Development of a tongue image-based machine learning tool for the diagnosis of acute respiratory tract infection

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Abstract

Background: Tongue characteristics, widely utilized in traditional Chinese medicine for health assessment, have been shown to correlate with specific respiratory infections. With the ongoing global spread of Human adenoviruses (HAdVs), COVID-19, and other seasonal respiratory viruses, this study aims to enhance the convenience and cost-effectiveness of respiratory infection diagnoses by developing prediction models based on tongue characteristics.

Method: This study utilized deep learning to extract features from 280 tongue images collected from COVID-19 patients, HAdVs patients, and healthy individuals. Machine learning diagnostic models were subsequently trained on these tongue characteristics to distinguish between normal cases and those indicative of COVID-19 and HAdVs infections. The key features identified by the machine learning algorithms were further visualized in a two-dimensional space.

Result: Nine significant tongue features were identified: tongue coating color (red, green, blue), the presence of tooth marks, tongue coating crack ratio, tongue coating moisture level, texture directionality, texture roughness, and texture contrast. Diagnostic models trained on these features achieved an area under the precision-recall curve exceeding 70%, with the area under the receiver operating characteristic curve surpassing 80% for general performance. The SHAP value revealed that tongue color, moisture level, and texture direction were the most influential features.

Conclusion: Our findings demonstrate the potential of tongue diagnosis in identifying pathogens responsible for acute respiratory tract infections at the time of admission. This approach holds significant clinical implications, offering the potential to reduce clinician workloads while improving diagnostic accuracy and the overall quality of medical care.

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Title page

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Abstract

Background: Tongue characteristics, widely utilized in traditional Chinese medicine for health assessment, have been shown to correlate with specific respiratory infections. With the ongoing global spread of Human adenoviruses (HAdVs), COVID-19, and other seasonal respiratory viruses, this study aims to enhance the convenience and cost-effectiveness of respiratory infection diagnoses by developing prediction models based on tongue characteristics.

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Conclusion: Our findings demonstrate the potential of tongue diagnosis in identifying pathogens responsible for acute respiratory tract infections at the time of admission. This approach holds significant clinical implications, offering the potential to reduce clinician workloads while improving diagnostic accuracy and the overall quality of medical care.

Keywords: Tongue diagnosis, Human adenoviruses, COVID-19, image feature extraction, Machine learning, Traditional Chinese medicine

Introduction

Human adenoviruses (HAdVs) are prominent respiratory pathogens affecting individuals of all ages, leading to acute upper and lower respiratory tract diseases such as pneumonia and bronchitis[1]. Nearly half (45.71%) of acute respiratory tract infection (ARTI) outbreaks between 2009 and 2020 were attributed to HAdV-7 [2]in China. Since 2020, a temporary decline in HAdVs activity has been noted due to the rapid global spread of coronavirus disease 2019 (COVID-19) and subsequent public health measures [3, 4]. As COVID-19 persists in its global circulation, a resurgence of HAdVs and other seasonal respiratory virus infections has occurred [5]. The clinical presentations of ARTI caused by HAdVs and COVID-19 are similar, often presenting as mild symptoms such as fever, rhinorrhea, cough, and sore throat, which poses a significant diagnostic challenge in the absence of viral testing. HAdVs are particularly prone to causing acute respiratory infections in children, including pharyngitis, tonsillitis, pharyngo-conjunctival fever, bronchitis, and pneumonia, compared to COVID-19 [6]. Moreover, recent studies indicate that mixed respiratory viral infections may lead to more severe disease outcomes than single infections [7]. Given the tendency of many ARTI patients to self-medicate, it is essential to develop methods to differentiate between these common viral infections. Such differentiation could promote timely medical consultation and help reduce the transmission of adenovirus to children.

Tongue image diagnosis is a straightforward, non-invasive, and valuable diagnostic method employed in traditional Chinese medicine (TCM) [8]. Key characteristics assessed during tongue diagnosis include the color, size, and shape of the tongue, along with the color, thickness, and moisture level of the tongue coating. According to the TCM theory, in patients with respiratory infections, a white tongue coating typically signifies the wind-cold attacking the lung syndrome, while a red-tipped tongue with a yellow coating may indicate the wind-heat invading lung syndrome [9]. Previous studies have shown that a fissured or non-papillated tongue, prominent papillae, and strawberry tongue are oral manifestations associated with COVID-19 [10-13]. In contrast, tongue symptoms are rarely documented in HAdVs patients. Due to the convenience and cost-effectiveness of tongue imaging as a diagnostic tool, studying the relationship between tongue image changes and the differential diagnosis of COVID-19 and adenoviral respiratory infections has significant research value.

