

Survival after recurrence of breast cancer

A multistate model compared to Kaplan-Meier

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Background

- Kaplan-Meier Estimator (KM) as non-parametric method is well known with very few restrictions
- Complex adjustments e.g. for age/grade/... need further assumptions (A)
- Multistate Models (MS) allow for more complexity and deeper insights

Data

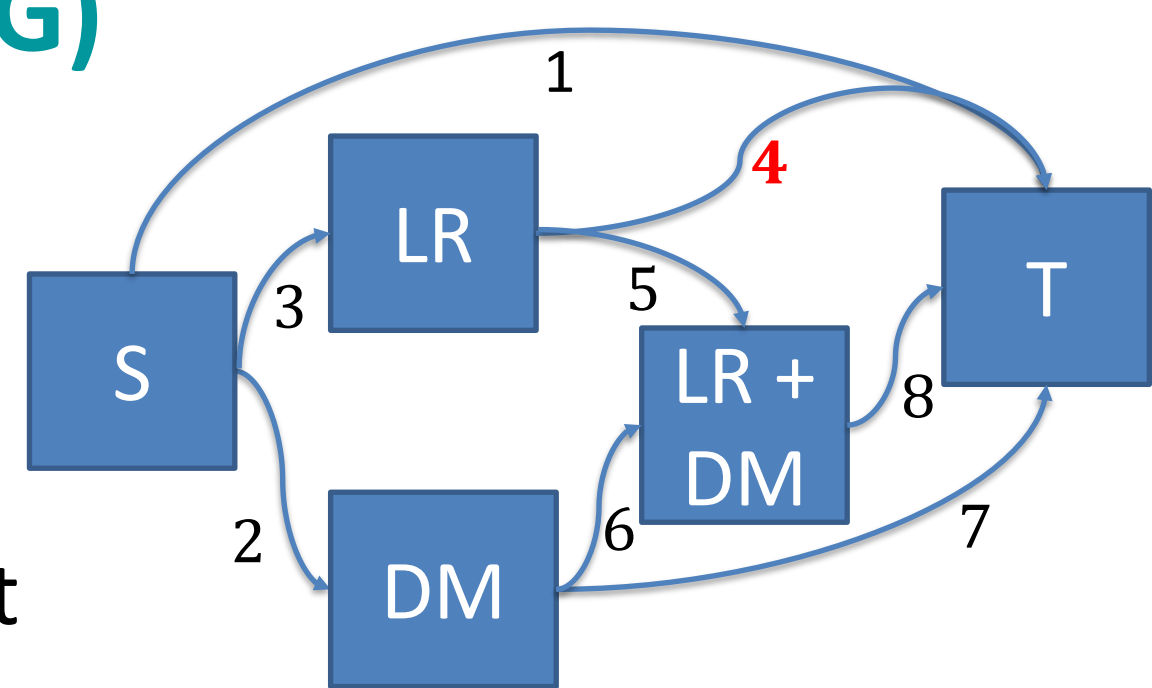
- Focus on female patients of 4 OSP centers
- Diagnosis: 2003-2024 with ICD C50/D05
- Model adjustment (following Putter) for:

Case	n	%
Complete	10428	83,1
Incomplete	2115	16,9
Total	12543	100
- Center: A/B/C/D, Age, Tumorsize, Grading 1/2/3, Nodalstatus 0/1, Chemo y/n, Treatment: BCT, BCT+RT, MAS, MAS+RT, BCT-MAS, BCT-MAS+RT, Adjuvant: y/n
- Further information see QR-Code

Variable	N	Mean	sd	Median	Min	Max
Age at Diag	12543	60,03	12,96	59,92	18,23	100,41
Tumor Size (mm)	10625	23,78	13,89	16,00	0,00	173,00

Directed Acyclic Graph (DAG)

