



# Identifying SHAP's added value to PK covariate modeling on a small dataset

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## Introduction and objective

To reduce the time required for covariate model building, SHapley Additive exPlanations (SHAP) [1] has recently gained the interest of pharmacometricians for its ability to both detect important covariates and decipher covariate-to-PK-parameter relationships [2, 3, 4, 5, 6]. However, computing exact SHAP values can require exponential time complexity, which leads to question its added value. The objective of this project is to examine whether SHAP correctly identifies true covariates and their relationships to PK parameters in the case of a small dataset.

## Data

A dataset was generated using original moxonidine clinical study data from 74 patients with 9 covariates (5 categorical and 4 continuous). PK concentrations were simulated with a one-compartment model with inter-occasion variability on clearance (CL) and volume of distribution (V), inter-individual variability on CL, V and absorption rate constant (KA), and linear effects of creatinine clearance (CLCR) on CL and weight (WT) on V.

## Methods

Multi-Layer Perceptron (MLP), Random Forests (RF), Support Vector Regression (SVR) and XGBoost (XGB) were trained and evaluated through normalized root mean squared error (NRMSE) on their ability to correctly predict CL and V at baseline.

### I – Covariate identification

SHAP covariate ranking was computed for all models based on the mean absolute SHAP ( $\text{mean}(|\text{SHAP}|)$ ) values and the 90% middle span of the SHAP values ( $\text{span}(\text{SHAP}, 90\%)$ ). **SHAP's ability to correctly rank covariates was assessed through ability to identify the true covariate as the top ranked one with both  $\text{mean}(|\text{SHAP}|)$  and  $\text{span}(\text{SHAP}, 90\%)$ .** SHAP ranking was compared to feature permutation importance with Random Forests, Gini importance and LASSO.

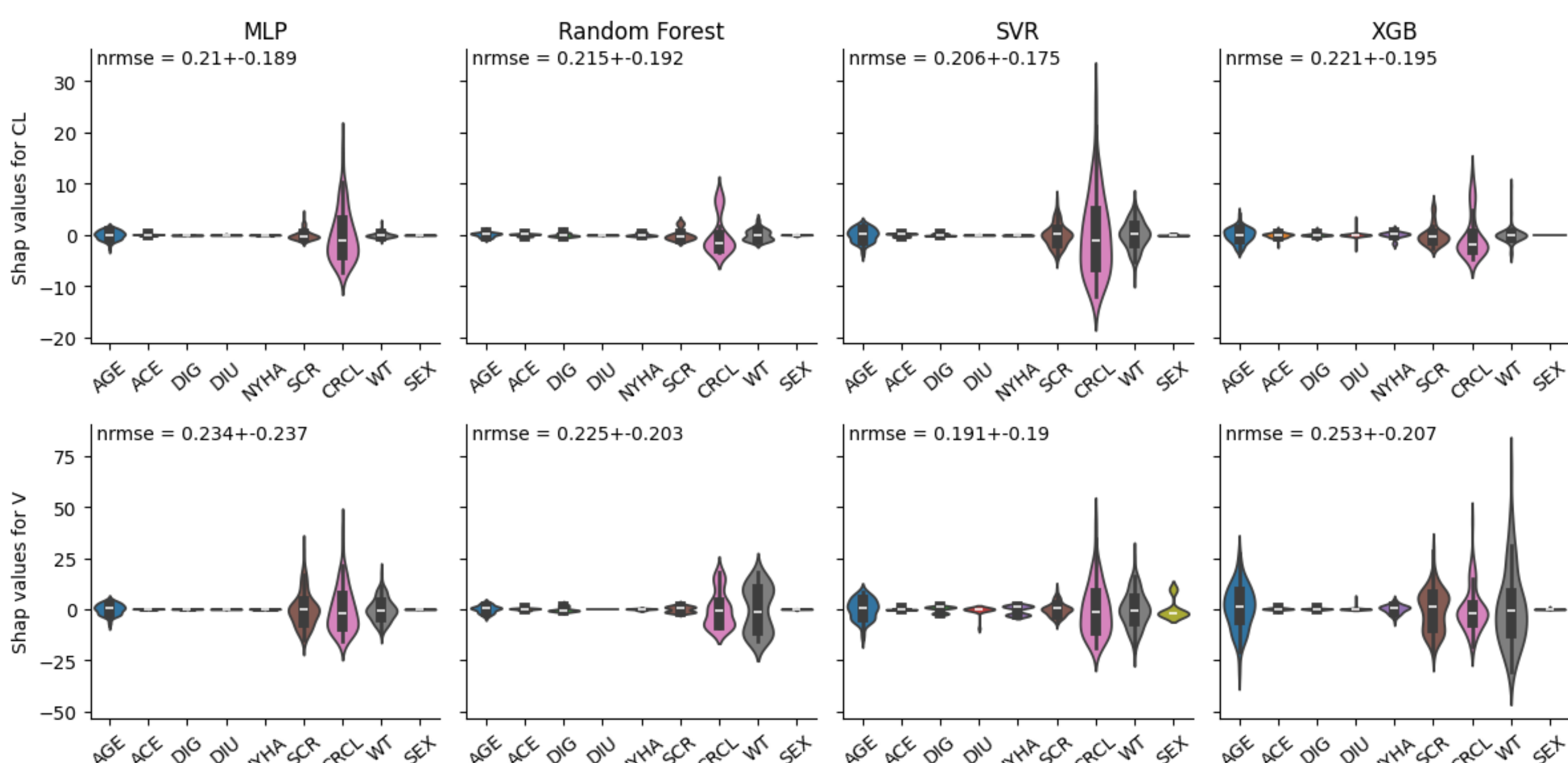
### II – Covariate-to-PK-parameter relationship identification