As a traditional diagnostic technique, tongue diagnosis involves the collection of disease-related information by a Traditional Chinese Medicine (TCM) practitioner through the observation of tongue characteristics. Consequently, its effectiveness depends on the practitioner's experience and expertise. The advent of Artificial Intelligence (AI) image processing has significantly enhanced tongue diagnosis, particularly in the areas of standardized feature extraction and analysis, demonstrating promising applications in predicting gastrointestinal disorders [14-17]. Research on using this method to diagnose respiratory infections remains limited. To address this, we compiled a dataset of tongue images from 57 COVID-19 patients, 85 HAdVs patients, and 30 healthy individuals. Then, we developed and validated AI deep learning models to assess the diagnostic value of tongue images by identifying specific features such as color, coating, fissures, papillae, tooth marks, and granules. Utilizing these tongue characteristics, we developed four machine learning diagnostic models: logistic regression (LR), Random Forest (RF), Gradient Boosting Model (GBM), and Extreme Gradient Boosting (XGBoost). Our study aims to offer valuable insights that enhance respiratory tract infections diagnostic accuracy and refine traditional practices.

Method

Study Sample

Our study was conducted between November 2020 and January 2021 at the Department of

Traditional Chinese Medicine Hepatology, which is in the Fifth Medical Center of PLA General Hospital.

The inclusion criteria include:

1. Participants whose age is between 18 and 80 years old.
2. Participants willing to participate in tongue image photography signed an informed consent form.

The exclusion criteria for this study include:

1. Individuals who were unable to describe their condition clearly due to mental factors or could not cooperate with the collection of tongue diagnosis images.
2. Participants with severe acute complications, such as serious electrolyte imbalance and acidosis; patients with other serious internal diseases, such as tumors, immune system disorders, or hematologic diseases; and individuals taking medications, such as steroids, that affect glucose metabolism.
3. Pregnant women and nursing mothers were excluded.

After applying the inclusion and exclusion criteria, 172 participants were included in the study. Of these, 57 were diagnosed with COVID-19, 85 with adenovirus, and 30 were assigned to the control group. Meanwhile, all the patients had complete clinical data and demonstrated high compliance, while control group participants had no history of chronic or acute diseases in the past three months (**Figure 1**).

Outcome definition

A confirmed case of COVID-19 is defined as a suspected case that yields a positive result on a real-time reverse-transcription polymerase chain reaction (RT-PCR) assay using respiratory specimens [18]. In this study, all patients with adenovirus infection met the diagnostic criteria outlined in the

"Adenovirus Infection Diagnosis and Treatment Guidelines" issued in 2013 [19]. According to these guidelines, the criteria include (1) a real-time PCR test on throat swab samples that detects adenovirus-specific nucleic acids, (2) the presence of adenovirus-specific IgM antibodies in the serum, and (3) a four-fold or greater increase in adenovirus-specific IgG antibodies in paired serum samples collected during the acute and recovery phases. The selection of diagnostic tests was based on clinical judgment. These tests were conducted on various specimen types, including nasopharyngeal swabs, throat swabs, sputum samples, pleural effusion samples, and bronchoalveolar lavage fluid samples.

Tongue image collection

Collecting tongue images was conducted either before a meal or 2 hours afterward. Before being photographed, participants were instructed not to eat any food or drink any colored beverages. During the examination, participants were asked to sit with their mouths open, and their tongues extended, ensuring the tongue body relaxed, the surface flat, and the tip drooping. A color correction card was held within the camera's view during image capture to prevent external lighting from affecting the quality of the photograph. If a retake was necessary, the participants were advised to rest for 3-5 minutes before recollecting the image. The final choice for storage was the best-quality image. A digital diagnostic system was used to collect and analyze all tongue images.

