

Meta-analysis of rifampicin exposure and mortality in three randomized controlled phase II tuberculosis meningitis trials

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Background

Tuberculosis meningitis (TBM) is the most severe form of tuberculosis, with up to 50% mortality mostly within the first 2 weeks after presentation of disease [1]. The currently recommended treatment consists of a 4-drug combination: rifampicin (RIF), isoniazid, ethambutol and pyrazinamide. Recent studies suggest that an **intensified regimen with higher RIF doses** during the first critical days of treatment may **improve outcome**.

Objective

- Characterize population PK of high-dose RIF in plasma and cerebrospinal fluid (CSF)
- Investigate predictors of PK variability
- Evaluate a link between individual RIF exposures and 6-month mortality

Methods

An individual patient data meta-analysis including three randomized controlled phase II trials performed in the same center in Bandung, Indonesia [2-4] was conducted. The studies compared the standard RIF oral dose of 450 mg to intensified 14 or 30-days regimens including 750, 900 or 1350 mg oral RIF, or an intravenous RIF infusion (1.5h) of 600 mg. Rich plasma PK sampling were performed at day 2±1 and for two of the studies also at day 12±3. A single lumbar puncture was performed at PK days for quantification of RIF and metabolites in CSF as described in the original publications [2-4].

The 6-month survival was described with time-to-event models. The exposure-response analysis was performed sequentially using NONMEM 7.3.

Results

PK

The PK dataset included **133 individuals** and 1266 RIF observations of which 1150 (170 from CSF) were above the limit of quantification. The structure of the final model is described in Figure 1 and VPCs in Figure 2.

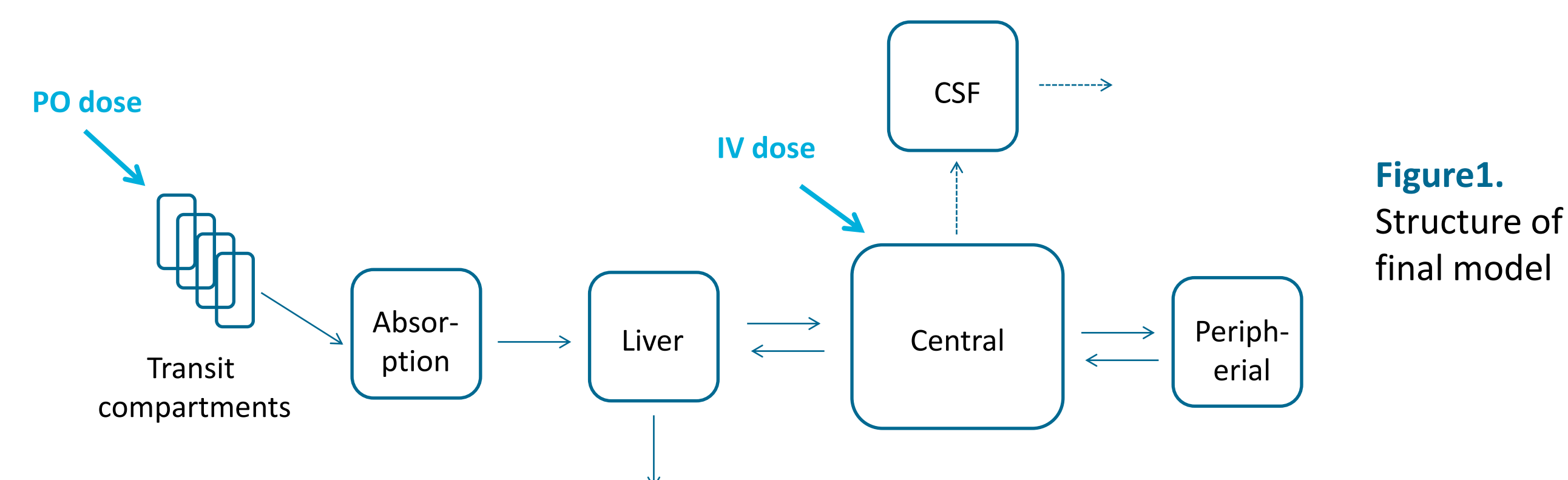


Figure1.
Structure of final model

- Allometric scaling with fat-free mass and fixed coefficients was included
- Intrinsic clearance (CL_{int}) saturable following Michaelis-Menten kinetics [5, 6]
- Autoinduction: separate CL_{int} estimated for samples after day 7, 48% (28-68) higher
- Bioavailability: 78% (71-84)
- Volume of distribution: 19% (12-27) lower after day 7 (improved disease status)

