Comparison of Non-compartmental Analysis Estimation and Population Pharmacokinetic Predictions of Exposure Changes as a Function of Renal Impairment

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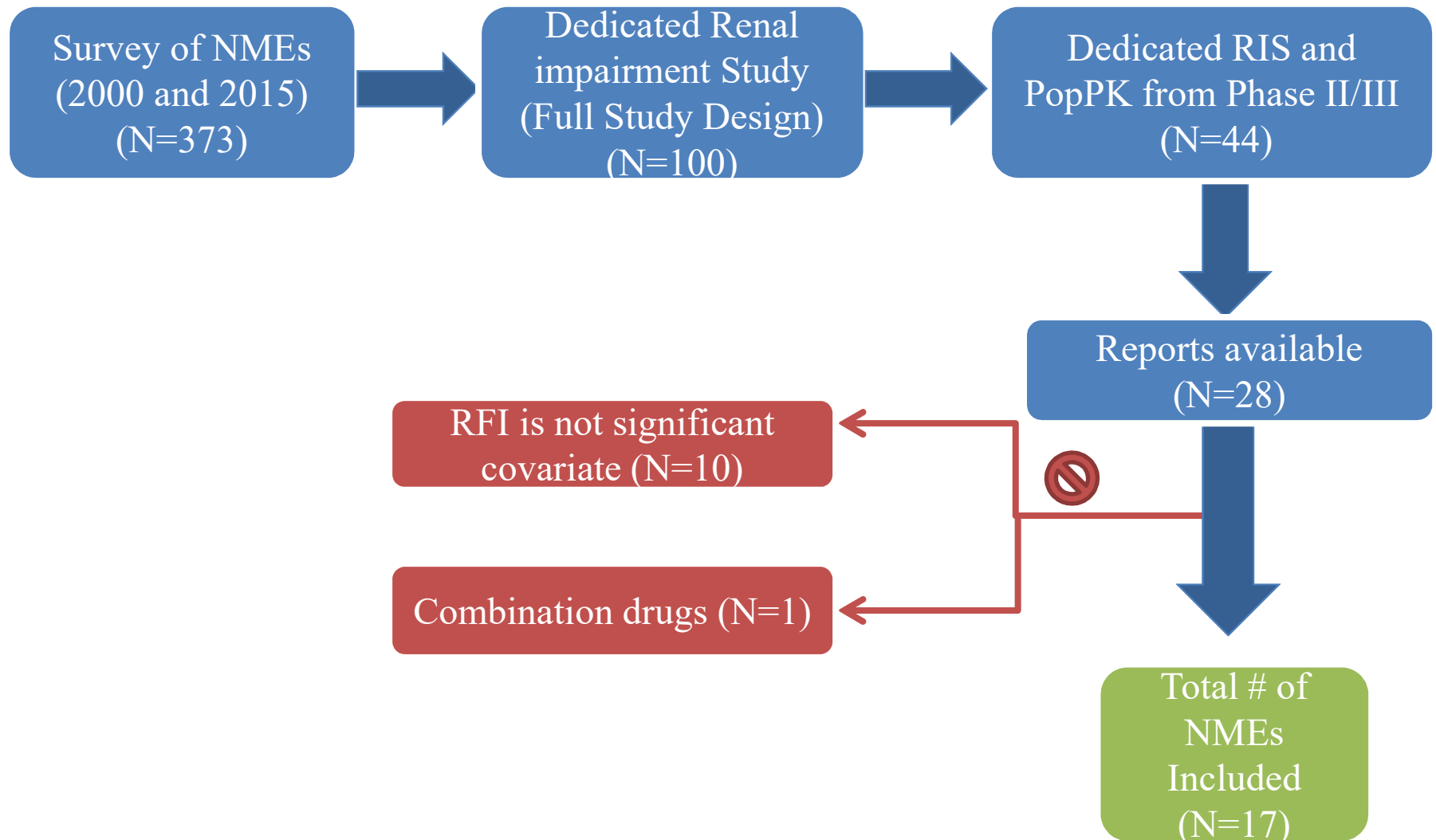
US Food and Drug Administration