Tongue image-based AI deep learning models

In this study, four key factors were primarily selected for detection: the tongue body, the coating, the teeth mark, and the fissures. To develop a target detection algorithm for tongue diagnosis images, the YOLOv4 object detection framework was employed [20]. Through extensive experimentation with this algorithm, the optimal combination was identified to enhance the accuracy of the Convolutional

Neural Network (CNN), enabling more precise and reliable assessments of tongue features relevant to medical diagnosis [21]. We also increased the sample size and improved the model's generalization using image preprocessing techniques, including random cropping, horizontal flipping, and color distortion [22]. This preprocessing yielded sample images with various tongue characteristics, including color, coating, fissures, prickles, tooth marks, and granules, categorized under data labels 1-20 (**Supplemental Table 1**).

We trained our neural network with two datasets, VOC 2007 and 2012. The training batch size was 32 images, and two NVIDIA 1080 8G GPUs were used. Each group was segmented individually for different tongue features, including tongue coating (color, shape, moisture), fissures (cracks ratio), prickles, tooth marks, and granules (shape, reflectivity).

Tongue image feature definition

The color of the tongue coating was calculated by taking the mean RGB (Red, Green, Blue) values within a specified area, providing insights into the tongue's health condition. Tooth marks were identified using the object detection algorithm, with a confidence threshold set at 0.6 to determine the presence and count of tooth marks. The proportion of cracks in the tongue coating was calculated by segmenting and merging areas where multiple fine cracks intersect, thus determining the area occupied by these cracks relative to the total area of the tongue coating. The moisture level of the tongue coating was assessed by identifying reflective areas where brightness exceeds a threshold value of 170, helping to evaluate the hydration status of the tongue. The texture features of the tongue coating were extracted using Tamura texture features, which focus on describing the textural characteristics of the tongue coating in terms of coarseness, contrast, directionality, and roughness [23]. In this study, coarseness refers to texture coarseness and is calculated based on the size of the elements. A larger element size or fewer repetitions of the element indicates a coarser texture. Contrast is primarily derived from the image grayscale, while directionality refers to the degree of alignment within the elements.

Statistical Analysis

We obtained 280 tongue images from these participants, each contributing up to seven images. Only images taken on the baseline day were retained for this study, and we took the average value of the extracted features in the images if participants had more than one image on the baseline day. There were 21 images with quality issues, including 11 unidentifiable images (all characteristic values were zero) and 10 unclear images (most characteristic values were zero). We applied a mean imputation technique to these images, averaging the image parameters based on outcome category and symptom severity [24]. We conducted comparative analyses across three groups to examine variations in tongue features, including color, texture, moisture, and morphology.

The data was divided into two subsets, with 70% allocated for training and 30% reserved for internal validation, to address potential overfitting concerns. Advanced machine learning models were used to analyze tongue images and classify them into three categories: COVID-19, adenovirus, and normal. We used several models in our analysis, including Gradient Boosting Machines (GBM), Random Forest, Logistic Regression, and XGBoost. To fit each model, we applied 5-fold cross-validation on the training set. We evaluated the models' performance using two metrics: the area under the receiver operating characteristic curve (AUC) and the area under the precision-recall curve (AUCPR) [25].

An importance variable rank was computed for each algorithm to identify the variables with the highest predictive power. Additionally, we created SHAP values that were calculated to indicate the contributing direction of the tongue image features [26]. Lastly, we projected the selected variables of tongue images into a two-dimensional space by a t-SNE plot to visually examine each group's clustering distribution [27].

All statistical analyses were performed using R Studio 4.2.0 software. Independent sample t-test was used to analyze the measurement data such as age and identified tongue image features. The count data were analyzed using the chi-square test. Results with $P < 0.05$ were considered statistically significant.

Ethics approval

The Ethics Committee of the Fifth Medical Center of the PLA General Hospital (2020074D) gave ethical approval.

Result

Characteristics of patients with each pathogen

Our research involved 172 participants; 58 had COVID-19, 84 were diagnosed with adenovirus, and 30 were in the control group. Table 1 shows the main descriptive sociodemographic variables (sex and age). The average age in our sample was 23.65 (±9.61) years old (**Table 1**).

Tongue image feature extraction and definition

We employed transfer learning techniques using weights obtained from training on the VOC 07 and 12 datasets, which enabled the model to improve its understanding of general object detection. After 60,000 iterations with a learning rate of 0.0001, the average loss was reduced to 0.2867

(**Supplemental Figure 1**). Compared to the proposed Fast-RNN and Faster-RCNN, the SSD architecture demonstrates higher accuracy across 20 labeled datasets (**Supplemental Figure 2**). After applying our feature extraction architecture, nine features of tongue images were identified: tongue coating color values (red, green, blue), the presence of tooth marks, tongue coating crack ratio, tongue coating moisture level, texture directionality, texture roughness, and texture contrast (**Supplemental Table 3**).

