

Highlights

Machine learning model for predicting the visit duration of urticaria based on clinical laboratory data

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- A machine learning model was built to predict the visit duration of urticaria based on clinical laboratory data.
- Inversed trend of shapley values of laboratory data in different phase of disease was observed.

Machine learning model for predicting the visit duration of urticaria based on clinical laboratory data

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Abstract

Background: Urticaria is a common condition presenting with wheals, angioedema, or both, driven by mast cell degranulation. The duration of urticaria, particularly chronic spontaneous urticaria (CSU), is crucial for effective patient management and treatment planning. This study aimed to build a machine learning model for predicting the visit duration of urticaria based on clinical laboratory data and to identify the factors that contribute to prolonged episodes of chronic urticaria.

Method:

Results:

Conclusion:

Keywords:

1. Introduction

Urticaria is a common condition presenting with wheals, angioedema, or both, driven by mast cell degranulation(Zuberbier et al., 2021; Radonjic-Hoesli et al., 2018; Ring and Grosber, 2012). The lifetime prevalence for acute urticaria is approximately 20% (Zuberbier et al., 2021).

Urticaria is classified based on duration and triggers. Acute urticaria lasts less than 6 weeks, often triggered by specific causes like drugs, food, or infections. While chronic urticaria lasts more than 6 weeks and can be further classified into chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU)(Zuberbier et al., 2021; Ring and Grosber, 2012).

CSU is characterized by the spontaneous occurrence of wheals and/or angioedema without a specific trigger and often associated with autoimmune mechanisms(Schettini et al., 2023), while CIndU is triggered by specific stimuli like cold, heat, or pressure(Pozderac et al., 2020).

The prevalence of CSU is approximately 0.5% in general population, and is less prevalent in children compared to adults(Balp et al., 2015; Poddighe, 2019; Labbene and Tekou, 2023). Some patients with CSU experience trigger-induced wheals, angioedema, or both. Up to 36% of

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patients with CSU have been reported to react concomitantly to physical trigger tests(Dressler et al., 2018). These triggers are not definite, as their presence does not always induce signs and symptoms and because wheals, angioedema, or both also occur without them, that is, spontaneously. Some patients can present with more than one subtype of urticaria(Zuberbier et al., 2021).

Chronic urticaria significantly impairs quality of life, affecting work and school performance. It is considered a severe allergic disease due to its disabling nature and high disease burden(Zuberbier et al., 2021). Duration of CSU greater than 3 years are associated with better responses to second-generation antihistamines and other treatments(Chiang et al., 2022). Predicting the duration of urticaria, particularly chronic spontaneous urticaria (CSU), is crucial for effective patient management and treatment planning.

Several clinical features have been associated with the severity and duration of chronic spontaneous urticaria (CSU). Higher age at onset, female gender, longer disease duration, and hypersensitivity to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) are linked to more severe CSU and prolonged time to remission (SanchezBorges et al., 2017; Rabelo-Filardi et al., 2013). Patients exhibiting concomitant CIndU and recurrent angioedema also tend to experience longer durations of CSU (SanchezBorges et al., 2017; Curto-Barredo et al., 2018). Moreover, patients with multiple allergic conditions are more likely to have prolonged episodes of urticaria (Lin et al., 2011).

Potential biomarkers for CSU severity and duration have been identified. Positive autologous serum skin test (ASST) results, basophil counts, levels of inflammatory markers, activation markers of the extrinsic coagulation pathway, immunoglobulin E (IgE), eosinophils counts, and vitamin D levels are all associated with the disease's severity and duration (SanchezBorges et al., 2017; Rabelo-Filardi et al., 2013; Kolkhir et al., 2019). Specifically, plasma levels of prothrombin fragment, D-dimer, and C-reactive protein (CRP) may serve as markers of CSU severity (Rabelo-Filardi et al., 2013). Serum diamine oxidase (DAO) levels have been linked to the response to antihistamines and dietary interventions, indicating a potential role in predicting disease duration (Chiang et al., 2022).

Metabolic factors also play a role, with high waist circumference (WC), rather than high body mass index (BMI), emerging as a predictive risk factor for longer disease duration in CSU patients (Kim et al., 2021).

The aim of this study was to build a machine learning model for predicting the visit duration of urticaria based on clinical laboratory data and to identify the factors can contribute to prolonged episodes of chronic urticaria by analyzing the importance of variables in the model, hoping to provide a reference for the clinical management of urticaria.

2. Methods

2.1. Patients

patients with urticaria were recruited from the urticaria specialty clinic of the dermatology department of Shanghai XinHua Hospital affiliated to Shanghai Jiao Tong University School of Medicine from January 2018 to December 2024. The inclusion criteria were as follows: (1) patients diagnosed with urticaria according to the EAACI/GA2LEN/EDF/WAO guidelines(Zuberbier et al., 2021); (2) patients with complete clinical and laboratory data; (3) patients with stable follow-up history, indicated by at least 3 times of follow-up visits. the exclusion criteria were as follows: (1) patients with other skin diseases; (2) patients with severe systemic diseases; (3) patients with incomplete clinical data. The study was approved by the ethics committee

of Shanghai XinHua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, and all patients provided written informed consent.

2.2. Data collection and management

the data of patients with urticaria were collected from the electronic medical record system of the hospital, including demographic data, clinical data, laboratory data. the data were stored in a mysql database for subsequent analysis as follows: (1) Patients: containing basic information of each unique patient; (2) OutpatientNumbers: storing relationship between outpatient numbers with unique patient; (3) PatientVisits: containing visit events records; (4) PatientExaminations: containing the examination events records; (5) ExaminationItems: a dictionary table describing the examination items. the database schema is shown in database. Database markup language (DBML) describing the database schema is shown in supplementary materials.

2.3. Feature extraction and feature engineering

Visit duration, calculated by the difference between the first visit date and the last visit date in the urticaria specialty clinic, was the target variable. We suppose that the visit duration of a patient at the urticaria specialty clinic is a surrogate for the disease duration of urticaria. The following features were extracted from the database: (1) demographic data: gender, first visit age; (2) clinical data: whether the patient having concomitant inducible urticaria; (3) laboratory data: results from common blood tests, CRP, immunoglobulin, 25-hydroxyvitamin D, Thyroid function, autoantibodies, coagulation function, common urine tests, and allergen specific IgE tests. For laboratory data, 2 types of data were extracted: time-independent data and time-dependent data. Time-independent data are average values of laboratory data during the whole follow-up period, while time-dependent data are average values of laboratory data during pre-clincial phase (before the onset of urticaria), acute phase (within 6 weeks after the onset of urticaria), and chronic phase (after 6 weeks of the onset of urticaria). 2 datasets were generated: one with time-independent data and one with time-dependent data, and were compared for prediction performance in the model development process. The sql queries for data are shown in feature_extraction.sql in supplementary materials.

