Identifying Predictive Factors of Patient Dropout in Alzheimer's Disease Clinical Trials

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CONCLUSIONS

- A limited set of patient and site features can be used to estimate patient dropout risk within 3, 6, and 12 months of randomization
- Important interactions exist between patient and site factors which should be considered in the evaluation of patient dropout risk
- Previous findings of patient and site factors associated with dropout[2–5] are reflected in this study, in addition to new factors such as site location characteristics and anxiety before/during the trial
- Many of these risk factors remain for dropouts that resulted from reasons other than AE/death
- Further investigation into these and other factors associated with patient dropout is warranted to improve understanding and to further define patient retention strategies in AD trials

RESULTS

Study population

- 8103 patients from 665 clinical trial sites in 7 completed, phase 3, interventional (oral) AD trials were included in the analysis **(Table 1)**
- The treatment period across trials was 1.4 ± 1.6 years (mean ± SD) and the dropout rate was 21.2 ± 10.8%

Table 1. Patient and Site Characteristics

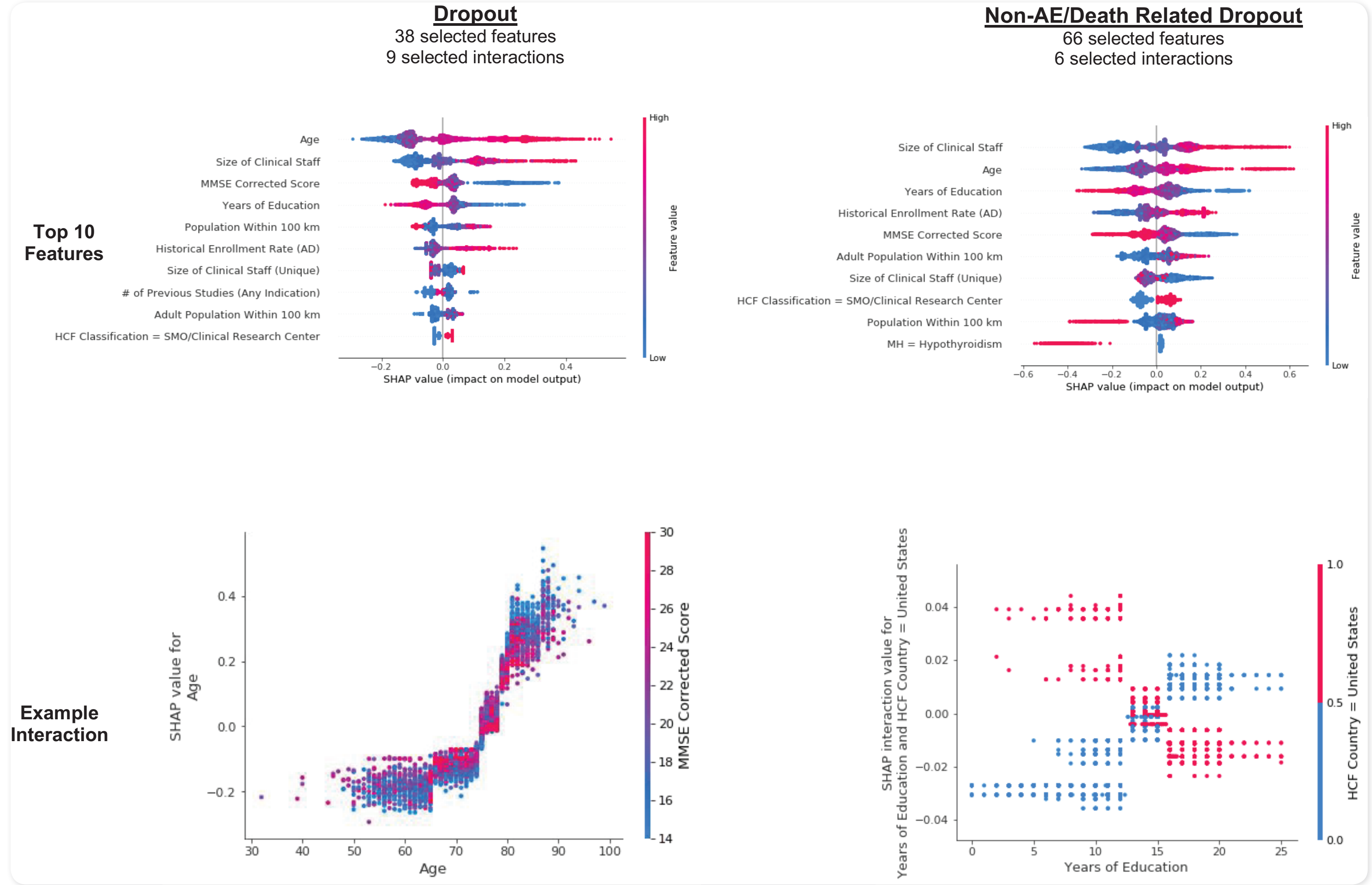
Patients	Dropout (N = 1982)	Complete (N = 6121)
Age (mean ± SD)	74.5 ± 7.1	73.2 ± 7.5
Sex: Female	1133 (57.2%)	3598 (58.8%)
Race		
White	1817 (91.7%)	5596 (91.4%)
Asian	57 (2.9%)	240 (3.9%)
Black	62 (3.1%)	101 (1.7%)
Missing/Other	46 (2.3%)	184 (3.0%)
Education	14.0 ± 3.5	13.8 ± 3.8
Year of Enrollment		
2010-2014	1187 (59.9%)	2824 (46.1%)
2015-2018	795 (40.1%)	3297 (53.9%)
MMSE (mean ± SD)	24.7 ± 5.8	25.0 ± 5.2