To assess whether SHAP brought information on the functional relationship between covariates and PK parameters, SHAP values and individual PK values were plotted against each covariate and compared.

## Results

### I – Covariate identification

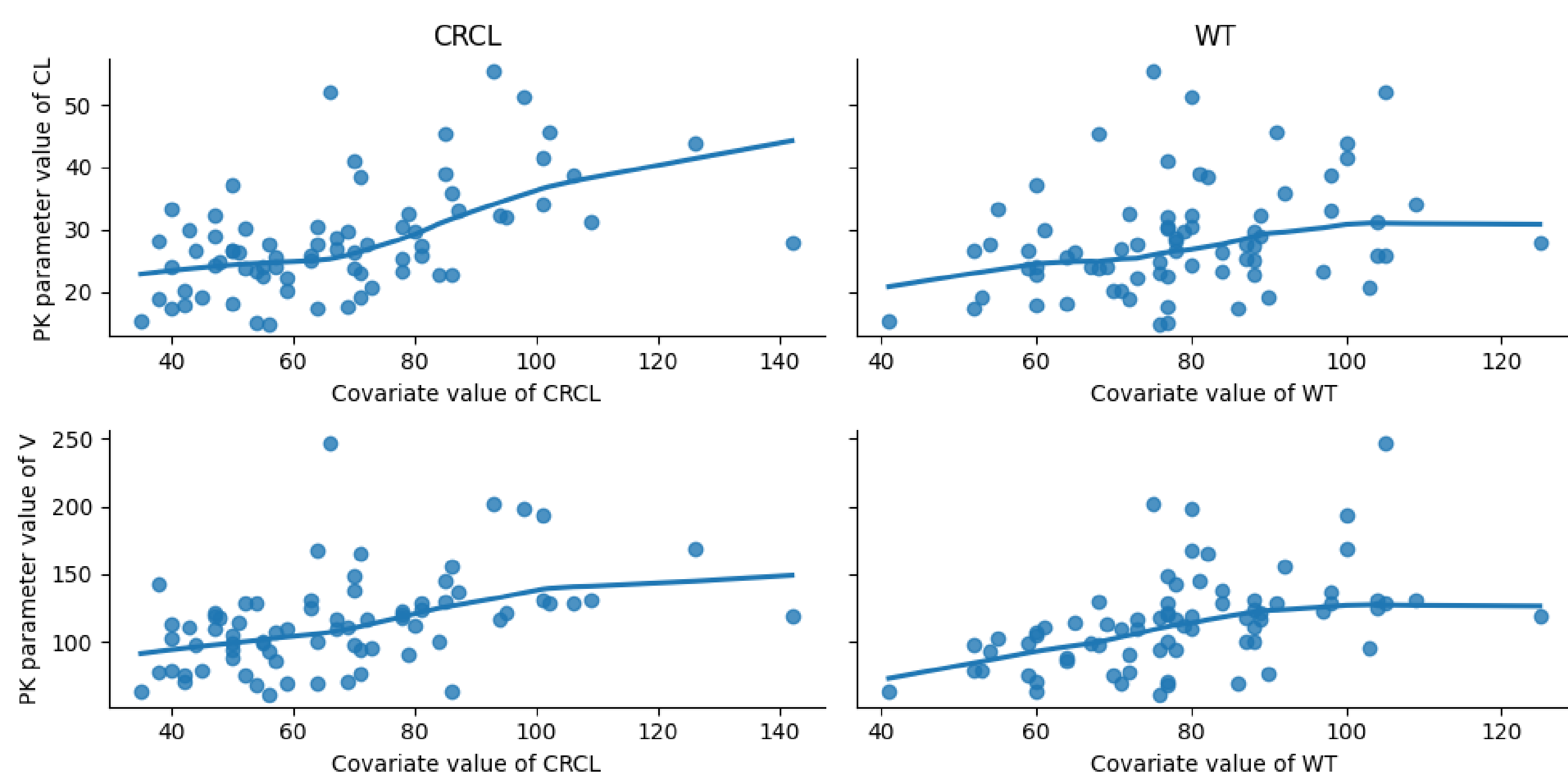
#### a. SHAP values distributions for all ML models