2.4. Model development and comparison

Dataset was split into training set and external test set with a ratio of 7:3. 5 models were adopted for comparison: Xgboost, random forest, adaboost, gradient boosting machine (GBM), and support vector machine (SVM). Hyperparameter optimization on 10 model settings (5 models multiply 2 datasets) was performed using TPE algorithm by nni package in python, which is a bayesian optimization algorithm that uses tree-structured parzen estimator to model the objective function and suggest the next set of hyperparameters to evaluate based on the previous results. Internal 5 fold cross-validation was employed to discern the most suitable hyperparameters for each distinct model, individually applied to each model settings for enhanced performance. The performance of the model and data was evaluated by receiver operating characteristic (ROC) curve, area under the curve (AUC), accuracy, precision, recall and F1 score on different cutoffs of disease duration. The sensitivity, specificity, PPV, NPV, accuracy, and F1 score were calculated at the optimal cutoff value that maximized the Youden index. The model and data with the best performance were selected for further analysis.

2.5. feature selection

Too many features can lead to overfitting and reduce the interpretability of the model. Therefore, feature selection was performed on final model for further optimization. Although, feature importances can be evaluated directly from the boosted trees, these importances have been shown to be local and inconsistent. A SHAP score inspired by Shapley values can combine different explanation models and provide a global feature importance score that is consistent across different test sets. However, other than to arbitrarily select an importance threshold beyond which features are considered unimportant, SHAP analysis does not offer an algorithmic way to filter a large feature set to a limited set of important features. Boruta algorithm is a wrapper method that determine the importance of features by comparing the importance of original features with their shuffled copies. If importance of an original feature is significantly greater than its shuffled copy, that feature is deemed important (Kursa and Rudnicki, 2010).

In this study, Boruta algorithm was performed on the final model, with max iteration set to 50 and repetition for 15 times. The confirmed features list and importance rank were recorded for each run. The overlap of confirmed features across runs was calculated to determine the final feature list. For time dependent data, once a laboratory item was confirmed as important in any phase of disease, the feature of the same lab item in other phase of disease was also considered as important. That is to say, when top 10 items were selected, the features representing different phases of that item were all included in the final model, which is at most 30 features for time dependent data. The model performance on different number of top items, ranked by the average importance score, were compared to determine the optimal number of features for the final model.

2.6. Model explanation

It is challenging to get the correct interpretation of a ML model. The SHAP method is an approach that could rank the importance of input features and explain the results of the prediction model, and it is implemented to overcome the “black-box” issue (Lundberg and Lee, 2017). The shapley value of each laboratory item in different phase of disease were compared to reveal various predicting ability. Some of the features were further analyzed with different age populations to explore the potential age effect on the predicting ability of laboratory data.

3. Results

3.1. Patient characteristics

This retrospective study included 3954 patients with urticaria. Of the 9921 patients who visited the urticaria specialty clinic and met the inclusion criteria from January 2018 to December 2024, 3954 patients were selected for time independent dataset and 1948 patients were selected for time dependent dataset, the rest were excluded due to serious missing data. 3954 patients in time independent data and 1948 patients time dependent data were allocated into separate derivation and external validation sets with a ratio of 7:3, respectively. The comparison of demographic and clinical variables among the training and external validation sets is shown in Table Appendix A for time independent dataset and Table Appendix A for time dependent dataset. No substantial differences were observed between the training set and the external test set across the majority of features in either time independent or time dependent data. Details of the study design are displayed in Figure 1.

Table 1 delineates the disparities between groups regarding the disease duration of patients in time independent Dataset. Among the 3954 patients, 2027 patients had a visit duration of less than 100 days, while 1927 patients had a visit duration of 100 days or more. The mean visit duration was 25.37 days for the short duration group and 604.32 days for the long duration group. The comparison of clinical characteristics between patients with short and prolonged visit duration in the time-independent dataset (Table 1) highlights several trends that align with findings from previous studies on chronic spontaneous urticaria (CSU). In this analysis, immunoglobulin E (IgE) (131.65 ± 242.00 in good outcome vs 152.28 ± 346.75 in poor outcome), eosinophils percentage (1.55 ± 2.02 in good outcome vs 2.31 ± 2.37 in poor outcome), eosinophils counts (128.60 ± 141.68 in good outcome vs 162.83 ± 190.02 in poor outcome), and basophil percentage (0.25 ± 0.22 in good outcome vs 0.32 ± 0.24 in poor outcome) were significantly higher in patients with poor outcomes, which is consistent with previous studies that have linked these markers to CSU severity and duration (SanchezBorges et al., 2017; Rabelo-Filardi et al., 2013; Kolkhir et al., 2019). In contrast, C-reactive protein (CRP) levels were significantly lower in patients with poor outcomes (13.03 ± 19.62 in good outcome vs 7.71 ± 10.23 in poor outcome), which contradicts previous findings that have associated higher CRP levels with CSU severity (Rabelo-Filardi et al., 2013). However, this discrepancy could reflect the complexity of CRP as an inflammatory marker that may vary across different disease stages or subgroups of patients. In time dependent data, which is shown in supplementary Table Appendix A, CRP presented various trends in different phases of disease, with significantly lower CRP levels in acute phase (10.21 ± 10.95 in good outcome vs 8.95 ± 8.22 in poor outcome) and higher CRP levels in chronic phase (5.39 ± 4.84 in good outcome vs 6.47 ± 8.81 in poor outcome) in patients with poor outcomes. This finding suggests that the predictive ability of CRP may be influenced by the disease phase, which could explain the inconsistent results observed in the time-independent dataset.

3.2. Comparison of multiple models on time-dependent and time-independent data

Time independent and Time dependent data, combined with 5 different models (XGBoost, Random Forest, AdaBoost, GBM, SVM), were used to generate 10 machine learning models to predict the disease duration of urticaria. Although most models utilized in this study is based on regression trees, their performance in directly predicting continuous numeric values in the regression task was suboptimal, which is likely due to the complexity of the underlying data distribution and model constraints. The predicted values, while not accurate for continuous outcome prediction, can still be utilized for binary classification tasks by applying an optimal threshold. Specifically, the model's output is better suited for classification of disease duration when applying a predefined threshold that maximizes the classification performance (e.g., based on ROC-AUC or Youden's index). Therefore we use binary classification task to evaluate the model performance. Among the 10 models, the XGBoost model with time-dependent data ($AUC = 0.906 \pm 0.013$ for 42, $AUC = 0.926 \pm 0.013$ for 100, $AUC = 0.884 \pm 0.018$ for 365) has the best predictive effect for disease duration, followed by the Random Forest model with time-dependent data ($AUC = 0.933 \pm 0.025$ for 42, $AUC = 0.922 \pm 0.028$ for 100, $AUC = 0.837 \pm 0.037$ for 365). The ROC curves for the top three best-performing ML models are presented in Figure 2. The discriminative performances and ROC curves of all 10 models are listed in Supplementary Table Appendix A, and Supplementary Figure Appendix A, respectively.