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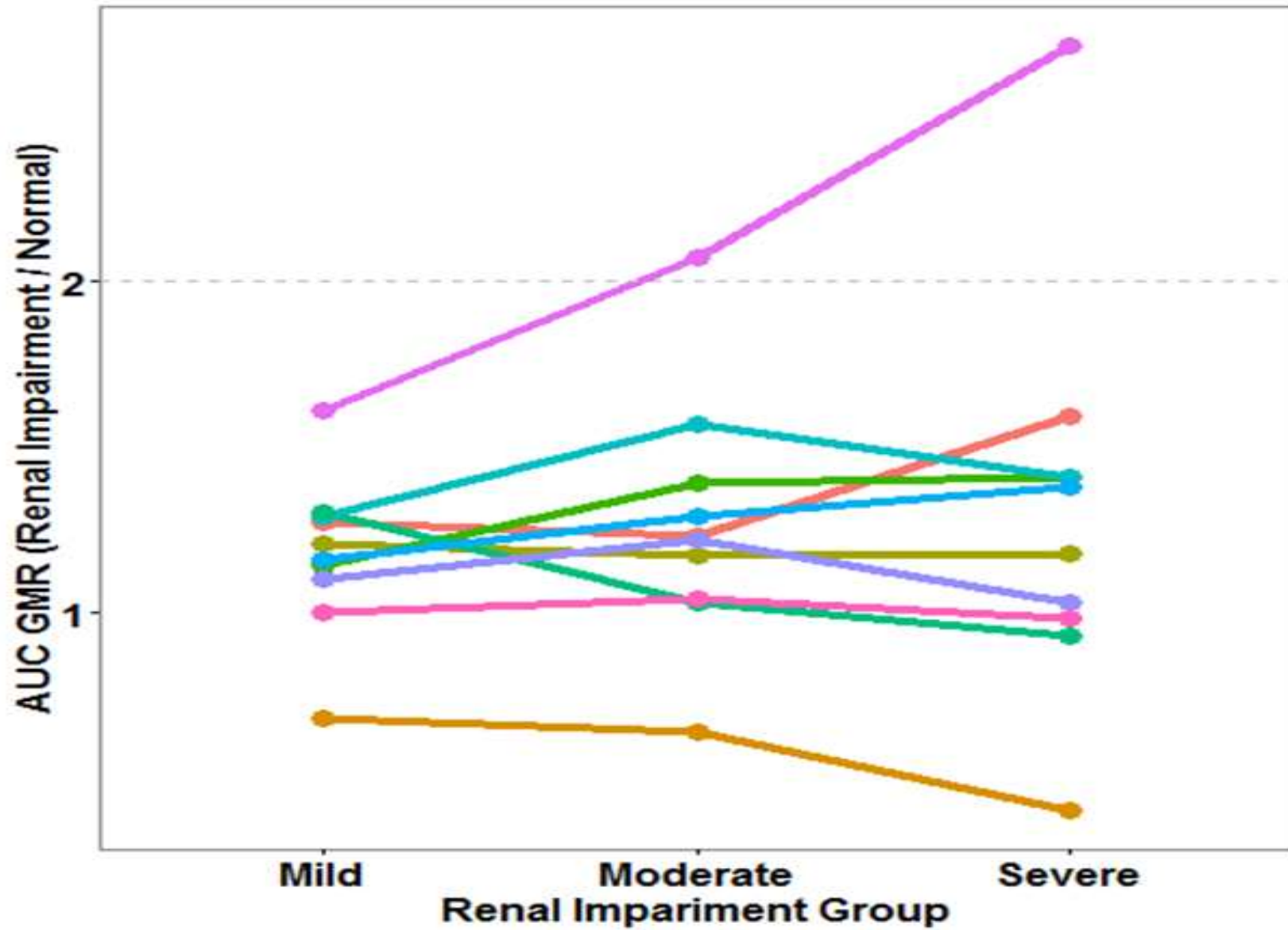
Research Objective