Sites	N = 665
Number of Previous AD Trials (mean ± SD)	1.0 ± 1.7
Size of Clinical Staff (mean ± SD)	306 ± 150
Number of Countries (mean ± SD)	12 ± 7
Top countries: 1. US 2. UK 3. Italy 4. Germany 5. Poland	
Population Density within 50km	
High (>1.5M)	433 (65.1%)
Med (750K to 1.5M)	116 (17.4%)
Low (<750K)	116 (17.4%)
Facility Type	
SMO/Clinical Research Center	185 (27.8%)
Hospital/Medical Center	179 (26.9%)
Academic Hospital/Medical Center	174 (26.2%)
Private or Group Practice/Clinic	113 (17.0%)
Other	14 (2.1%)

Feature Selection

- Size of clinical staff*, patient age, and years of education were among the most important features identified for prediction of dropout, and specifically, non-AE/death related dropout
- The risk associated with low MMSE score at baseline varied with age where older patients (>80 years) with low baseline MMSE scores had a higher risk of dropout
- Fewer years of education (≤15 years) for patients in the US was associated with a higher risk of non-AE/death related dropout

Figure 2. Shapley Values for Top Features and Selected Interactions From XGBoost Models Trained on the "Full Data"

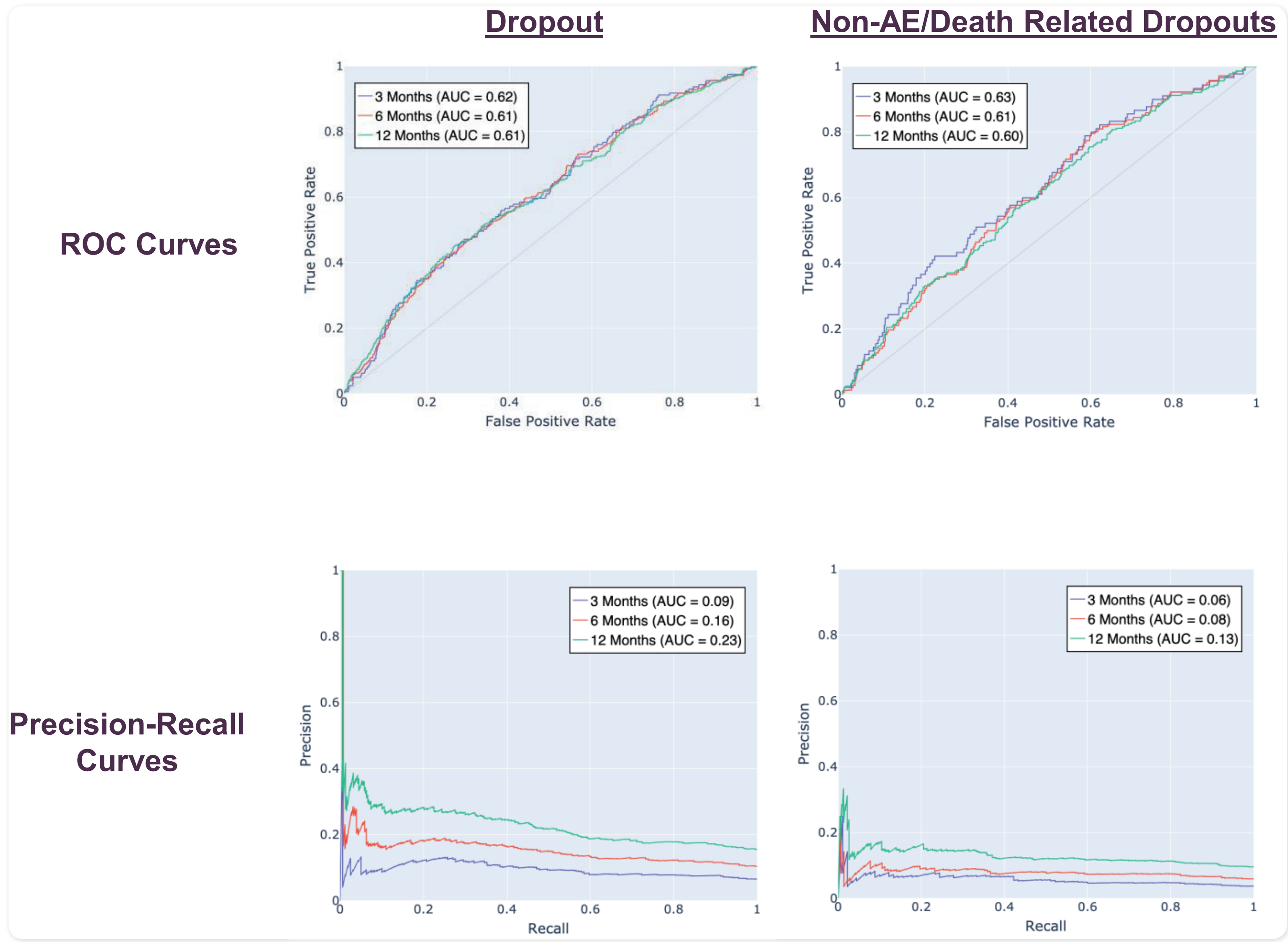


*Size of clinical staff is estimated based on the average number of Medidata Rave users per study at a site.

Model Performance

- The models were observed to predict dropouts at an acceptable level above random guessing with an ROC-AUC ≥0.60 within 3, 6, and 12 months
- However, the probability of dropout was typically overestimated, leading to more false positives and reduced precision overall (PR-AUC <0.24)

