Preplanned Studies

Developing Machine Learning Models Based on Clinical Manifestations to Predict Influenza — Chongqing Municipality, China, 2022–2023

Qianqian Zeng[1,&]; Hongyu Zhou[2,&]; Jiang Long[3]; Yi Jian[4]; Li Feng[5]; Liangbo Hu[6]; Hongyu Zhou[6]; Weimin Zhu[1]; Zhe Yuan[1]; Yajuan Chen[1]; Guangzhao Yi[1,#]

Summary

What is already known about this topic?

Current evidence regarding which clinical manifestations best predict influenza requires refinement, particularly considering regional variations in disease presentation and their importance for early diagnosis and surveillance.

What is added by this report?

The optimal machine learning model identified key influenza predictors, including epidemiological characteristics, critical symptoms and signs, and age. Based on this model, we introduced a new influenza-like illness (ILI) definition characterized by fever (≥ 37.9 °C) with either cough or rhinorrhea.

What are the implications for public health practice?

These findings provide evidence-based clinical manifestations for influenza prediction and offer an optimized definition of ILI for improved surveillance and early detection.

ABSTRACT

Introduction: Clinical manifestations are essential for early diagnosis of influenza-like illness (ILI). Machine learning models for influenza prediction were developed and a new ILI definition was introduced.

Methods: A retrospective cohort study was conducted at three hospitals in southwest China during June 2022 and May 2023. Artificial intelligence was used to extract variables from medical records and XGBOOST algorithm was used to develop prediction models for the total population and three age subgroups. A new ILI definition was introduced based on the optimal model and its performance was compared with WHO, China CDC, and USA CDC definitions.

Results: Totally 200,135 patients were included. 4,249 (36.2%) were confirmed influenza. The predictors of the optimal model included epidemiological characteristics, important symptoms and signs, and age for the total population [Area under curve (AUC) 0.734 (0.710–0.750), accuracy 0.689 (0.669–0.772)]. The new ILI definition was fever (≥ 37.9 °C) with cough or rhinorrhea, and its AUC, sensitivity, and specificity for diagnosing influenza were 0.618 (0.598–0.639), 0.665 and 0.572, outperformed the WHO, China CDC, and USA CDC definitions (P<0.05).

Conclusions: Fever, cough, and rhinorrhea maybe the most important indicators for influenza surveillance.

Influenza poses a significant public health threat. Early identification of influenza based on clinical manifestations is crucial for optimal treatment outcomes and prognosis (*1*). Influenza surveillance serves as a critical component for outbreak early warning systems and timely implementation of preventive and control measures (*2*). The World Health Organization (WHO) established a global symptom surveillance network for influenza in 1952, known as influenza-like illness (ILI) surveillance (*3*). However, limited research has evaluated the performance of ILI definition in influenza surveillance using large-scale data from Chinese populations. To address this gap, a retrospective cohort study was conducted at three tertiary comprehensive and influenza sentinel hospitals in Chongqing Municipality, China, between June 2022 and May 2023 (Supplementary Material, available at https://weekly.chinacdc.cn/). Our findings demonstrate that body temperature, cough, and rhinorrhea may be the most important clinical indicators for influenza diagnosis and ILI surveillance.

The study cohort comprised all patients who visited the emergency departments or fever clinics of the three participating hospitals during the study period. Exclusion criteria included: 1) patients who returned to either department for respiratory illness within one month, and 2) patients lacking diagnosis, chief complaint, or present illness history documentation. Laboratory confirmation of influenza infection followed established diagnostic criteria (*4*). A total of 27 symptom and sign variables were extracted (Supplementary Table S1, available at https://weekly.chinacdc.cn/) from the electronic medical record (EMR) information systems of the outpatient and emergency departments. CongRong (Supplementary Material), an artificial intelligence (AI) assistant and pre-trained large language model, was utilized to extract symptom variables for database construction.

The model development and validation dataset comprised cases with confirmed influenza laboratory testing results. Important variables were identified using the boruta algorithm, and machine learning models were developed for three age subgroups (0–14 years, 15–64 years, and ≥65 years) and the total population using eXtreme Gradient Boosting (XGBOOST) algorithm (*5*). For each age group, four models based on different combinations of epidemiological and other variables were constructed , following the process outlined in Supplementary Figure S1 (available at https://weekly.chinacdc.cn/). The resulting 16 candidate models were evaluated using the testing dataset (Table 1). The model with the highest area under curve (AUC) of the receiver operating characteristic (ROC) curve was designated as optimal. To interpret the machine learning models, SHapley Additive exPlanations (SHAP) values were employed to quantify the direction and magnitude (mean SHAP value) of important variables in the optimal model (*5*).

TABLE 1. Performance of machine learning-based prediction models for influenza in the testing dataset.