All tongue coating color values (red, green, blue) differed significantly across groups ($P < 0.001$) (**Table 1**). Adenovirus patients had the highest values, especially in the red component, which may indicate more pronounced inflammation or other specific clinical features related to adenovirus infections. The presence of tooth marks varied across groups, with the highest prevalence of two tooth marks in the COVID-19 group (36.2%). While not statistically significant, the COVID-19 group showed a higher crack ratio (1.44), which may correlate with other symptoms or manifestations of the illness. Tongue coating moisture levels also showed significant differences across groups, with the adenovirus group showing the lowest average moisture level($P = 0.07$). The density plot suggested distinct patterns in tongue features among individuals with COVID-19, adenovirus, and those in the control group, demonstrating the potential of these features in differentiating respiratory viral infections (**Figure 2**).

Diagnostic performance results

The tree-based and boosting models achieved over 70% AUCPR performance, with AUC exceeding 80% for general performance. The GBM achieved the highest AUC value of 0.888 and AUCPR value of 0.764. XGBoost came in second with an AUC value of 0.872 and an AUCPR value of 0.751, followed closely by Random Forest with an AUC value of 0.872 and an AUCPR value of 0.747. However, Logistic Regression showed a relatively worse performance, with an AUC value of

0.812 and an AUCPR value of 0.668. These results suggested that the ensemble methods may be more effective in handling complex patterns within our data (**Supplemental Table 4**).

Explaining the rationale behind the predicted models

Based on SHAP values, several factors contribute to diagnosing adenovirus and COVID-19, including the color of tongue coating, moisture level, and texture direction. The feature importance plots indicate that the most significant variables are tongue color, moisture level, and texture direction (**Figure 3**). Specifically, a red tongue coating helps identify adenovirus cases, while a green tongue coating is beneficial for identifying COVID-19 cases (**Figure 4**). Additionally, the t-SNE plot projects these variables into a two-dimensional space and color codes each group. The distribution of patients with COVID-19 and adenovirus differs within the t-SNE space, showing some overlap, while the control group is between the two infectious cases (**Figure 5**).

Discussion

In recent years, the concurrent prevalence of respiratory infectious diseases such as COVID-19 and HAdVs has made it challenging to establish a differential diagnosis without pathogenic testing, thereby impacting the efficacy of the treatment [28]. Tongue image diagnosis has emerged as an effective, non-invasive method for auxiliary diagnosis that can be conducted in various settings, catering to the global demands of primary healthcare systems [29]. In this study, we developed machine-learning models that utilize tongue images to predict ARI pathogens. The accuracy of these models exceeded 80%, with feature importance plots revealing tongue color, moisture level, and tongue texture direction as pivotal variables. We then projected the tongue images features of the three groups of participants into a lower-dimensional space by t-SNE plot. The resulting clusters of COVID-19 and adenovirus were notably distinct, suggesting that the tongue image parameters we extracted contribute significantly to the diagnosis of ARIs. This non-invasive, convenient, and rapid approach has the potential to mitigate unnecessary diagnostic procedures and reduce healthcare costs.

The constructability of a risk warning model using tongue diagnosis data has been validated in research on diabetes, depression, and cancers [30-32]. Our study is pioneering in applying AI deep learning techniques to investigate the diagnostic value of tongue images in acute respiratory tract infection diagnosis and can be integrated into clinical practice to aid decision-making and alleviate physician burden. Previous research by Mai et al. aimed to predict common respiratory viruses in the United States by combining natural language processing (NLP) tools with Machine Learning techniques [33]. However, the model's prediction performance of HAdVs was moderate, with an AUROC of 0.53 [33]. Chen et al. utilized an XGBoost model, incorporating demographic, physical examination, laboratory, and vital sign data, to predict HAdVs in hospitalized children with respiratory symptoms, achieving an AUROC of 0.82 [34]. Our model exhibited superior performance, achieving an AUROC of 0.87, following the inclusion of various features in its development. In contrast to models established in previous studies, the model developed in this paper benefited from the utilization of non-invasive tongue image data, obviating the need for laboratory examination indicators. By utilizing the YOLOv4 object detection framework for image feature extraction and integrating ensemble learning algorithms (i.e., GBM, XGBoost), we have demonstrated the clinical utility of tongue images. All four models exhibited discriminative validity over tongue images, indicating that tongue images can serve as a reliable tool for ARTI diagnosis and are robust across different AI deep learning model types.

