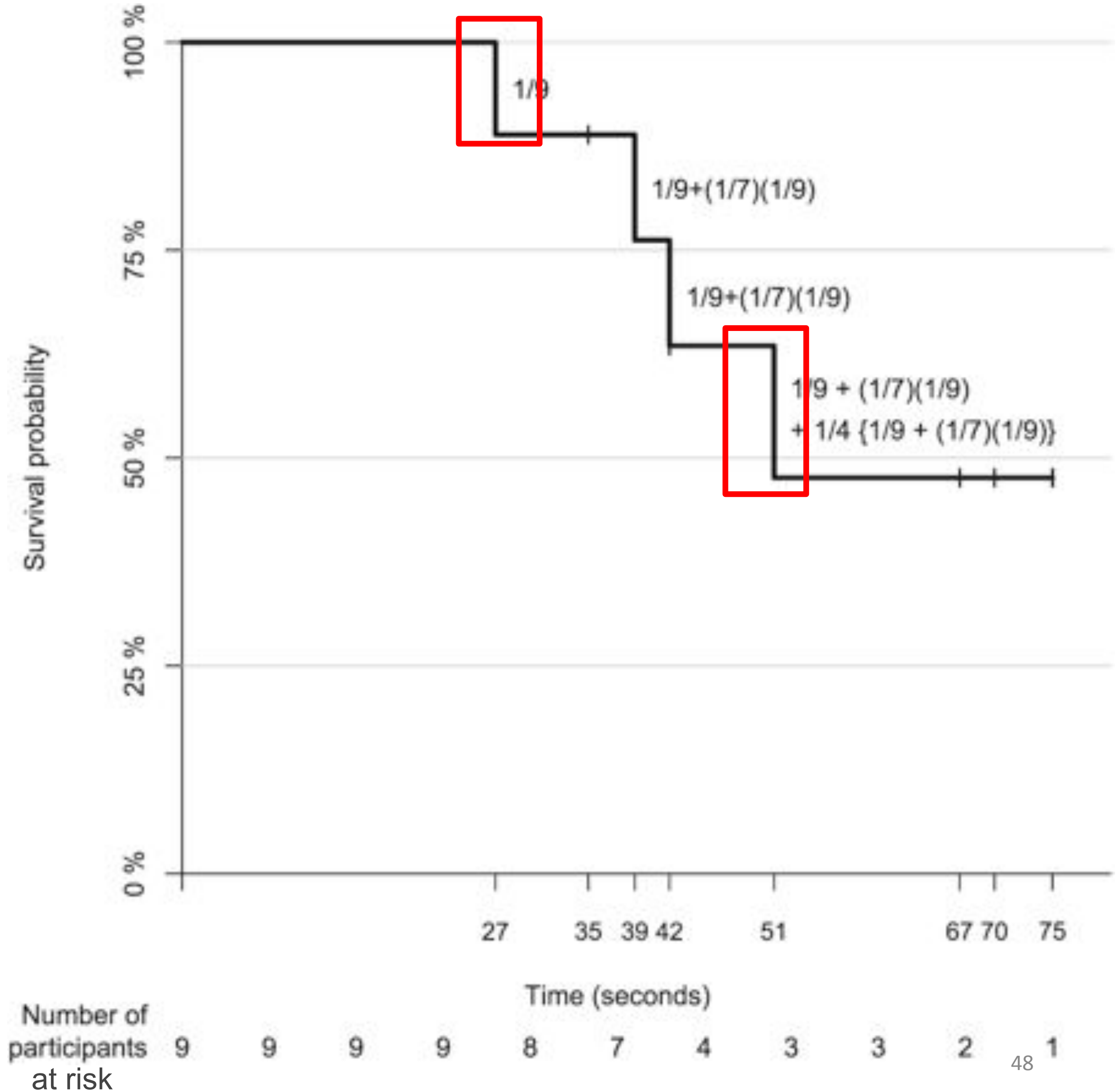


Q2. Why does the step size (vertical distance 'dropped') *increase* over time?