Dataset	Models	Accuracy (95% *CI*)	AUC (95% *CI*)	Threshold†	Sensitivity	Specificity
Total population						
	Model_1	0.689 (0.669, 0.772)	0.734 (0.710, 0.750)	0.500	0.541	0.769
	Model_2	0.685 (0.666, 0.703)	0.728 (0.707, 0.749)	0.486	0.525	0.771
	Model_3	0.679 (0.660, 0.698)	0.723 (0.703, 0.744)	0.496	0.535	0.758
	Model_4	0.651 (0.638, 0.670)	0.664 (0.642, 0.687)*	0.483	0.460	0.754
0–14 years age group						
	Model_1	0.607 (0.550, 0.662)	0.680 (0.621, 0.740)	0.500	0.708	0.543
	Model_2	0.604 (0.547, 0.659)	0.680 (0.621, 0.739)	0.499	0.692	0.548
	Model_3	0.604 (0.547, 0.659)	0.654 (0.593, 0.715)	0.469	0.717	0.532
	Model_4	0.588 (0.530, 0.643)	0.631 (0.568, 0.693)*	0.494	0.583	0.590
15–64 years age group						
	Model_1	0.701 (0.680, 0.722)	0.747 (0.724, 0.769)	0.516	0.475	0.826
	Model_2	0.693 (0.672, 0.714)	0.748 (0.726, 0.770)	0.510	0.470	0.816
	Model_3	0.687 (0.666, 0.708)	0.731 (0.708, 0.753)*	0.484	0.502	0.790
	Model_4	0.650 (0.628, 0.671)	0.679 (0.654, 0.704)*	0.463	0.426	0.773
≥65 years age group						
	Model_1	0.711 (0.629, 0.784)	0.791 (0.719, 0.864)*	0.531	0.656	0.756
	Model_2	0.704 (0.622, 0.778)	0.750 (0.669, 0.830)*	0.502	0.641	0.756
	Model_3	0.578 (0.492, 0.660)	0.719 (0.635, 0.803)*	0.570	0.422	0.705
	Model_4	0.542 (0.457, 0.626)	0.600 (0.507, 0.693)*	0.531	0.484	0.590

Note: Model_1 included two epidemiological characteristics and other important variables.
Model_2 included visiting during a specific week of epidemic season and other important variables.
Model_3 included visiting during the epidemic season and other important variables.
Model_4 included important variables except epidemiological characteristics.
Abbreviation: *CI*=confidence interval.
* The difference between this model and others was statistically significant in the same group ($P<0.05$).
† The maximum Youden index was used to determine the optimal threshold for influenza prediction.

Based on the most significant symptoms and signs positively associated with influenza (indicated by higher importance value with a positive SHAP value) in the optimal model for the total population, a new ILI definition was developed. The diagnostic performance of the new definition alongside existing WHO, China CDC, and USA CDC ILI definitions was evaluated using the testing dataset. Additionally, cross-correlation analysis of time series between ILI cases under these definitions and confirmed influenza cases was conducted using the cross-correlation function from the Stats package.

All statistical analyses were performed using R software version 4.3.2 (R foundation, Vienna, Austria). Continuous variables were compared using t-tests or Kruskal-Wallis tests as appropriate. Categorical variables were analyzed using chi-squared tests or Fisher's exact tests. The pROC package was employed to determine the optimal body temperature cut-off value (maximum Youden index) and compare model AUC values using the DeLong method.

After data extraction and processing, we established a comprehensive database comprising 200,135 cases. The CongRong model demonstrated exceptional performance in symptom variable extraction, achieving an accuracy of 0.997, sensitivity of 0.991, and specificity of 0.998 in the testing dataset (Supplementary Table S2, available at https://weekly.chinacdc.cn/). From the influenza sub-dataset used for developing and validating infection prediction models (n=11,753; Supplementary Figure S1), we identified 4,249 (36.2%) influenza-positive cases in the total population, with positivity rates of 41.6%, 34.9%, and 41.5% in the 0–14 years, 15–64 years, and ≥65 years age groups, respectively (Supplementary Table S1).

The Boruta algorithm identified distinct sets of important candidate variables for modeling: 18 for the total population, and 7, 16, and 8 variables for the 0–14 years, 15–64 years, and ≥65 years age groups, respectively (Figure 1). The predictive performance metrics of all 16 machine learning models are presented in Table 1. For the total population, model_1 emerged as the optimal prediction model, achieving an accuracy of 0.689 (0.669, 0.772) and an AUC of 0.734 (0.710, 0.750). The most influential predictors in this model included body temperature, age, visiting during the epidemic season, visiting during a certain week of epidemic season, cough, and rhinorrhea, with all factors except age showing strong positive associations with influenza (Figure 1). In the 0–14 years age group, model_1 performed optimally, with body temperature, visiting during a certain week of epidemic season, rhinorrhea, visiting during epidemic season, and cough emerge as the most significant predictors, all demonstrating strong positive correlations with influenza (Figure 1). For the 15–64 years age group, model_2 proved most effective, with body temperature, visiting during a certain week of epidemic season, age, cough, and rhinorrhea identified as key predictor, all except age showing strong positive associations with influenza (Figure 1). In the ≥65 years age group, model_1 demonstrated optimal performance, with visiting during epidemic season, visiting during a certain week of epidemic season, body

