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A multistate model for the analysis of clinical outcomes in nosocomial pneumonia patients

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Background

- COMBINE: part of IMI AMR Accelerator, aims to develop approaches for improving the **translation** of **preclinical** results into **clinical** outcomes
- Analyses of antibiotic clinical trial outcomes usually lack an assessment of longitudinal information
- This work aimed to develop a **multistate** model for **pneumonia** clinical data that assessed the relationship of clinical outcomes over time (at end-of-treatment and at end-of-study) and disease progression by evaluating early predictors

Conclusions

- The developed **multistate** model successfully **described** pneumonia **clinical outcomes**
- The **risk of death** over time follows different functions depending on the patient state, presenting a **constant** hazard for patients in the ***cure*** state and a **time-dependent** hazard (Weibull) for those in the ***failure*** state
- Early predictors (**APACHEII** score, **creatinine clearance** and **age**) that can influence the probability of patients transiting to another state were found
- This model is an **initial step** towards a framework which eventually aims to translate quantitative drug effect information (i.e., bacterial load) from preclinical results to improve design and prediction of clinical trials

Multistate models

Standard outcome analysis

- **Univariate statistical** tests (e.g. t-test)
  - Only at the end of the measured outcome
- **Kaplan-Meier** curves
  - Handles censored data
- **Cox** proportional hazards model
  - Describes the effect of covariates on the hazard
  - Can handle continuous covariates
- **Parametric time-to-event** model
  - Describes the underlying baseline hazard
  - Can be used for simulations

Limitations

- **Statistical tests (e.g. t-test)**
  - Does not handle censored data
- **Kaplan-Meier curves**
  - Continuous covariates need to be categorized for their assessment
- **Cox proportional hazards model**
  - Baseline hazard is not estimated
- **Parametric time-to-event model**
  - Biased estimation of the death hazard when several clinical outcomes are present (competing risks)

Multistate models

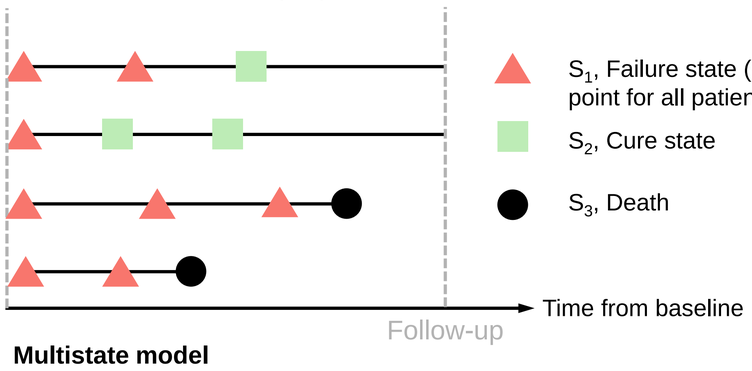
- Considers all **longitudinal** information
- Allows the exploration of **covariate effects** on transitions between **intermediate states** instead of a single effect on the general risk of death
- Bias by **competing risks** is **avoided** by estimating different transition rates to the different states, allowing to distinguish between the risk of death for ill patients and the one for healthier patients
- This **methodology** has **already** been **applied** in other works related to anti-infectives[1], as well as in other fields such as oncology[2]

Methods

Clinical outcomes from a phase IV study[3]

- End-of-treatment (EOT) visit
- End-of-study visit: 7-30 days after EOT
- Overall survival: 60 days after EOT

Patient states were derived from the clinical outcomes and overall survival data. Four example patients can be found below:



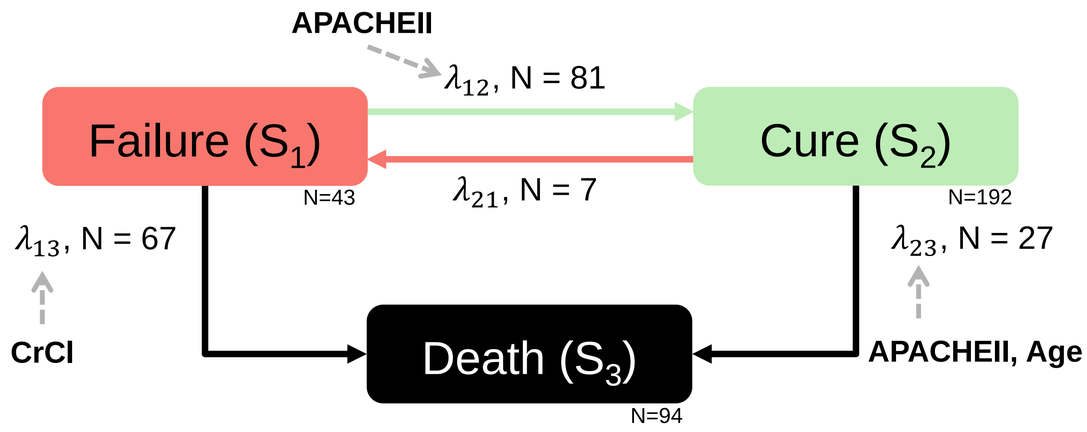
Multistate model

- Patients can transit from failure (S_1) to cure (S_2) or vice versa
- Death can happen from any of the states up to follow-up
- Transition rates λ_{ij}: probabilities of patients transiting from state *i* to state *j* over time
- Baseline covariates tested as predictors on transition rates λ_{ij}

Baseline covariates

- Minimum Inhibitory Concentration for the study drugs
- Age, sex, weight, creatinine clearance (Cockcroft-Gault)
- White blood cell counts
- Clinical scores: APACHEII, CPIS

Results

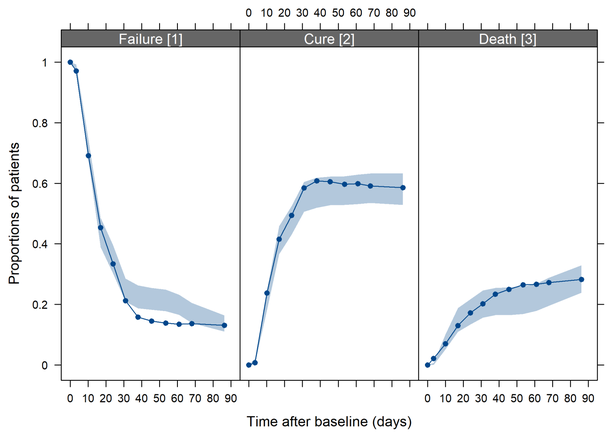


Data and model features

- A total of 329 patients with 896 observations were analyzed
- Transition rates between states followed a constant function except for the one between *failure* and *death* (λ_{13}, Weibull function), that increased over time
- The probability of transiting from ***failure*** **to** ***cure*** (λ_{12}) was lower for **high APACHEII** scores (29) with respect to a median of 17 (HR = 0.72)
- The risk of **dying** when in the ***failure*** state (λ_{13}) was higher for **low creatinine clearance** (CrCl) values (17 mL/min) compared to a median CrCl of 85 mL/min (HR = 1.61)
- The probability of **dying** when in the ***cure*** state (λ_{23}) was larger for **high APACHEII** scores and for **older** patients (86 years) than for those with median age (65 years) (HR = 3.57 and 2.94, respectively)

Visual predictive checks stratified by model state

Dots/lines: observed proportions. Areas: simulated proportions



[1]: Peng Y, Minichmayr IK, Liu H, Xie F, Friberg LE. Multistate modeling for survival analysis in critically ill patients treated with meropenem. CPT Pharmacomet Syst Pharmacol. 2024;13(2):222-233. doi:10.1002/psp4.13072
[2]: Krishnan SM, Friberg LE, Bruno R, Beyer U, Jin JY, Karlsson MO. Multistate model for pharmacometric analyses of overall survival in HER2-negative breast cancer patients treated with docetaxel. CPT Pharmacomet Syst Pharmacol. 2021;10(10):1255-1266. doi:10.1002/PSP4.12693
[3]: Wunderink RG, Niederman MS, Kollef MH, et al. Linezolid in Methicillin-Resistant Staphylococcus aureus Nosocomial Pneumonia: A Randomized, Controlled Study. Clin Infect Dis. 2012;54(5):621-629. doi:10.1093/cid/cir895

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