

Comparative Analysis of Clinical, Laboratory, and Chest CT Features Between COVID-19 and H1N1 Pneumonia: A Large-Scale Retrospective Study with Machine Learning Integration

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Abstract

Background

Concurrent COVID-19 and influenza A(H1N1) epidemics since late 2019 have complicated early differentiation because of overlapping clinical and imaging features. Viral evolution, shifting population immunity, and emerging variants may have altered imaging phenotypes, underscoring the need for contemporary data. We aimed to compare clinical, laboratory, and CT characteristics between COVID-19 and H1N1 pneumonia, identify independent predictors for each diagnosis, and explore machine learning (ML) models for differentiation.

Methods

This retrospective study included 612 patients (442 H1N1, 170 COVID-19) diagnosed between January 2023 and December 2025. Clinical, laboratory, and chest CT features were comprehensively analyzed. Between-group differences were assessed by χ^2 test or Mann-Whitney U test. Multivariable logistic regression was performed to identify the independent predictive factors. Least absolute shrinkage and selection operator regression was used for feature selection. Five ML algorithms were trained (70% of cohort) and tested (30%). Model performance was assessed using area under the receiver operating characteristic curve (AUC).

Results

Parenchymal involvement was more frequent in COVID-19 than in H1N1 pneumonia (91.2% vs 74.7%; $P < 0.001$), with higher rates of ground-glass opacities, interlobular septal thickening, and crazy-paving pattern. Airway involvement was more frequent in H1N1 pneumonia (48.2% vs 34.7%; $P = 0.003$), including higher rates of bronchial wall thickening, centrilobular nodules, and tree-in-bud nodules. On multivariable analysis, upper lobe involvement (OR = 2.19; 95% CI: 1.04, 4.65) and parenchymal involvement (OR = 3.44; 95% CI: 1.67, 7.10) were independent predictors of COVID-19. Tree-in-bud nodules (OR = 0.30; 95% CI: 0.12, 0.77), lymphadenopathy (OR = 0.29; 95% CI: 0.06, 0.81), and disorders of consciousness (OR = 0.20; 95% CI: 0.07, 0.61) were independently associated with H1N1 pneumonia. Among five ML models, the random forest model achieved the highest performance, with an AUC of 0.71 (95% CI: 0.58, 0.85) for differentiation.

Conclusion

Upper lobe involvement and parenchymal involvement are independent predictors of COVID-19, whereas tree-in-bud nodules, lymphadenopathy, and disorders of consciousness are independently associated with H1N1 pneumonia. These imaging and clinical features may facilitate early differential diagnosis.

Introduction

Since late 2019, the emergence and continued circulation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), along with seasonal H1N1 influenza, have produced overlapping epidemics of viral pneumonia during Northern Hemisphere winters[1]. Clinically, both coronavirus disease 2019 (COVID-19) and H1N1 pneumonia present with nonspecific symptoms—including fever, cough, myalgia, and dyspnea—and share common laboratory findings, such as lymphopenia and elevated inflammatory markers[2, 3], posing substantial diagnostic challenges. However, the available antivirals, therapeutic windows, and eligibility criteria differ substantially between the two infections.

Reverse transcription-polymerase chain reaction (RT-PCR) remains the diagnostic gold standard for both H1N1 and COVID-19. Nevertheless, false-negative rates ranging from 20% to 30% have been documented during early infection, attributable to suboptimal sampling techniques, low viral load, or inappropriate timing of specimen collection[4, 5]. Furthermore, delays in turnaround time—often 24 to 48 hours in routine clinical settings—substantially limit the utility of RT-PCR in time-sensitive clinical decisions, particularly in emergency department and intensive care unit settings where rapid therapeutic intervention is critical.

Chest computed tomography (CT) plays a pivotal role in the evaluation of patients with suspected viral pneumonia. Prior studies[6, 7] have suggested that H1N1 and COVID-19 pneumonia often demonstrate overlapping imaging findings, including bilateral ground-glass opacities (GGOs) and consolidation. Certain distinguishing features have been proposed: COVID-19 pneumonia frequently demonstrates peripheral distribution with lower lobe predominance[8, 9], whereas H1N1 pneumonia more commonly shows peribronchovascular distribution[10, 11]. However, the majority of these comparative studies were conducted during the early pandemic period (2020) and involved small cohorts, raising concerns about selection bias and limited generalizability to contemporary patient populations. Moreover, viral evolution, changing population immunity through vaccination and prior infection, and the emergence of novel variants have potentially altered the imaging phenotype of these infections, highlighting the urgent need for contemporary data.

Machine learning (ML) models have demonstrated considerable promise in medical imaging analysis, with applications spanning disease detection, severity stratification, and outcome prediction[12, 13]. Several studies have proposed ML models for COVID-19 diagnosis using CT[13–15]. However, the potential of integrating clinical, laboratory, and CT features using ML techniques to differentiate COVID-19 from H1N1 pneumonia remains unexplored.

In the current study, we conducted a large-scale retrospective analysis of 612 patients with laboratory-confirmed H1N1 or COVID-19 pneumonia between January 2023 and December 2025. Our objectives were: (1) to systematically compare clinical, laboratory, and chest CT features between the two viral pneumonias; (2) to identify independent clinical and imaging predictors of each diagnosis using multivariable logistic regression; and (3) to explore and compare multiple ML algorithms for differentiating COVID-19 from H1N1 pneumonia.

Materials and Methods

Participants

This retrospective study was approved by the Institutional Review Board of our institution, with a waiver of informed consent due to the anonymized data. All procedures were performed in accordance with the Declaration of Helsinki and relevant ethical guidelines.

We enrolled patients with RT-PCR–confirmed H1N1 or SARS-CoV-2 infection at our institution between January 2023 and December 2025. All nasopharyngeal swab specimens were tested per national guidelines. Of 4,996 initial patients (3,648 H1N1, 1,348 COVID-19), we excluded those with (a) absence of chest CT examination within 7 days of symptom onset; (b) normal chest CT findings; c) incomplete clinical or laboratory data; or (d) co-infection with other respiratory pathogens. The final cohort comprised 442 patients with H1N1 pneumonia and 170 patients with COVID-19, none of whom received antiviral therapy prior to CT examination. The patient flowchart is presented in Fig. 1.

Clinical Data Acquisition

Demographic characteristics, clinical symptoms, and laboratory findings were extracted from electronic medical records. Collected variables included age, sex, symptoms, comorbidities, and the following laboratory parameters: leukocyte count, neutrophil count, neutrophil percentage, lymphocyte count, lymphocyte percentage, C-reactive protein (CRP), interleukin-6 (IL-6), and erythrocyte sedimentation rate (ESR).

CT Image Acquisition

Chest CT was performed on a dual-source scanner (SOMATOM Definition Flash; Siemens Healthineers) with the patient in the supine position during a single inspiratory breath hold. The acquisition parameters were as follows: tube voltage, 100–120 kV; tube current, automatic modulation; pitch, 1.2; gantry rotation time, 0.28 seconds; slice thickness, 0.6 mm; detector configuration, $2 \times 64 \times 0.6$ mm; and image matrix, 512×512 . Images were reconstructed in transverse, sagittal, and coronal planes with a slice thickness of 1.0 mm and an increment of 1.0 mm. All images were displayed with lung (window width, 1500 HU; window level, – 500 HU) and mediastinal (window width, 400 HU; window level, 40 HU) window settings.

