PAGE poster, 2024

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Assessing clinical outcomes of nosocomial pneumonia patients with a pharmacometric multistate model

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Background

- Analyses of antibiotic clinical trial outcomes (clinical and/or microbiological) usually **lack** an **assessment** of **longitudinal** information
- COMBINE: part of IMI AMR Accelerator, aims to develop approaches for improving the **translation** of **preclinical** results into **clinical** outcomes
- 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 on the transitions between clinical states

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
- **High APACHE II** scores decreased the probability of getting cured and increased the risk of dying once cured, **low creatinine clearance** increased the hazard of dying from the failure state and **older patients** had a higher risk of dying even if they were cured.
- This model is **one step** towards a framework which aims to translate quantitative drug effect information (i.e., bacterial load) from preclinical results to improve design and prediction of clinical trials

Multistate models

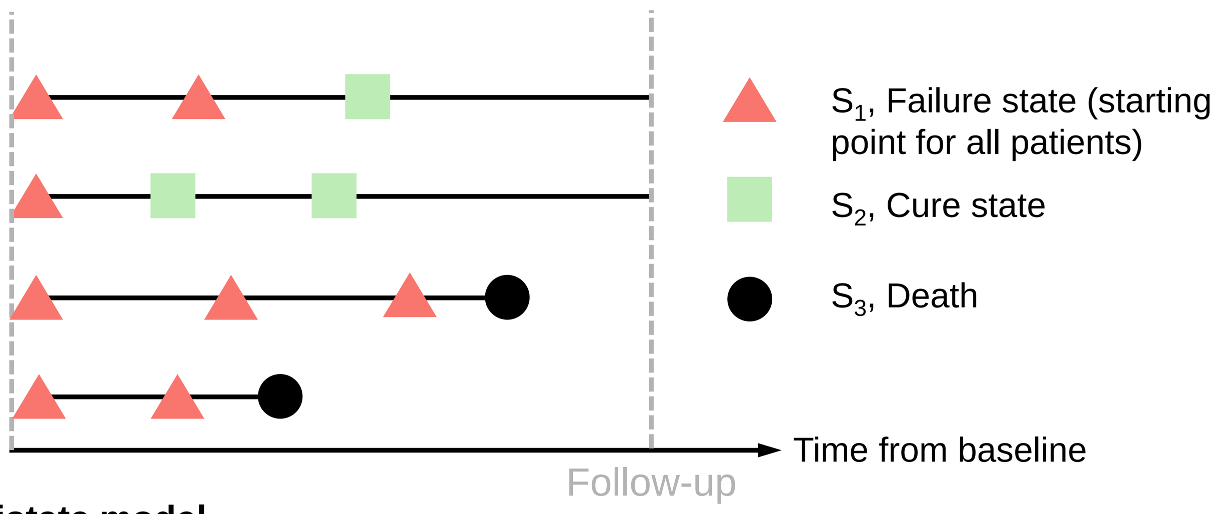
- Analysis of all **longitudinal clinical** outcome data
- Allows the exploration of **covariate effects** on transitions between intermediate states **during and after treatment** instead of a single effect on the general risk of death
- Bias due **competing risks** is **reduced** by estimating different 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** to other fields such as oncology[1] , as well as to anti-infectives without considering clinical outcomes[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 (S_3) 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}