3.3. Feature selection and final model

Xgboost with time dependent data, as the best performing model, was selected for further optimization. Feature importance ranking by Boruta algorithm are shown in Figure 3 and Sup-

Characteristic	Good Outcome	Poor Outcome	P-value
Number of patients	2027	1927	
Outcome	25.37 ± 25.09	604.32 ± 437.04	0.000 ↑
Gender	0: 64.7%, 1: 35.3%	0: 61.1%, 1: 38.9%	0.023
First Visit Age	30.12 ± 21.79	28.11 ± 23.61	0.005 ↓
CI nd U	0: 99.3%, 1: 0.7%	0: 97.2%, 1: 2.8%	0.000
Lymphocytes Percentage	28.98 ± 14.05	34.02 ± 13.88	0.000 ↑
Neutrophils Percentage	63.13 ± 15.68	56.63 ± 14.97	0.000 ↓
Monocytes Percentage	6.18 ± 1.64	6.49 ± 1.67	0.000 ↑
Mean Corpuscular Hemoglobin Concentration	335.62 ± 10.51	336.93 ± 10.30	0.000 ↑
Platelet Count	263.47 ± 74.09	256.73 ± 68.96	0.003 ↓
White Blood Cell Count	10.31 ± 3.00	9.35 ± 2.39	0.000 ↓
Mean Corpuscular Hemoglobin	29.07 ± 2.33	28.98 ± 2.30	0.202
Mean Corpuscular Volume	86.66 ± 6.65	85.99 ± 6.67	0.002 ↓
Hemoglobin	130.03 ± 9.16	130.20 ± 8.46	0.546
Eosinophils Percentage	1.55 ± 2.02	2.31 ± 2.37	0.000 ↑
Basophils Percentage	0.25 ± 0.22	0.32 ± 0.24	0.000 ↑
Absolute Eosinophil Count	0.13 ± 0.20	0.18 ± 0.21	0.000 ↑
Absolute Lymphocyte Count	2.61 ± 1.12	2.83 ± 1.29	0.000 ↑
Mean Platelet Volume	9.14 ± 1.39	9.02 ± 1.39	0.007 ↓
Platelet Distribution Width	12.72 ± 1.96	12.57 ± 1.94	0.020
Eosinophil Count Absolute	128.60 ± 141.68	162.83 ± 190.02	0.000 ↑
CR eactive Protein	13.03 ± 19.62	7.71 ± 10.23	0.000 ↓
Immunoglobulin E	131.65 ± 242.00	152.28 ± 346.75	0.029
SMRNP	1.18 ± 2.16	1.22 ± 1.84	0.576
Anti SSA	1.42 ± 5.44	1.58 ± 5.68	0.363
Anti Jo 1	1.08 ± 1.77	1.12 ± 2.06	0.534
Nucleosome	0.57 ± 0.34	0.65 ± 0.43	0.000 ↑
Ribosomal PP rotein	1.07 ± 0.71	1.17 ± 2.13	0.050
Ro 52	2.10 ± 5.90	2.23 ± 6.81	0.515

Table 1: Comparison of the characteristics between patients with good and poor outcomes in the time independent dataset
continuous variables are presented as mean ± standard deviation, categorical variables are presented as number (percentage)
good outcome is defined as visit duration < 100 days, poor outcome is defined as visit duration ≥ 100 days

plementary Table Appendix A. A total of 38 laboratory items were confirmed as important by Boruta algorithm, as shown in Supplementary Table Appendix A.

During the process of reducing features based on the feature importance, the changes in AUCs for the model shows that the model maintain robust performance until the number of items reduced to less than 10, as shown in Figure 4 A-C. The 25-item model shows the best performance in internal validation set with AUC of 0.914, 0.939, 0.899 for 42, 100, 365 cutoffs, respectively. The 25-item model were selected as the final model, and showed a stable performance in external test set with AUC of 0.887, 0.898, 0.809 for 42, 100, 365 cutoffs, as shown in Figure 3 4 D-F.

3.4. Model explanation

The SHAP analysis was performed on the final model with 25 top items. The heatmap shows shap values of the top 25 features on 300 samples from dataset, with the samples ordered by hierarchical clustering based on the similarity of shap values, and the corresponding model output and global importance of each feature, shown in Figure 5.

3.4.1. SHAP analysis reveals alignment with previous studies while discovering phase-specific trends

SHAP analysis on well-known markers of CSU severity and duration, such as eosinophils, basophils, and CRP, revealed consistent trends with previous studies while providing insights on how those markers in different phase can have different predicting ability. A high value in Basophils percentage during chronic phase of disease pushed the model output towards a longer visit duration, a trend that was proved by previous studies (SanchezBorges et al., 2017), while a high Eosinophils percentage during the preclinical phase of disease had the opposite effect, as shown in Figure 6 A. The increasing CRP levels in the chronic phase of disease was having positive effect on the model output, same as the previous studies that have associated higher CRP levels with CSU severity (Rabelo-Filardi et al., 2013), while the extreme high CRP levels in the acute phase of disease was having negative effect on the model output, as shown in Figure 6 B. High immunoglobulin E levels in the chronic phase of disease was having positive effect on the model output, which is consistent with previous studies that have linked high IgE levels to CSU severity and duration (SanchezBorges et al., 2017), while having no effect in the acute phase of disease, as shown in Figure 6 C. It has been discovered that lymphocytes count is reduced in acute urticaria compared with healthy control. But whether a lower lymphocytes count is associated with severity and duration of CSU is still unknown. SHAP analysis shows that a low lymphocytes count in the preclinical and acute phase is having positive effect on the model output, while having negative effect in the chronic phase, as shown in Figure 6 D.

Thyroid dysfunction is a common comorbidity in patients with chronic urticaria, and it has been reported that reducing thyroxine dose may cause flare-ups of chronic urticaria and angio-oedema, suggesting a possible link between thyroid function and urticaria severity (Dunkley and Jawad, 2003). Our study shows that a high TSH level in the chronic phase of disease is having negative effect on the model output, as shown in Figure 6 E.

