

Systematic Evaluation of Voriconazole Pharmacokinetic Models without Pharmacogenetic Information for Bayesian Forecasting in Critically Ill Patients

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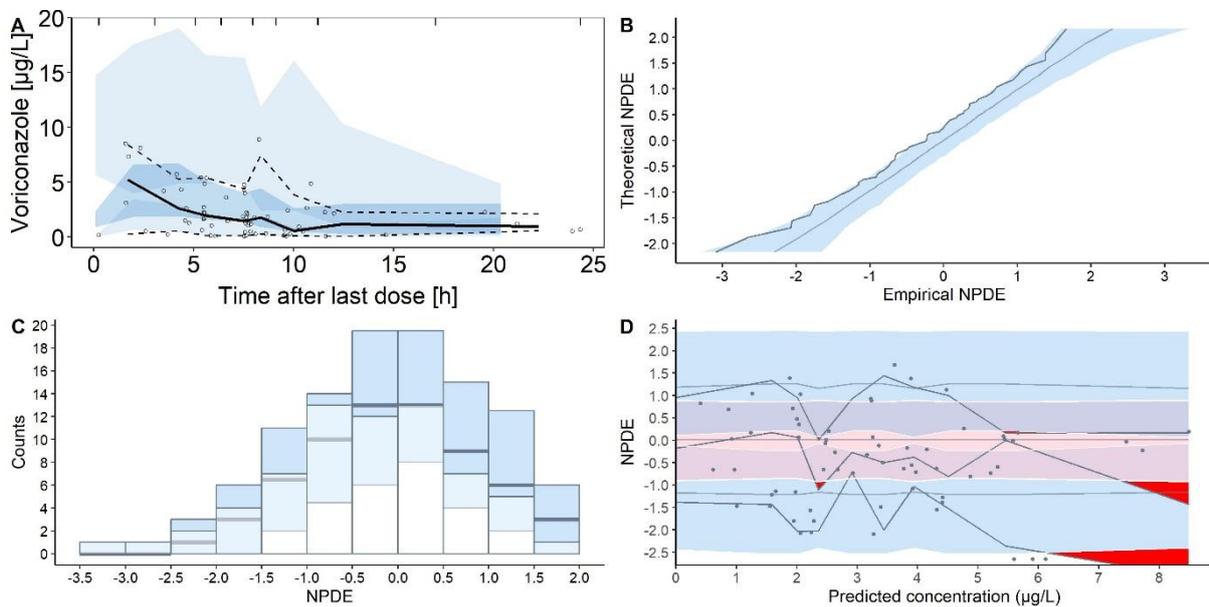


Figure S1. Graphical evaluation of the model by Chen et al. **A:** Visual predictive check. Light blue shaded regions: 90% prediction bands associated with the 5th and 95th percentiles of pharmacokinetic (PK) model simulations (N=1000 iterations). Dark blue region: 90% prediction band associated with the 50th percentile of PK model simulations. Dashed lines: 5th and 95th percentiles of observed data; solid line: 50th percentile of observed data. Dots: observed data. **B:** Quantile-Quantile plot. Theoretical Normalised Prediction Distribution Error (NPDE) vs empirical NPDE; light blue shaded region: Simulation based 95% prediction interval (N=1000 iterations) with 50th percentile (straight solid line); solid line: 50th percentile of the empirical NPDE; **C:** Theoretical vs empirical NPDE; light blue shaded region: 90% simulation based (N=1000) prediction interval; solid line: 50th percentile; white histogram: Empirical NPDE; **D:** Theoretical and empirical NPDE distribution vs. predicted voriconazole concentration. dots: observed concentrations; lines: 5th, 50th and 95th percentiles of observed concentrations; blue areas: 90% prediction intervals of the 5th and 95th percentiles; light red area: 90% prediction interval of the 50th percentile; the dark red area indicates a mismatch of the model.