CT Image Analysis

All chest CT examinations were independently interpreted by two board-certified thoracic radiologists with 13 and 9 years of post-certification experience in thoracic imaging, respectively. Both readers were blinded to clinical data, laboratory findings, and virologic results. Discrepancies between the two readers

were resolved by consensus consultation, with a third senior radiologist available for adjudication if needed. The following imaging characteristics were evaluated:

1. Lesion distribution: laterality (unilateral/bilateral); lobar involvement (upper/middle/lower lobe); zonal predominance (peripheral = outer one-third of the lung; central = inner two-thirds; combined peripheral and central); and number of involved lobes (1–5).
2. Signs of pulmonary parenchymal involvement: GGOs, consolidation, interlobular septal thickening, crazy-paving pattern (GGOs with superimposed interlobular and intralobular septal thickening), linear opacities, traction bronchiectasis, air bronchogram, and the head-cheese sign (coexistence of normal lung attenuation, GGOs, and consolidation) (Fig. 2).
3. Signs of airway involvement: tree-in-bud nodules, centrilobular nodules, bronchial wall thickening, bronchial narrowing, and mucus plugging (Fig. 3).
4. Additional pulmonary findings: subpleural sparing (relative preservation of the lung immediately beneath the pleura) and volume loss (evidenced by fissure displacement, mediastinal shift, or hemidiaphragm elevation).
5. Extrapulmonary findings: pleural effusion, pericardial effusion, and mediastinal or hilar lymphadenopathy (defined as short-axis diameter ≥ 10 mm on axial images).

ML Model Development

The cohort of 612 patients was randomly divided into training (70%, $n = 428$) and test (30%, $n = 184$) sets, stratified by final diagnosis to maintain class balance. For feature selection, 52 parameters were available: 14 clinical characteristics, 5 laboratory parameters, and 33 chest CT features. Least absolute shrinkage and selection operator (LASSO) regression with 5-fold cross-validation was employed to identify the subset of features associated with differential diagnosis. The regularization parameter (λ) was selected based on minimum cross-validation error. Five supervised ML algorithms were trained and compared using the training set: random forest (RF), logistic regression (LR), support vector machine (SVM), extreme gradient boosting (XGBoost), and k-nearest neighbors (KNN). Hyperparameter tuning was performed using grid search with 5-fold cross-validation on the training set.

Statistical Analysis

Continuous variables were expressed as median and interquartile range (IQR; 25th–75th percentiles) and were compared between the H1N1 and COVID-19 groups using the Mann–Whitney U test. Categorical variables were presented as frequencies and percentages and were compared using the χ^2 test or Fisher's exact test when expected cell counts were < 5 . Relevant variables were first analyzed using univariate logistic regression to calculate unadjusted odds ratios (ORs) and 95% confidence intervals (CIs). Statistically significant factors from univariate analysis were then entered into multivariate logistic regression analysis using the enter method to identify the independent predictors of COVID-19 versus H1N1 pneumonia.

Model discrimination was assessed using the area under the receiver operating characteristic (ROC) curve (AUC) and its 95% CI, calculated using the DeLong method. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and F1 score were calculated for each model at the optimal probability threshold determined by the Youden index.

All analyses were performed using IBM SPSS Statistics software (version 26.0; IBM, Armonk, NY). ML models were built using R (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria). Two-sided $P < 0.05$ was considered statistically significant.

Results

Demographics, Clinical Characteristics, and Laboratory Findings

Baseline demographics and comorbidities showed no significant differences between H1N1 and COVID-19 groups (Table 1). Disorders of consciousness were more frequent in the H1N1 group than in COVID-19 group (7.7% vs 2.4%; $P = 0.014$), whereas other symptoms—including fever, cough, dyspnea, and infection shock—did not differ significantly. All evaluated laboratory parameters, including leukocyte count, neutrophil count, neutrophil percentage, lymphocyte count, lymphocyte percentage, CRP, IL-6, and ESR, were comparable between groups (all $P > 0.05$) (Table 2).

Table 1
Demographic and Clinical Characteristics of Patients with H1N1 and COVID-19 Pneumonia

Variable	H1N1		COVID-19		P-values
	n (442)	%	n (170)	%	
Sex(male)	174	39.4	65	38.2	0.797
Age (y)*	66.0	(49.0, 77.3)	65.5	(29.8, 79.5)	0.742
Fever	313	70.8	126	74.1	0.416
Cough	252	57.0	95	55.9	0.800
Dyspnea at rest	103	23.3	42	24.7	0.715
Disorders of consciousness	34	7.7	4	2.4	0.014
Infection shock	8	1.8	1	0.6	0.453
Comorbidities	183	41.4	68	40.0	0.752
Malignant tumor	57	12.9	19	11.2	0.563
Cardiovascular disease	128	29.0	43	25.3	0.365
Diabetes	57	12.9	19	11.2	0.563
Chronic kidney failure	25	5.7	5	2.9	0.164
Chronic liver disease	17	3.8	9	5.3	0.426
Arthritis	5	1.1	0	0.0	0.373
Note. — Unless otherwise indicated, data were numbers and percentages of patients, and were compared between the two groups using the χ^2 test.					

* Data were median and quartiles (25th and 75th percentiles), and were compared between the two groups using the Mann-Whitney's U-test.

Table 2
Laboratory Findings in Patients with H1N1 and COVID-19 Pneumonia

Variable	H1N1	COVID-19	P-value
	median (25th, 75th)	median (25th, 75th)	
Leukocyte count (×10 ⁹ /L)	7.5 (4.7, 9.4)	5.7 (3.3, 12.8)	0.495
Neutrophil count (×10 ⁹ /L)	5.8 (3.9, 7.5)	3.9 (1.7, 11.7)	0.300
Neutrophil percentage (%)	83.1 (72.1, 88.0)	68.2 (47.3, 87.9)	0.249
Lymphocyte count (×10 ⁹ /L)	0.7 (0.3, 1.4)	1.0 (0.8, 1.4)	0.125
Lymphocyte percentage (%)	9.9 (5.5, 16.1)	22.5 (8.2, 35.8)	0.895
CRP	34.2 (8.3, 63.7)	16.9 (6.0, 52.6)	0.204
IL-6	37.7 (17.6, 67.8)	9.7 (8.2, 74.7)	0.094
ESR	56.5 (44.0, 74.8)	40.0 (15.5, 70.5)	0.172
Note. — Data were compared between the two groups using the Mann-Whitney's U-test. CRP = C-reactive protein; IL-6 = interleukin-6; ESR = erythrocyte sedimentation rate.			

Chest CT Findings

The initial chest CT findings are detailed in Table 3.

