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Enclosure:

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Development of a Machine Learning Model Predicting Response to Aripiprazole Once-Monthly in Patients Diagnosed With Schizophrenia

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Background

- The antipsychotic aripiprazole is available as a once-daily oral tablet and as extended-release suspensions of aripiprazole monohydrate administered intramuscularly either once monthly or once every 2 months.¹⁻³
- In the United States, aripiprazole once-monthly 400 mg (AOM 400) is approved for the treatment of schizophrenia in adults and for the maintenance monotherapy treatment of bipolar I disorder (BP-I) in adults.²
- Evidence from clinical trials and real-world studies shows that maintenance treatment with AOM 400 in patients diagnosed with schizophrenia delays relapse, improves functioning and health-related quality of life, and is well tolerated.⁴⁻⁸
- Understanding factors that might predict response to AOM 400 in the treatment of schizophrenia may help clinicians to provide more individualized care to patients initiating treatment, with the aim of optimizing outcomes. This may be especially beneficial for patients who are earlier in their treatment journey, since recurring relapse is associated with poorer outcomes.^{9,10}
- Traditionally, statistical techniques such as regression modeling have been used to explore treatment-response relationships, relying on *a priori* hypotheses about which factors to investigate. Newer methodologies involving machine learning may improve this process by detecting complex, data-driven patterns that are not limited to predefined assumptions.^{11,12}
- In prior studies, machine learning demonstrated clinical utility for predicting response to antipsychotics, including aripiprazole, in patients diagnosed with schizophrenia.^{13,14}
- The current study builds on these findings by using machine learning to identify factors that predict response to AOM 400, with a view to identifying factors that clinicians may be able to monitor and target to improve treatment outcomes.

Here, we describe the development of a machine learning model to identify baseline factors predictive of response to AOM 400 in patients diagnosed with schizophrenia using data from a clinical trial.

A separate model to identify baseline factors predictive of response to AOM 400 versus placebo in patients diagnosed with BP-I has also been developed using data from a clinical trial, with results reported in poster 64.

Methods





Source data

- Baseline information used for the development of the model was derived from patients enrolled in a pre-post study that compared hospitalization rates in the 6-month periods before and after switching from oral antipsychotic treatment to AOM 400¹⁵ (Supplementary Figure 1; please scan the QR code to access supplementary content).
- The study included 433 patients diagnosed with schizophrenia. Of these, 38 (8.8%) were hospitalized in the 6-month period following a switch to AOM 400.¹⁵

Variable screening

- A list of potential variables, encompassing demographic characteristics, vital signs, medical/disease history, and data from clinician-rated and patient-reported outcome measures, are shown in **Box 1**. These variables reflected the entirety of baseline data collected during the study.
- A univariate analysis was conducted to associate each variable, one at a time, to the outcome of hospitalization in the 6-month period following the switch to AOM 400. Variables meeting predefined thresholds were carried forward to the predictive modeling step.
- The goal of variable screening was to narrow the dataset to only the most relevant baseline factors, reducing 'noise' and improving the model's ability to identify meaningful predictors of treatment response.¹⁶

Box 1: Baseline variables screened in univariate analysis

Demographics		<ul style="list-style-type: none">AgeGenderRace	<ul style="list-style-type: none">EthnicityHeight
Vital signs		<ul style="list-style-type: none">BMI/weightHeart rateStanding/supine diastolic/systolic blood pressure	
Medical and disease history		<ul style="list-style-type: none">Hospitalization/ER visits in the 6-month preswitch periodDiagnosis history of prevalent diseases* including hypertension, insomnia, anxiety, asthma, depression, seasonal allergies, and obesity	
Clinician-rated and patient-reported outcome measures		<ul style="list-style-type: none">PANSS including matched BPRSCGI-SQLSSWN-SDAI	<ul style="list-style-type: none">AIMSBARSSASCSSRS

