Application of Machine Learning Approach to Pharmacokinetic/Pharmacodynamic Analysis of Lusutrombopag

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Introduction and Objective

- Machine leaning (ML) is an approach to provide a powerful computational efficiency and is expected to complement pharmacometric analyses in drug development [1].
- In pharmacokinetic/pharmacodynamic (PK/PD) analyses using time-course data, compartment model analysis is standardly used and work reasonably. However, this analysis would be time-consuming for model building in some cases where the numbers of subject, compartments, and/or covariates are large. Machine leaning approach may increase efficiency for the PK/PD analyses.
- The aim of this study was to apply ML approach for model building and covariate selection in the PK/PD analysis of lusutrombopag, a thrombopoietin receptor agonist, and to compare predictive performance with the PK/PD compartment model of lusutombopag.

Methods

ML Approach

- Gradient Boosting Decision Tree, using Python LightGBM [2]

Data

- Platelet count data from thrombocytopenic patients with chronic liver disease after 0.25 – 4 mg dose of lusurombopag once daily for 7 days with the stopping criteria based on platelet counts in clinical trials [3].
- Learning data: 2520 platelet count data from the 253 thrombocytopenic patients
- Test data: 1006 platelet count data from 94 thrombocytopenic patients

Impact of features on model prediction

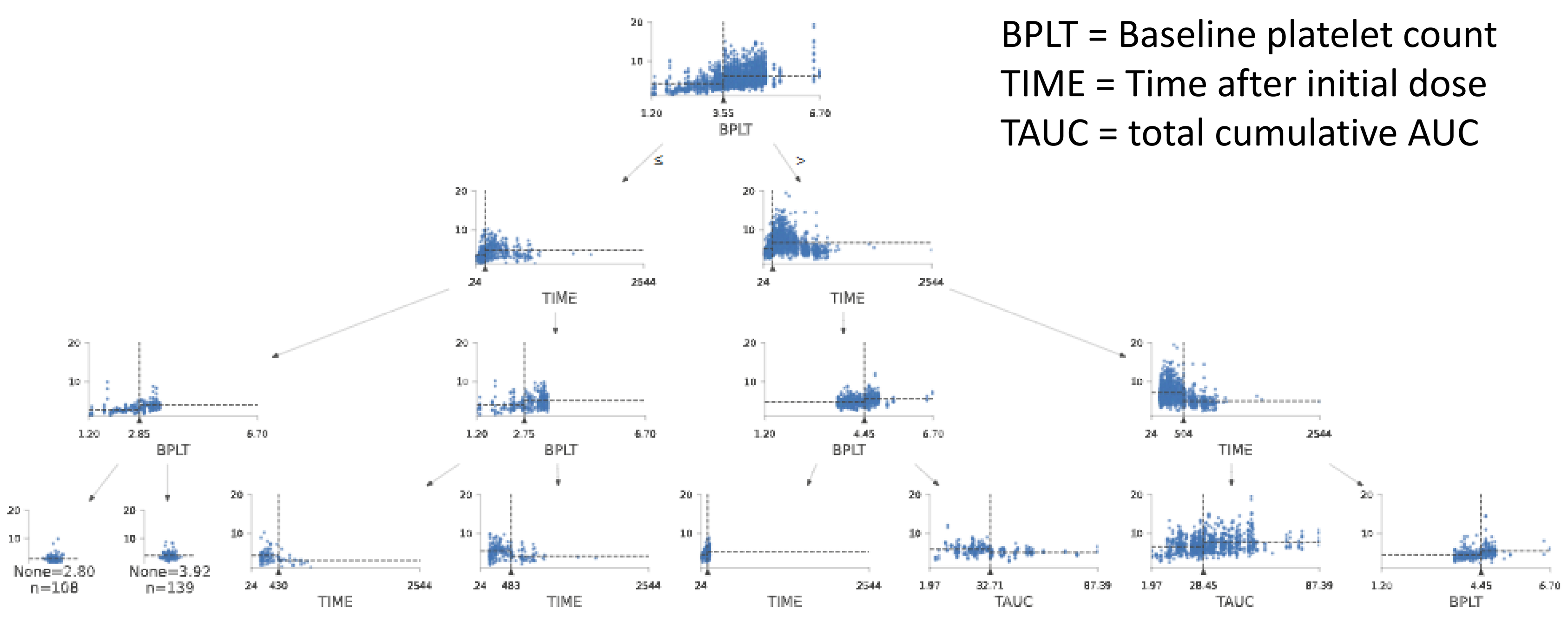
- The impact of features on platelet count profiles were evaluated using SHapley Additive exPlanation (SHAP) values [4].
- Tested features: time after initial dose (TAID), total cumulative area under the plasma drug concentration-time curve (TAUC) of lusutrombopag during the study, Child-Pugh score, baseline platelet counts (BPLT), age, sex, and ethnicity (Japanese or non-Japanese patients)

Comparison with PK/PD compartment model

- The predictive performance of the selected model using LightGBM was compared with that of the PK/PD compartment model which had the same structure as the reported PK/PD model of lusutrombopag (3-compartment PK model and 5-compartment PD model) [3].

Results

- The first 3 selected features of developed tree model using LightGBM were BPLT, TAID, and TAUC.



BPLT = Baseline platelet count
TIME = Time after initial dose
TAUC = total cumulative AUC

Figure 1. The First 3 Selected Features of Developed Tree Model Using LightGBM

Conclusion

- The ML could be applied for describing platelet count profiles after lusutrombopag dose and selecting features on the change in platelet counts.
- The run time up to completion was very fast for developing the model by using LightGBM (a few seconds per run), which would be an advantage of the ML.
- The ML would be an alternative for PK/PD analyses and is expected to provide a powerful computational efficiency.

Reference

1. McComb A et al. Br J Clin Pharmacol. 2022. 88:1482-99.
2. Ke, G. et al. NIPS 2017. 3149–57.
3. Katsube T et al. Clin Pharmacokinet. 2019. 58:1469-82.
4. Lundberg SM et al. NIPS 2017. 4768–77.

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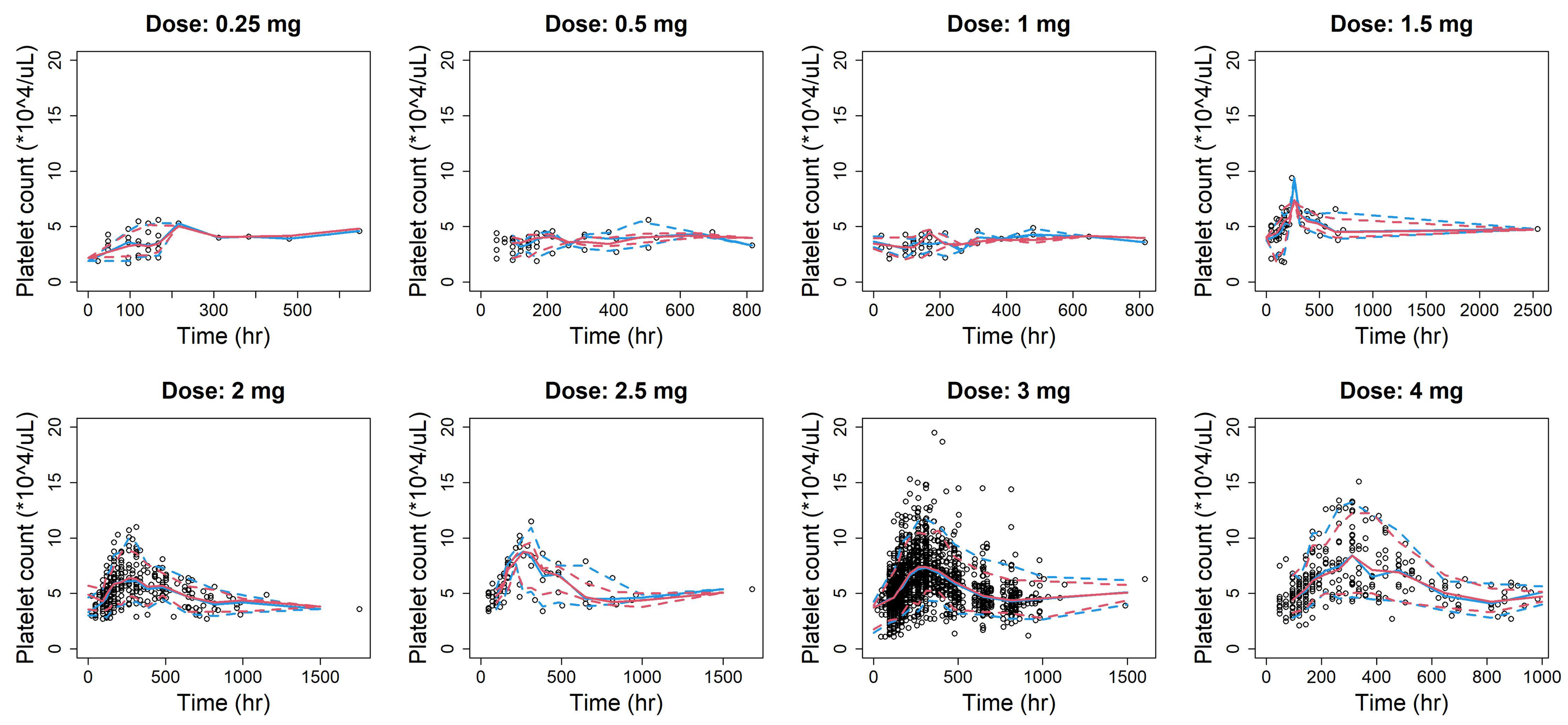
Results

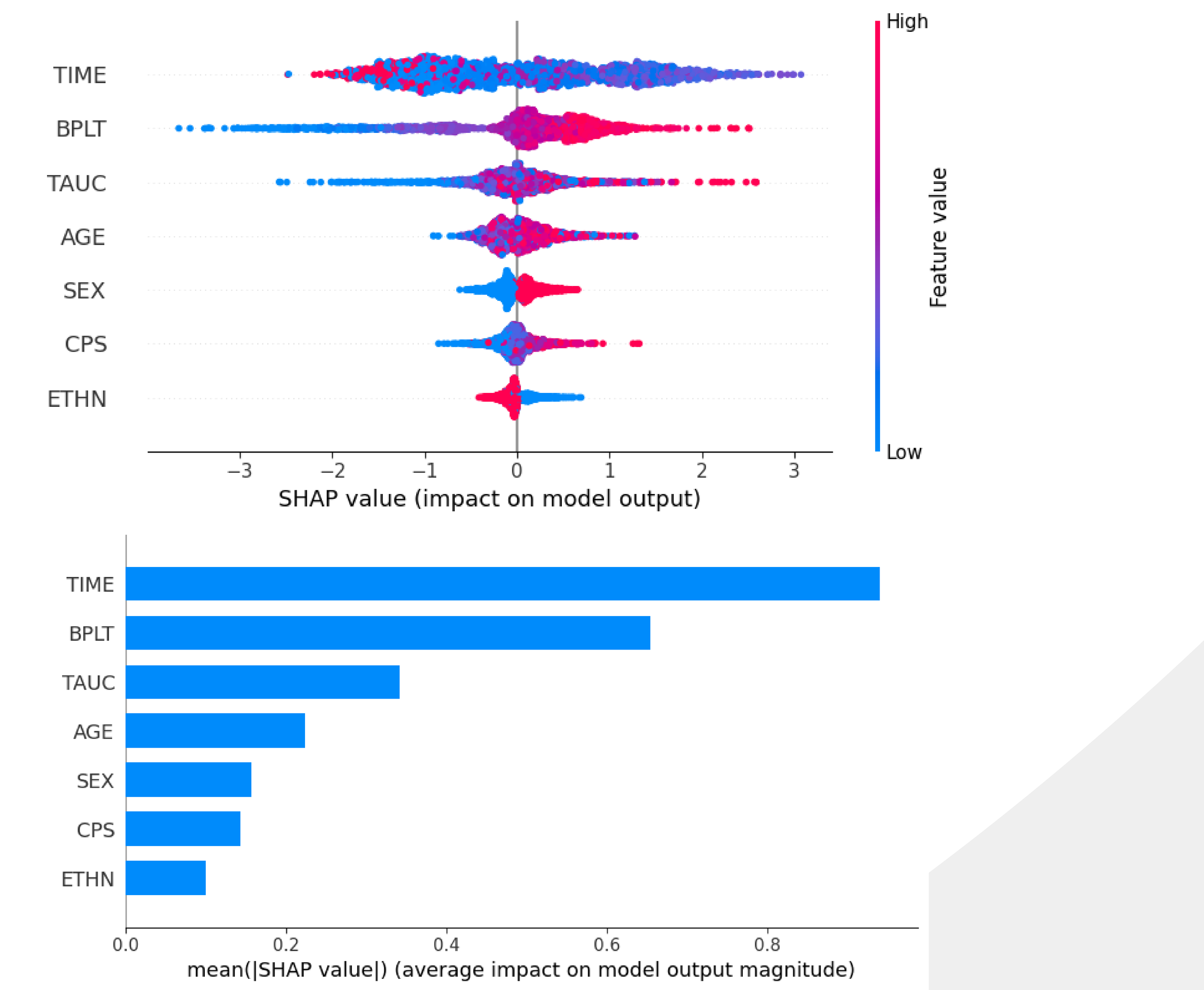
- The developed model using LightGBM well described platelet counts by dose (0.5 – 4 mg) for the training data (Figure 2).



Circles: observed data of platelet counts.
Solid lines: median. Dotted lines: 5th and 95th percentiles.
Red lines for model prediction. Blue lines for observation.

Figure 2. Predictions and Observations for Time Courses of Platelet Counts in Training Data Using LightGBM Model

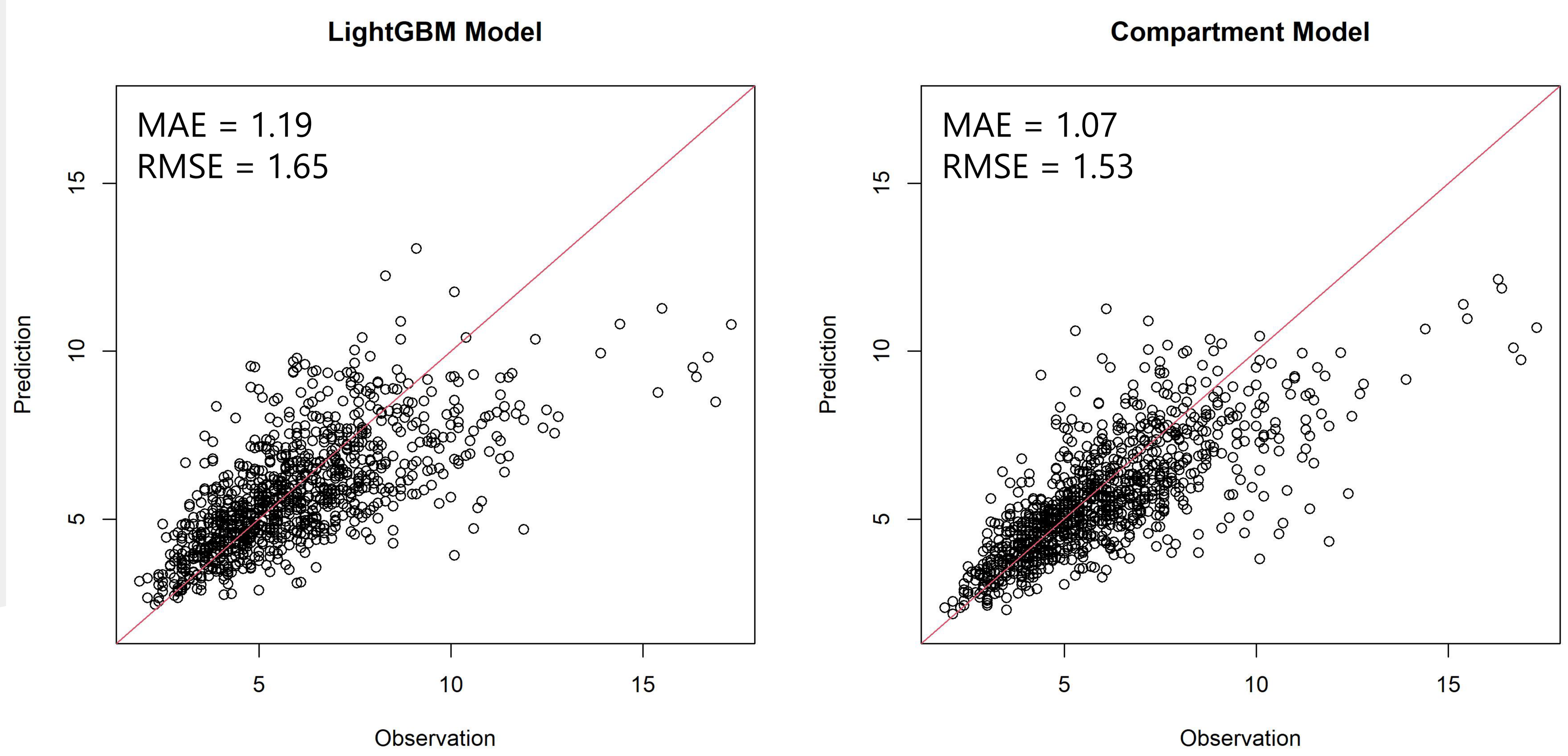
- The fluctuations of SHAP values were larger for TAID, BPLT, and TAUC in the LightGBM model (Figure 3, upper)
- The absolute mean SHAP value was the highest for TAID, followed in order by BPLT, and TAUC (Figure 3, lower).
- The above 3 features were consistent with influential covariates based on the previous PK/PD modeling of lusutrombopag [3].



TIME = Time after initial dose, BPLT =Baseline platelet counts,
TAUC = Total cumulative AUC, CPS = Child-Pugh score, ETHN = Ethnicity (Japanese or Non-Japanese)

Figure 3. SHAP Values for Impact of Each Features on Platelet Count Profiles

- The predictive performance for platelet counts of the test data was comparable between the LightGBM model and the PK/PD compartment model (Figure 4).



MAE = Mean absolute error, RMSE = root mean squared error

Figure 4. Predictive Performance of LightGBM Model and PK/PD Compartment Model for Platelet Counts of Test Data