Previous research has validated the use of objective tongue image acquisition equipment, methods, and data analysis techniques[35]. Research on AI in Traditional Chinese Medicine (TCM) tongue diagnosis has predominantly focused on standardizing tongue diagnosis to minimize human errors [35]. Xu et al. developed a multitask joint learning model for segmenting and classifying tongue images, utilizing a deep neural network to optimally extract tongue image features [36]. Meng et al. proposed a novel feature extraction framework, termed constrained high dispersal neural networks, to extract unbiased features and minimize human labor in TCM tongue image diagnosis [37]. This study employed the YOLOv4 framework, which excelled in extracting high-level image features, thereby enhancing the model's capacity to identify intricate patterns and subtle variations [38]. This integration, coupled with the fusion of ensemble learning algorithms, harnesses the complementary strengths of clinical and image-derived features, effectively addressing the limitations of each modality in isolation [39]. Consequently, the model gains enhanced discriminative power, leading to more accurate predictions of ARTI.

The analysis of feature importance in Machine Learning models (GBM, XGBoost, random forest) revealed that a red tongue coat is most indicative of HAdVs and normal individuals, while the green color is more suggestive of COVID-19 cases. Furthermore, statistical analysis of the tongue images of the three groups showed that COVID-19 group had a higher moisture level and lower contrast rate, suggesting that the COVID -19 patients are more likely to have a thicker and greasier tongue coating compared to the other two groups. Our findings align with the TCM theory. According to TCM, COVID-19 is classified as a "cold-dampness" disease, characterized by a tongue that is pale red or dark and thick white greasy coating. HAdVs are considered as "warm" diseases in TCM, typically presenting with red and dry tongues. The thickness and dryness of the tongue coating can also indicate the severity of the disease and the extent of fluid damage. Epidemiological studies conducted in China, the UK, and Ukraine have yielded analogous findings; the predominant tongue colors observed were pale pink and dark red, with the most frequently encountered tongue coating being thin and greasy [40-42]. Therefore, a patient presenting with acute respiratory symptoms and a red tongue devoid of a thick, greasy coating are more likely to have an HAdVs infection. Such observations could guide healthcare professionals in suggesting preventive measures, like isolation or improved hygiene, to avert transmission to susceptible household members, including children and the elderly. The incorporation of tongue image analysis into clinical practice allows healthcare providers to make informed judgments about the need for additional diagnostic tests, potentially reducing unnecessary interventions and healthcare expenses.

Hypothetically, the SARS-CoV-2 virus may induce alterations in the expression levels of genes coding for apoptosis of epithelial cells, resulting in the accumulation of oral epithelial cells and increasing tongue coating thickness. Wang et al. found a correlation between tongue coating thickness in COVID-19 patients and levels of white blood cells (WBC) as well as the neutrophil-to-lymphocyte ratio [43]. Conversely, in febrile patients without COVID-19, the presence of slimy or greasy tongue fur was associated with the level of C-reactive protein [43]. Additionally, studies have indicated that greasy tongue fur is associated with higher blood fibrinogen levels in stroke patients and with increased activity of glossal epithelial cells and vascular permeability in rodent models [44, 45].

It is important to acknowledge several limitations of this study that may impact the generalizability of its findings. Our dataset has a moderate sample size, and we further split it into training and validation subsets, this could introduce bias due to the limited number of samples used for model validation. Furthermore, the COVID-19 pandemic's operational constraints necessitated data collection at a single tertiary hospital. However, as a national referral center serving Beijing and surrounding provinces, our institution treats patients from geographically diverse regions, which partially mitigates concerns about population representativeness.