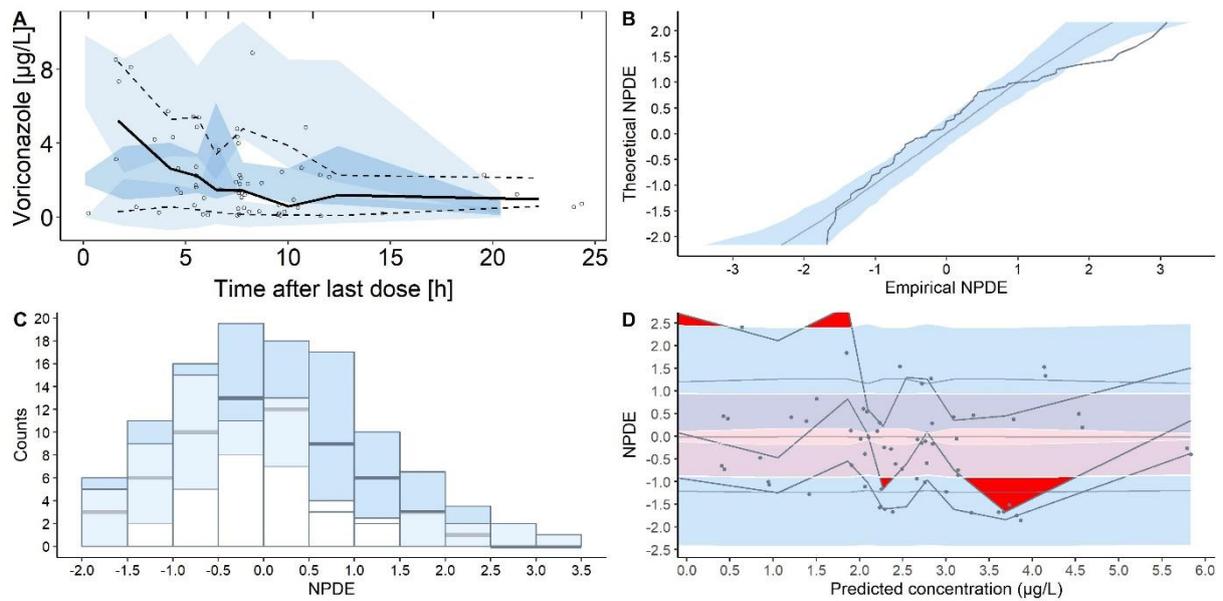


Figure S2. Graphical evaluation of the model by Chantharit et al. **A:** Visual predictive check. Light blue shaded regions: 90% prediction bands associated with the 5th and 95th percentiles of pharmacokinetic (PK) model simulations (N=1000 iterations). Dark blue region: 90% prediction band associated with the 50th percentile of PK model simulations. Dashed lines: 5th and 95th percentiles of observed data; solid line: 50th percentile of observed data. Dots: observed data. **B:** Quantile-Quantile plot. Theoretical Normalised Prediction Distribution Error (NPDE) vs empirical NPDE; light blue shaded region: Simulation based 95% prediction interval (N=1000 iterations) with 50th percentile (straight solid line); solid line: 50th percentile of the empirical NPDE; **C:** Theoretical vs empirical NPDE; light blue shaded region: 90% simulation based (N=1000) prediction interval; solid line: 50th percentile; white histogram: Empirical NPDE; **D:** Theoretical and empirical NPDE distribution vs. predicted voriconazole concentration. dots: observed concentrations; lines: 5th, 50th and 95th percentiles of observed concentrations; blue areas: 90% prediction intervals of the 5th and 95th percentiles; light red area: 90% prediction interval of the 50th percentile; the dark red area indicates a mismatch of the model.

