Simple parametric analysis for a multi-state model in hospital epidemiology

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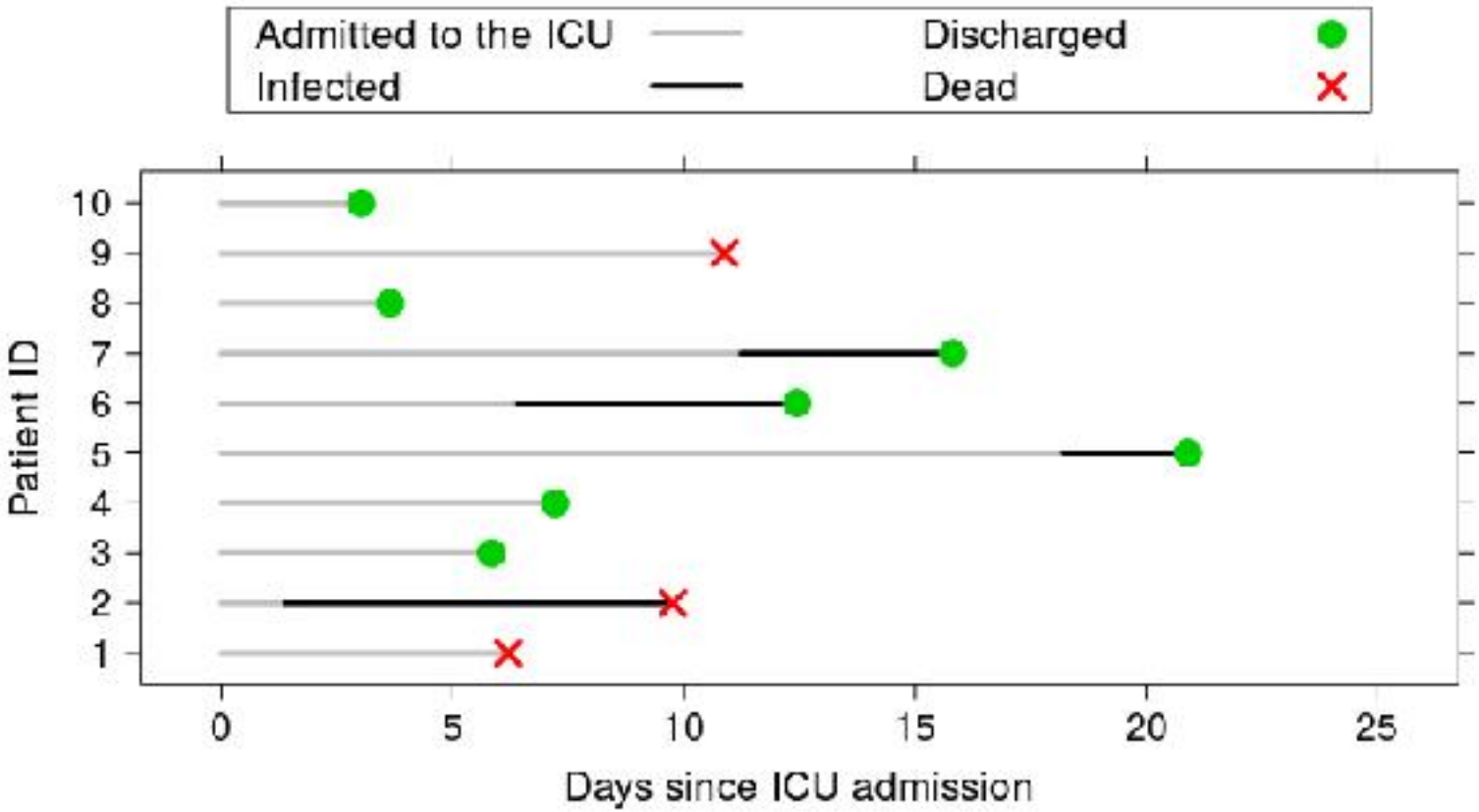
- **Key message:**
  - When analysing a new dataset try to start out simple
- **Questions to discuss during the day:**
  - How do others bridge the gap between simplification and misspecification?
  - How do others bridge the gap between correct (but complex) modelling and interpretability?

Motivating example: Sample of the SIR-3 study



- Observational cohort study from the Charite university hospital in Berlin Germany on hospital-acquired pneumonia in intensive care
- Investigate burden of hospital-acquired infection