Conclusion

This study illustrates the utility of AI in helping clinicians identify potential pathogens in ARTI at the time of admission. The results were interpretable and relevant to clinical practice. With our model's superior accuracy, clinicians may avoid unnecessary medical costs and diagnostic tests while maintaining accurate diagnoses. Our method can potentially alleviate clinicians' workloads and enhance the overall quality of medical care.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Informed consent

Informed consent was waived by the Fifth Medical Center of the PLA General Hospital. Our manuscript does not contain individual person's data. Therefore, consent to publish does not apply.

Data availability

The datasets generated and analyzed in this study are not available for public access due to data-sharing agreements with the participating hospitals.

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Author Contributions Statement

Q.C. and Y.L. conceptualized and designed the study, as well as drafted the main manuscript text. Z.W., L.L. and R.W. collected the tongue image data and curated the dataset. F.X. developed and implemented the machine learning models. X.C. contributed to data visualization and statistical analysis. W.Y. and R.W. supervised the overall study and provided critical revisions to the manuscript. All authors reviewed and approved the final manuscript.

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Table 1 Study sample and extracted feature characteristics

Variables	Control (N=30)	COVID-19 (N=58)	Adenovirus (N=84)	p value
Gender: men	13 (43.3%)	36 (62.1%)	83 (98.8%)	< 0.001
Age	27.20 (7.95)	47.62 (15.79)	23.65 (9.61)	< 0.001
Tongue coating				
Red	119.02 (16.53)	109.75 (22.60)	149.23 (20.42)	< 0.001
Green	93.33 (13.79)	77.65 (21.16)	110.83 (20.69)	< 0.001
Blue	97.12 (19.69)	79.20 (22.04)	114.17 (25.36)	< 0.001
Toothmarks				0.049
0	20 (66.7%)	20 (34.5%)	33 (39.3%)	
1	6 (20.0%)	17 (29.3%)	24 (28.6%)	
2	4 (13.3%)	21 (36.2%)	27 (32.1%)	
Crack Ratio	0.45 (1.01)	1.44 (2.40)	1.15 (1.98)	0.092
Moisture	0.13 (0.06)	0.14 (0.04)	0.07 (0.05)	< 0.001
Roughness	3.16 (0.21)	3.12 (0.19)	3.31 (0.21)	< 0.001
Texture Direction	40.65 (19.10)	29.91 (17.73)	34.83 (19.05)	0.036
Texture Contrast	17.09 (9.41)	12.49 (5.81)	24.60 (9.94)	< 0.001

Figure 1 Study process

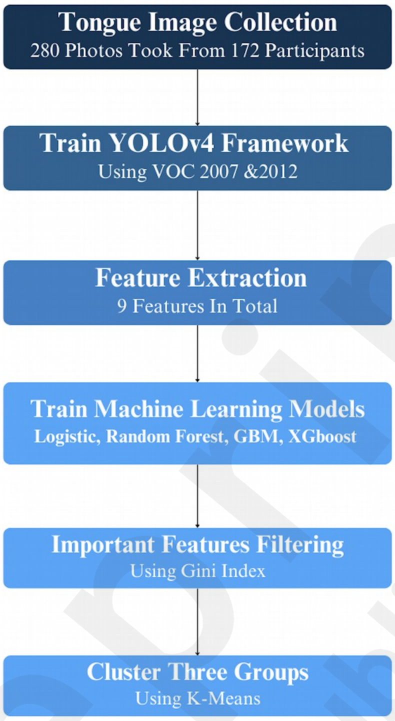


Figure 2 Extracted tongue image feature density plot.

