Cross-cohort prognosis of levodopa-induced dyskinesia in Parkinson's disease

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Background

In the treatment of Parkinson's disease (PD), the drug levodopa is often prescribed to relieve the motor symptoms of the disease[1]. However, prolonged levodopa usage often leads to adverse effects, including involuntary movements known as levodopa-induced dyskinesia (LID). While most PD patients develop LID during later disease stages, some patients remain free from this symptom despite continuous levodopa treatment[2]. The key molecular factors distinguishing affected from unaffected patients remain largely unknown but may provide targets for improved therapy.

Methods

Three large-scale, longitudinal PD cohorts (LUXPARK, PPMI, and ICEBERG) were used to build cross-cohort prediction models for LID prognosis, considering 4 years of follow-up clinical visits, to discover the potential risk and protective factors for LID development using baseline clinical assessments.
Apart from investigating predictive factors for LID in each cohort separately, we examine the similarities between cohorts to identify the most robust shared predictors.
Machine learning (ML) algorithms for binary classification and time-to-event analysis were implemented and applied using a nested 5-fold cross-validation including missing values imputation, normalization, categorical outcome encoding, undersampling, and feature selection.
SHAP value and SurvSHAP(t) analyses were performed to interpret the predictive value of the features.

Results

A. Predictive performance for optimal unbiased LID prognosis models (4-year follow-up) was measured as an average cross-validated AUC/C-index ± standard deviation (SD) and hold-out AUC/C-index for single cohort and multi-cohort analyses

Cohort	Classification		Time-to-event	
	Mean ± SD	Hold-out AUC	Mean ± SD	Hold-out C-index
LUXPARK	0.74 ± 0.028	0.795	0.85 ± 0.009	0.856
PPMI	0.70 ± 0.043	0.712	0.74 ± 0.026	0.734
ICEBERG	0.69 ± 0.074	0.763	0.71 ± 0.123	0.622
Cross-cohort	0.77 ± 0.037	0.743	0.78 ± 0.033	0.818
Leave-ICEBERG-out	0.79 ± 0.041	0.537	0.80 ± 0.024	0.613
Leave-PPMI-out	0.78 ± 0.039	0.678	0.86 ± 0.010	0.719

- **Left:** Area under the curve (AUC) scores serve as a measure of the predictive performance for the LID classification prognostic model.
- **Right:** The concordance index (C-index) serves as a measure of the predictive performance for the time-to-LID model.

B. Relevance and consistency of selected features for LID prognosis and time-to-LID occurrence

Baseline feature	Classification		Time-to-dyskinesia	
	Number of cohorts	Average frequency (%)	Number of cohorts	Average frequency (%)
Baseline dyskinesia	5	88.13	5	79.95
Duration of PD diagnosis to enrollment	3		4	57.15
MDS-UPDRS I - Urinary problems	3		4	52.24
Age of onset	4	35.88	3	
MDS-UPDRS II - Walking and balance	3	33.08	3	
Levodopa treatment		47.60	5	
MDS-UPDRS I – Fatigue	4	36.10		52.69
MDS-UPDRS III - Rigidity - RLE (ON)		35.09		52.50

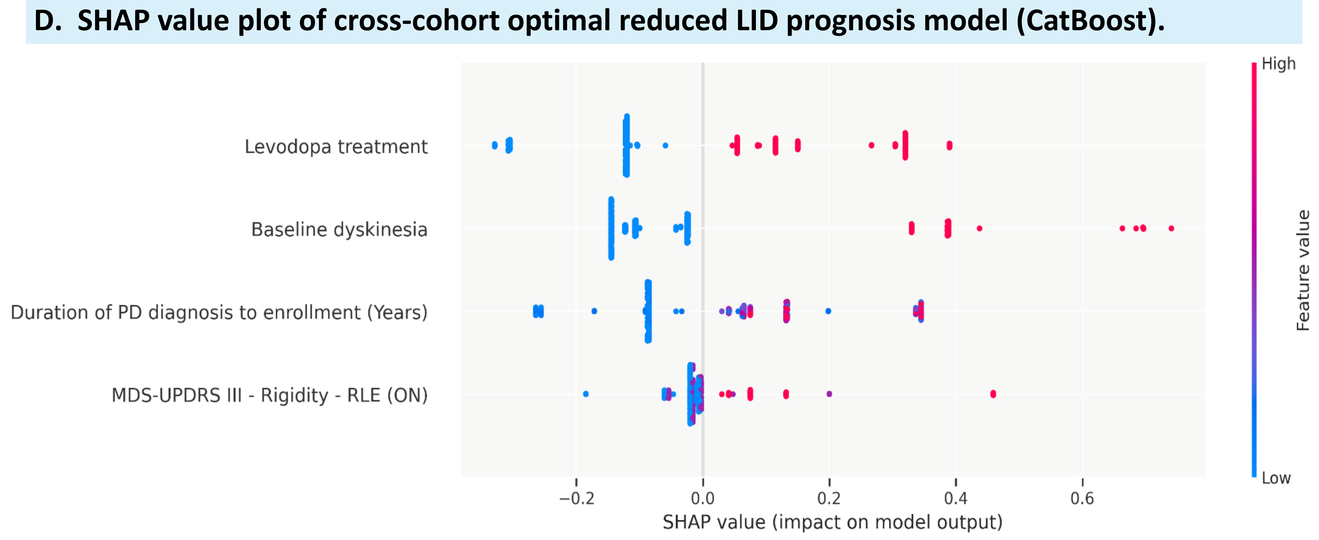
- Number of cohorts: *The number of cohorts for which the optimal model included the particular feature.*
- Average frequency (%): *The average frequency of selection for each cohort. The frequency was computed as the relative number of the occurrences of the predictive feature in each optimal model, across different normalization methods, feature selection methods, and undersampling techniques for each cohort.*

C. Predictive performance for optimal reduced LID prognosis model (4-year follow-up) was measured as average cross-validated AUC/C-index ± standard deviation (SD) and hold-out AUC/C-index for single cohort and multi-cohort analyses

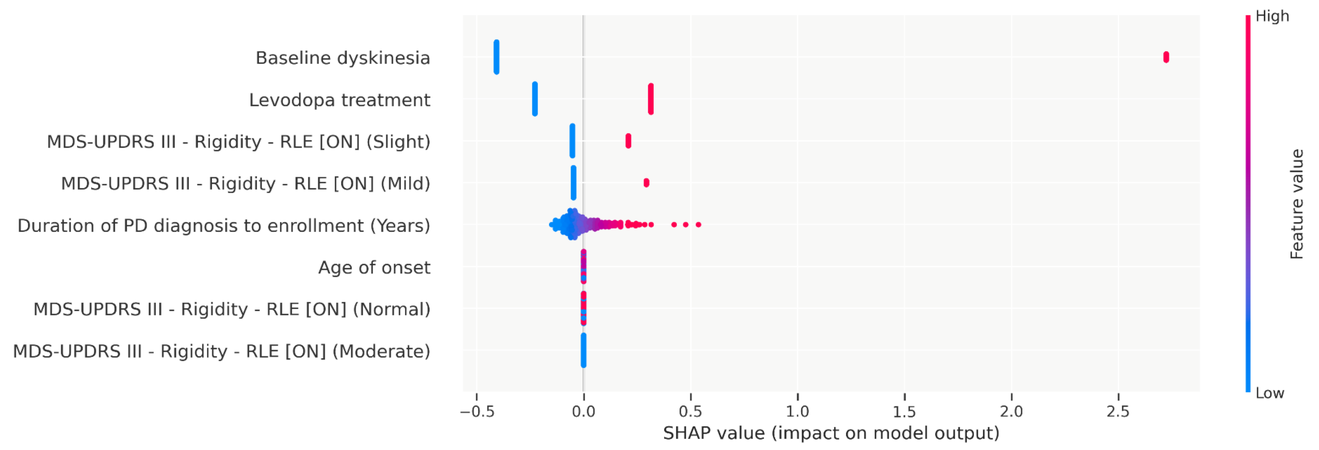
Cohort	Classification			Time-to-event		
	Mean ± SD	Hold-out AUC	p-values	Mean ± SD	Hold-out C-index	p-values
LUXPARK	0.74 ± 0.045	0.771	0.077	0.85 ± 0.034	0.865	0.675
PPMI	0.71 ± 0.067	0.736	0.654	0.72 ± 0.021	0.701	0.188
ICEBERG	0.72 ± 0.104	0.747	0.784	0.74 ± 0.133	0.601	0.842
Cross-cohort	0.75 ± 0.046	0.750	0.784	0.77 ± 0.034	0.793	0.061
Leave-ICEBERG-out	0.78 ± 0.015	0.590	0.456	0.79 ± 0.030	0.685	0.231
Leave-PPMI-out	0.75 ± 0.055	0.647	0.295	0.86 ± 0.017	0.715	0.742

- The performance of the prognostic models for the optimal unbiased model in Table A and the optimal reduced model for LID prognosis in each cohort is compared-
- Statistical tests: DeLong's test is used to compare model AUC scores, a one-shot nonparametric test is used to compare model C-index scores.

D. SHAP value plot of cross-cohort optimal reduced LID prognosis model (CatBoost).



E. SHAP value plot for the cross-cohort optimal reduced time-to-LID occurrence model (component-wise gradient boosting)



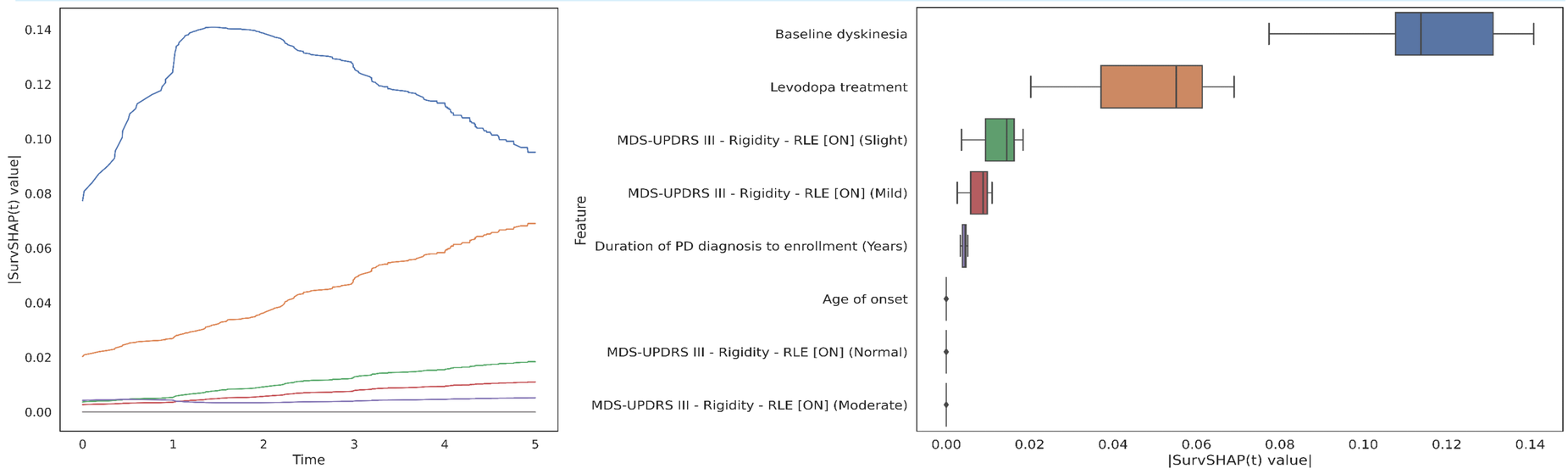
Discussions

- Baseline dyskinesia had a higher impact on short-term LID prognostics model.
- Age of PD onset had limited predictive power and might not be a primary driver of LID risk.
- Levodopa treatment and MDS-UPDRS III rigidity score suggested that the impact of these factors on LID risk intensifies over time.
- The reduced model of LID prognosis and time-to-LID occurrence model, both demonstrating similar prediction performance to the unbiased model, reinforce the efficiency of these simplified models.

In a nutshell …

- Cross-cohort ML analyses using comprehensive baseline clinical data can highlight potential LID risk factors and pave the way towards tailored interventions depending on the patient's disease duration, levodopa treatment, and symptoms of rigidity.
- The reduced optimal prognostic model provides an interpretable, yet highly predictive biomarker signature of LID development.
- The LID prognostic model may help to lay the ground for earlier therapeutic interventions against LID development in Parkinson's disease.

F. Time-dependent SHAP value, SurvSHAP(t) of cross-cohort optimal reduced time-to-LID occurrence model (component-wise gradient boosting)



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