Motivating example: Sample of the SIR-3 study

- Commonly used: Kaplan-Meier estimator for classical survival-model

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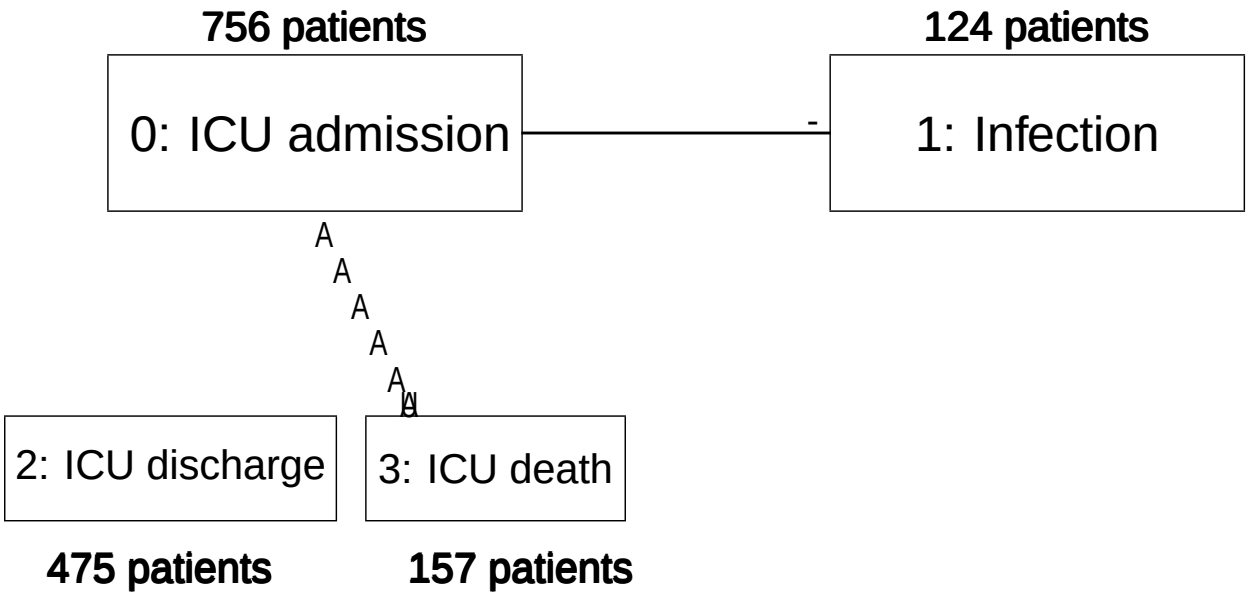

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- Source of bias! Kaplan-Meier estimator treats competing events as non-informative

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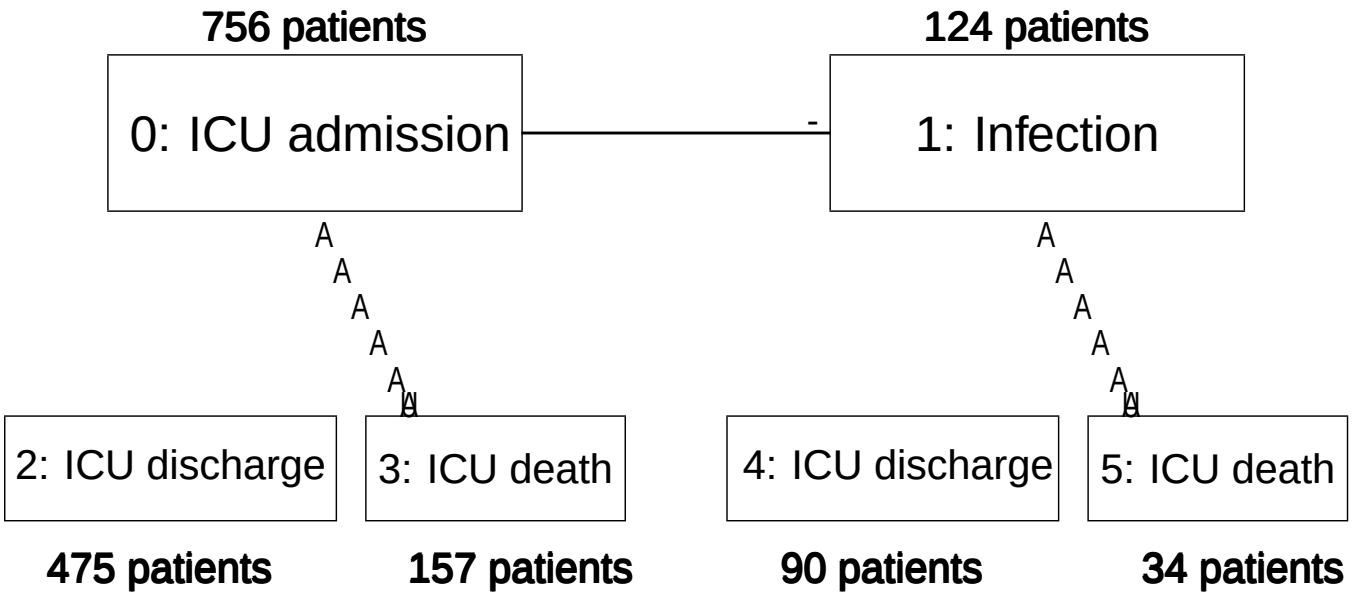

- Commonly used: Kaplan-Meier estimator for classical survival-model
- Source of bias! Kaplan-Meier estimator treats competing events as non-informative
- Watch out for: Competing risks bias, time-dependent bias