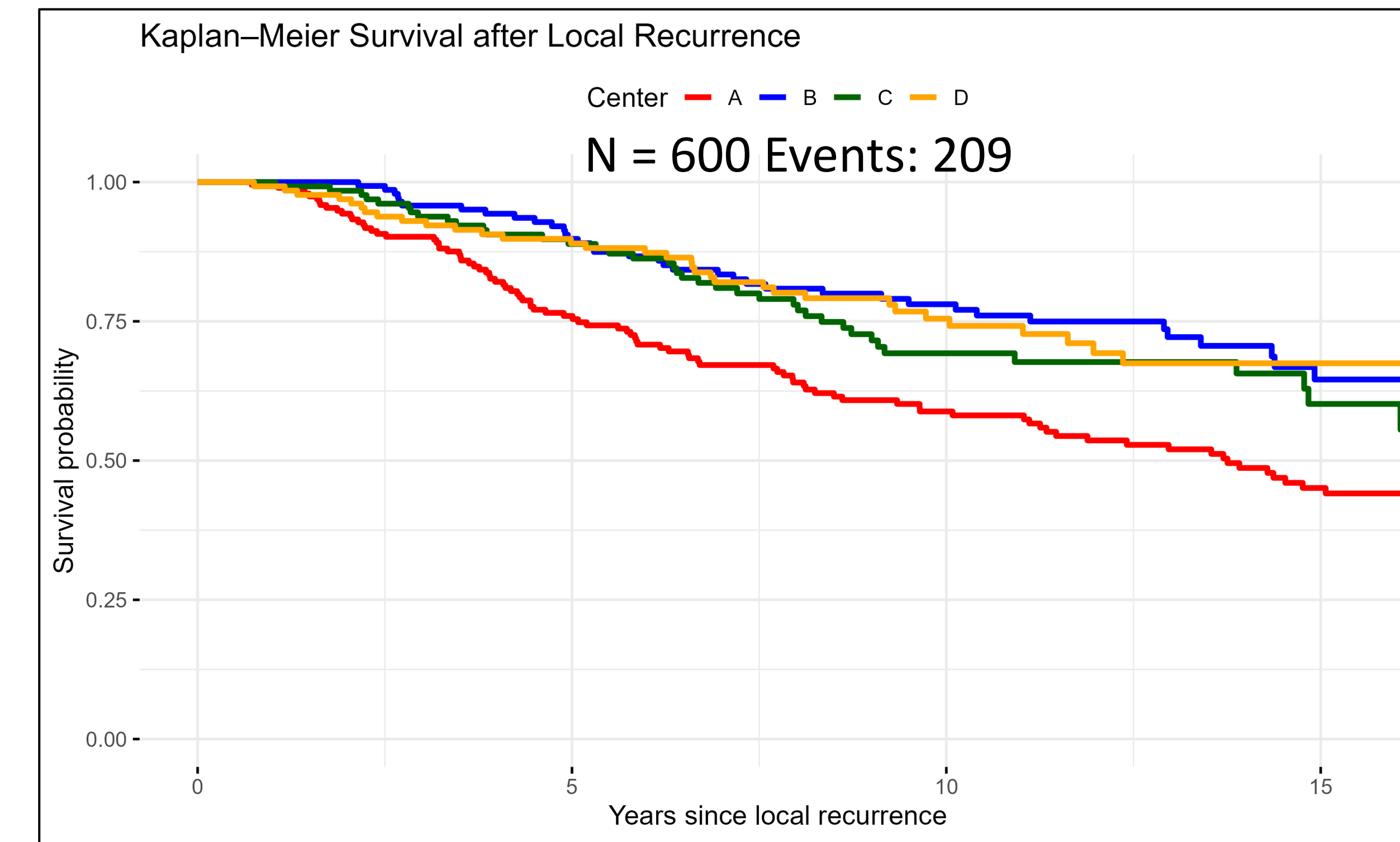
- DAG illustrates possible state transitions
- S: Start with Diagnosis C50/D05
- LR: Locoregional recurrent event
- DM: Distant metastasis
- T: Death as only absorbing eventtype
- Numbers refer to the correspondent transition



