

Bounded integer approach to model time-varying SOFA scores from patients with carbapenem resistant infections

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Background

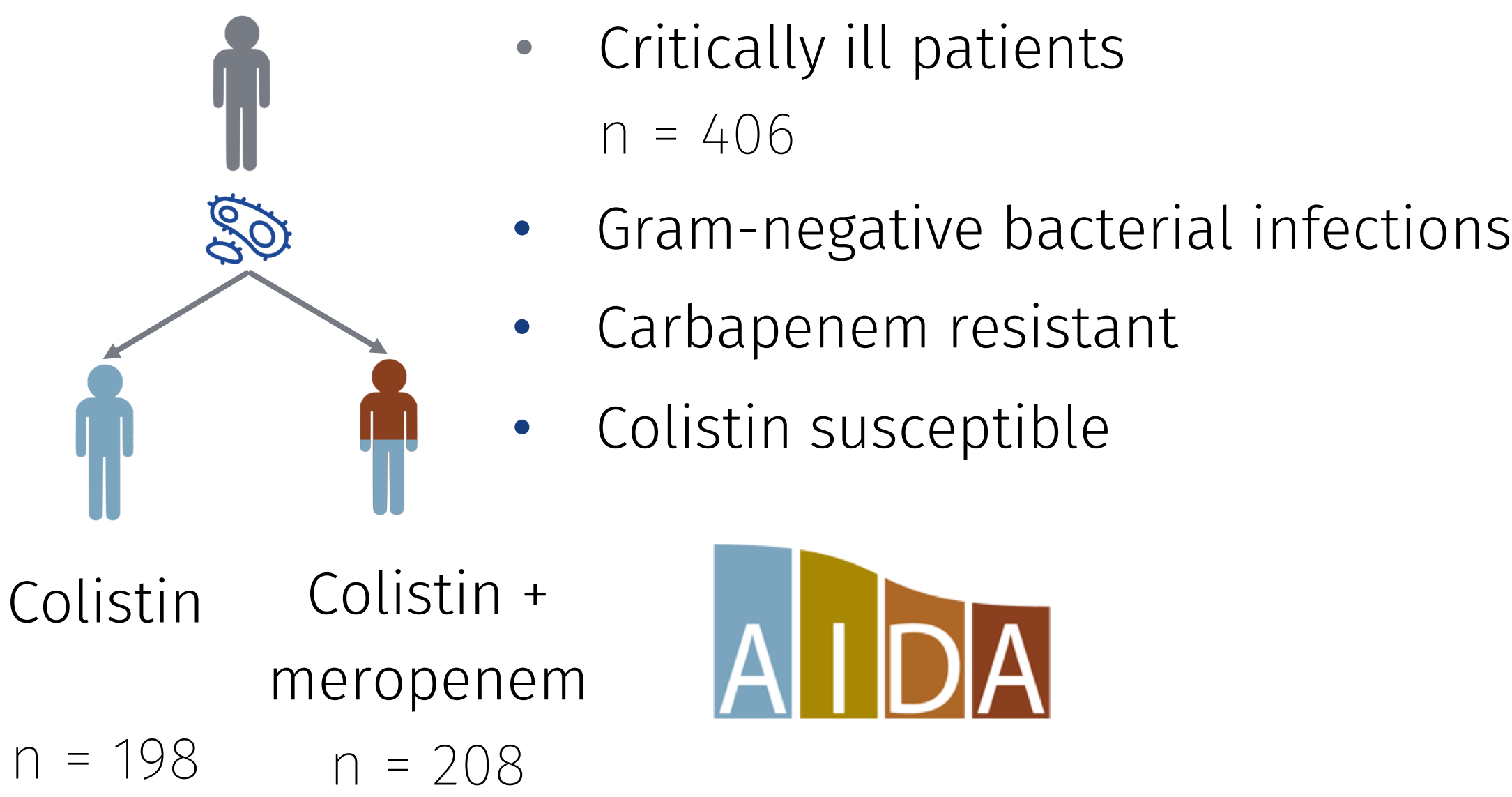
How can variables be analyzed efficiently in the clinical development of antibacterials

- One commonly used clinical score is SOFA (Sequential Organ Failure Assessment score).
- SOFA is a composite score ranging from 0 (normal organ function) to 24 (most abnormal organ function).
- SOFA describes renal, respiratory, cardiovascular, neurological, coagulation, and hepatic function.
- Colistin is used as a last-resort drug against resistant bacteria

Aim: Explore the ability of the Bounded Integer modelling approach to elucidate if colistin exposure has an influence on how SOFA score changes over time.

