

Pharmacometric analysis of symptom burden during anti-cancer therapy by a Markov modelling approach

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Introduction

The patient perspective is becoming increasingly important in the assessment of adverse drug events (ADE), as measured by the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [1]. Predicting patient-reported symptom burden can contribute to individualized optimization of therapeutic and supportive measures in cancer treatment. Continuous-time Markov models (CTMM) and minimal continuous-time Markov models (mCTMM) are well suited to describe toxicity-covariate relationships in combination with pharmacometric models [2].

Aim

To develop a modelling and simulation framework describing the symptom burden of patients treated with a continuous infusion fluorouracil (5-FU).

Methods

- In an observational study (5-FU-PRO) patients with colorectal cancer treated with a continuous infusion of 5-FU were assessed for symptom burden using a validated electronic questionnaire with selected PRO-CTCAE items [3].
- CTMMs and mCTMMs were developed to describe the severity of 16 measured PRO-CTCAE symptoms, e. g. diarrhea.
- Covariates were selected via forward inclusion (p value ≤ 0.05) and subsequent backward exclusion (p value ≤ 0.01).

Summary and Conclusions

- The time course of PRO-CTCAE symptom scores for diarrhea could be successfully described by continuous-time (CTMM) and minimal continuous-time Markov models (mCTMM).
- The covariates identified using the CTMM approach were found to be more plausible than those identified using the mCTMM approach.
- These findings indicate the need to distinguish covariate effects between forward and backward transition rates in PRO-CTCAE data.

Results

- In the period from November 2020 to December 2022, 42 patients were enrolled.
- 355 PRO-CTCAE questionnaires were collected.
- Severity grades 2 and 3 were combined for modeling purposes, as severity grade 3 was reported very rarely.
- In the covariate analysis, different covariates were identified with both approaches.

Parameter estimates of CTMM

Parameter	Estimate (RSE, %)	Bootstrap Median	Bootstrap 95 % CI
λ_{01}	0.07 (31 %)	0.07	0.02 to 0.28
λ_{10}	0.09 (20 %)	0.09	0.04 to 0.41
λ_{12}	0.01 (37 %)	0.01	0.01 to 0.05
λ_{21}	0.13 (20 %)	0.14	0.07 to 0.59
$\theta_{for\ Oxa}$	4.71 (42 %)	5.08	1.74 to 13.42
$\theta_{back\ Oxa}$	- 0.70 (31 %)	-0.63	- 0.88 to 0.01
$\theta_{for\ Diar}$	3.6 (61 %)	3.66	0.94 to 10.65
$\theta_{back\ Diar}$	- 0.80 (26 %)	-0.77	- 0.92 to - 0.15

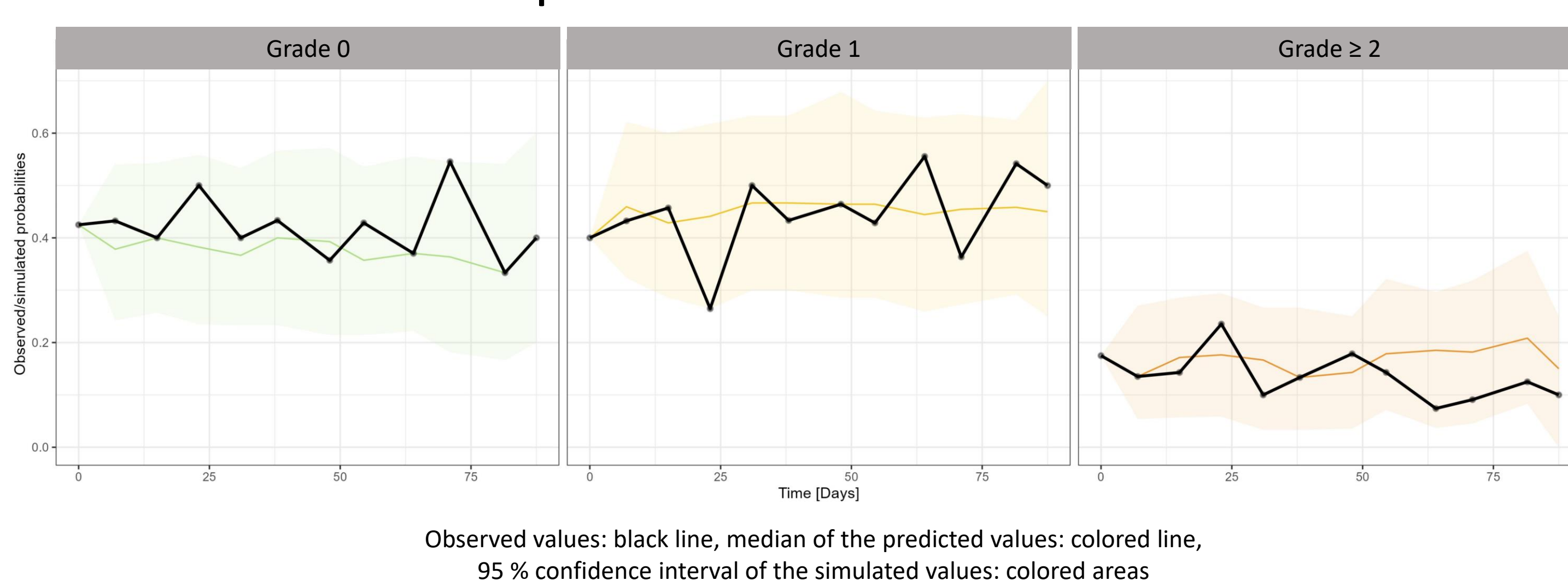
$\lambda_{n, n\pm 1}$ transition rate from grade n to grade n ± 1 , θ_{for} effect size on forward transition (from Grade n to Grade n + 1), θ_{back} effect size on backward transition (from Grade n to Grade n - 1), θ_{Oxa} effect size of comedication with oxaliplatin as covariate on the transition rate, θ_{Diar} effect size of diarrhea medication as covariate on the transition rate