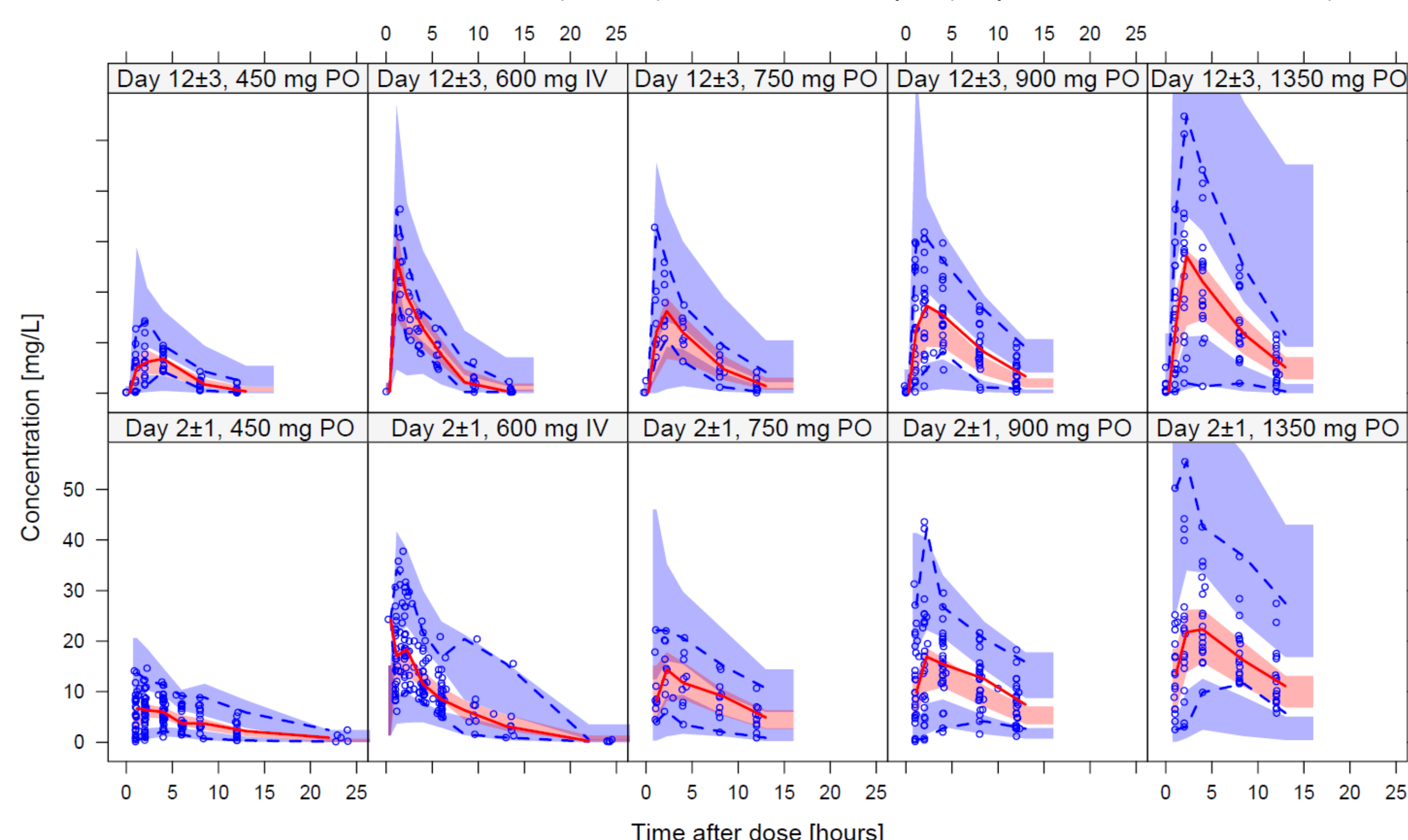


Figure 2. VPC showing 95% CIs and RIF plasma concentration per dose and sampling occasion.

RIF CSF concentrations were modeled with a partition coefficient and a half-life for the distribution between plasma and CSF, estimated to 5.5% (4.5-6.4) and 2.1 (1.3-2.9) hours, respectively.

- IIV in the partition coefficient 36% CV
- **Higher protein concentration in CSF** correlated to **higher CSF RIF concentrations**

PK-PD

The survival dataset included **148 individuals** of which 58 died and 15 dropped out before 6 months. The **hazard** model that best described the survival was a **exponentially declining function** (deltaOFV -91.2 and -24.3, compared to constant and Weibull functions, respectively).