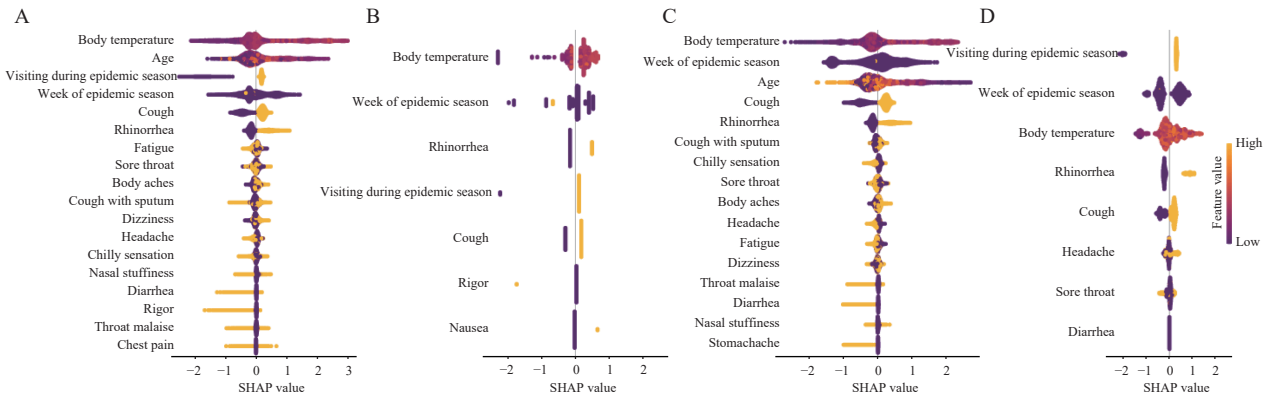

FIGURE 1. SHAP summary plot illustrating variable importance and directional relationships obtained from the optimal model for influenza prediction across the (A) total population, (B) 0–14 years group, (C) 15–64 years group, and (D) ≥65 years group.

Note: Variables with higher importance values (yellow) and positive SHAP values (right side) demonstrate positive associations, while those with higher importance values (yellow) and negative SHAP values (left side) indicate negative associations.

Abbreviation: SHAP=SHapley Additive exPlanations.

temperature, rhinorrhea, and cough emerging as the most important predictors, all showing strong positive correlations with influenza (Figure 1). The complete performance metrics for both testing and training datasets are detailed in Table 1 and Supplementary Table S3 (available at https://weekly.chinacdc.cn/), respectively.

Based on the most important symptoms and signs positively associated with influenza in the optimal model for the total population — body temperature, cough, and rhinorrhea — and using the identified cut-off value for body temperature of 37.9 °C, a new ILI definition was established: fever (≥37.9 °C) with either cough or rhinorrhea. This new definition significantly outperformed (P<0.001) the existing WHO, China CDC, and USA CDC definitions in diagnosing influenza, achieving an AUC of 0.618 (0.598, 0.639), accuracy of 0.605 (0.585, 0.625), sensitivity of 0.665, and specificity of 0.572 (Table 2). Time series analyses of ILI cases under the new, WHO, China CDC, and USA CDC definitions alongside confirmed influenza cases during the study period, revealed that the daily trend cross-correlation coefficients between ILI cases under the new, WHO, China CDC, and USA CDC definitions and influenza cases were 0.701 (P<0.05), 0.685 (P<0.05), 0.648 (P<0.05), and 0.653 (P<0.05) respectively, with peak correlations occurring simultaneously.

DISCUSSION

This study developed machine learning models for influenza prediction using data from three large sentinel hospitals in Chongqing, China, and identified an optimal model with the highest AUC. Based on the model's top three predictive symptoms (fever, cough, and rhinorrhea), a new ILI definition was proposed that demonstrated superior performance compared to existing WHO, China CDC, and USA CDC definitions. Our findings suggest that body temperature, cough, and rhinorrhea serve as crucial indicators for both early clinical diagnosis of influenza and ILI surveillance.

Our study employed XGBOOST, an advanced machine learning algorithm that has demonstrated superior performance in clinical and epidemiological studies compared to other approaches such as Ranger, Random Forest, Cforest, SVM, Artificial Neural Network, and Deep Learning (*5*–*6*). The SHAP value analysis of our optimal models revealed consistent important variables across all age subgroups and the total population, including epidemic season timing, body temperature, cough, and rhinorrhea, aligning with previous research findings (*5*,*7*–*9*). These results underscore two critical points: first, the importance of timely reporting of influenza epidemic trends by national and regional CDC authorities based on surveillance data; and second, the primary clinical indicators — body temperature, cough, and rhinorrhea — that clinicians should prioritize when diagnosing influenza during epidemic seasons.