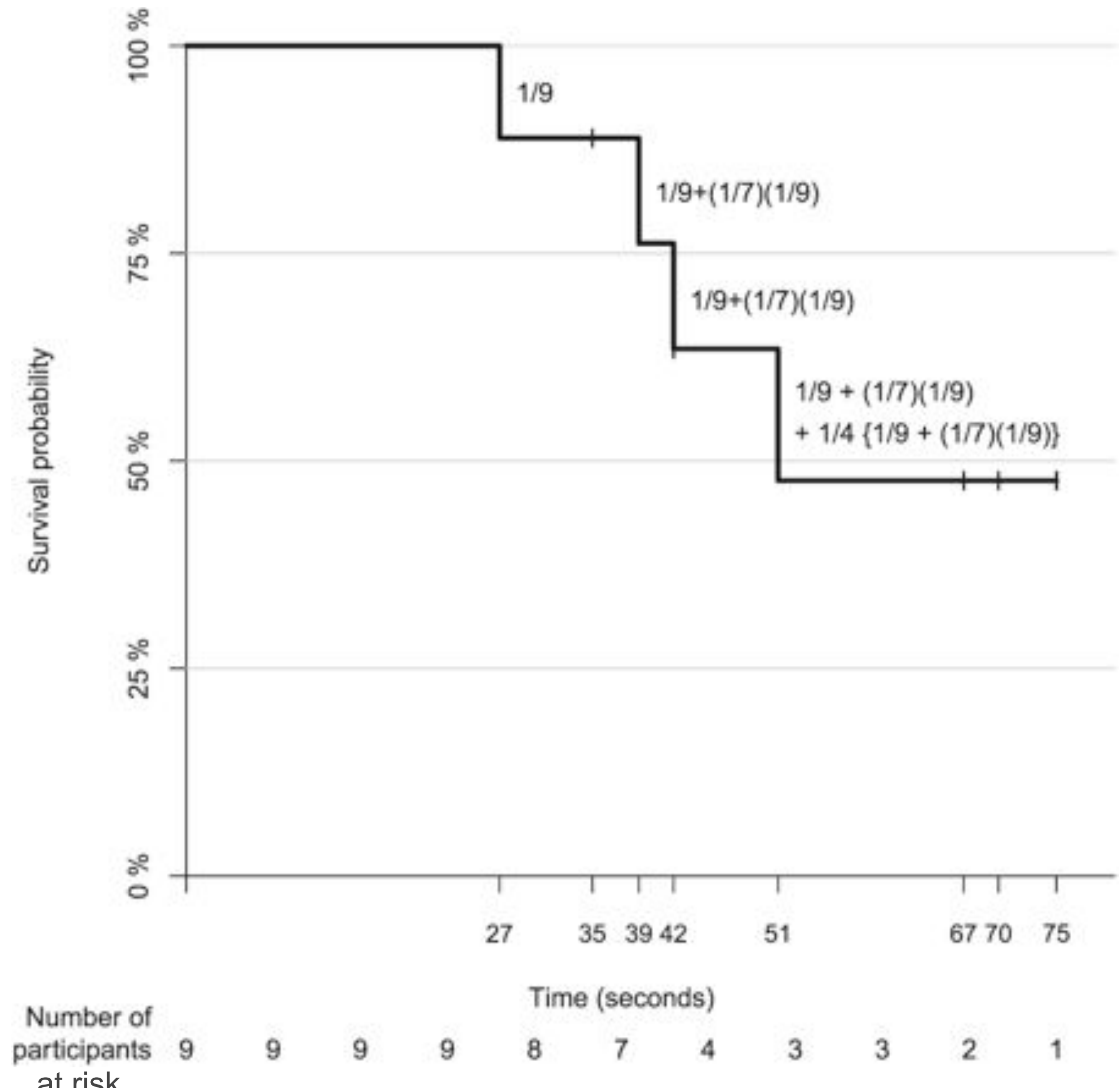


Q2. Why does the step size *increase* over time?

A. At time point of event occurrence, survival probability at that time point drops by individual contribution ***PLUS*** redistributed probability mass of others who were previously censored



Let’s now go through our completed table (next slide) together with this graph to understand this fully...



Time (sec)	Number of subjects	Number of events	Number lost to follow-up	Survival probability (%)	Calculation/Notes
0	9	0	0	100	everyone alive
27	9	1	0	88.9	1–1/9
35	8	0	1	88.9	no change
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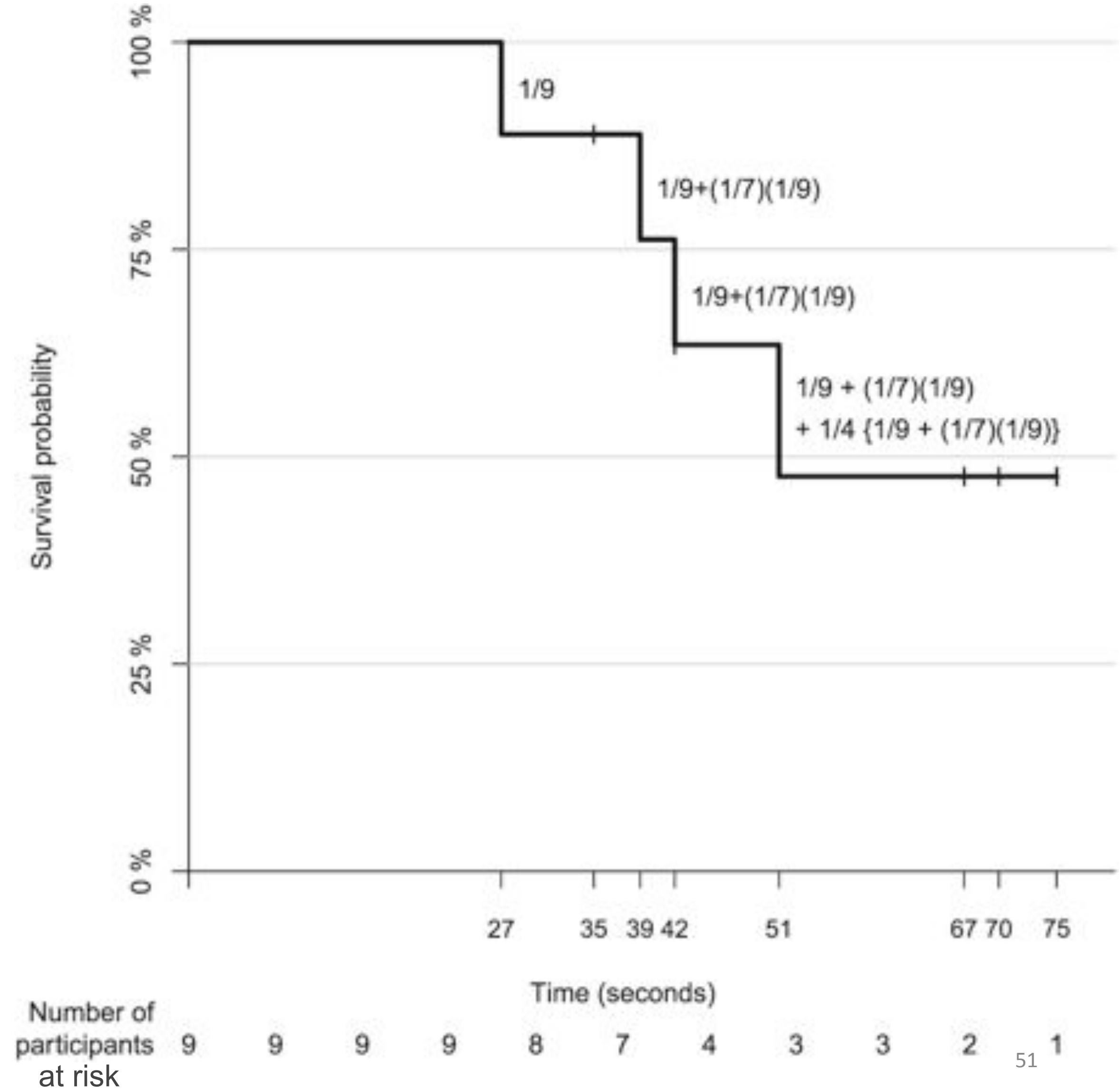
51	4	1	0	47.6	0.635–1/9 – 1/7*1/9 – 1/4*1/9 – 1/4*1/7*1/9
67	3	0	1	47.6	no change
70	2	0	1	47.6	no change
75	1	0	1	47.6	no change