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To compare exposure changes as a function of renal impairment utilizing

1. Non-compartmental analysis estimation
2. Population pharmacokinetics predictions

Methods: Inclusion/Exclusion Criteria

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Survey of NMEs (2000 and 2015) (N=373) → Dedicated Renal impairment Study (Full Study Design) (N=100) → Dedicated RIS and PopPK from Phase II/III (N=44)

↓

Reports available (N=28)

RFI is not significant covariate (N=10)

Combination drugs (N=1)

Total # of NMEs Included (N=17)

# Excluded Cases

Methods

- Renal impairment classification was based on C-G equation as follows:
  - Normal: CrCL ≥ 80 mL/min
  - Mild: CrCL ≥ 50-<80 mL/min
  - Moderate: CrCL ≥ 30-<50 mL/min
  - Severe: CrCL<30 mL/min
- Submitted PopPK models were used to predict observed AUC for each subject enrolled in RIS
  - 1000 simulation per subject
  - The non-parametric prediction interval for AUC GMR was calculated by computing the 5th and 95th percentiles of the model-based predicted GMR based on the 1000 simulations

Results: Description

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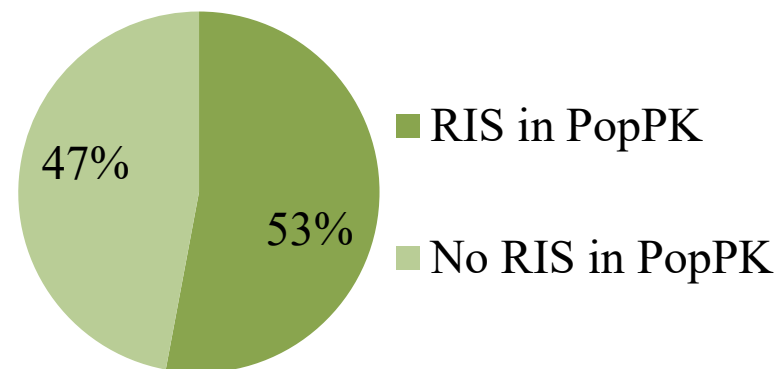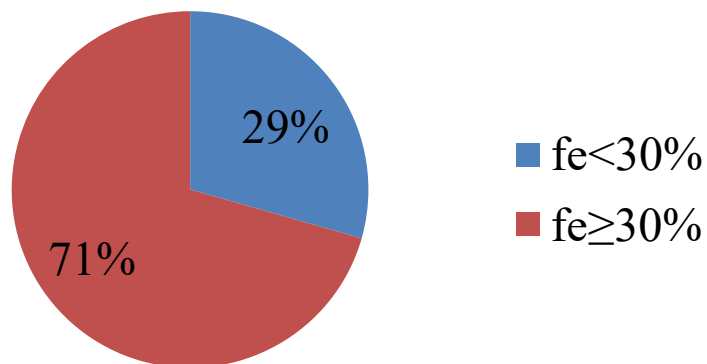
	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment
RIS				
Median Number of Subjects Included	8	8	7	6
PopPK				
Median Number of Subjects Included	636	166	12	4