The effect of individual RIF exposure (plasma and CSF AUC_{0-24h} and plasma C_{max}) on the hazard was evaluated with linear, power and Emax-relationships. **Plasma AUC_{0-24h} was the best performing exposure metric**. The effect on the hazard was coded:

$$h_i = h_b \cdot (1 - AUC_i / (AUC_{50} + AUC_i))$$

The AUC_{50} was estimated to 171 (RSE 86%) mg/L·h. Other covariates of importance were age and Glasgow Coma Scale status at baseline.

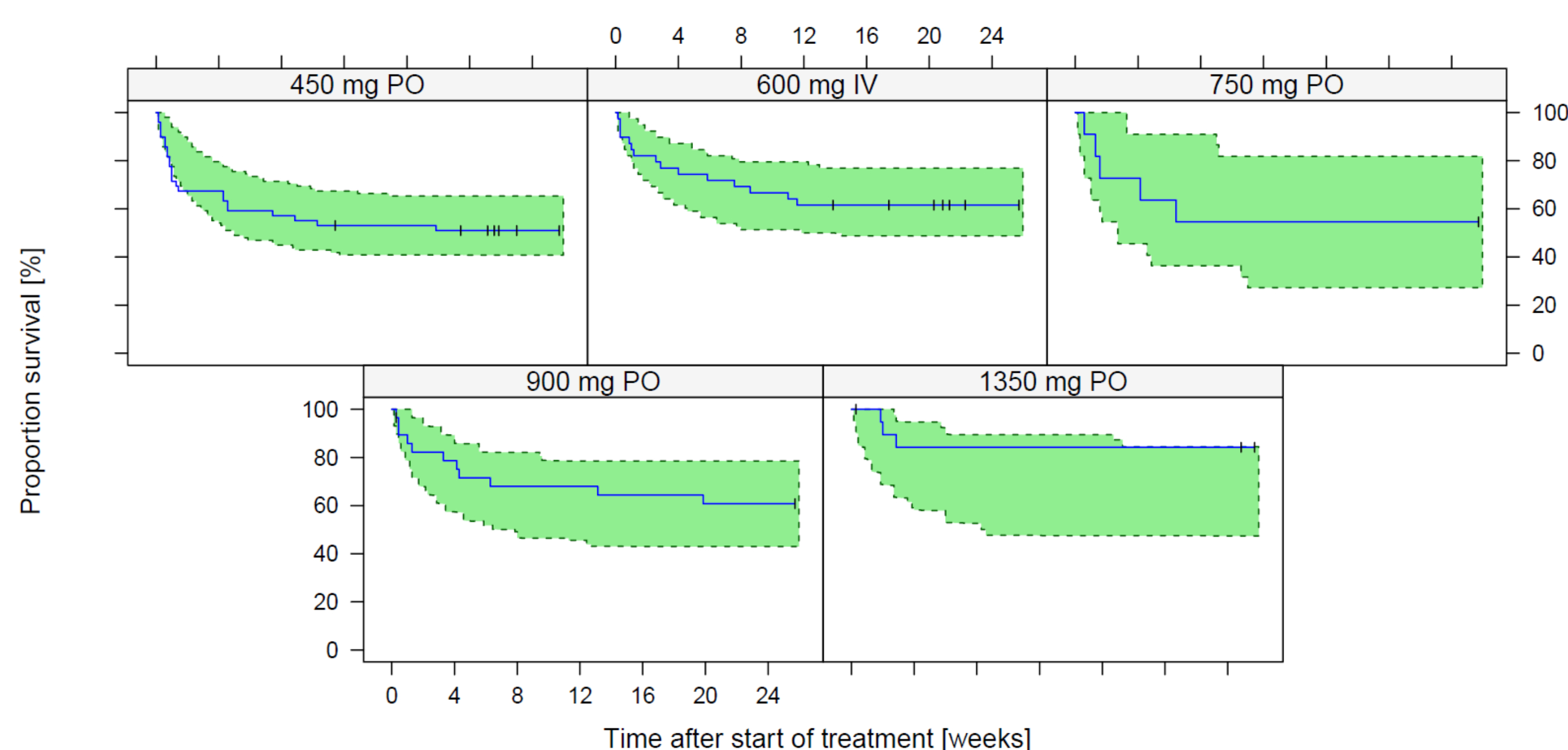


Figure 2. VPC of the final survival model per dose group showing 95% CIs.