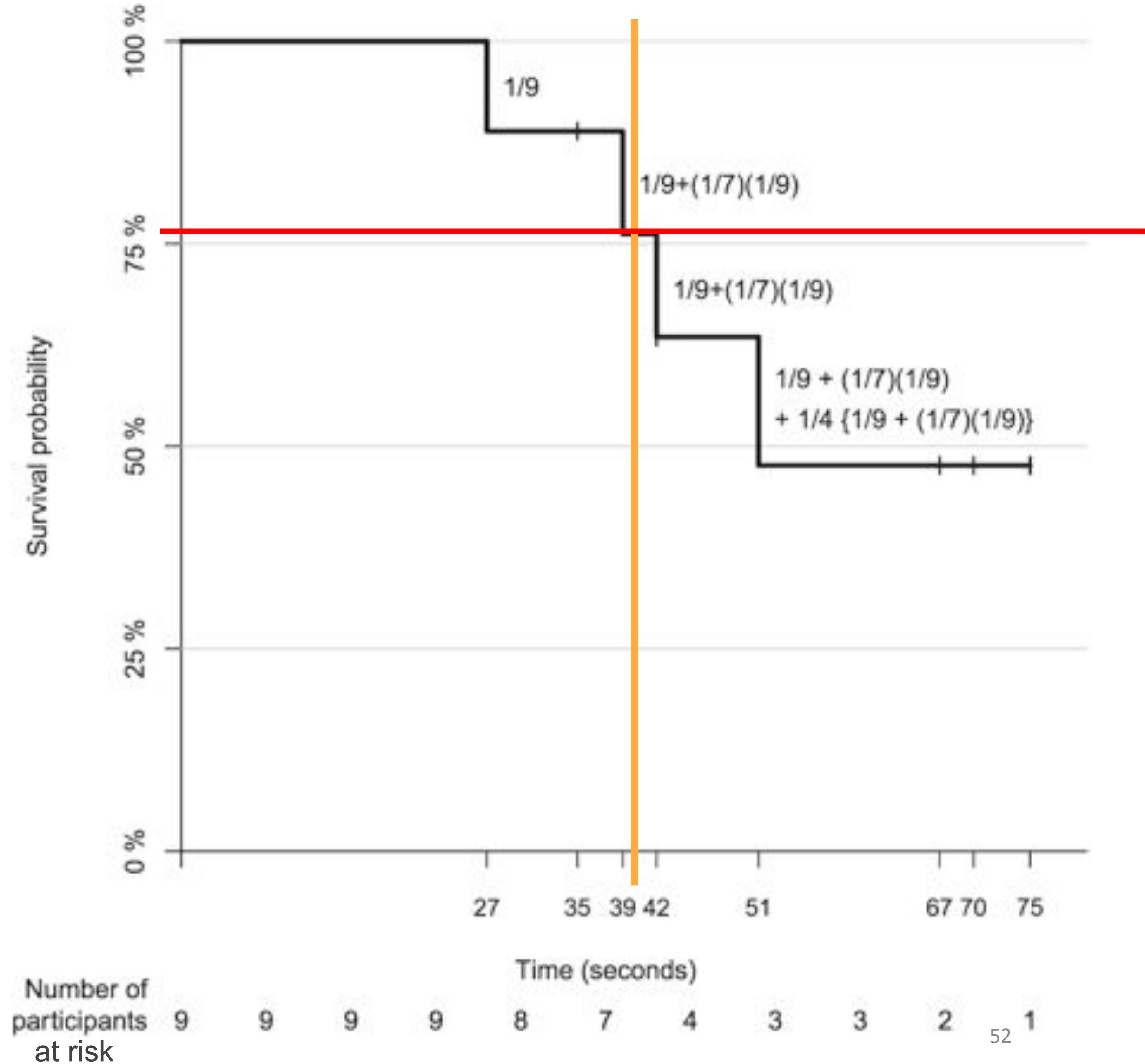
More questions:

Q3. In our study, what was the probability to survive 40 seconds?