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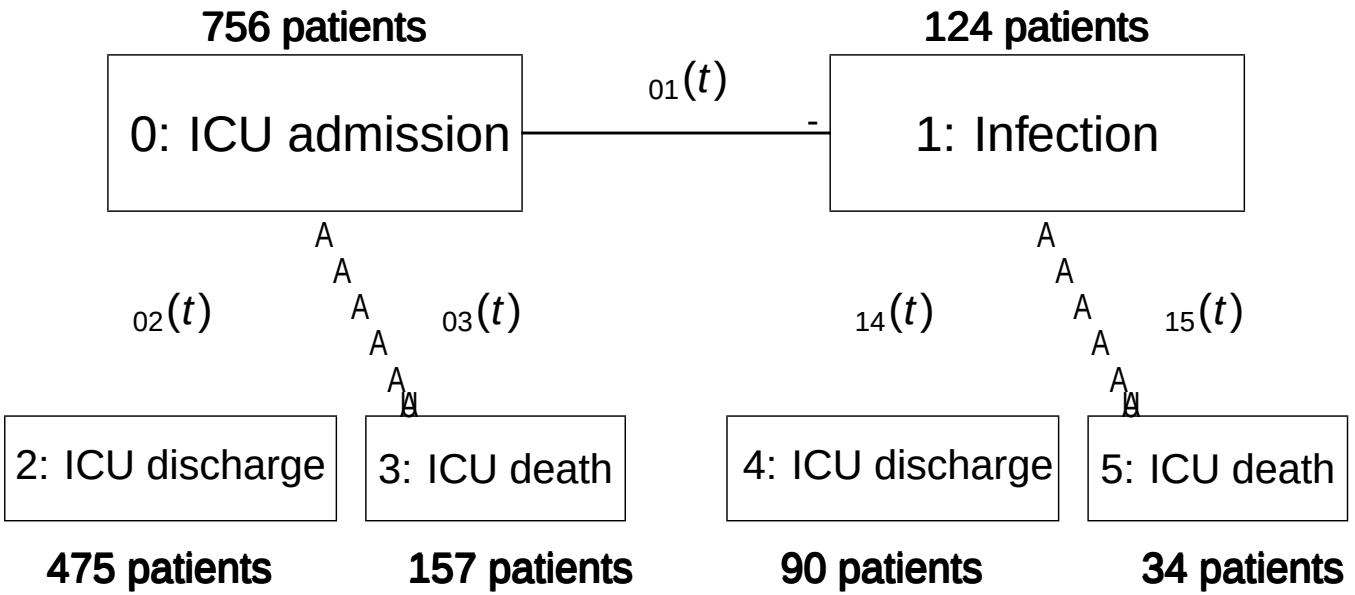

- Transition specific hazard rates $_{ij}(t); i; j \; 2 \; f0; 1; 2; 3; 4; 5g$
- Transition probabilities $P_{ij}(s; t)$
- Hazard ratios of infection, relative risk of death

Parametric estimation: Assuming constant hazards

- Assume $_{ij}(t) = \ _{ij}$ for all possible transitions
- Simple summary analysis

Occurrence of infection	
Incidence rate per day	01

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Occurrence of infection	
Incidence rate per day	01
Risk of infection	$_{01} = (\ _{01} + \ _{02} + \ _{03})$
Mortality	
Death hazard ratio of infection	$_{15} = \ _{03}$
Discharge hazard ratio of infection	$_{14} = \ _{02}$

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Occurrence of infection	
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Risk of infection	$_{01} = (\ _{01} + \ _{02} + \ _{03})$
Mortality	
Death hazard ratio of infection	$_{15} = \ _{03}$
Discharge hazard ratio of infection	$_{14} = \ _{02}$
ICU mortality risk of infected patients	$_{15} = (\ _{14} + \ _{15})$
ICU mortality risk of uninfected patients	$_{03} = (\ _{02} + \ _{03})$
ICU mortality risk ratio	$_{15} = \ _{03} \quad (\ _{02} + \ _{03}) = (\ _{14} + \ _{15})$

Parametric estimation: Assuming constant hazards

- Other quantities such as odds of infection/ICU death, extra length of hospital stay
- Even the transition probabilities of the extended illness-death model have closed mathematical forms!
- Example: $P_{ij}(s;t) = P_{ij}(0;\tau), \tau = t \quad s$
  - $P_{00}(s;t) = P_{00}(0;\tau) = \exp(\ (\ _{01} + \ _{02} + \ _{03})\tau)$
  - $P_{03}(s;t) = P_{03}(0;\tau) = \frac{_{03}}{_{01} + _{02} + _{03}}(1 \quad \exp(\ (\ _{01} + \ _{02} + \ _{03})\tau))$

Parametric estimation: Assuming constant hazards

- Estimate constant hazard rates with maximum likelihood estimator:

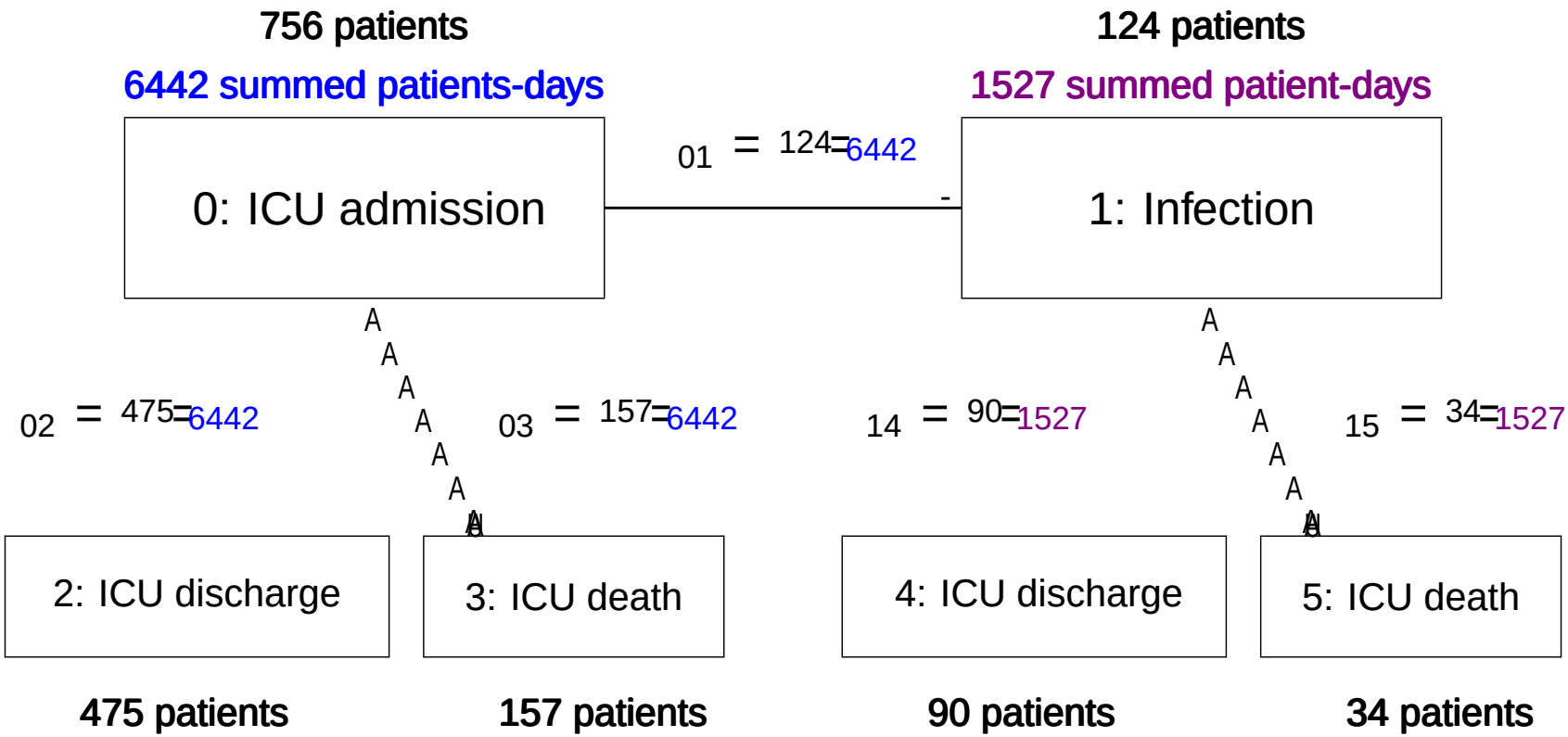
$$\hat{}_{ij} = \frac{\text{Number of } i \;!\; j \text{ transitions}}{\text{Summed patient-days in state } i}:$$

- Plug into the formulas

) **No sophisticated software is necessary for a basic multi-state analysis**

- All you need:
  - Summed patient days in state 0 and 1
  - Number of patients in each state at end of follow-up

