

External evaluation of published population pharmacokinetic models of adalimumab in inflammatory bowel disease patients

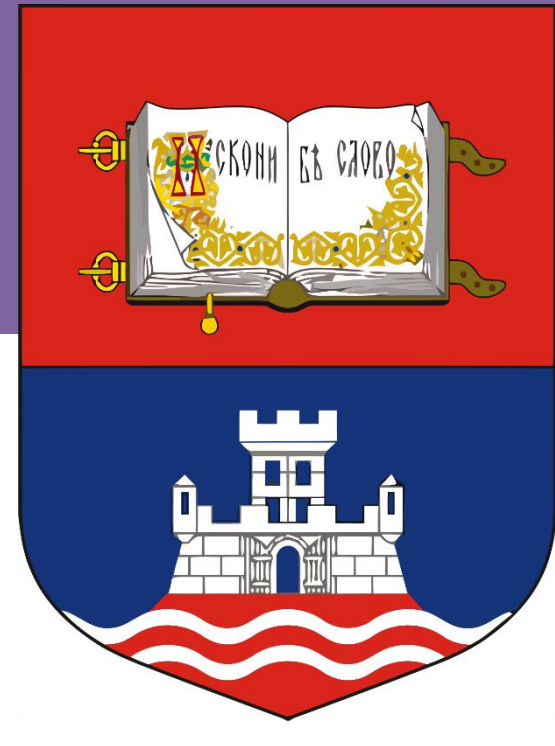


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Introduction

Adalimumab is a fully human monoclonal antibody that belongs to the group of tumor necrosis factor (TNF)-alpha inhibitors. It is approved for the treatment of patients with ulcerative colitis and Crohn's disease and other immune-related diseases characterized by inflammation [1]. However, a significant number of patients either do not respond to initial therapy with adalimumab or experience a loss of clinical response over time, leading to inadequate disease control [2]. Therefore, proactive therapeutic drug monitoring (TDM) and model-informed precision dosing techniques are essential to prevent therapy failure [3,4].