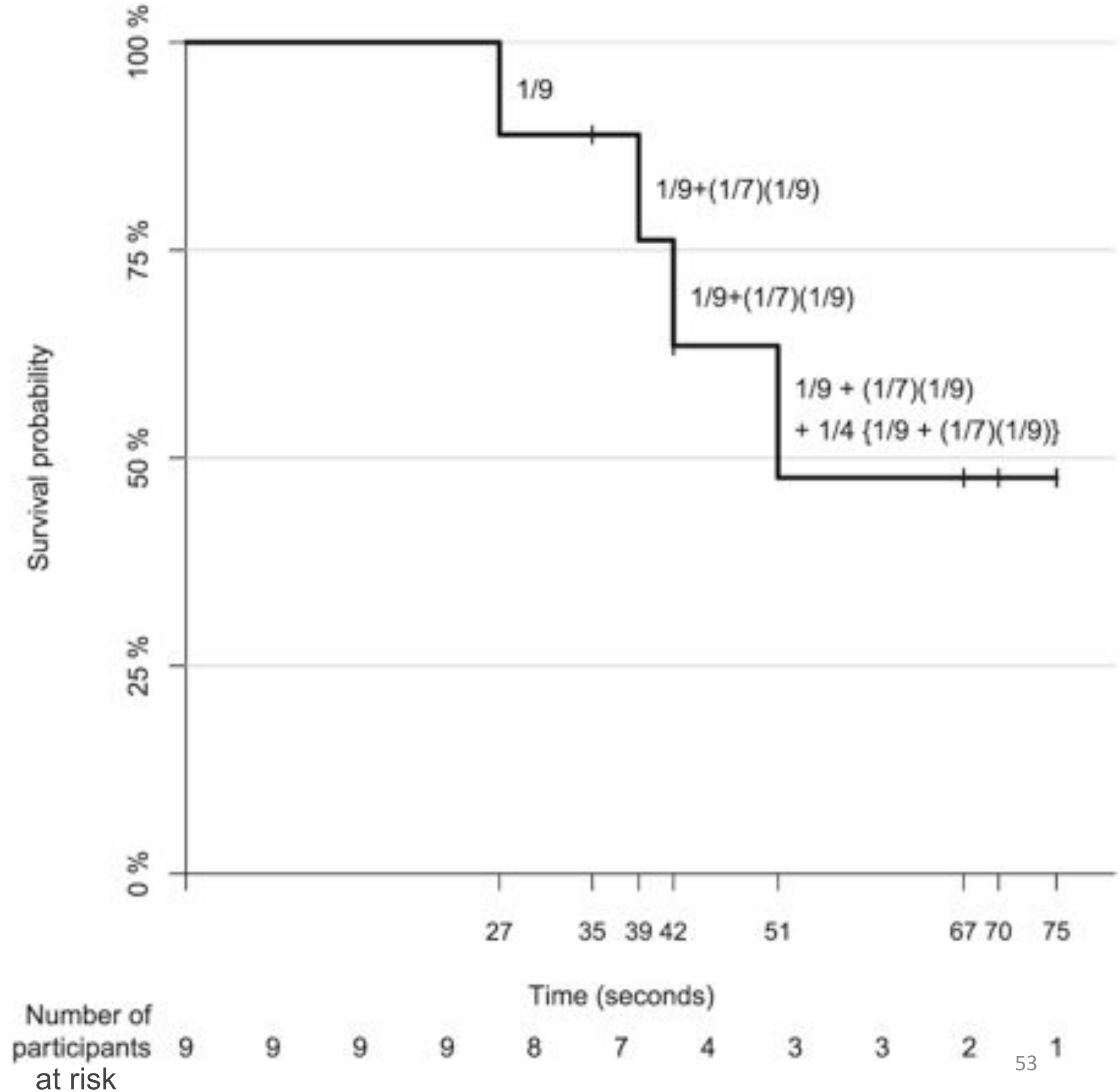


Q3. In our study, what was the probability to survive 40 seconds?

A. approx. 76%



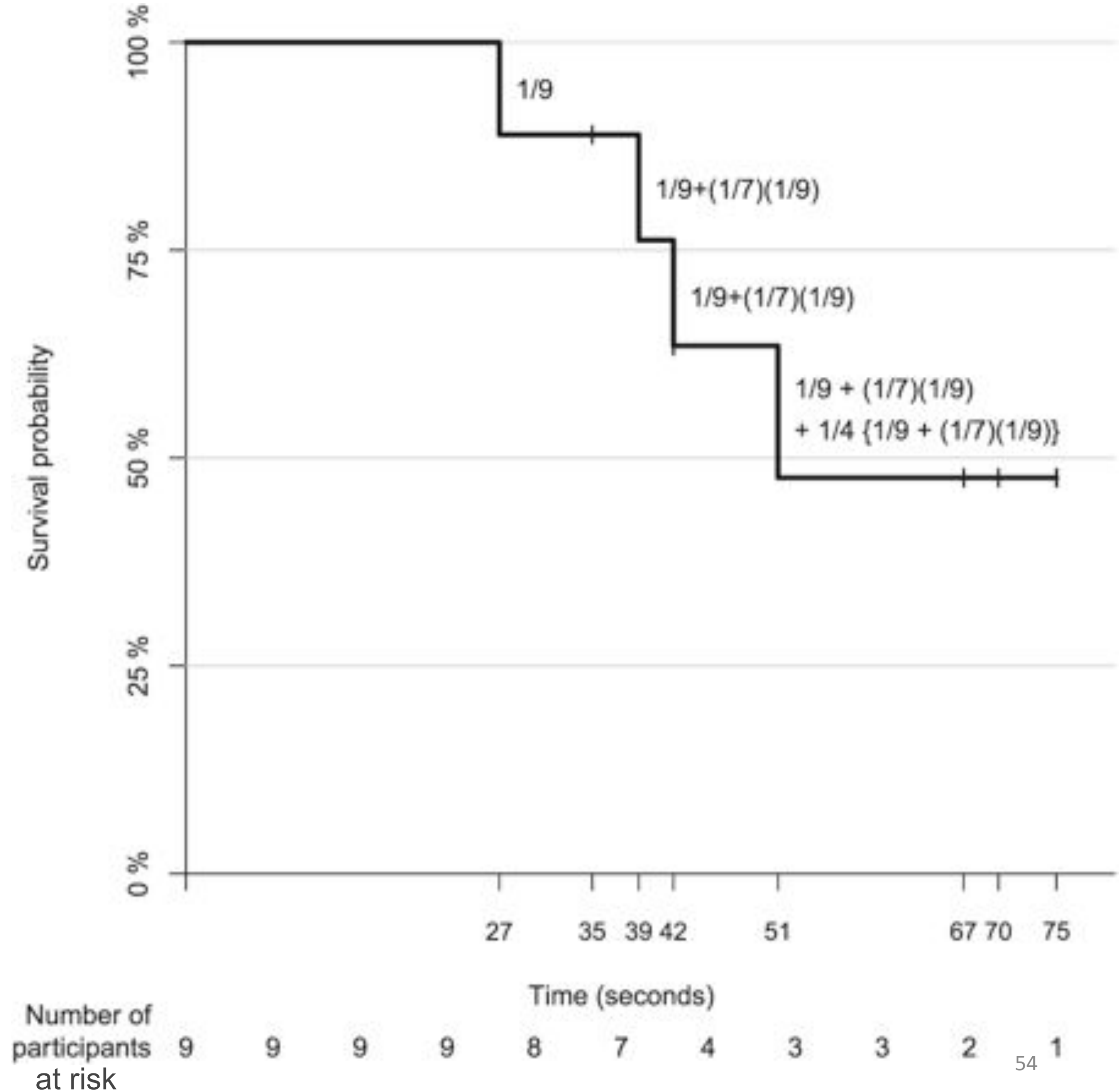
Q4. Why don't we see these distinct steps in similar looking plots in some scientific articles?