Results: Concordance
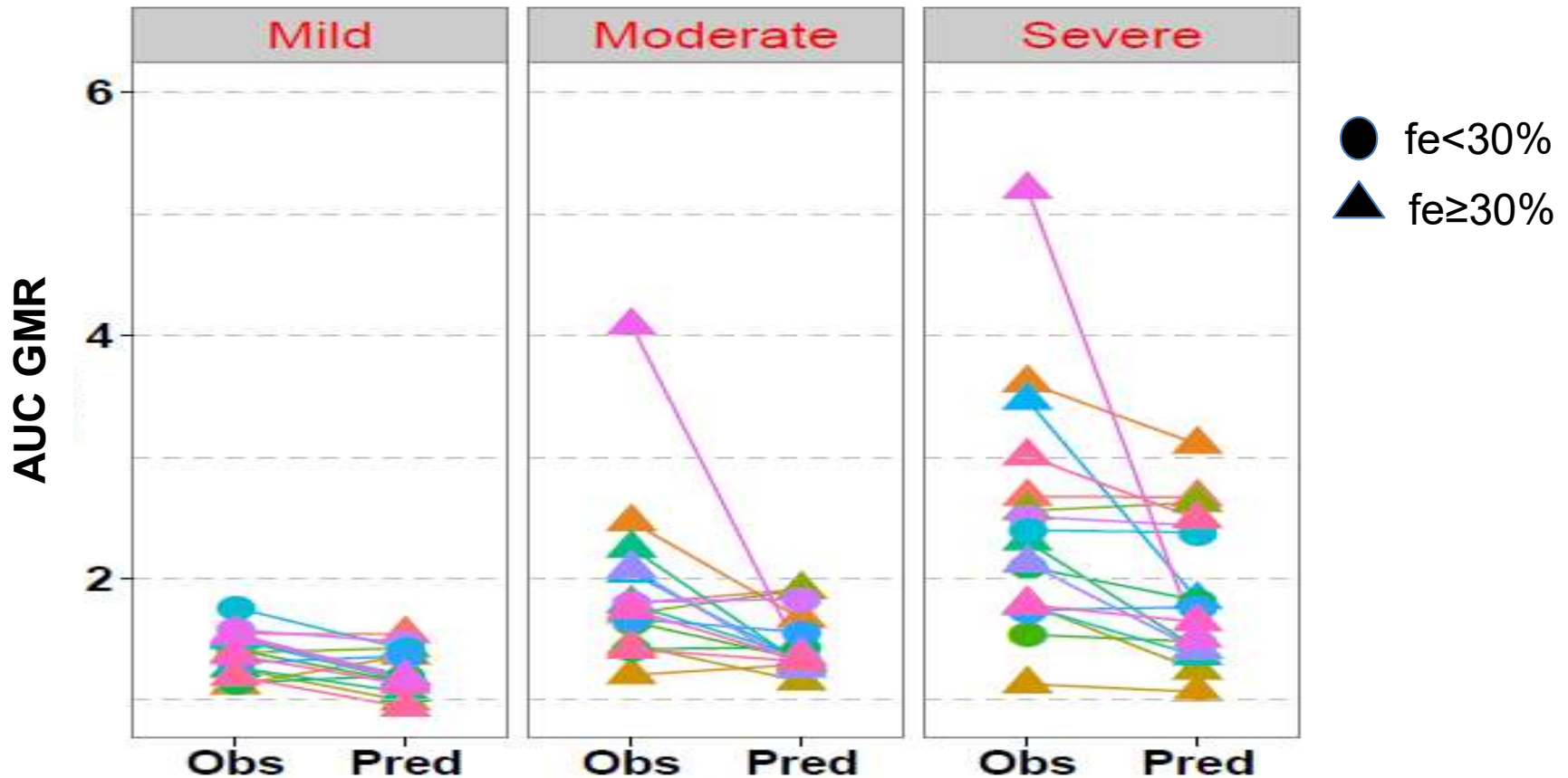
Number of Cases where AUC Geometric Mean Ratios (GMR) was not within the Same Fold		
Mild	**Moderate**	**Severe**
0/17 (0%)	4/16 (25%)	5/17 (29%)

Potential Factors for Differences

- Fraction excreted in urine.