Simulations predict 6-month mortality to be reduced from 49% as expected with the 450 mg dose (median exposure 48 mg/L·h) to **31%** expected with the 1350 mg (233 mg/L·h) (Figure 3).

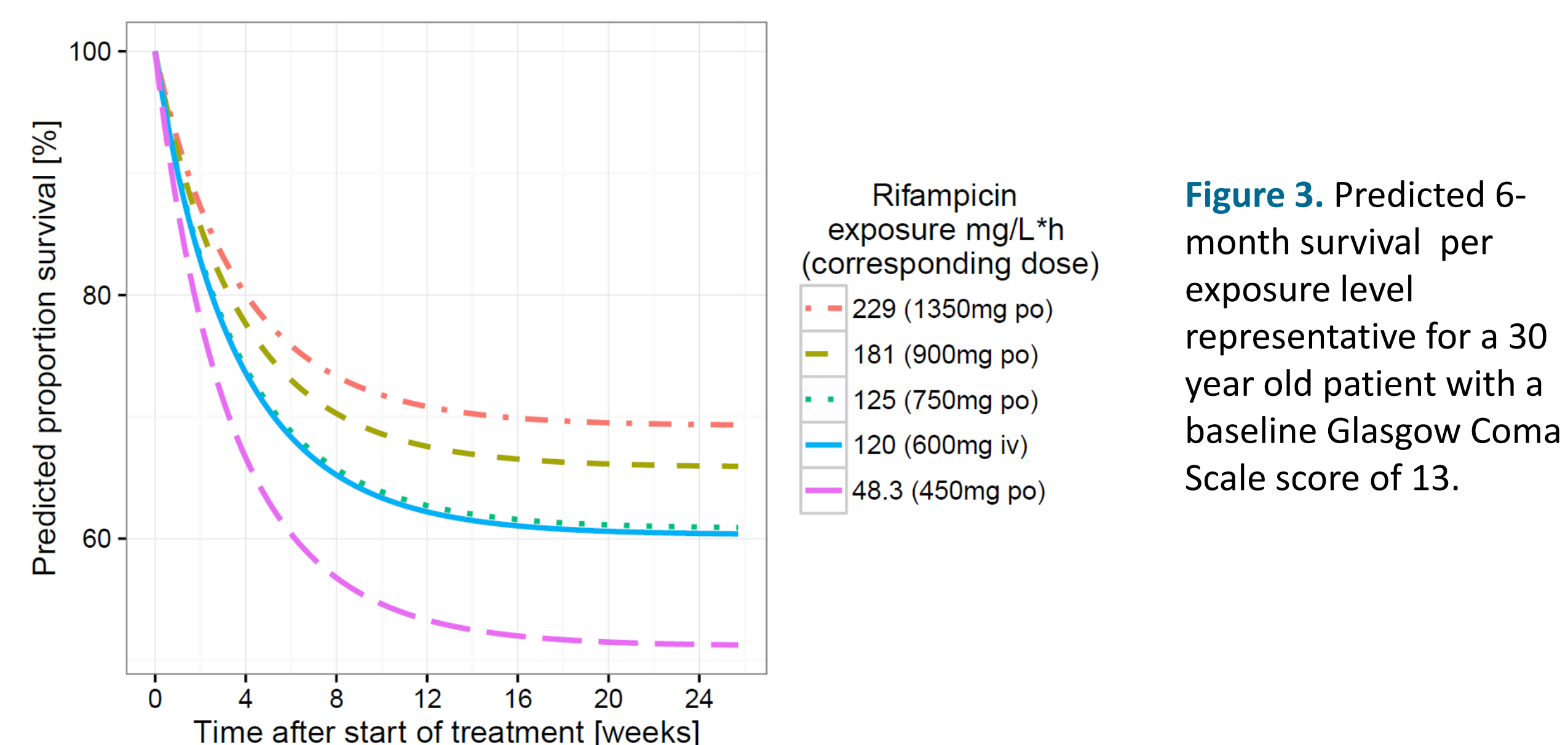


Figure 3. Predicted 6-month survival per exposure level representative for a 30 year old patient with a baseline Glasgow Coma Scale score of 13.

Conclusions

- **Higher RIF exposure during the first days of treatment decreases the risk of death in Indonesian TBM patients**
- **Maximal effect was not reached within the studied range of exposures**
- **The optimal dose of RIF in treatment of TBM should be further investigated in phase III type trials**

References

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