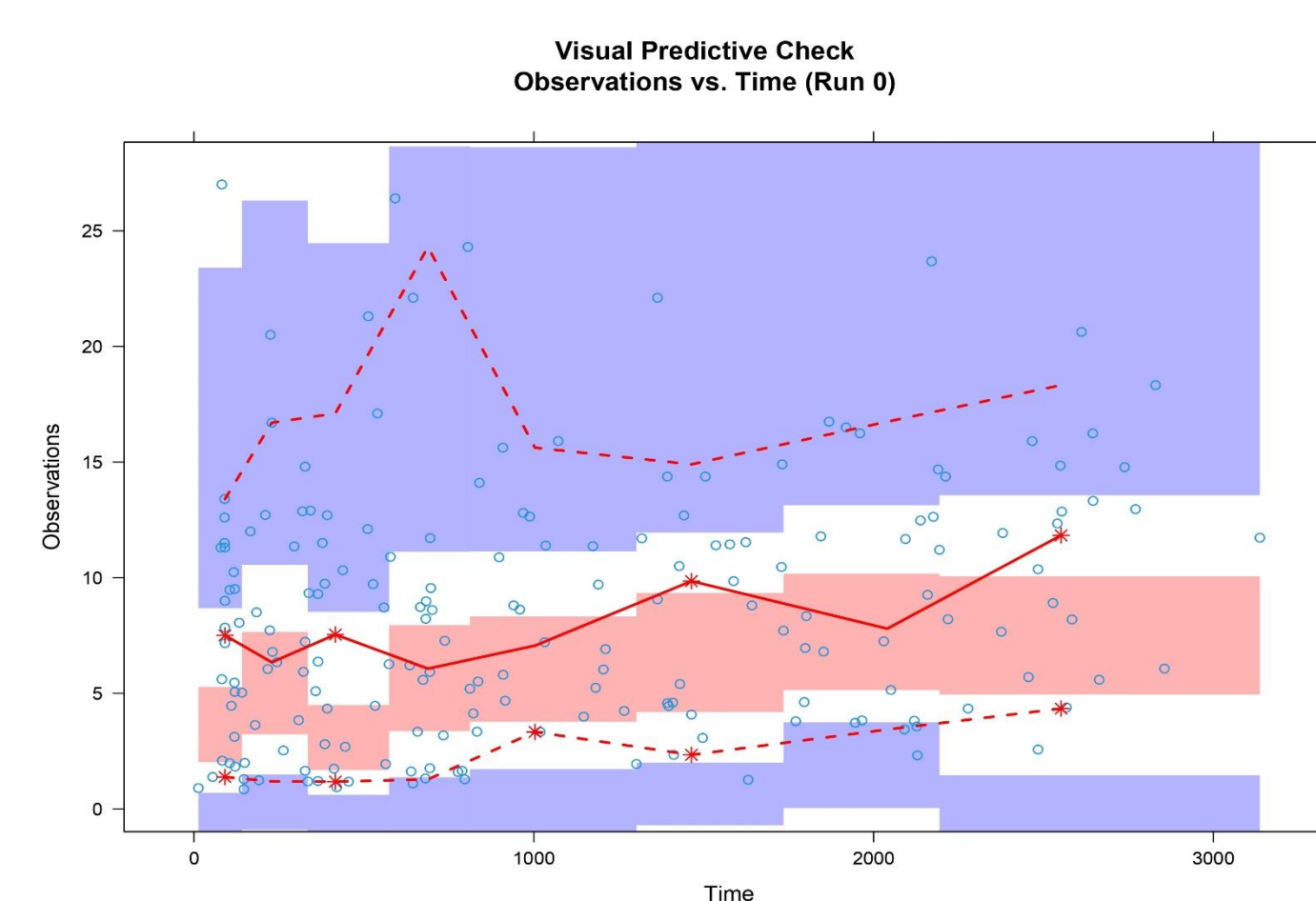
Objectives

The aim of this study is to evaluate the predictive performance and reliability of available adalimumab pharmacometric models using selected evaluation techniques. This assessment aims to determine their suitability for potential application in the clinical setting.

