

Comparison of different minimal continuous-time Markov model structures for the analysis of symptom burden during anti-cancer drug therapy

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Introduction

The patient perspective is becoming increasingly important in the assessment of adverse drug events (ADEs), 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 measures in cancer treatment. Minimal continuous-time Markov models (mCTMM) are well suited to describe toxicity-covariate relationships in combination with pharmacometric models [2].

Aim

Development of different mCTMMs to identify covariate influences on the occurrence of selected patient-reported ADEs in patients treated with fluorouracil (5-FU).

Summary and Conclusions

- The development of mCTMMs in combination with PRO-CTCAE symptom scores was feasible. The diarrhea model was improved by the inclusion of covariates.
- The two models with two mean equilibration times (METs) were less stable than the model with one MET, probably because the data was too sparse.
- For a better evaluation of the modifications, further analyses with larger data sets should be performed.

Methods

Study centers

- 5-FU dose
- 5-FU plasma concentrations
- Comedications



Patients

- Diagnosis of Colorectal Cancer
- Demographic Data
- Weekly PRO-CTCAE Questionnaires



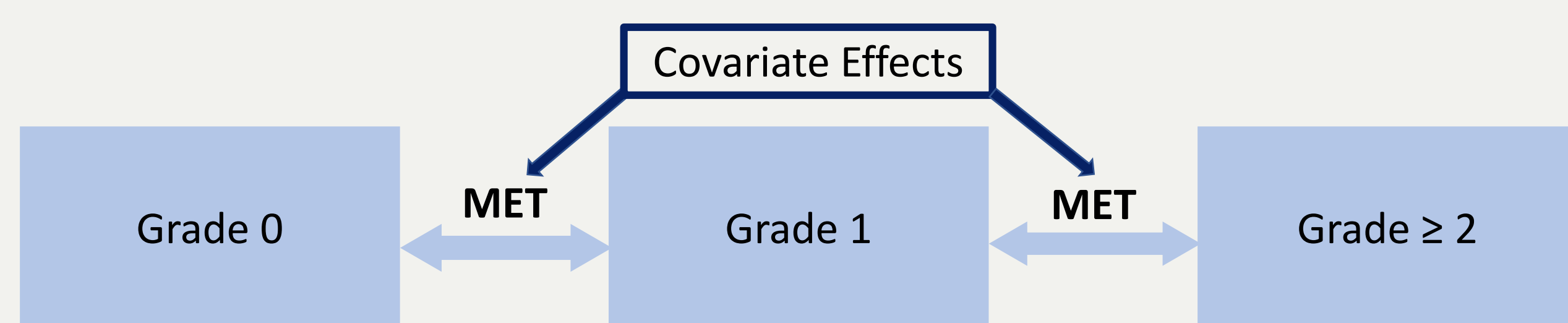
November 2020 to December 2022
Observation period: 12 Weeks

42 Patients
355 Questionnaires

Modelling

- mCTMMs were developed to describe the severity of the PRO-CTCAE symptom diarrhea. Severity grades 2 and 3 were combined for modeling purposes, as severity grade 3 was reported very rarely.
- Two mCTMMs with one mean equilibration time (MET) and two mCTMMs with two METs were developed.
- Covariate influences were tested on α_1 and MET
- Covariates were selected via forward inclusion (p value ≤ 0.05) and subsequent backward exclusion (p value ≤ 0.01).