3.4.2. correlation analysis with SHAP values facilitate independent impact of features

Other than single marker analysis, we also discover relationship between ne

3.4.3. SHAP analysis in different age groups shows novel age effect

4. Discussion

Although the pathogenesis of CSU is not yet fully understood, it is well established that its signs and symptoms are due to the activation of mast cells and basophils, leading to the release of histamine and other inflammatory mediators(Zuberbier et al., 2021).

Based on recent evidence, it is known that the causes of CSU include autoimmunity Type I (CSUaiTI, or “autoallergic CSU”; with IgE autoantibodies to self-antigens) and autoimmunity Type IIb (CSUaiTIIb; with mast cell-directed activating autoantibodies). In CSU due to unknown cause (CSUuc), as of yet unknown mechanisms are relevant for the degranulation of skin mast cell (MC)(Sella et al., 2023; Maronese et al., 2023).

The results of the basic tests performed in CSU can point to CSUaiTI vs CSUaiTIIb, with CRP more often elevated and eosinophil and basophil levels more often reduced in CSUaiTIIb(Xiang et al., 2023). Other underlying causes include active thyroid disease, infections, inflammatory processes, food, and drugs but these can be both cause as well as only aggravating factor(Kolkhir et al., 2021)

Eosinopenia in chronic spontaneous urticaria patients is associated with type IIb autoimmunity, high disease activity, and poor treatment response. (Kolkhir et al., 2019), especially in children (A et al., 2023).

Acute urticaria patients have abnormal cell immune responses, with lower numbers of CD3+ and CD4+ lymphocytes compared to healthy controls.(De-yu, 2009).

Chronic idiopathic urticaria is associated with a prominent infiltrate of T-lymphocytes, monocytes, and mast cells, suggesting potential interactions between these cells to cause mediator release.(Elias et al., 1986)

Reducing thyroxine dose may cause flare-ups of chronic urticaria and angio-oedema, suggesting a possible link between thyroid function and musculoskeletal conditions.(Dunkley and Jawad, 2003)

Mean platelet volume levels are higher in patients with chronic urticaria and correlate with its severity, suggesting coagulation and inflammation may play a role in the disease.(Aleem et al., 2015) Chronic urticaria with a positive autologous serum skin test is associated with higher clinical severity, increased platelet volume, and increased C-reactive protein levels.(Magen et al., 2010)

Neutrophilic urticarial dermatosis is a distinct cutaneous manifestation of neutrophilic aseptic disease, strongly associated with systemic diseases like Schnitzler syndrome, adult-onset Still disease, lupus erythematosus, and hereditary autoinflammatory fever syndromes.(Kieffer et al., 2009) Neutrophilic urticaria is common and not associated with other diseases, but its presence in biopsy samples may indicate rheumatic disease.(Llamas-Velasco et al., 2012)

5. code availability

Code for data extraction, model development, and model explanation are available at <https://github.com/jabberwockyang/UrticariaPrediction>

Appendix A. Supplementary data

Supplementary Table1: Comparison of the characteristic between the training set and external testing set data in the time independent dataset

Supplementary Table2: Comparison of the characteristic between the training set and external testing set data in the time dependent dataset

Supplementary Table 3: Comparison of the characteristic between the short duration group and long duration group in the time dependent dataset

Supplementary Table 4: The discriminative performances of all 10 models in 5 fold cross validation

Supplementary Figure 1: ROC curves of all 10 models in 5 fold cross validation

Supplementary Table 5: Feature importance ranking by Boruta algorithm

Supplementary Table 6: 38 laboratory items confirmed as important by Boruta algorithm

Supplementary Table 7: The performance of the final model on external test set

Appendix B. Acknowledgements

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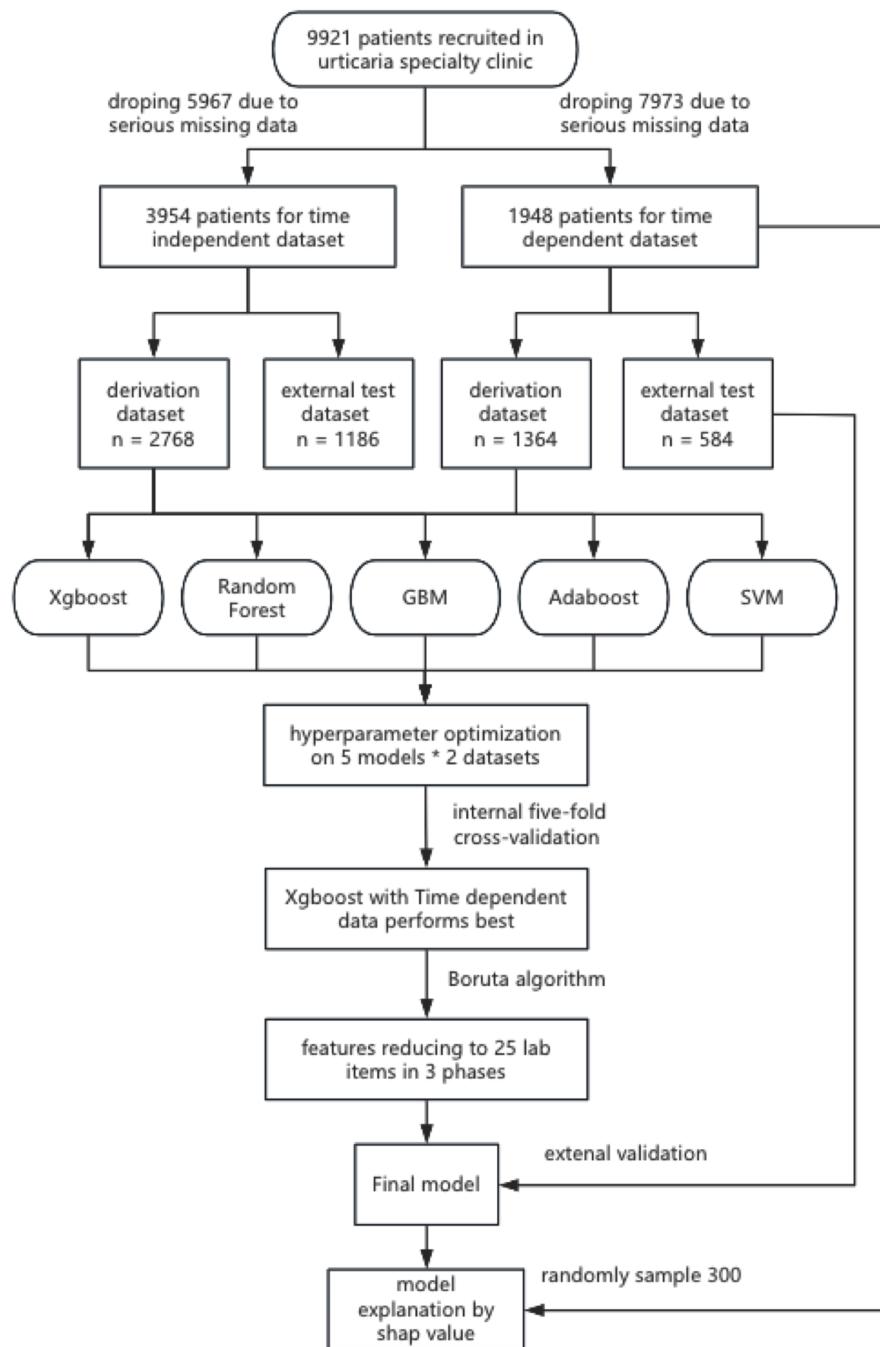