While ILI definitions vary across countries and WHO revised its definition in 2011 (*9*), our study aimed to establish a more accurate definition. Based on our optimal prediction model's identification of body temperature, cough, and rhinorrhea as the most significant positive predictors of influenza, with a body temperature threshold of 37.9 °C, we proposed defining ILI as fever (≥37.9 °C) with either cough or rhinorrhea. This new definition not only outperformed WHO, China CDC, and USA CDC definitions in our study but also showed the highest daily trend cross-correlation coefficient with confirmed influenza cases. Our temperature threshold of 37.9 °C closely approximates the 38.0 °C specified by WHO and China CDC, and the 37.8 °C by USA CDC. While our definition shares the core elements of fever and cough with existing definitions, it notably substitutes rhinorrhea for sore throat as an alternative criterion. This modification is supported by previous studies identifying rhinorrhea as a common influenza symptom occurring alongside cough (*10*–*11*), providing evidence-based justification for optimizing

TABLE 2. Performance of ILIs with the new, WHO, China CDC and USA CDC definitions in predicting influenza.

ILI	AUC (95% *CI*)	Accuracy (95% *CI*)	Sensitivity	Specificity
New ILI	0.618 (0.598, 0.639)*	0.605 (0.585, 0.625)	0.665	0.572
WHO ILI	0.599 (0.578, 0.620)	0.602 (0.583, 0.622)	0.587	0.611
China CDC ILI	0.592 (0.572, 0.613)	0.572 (0.551, 0.591)	0.661	0.522
USA CDC ILI	0.592 (0.571, 0.612)	0.560 (0.540, 0.580)	0.701	0.482

Abbreviation: ILI=influenza-like illness; *CI*=confidence interval; WHO=World Health Organization; AUC=area under curve.
* The difference in AUC between the new ILI definition and other definitions was statistically significant (P<0.001).

the ILI definition.

Our study has two primary limitations. First, its retrospective design may introduce inherent biases. Second, despite including multiple centers, the data remains geographically confined to one region. Future research should incorporate data from diverse regions and countries to validate these findings.

Conflicts of interest: No conflicts of interest.

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[#] Corresponding author: Guangzhao Yi, 202774@hospital.cqmu.edu.cn.

[1] The First Affiliated Hospital of Chongqing Medical University, Chongqing, China; [2] Chongqing Medical University, Chongqing, China; [3] Chongqing Center for Disease Control and Prevention, Chongqing, China; [4] Cloudwalk Technology, Chongqing, China; [5] People's Hospital of Chongqing Banan District, Chongqing, China; [6] The Affiliated Yongchuan Hospital of Chongqing Medical University, Chongqing, China.
[&] Joint first authors.

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SUPPLEMENTARY MATERIALS

Introduction to Participating Hospitals in this Study

The three hospitals are sentinel hospitals for influenza surveillance, located in the central, southern and western Chongqing, with 3,200, 1,500 and 1,200 beds, respectively; during the study, the number of visits in the emergency department was 27,262, 83,828 and 64,075, and the number of visits in the fever clinic was 16,303, 17,500 and 11,293, respectively.

Introduction of AI Assistant CongRong and Symptom Variables Extraction Process

As an AI assistant, CongRong is a pre-trained large language model with balanced capabilities in both Chinese and English. It is a transformer-based autoregressive model with 75 billion parameters, with a basic architecture similar to that of a new generation of open source large model, LLama 2. Regarding pre-training data, approximately 55% of data is consistent with that of LLama 2, primarily in English, comprising wiki, arXiv papers, code, e-books, and web content. The remaining 45% is primarily in Chinese, including Chinese encyclopedias, e-books, papers, and web content. CongRong's training ultimately consumed 1.5TB of tokenized pre-training data.

Data for the variables except body temperature were extracted from chief complaint, history of present illness and physical examination within the raw data by CongRong, an artificial intelligence (AI) assistant and pre-trained large language model, to obtain a database for analysis. In order to enable CongRong to better understand the unique expressions and professional terminology specific to this extraction task, we selected a sample dataset with 1,167 cases from the raw data to train and validate CongRong model: first, three clinicians read the medical records of the sample cases and recorded whether a patient exhibited any of the 26 symptoms (annotated positive 1 and negative 0); then the sample dataset was divided into a training dataset (n=854) and a testing dataset (n=313), and the training dataset was used to fine-tune the CongRong pre-trained model; finally, the CongRong pre-trained model was validated in the testing dataset.

The Definitions Involved in this Study

Epidemic season for influenza The start of an epidemic season was defined as the first week during which the infection (influenza) positive rate was higher than the average infection positive rate for the study period (a surveillance year) and remained above that level for at least four consecutive weeks; the end of an epidemic season was defined as the first week during which the infection (influenza) positive rate was lower than the average infection positive rate for the study period and remained below that level for at least four consecutive weeks (*1*,*2*).