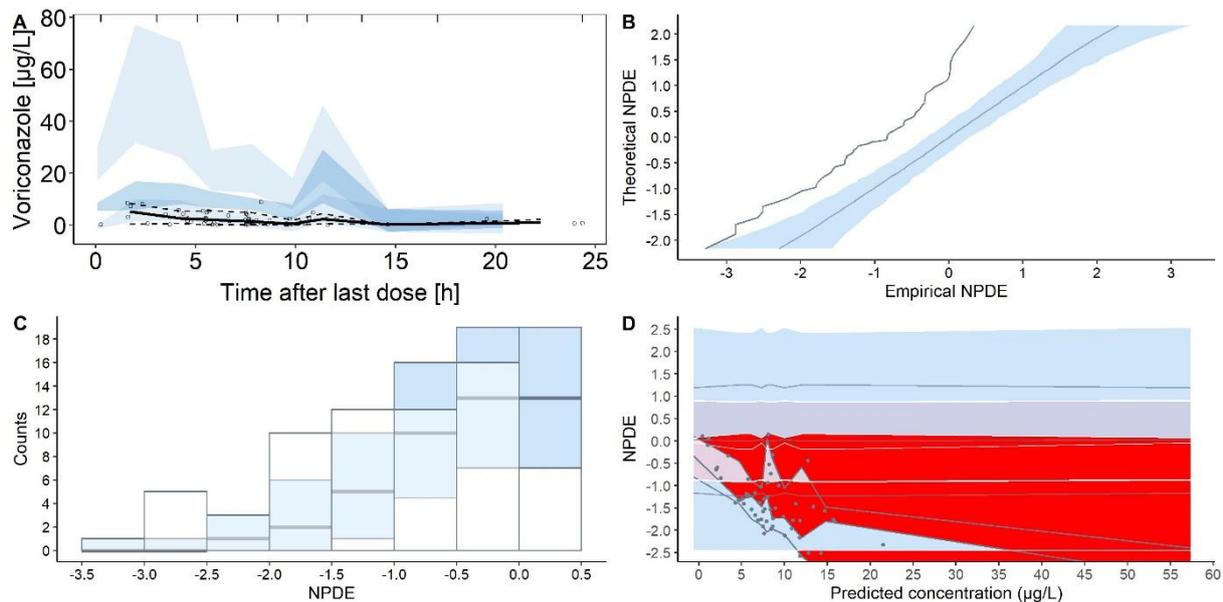


Figure S3. Graphical evaluation of the model by Khan-asa et al.. **A:** Visual predictive check. Light blue shaded regions: 90% prediction bands associated with the 5th and 95th percentiles of pharmacokinetic (PK) model simulations (N=1000 iterations). Dark blue region: 90% prediction band associated with the 50th percentile of PK model simulations. Dashed lines: 5th and 95th percentiles of observed data; solid line: 50th percentile of observed data. Dots: observed data. **B:** Quantile-Quantile plot. Theoretical Normalised Prediction Distribution Error (NPDE) vs empirical NPDE; light blue shaded region: Simulation based 95% prediction interval (N=1000 iterations) with 50th percentile (straight solid line); solid line: 50th percentile of the empirical NPDE; **C:** Theoretical vs empirical NPDE; light blue shaded region: 90% simulation based (N=1000) prediction interval; solid line: 50th percentile; white histogram: Empirical NPDE; **D:** Theoretical and empirical

NPDE distribution vs. predicted voriconazole concentration. dots: observed concentrations; lines: 5th, 50th and 95th percentiles of observed concentrations; blue areas: 90% prediction intervals of the 5th and 95th percentiles; light red area: 90% prediction interval of the 50th percentile; the dark red area indicates a mismatch of the model.