Lesion distribution

Bilateral pulmonary involvement was common in both groups (77.8% of H1N1 patients vs 84.1% of COVID-19 patients; $P = 0.084$). Upper lobe involvement was significantly more common in COVID-19 than in H1N1 (87.6% vs 72.4%; $P < 0.001$), as was middle lobe involvement (73.5% vs 64.7%; $P = 0.037$). Lower lobe involvement was the most common pattern in both groups (92.4% in COVID-19 vs 91.0% in H1N1; $P = 0.581$). Regarding zonal distribution, combined peripheral and central involvement was more common in COVID-19 pneumonia (77.1% vs 68.1%; $P = 0.029$), whereas central predominance was more frequent in H1N1 pneumonia (17.6% vs 7.6%; $P = 0.002$).

Parenchymal involvement

Parenchymal involvement was significantly more common in COVID-19 pneumonia than in H1N1 pneumonia (91.2% vs 74.7%; $P < 0.001$). Specifically, COVID-19 patients demonstrated higher rates of GGOs, interlobular septal thickening, and crazy-paving pattern (all $P < 0.05$). Consolidation, linear opacities, traction bronchiectasis, air bronchogram, and head-cheese sign showed no significant differences between groups.

Airway involvement

Airway involvement was more frequent in H1N1 pneumonia (48.2% vs 34.7%; $P = 0.003$), with higher rates of bronchial wall thickening, centrilobular nodules, and tree-in-bud nodules (all $P < 0.05$). Bronchial narrowing and mucus plugging showed no significant differences between groups.

Additional and extrapulmonary findings

Mediastinal or hilar lymphadenopathy was more frequent in H1N1 pneumonia (5.4% vs 1.8%; $P = 0.048$). Subpleural sparing, volume loss, pleural and pericardial effusions showed no significant differences.

Table 3
Initial Chest CT Findings in Patients with H1N1 and COVID-19 Pneumonia

CT presentations	H1N1		COVID-19		P-values
	n (442)	%	n (170)	%	
Lesion distribution					
Unilateral/ Bilateral					0.084
Unilateral	98	22.2	27	15.9	
Bilateral	344	77.8	143	84.1	
Number of lobes					0.012
One lobe	81	18.3	16	9.4	
Two lobes	65	14.7	19	11.2	
Three lobes	40	9.0	14	8.2	
Four lobes	60	13.6	21	12.4	
Five lobes	196	44.3	100	58.8	
Upper lobar	320	72.4	149	87.6	< 0.001
Middle lobar	286	64.7	125	73.5	0.037
Lower lobar	402	91.0	157	92.4	0.581
Peripheral	63	14.3	26	15.3	0.744
Central	78	17.6	13	7.6	0.002
Peripheral and central	301	68.1	131	77.1	0.029
Parenchymal involvement	330	74.7	155	91.2	< 0.001
Ground-glass opacities	318	71.9	146	85.9	< 0.001
Interlobular septal thickening	125	28.3	94	55.3	< 0.001
Crazy-paving sign	109	24.7	90	52.9	< 0.001
Consolidation	305	69.0	107	62.9	0.152
Air bronchogram	116	26.2	52	30.6	0.281
Linear opacities	140	31.7	44	25.9	0.162
Head cheese sign	3	0.7	2	1.2	0.911
Traction bronchiectasis	72	16.3	35	20.6	0.210
Note. — Data were compared between the two groups using the χ^2 test.					

CT presentations	H1N1		COVID-19		P-values
	n (442)	%	n (170)	%	
Airway involvement	213	48.2	59	34.7	0.003
Bronchial narrowing	102	23.1	27	15.9	0.051
Bronchial wall thickening	150	33.9	37	21.8	0.003
Mucus plugging	15	3.4	3	1.8	0.285
Centrilobular nodules	106	24.0	21	12.4	0.001
Tree-in-bud nodules	93	21.0	12	7.1	< 0.001
Additional pulmonary findings					
Lung volume loss	38	8.6	22	12.9	0.106
Subpleural sparing	19	4.3	2	1.2	0.057
Extrapulmonary findings					
Pleural effusion	140	31.7	56	32.9	0.764
Pericardial effusion	49	11.1	23	13.5	0.401
Lymphadenopathy	24	5.4	3	1.8	0.048
Note. — Data were compared between the two groups using the χ^2 test.					

Univariate and Multivariate Logistic Regression Analysis

The results of univariate and multivariate logistic regression analysis are presented in Table 4. Upper lobe involvement (OR = 2.19; 95% CI: 1.04, 4.65; $P = 0.040$) and parenchymal involvement (OR = 3.44; 95% CI: 1.67, 7.10; $P < 0.001$) were identified as independent predictors of COVID-19 pneumonia. Tree-in-bud nodules (OR = 0.30; 95% CI: 0.12, 0.77; $P = 0.007$), lymphadenopathy (OR = 0.29; 95% CI: 0.06, 0.81; $P = 0.022$), and disorders of consciousness (OR = 0.20; 95% CI: 0.07, 0.61; $P = 0.005$) were independently associated with H1N1 pneumonia.

Table 4

Univariate and Multivariate regression analysis for differentiating COVID-19 from H1N1 pneumonia

Variable	Univariable Analysis (n = 612)			Multivariable Analysis (n = 612)		
	OR	95% CI	P-value	OR	95% CI	P-value
Upper lobar	2.71	1.64–4.47	< 0.001	2.19	1.04–4.65	0.040
Middle lobar	1.52	1.02–2.24	0.038	0.81	0.40–1.66	0.567
Central	0.39	0.21–0.72	0.002	0.62	0.25–1.51	0.292
Peripheral and central	1.57	1.05–2.37	0.034	0.84	0.47–1.51	0.561
Parenchymal involvement	3.51	1.98–6.21	< 0.001	3.44	1.67–7.10	< 0.001
Ground-glass opacities	2.37	1.47–3.83	< 0.001	0.75	0.387–1.46	0.400
Interlobular septal thickening	3.14	2.17–4.53	< 0.001	1.34	0.55–3.25	0.520
Crazy-paving sign	3.44	2.37–4.98	< 0.001	1.92	0.77–4.75	0.160
Airway involvement	0.57	0.40–0.83	0.003	0.72	0.40–1.30	0.270
Bronchial wall thickening	0.54	0.36–0.82	0.004	0.83	0.38–1.84	0.645
Centrilobular nodules	0.45	0.27–0.74	0.002	1.61	0.72–3.59	0.246
Tree-in-bud nodules	0.29	0.15–0.54	< 0.001	0.30	0.12–0.77	0.007
Lymphadenopathy	0.31	0.09–1.05	0.041	0.29	0.06–0.81	0.022
Disorders of consciousness	0.29	0.10–0.83	0.021	0.20	0.07–0.61	0.005

Note. — OR = odds ratio; CI = confidence interval.

Feature Selection Using LASSO Regression

The LASSO regression identified 19 variables associated with the differential diagnosis of COVID-19 versus H1N1 pneumonia. These included 13 CT features (middle lobe involvement, lower lobe

involvement, number of involved lobes [2, 4, 5], parenchymal involvement, interlobular septal thickening, bronchial narrowing, mucus plugging, head-cheese sign, lung volume loss, subpleural sparing, lymphadenopathy) and 6 clinical characteristics (infection shock, disorders of consciousness, chronic liver disease, chronic kidney failure, cardiovascular disease, diabetes). The LASSO coefficient paths, cross-validation performance, and feature importance rankings are presented in Fig. 4A–4C.