We collected two epidemiological characteristics variables included visiting during respective epidemic season of influenza and visiting during a certain week of epidemic season. According to the definition of epidemic season, we determined that the study period included two influenza seasons with a total of 12 weeks.

Influenza-like illness defined by WHO An acute respiratory illness with a measured temperature of ≥38°C and cough, with onset within the past 10 days (*3*).

Influenza-like illness defined by China CDC Fever (≥38.0°C) with cough or sore throat (*4*).

Influenza-like illness defined by USA CDC Fever (≥37.8°C) and a cough and/or a sore throat (*5*).

SUPPLEMENTARY TABLE S1. Characteristics of patients undergoing influenza laboratory testing.

Variables	Total (*N*=11,753)	Total		0–14 years group		15–64 years group		≥65 years group	
		Influenza negative (*N*=7,504)	Influenza positive (*N*=4,249)	Influenza negative (*N*=901)	Influenza positive (*N*=641)	Influenza negative (*N*=6,187)	Influenza positive (*N*=3,313)	Influenza negative (*N*=416)	Influenza positive (*N*=295)
Age, years, median (IQR)	25 (17–36)	25 (17–35)	26 (17–36)	8 (4–14)	6 (3–14)*	26 (19–35)	27 (20–36)*	73 (68–78)	73 (69–80)
Female	6,079 (51.7)	3,988 (53.1)	2,091 (49.2)*	430 (47.7)	280 (43.7)	3,347 (54.1)	1,676 (50.6)*	211 (50.7)	135 (45.8)
Visiting during epidemic season, *n* (%)	10,006 (85.1)	5,906 (78.7)	4,100 (96.5)*	808 (89.7)	631 (98.4)*	4,818 (77.9)	3,181 (96.0)*	280 (67.3)	288 (97.6)*
Visiting during a certain week of epidemic season, *n* (%)									
The first influenza season									
1	96 (0.8)	59 (0.8)	37 (0.9)*	35 (3.9)	16 (2.5)*	23 (0.4)	17 (0.5)*	1 (0.2)	4 (1.4)*
2	935 (8.0)	395 (5.3)	540 (12.7)	68 (7.5)	91 (14.2)	280 (4.5)	380 (11.5)	47 (11.3)	69 (23.4)
3	1,209 (10.3)	509 (6.8)	700 (16.5)	111 (12.3)	158 (24.6)	350 (5.7)	454 (13.7)	48 (11.5)	88 (29.8)
4	862 (7.3)	451 (6.0)	411 (9.7)	139 (15.4)	141 (22.0)	270 (4.4)	237 (7.2)	42 (10.1)	33 (11.2)
5	335 (2.9)	229 (3.1)	106 (2.5)	71 (7.9)	32 (5.0)	143 (2.3)	63 (1.9)	15 (3.6)	11 (3.7)
The second influenza season									
1	336 (2.9)	220 (2.9)	116 (2.7)	22 (2.4)	20 (3.1)	194 (3.1)	94 (2.8)	4 (1.0)	2 (0.7)
2	1,121 (9.5)	728 (9.7)	393 (9.2)	77 (8.5)	56 (8.7)	640 (10.3)	332 (10.0)	11 (2.6)	5 (1.7)
3	1,521 (12.9)	933 (12.4)	588 (13.8)	117 (13.0)	61 (9.5)	795 (12.8)	511 (15.4)	21 (5.0)	16 (5.4)
4	1,298 (11.0)	787 (10.5)	511 (12.0)	76 (8.4)	39 (6.1)	684 (11.1)	446 (13.5)	27 (6.5)	26 (8.8)
5	1,086 (9.2)	742 (9.9)	344 (8.1)	59 (6.5)	9 (1.4)	658 (10.6)	322 (9.7)	25 (6.0)	13 (4.4)
6	787 (6.7)	546 (7.3)	241 (5.7)	21 (2.3)	8 (1.2)	497 (8.0)	222 (6.7)	28 (6.7)	11 (3.7)
7	420 (3.6)	307 (4.1)	113 (2.7)	12 (1.3)	0 (0)	284 (4.6)	103 (3.1)	11 (2.6)	10 (3.4)
Symptoms and signs, *n* (%)									
Body temperature, °C, mean±SD	38.3±0.9	38.2±1.0	38.5±0.8*	38.5±1.0	38.9±0.8*	38.2±1.0	38.5±0.8*	38.1±1.0	38.3±0.8*
Body aches	5,243 (44.6)	3,247 (43.3)	1,996 (47.0)*	144 (16.0)	89 (13.9)	2,960 (47.8)	1,796 (54.2)*	143 (34.4)	111 (37.6)
Fatigue	4,970 (42.3)	3,096 (41.3)	1,874 (44.1)*	145 (16.1)	102 (15.9)	2,774 (44.8)	1,634 (49.3)*	177 (42.5)	138 (46.8)
Chilly sensation	3,712 (31.6)	2351 (31.3)	1,361 (32.0)	118 (13.1)	75 (11.7)	2,104 (34.0)	1,197 (36.1)*	129 (31.0)	89 (30.2)
Rigor	308 (2.6)	227 (3.0)	81 (1.9)*	23 (2.6)	7 (1.1)	180 (2.9)	66 (2.0)*	24 (5.8)	8 (2.7)
Sleepiness	14 (0.1)	9 (0.1)	5 (0.1)*	0 (0)	0 (0)	5 (0.1)	3 (0.1)	4 (1.0)	2 (0.7)
Headache	4,037 (34.3)	2,474 (33.0)	1,563 (36.8)*	131 (14.5)	97 (15.1)	2,242 (36.2)	1,371 (41.4)*	101 (24.3)	95 (32.2)*
Dizziness	4,605 (39.2)	2,799 (37.3)	1,806 (42.5)*	191 (21.2)	139 (21.7)	2,478 (40.1)	1,547 (46.7)*	130 (31.3)	120 (40.7)*
Cough	7,236 (61.6)	4,055 (54.0)	3,181 (74.9)*	504 (55.9)	436 (68.0)*	3,320 (53.7)	2,525 (76.2)*	231 (55.5)	220 (74.6)*
Cough with sputum	3,967 (33.8)	2,218 (29.6)	1,749 (41.2)*	190 (21.1)	122 (19.0)	1,870 (30.2)	1,468 (44.3)*	158 (38.0)	159 (53.9)*
Sore throat	5,270 (44.8)	3,206 (42.7)	2,064 (48.6)*	200 (22.2)	138 (21.5)	2,921 (47.2)	1,829 (55.2)	85 (20.4)	97 (32.9)*
Throat malaise†	646 (5.5)	423 (5.6)	223 (5.2)*	12 (1.3)	10 (1.6)	393 (6.4)	198 (6.0)	18 (4.3)	15 (5.1)
Rhinorrhea	2,946 (25.1)	1,523 (20.3)	1,423 (33.5)*	176 (19.5)	198 (30.9)*	1,289 (20.8)	1,139 (34.4)*	58 (13.9)	86 (29.2)*