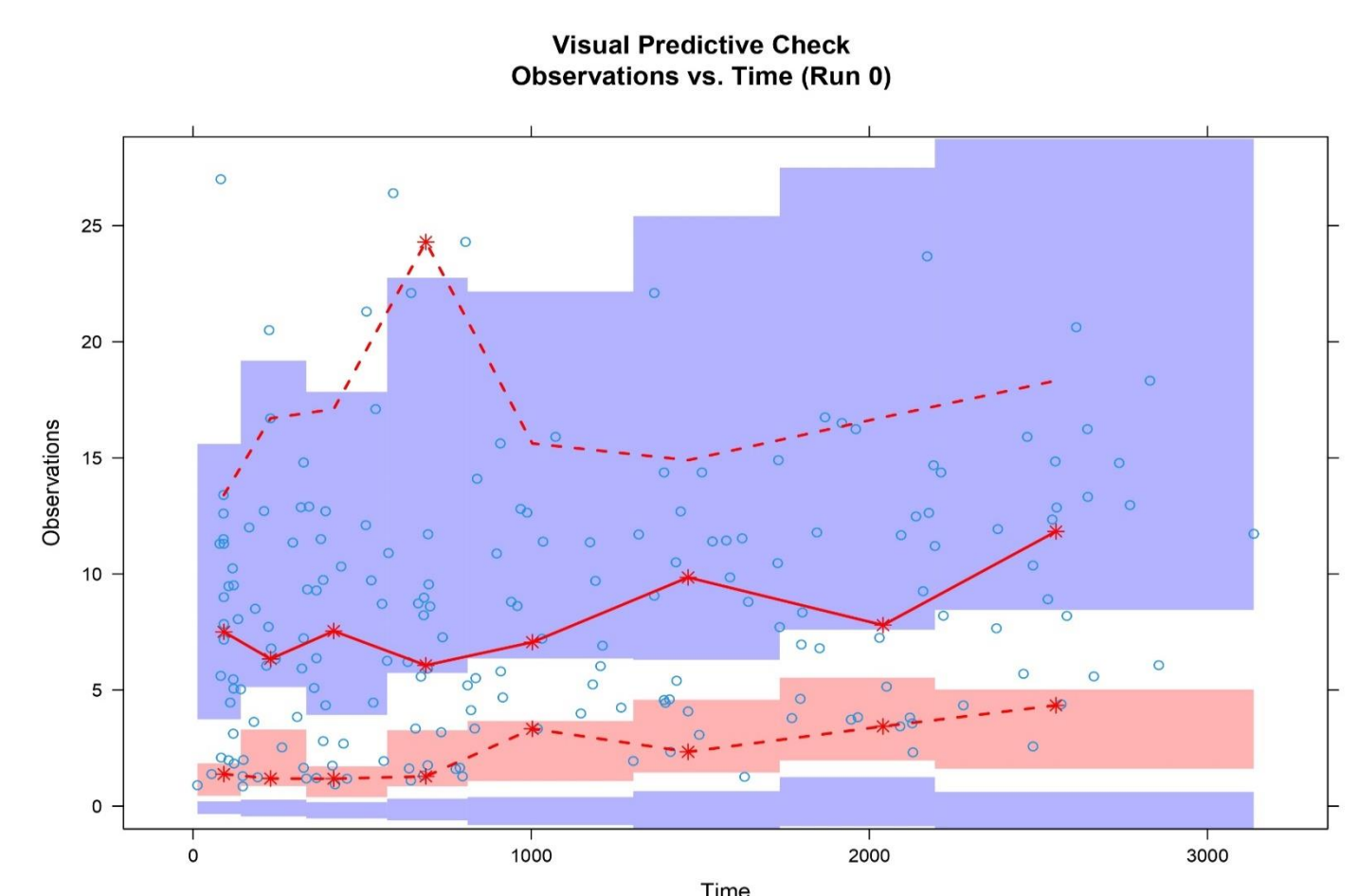
Results

Our PubMed search yielded a total of 9 models, with 3 developed in Monolix® and 6 in NONMEM®. After considering the covariates available in our dataset and the compatibility of published models with our data format, we selected the following models for external evaluation: Berends et al. [5], Marquez-Megias et al. [6], Ternant et al. [7], de Klaver et al. [8]. Our dataset for external model evaluation comprised 48 patients, with a mean age of 37.70 years (range: 21 – 61) including 28 females (58.33%). The