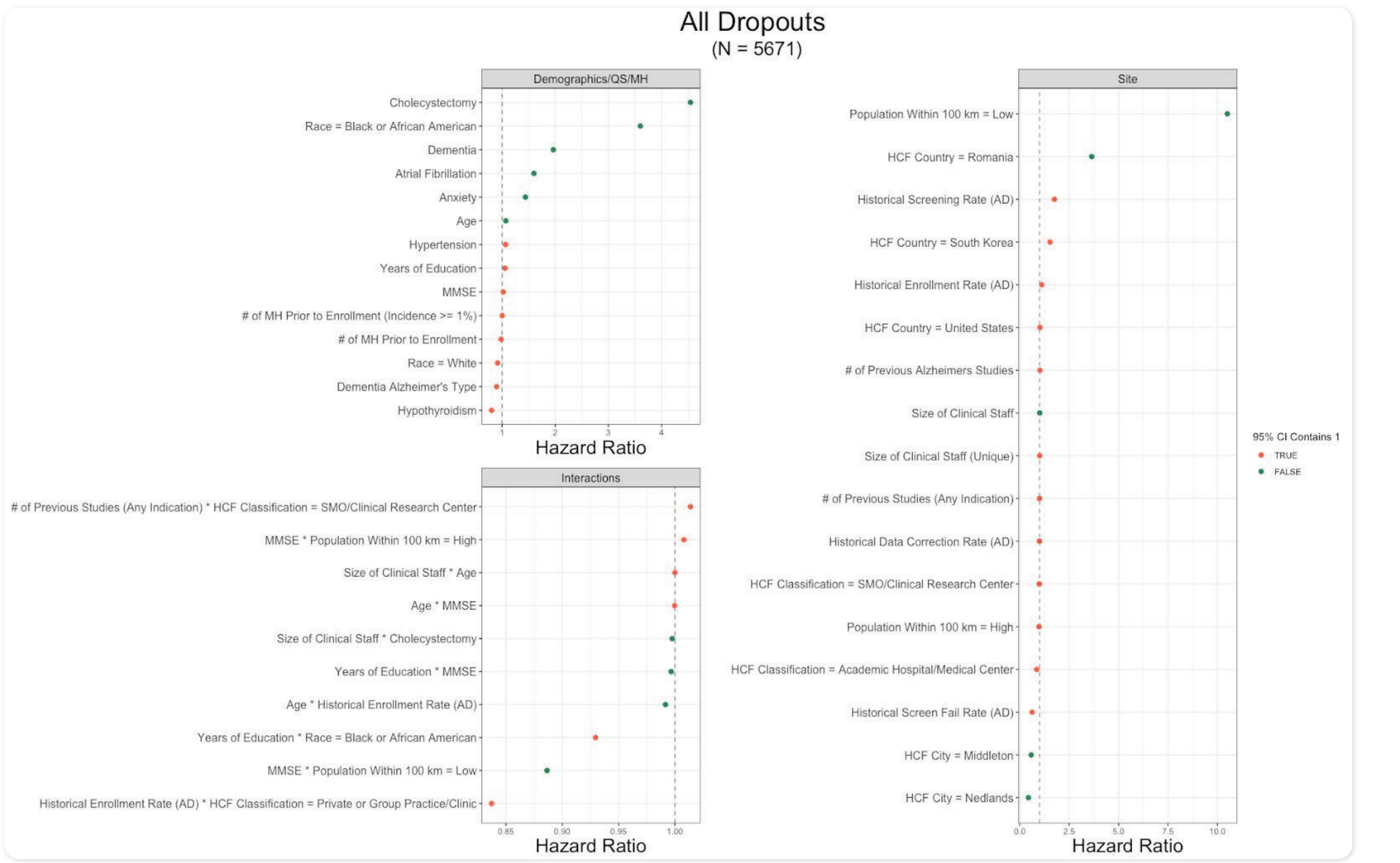
Figure 3. ROC and PR Curves for the Multivariate Cox Proportional Hazards Models Trained on "Full Data"



Predictive Factors

- Patient age (adjusted hazard ratio [HR] 1.07, $P = .005$), race (HR = 3.60, $P = .04$), certain medical histories (eg, cholecystectomy [HR = 4.54, $P = .004$], anxiety [HR = 1.44, $P = .006$]), low surrounding population density (HR = 10.50, $P = .04$), and the size of clinical staff (HR = 1.01, $P = .02$) were among the factors associated with increased risk of dropout at the time of randomization
- Patients in the US had increased risk of non-AE/death related dropout (HR = 3.02, $P = .03$); however, more years of education reduced this risk (HR = 0.95, $P = .02$)
- Patients with a friend as a caregiver had increased risk of dropout (HR = 1.91, $P = .001$)
- Experiences of certain AEs during the trial (eg, anxiety [HR = 1.54, p=0.04], agitation [HR = 2.47, $P < .0001$]) as well as an increased number of SAEs experienced by the patient (HR = 1.27, $P = .0001$) increased the risk of non-AE/death related dropout

