

Exploring the Impact of Clinical Covariates on Population Pharmacokinetic Modeling of Vancomycin in High-Flux Intermittent Hemodialysis

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Introduction

Intravenous vancomycin in hemodialysis (HD)
10 fold risk of severe MRSA infection¹ **75.9** % mortality rate in HD patients with sepsis² **15-20** mg/L target pre-HD level as per 2020 IDSA consensus³

Several population pharmacokinetic (popPK) models have been developed, but none proved adequate for our population⁴

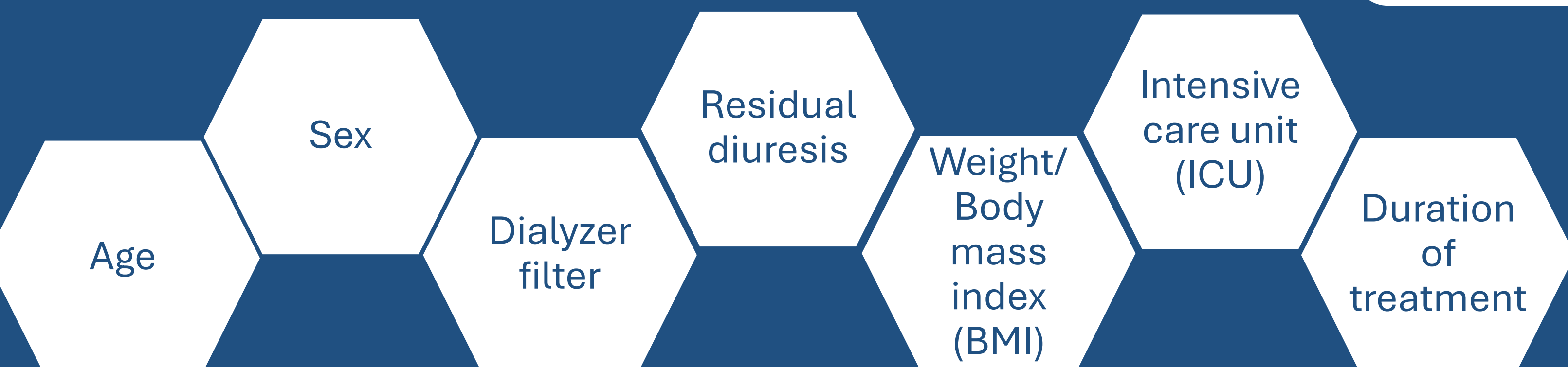
Bae et al. (2019)⁵
Goti et al. (2018)⁶
Hui et al. (2019)⁷
Oda et al. (2023)⁸

Bias ±30%
Imprecision >40%
(bias and imprecision based on weighted median)

Objectives

- Compare population predictions according to clinical covariates
- Identify clinical predictors of poor predictive performance

Clinical covariates



Methods

Population predictions of original models

Refinement with local dataset

only ¾ models converged

Population predictions of refined models

Comparison of predictive performance

Multivariate logistic regression

Stratified according to clinical covariates

- GOF
- MDPE, MDAPE

Outcomes (Y):

- Overprediction (PE > 20%)
- Under prediction (PE < - 20%)
- Imprecision (|PE| > 30%)

Predictors (X): Clinical covariates
Logistic regression performed with generalized estimating equations approach with exchangeable correlation matrix

