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.

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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), and vitamin D levels are all associated with the disease's severity and duration (SanchezBorges et al., 2017; Rabelo-Filardi et al., 2013). 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, was the target variable. The following features were extracted from the database: (1) demographic data: gender, first visit age; (2) clinical data: 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 durting preclincial 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 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 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 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 cuttoffs 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 evalutated directly from the boosted trees, these importances have been

shown to be local and inconsistent. A SHAP score inspired by Shapley values can combines 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 features is deemed important.

In this study, Boruta algorithm was run on the final model, with max iteration set to 50 and repeated 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

The shapley value of each laboratory item in different phase of disease were compared to reveal various predicting ability of laboratory data in different phase of disease. To further verify the tendency oberserved in shapley values, kernal density estimation was used to visualize the distribution of average values of laboratory data in different phase of disease for patients with different disease duration. Shapley values together with kernal density estimation were used to explain the model and provide insights for clinical practice. 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

Table 1 and Table 2 delineates the disparities between groups regarding the disease duration of patients in dataset.

Table Appendix A and table Appendix A provides a comparison of the baseline characteristic between the training set and external testing set data. 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.

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

Characteristic	Good Outcome	Poor Outcome	P-value
Number of patients	1202	746	
Outcome	14.68 ± 22.61	631.42 ± 448.34	0.000 ↑
Gender	0: 84.6%, 1: 15.4%	0: 77.3%, 1: 22.7%	0.000
First Visit Age	22.60 ± 21.58	22.26 ± 23.12	0.746
CI nd U	0: 99.4%, 1: 0.6%	0: 98.5%, 1: 1.5%	0.079
Lymphocytes Percentage chronic	35.37 ± 9.29	36.50 ± 11.95	0.019
Lymphocytes Percentage acute	32.37 ± 14.25	34.65 ± 13.91	0.001 ↑
Lymphocytes Percentage preclinical	37.86 ± 14.45	40.34 ± 15.16	0.000 ↑
Neutrophils Percentage preclinical	51.40 ± 15.89	48.94 ± 16.49	0.001 ↓
Neutrophils Percentage chronic	54.34 ± 10.18	53.71 ± 12.76	0.229
Neutrophils Percentage acute	59.48 ± 15.77	56.92 ± 14.85	0.000 ↓
Monocytes Percentage chronic	6.53 ± 0.77	6.53 ± 1.22	0.980
Monocytes Percentage acute	6.23 ± 1.08	6.23 ± 1.04	0.937
Monocytes Percentage preclinical	6.66 ± 1.03	6.70 ± 0.82	0.359
Mean Corpuscular Hemoglobin Concentration chronic	333.82 ± 4.53	334.04 ± 8.74	0.457
Mean Corpuscular Hemoglobin Concentration acute	336.49 ± 12.49	338.59 ± 12.85	0.000 ↑
Mean Corpuscular Hemoglobin Concentration preclinical	343.26 ± 6.90	343.88 ± 7.38	0.058
Platelet Count chronic	253.50 ± 31.29	257.54 ± 57.28	0.044
Platelet Count acute	260.29 ± 69.51	258.81 ± 62.12	0.634
Platelet Count preclinical	252.05 ± 52.40	255.30 ± 50.00	0.176
White Blood Cell Count acute	10.06 ± 3.20	9.56 ± 2.56	0.000 ↓
White Blood Cell Count chronic	8.44 ± 1.00	8.67 ± 2.31	0.003 ↑
White Blood Cell Count preclinical	8.65 ± 2.05	8.52 ± 1.81	0.179
Mean Corpuscular Hemoglobin chronic	28.93 ± 1.41	28.79 ± 1.75	0.064
Mean Corpuscular Hemoglobin preclinical	28.47 ± 1.63	28.30 ± 1.73	0.027
Mean Corpuscular Hemoglobin acute	28.60 ± 2.03	28.64 ± 2.04	0.686
Mean Corpuscular Volume chronic	86.62 ± 4.32	86.02 ± 5.27	0.006 ↓
Mean Corpuscular Volume acute	85.02 ± 6.22	84.57 ± 5.81	0.113
Mean Corpuscular Volume preclinical	83.11 ± 5.43	82.44 ± 5.83	0.010
Hemoglobin acute	129.24 ± 9.96	129.41 ± 7.91	0.690
Hemoglobin chronic	130.22 ± 4.78	129.84 ± 7.44	0.171
Hemoglobin preclinical	128.17 ± 7.15	127.20 ± 8.29	0.006 ↓