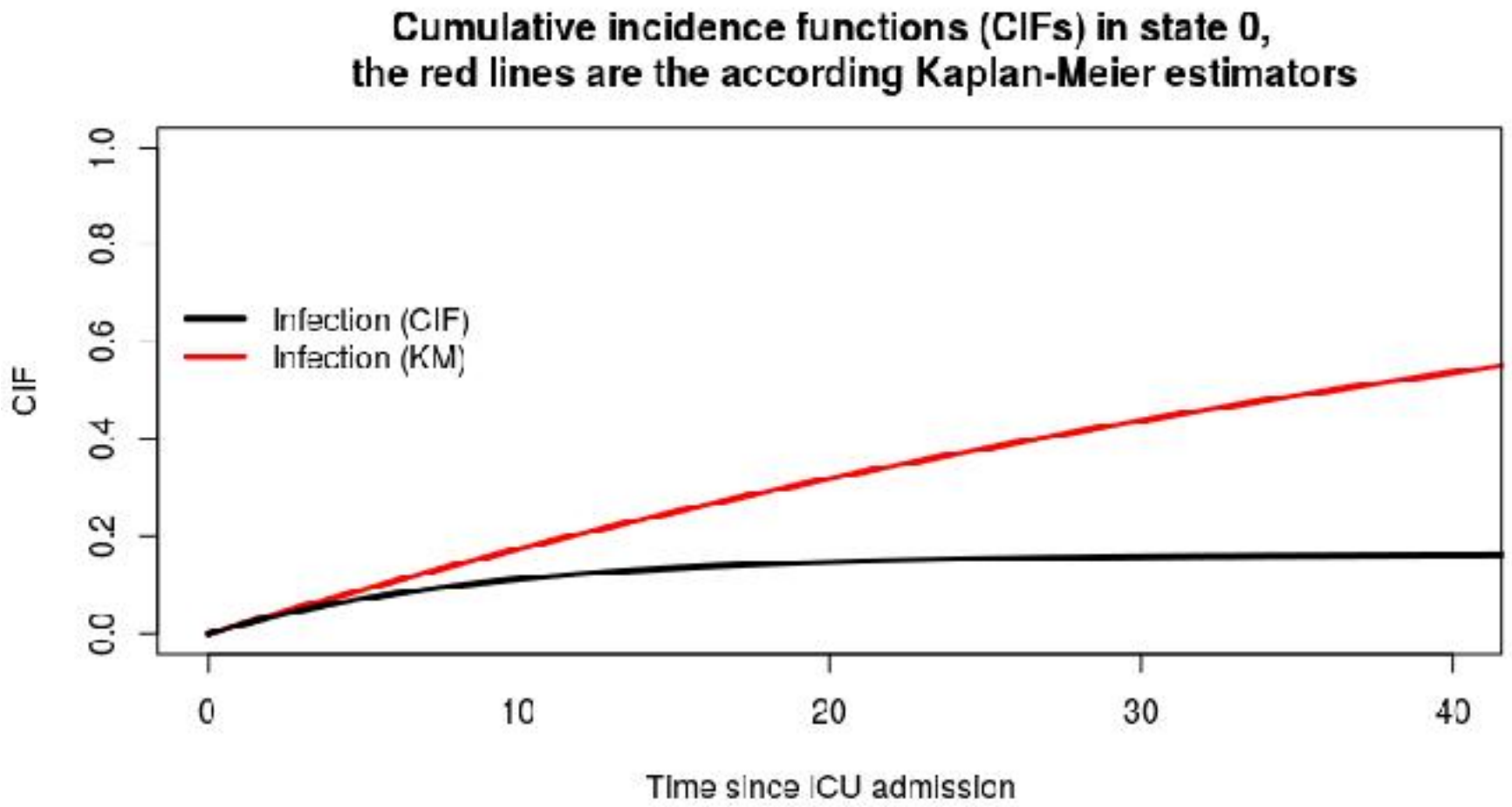
Applied to the sample of the SIR-3 study



Data example: Summary analysis of sample of SIR-3 study

Occurrence of infection	
Incidence rate per day	0.019
Risk of infection	16.4%
Mortality	
Death hazard ratio of infection	0.91
Discharge hazard ratio of infection	**0.80**
ICU mortality risk of infected patients	27.4%
ICU mortality risk of uninfected patients	24.8%
ICU mortality risk ratio	1.11