Results

Refined models predictive performance
Bias±10% Imprecision<30%

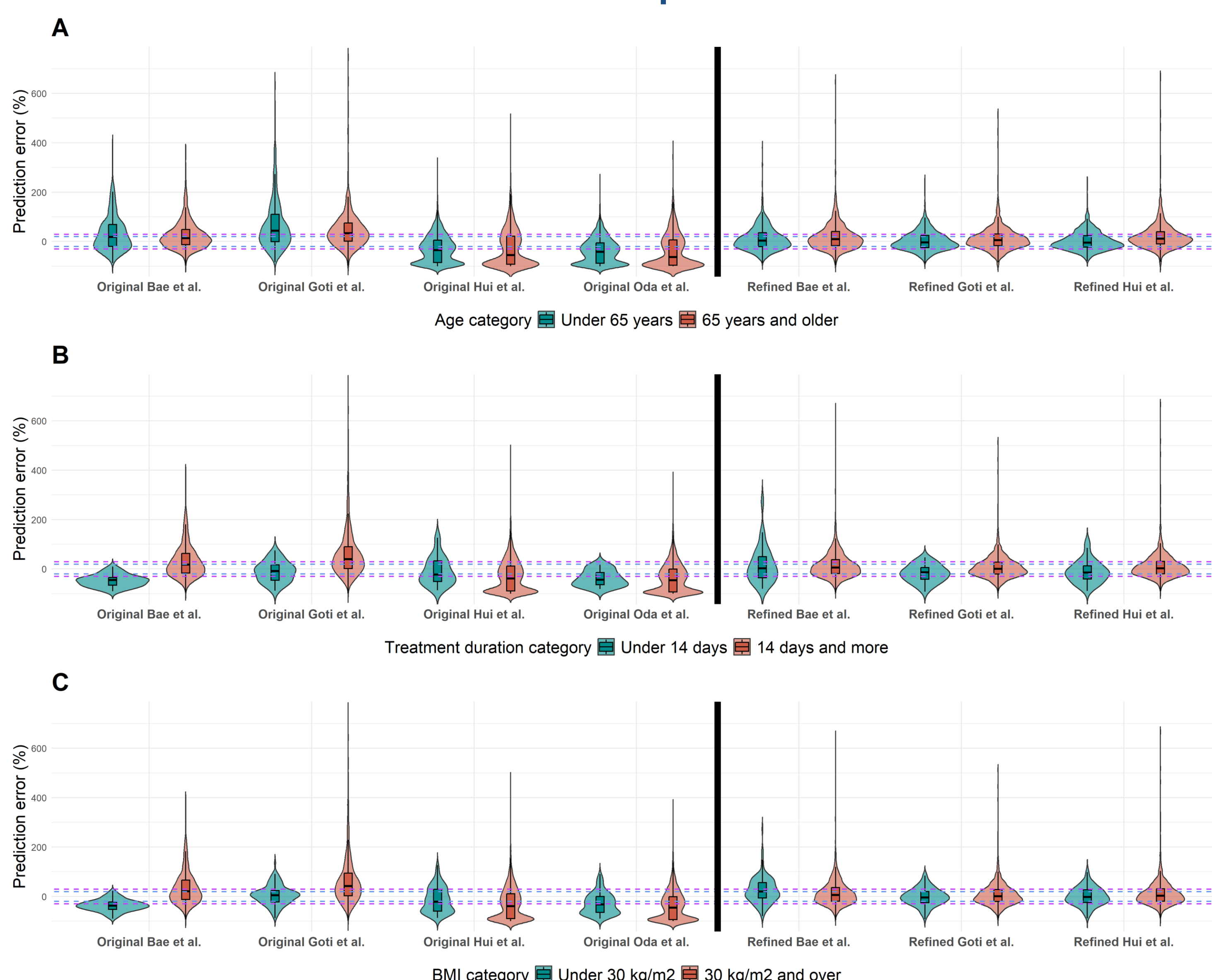


Figure 1. Violin/box plots of prediction errors according to (A) age, (B) treatment duration and (C) BMI categories. ± 20% and ± 30% thresholds are depicted by dashed blue and horizontal lines, respectively.

