



## Aim

- To explore
- How well population PK (Pop PK) models in rich data setting characterize NCA parameters Cmax and AUC(0-t)
  - The influence of chosen absorption delay model on the characterization

## Methods

Original and alternative PopPK models with respect to absorption (no delay, lagtime or transit compartment) evaluated using NONMEM 7.3 [1] for 5 data sets with rich sampling [Table 1].

For each model data sets simulated (n=1000) using *nca* in PsN [7].

The *ncappc* package [8] generated

- Population level metrics (Pop\_Mean, NPDE\_Mean and NPDE\_SD), across drugs and NCA parameters for each model
- Individual level metrics (PPC\_Outlier, NPDE\_Outlier) across individuals, drugs and NCA parameters

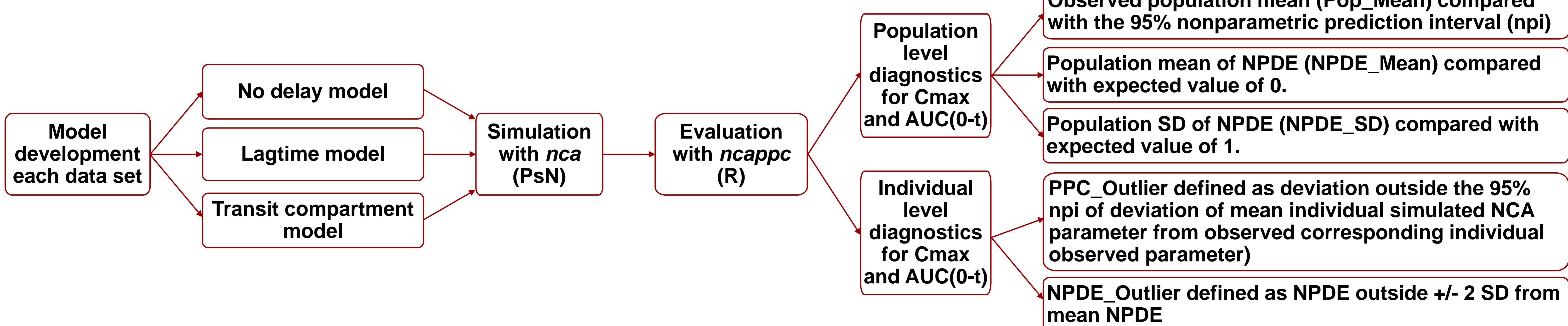
## Conclusion

- Evaluation of NCA metrics was facilitated by PsN and the *ncappc* package
- PopPK models described the mean and interindividual variability in Cmax and AUC(0-t) reasonably well
- Choice of model affected quality of both Cmax and AUC(0-t) simulations

Table 1	Number of subjects, administration route, dose level. Data selected for evaluation
Glibenclamide [2]	N=8, oral&iv, SD, 3.5 mg. Oral data
Melagatran [3]	N=61, oral, MD, 76.01 mg. Data at steady state from SPORTIF IV and VI studies
Prazosin [4]	N=64, oral, MD, 1000–10000 mg (5 dose levels). Data at steady state
Moxonidine [5]	N=74, oral, SD&MD, 200 ug. SD data
Ethambutol [6]	N=129, oral, MD, 800–500 mg, 4 dose levels). Data at steady state from Brewelskloof Hospital

SD single dose, MD multiple doses

## Overview of methods



## Results

The transit compartment model resulted in the best fit for all drugs based on the OFV with reduction in OFV versus no delay ranged from 237 to 662 (Figure 1). The transit model performed well for Cmax and AUC(0-t) for 5 and 4 data sets, respectively, for Pop\_Mean (95% npi covered observed mean), and for 2 out of 5 drugs for both NPDE\_Mean and NPDE\_SD. Thus, 8 out of 30 metrics were outside the 95% PIs. For the lagtime and no delay models, the corresponding values were 10/30 and 17/30 (Figure 2).