Continued

Variables	Total (*N*=11,753)	Total		0–14 years group		15–64 years group		≥65 years group	
		Influenza negative (*N*=7,504)	Influenza positive (*N*=4,249)	Influenza negative (*N*=901)	Influenza positive (*N*=641)	Influenza negative (*N*=6,187)	Influenza positive (*N*=3,313)	Influenza negative (*N*=416)	Influenza positive (*N*=295)
Nasal stuffiness	1149 (9.8)	702 (9.4)	447 (10.5)*	89 (9.9)	57 (8.9)	597 (9.6)	374 (11.3)*	16 (3.8)	16 (5.4)
Hemoptysis	7 (0.1)	5 (0.1)	2 (0.05)	0 (0)	0 (0)	3 (0.05)	1 (0.03)	2 (0.5)	1 (0.3)
Chest pain	231 (2.0)	135 (1.8)	96 (2.3)	6 (0.7)	1 (0.2)	118 (1.9)	83 (2.5)	11 (2.6)	12 (4.1)
Shortness of breath	195 (1.7)	121 (1.6)	74 (1.7)	3 (0.3)	1 (0.2)	94 (1.5)	48 (1.4)	24 (5.8)	25 (8.5)
Dyspnea	91 (0.8)	54 (0.7)	37 (0.9)	0 (0)	0 (0)	40 (0.6)	31 (0.9)	14 (3.4)	6 (2.0)
Palpitation	198 (1.7)	135 (1.8)	63 (1.5)	2 (0.2)	4 (0.6)	115 (1.9)	51 (1.5)	18 (4.3)	8 (2.7)
Diarrhea	397 (3.4)	304 (4.1)	93 (2.2)*	14 (1.6)	6 (0.9)	268 (4.3)	79 (2.4)*	22 (5.3)	8 (2.7)
Stomachache	265 (2.3)	195 (2.6)	70 (1.6)*	34 (3.8)	27 (4.2)	144 (2.3)	38 (1.1)*	17 (4.1)	5 (1.7)
Nausea	811 (6.9)	515 (6.9)	296 (7.0)	22 (2.4)	32 (5.0)*	457 (7.4)	238 (7.2)	36 (8.7)	26 (8.8)
Vomiting	585 (5.0)	389 (5.2)	196 (4.6)	56 (6.2)	42 (6.6)	297 (4.8)	126 (3.8)*	36 (8.7)	28 (9.5)
Conjunctivitis	3 (0.03)	3 (0.04)	0 (0)	0 (0)	0 (0)	3 (0.05)	0 (0)	0 (0)	0 (0)
Impaired sense of smell	4 (0.03)	4 (0.1)	0 (0)	0 (0)	0 (0)	2 (0.03)	0 (0)	2 (0.5)	0 (0)
Impaired taste	16 (0.1)	14 (0.2)	2 (0.05)	0 (0)	0 (0)	13 (0.2)	1 (0.03)	1 (0.2)	1 (0.3)
Rash	42 (0.4)	32 (0.4)	10 (0.2)	6 (0.7)	3 (0.5)	23 (0.4)	7 (0.2)	3 (0.7)	0 (0)

Abbreviation: IQR=interquartile range; SD=standard deviation.