Model Performance

The performance metrics of the five ML models on the independent test set (n = 184) are summarized in Table 5 and Fig. 4D–4F.

All ML models demonstrated moderate discrimination, with AUC values ranging from 0.60 to 0.71. The RF model achieved the highest performance, with an AUC of 0.71, sensitivity of 52.2%, specificity of 81.5%, PPV of 54.6%, NPV of 80.0%, accuracy of 72.7%, and F1 score of 0.53. LR, SVM, XGBoost and KNN achieved an AUC of 0.69, 0.68, 0.66 and 0.60, respectively. Calibration curves demonstrated that all models tended to underestimate the probability of COVID-19 in the intermediate probability range, with the RF model showing the best calibration properties overall.

Table 5
Performance Characteristics of Machine Learning Models for Predicting COVID-19 from H1N1 pneumonia

Metric	RF	LR	SVM	XGBoost	KNN
AUC	0.71	0.69	0.68	0.66	0.60
Sensitivity (%)	52.2	43.5	60.9	52.2	47.8
Specificity (%)	81.5	79.6	72.2	64.8	68.5
PPV (%)	54.6	47.6	48.3	38.7	39.3
NPV (%)	80.0	76.8	81.3	76.1	75.5
Accuracy (%)	72.7	68.8	68.8	61.0	62.3
F1 score	0.53	0.45	0.54	0.44	0.43
Note. – AUC = area under the receiver operating characteristic curve; PPV = positive predictive value; NPV = negative predictive value; RF = random forest; LR = logistic regression; SVM = support vector machine; XGBoost = extreme gradient boosting; KNN = k-nearest neighbor.					

Discussion

In this large-scale comparative study of 612 patients (170 with COVID-19, 442 with H1N1 pneumonia) enrolled after the peak of the COVID-19 pandemic, we comprehensively analyzed the clinical, laboratory, and CT features of these two viral pneumonias. Multivariable logistic regression analysis revealed that upper lobe involvement and parenchymal involvement were independent predictors of COVID-19,

whereas tree-in-bud nodules, lymphadenopathy, and disorders of consciousness were independently associated with H1N1. We further developed and compared five ML-based classification models, all of which demonstrated moderate performance. The random forest model achieved the highest discrimination, with an AUC of 0.71.

In our cohort, lower lobe involvement was most common in both groups. However, upper lobe involvement was significantly more frequent in COVID-19 than in H1N1 and independently predicted COVID-19. This finding contrasts with early pandemic reports that emphasized lower lobe and peripheral predominance[8, 16], yet aligns with recent studies demonstrating that COVID-19 now frequently involves multiple lobes without strict lower lobe preference[17, 18]. This discrepancy likely reflects differences in viral strains (from the initial index strain to later variants with altered tissue tropism)[17], population immunity (initially negligible, now modified by vaccination and prior infection), and study design (including patient selection and disease severity)[19].

Parenchymal involvement was more frequent in COVID-19 than in H1N1 pneumonia and independently predicted COVID-19. Specifically, COVID-19 patients demonstrated higher rates of GGOs, interlobular septal thickening, and the crazy-paving pattern. These findings agree with a meta-analysis of 148 patients showing that GGOs and consolidation are more common in COVID-19 than in H1N1 pneumonia[20]. The imaging features observed in COVID-19 reflect the pathophysiology of SARS-CoV-2. Hamming et al.[21] demonstrated that SARS-CoV-2 enters host cells via angiotensin-converting enzyme 2 (ACE2) receptors, which are predominantly expressed on type II alveolar epithelial cells. This alveolar predilection leads to diffuse alveolar damage and edema, which manifests as GGOs on CT[22]. As the disease progresses, proteinaceous exudate fills the alveolar spaces and extends into the interlobular septa, resulting in the interlobular septal thickening and the characteristic crazy-paving pattern observed on imaging[23, 24]. Further exacerbation of alveolar edema leads to consolidation, representing the dynamic evolution of pulmonary pathology in severe infections.

We found that airway involvement was significantly more prevalent in H1N1 pneumonia, including bronchial wall thickening, centrilobular nodules, and tree-in-bud nodules. Multivariable analysis confirmed tree-in-bud nodules as an independent predictor of H1N1 pneumonia. These findings are consistent with prior studies[11, 25] demonstrating that airway involvement —particularly tree-in-bud nodules, bronchial wall thickening, and air trapping— is significantly more common in H1N1 than in COVID-19 pneumonia. The radiological differences between these two viral pneumonias align with their distinct viral tropism. Unlike SARS-CoV-2, which binds to ACE2 receptors on type II alveolar cells, influenza A viruses preferentially bind to α 2,6-linked sialic acid receptors, which are abundant on ciliated epithelial cells lining the trachea, bronchi, and bronchioles[26]. Histopathologic studies of fatal H1N1 cases[27–29] have demonstrated robust viral antigen expression in airway epithelium with lower alveolar expression, leading to necrotizing bronchiolitis and peribronchiolar inflammation[30, 31], which correlate with CT findings of small airways involvement[6, 32]. Thus, the presence of these airway involvement findings, particularly tree-in-bud nodules, should raise suspicion for H1N1 rather than COVID-19 in the appropriate clinical context.

Lymphadenopathy was more common in H1N1 than in COVID-19, consistent with Şimşek and Özmen[19], who reported mediastinal lymphadenopathy in 24% of H1N1 patients compared to 1.8% of COVID-19 patients. In our multivariable analysis, lymphadenopathy was independently associated with H1N1. Given the low event counts (only 27 cases of lymphadenopathy in the entire cohort, including only 3 COVID-19 patients) and potential for model overfitting in the setting of rare events, this finding should be interpreted with caution. The clinical utility of lymphadenopathy as a discriminating feature may be limited by its low prevalence in both groups.

Disorders of consciousness were significantly more common in H1N1 than in COVID-19 and emerged as an independent predictor of H1N1 in our multivariable model. The pathogenesis of neurologic involvement in influenza is thought to involve cytokine-mediated inflammation, direct viral invasion of the central nervous system, or metabolic derangements secondary to severe respiratory compromise[33]. The higher prevalence of consciousness disorders in H1N1 may reflect a more pronounced systemic inflammatory response or greater neurotropism compared with COVID-19. Alternatively, this difference could be confounded by baseline illness severity, comorbidities, or differences in clinical management between the two infection groups, factors that our study may not have fully captured.

Our exploration of five ML algorithms for differential diagnosis revealed moderate performance. The RF model achieved the highest discrimination (AUC = 0.71), with a specificity of 81.5% and NPV of 80%. The relatively modest performance of our ML models compared to previous studies focusing exclusively on COVID-19 diagnosis[34, 35] may be attributed to several factors. First, the task of differentiating two specific viral pneumonias with overlapping clinical and radiological features is inherently more challenging than binary classification between viral pneumonia and healthy controls. Second, the absence of significant laboratory differences between groups removed a potentially informative feature domain. Third, the class imbalance in our cohort may have affected model training.