Q4. Why don't we see these distinct steps in some scientific articles?

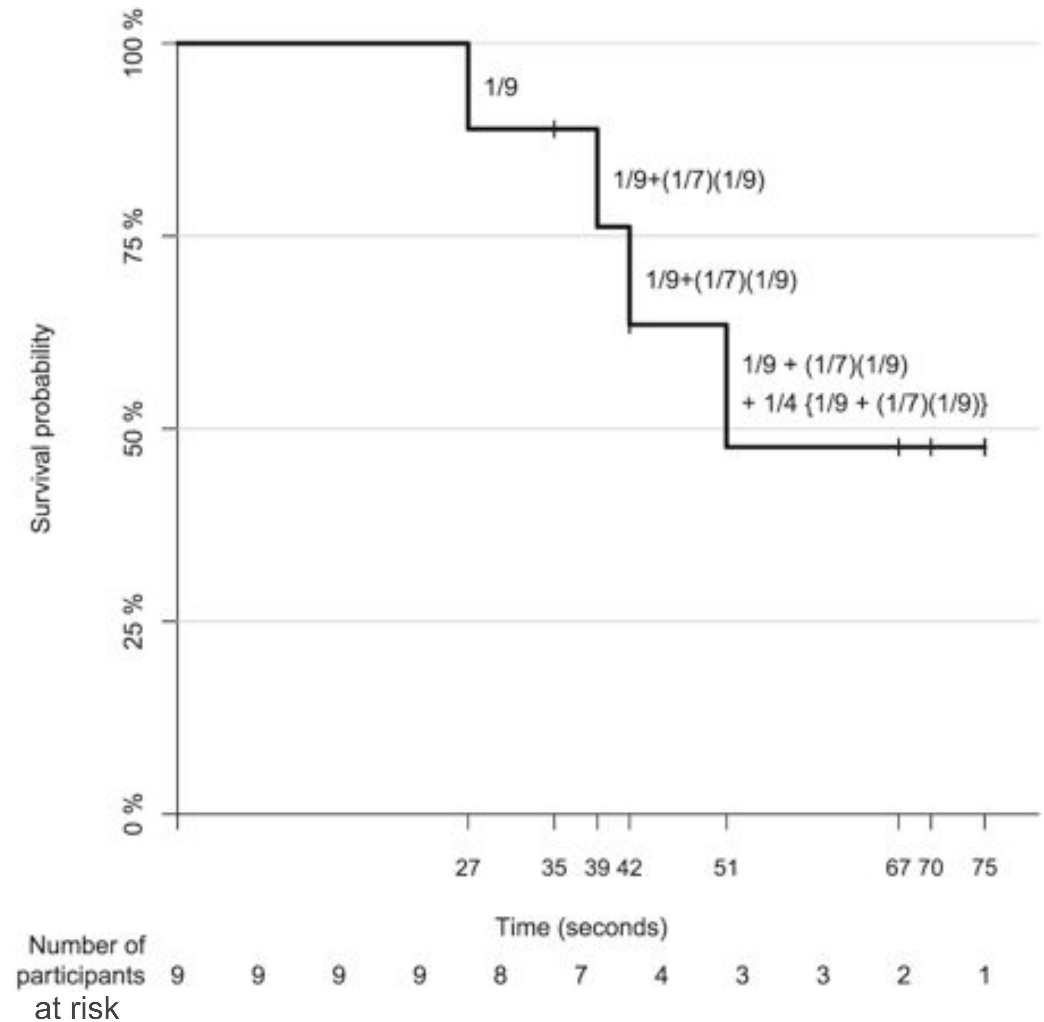
Two possibilities:

1. Didn't use a step function like Kaplan-Meier
2. Too large of a sample size to see steps (we need to zoom in)



Other notes:

- Useful to include number of participants at risk below graph (below time axis)
- Fewer participants at risk on right-hand side of curve = curve less reliable at the end (& wider confidence intervals)



Let’s recap the key definitions:

- **Survival time** = time btwn. study start & event or censoring
  - Note: participants may have different enrollment (start) dates!
- **Censoring** = no event has yet occurred at indiv. stop time
  - This can occur at **end** of study or
  - Due to loss to follow up at some point **during** the study
  - e.g. stop answering correspondence, no longer consent to participate, death for unrelated reasons, move away
- **Endpoint =** event = outcome. Must be defined in advance!
- ***New concept:*** **Overall survival vs. disease-specific survival**
  - Time from diagnosis to death for any reason vs.
  - Time from disease diagnosis to cause-specific death

From your reading...