* The difference between influenza-positive and -negative cases was statistically significant ($P<0.05$).

† Pharyngeal discomfort included feelings of dryness, itching, and other discomfort in the throat, excluding sore throat.

SUPPLEMENTARY TABLE S2. The performance of CongRong pre-trained model in this study.

Symptoms	Accuracy	Sensitivity	Specificity
Body aches	0.997	1.000	0.996
Fatigue	0.997	0.987	1.000
Chills	0.994	1.000	0.993
Rigor	1.000	1.000	1.000
Somnolence	1.000	−	1.000
Headache	0.994	0.985	0.996
Dizziness	1.000	1.000	1.000
Cough	0.994	0.991	0.995
Expectoration	1.000	1.000	1.000
Sore throat	1.000	1.000	1.000
Pharyngeal discomfort	0.997	1.000	0.997
Rhinorrhea	0.994	0.949	1.000
Nasal congestion	1.000	1.000	1.000
Hemoptysis	1.000	1.000	1.000
Chest pain	1.000	1.000	1.000
Shortness of breath	0.994	1.000	0.993
Dyspnea	1.000	1.000	1.008
Palpitation	1.000	1.000	1.000
Diarrhea	0.997	1.000	0.997
Abdominal pain	0.994	1.000	0.993
Nausea	0.997	1.000	0.997
Vomiting	0.994	0.931	1.000
Conjunctivitis	1.000	1.000	1.000
Impaired sense of smell	1.000	1.000	1.000
Impaired taste	0.997	1.000	0.997
Erythra	1.000	1.000	1.000
Total	0.997	0.991	0.998

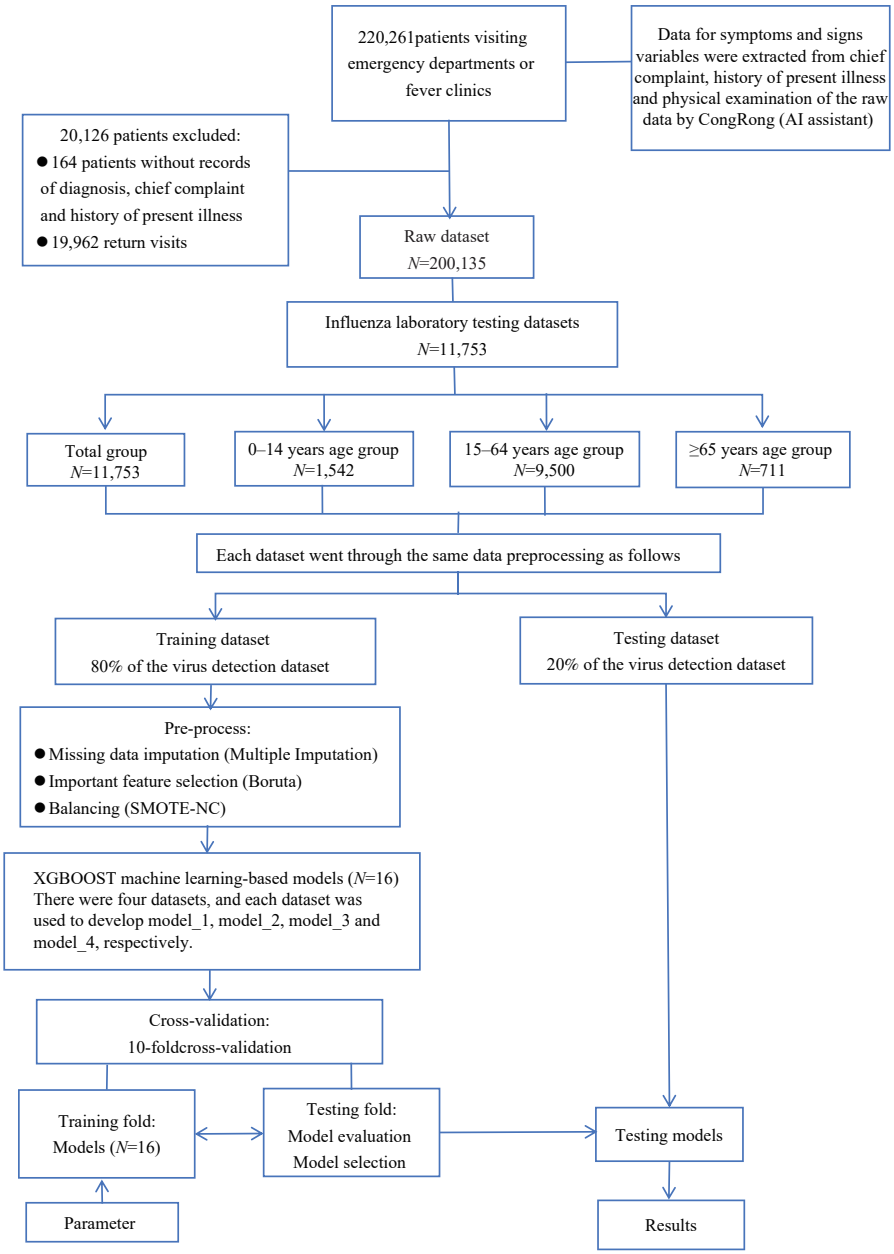
Note: −: There were no patients with positive somnolence in the model training set.