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

Time independent and Time dependent data were used to generate 5 machine learning models to predict the disease duration of urticaria. Among the 10 models, Xgboost model with time dependent data (AUC =) has the best predictive effect for disease duration, followed by random forest with time dependent data (AUC =) the ROC curves for the top three best-performing ML models are presented in Figure 1. 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 2 and Supplementary 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 important ranking, the changes in AUCs for the model shows that the model maintain robust performance unitil the number of items reduced to less than 10, as shown in Figure 3 A-C. Top 25 items were selected as the final model, validation on external test set showed a stable performance with AUC of 0.85, as shown in Figure 3 3 D-F.

3.4. Model explanation

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)

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: 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 4: Feature importance ranking by Boruta algorithm

Supplementary Table 5: 38 laboratory items confirmed as important by Boruta algorithm

Supplementary Table 6: The performance of the final model on external test set

Appendix B. Acknowledgements

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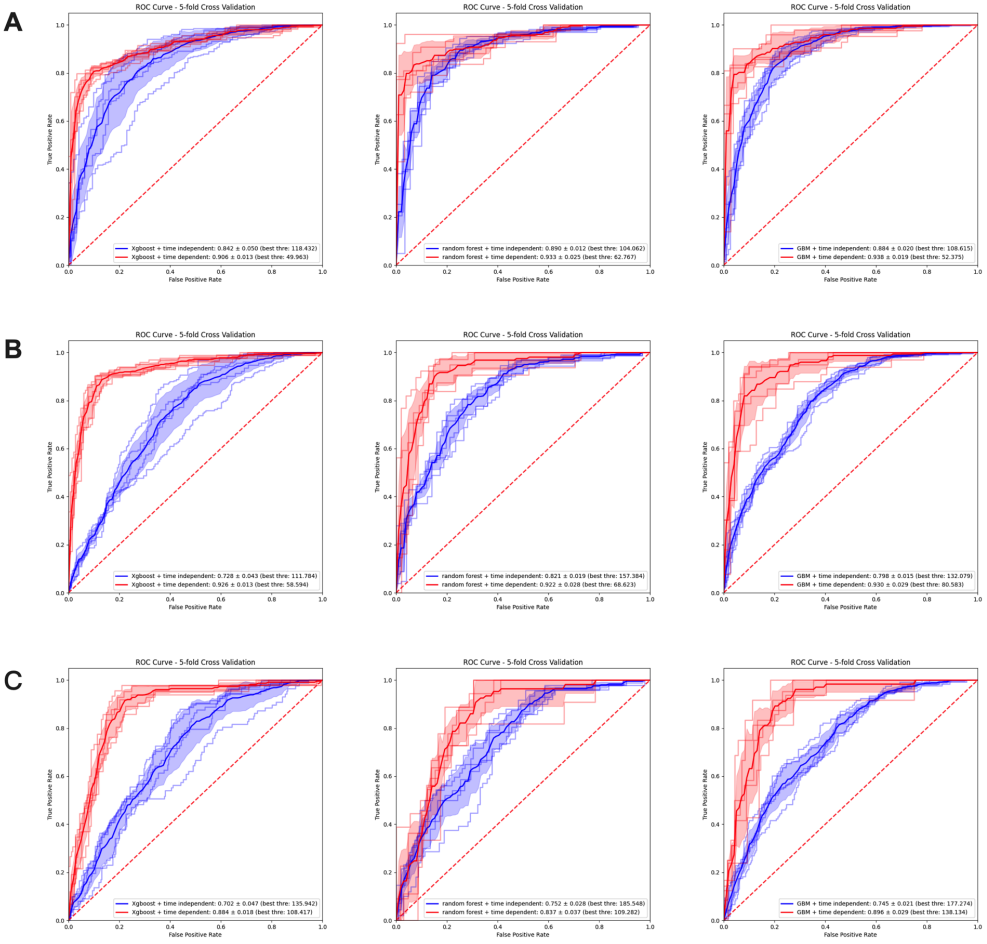