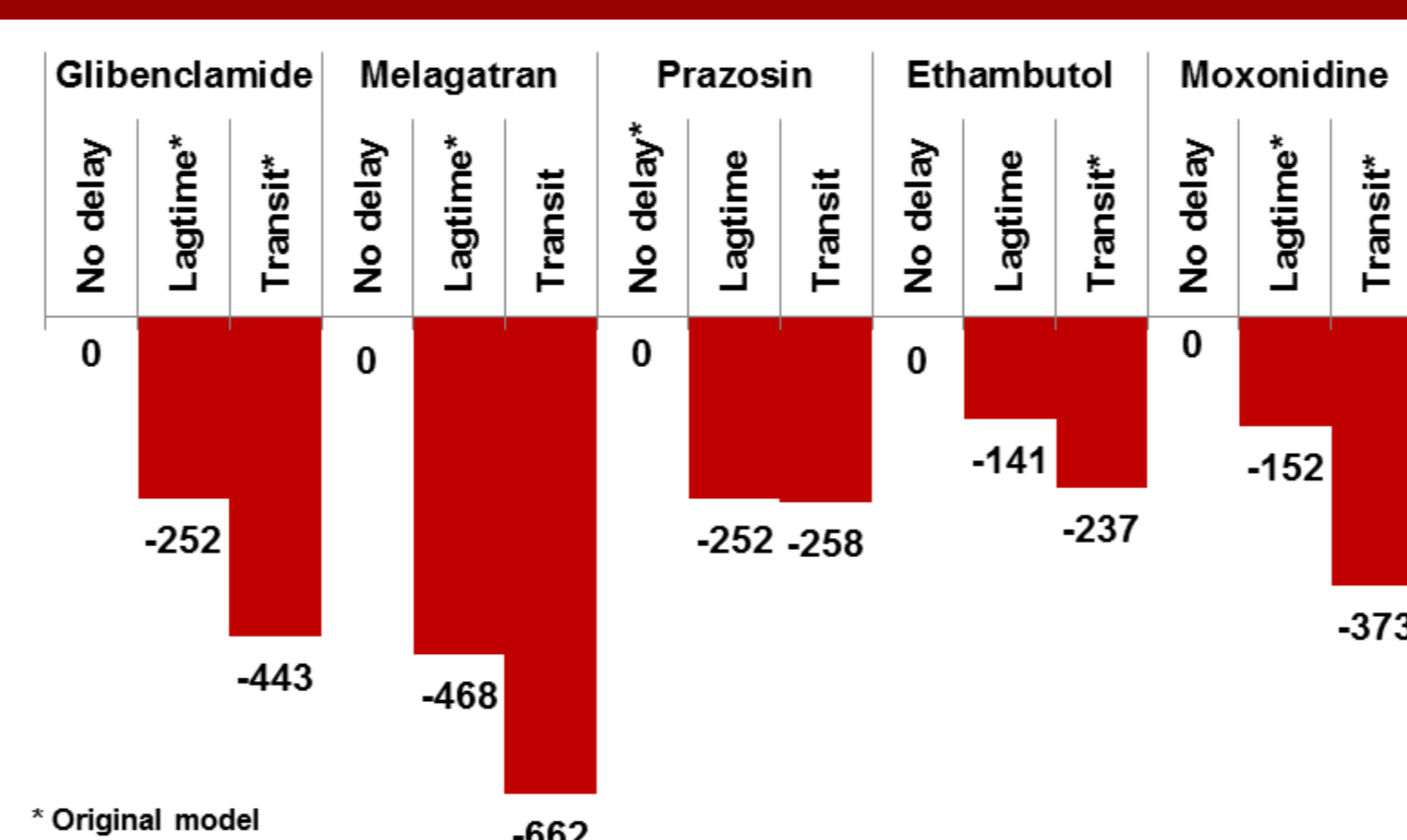


Figure 1. The comparison of the models based on  $\Delta$ OFV (versus no delay model).

For Cmax, across all models, the percentage identified individual subject outliers were in agreement with expectations; PPC\_Outlier 3.6–6.2% vs expected 5%, and NPDE\_Outlier 3.6–5.7% vs expected 4.5%.

Corresponding PPC\_Outlier and NPDE\_Outlier values for AUC(0-t) were 2.7%–3.9%, and 2.7–3.3%, respectively (Figure 3).