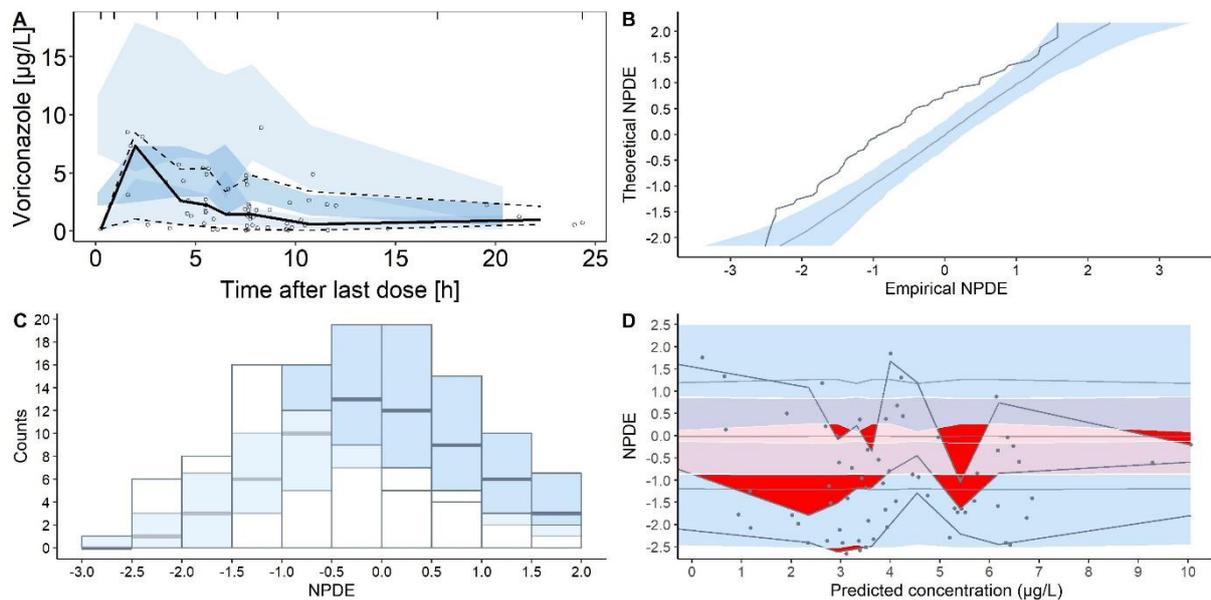


Figure S4. Graphical evaluation of the model by Pascual et al. **A:** Visual predictive check. Light blue shaded regions: 90% prediction bands associated with the 5th and 95th percentiles of pharmacokinetic (PK) model simulations (N=1000 iterations). Dark blue region: 90% prediction band associated with the 50th percentile of PK model simulations. Dashed lines: 5th and 95th percentiles of observed data; solid line: 50th percentile of observed data. Dots: observed data. **B:** Quantile-Quantile plot. Theoretical Normalised Prediction Distribution Error (NPDE) vs empirical NPDE; light blue shaded region: Simulation based 95% prediction interval (N=1000 iterations) with 50th percentile (straight solid line); solid line: 50th percentile of the empirical NPDE; **C:** Theoretical vs empirical NPDE; light blue shaded region: 90% simulation based (N=1000) prediction interval; solid line: 50th percentile; white histogram: Empirical NPDE; **D:** Theoretical and empirical NPDE distribution vs. predicted voriconazole concentration. dots: observed concentrations; lines: 5th, 50th and 95th percentiles of observed concentrations; blue areas: 90% prediction intervals of the 5th and 95th percentiles; light red area: 90% prediction interval of the 50th percentile; the dark red area indicates a mismatch of the model.

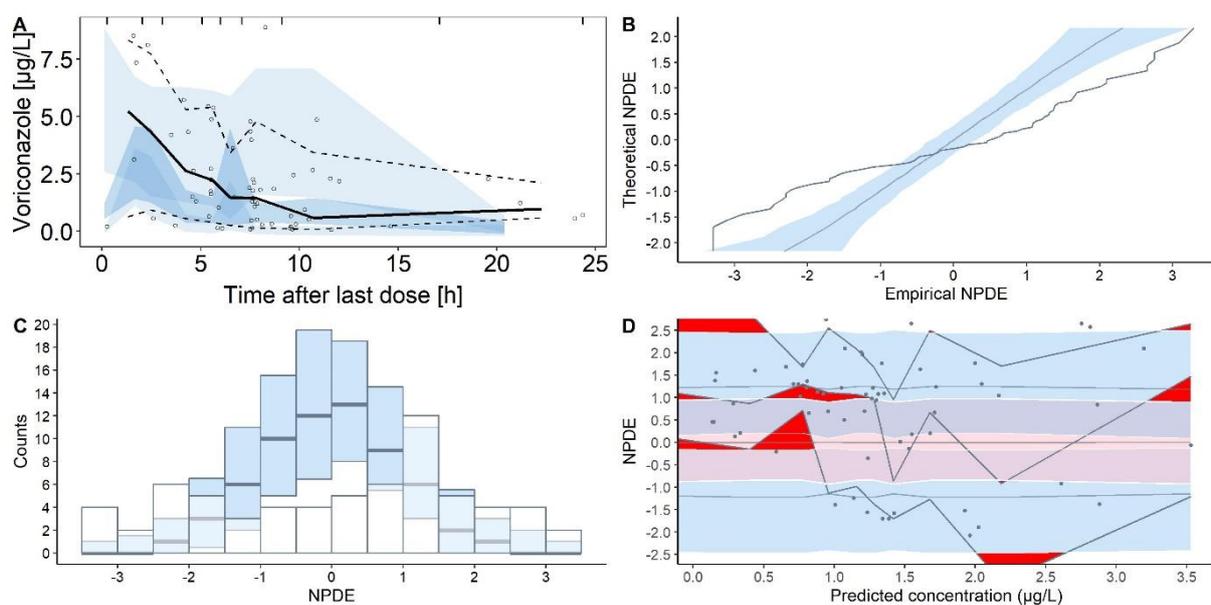


Figure S5. Graphical evaluation of the model by Perez-Pitarch et al.. **A:** Visual predictive check. Light blue shaded regions: 90% prediction bands associated with the 5th and 95th percentiles of pharmacokinetic (PK) model simulations (N=1000