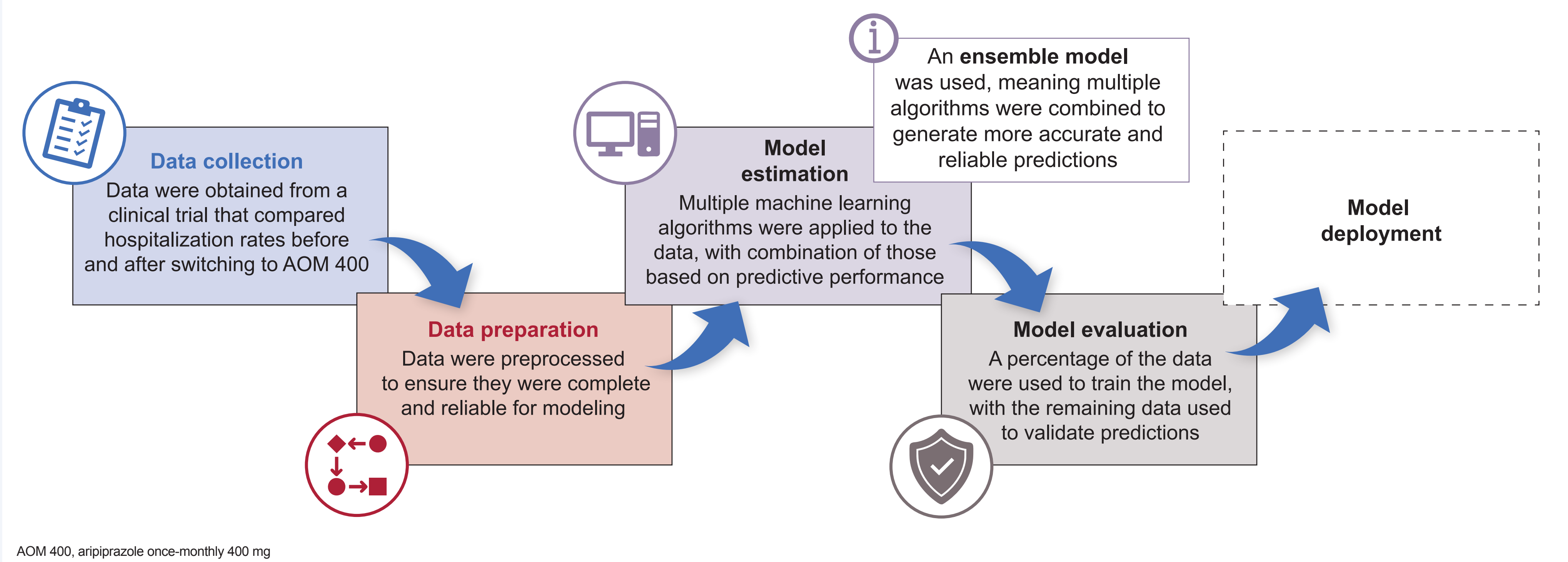
*Present in >30 patients
AIMS: Abnormal Involuntary Movement Scale; BARS: Barnes Akathisia Rating Scale; BMI: body mass index; BPRS: Brief Psychiatric Rating Scale (older version); CGI-S: Clinical Global Impression – Severity; CSSRS: Columbia Suicide Severity Rating Scale; DAI: Drug Attitude Inventory; ER: emergency room; PANSS: Positive and Negative Syndrome Scale; QLS: Quality of Life Scale; SAS: Simpson-Angus Scale; SWN-S: Subjective Well-being under Neuroleptic Treatment – Short Form

Methods (continued)

Predictive modeling

- Key steps in the predictive modeling process are shown in **Figure 1**.
- Premodeling steps were undertaken to address missing data and the overall low frequency of hospitalization events in the 6-month post-switch period.
- Commonly used binary machine learning algorithms with demonstrated predictive capability were evaluated for inclusion in an ensemble model. The ensemble was refined through iterative exclusion of classifiers with a weight of zero (indicating a trivial contribution to the model's predictive capability).
- Similar to the work of others,¹⁴ data were randomly split into 70% for training the ensemble model and 30% for out-of-sample validation.
- Model performance was assessed using standard metrics, including those appropriate for imbalanced data. The importance of each variable in the final model was reported using SHapley Additive exPlanations.
- The established model was used to generate partial dependence plots (PDPs) illustrating the likelihood of nonhospitalization according to influential variables, while holding all other variables constant at population mean values.

Figure 1: Key steps in the predictive modeling process



Results

- Overall, 163 baseline variables were considered (Supplementary Table 1; please scan the QR code to access supplementary content); of these, 37 were carried forward to the predictive modeling step.
- Three classifiers were included in the final ensemble model, each contributing to prediction accuracy based on their nonzero weighting (Table 1).
- The final model demonstrated a strong performance (Table 2 and Figure 2).
- The importance ranking of each of the 37 variables included in the final predictive model is shown in **Figure 3**.
- A PDP depicting the model-predicted likelihood of nonhospitalization as a function of the top two ranked variables (ie, Positive and Negative Syndrome Scale [PANSS] items 'G12, Lack of judgment and insight' and 'P7, Hostility') is shown in **Figure 4**.
- A PDP depicting the model-predicted likelihood of nonhospitalization as a function of influential Quality of Life Scale (QLS) variables (ie, 'Extent of occupational role functioning' and 'Sociosexual relations') is shown in **Supplementary Figure 2** (please scan the QR code to access supplementary content).