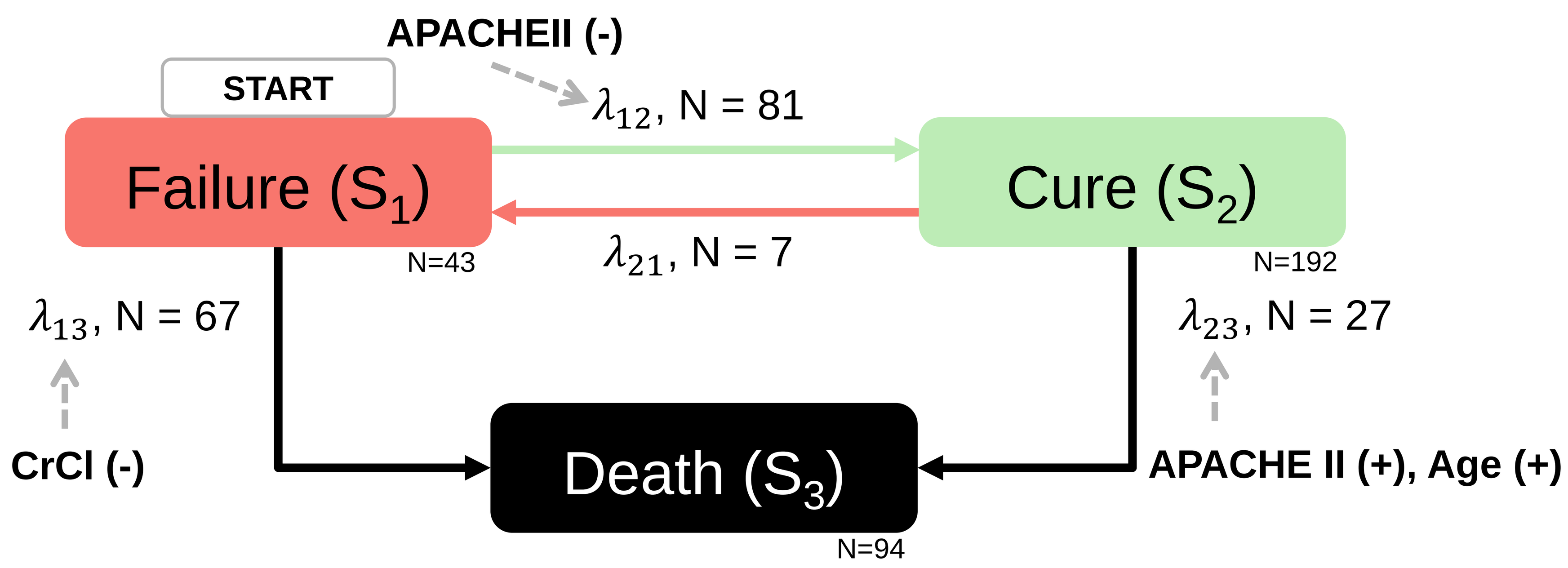
Baseline covariates

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

Model building and selection

- Models were selected upon the objective function value (OFV) and visual predictive checks (VPCs). Parameter uncertainty was evaluated by running non-parametric bootstraps
- Developed in NONMEM. Data processing and plots were carried out in R. Perl-Speaks-NONMEM (PsN) was used for model selection and evaluation

Results



Data and model features

- A total of 329 patients with 896 observations were analyzed
- A **step function** was included to consider differences in transition rates **during** and **after treatment**
  - Few patients died when in the *cure* state during treatment, thus the transition (λ_{23}) was removed from the model
  - The rates from *failure* to *cure* (λ_{12}) and vice versa (λ_{21}) were not significantly different during treatment
- **Transition rates** between states followed a **constant** function except for the one between ***failure*** and ***death*** (λ_{13}, **Weibull** function), that increased over time since randomization
  - Constant function: $\lambda_{ij} = scale_{ij}$; Weibull function: $\lambda_{ij} = scale_{ij} * shape_{ij} * \left(scale_{ij} * T\right)^{shape_{ij}-1}$
- The probability of transiting from ***failure* to *cure*** (λ_{12}) was lower for **high APACHE II** 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 higher for **high APACHE II** scores and for **older** patients (86 years) than for those with median age (65 years) (HR = 3.57 and 2.94, respectively)