Parametric cumulative incidence functions to demonstrate competing-risks bias



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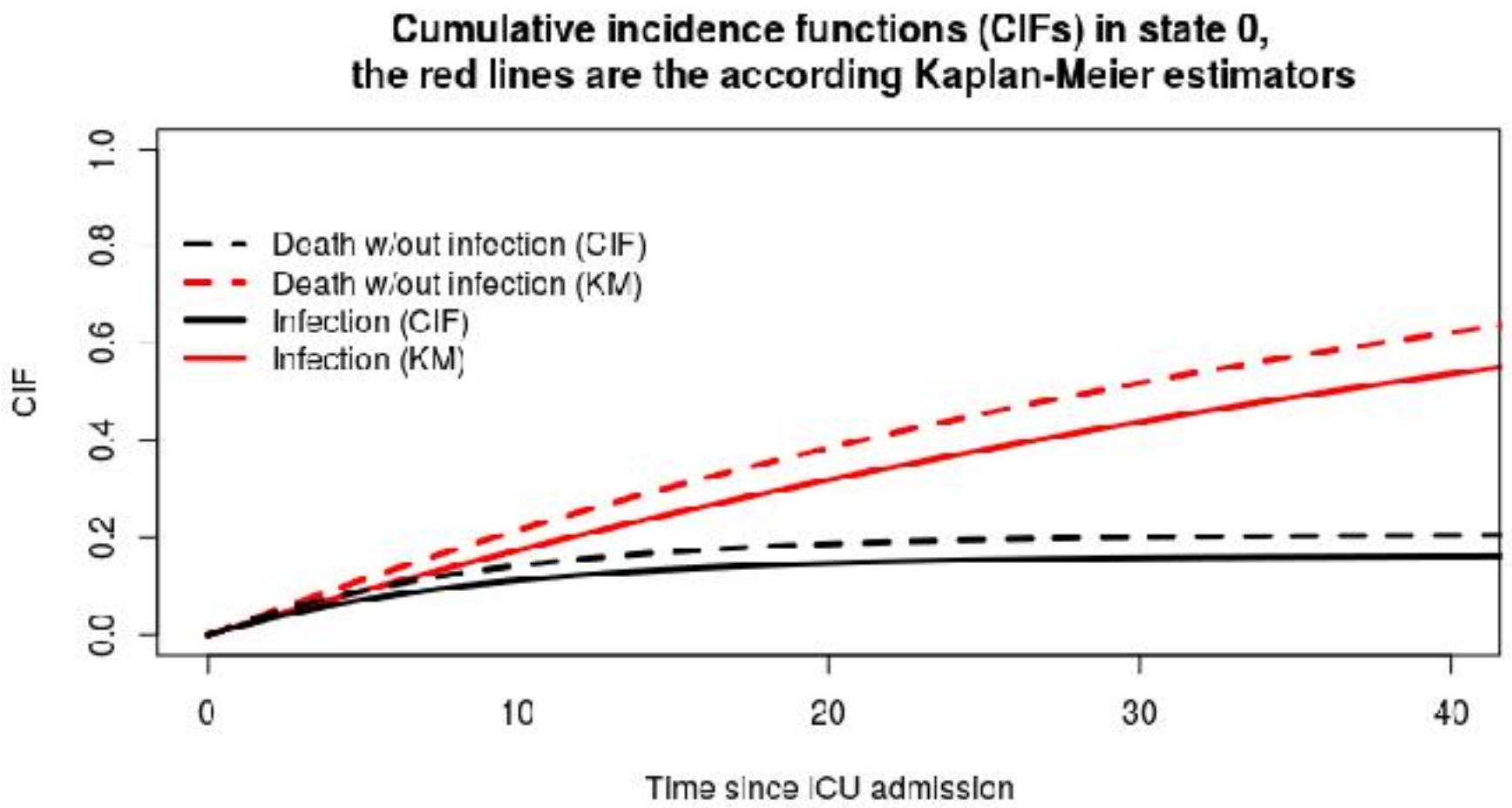

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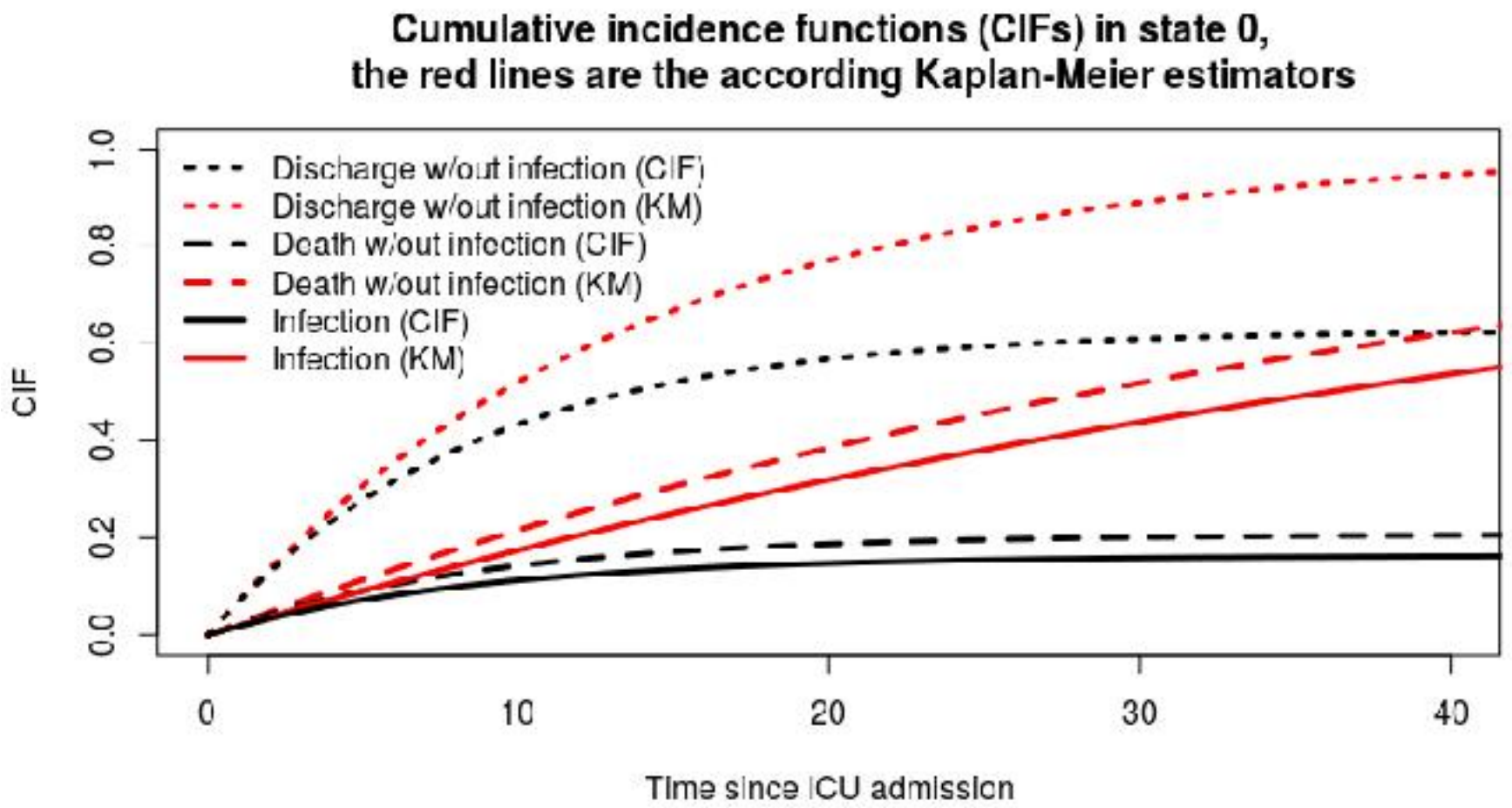