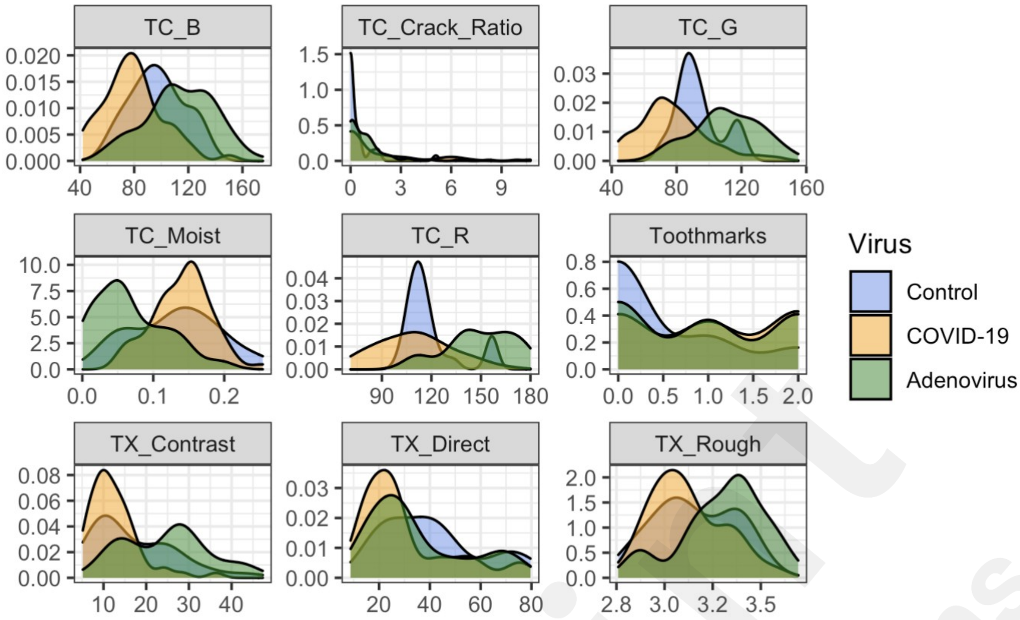


Figure 3 Mean SHAP value over the random forest, GMB, Xgboost. A longer bar indicates the variable is of higher importance in model performance.

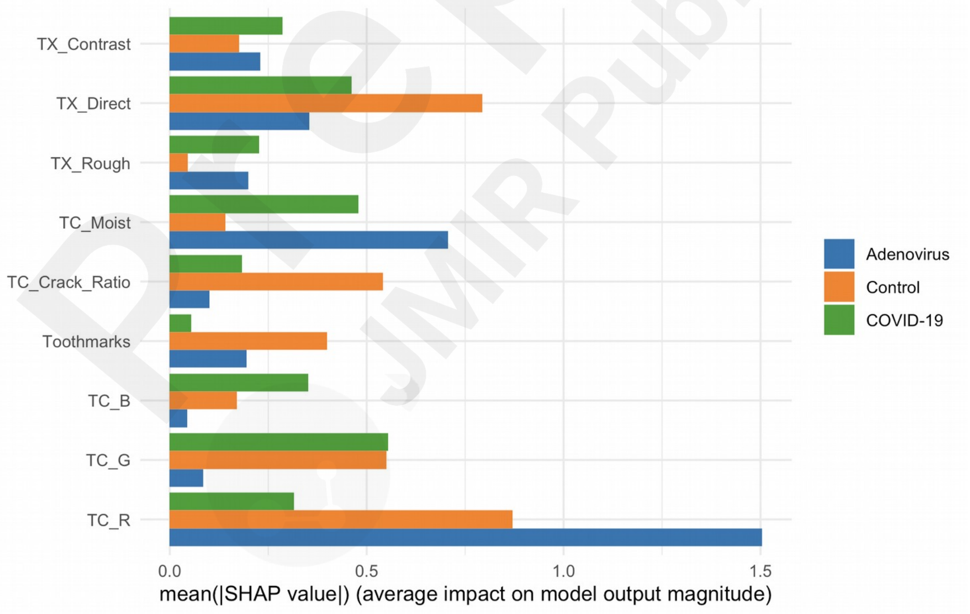


Figure 4 In the graphs, each SHAP value is represented by a point, with blue points indicating lower covariate values and red points representing higher covariate values.