- Typically, curves for 2 groups are compared
  - Which therapy would you recommend based on results?

Kaplan–Meier curve for 33 children and adolescents with medulloblastoma and metastasis status M1

Maintenance chemotherapy: 10-year survival rate = 70%, median survival rate cannot be determined

Sandwich chemotherapy: 10-year survival rate = 36%, median survival rate = 2.9 years

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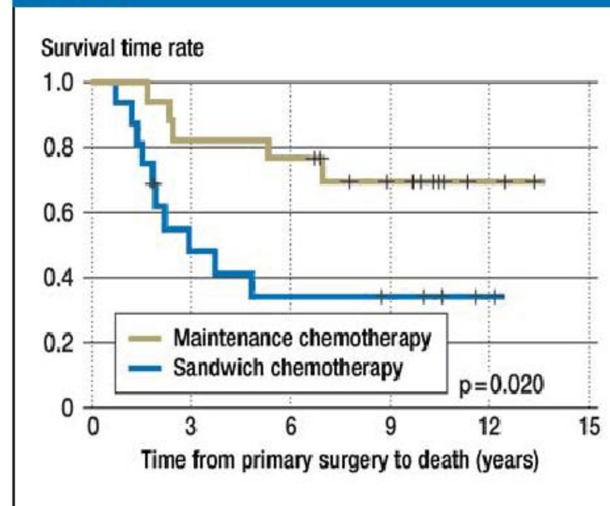
FIGURE 2

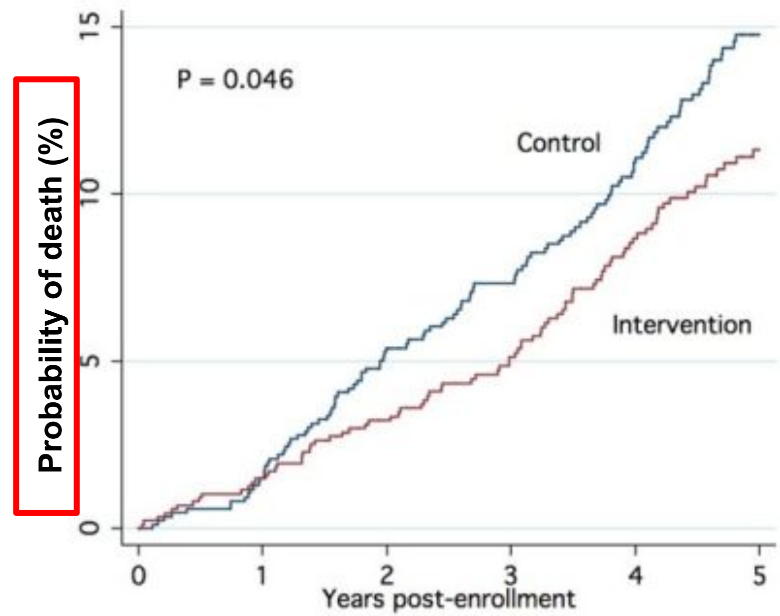


Zwiener, I; Blettner, M; Hommel, G **Survival Analysis: Part 15 of a Series on Evaluation of Scientific Publications** Dtsch Arztebl Int 2011; 108(10): 163-9; DOI: 10.3238/arztebl.2011.0163

Upside-down curves?? Don’t panic…

They are showing cumulative mortality instead of survival

= 1 minus the Kaplan Meier estimate
= 1- S(t)



Number at Risk (Deaths)

Control	863	(13)	850	(33)	766	(15)	712	(27)	617	(23)	398
Intervention	873	(13)	860	(15)	792	(15)	738	(27)	642	(16)	417

Effect of a community-based nursing intervention on mortality in chronically ill older adults: a randomized controlled trial.

Coburn KD, Marcantonio S, Lazansky R, Keller M, Davis N - PLoS Med. (2012)

Note: y-axis label corrected by JR

3 Assumptions of the Kaplan-Meier method

1. Everyone in study will have the event eventually
   - This can problematic if we have **competing risks**
   - If we use a single, disease-only endpoint, there are other endpoints that will 'compete' with this endpoint
     - Makes it less likely/impossible for participant to have endpoint of interest
   - In traditional K-M method, competing events (e.g. death) are censored
     - This can introduce bias, depending on nature and # of competing events
     - Reflects purely hypothetical population where individuals could not die without the disease (not realistic!)

Use alternative methods designed for CRs

- Inference for disease risks and rates can be made 'in the presence of the competing risk of dying'.
- Example: Outcome of interest = recurrent stroke in cohort of stroke patients
- What to do? (beyond scope of MET2…)
    - Use Nelson-Aalen(-Johansen) & other advanced estimator methods
    - Use a combined endpoint instead (e.g. time to ischemic stroke **or** myocardial infarction **or** death, whichever comes first
    - Keep follow-up time short
    - Detailed example: Andersen PK, et al. Competing risks in epidemiology Int J Epidemiol. 2012.