This study has several limitations. First, the single-center, retrospective design may have introduced selection bias and limits generalizability. Second, the H1N1 cohort was substantially larger than the COVID-19 cohort, reflecting the relative prevalence of these infections during the study period (January 2023 to December 2025); this class imbalance may have limited our statistical power to detect additional discriminating features and may have affected model training. Third, we did not account for pneumonia severity or clinical outcome, which could have biased the cohort composition and affected model performance. Fourth, the ML models showed only moderate performance, and their clinical utility requires further validation in prospective, multi-center studies.

In conclusion, upper lobe involvement and parenchymal involvement were independent predictors of COVID-19, whereas tree-in-bud nodules, lymphadenopathy, and disorders of consciousness were independently associated with H1N1 pneumonia. These imaging and clinical features may assist in early differential diagnosis. Future multi-center and prospective studies are needed to validate these findings.

Abbreviations

SARS-CoV-2
Severe acute respiratory syndrome coronavirus 2
COVID-19
Coronavirus disease 2019
H1N1
Influenza A
RT-PCR
Reverse transcription-polymerase chain reaction
CT
Computed tomography
GGOs
Ground-glass opacities
ML
Machine learning
CRP
C-reactive protein erythrocyte
IL-6
Interleukin-6
ESR
Erythrocyte sedimentation rate
LASSO
Least absolute shrinkage and selection operator
RF
Random forest
LR
Logistic regression
SVM
Support vector machine
XGBoost
Extreme gradient boosting
KNN
K-nearest neighbors
IQR
Interquartile range
ORs
Odds ratios
CIs
Confidence intervals
AUC
Area under the receiver operating characteristic curve

ROC
Receiver operating characteristic
PPV
Positive predictive value
NPV
Negative predictive value
ACE2
Angiotensin-converting enzyme 2

Declarations

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Consent for publication Not applicable.

Competing interests The authors declare that they have no competing interests.

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References

1. Di Pietro C, Haberman AM, Lindenbach BD, Smith PC, Bruscia EM, et al. Prior Influenza Infection Mitigates SARS-CoV-2 Disease in Syrian Hamsters. *Viruses*. 2024;246. <https://doi.org/10.3390/v16020246>.
2. Song X, Delaney M, Shah RK, Campos JM, Wessel DL et al. Comparison of Clinical Features of COVID-19 vs Seasonal Influenza A and B in US Children. *JAMA Netw Open* 2020.Vol:e2020495. <https://doi.org/10.1001/jamanetworkopen.2020.20495>
3. Deng LS, Yuan J, Ding L, Chen YL, Zhao CH, et al. Comparison of patients hospitalized with COVID-19, H7N9 and H1N1. *Infect Dis Poverty*. 2020. <https://doi.org/10.1186/s40249-020-00781-5>. 163.
4. Arevalo-Rodriguez I, Buitrago-Garcia D, Simancas-Racines D, Zambrano-Achig P, Del Campo R, et al. False-negative results of initial RT-PCR assays for COVID-19: A systematic review. *PLoS ONE*. 2020;e0242958. <https://doi.org/10.1371/journal.pone.0242958>.
5. Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction-Based SARS-CoV-2 Tests by Time Since Exposure. *Ann Intern Med*. 2020. <https://doi.org/10.7326/M20-1495>. 262 – 67.
6. Koo HJ, Lim S, Choe J, Choi SH, Sung H et al. Radiographic and CT Features of Viral Pneumonia. *Radiographics*. 2018.Vol:719 – 39. <https://doi.org/10.1148/rg.2018170048>
7. Shen C, Tan M, Song X, Zhang G, Liang J, et al. Comparative Analysis of Early-Stage Clinical Features Between COVID-19 and Influenza A H1N1 Virus Pneumonia. *Front Public Health*. 2020. <https://doi.org/10.3389/fpubh.2020.00206>. 206.
8. Bernheim A, Mei X, Huang M, Yang Y, Fayad ZA, et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. *Radiology*. 2020;200463. <https://doi.org/10.1148/radiol.2020200463>.
9. Caruso D, Polidori T, Guido G, Nicolai M, Bracci B, et al. Typical and atypical COVID-19 computed tomography findings. *World J Clin Cases*. 2020. <https://doi.org/10.12998/wjcc.v8.i15.3177>. 3177-87.
10. Ajlan AM, Quiney B, Nicolaou S, Muller NL. Swine-origin influenza A (H1N1) viral infection: radiographic and CT findings. *AJR Am J Roentgenol*. 2009;1494–99. <https://doi.org/10.2214/AJR.09.3625>.
11. Samir A, Naguib NNN, Elnekeidy A, Baess AI, Shawky A. COVID-19 versus H1N1: challenges in radiological diagnosis—comparative study on 130 patients using chest HRCT. *Egypt J Radiol Nuclear Med* 2021 Vol:77–86. <https://doi.org/10.1186/s43055-021-00455-8>

12. Mushtaq J, Pennella R, Lavallo S, Colarieti A, Steidler S et al. Initial chest radiographs and artificial intelligence (AI) predict clinical outcomes in COVID-19 patients: analysis of 697 Italian patients. *Eur Radiol* 2021 Vol:1770–79. <https://doi.org/10.1007/s00330-020-07269-8>
13. Purkayastha S, Xiao Y, Jiao Z, Thepumnoeysuk R, Halsey K, et al. Machine Learning-Based Prediction of COVID-19 Severity and Progression to Critical Illness Using CT Imaging and Clinical Data. *Korean J Radiol*. 2021;1213–24. <https://doi.org/10.3348/kjr.2020.1104>.
14. Mortani Barbosa EJ Jr., Georgescu B, Chaganti S, Aleman GB, Cabrero JB et al. Machine learning automatically detects COVID-19 using chest CTs in a large multicenter cohort. *Eur Radiol* 2021 Vol:8775–85. <https://doi.org/10.1007/s00330-021-07937-3>
15. Albataineh Z, Aldrweesh F, Alzubaidi MA. COVID-19 CT-images diagnosis and severity assessment using machine learning algorithm. *Cluster Comput* 2023 Vol:1–16. <https://doi.org/10.1007/s10586-023-03972-5>
16. Shi H, Han X, Jiang N, Cao Y, Alwalid O et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. *Lancet Infect Dis* 2020.425 – 34. [https://doi.org/10.1016/S1473-3099\(20\)30086-4](https://doi.org/10.1016/S1473-3099(20)30086-4)
17. Yoon SH, Lee JH, Kim BN. Chest CT Findings in Hospitalized Patients with SARS-CoV-2: Delta versus Omicron Variants. *Radiology*. 2023.Vol:252 – 60. <https://doi.org/10.1148/radiol.220676>
18. Smejkal P, Hruby F, Hornakova A. The importance of screening asymptomatic patients admitted to healthcare facilities during the COVID-19 pandemic. *Cent Eur J Public Health*. 2025.170 – 75. <https://doi.org/10.21101/cejph.a8739>
19. Şimşek S, Özmen CA. Comparison of Chest Computed Tomography Findings in Patients with H1N1 and Coronavirus Disease-2019 Pneumonia. *Gazi Med J*. 2024. <https://doi.org/10.12996/gmj.2023.3813>. 228 – 35.
20. Velez-Ramirez LN, Jimenez-Zarazua O, Gonzalez-Najera LE, Flores-Saldana GA, Valdez-Escobedo A, et al. Comparison of Tomographic Findings in Patients with Influenza A (H1N1) and COVID-19. *Diagnostics (Basel)*. 2025;1430. <https://doi.org/10.3390/diagnostics15111430>.
21. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol*. 2004;631–7. <https://doi.org/10.1002/path.1570>.
22. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. *Lancet Infect Dis* 2020 Vol:1135–40. [https://doi.org/10.1016/S1473-3099\(20\)30434-5](https://doi.org/10.1016/S1473-3099(20)30434-5)
23. Tian S, Xiong Y, Liu H, Niu L, Guo J et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. *Mod Pathol* 2020 Vol:1007–14. <https://doi.org/10.1038/s41379-020-0536-x>
24. Pan F, Ye T, Sun P, Gui S, Liang B et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). *Radiology*. 2020.Vol:715 – 21. <https://doi.org/10.1148/radiol.2020200370>