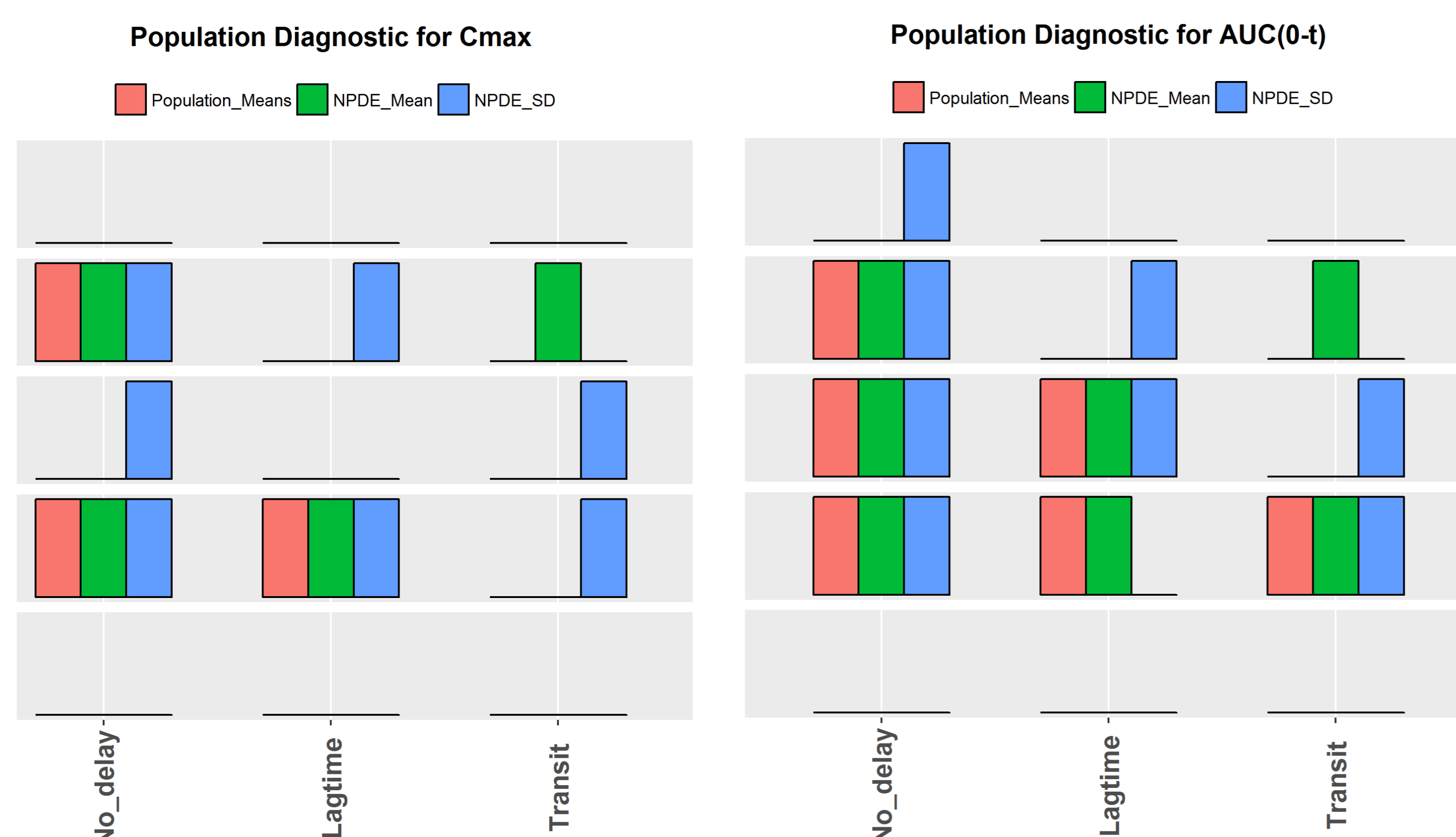


Figure 2. The population diagnostics for Cmax (left) and AUC(0-t) (right) for each drug and model. **Pop\_Mean with color** → The 95% npi of simulated mean did not cover observed mean; **NPDE\_Mean with color** → The 95% CI of the NPDE\_Mean did not include the theoretical value of 0; **NPDE\_SD with color** → The 95% CI of the NPDE\_SD did not include the theoretical value of 1.