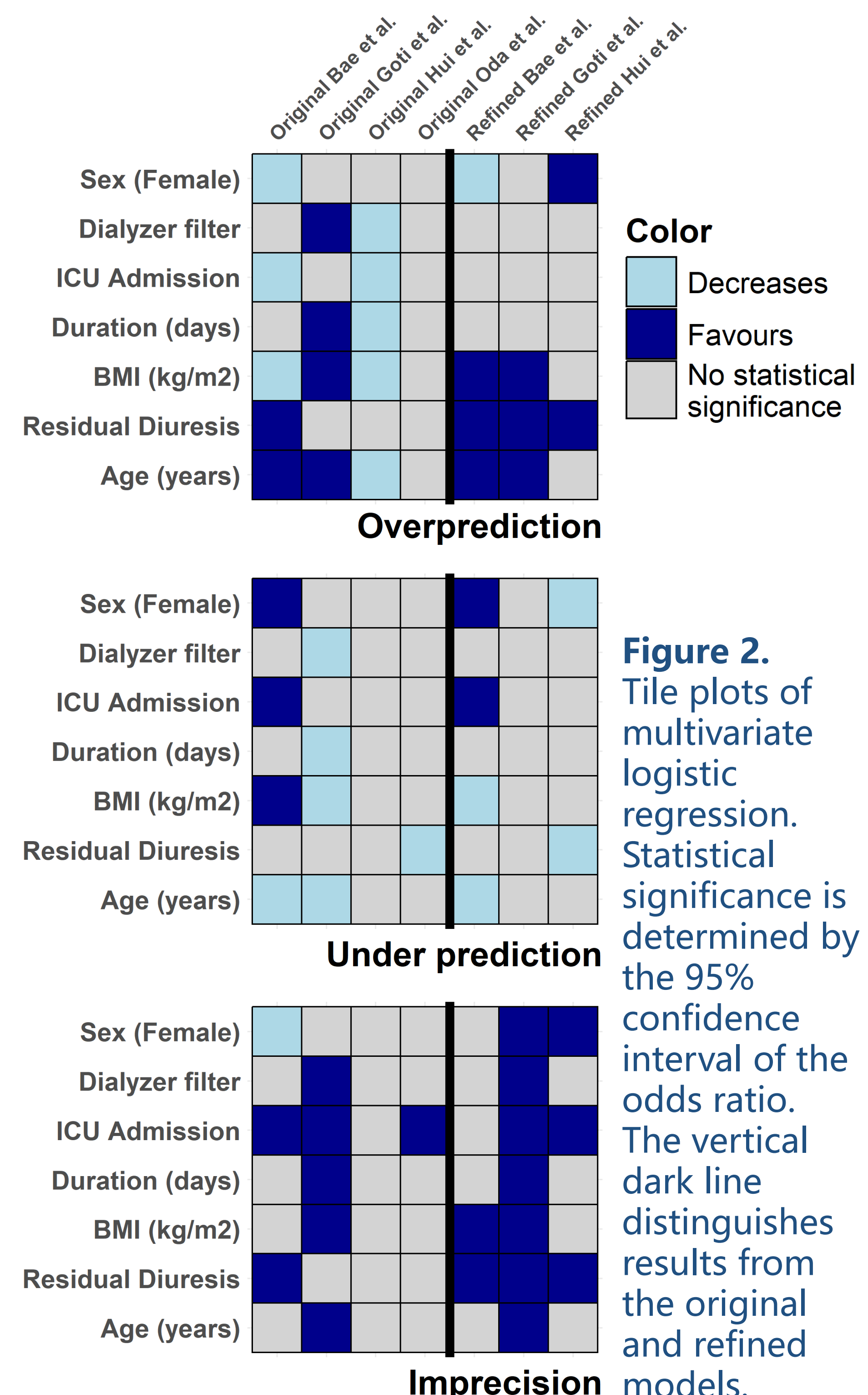


Figure 2. Tile plots of multivariate logistic regression. Statistical significance is determined by the 95% confidence interval of the odds ratio. The vertical dark line distinguishes results from the original and refined models.

Key findings

Comparison of Predictive Performance

- Visual assessment suggest older age (≥65 years), higher BMI (≥30 kg/m²) and late-stage treatment (≥14 days) as potential sources of bias and imprecision in the original models.

Multivariable Logistic Regression:

- Logistic regression analysis identified several clinical covariates associated with poor performance in the original models. Residual diuresis, advanced age and elevated BMI remained statistically significant predictors following model refinement.

Conclusion: Our findings indicate that model refinement alone is insufficient. Residual diuresis, age and BMI should be prioritized for inclusion in future popPK model development.

References

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