iterations). Dark blue region: 90% prediction band associated with the 50th percentile of PK model simulations. Dashed lines: 5th and 95th percentiles of observed data; solid line: 50th percentile of observed data. Dots: observed data. **B**: Quantile-Quantile plot. Theoretical Normalised Prediction Distribution Error (NPDE) vs empirical NPDE; light blue shaded region: Simulation based 95% prediction interval (N=1000 iterations) with 50th percentile (straight solid line); solid line: 50th percentile of the empirical NPDE; **C**: Theoretical vs empirical NPDE; light blue shaded region: 90% simulation based (N=1000) prediction interval; solid line: 50th percentile; white histogram: Empirical NPDE; **D**: Theoretical and empirical NPDE distribution vs. predicted voriconazole concentration. dots: observed concentrations; lines: 5th, 50th and 95th percentiles of observed concentrations; blue areas: 90% prediction intervals of the 5th and 95th percentiles; light red area: 90% prediction interval of the 50th percentile; the dark red area indicates a mismatch of the model.

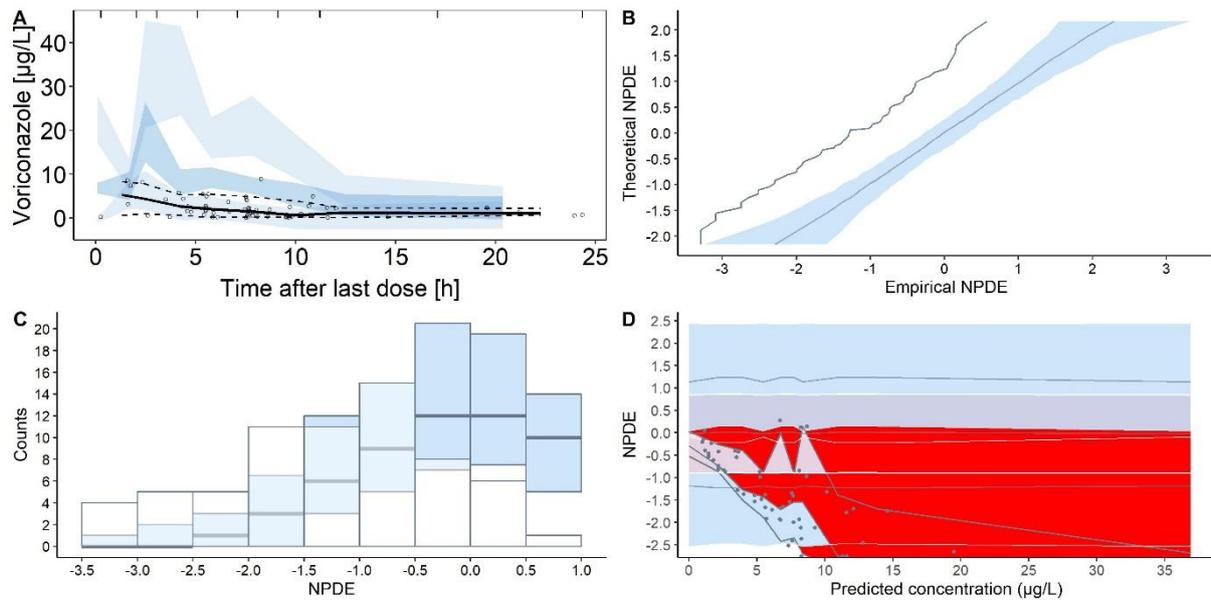


Figure S6. Graphical evaluation of the model by Tang et al. 2019. **A**: Visual predictive check. Light blue shaded regions: 90% prediction bands associated with the 5th and 95th percentiles of pharmacokinetic (PK) model simulations (N=1000 iterations). Dark blue region: 90% prediction band associated with the 50th percentile of PK model simulations. Dashed lines: 5th and 95th percentiles of observed data; solid line: 50th percentile of observed data. Dots: observed data. **B**: Quantile-Quantile plot. Theoretical Normalised Prediction Distribution Error (NPDE) vs empirical NPDE; light blue shaded region: Simulation based 95% prediction interval (N=1000 iterations) with 50th percentile (straight solid line); solid line: 50th percentile of the empirical NPDE; **C**: Theoretical vs empirical NPDE; light blue shaded region: 90% simulation based (N=1000) prediction interval; solid line: 50th percentile; white histogram: Empirical NPDE; **D**: Theoretical and empirical NPDE distribution vs. predicted voriconazole concentration. dots: observed concentrations; lines: 5th, 50th and 95th percentiles of observed concentrations; blue areas: 90% prediction intervals of the 5th and 95th percentiles; light red area: 90% prediction interval of the 50th percentile; the dark red area indicates a mismatch of the model.