25. Eslambolchi A, Maliglig A, Gupta A, Gholamrezanezhad A. COVID-19 or non-COVID viral pneumonia: How to differentiate based on the radiologic findings? *World J Radiol.* 2020;289–301. <https://doi.org/10.4329/wjr.v12.i12.289>.
26. Krammer F, Smith GJD, Fouchier RAM, Peiris M, Kedzierska K, et al. *Influenza Nat Rev Dis Primers.* 2018. <https://doi.org/10.1038/s41572-018-0002-y>. 3.
27. Nakajima N, Sato Y, Katano H, Hasegawa H, Kumasaka T, et al. Histopathological and immunohistochemical findings of 20 autopsy cases with 2009 H1N1 virus infection. *Mod Pathol.* 2012;1–13. <https://doi.org/10.1038/modpathol.2011.125>.
28. Shieh WJ, Blau DM, Denison AM, Deleon-Carnes M, Adem P, et al. 2009 pandemic influenza A (H1N1): pathology and pathogenesis of 100 fatal cases in the United States. *Am J Pathol.* 2010. <https://doi.org/10.2353/ajpath.2010.100115>. 166 – 75.
29. Shelke VN, Kolhapure RM, Kadam D, Sangle S, Chadha MC, et al. Pathologic study of pandemic influenza A (H1N1) 2009 cases from India. *Pathol Int.* 2012;36–42. <https://doi.org/10.1111/j.1440-1827.2011.02751.x>.
30. Thompson AJ, Paulson JC. Adaptation of influenza viruses to human airway receptors. *J Biol Chem.* 2021. <https://doi.org/10.1074/jbc.REV120.013309>. 100017.
31. Kim YS, Kang UR, Kim YH. The Spectrum of CT Findings of COVID-19 Pneumonia: Acute Alveolar Insult and Organizing Pneumonia as Different Phases of Lung Injury and Repair. *Taehan Yongsang Uihakhoe Chi.* 2021. <https://doi.org/10.3348/jksr.2020.0142>. 359 – 70.
32. Koo HJ, Choi SH, Sung H, Choe J, Do KH. RadioGraphics Update: Radiographic and CT Features of Viral Pneumonia. *Radiographics* 2020 VolE8-E15. <https://doi.org/10.1148/rg.2020200097>
33. Barbosa-Silva MC, Lima MN, Battaglini D, Robba C, Pelosi P, et al. Infectious disease-associated encephalopathies. *Crit Care.* 2021. <https://doi.org/10.1186/s13054-021-03659-6>. 236.
34. Murota M, Johkoh T, Lee KS, Franquet T, Kondoh Y et al. Influenza H1N1 virus-associated pneumonia often resembles rapidly progressive interstitial lung disease seen in collagen vascular diseases and COVID-19 pneumonia; CT-pathologic correlation in 24 patients. *Eur J Radiol Open* 2020 Vol:100297. <https://doi.org/10.1016/j.ejro.2020.100297>
35. Mahaboob Basha S, Lira Neto AV, Alshathri S, Elaziz MA, Hashmitha Mohisin S, et al. Multithreshold Segmentation and Machine Learning Based Approach to Differentiate COVID-19 from Viral Pneumonia. *Comput Intell Neurosci.* 2022. <https://doi.org/10.1155/2022/2728866>. 2728866.