- Inclusion of RIS data in PopPK model development

- Number of subjects with renal impairment in phase II/III trials

- Covariate model
  – Inclusion of correlated covariates

Results: Colinearity of Covariates was a Major Factor in Differences
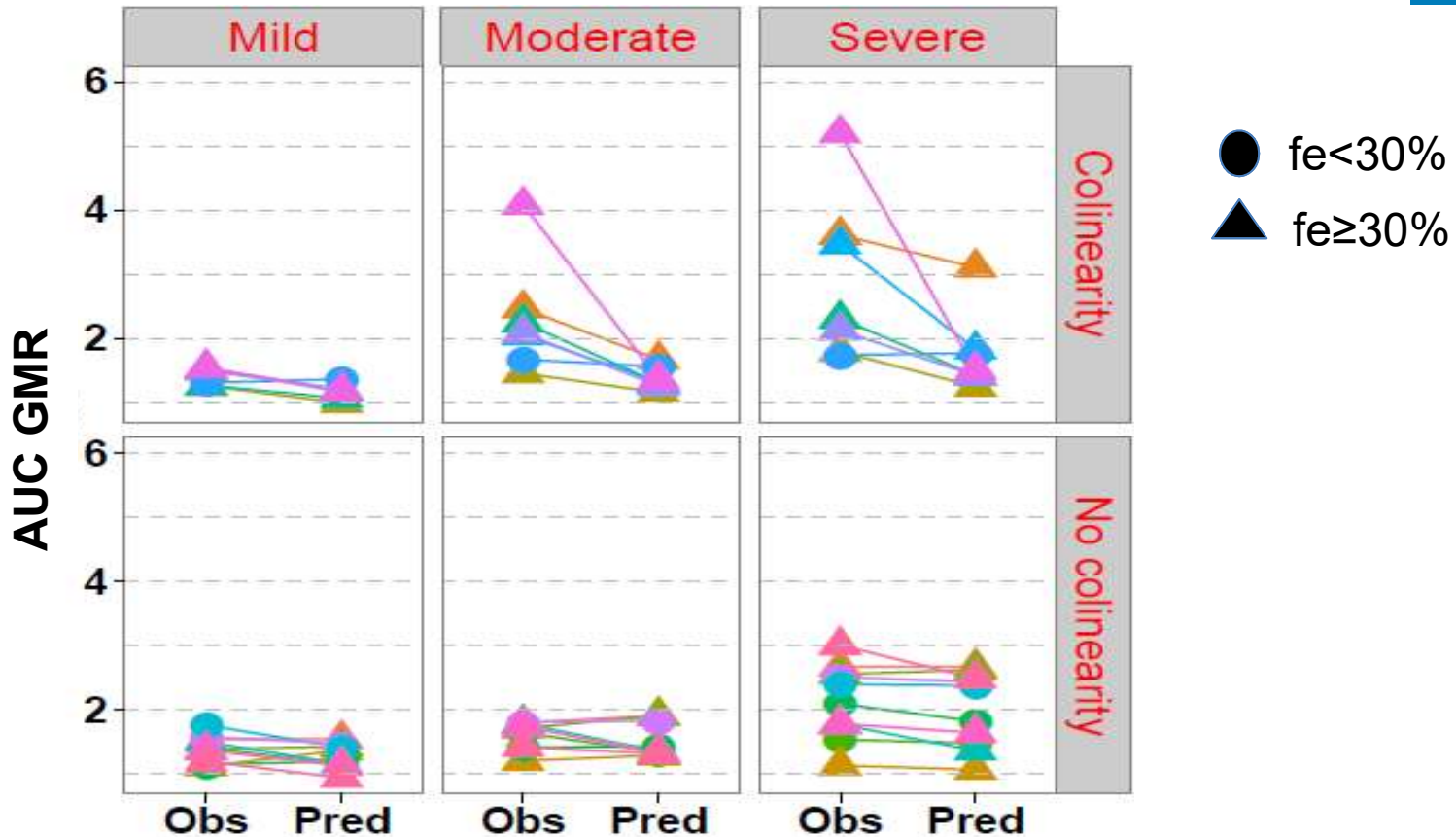
Number of Cases where AUC Geometric Mean Ratios (GMR) was not within the Same Fold

	Mild	Moderate	Severe
Colinearity	0/7 (0%)	4/7 (57%)	4/7 (57%)
No colinearity	0/10 (0%)	0/9 (0%)	1/10 (10%)

Conclusions

- In general, there is a good concordance between PopPK and NCA results

- Inclusion of correlated covariates in model development increases the discordance between PopPK predictions and NCA analysis

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