majority of patients were diagnosed with Crohn's disease (44,91.66%). A total of 190 concentrations were included in the evaluation.

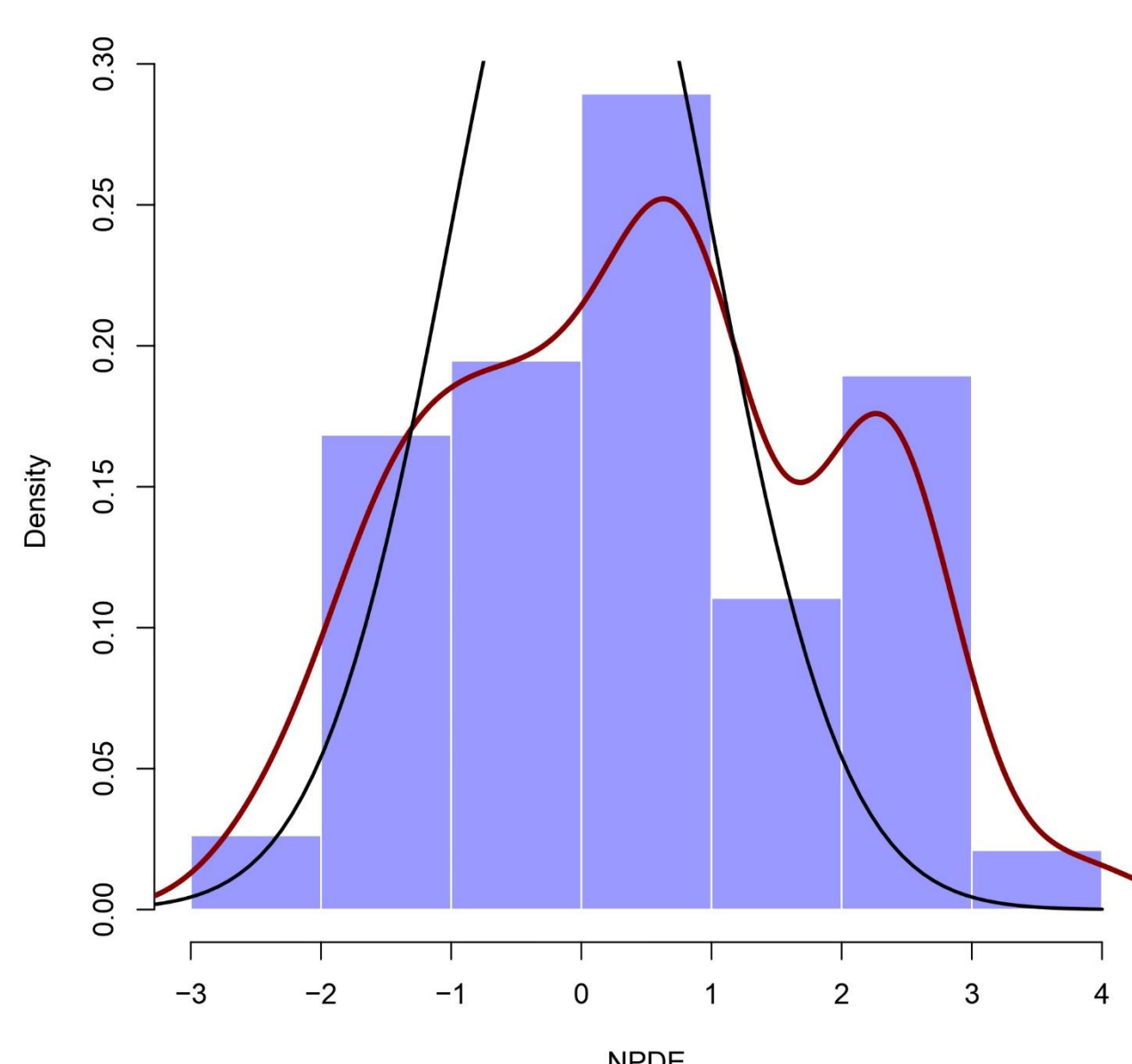
Model/parameters	PRED		IPRED	
	MPE (95% CI)	RMSPE	MPE (95% CI)	RMSPE
Berends et al. 2018	-2.54 (-3.52 – -1.57)	7.3	-1.05 (-1.36 – -0.73)	2.45
Marquez – Megias et al. 2023	-5.59 (-6.44 – -4.74)	8.18	-2.76 (-3.13 – -2.39)	3.8
Ternant et al. 2015	-2.31 (-3.25 – -1.38)	6.95	-0.32 (-0.57 – -0.06)	1.81
Klaver et al. 2023	-0.67 (-1.66 – 0.32)	6.96	-0.32 (-0.55 – -0.099)	1.6