Figures

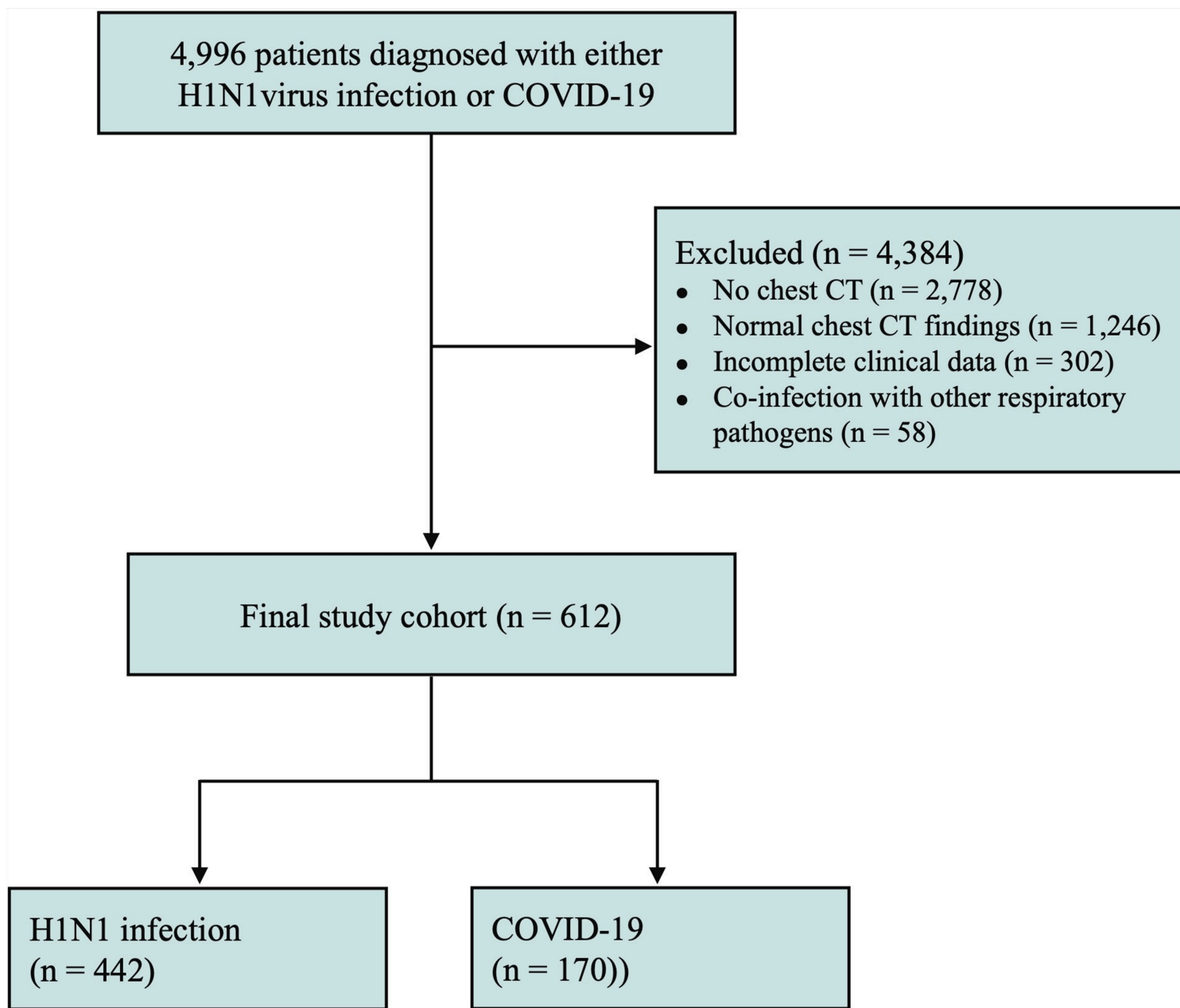


Figure 1

Flow diagram for the patients' inclusion and exclusion criteria

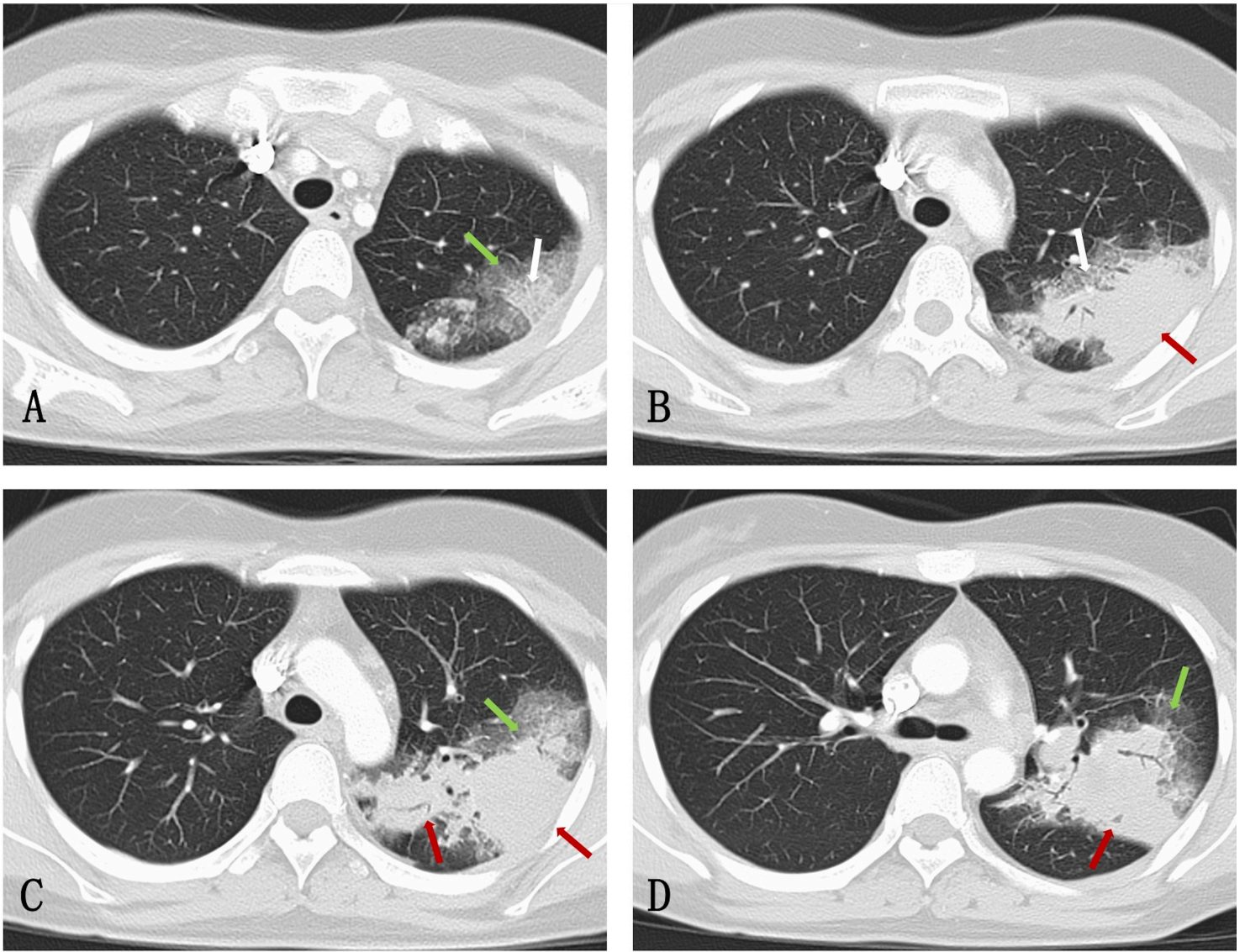


Figure 2

A 27-year-old woman with COVID-19 pneumonia who presented with fever and cough. (A-D) Axial chest CT images (lung window) demonstrate extensive consolidation (red arrow), ground-glass opacities (GGOs, green arrow), and crazy-paving pattern (GGOs with superimposed interlobular and intralobular septal thickening, white arrow) in the left upper lobe.