Table 1: Final ensemble model

Final ensemble model	Weight
Random forests	0.001
eXtreme Gradient Boosting	0.406
Kernel-based Support Vector Machine	0.593

- In total, nine machine learning algorithms were evaluated for inclusion, with predictions from three of the algorithms combined in an ensemble model.
- Each algorithm was assigned a weight reflecting how much it contributed to improving the overall accuracy of the combined model (a higher weight = a greater contribution to prediction accuracy).

All other binary classifiers tested had a weight of zero.

Table 2: Model performance metrics

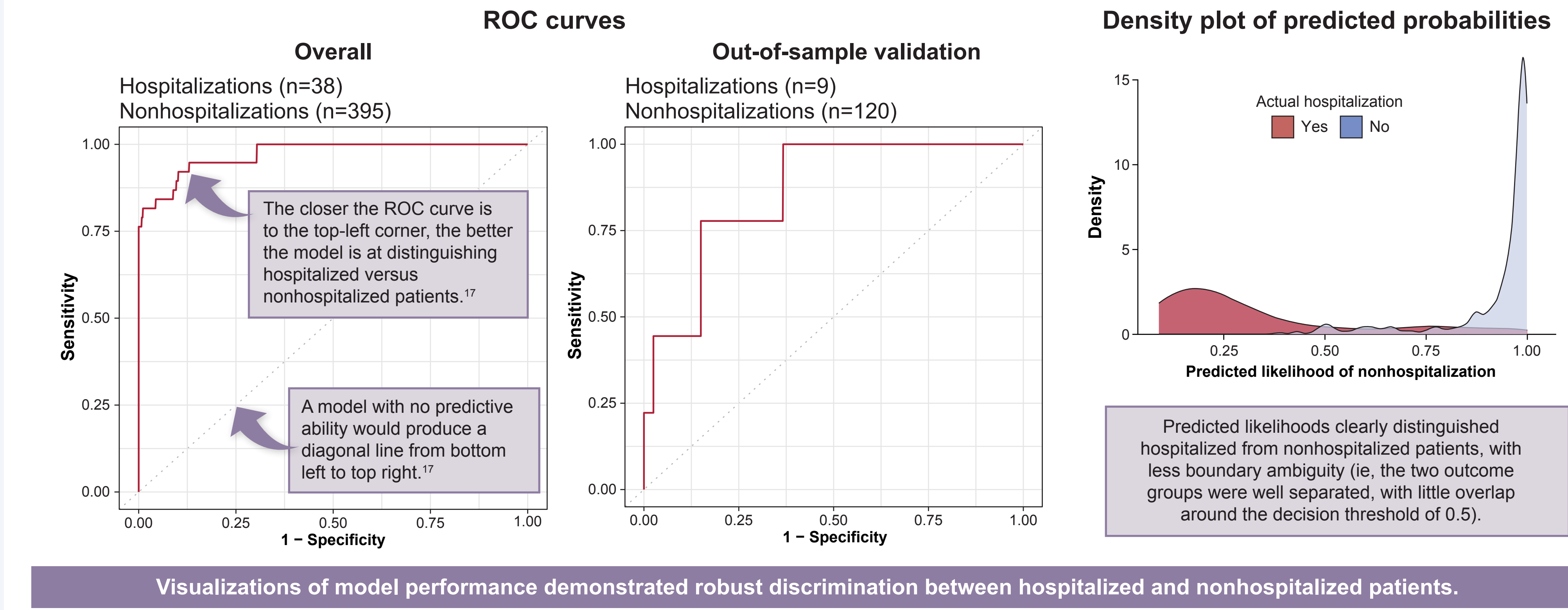
	Accuracy	Sensitivity	Specificity	F1-score	AUC (ROC)	AUC (PRC)
Overall N=433 (38 hospitalizations, 395 nonhospitalizations)	0.9	0.92	0.9	0.62	0.97	0.89
Out-of-sample validation, random 30% split, n=129 (9 hospitalizations, 120 nonhospitalizations)	0.84	0.78	0.84	0.4	0.86	0.44

- AUC-PRC in out-of-sample validation was 0.44, which was considered robust for highly imbalanced, rare-event binary classification (ie, 38 hospitalizations in 433 patients).
- An AUC-PRC value of 0.44 indicates the model was ~six times better than that expected from random chance.
- The model showed strong overall accuracy and an excellent ability to distinguish between patients who were hospitalized and those who were not.