Figure 1: Study design

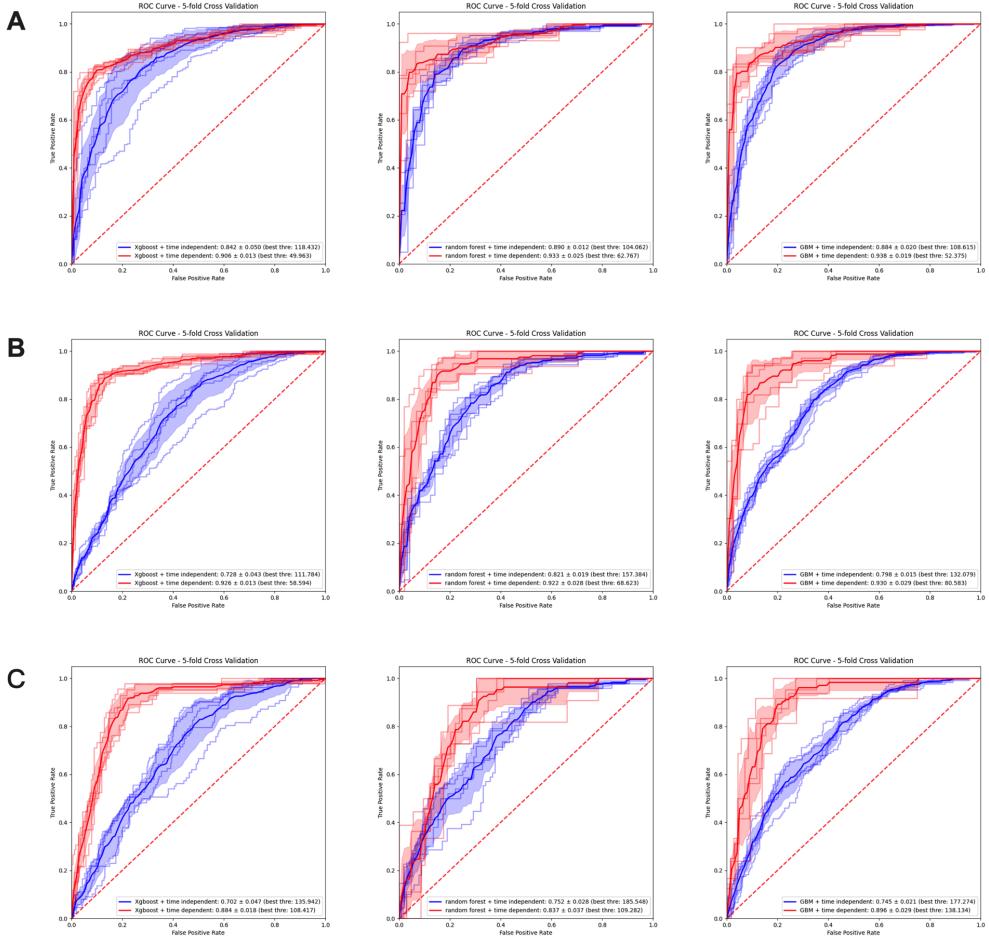


Figure 2: ROC curves for 5-fold cross-validation results for three different models (XGBoost, Random Forest, and GBM) at three binary classification thresholds (42, 100, and 365). Each row (A, B, and C) represents the results for a specific threshold. The models' performances are plotted with time-independent and time-dependent datasets, where red indicates the time-independent dataset and blue represents the time-dependent dataset. The shaded areas represent the 95% confidence intervals.

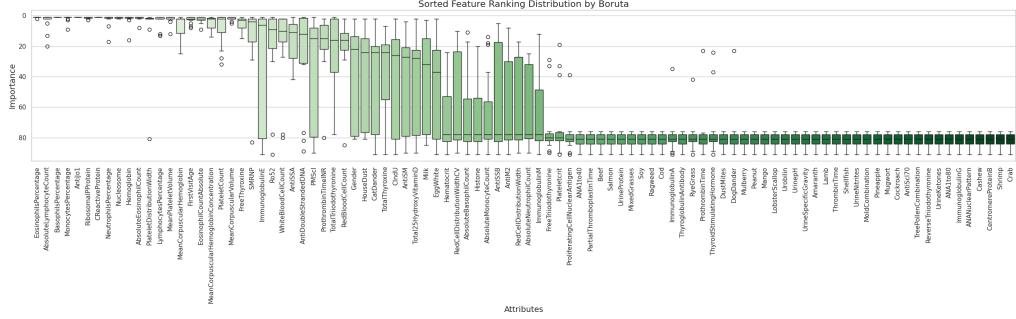


Figure 3: Boxplot representing averaged feature ranking distribution for each laboratory item generated by the Boruta algorithm over 15 iterations. The ranking value for each laboratory item is averaged for 3 different phases of disease. The y-axis shows the importance rank, with lower values indicating higher importance, while the x-axis lists the laboratory items names.