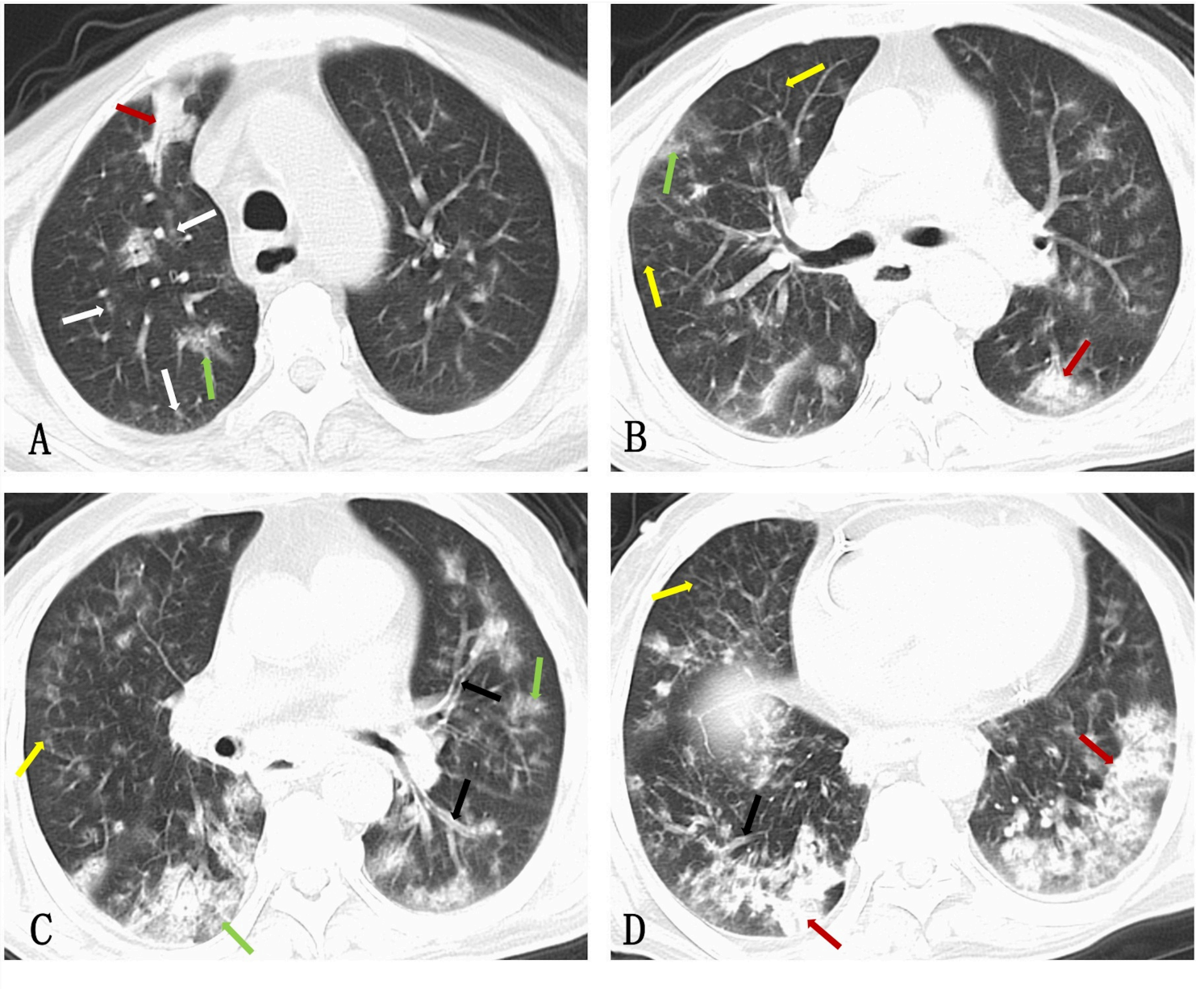


Figure 3

A 67-year-old man with H1N1 pneumonia and a 5-month history of esophageal carcinoma who presented with fever and productive cough. (A–D) Axial chest CT images (lung window) demonstrate diffuse tree-in-bud nodules (yellow arrow), centrilobular nodules (white arrow), bronchial wall thickening (black arrow), scattered GGOs (green arrow), and multifocal consolidation (red arrow).

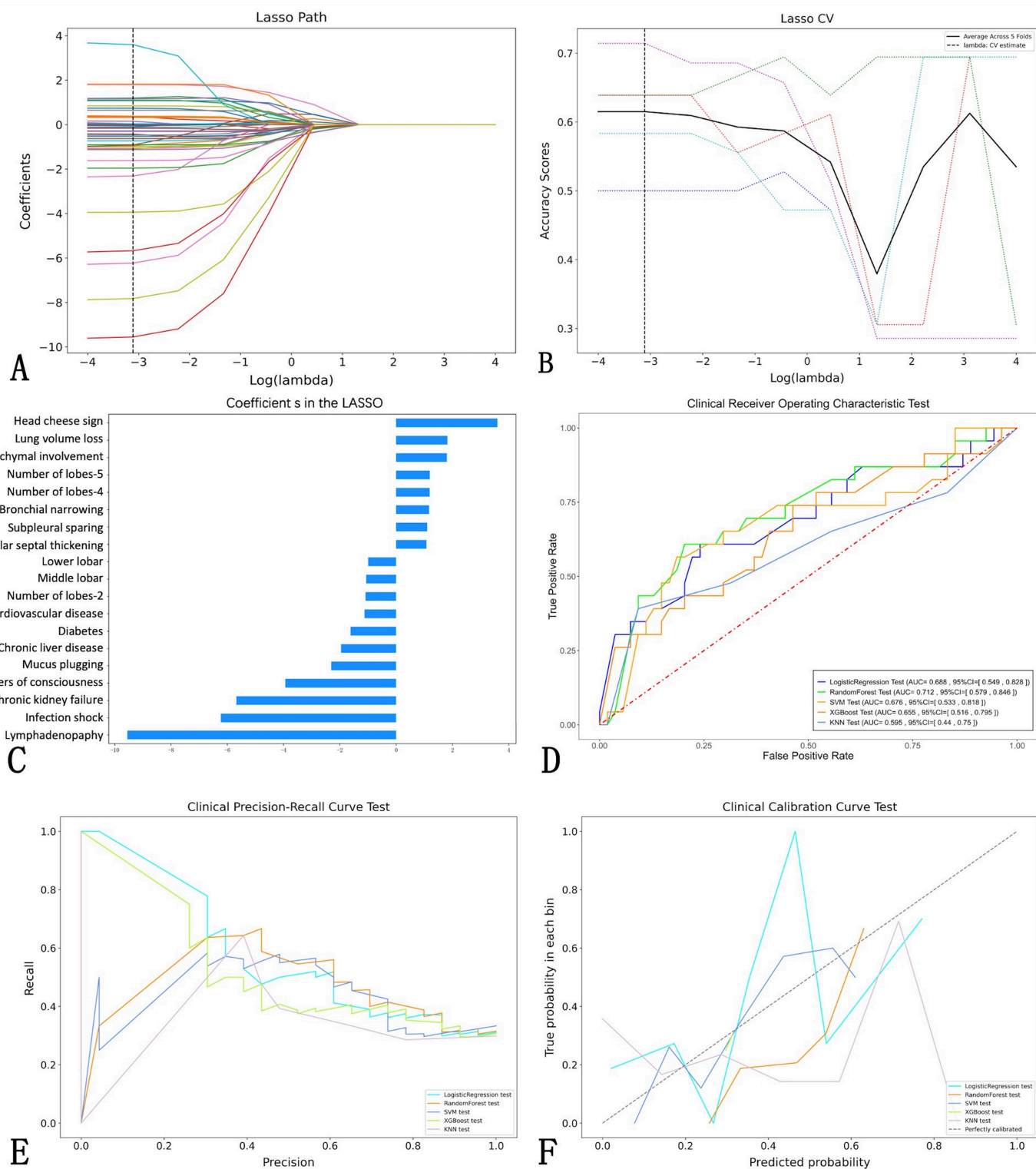


Figure 4

(A) Least absolute shrinkage and selection operator (LASSO) coefficient paths for clinical and imaging features in differentiating COVID-19 from H1N1 pneumonia. (B) Cross-validation performance of the LASSO model. (C) LASSO coefficient bar plot of the 19 selected features. Positive coefficients are associated with a higher probability of COVID-19, whereas negative coefficients are associated with H1N1 pneumonia. The length of each bar reflects the relative contribution of the feature to the predictive

model. (D) Receiver operating characteristic (ROC) curves of five ML models on the test set for distinguishing COVID-19 from H1N1 pneumonia. (E) Precision-recall curves of five ML models on the test set. (F) Calibration curves of predicted probabilities from five ML models on the test set.