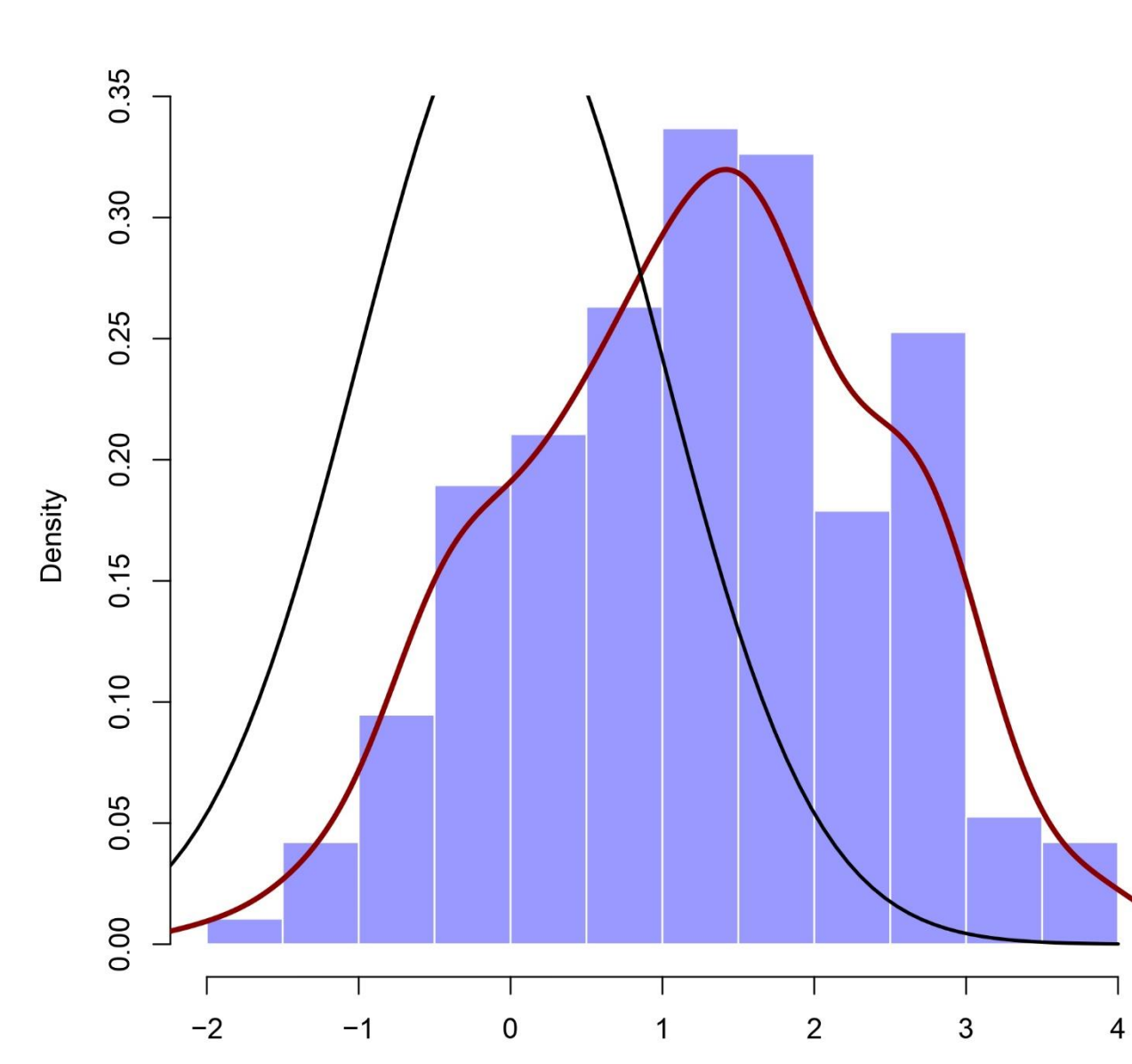
Berends et al. 2018



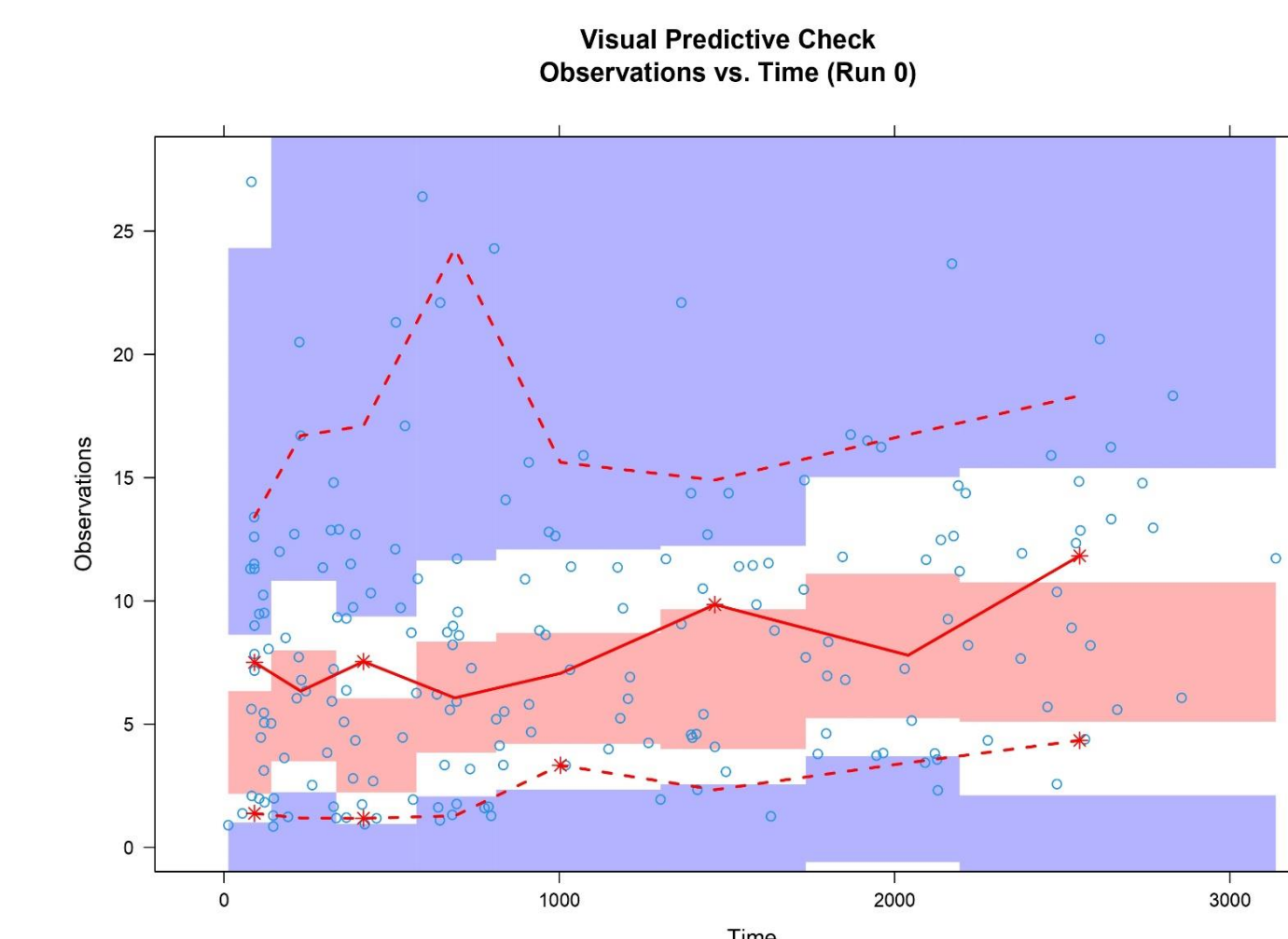
Marquez – Megias et al. 2023



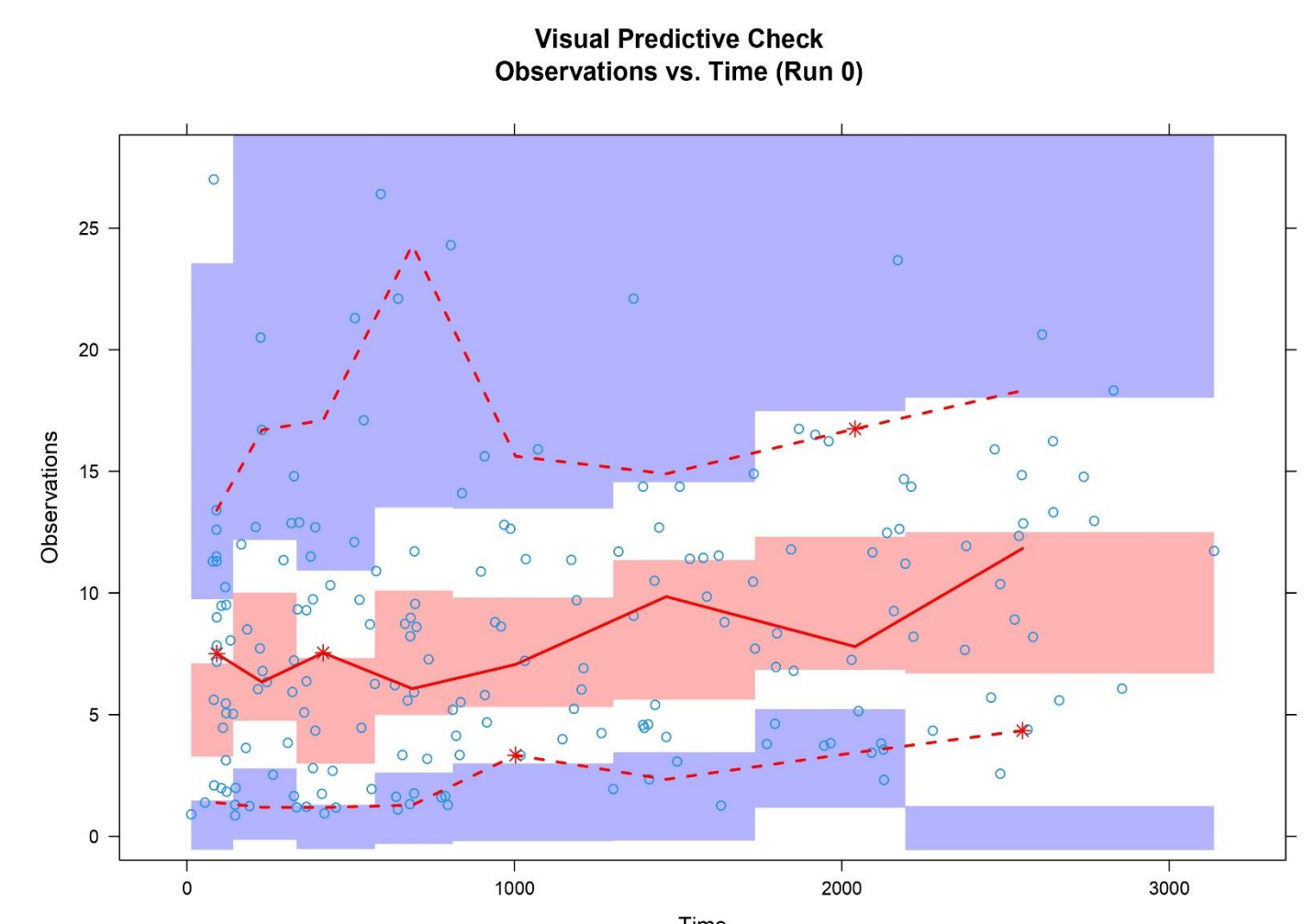
Berends et al. 2018



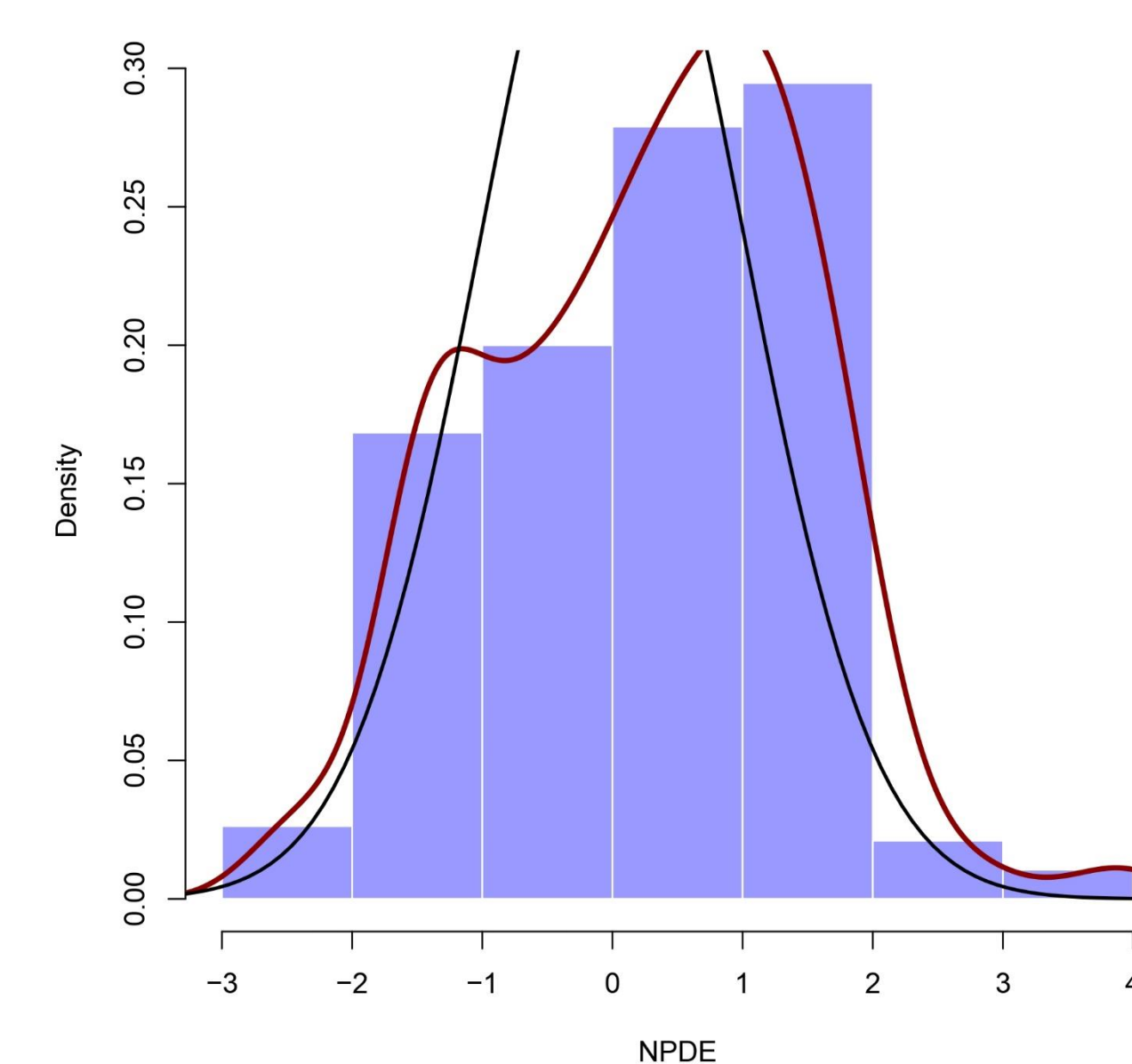
Marquez – Megias et al. 2023



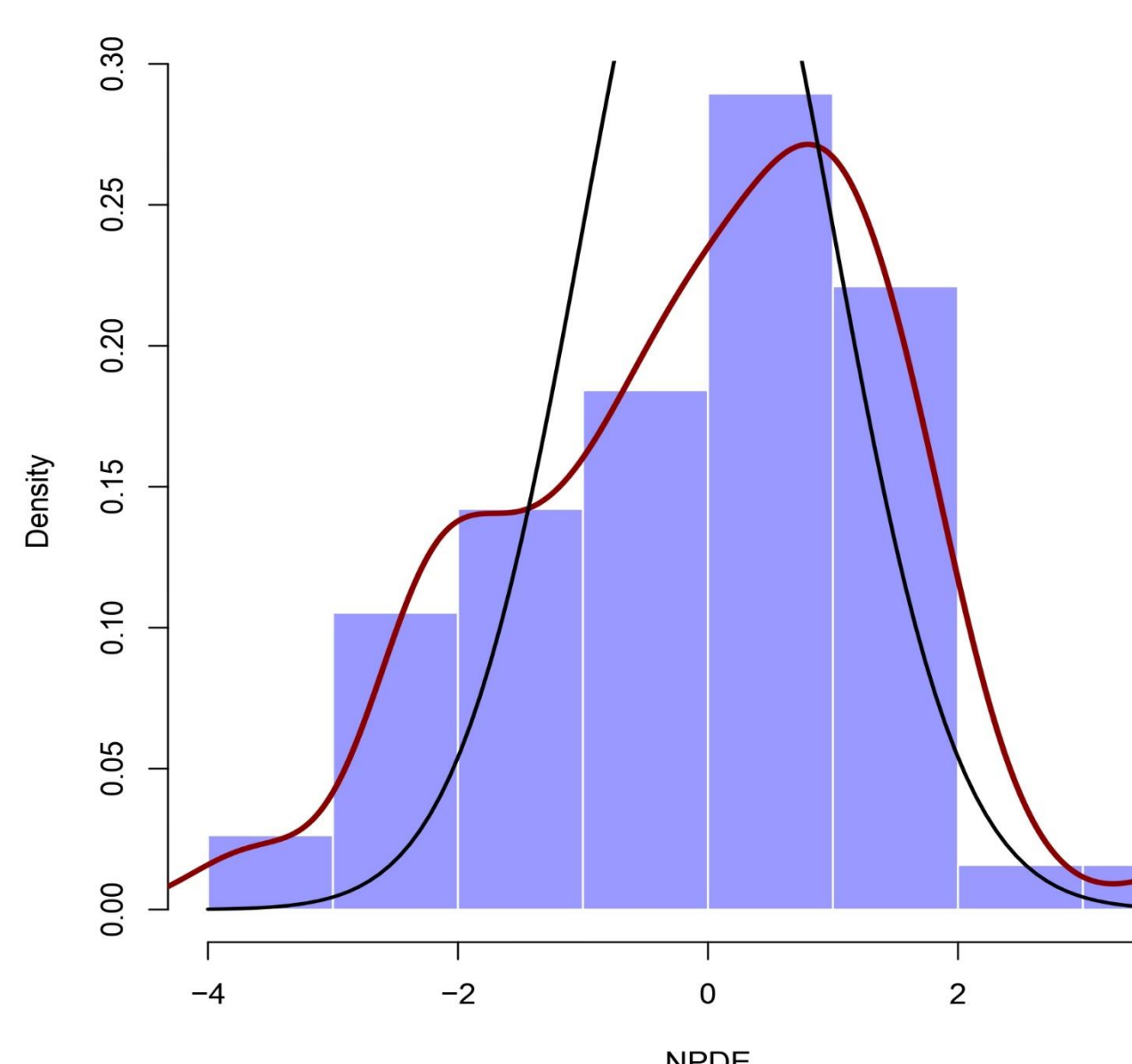
Ternant et al. 2015



Klaver et al. 2023



Ternant et al. 2015



Klaver et al. 2023

Evaluation of Berends et al., Marquez-Megias et al., and Ternant et al. models revealed bias in both PRED and IPRED predictions, although precision in prediction was observed as RMSPE values were also small for these models. The VPC and NPDE plots showed that Klaver et al. model performed better than the other three models.

Conclusion

Based on the analysis of goodness-of-fit plots, VPCs, NPDEs and calculated MPE and RMSPE, the model developed by de Klaver et al. demonstrates the most accurate prediction of PRED of adalimumab in our patient population. These findings underscore the need for additional population pharmacokinetic models of adalimumab. Additional models are essential to comprehensively identify all potential sources of variability and, consequently, enhance the accuracy of individual predictions.

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Acknowledgement: This research was supported by the Science Fund of the Republic of Serbia, grant no. 6777, project: Improving Clinical Outcomes with Precision Dosing in Patients with Inflammatory Bowel Disease Through Investigating Variability of Monoclonal Antibodies Based on Population Pharmacokinetic-Pharmacodynamic Modeling - optYmAb.