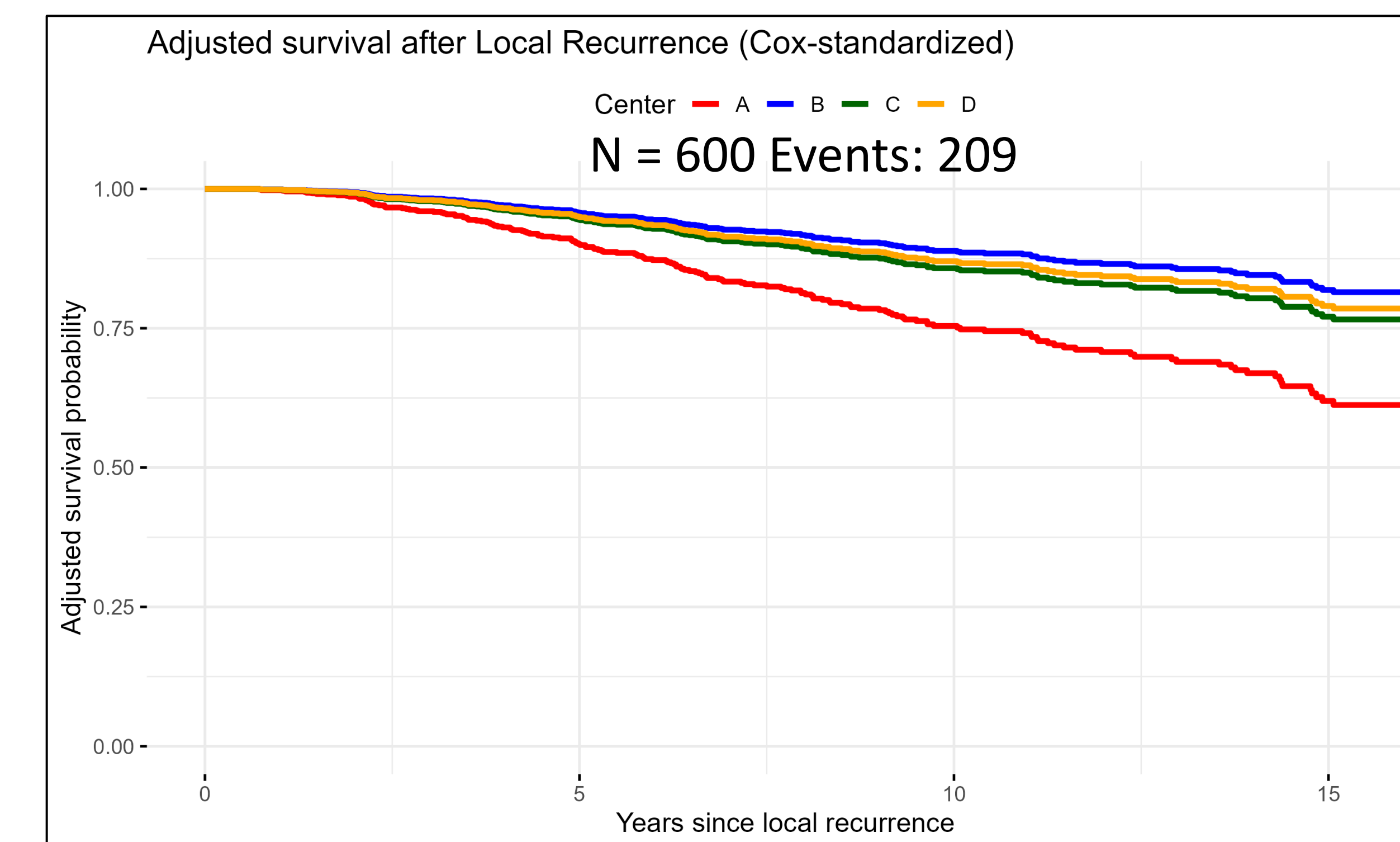
	LR	DM	LR+DM	Death	none	Enter
Start	600	778	0	1581	9584	12543
LR			156	80	364	600
DM			75	551	152	778
LR+DM				234	77	311
Death					2446	2446

- KM model only transition 4
- MS model incorporates all transitions

Kaplan-Meier Estimation



- Unadjusted or stratified, usually unbiased (A: independent censoring)
- Competing events lead to biased estimates
- Crossing curves can be an indicator for non-proportional hazards (A)
- Test: Schoenfeld-Residual, here χ^2 : 5.95, df: 4, p = 0.2
- Therefore, for centers in this case the baseline hazards are proportional "enough"