Method: Data

Data were available from a clinical trial

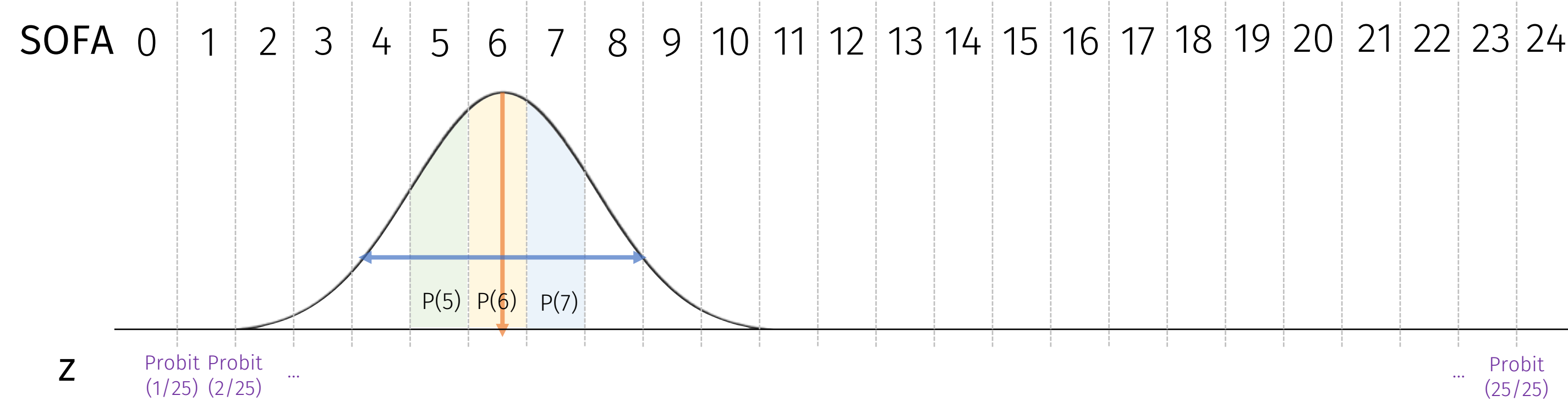


- Dependent variable: SOFA
- Independent variable: Time (Four time-points: Onset of infection, Randomization (day 0), day 7, and day 14)
- Covariates:
 - Treatment: Colistin exposure ($\bar{c}_{pl}$) and arm
 - Demographics: Age, sex, weight, and height
 - Lab: Creatinine, albumin, and urea
 - Infection: Pathogen, infection site, and Minimum Inhibitory Concentration (MIC, colistin/meropenem)

Analysis

Bounded Integer model was fit to SOFA scores

- Divide a $N(0,1)$ distribution into k parts of equal size, where k = number of scores (categories)
- Estimate mean and standard deviation (SD) of the z-distribution of the SOFA scores with IIV.
- Area within cut-offs = Probability of observing the score, $P(\text{score})$