➔ All models had similar performances (range(NRMSE) = [20.6%, 22.1%] for CL). SVR performed the best on average across all PK parameters (NRMSE $\approx$ 20%). However, the SVR's SHAP values failed at identifying the true covariates. Random Forest had slightly worse performances (NRMSE $\approx$ 21.5%) but was the only model for which SHAP values correctly identified the true covariates.

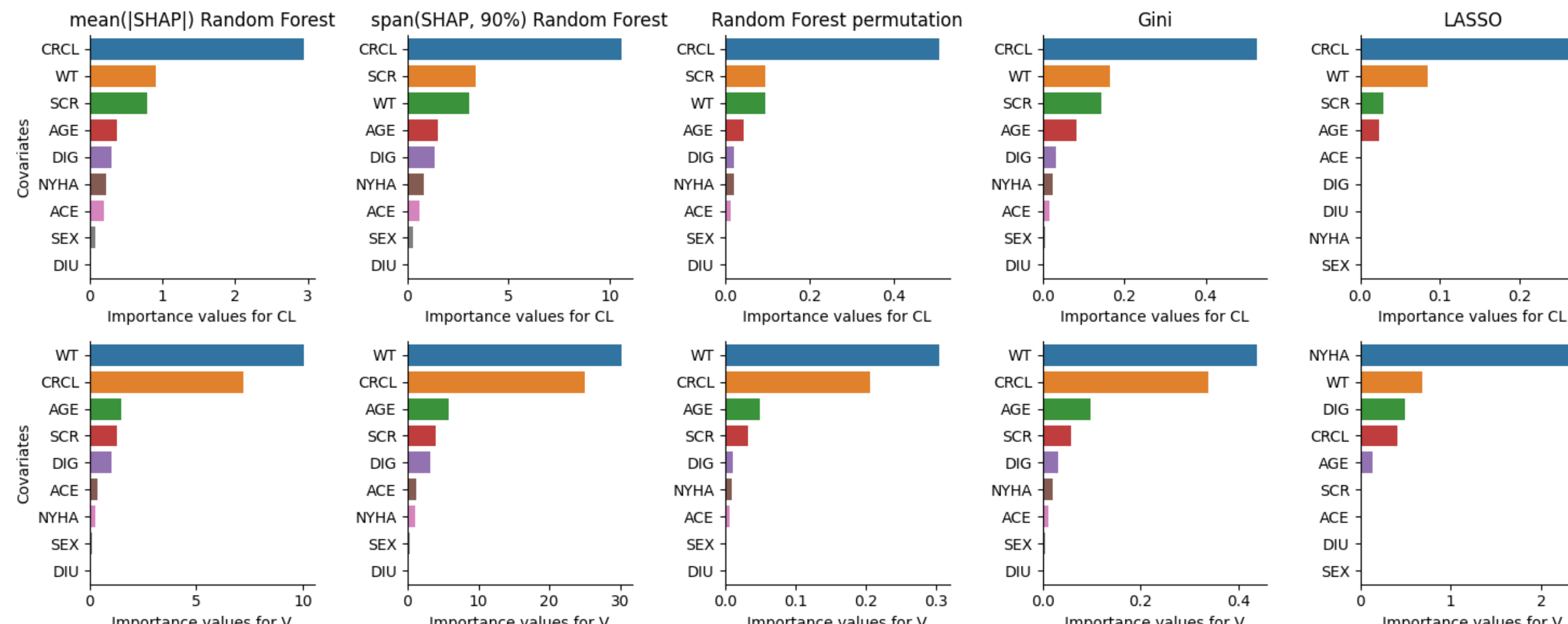
### II – Covariate-to-PK-parameter relationship identification

#### a. PK parameters versus covariates



➔ SHAP values correctly and clearly suggested a linear relationship between covariates and PK parameters with all machine learning models. Although a linear functional form could have been suspected from the PK-parameter-to-covariate plots, SHAP values suggested it with much more confidence.