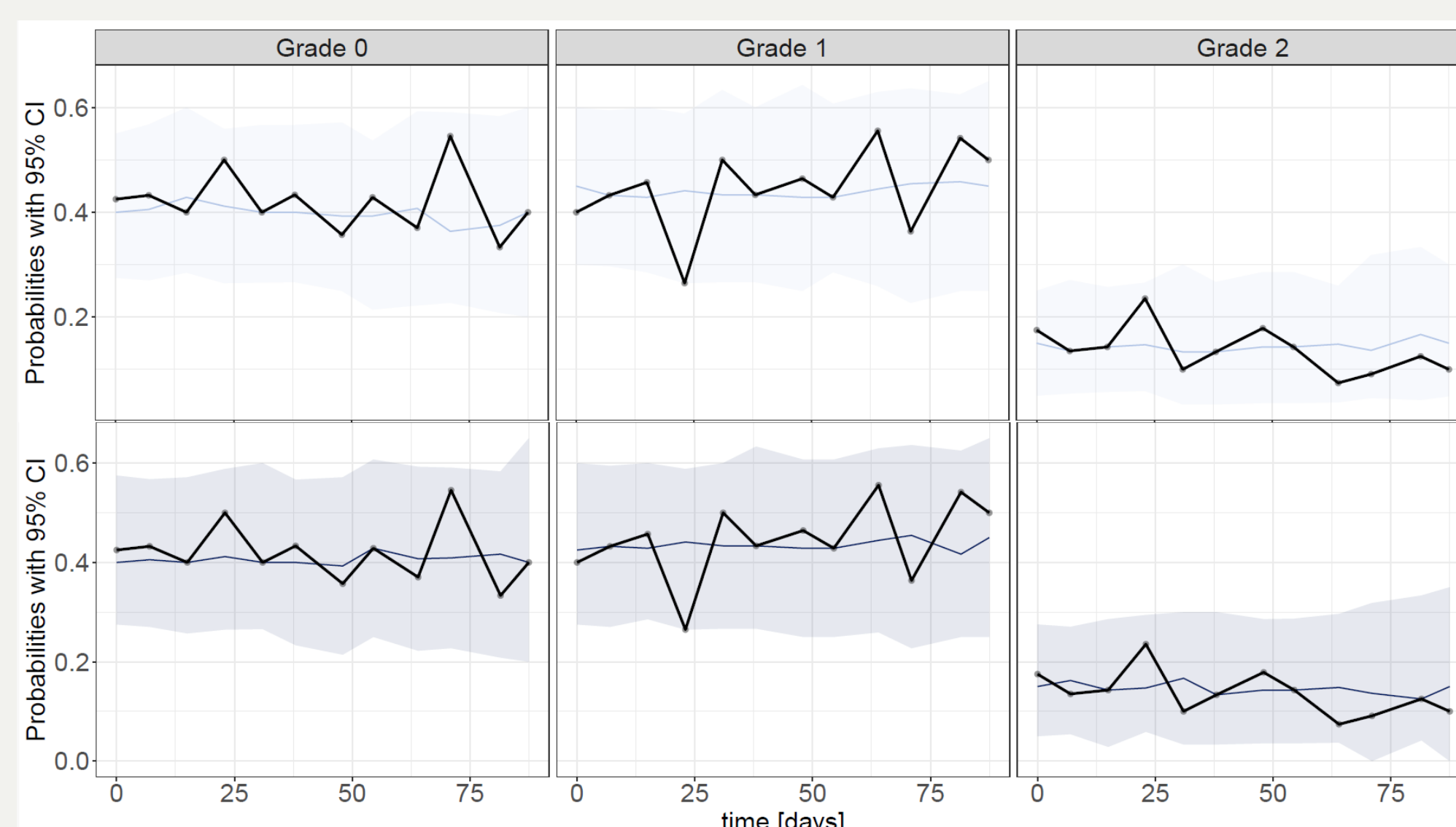
Results



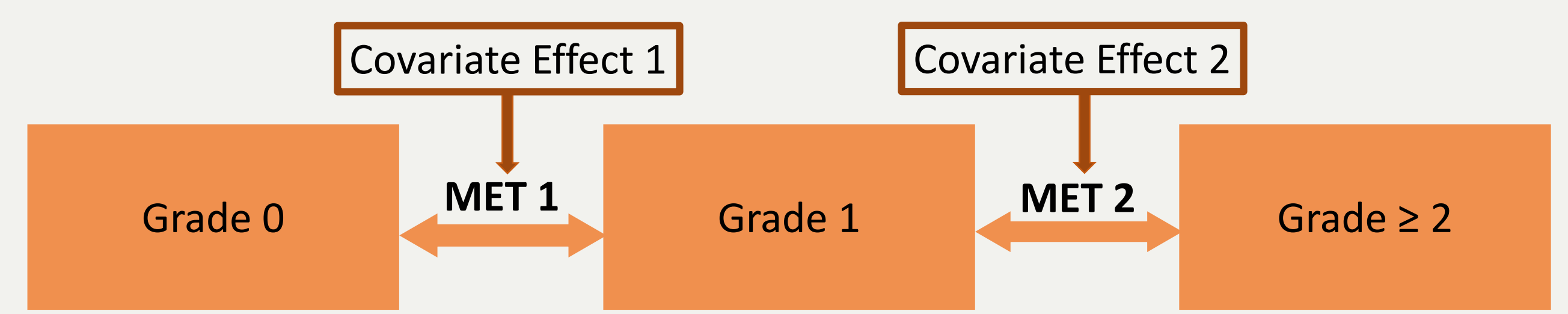
One mean equilibration time (MET)

Parameter	Model 1 Estimate (RSE, %)	Model 2 Estimate (RSE, %)
α_1	0.563 (34 %)	0.352 (42 %)
b_2	- 2.39 (8 %)	- 2.05 (9 %)
MET	5.83 (14 %)	3.28 (19 %)
θ_{Age}	-0.574 (25 %)	-
θ_{BSA}	- 2.33 (30 %)	-
θ_{Bol}	- 1.39 (32 %)	-
θ_{Sex}	-	2.03 (38 %)
θ_{DIAR}	-	- 1.7 (14 %)

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, θ_{Sex} effect size of sex, θ_{DIAR} effect size of diarrhea medication