Structural model:

```
MEAN = THETA(1) + ETA(1) ; Mean z-value for the individual
COV_1 = THETA(3) + ETA(3) ; Time (disease progression)
COV_2 = THETA(4) + ETA(4) ; Colistin exposure during first 24 h
COV_3 = THETA(5) + ETA(5) ; log(MIC_meropenem)

COV1 = TIME * COV_1 ; Time since randomization
COV2 = (C_avg_24 - 2) * COV_2
COV3 = (log_MIC_meropenem - 4.5) * COV_3
IPRED = MEAN + COV1 + COV2 + COV3 ; f(Theta, Eta, time, covariates)
SD = THETA(2) + EXP(ETA(2)) ; SD of the Distribution over the Scores.
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Individual score predictions:

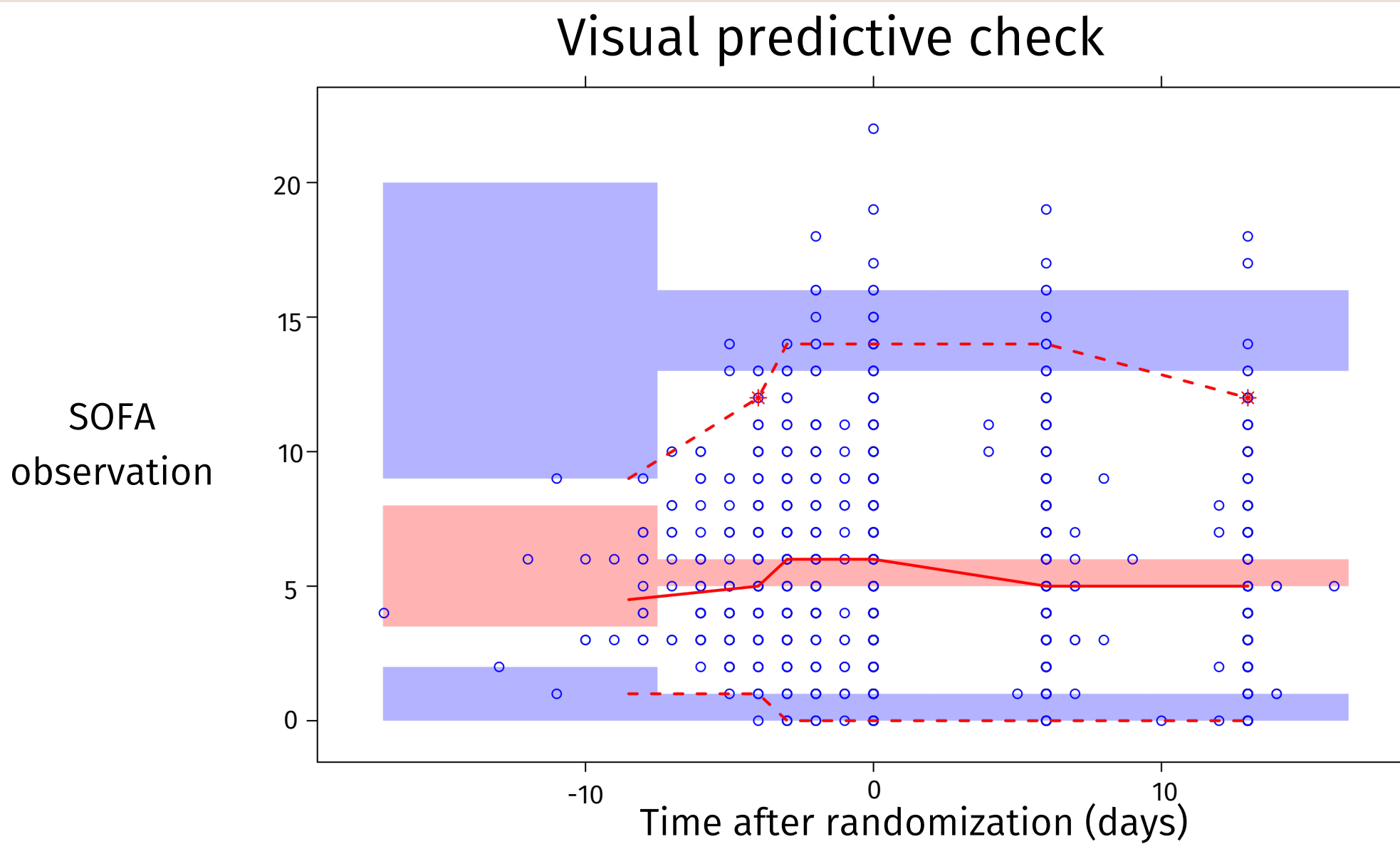
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P(0) = PHI((CO1 - IPRED) / SD) ; Cut-offs: CO(m) = Probit(m/k), m = 1, 2, ..., k
P(1) = PHI((CO2 - IPRED) / SD) - PHI((CO1 - IPRED) / SD)
...
P(23) = PHI((CO24 - IPRED) / SD) - PHI((CO23 - IPRED) / SD)
P(24) = 1 - PHI((CO24 - IPRED) / SD)

PPRED = 0 * P(0) + 1 * P(1) + ... + 23 * P(23) + 24 * P(24)
```

Software: NONMEM 7.4.3 and PsN 4.8.8

Results

The model described the data well



Significant predictors:

Name	Hazard Ratio [95% CI]	Estimates	Relative Standard Error	Interindividual variability (ω)	Relative Standard Error
Mean z-value		-0.685	4%	0.447	4%
Standard deviation		0.179	4%	0.577	8%
Time [day ⁻¹]		-0.004	30%		
$\bar{c}_{pl}$, colistin (Randomization - 24h) [L mg ⁻¹]	1.05 [1.01 1.08]	0.015	35%		
ln(MIC _{meropenem}) [L mg ⁻¹]	1.08 [1.02 1.14]	0.064	35%		

Conclusions:

- The Bounded Integer modelling approach was successfully applied on SOFA score data.
- The model could characterize the reduction in SOFA score over 14 days for the typical patient, as well as the variability between patients.
- The model indicated that high colistin exposure was associated with a high SOFA score. This finding might be confounded by kidney function because both colistin concentration and SOFA score increase with reduced kidney function.