Figure 1: Figure Caption

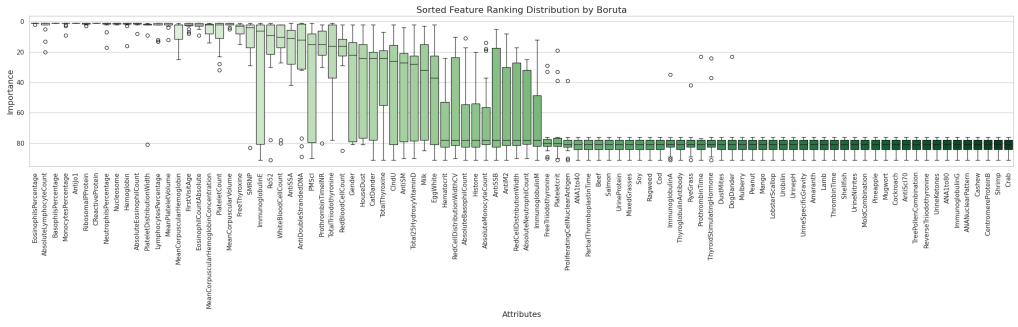

Figure 2: Figure Caption

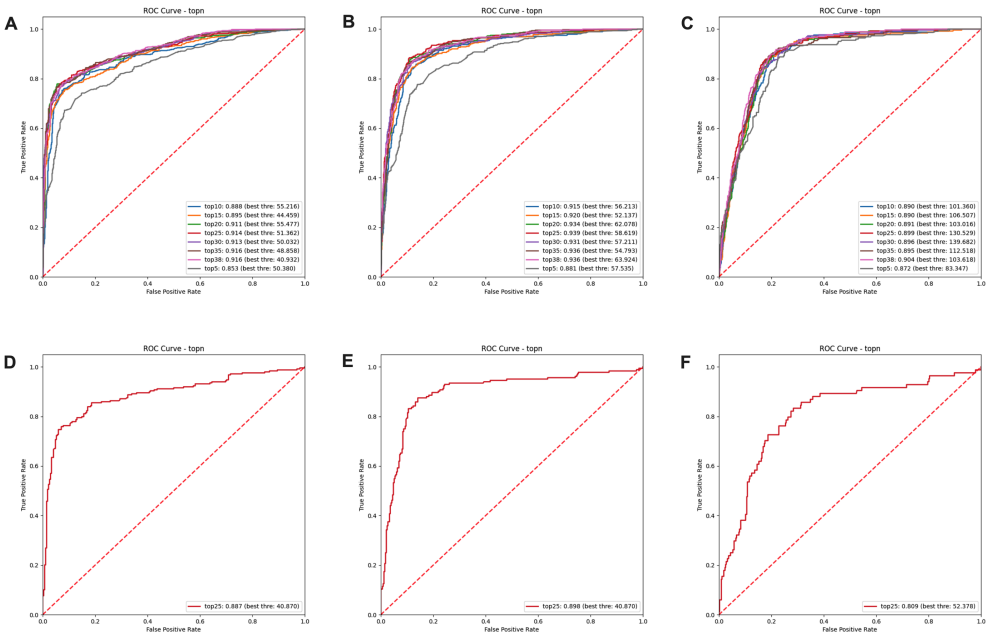

Figure 3: Figure Caption