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Summary

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) Provides first insights into data structure and time-dynamics
- Competing risks bias, time-dependent bias are avoided
- Method can be used for reanalysis of published data and meta analysis

) In publications: always provide mean length of stay spent in the transient states and the number of observed events!
- Method applicable to any other data setting with competing risks and binary exposure

Conclusion

Start simple,

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Start simple,
then increase complexity

References

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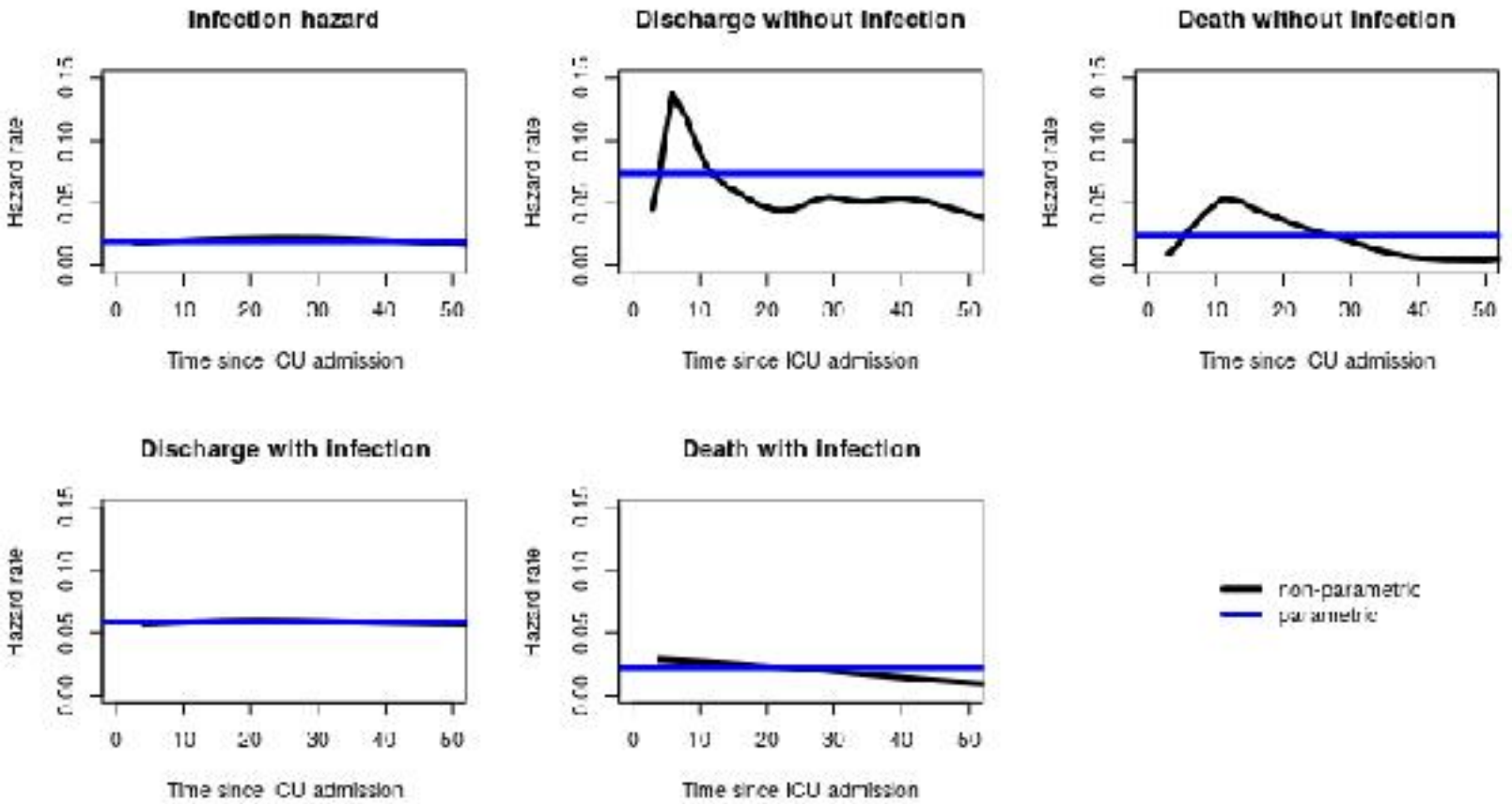
Non-parametric estimation in multi-state models