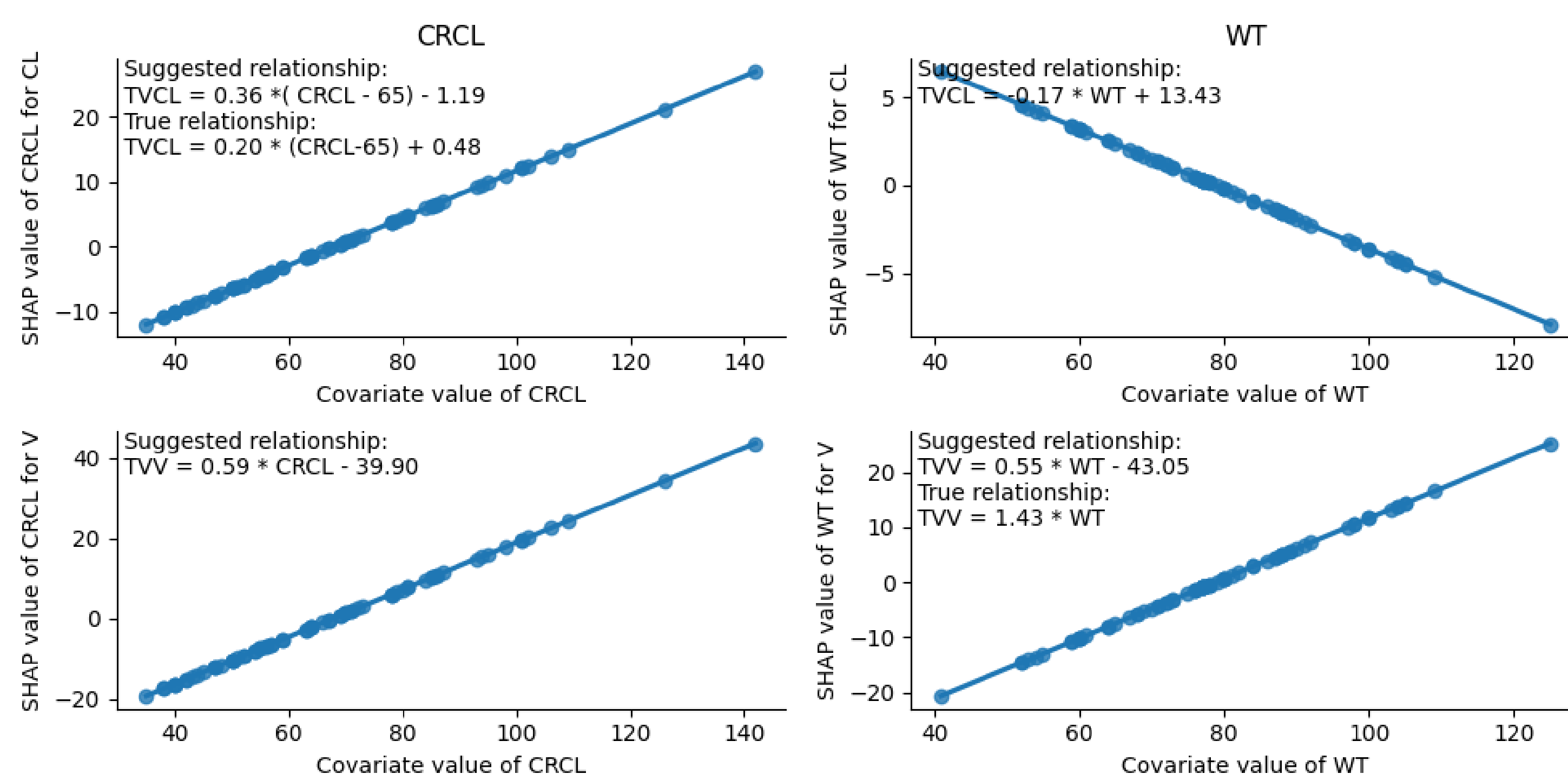
#### b. Random Forest's SHAP values versus classical feature selection methods



➔ Gini importance and RF permutation importance, which are both based on Random Forests, as well as Random Forest's SHAP are the only methods that correctly identified the true covariates. LASSO did not identify the true covariates.

Thus, whether using SHAP or classical feature selection methods, only Random Forests based methods have successfully identified the true covariates.

#### b. SVR's SHAP values versus covariates



## Conclusion

With this dataset, SHAP did not demonstrate the potential to be a complete full model alternative to classical covariate analyses. In such cases of small datasets, the computational time of SHAP remains low enough for it to be worth the information it brings on the functional form between covariates and PK parameters. Unfortunately, this computational time grows exponentially with covariates and extra patients in the dataset. In order to confirm or infirm these results, SHAP should be evaluated on a benchmark of different simulated scenarios.

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