3 Assumptions of the Kaplan-Meier method, contd.

2. Censored observations distribute their weight (probability mass) equally among those still at risk

- Regardless of distribution of other covariates! (e.g. sex, lung capacity, age, etc.)
- We do not know what happened to the censored participants- we **estimate** their experience **based** on remaining participants
- Independent censoring assumption:
  - "An individual censored at time t_i should be representative for those still at risk at that time. In other words, those censored should not be individuals with systematically high or low risk of event (Andersen, Int J Epidemiol 2012)

3 Assumptions of the Kaplan-Meier method

3. Non-informative censoring

- = Censoring status **is not** related to person's future

- If people who are censored die quicker than those who remain in the study, we have a problem!

Log-rank test

- Statistical comparison of survival times between 2 groups
  - an extended form also available for 3+ groups
- i.e. ‘statistically significant’ difference between groups?
  - at *a priori* signif. level -- (is this always useful?)
- Comparison made *over the entire observation period*--
  - Not just at one time point!
- Factors in the number of events per group
  - More events = lower p-value, since p-val conflates effect size and study size (same limitation as other stat. tests)
- Univariate: doesn’t consider the impact of other covariates!

Again, from your reading...

Q: p=0.020 = result from log-rank test means…?

Kaplan–Meier curve for 33 children and adolescents with medulloblastoma and metastasis status M1

Maintenance chemotherapy:	10-year survival rate = 70%, median survival rate cannot be determined
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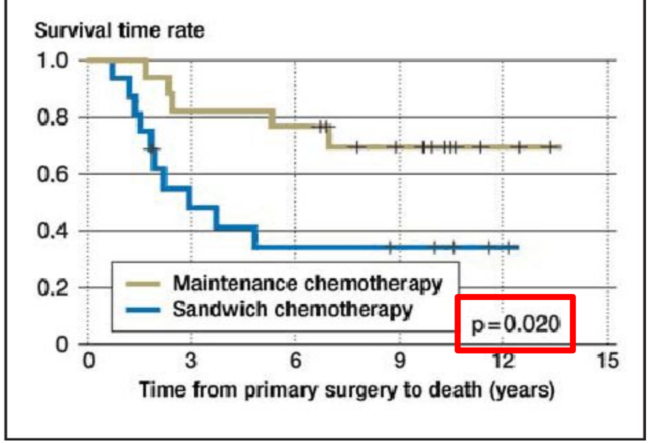

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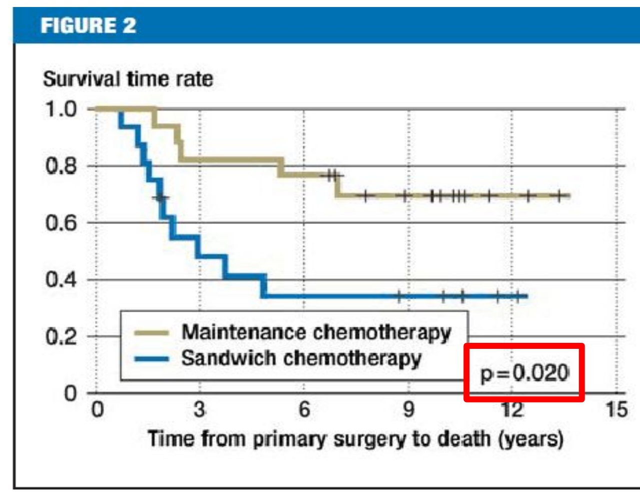

A: Stat. significant difference between groups (at alpha=0.05 significance level)

Another drawback to Kaplan-Meier / log-rank

- Useful only when the predictor variable is categorical (e.g.: treatment A vs treatment B).
  - What could we do if we wanted to run a K-M with a continuous variable like BMI?
  - What about something with many categories like education level?

Hazard & hazard function

- **Hazard** is the ***instantaneous* risk of suffering an event at exactly time (*t*)**
- e.g. instantaneous speed of dying/risk of death (Titanic)
- This risk may change over time, thus *dependent on t*
  - *E.g. time from medication administration to occurrence of adverse effect: nausea*
- The hazard **function**, **h(t)**, summarizes this hazard for ALL time points
- The hazard estimates the incidence rate (review):
  - Incidence rate (IR) = ???

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- The hazard estimates the incidence rate (review):
    - Incidence rate (IR) = # events / person-time

Hazard ratio: $h_A(t)/h_B(t)$

- The **hazard ratio (HR)** is the **hazard function in group A divided by the hazard function in group B** and is used to compare survival times.
- The HR estimates the incidence rate ratio (IRR)
  - Recall: IRR is a ratio of IR in one group vs. the other

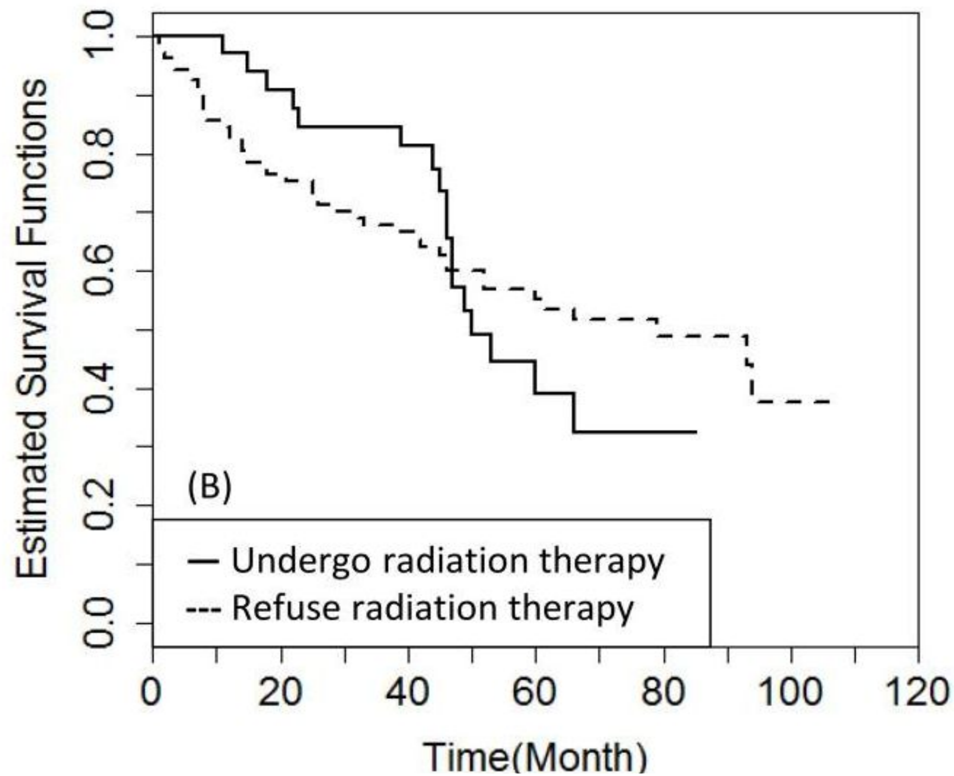
- HR > 1: the hazard of having an event is **higher** in group A compared to group B.
- HR = 1: hazards are the same in both groups
- HR < 1: the hazard of having an event is **lower** in group A compared to group B.