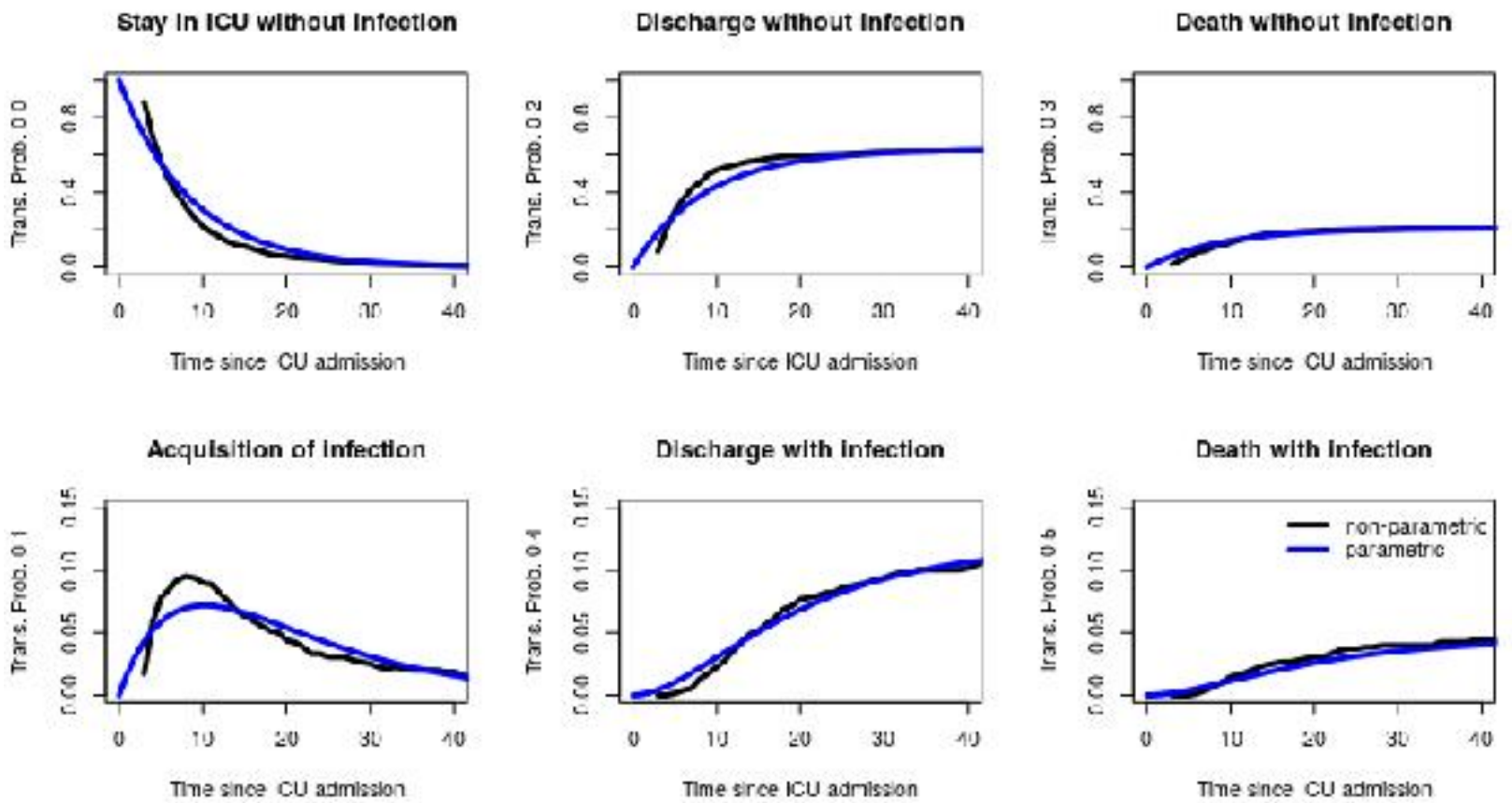
- Nelson-Aalen estimator of cumulative transition-specific hazards
  R-package: mvna
- Aalen-Johansen estimator of transition-probabilities
  R-package: etm, mstate
- Smoothing methods can be used to obtain the transition-specific hazard rates
  R-package: bshazard
- Cox proportional hazards model to estimate hazard ratios
  R-package: survival

) For more details and application see ”Competing risks and Multistate models with R” by Beyersmann et al. (2011)

Misspecification due to false assumption of constant hazards?



Parametric and non-parametric transition probabilities from state 0



Data example: Summary analysis of sample of SIR-3 study

Occurrence of infection / length of stay due to infection	
Incidence rate per day	0.019
Risk of infection	16.4%
Change in length of stay due to infection (cLOS)	1.77 days

- cLOS in naive approach (time-dependent bias):

(?LOS of infected patients) (?LOS of uninfected patients) =

21:0 8:5 = 12:5