Parameter estimates of mCTMM

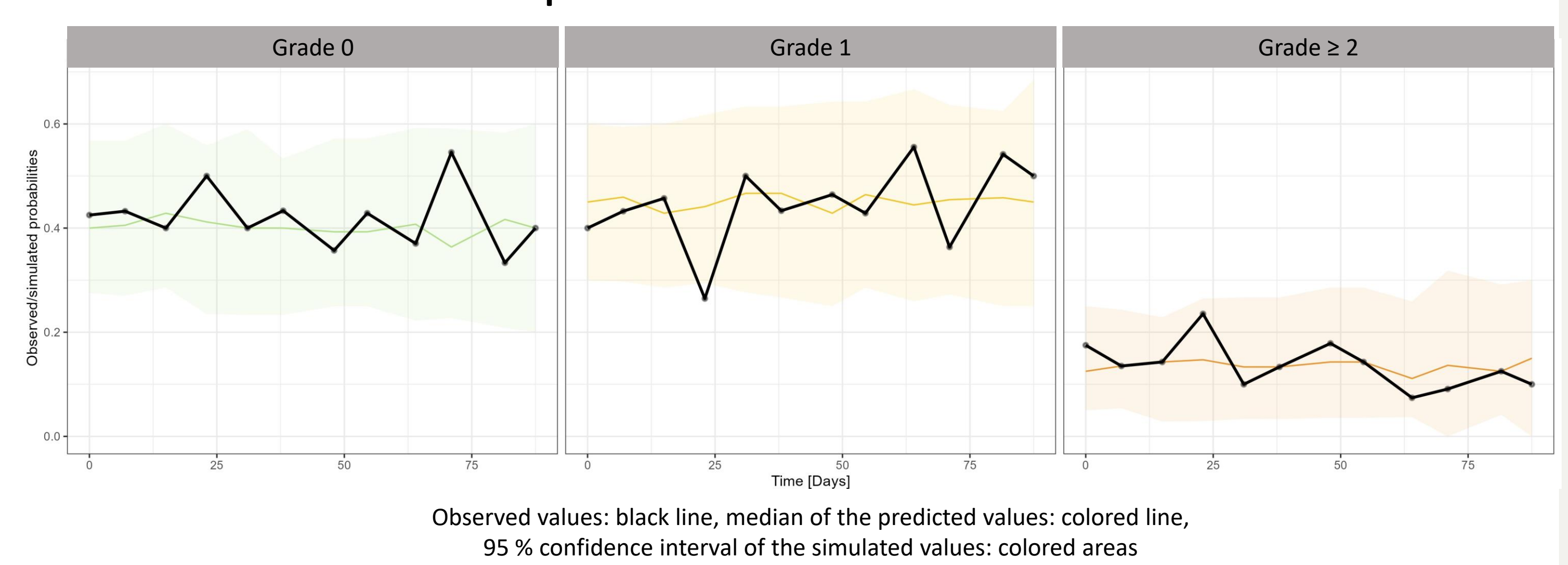
Parameter	Estimate (RSE, %)	Bootstrap Median	Bootstrap 95 % CI
α_1	0.55 (38 %)	0.55	0.09 to 1.24
b_2	- 2.45 (9 %)	- 2.48	- 3.08 to - 2.02
$MET [days]$	6.47 (36 %)	6.88	1.36 to 14.01
ω_{MET}	2.21 (47 %)	2.04	0.65 to 6.81
θ_{Age}	- 0.07 (22 %)	- 0.06	- 0.11 to 0.02
θ_{BSA}	- 3.29 (24 %)	- 2.94	- 5.43 to - 0.53
θ_{Bol}	- 1.68 (36 %)	- 1.43	- 4.90 to 0.89

α_1 Intercept parameter for Diarrhea grade 1 on the logit scale, b_n parameter for grade n such that $\alpha_n = \alpha_{n-1} + b_n$, MET mean equilibration time, θ_{Age} effect size of age as covariate on the logit scale, θ_{BSA} effect size of body surface area, θ_{Bol} effect size of bolus administration of 5-FU, ω_{MET} standard deviation of the interindividual variability of MET.

Visual predictive check of the final CTMM



Visual predictive check of the final mCTMM



References

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