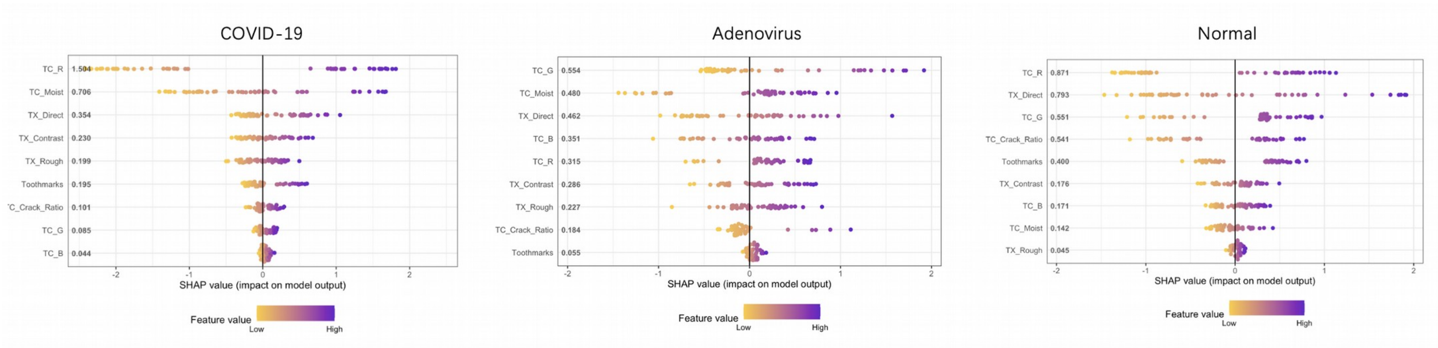
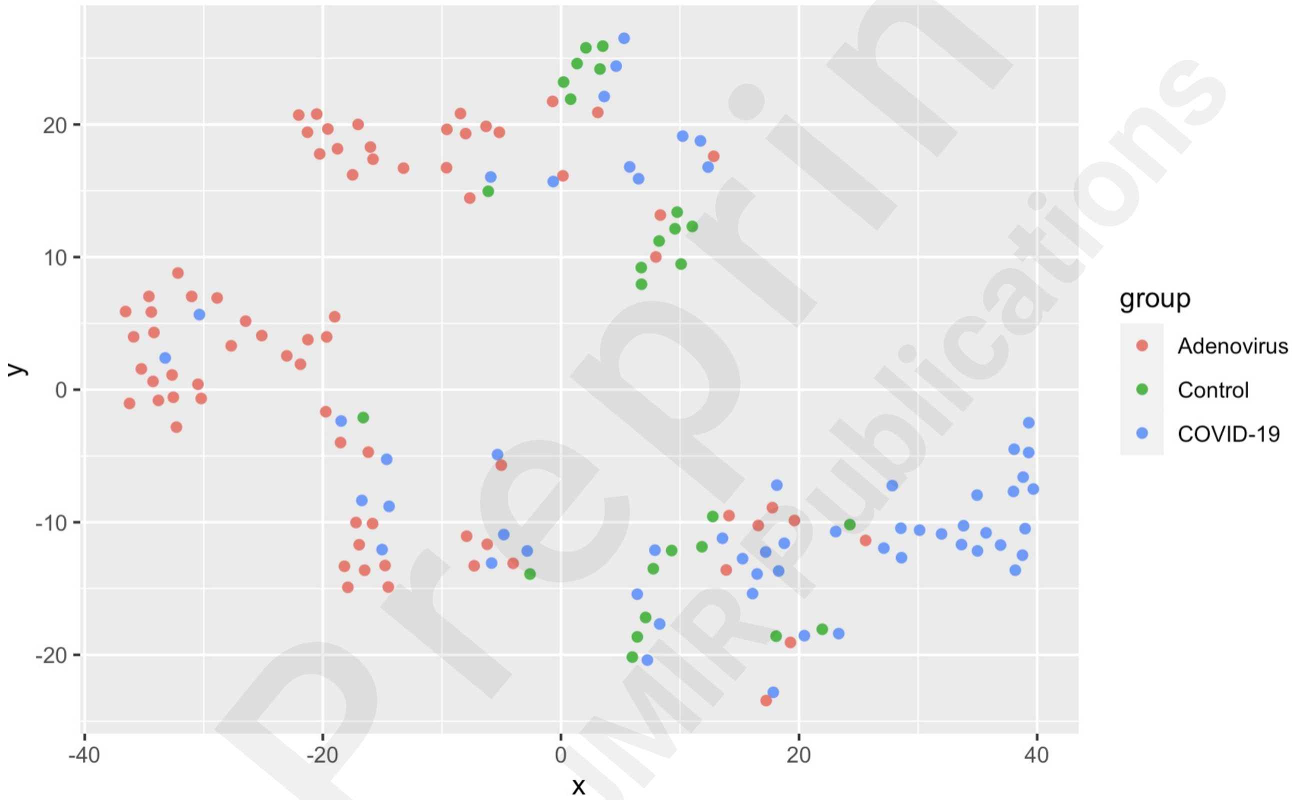


Figure 5 t-SNE plot: Adenovirus is marked in red, Control is in green, and COVID-19 is in blue.



Supplementary Files