AUC, area under the curve; AUC-PRC, area under the precision-recall curve; PRC, precision-recall curve; ROC, receiver-operating characteristic

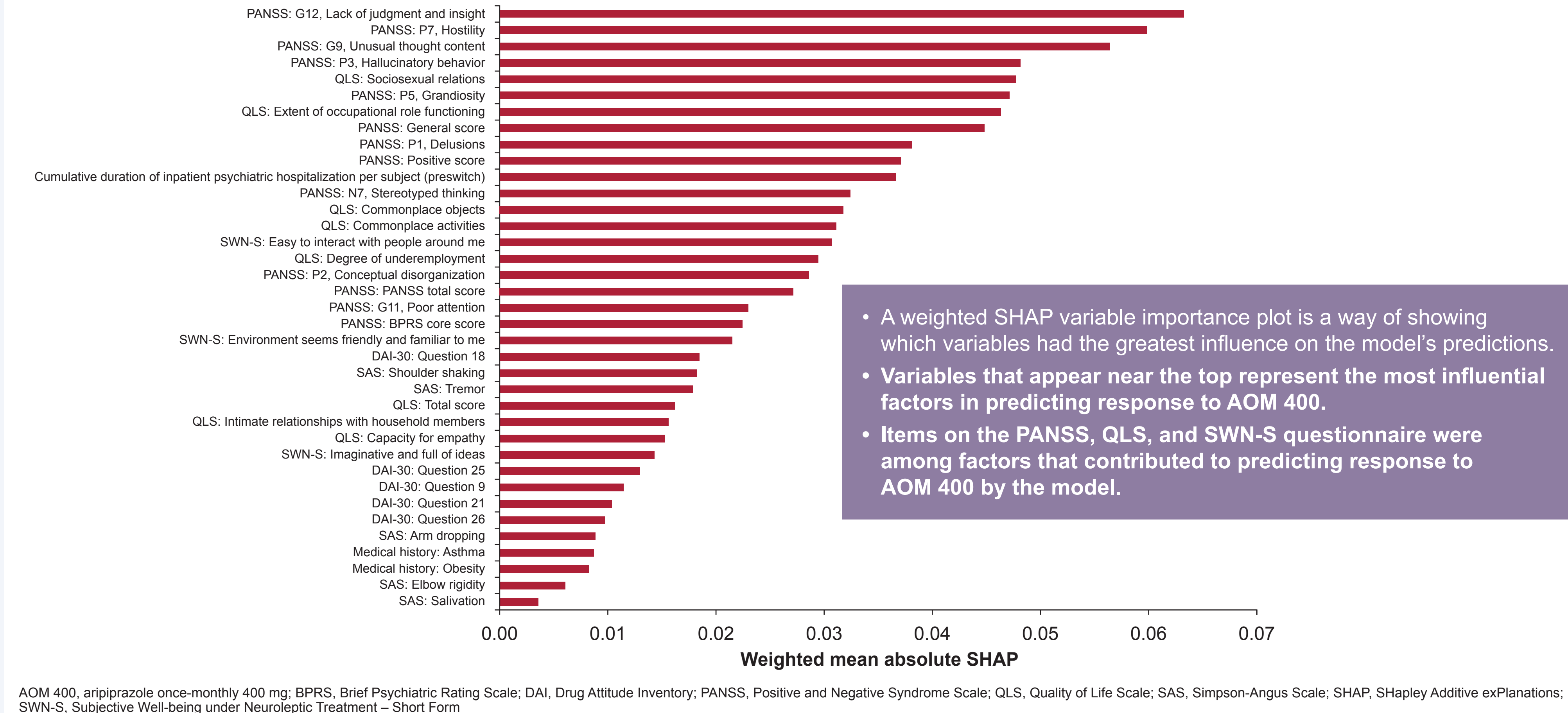
Results (continued)

Figure 2: Model performance plots



ROC, receiver-operating characteristic

Figure 3: Variable importance ranking



AOM 400, aripiprazole once-monthly 400 mg; BPRS, Brief Psychiatric Rating Scale; DAI, Drug Attitude Inventory; PANSS, Positive and Negative Syndrome Scale; QLS, Quality of Life Scale; SAS, Simpson-Angus Scale; SHAP, SHapley Additive exPlanations; SWN-S, Subjective Well-being under Neuroleptic Treatment – Short Form

Figure 4: Likelihood of nonhospitalization according to influential variables related to the PANSS