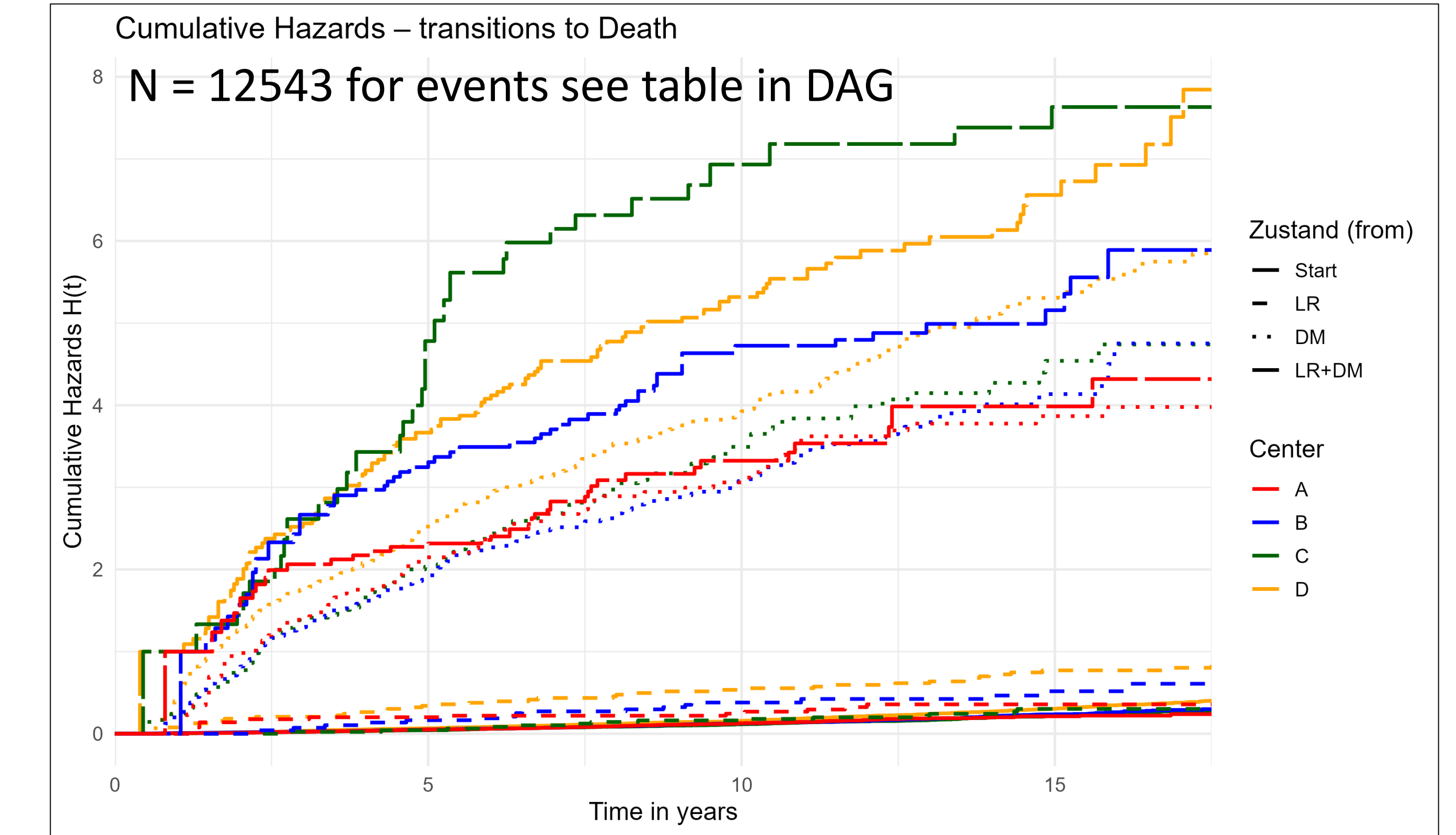


- Adjusted or stratified, unbiased only if assumptions are kept
- Most common adjustment: Cox proportional hazard model
- We gain global baseline hazards adjusted by covariates
- Proportional hazards are "forced"
- Sometimes with anomalies e.g. a survival of more then 100%

Multistate Model

- Allows to adjust for competing events
- Gives insight to each variables impact in every state
- Cumulated Hazards Higher value corresponds with higher probability of transition
- Able to plot for each transition
- Here transitions 1,4,7,8 (see DAG)