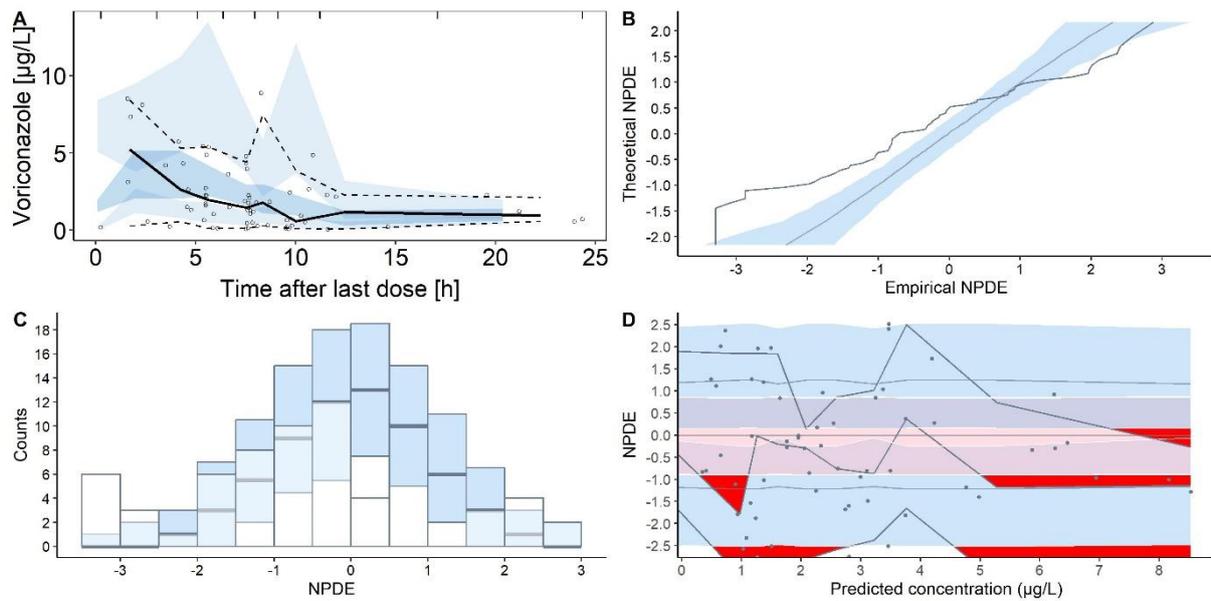


Figure S7. Graphical evaluation of the model by Tang et al. 2021. **A:** Visual predictive check. Light blue shaded regions: 90% prediction bands associated with the 5th and 95th percentiles of pharmacokinetic (PK) model simulations (N=1000 iterations). Dark blue region: 90% prediction band associated with the 50th percentile of PK model simulations. Dashed lines: 5th and 95th percentiles of observed data; solid line: 50th percentile of observed data. Dots: observed data. **B:** Quantile-Quantile plot. Theoretical Normalised Prediction Distribution Error (NPDE) vs empirical NPDE; light blue shaded region: Simulation based 95% prediction interval (N=1000 iterations) with 50th percentile (straight solid line); solid line: 50th percentile of the empirical NPDE; **C:** Theoretical vs empirical NPDE; light blue shaded region: 90% simulation based (N=1000) prediction interval; solid line: 50th percentile; white histogram: Empirical NPDE; **D:** Theoretical and empirical NPDE distribution vs. predicted voriconazole concentration. dots: observed concentrations; lines: 5th, 50th and 95th percentiles of observed concentrations; blue areas: 90% prediction intervals of the 5th and 95th percentiles; light red area: 90% prediction interval of the 50th percentile; the dark red area indicates a mismatch of the model.