SUPPLEMENTARY TABLE S3. Performance of machine learning-based prediction models for influenza in the training dataset.

Dataset	Models	Accuracy (95% *CI*)	AUC (95% *CI*)	Threshold*	Sensitivity	Specificity
Total population						
	Model_1	0.841 (0.835, 0.848)	0.926 (0.922, 0.931)	0.500	0.833	0.849
	Model_2	0.856 (0.849, 0.862)	0.934 (0.930, 0.938)	0.486	0.845	0.867
	Model_3	0.795 (0.787, 0.802)	0.890 (0.884, 0.895)	0.496	0.778	0.812
	Model_4	0.826 (0.820, 0.833)	0.910 (0.905, 0.915)	0.483	0.798	0.855
0–14 years age group						
	Model_1	0.703 (0.678, 0.726)	0.762 (0.738, 0.787)	0.500	0.794	0.612
	Model_2	0.700 (0.675, 0.724)	0.762 (0.738, 0.787)	0.499	0.787	0.613
	Model_3	0.692 (0.668, 0.716)	0.780 (0.757, 0.803)	0.469	0.798	0.586
	Model_4	0.671 (0.646, 0.696)	0.742 (0.717, 0.767)	0.494	0.698	0.644
15–64 years age group						
	Model_1	0.838 (0.831, 0.845)	0.923 (0.918, 0.928)	0.516	0.793	0.883
	Model_2	0.828 (0.820, 0.835)	0.911 (0.905, 0.916)	0.510	0.786	0.869
	Model_3	0.807 (0.799, 0.815)	0.897 (0.891, 0.903)	0.484	0.790	0.823
	Model_4	0.813 (0.805, 0.820)	0.898 (0.892, 0.904)	0.463	0.786	0.839
≥65 years age group						
	Model_1	0.778 (0.745, 0.809)	0.848 (0.820, 0.877)	0.531	0.793	0.763
	Model_2	0.802 (0.770, 0.831)	0.871 (0.844, 0.897)	0.502	0.802	0.802
	Model_3	0.836 (0.806, 0.863)	0.924 (0.906, 0.942)	0.570	0.817	0.855
	Model_4	0.772 (0.739, 0.803)	0.860 (0.833, 0.887)	0.470	0.784	0.760

Abbreviation: *CI*=confidence interval.

* The maximum Youden index was used to determine the optimal threshold for influenza prediction.



SUPPLEMENTARY FIGURE S1. Flow chart for patient enrollment, dataset establishment, and statistical analysis of prediction models for influenza in this study.

Note: Data preprocessing: the sub-dataset for developing and validating the influenza prediction models consisted of data from cases that underwent influenza laboratory testing. First, the sub-dataset was randomly partitioned into an 80% training dataset and a 20% testing dataset, stratified by infection status. Second, missing values in the training dataset were imputed using multiple imputation via the Mice package. Third, the training dataset was used to extract important candidate variables and remove unimportant variables using the Boruta algorithm. Finally, the data were balanced using the synthetic minority oversampling technique for nominal and continuous algorithm via the Themis package. Machine learning-based modeling: after data preprocessing, we developed four candidate models on each training dataset of the total population and three age subgroups (0–14 years, 15–64 years, and ≥65 years) to predict influenza. The independent variables included in the four models were combinations of two epidemiological characteristics variables and other important variables extracted by the Boruta algorithm. We performed ten-fold cross-validations to tune the parameters using the Caret package and developed machine learning-based models on each training dataset using XGBOOST algorithm. Model_1 included two epidemiological characteristics and other important variables. Model_2 included visiting during a certain week of epidemic season and other important variables. Model_3 included visiting during epidemic season and other important variables. Model_4 included important variables except epidemiological characteristics.

Abbreviation: AI=artificial intelligence; SMOTE-NC=Synthetic Minority Oversampling Technique for Nominal and Continuous.

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