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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

Multistate models

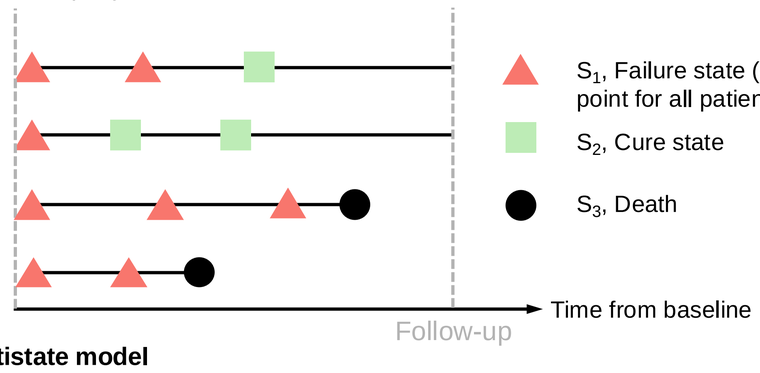
- Analysis of all **longitudinal clinical** outcome data
- Allows the exploration of **covariate effects** on transitions between intermediate states **during and after treatment** instead of a single effect on the general risk of death
- Bias due **competing risks** is **reduced** by estimating different 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

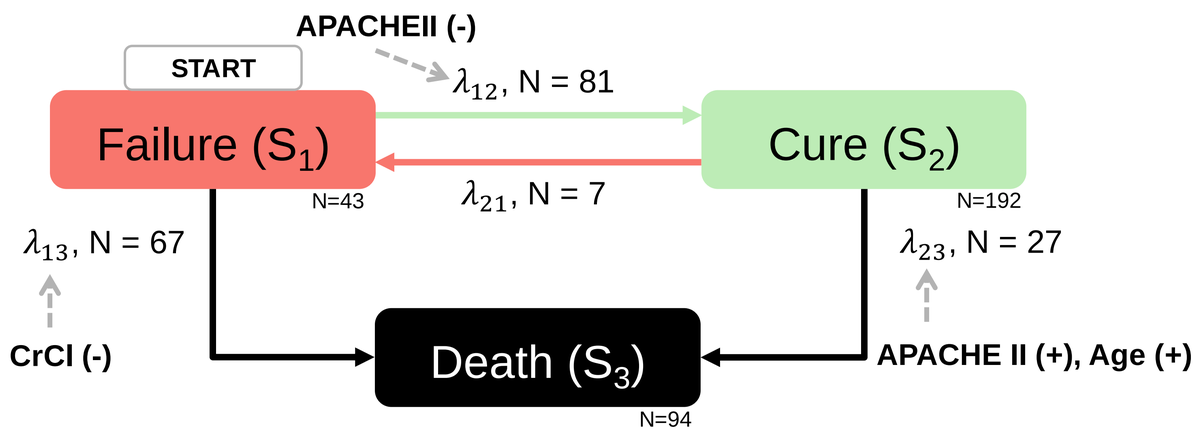
Model building and selection

- 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

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

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

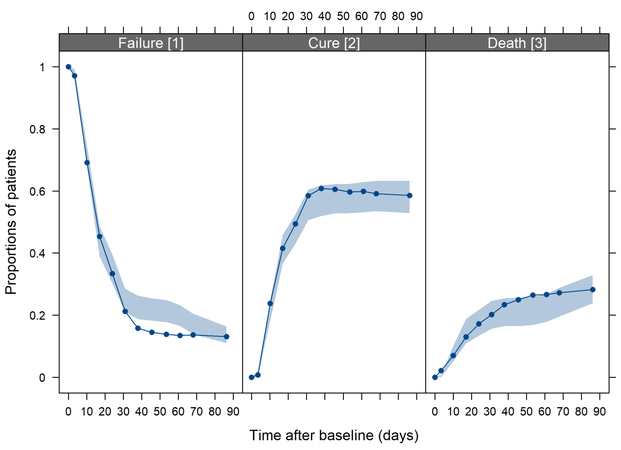
Parameter	Description	Value	95% CI (Bootstrap[a])
During treatment (median treatment duration: 8.5 days)			
$scale_{12\_21}$	*Failure* → *cure* and vice versa	0.122	0.0684 – 0.292
$scale_{13}$	*Failure* → *death*	0.0595	0.0269 – 0.0907
$shape_{13}$		1.83	1.22 – 3.43
After treatment			
$scale_{12}$	*Failure* → *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

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