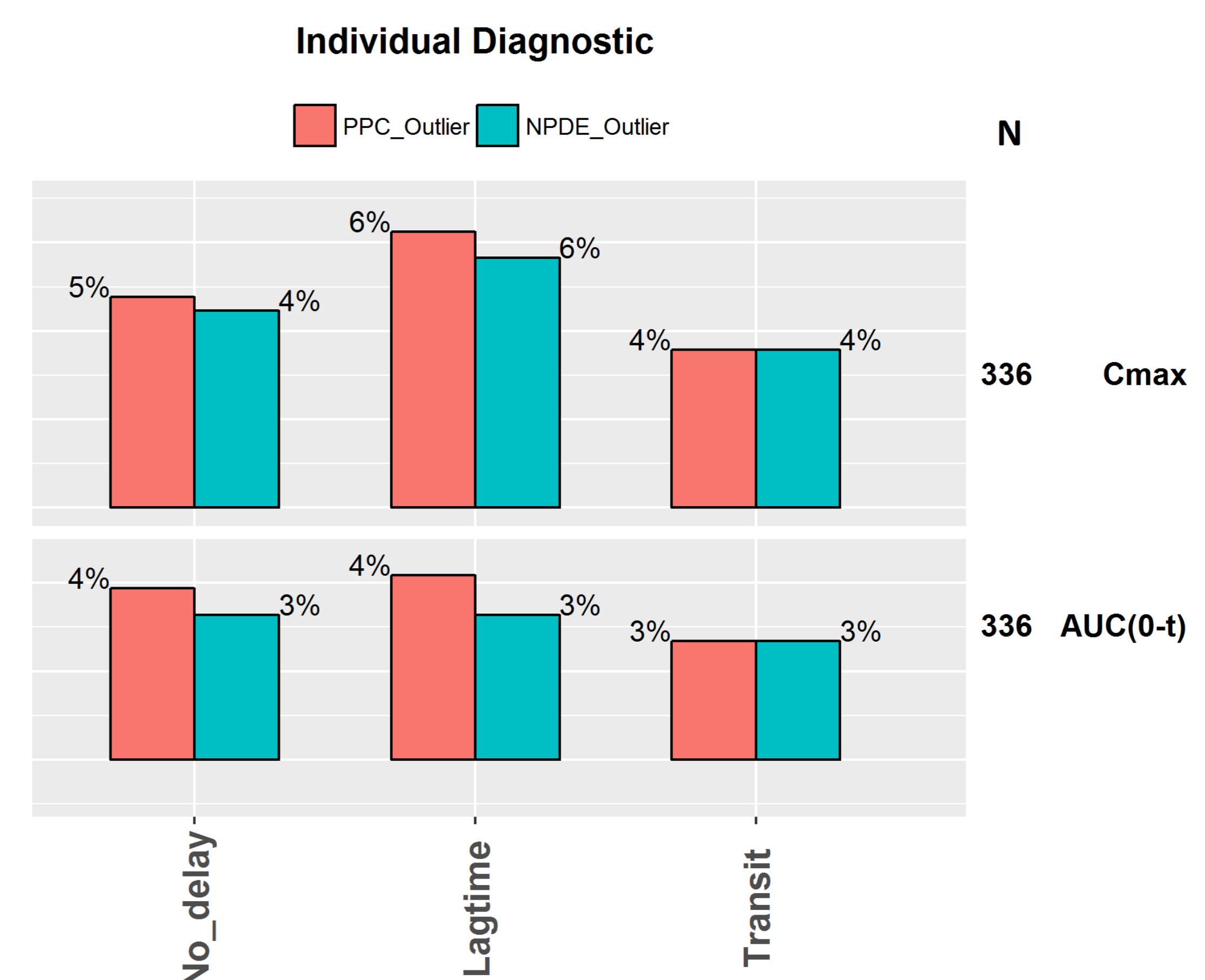


Figure 3. The individual diagnostics for Cmax and AUC(0-t) for all models.

## References

- [1] Beal SL et al. NONMEM Users Guides. 1989-2011. Icon Development Solutions, Ellicott City, Maryland, USA. [2] Savic et al. J Pharmacokinet Pharmacodyn. 2007;34(5):711-26. [3] Bååthe et al. Clin Pharmacokinet. 2006;45(8):803-19. [4] Karlsson MO et al. J Pharmacokinet Biopharm. 1993;21(6):735-50. [5] Karlsson MO et al. J Pharmacokinet Biopharm. 1998;26(2):207-46. [6] Jönsson S et al. Antimicrob Agents Chemother. 2011;55(9):4230-7. [7] Keizer RJ et al. CPT Pharmacometrics Syst Pharmacol. 2013;2:e50 [http://psn.sourceforge.net]. [8] Acharya C et al. Comput Methods Programs Biomed. 2016;127:83-93.