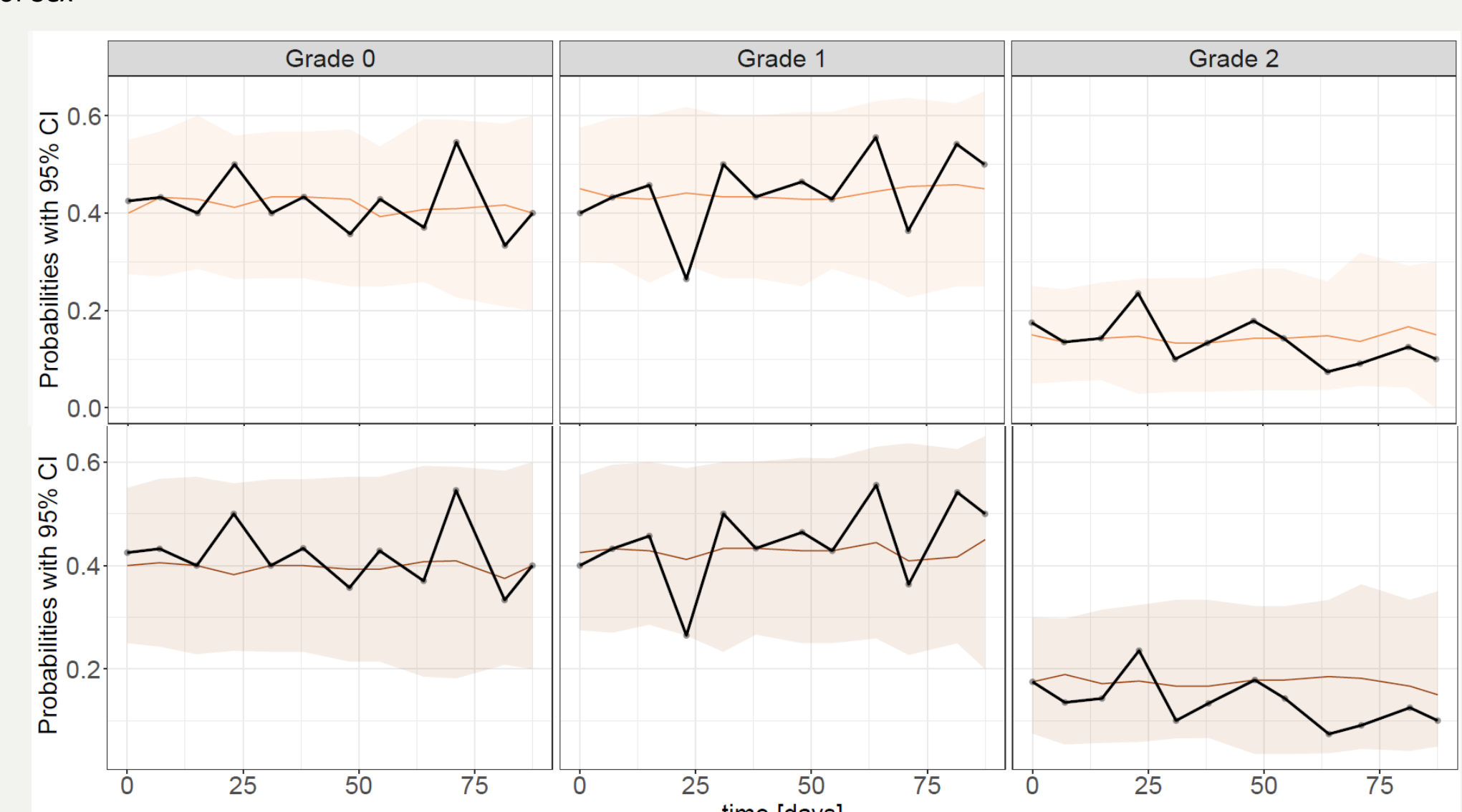
Observed values: black line, median of the predicted values: colored line, 95 % confidence interval of the simulated values: colored areas,
Top left: Model 1
Bottom left: Model 2
Top right: Model 3
Bottom right: Model 4



Two mean equilibration times (METs)

Parameter	Model 3 Estimate (RSE, %)	Model 4 Estimate (RSE, %)
α_1	0.581 (34 %)	0.429 (33 %)
b_2	- 2.45 (8 %)	- 1.96 (11 %)
$MET 1$	6.85 (16 %)	0.665 (362 %)
$MET 2$	3.96 (35 %)	5.42 (26 %)
θ_{Age}	- 0.628 (23 %)	-
θ_{BSA}	- 2.58 (28 %)	-
θ_{Bol}	- 1.51 (32 %)	-
θ_{Sex1}	-	12.2 (393 %)
θ_{Sex2}	-	2.3 (80 %)

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, θ_{Sex} effect size of Sex



References

- Minasian L, O'Mara A, Mitchell SA. Patient Relat Outcome Meas 2022; 13: 249-258
- Schindler, E, Karlsson MO. AAPS J 2017; 19: 1424-143

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