Proportional hazards assumption

- Hazard (e.g. speed of dying) in one group must permanently exceed that of the other *to the same extent*
  - The hazard may vary over time but the variations must be the same in both groups
- Graphically: K-M curves should **not** cross
- Check your assumptions:
  - Graphical approach: ln(-ln) survivor curves of the subgroups, Schoenfeld residuals
  - Goodness-of-fit tests
  - Time-dependent variables
- This assumption needed for log-rank test and Cox regression

Proportional hazards assumption violated- example

- Crossing Kaplan-Meier curves means proportional hazards assumption is violated, but still interesting finding!
- Interpretation somewhat more complex
  - Here: early benefit of radiation therapy, but not long-term



From: Li, H., Han, D., Hou, Y., Chen, H., & Chen, Z. (2015). Statistical Inference Methods for Two Crossing Survival Curves: A Comparison of Methods. *PLoS ONE*, *10*(1), e0116774. http://doi.org/10.1371/journal.pone.0116774

Is Kaplan-Meier a regression model?

- No, it is a step function
- Graphic representation of raw data, no adjustments
  - You can't perform multivariable analysis (ie. you can't adjust for age, sex, etc.) on a Kaplan-Meier! It is a crude **visualization** technique
  - Important to keep in mind when interpreting
- Is constructed from a life table
- Does not give us a point estimate
  - We can only calculate p-value via log-rank test: is there a "significant difference" between groups or not?

    However… we have Cox regression to help us do these things!

Cox proportional hazards regression

- Time-to-event analysis, models the incident rate ratio (IRR) as a “hazard ratio” (HR)
- Because we need person-time, we can only use it in studies with detailed person-time information (e.g. cohort, RCT…)

Cox regression

- Can model the effects of different variables on survival time simultaneously
  - Continuous (e.g. age at diagnosis)
  - Binary (treatment-yes or no)
  - Categorical (stage at diagnosis) …etc.
- Means we can control for confounding as in other regression models by including additional indep. variables in the model
- Proportional hazards assumption required! (Inspect K-M curves & check assumption!)

Recall....

- Linear regression:

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots \beta_k X_k + \varepsilon$$

- Logistic regression:

$$ln\left(\frac{Prob(Y=1)}{1-Prob(Y=1)}\right) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots \beta_k X_k$$

Natural logarithm

Cox regression has a similar equation...

$$ln\left(\frac{h(t)}{h_0(t)}\right) = \beta_1 X_1 + \beta_2 X_2 + \ldots \beta_k X_k$$

Natural log (ln) of the hazard at time *t* divided by the hazard at time t for a person with the value of zero for all independent variables

HR: How might this be calculated?

Cox PH regression model cont'd

X = exposure

$$HR = \frac{h(t, X=1)}{h(t, X=0)} = \frac{h_0(t) \cdot \exp(ß \cdot 1)}{h_0(t) \cdot \exp(ß \cdot 0)} = \frac{h_0(t) \cdot \exp(ß)}{h_0(t)} = \exp(ß)$$

- The Cox model is a semiparametric model.
- The baseline hazard function must be positive
- Cox PH only assumes that the ratio of two hazards is ***constant***
- Final expression of the HR does not contain time t (independent of time)
- This means: once model is fitted and we know value for X, the value of HR is **not** time varying

Cox PH regression model cont'd

$$ln\left(\frac{h(t)}{h_0(t)}\right) = \beta_1 X_1 + \beta_2 X_2 + \ldots \beta_k X_k$$

- HR: Hazard ratio given in statistical program output (adjusted for any covariates (X_2, X_3, etc.) you include in the model)
- As in logistic regression, simply take the anti-(natural) logarithm of the regression coeff. of interest (for exposure)

HR for exposure (X_1)= $e^{ß1}$

*will be practiced in R Seminars!

Final points

- **Like in logistic regression models, the # events (outcomes),** not sample size, is key! (# variables << # events)
- Possible bias due to distribution of censored patients in each group (differential loss to follow-up)
    - In other words, if our censoring becomes ***informative*** = problematic!
    - e.g. if censored participants die more frequently than non-censored, this would result in an underestimation of true event rate, which may be differential based on the exposure!
- Look out for mistakes in the literature… be a critical reader!

Further reading

Recommended books:

- Kleinbaum D & Klein M. 2012. Survival Analysis, a self-learning text. 3rd Edition. Springer.
- Collett D. Modeling survival data in medical research. 2nd edition. London: Chapman and Hall 2003.