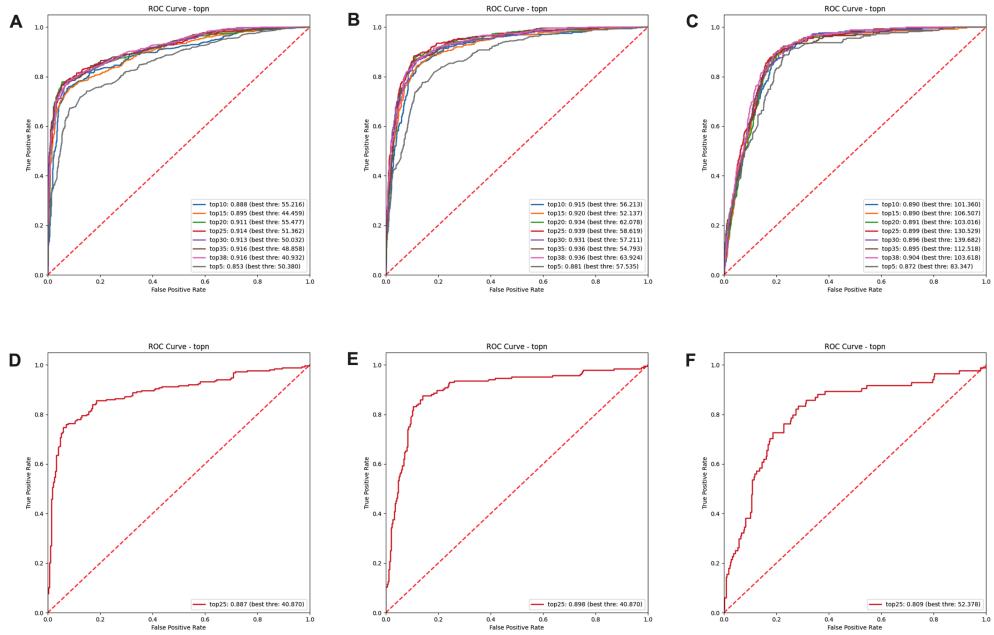


Figure 4: Panels A, B, and C display the ROC curves for the model as the number of top items is reduced based on the average importance score at cutoff values of 42, 100, and 365, respectively. Panels D, E, and F show the ROC curves for the final model with 25 top items on external test set at cutoff values of 42, 100, and 365, respectively.

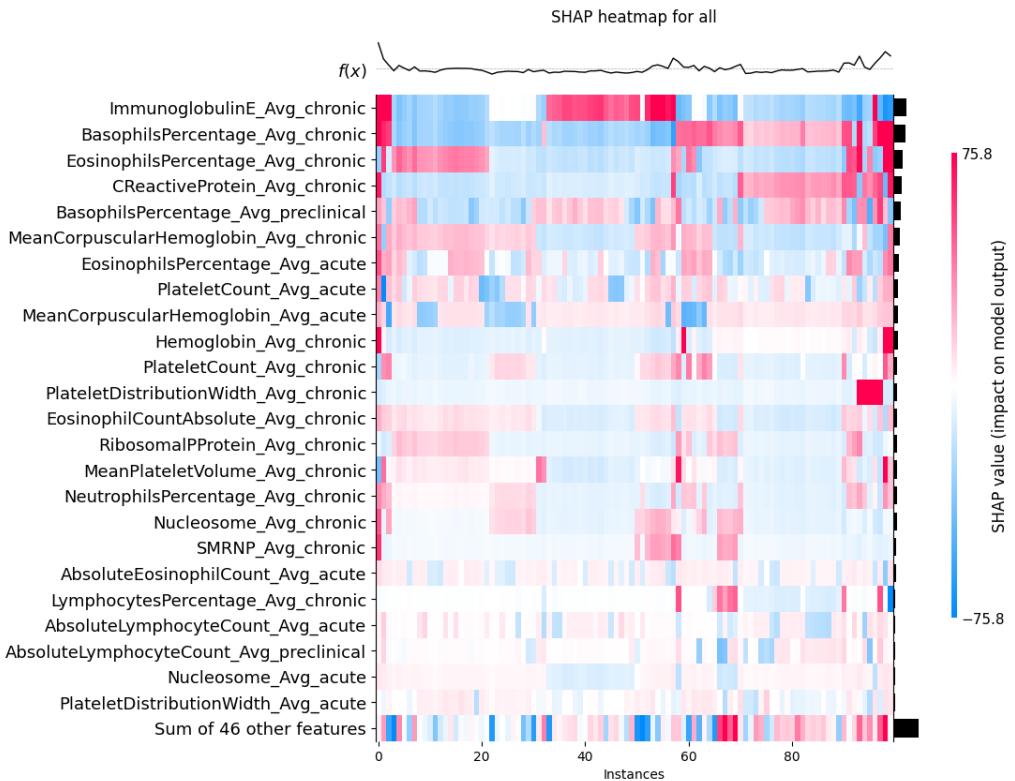


Figure 5: a heatmap plot with the instances on the x-axis, the model inputs on the y-axis, and the SHAP values encoded on a color scale. The samples are ordered based on a hierarchical clustering by their explanation similarity. This results in samples that have the same model output for the same reason getting grouped together. The output of the model is shown above the heatmap matrix, and the global importance of each model input shown as a bar plot on the right hand side of the plot.