Figure 4. Adjusted Hazard Ratios for Patient and Site Factors Associated With Dropout in the Multivariate Cox Proportional Hazards Model Trained on "Full Data"



INTRODUCTION

Background

- Patient dropout is a common challenge in Alzheimer's Disease (AD) clinical trials that can lead to trial delays, increased costs, and potentially biased trial results[1]
- Previous studies have shown that certain patient and site characteristics influence the risk of patient dropout in AD trials, such as age[2,3], race[2,4], education[2,4], site facility type[4], and caregiver relationship[5]
- The objectives of this analysis were to use pooled clinical trial data to evaluate how well dropout risk can be predicted at the time of randomization and to identify additional predictive factors of patient dropout in AD trials
- Predictive models and an understanding of dropout risk factors can be used to improve operational aspects of future trial designs as well as to support patients with retention strategies during future trials

METHODS

- Phase 3, interventional AD trials were selected from the Medidata Enterprise Data Store (MEDS), comprised of 23000+ historical clinical trials
- Demographics, years of education, medical history, adverse events, questionnaires (ie, MMSE, ADCS-ADL, RUD-Lite), and operational data elements (eg, site characteristics and historical performance) were standardized across trials using proprietary machine learning algorithms combined with human review
- Patients were randomly split into a 70/30 train-test split for the analysis. Equal representation of studies and dropout rates were ensured between the train and test sets
- Several multivariate Cox proportional hazards models were explored to predict the risk of dropout within 3, 6, and 12 months of randomization and to evaluate the effects of patient and site level factors on dropout **(Figure 1)**
  - Stratification and non-linear transformations were used respectively to correct categorical and continuous variables that violated the proportional hazards assumption

METHODS

Figure 1. Methods Overview

Objectives	Model	Data	Outcomes
1. Feature selection and identification of interactions	XGBoost w/Cox Proportional Hazards objective function	8103 patients w/MMSE scores "Full Data"	Dropout
			Non-AE/Death Dropout
		4630 patients w/MMSE + ADCS-ADL + RUD-Lite scores "QS Data"	Dropout
			Non-AE/Death Dropout
2. Assess predictive power and impact of baseline features	Cox Proportional Hazards Regression	8103 patients w/MMSE scores "Full Data"	Dropout
			Non-AE/Death Dropout
		4630 patients w/MMSE + ADCS-ADL + RUD-Lite scores "QS Data"	Dropout
			Non-AE/Death Dropout
3. Assess impact of time-varying features	Time-variant Cox Proportional Hazards Regression	8103 patients w/MMSE scores "Full Data"	Dropout
			Non-AE/Death Dropout
		4630 patients w/MMSE + ADCS-ADL + RUD-Lite scores "QS Data"	Dropout
			Non-AE/Death Dropout

DISCLOSURES

Presented at the Alzheimer's Association International Conference, July 26–30, 2021, Denver, Colorado, United States and Online

AbbVie and Medidata Disclosure:

AbbVie funded the research for this study and participated in the interpretation of data. Medidata's data contributions were analyzed for the research. AbbVie and Medidata participated in the study design and study research; and writing, reviewing, and approving this abstract for submission. All authors had access to the data; participated in the development, review, and approval of this presentation, and agreed to submit this presentation.

Disclosures:

PJA, LB, IA, JL, HL, CA, and **FM** are salaried employees of Acorn AI, by Medidata, a Dassault Systèmes company.

NF and **HF** are employees of AbbVie and may hold AbbVie stock and/or stock options.

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