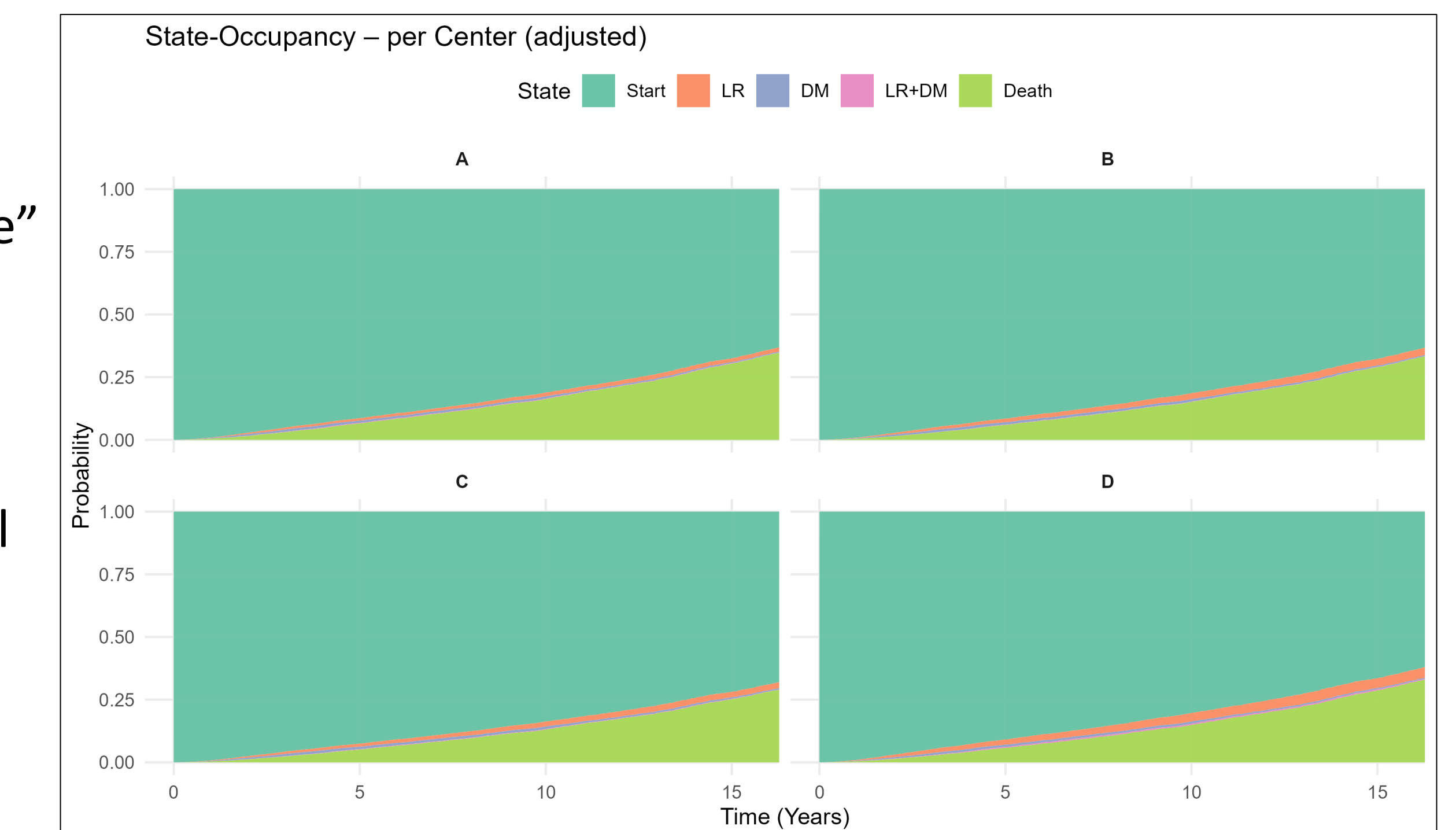
Variable	coef	exp(coef)	se(coef)
age_diag.1	0,01	1,01	0,00
age_diag.2	0,02	1,02	0,00
age_diag.3	0,09	1,10	0,00
...			
age_diag.5	0,05	1,05	0,01
...			
Chemo.2	0,77	2,16	0,11
Chemo.3	-0,22	0,80	0,08
Chemo.4	0,66	1,93	0,24



- All Estimands in leftside table are p<0.01 and show a brief excerpt (120 Coefficients in total [8*(3+2+1+1+5+1+1+1)])
- Age has for transitions 3 the largest hazard ratio compared to other transitions

Prediction with a Multistate Model

- Similar to adjusted KM: In both cases "average" patient or patient with specific covariates
- Stratified by center, probability to be in a certain state, starting at diagnosis
- While difference in KM seems huge MS model give more context
- Probability to transit to LR rather small
- Probability to transit into state Death overall comparable



Keypoints

- KM often used but assumptions rarely questioned
- Choose method according to data and research question
- Here: „Pure“ KM and adjusted → 600 patients
- Adjusted KM → misleading survival curve
- Also be aware: adjusted KM curves are often a subset/ "average" patient
- MS models are more flexible and incorporate all data → 12.543 patients
- More complex to interpret
- Allow to understand connections better and the effect of variables in different states