Parameter estimates and uncertainty of the multistate model

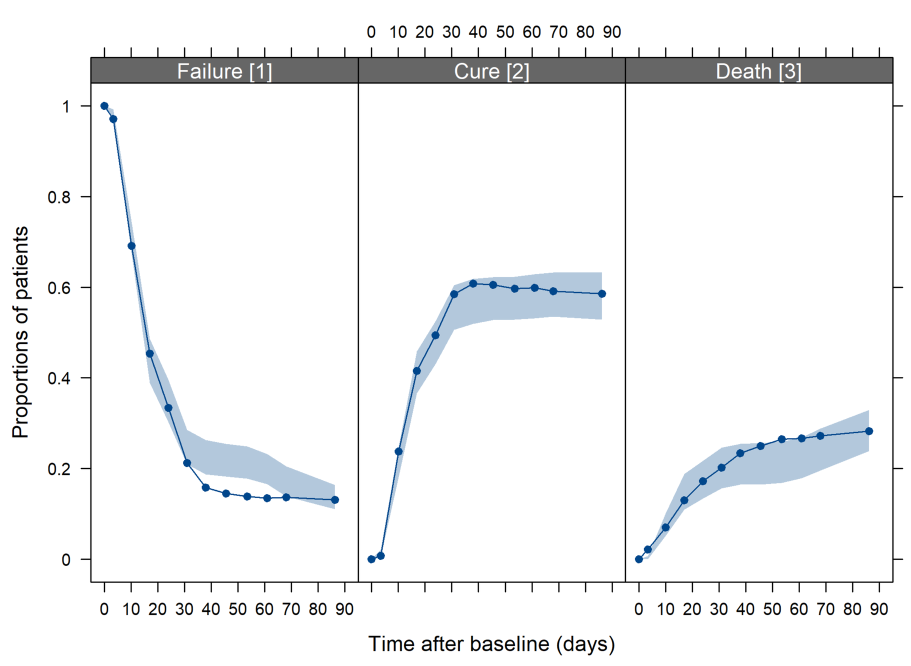
Parameter	Description	Value	95% CI (Bootstrap[a])
During treatment (median treatment duration: 8.5 days)			
$scale_{12\_21}$	*Failure* → *cure* and vice versa	0.122	0.0684 – 0.292
$scale_{13}$	*Failure* → *death*	0.0595	0.0269 – 0.0907
$shape_{13}$		1.83	1.22 – 3.43
After treatment			
$scale_{12}$	*Failure* → *cure*	0.0649	0.0556 – 0.0759
$scale_{21}$	*Cure* → *failure*	0.00552	0.00229 – 0.00991
$scale_{13}$	*Failure* → *death*	0.0179	0.0133 – 0.0232
$shape_{13}$		1.54	1.33 – 1.85
$scale_{23}$	*Cure* → *death*	0.00129	0.000296 – 0.0180
Relationship between transition rates and covariates[b]			
$\beta_{APACHEII\_12}$	Effect of APACHE II on *failure* → *cure* with respect to median (17)	-0.0278	-0.0486 – -0.00803
$\beta_{APACHEII\_23}$	Effect of APACHE II on cure → death with respect to median (17)	0.106	0.0414 – 0.193
β_{CrCl_13}	Effect of CrCl on failure →death with respect to median (85 mL/min)	-0.00716	-0.0127 – -0.00282
β_{Age_23}	Effect of age on cure → death with respect to median (65 years)	0.0514	0.0185 – 0.126

Abbreviations: CI, confidence interval; CrCl, creatinine clearance.

[a]A total of 1000 samples were run for the non-parametric bootstrap.

[b]Covariate effect included as $\lambda_{ij} * e^{[\beta_{COV} * (COV_k - COV_{median})]}$, where COV_k and COV_{median} are the individual baseline covariate value for the patient *k* and the median covariate value, respectively.

Visual predictive checks stratified by model state



A total of 1000 samples were run. Dots/lines: observed proportions of patients over time. Areas: 95% confidence interval of simulated proportions of patients over time.

[1]: 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

[2]: 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

[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

Acknowledgements: This work has received support from the EU/EFPIA Innovative Medicines Initiative 2 Joint Undertaking (COMBINE grant n° 853967) This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA companies' in kind contribution. The computations were enabled by resources provided by the National Academic Infrastructure for Supercomputing in Sweden (NAISS) at Uppsala Multidisciplinary Center for Advanced Computational Science (UPPMAX), partially funded by the Swedish Research Council through grant agreement no. 2022-06725.

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