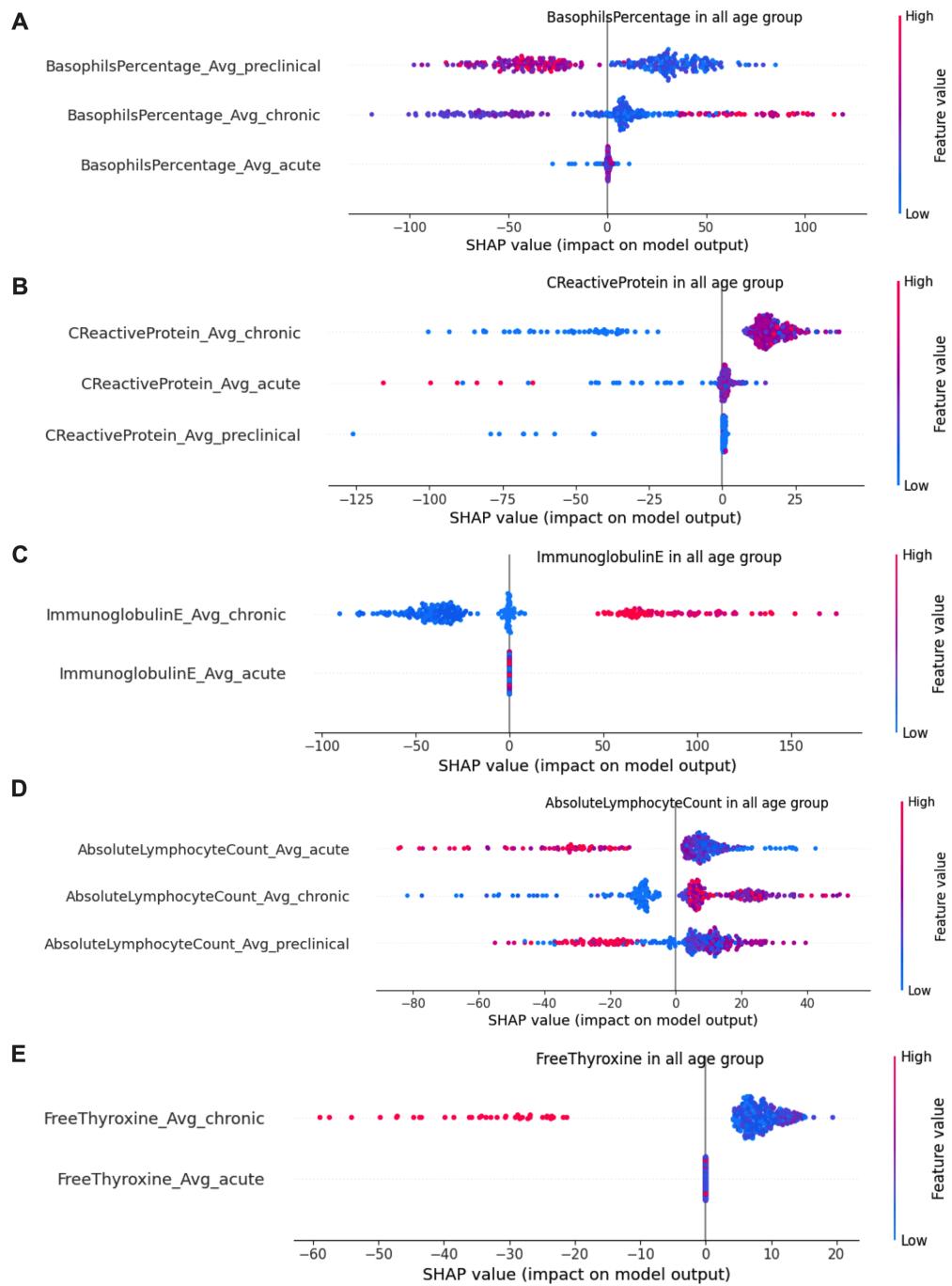


Figure 6:

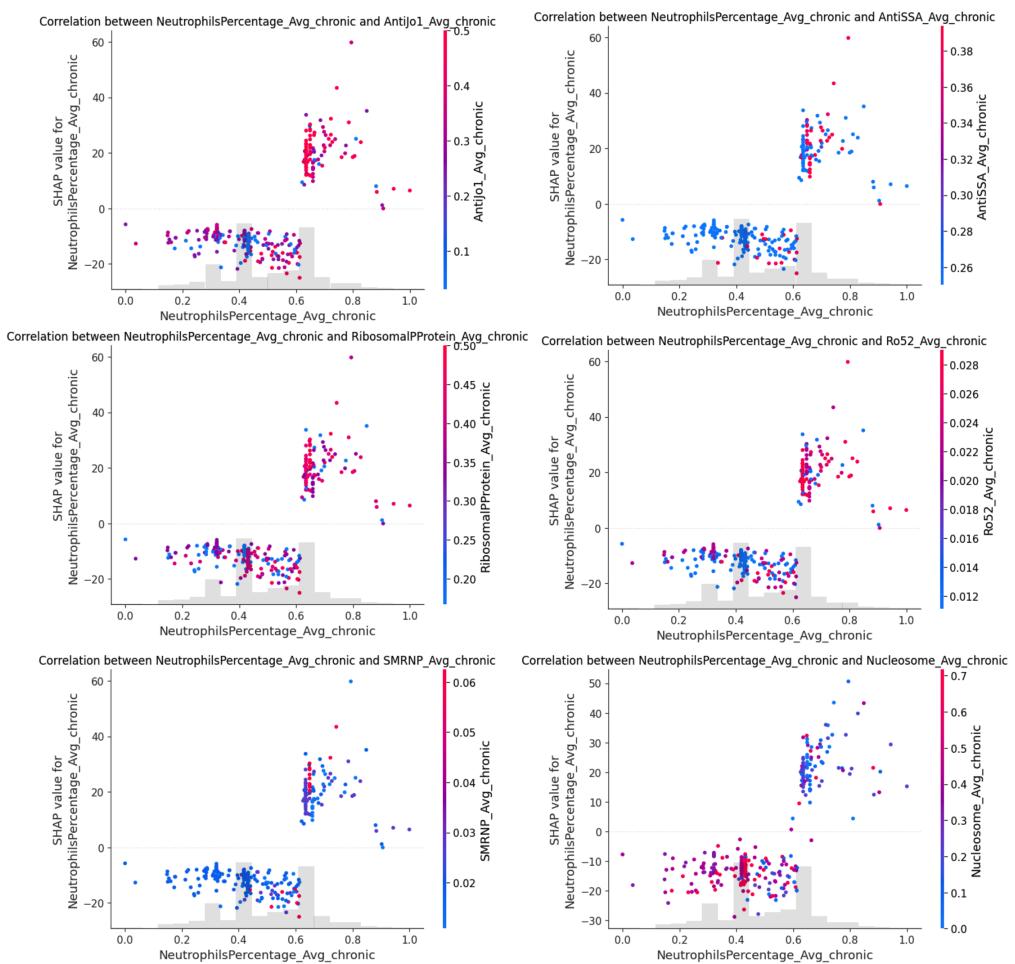


Figure 7:

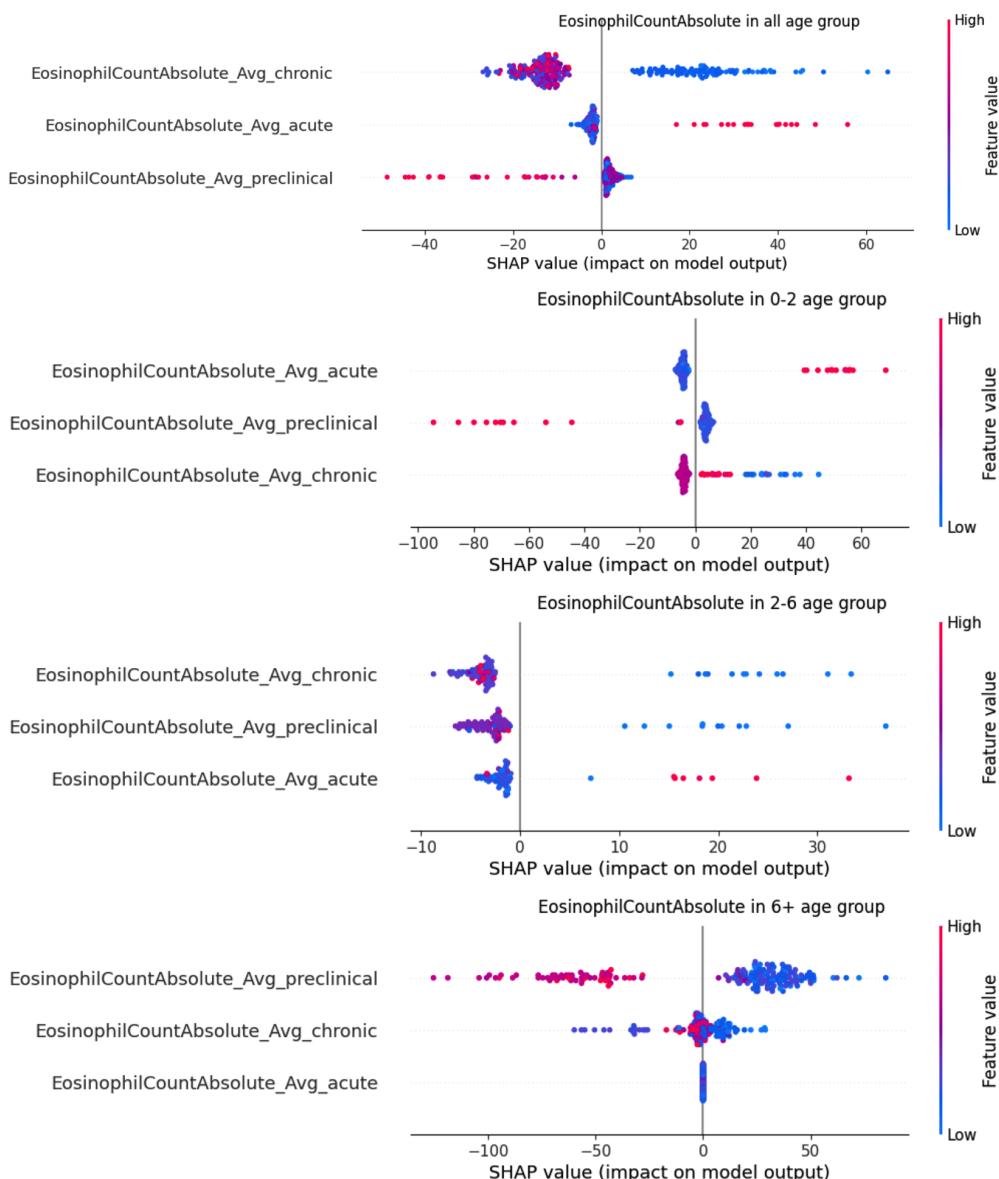


Figure 8:

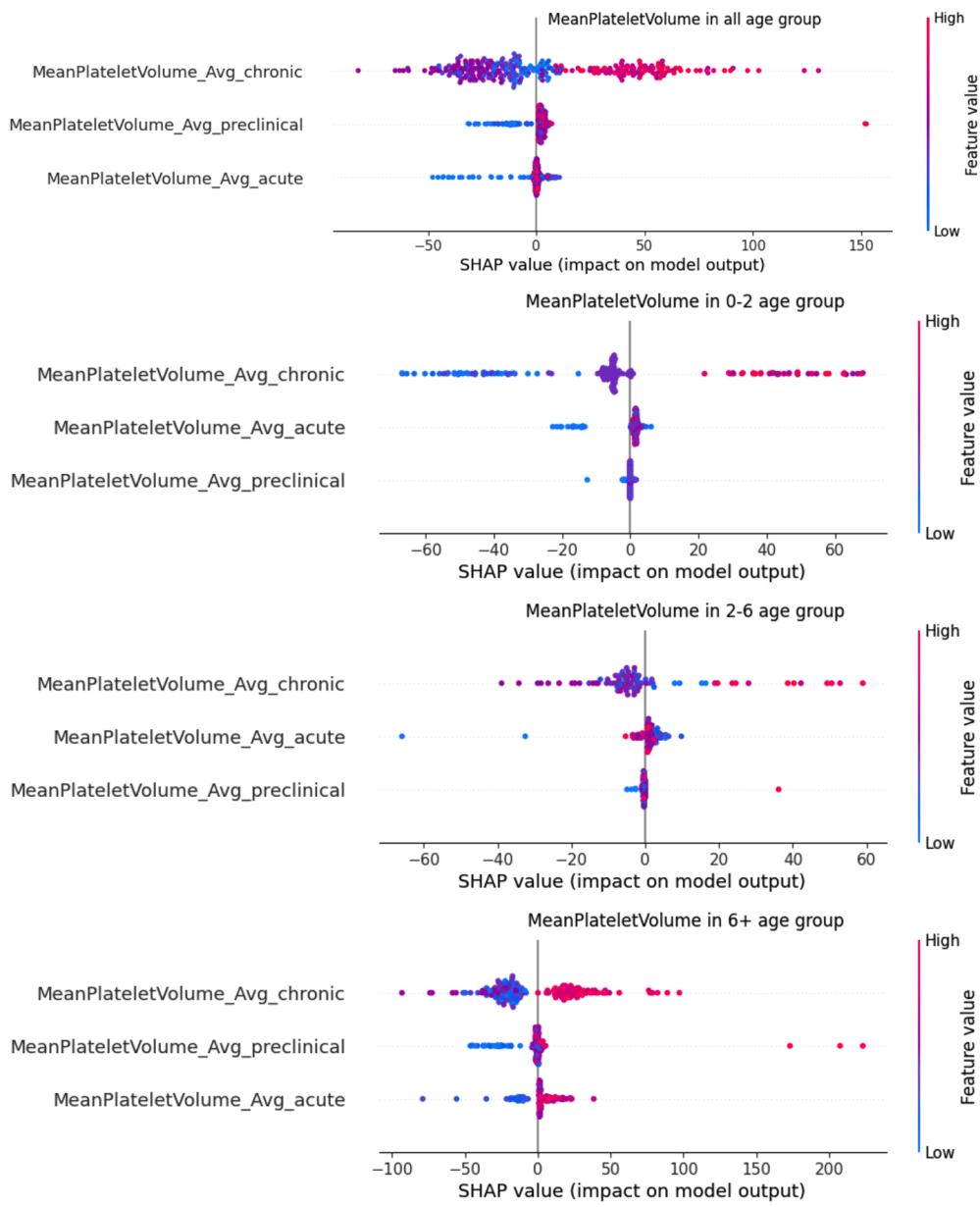


Figure 9: