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*Original Article*

# Combined CT score, blood mononuclear cell count, LDH, and plasma D-dimer for viral pneumonia diagnosis: a retrospective study

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**Abstract:** Objective: Due to a continued increase in viral pneumonia incidence and resulting high mortality, fast and accurate diagnosis is important for effective management. This investigation examined the significance of blood biomarkers and the CT score in the early diagnosis of viral pneumonia. Methods: Patients who were hospitalized due to radiologically-confirmed pneumonia and underwent virus antigen rapid test were enrolled. Their clinical information was compared. Blood mononuclear cell count, LDH, and plasma D-dimer were obtained. To evaluate the utility of biomarker levels in differentiating viral pneumonia from other pneumonia, ROC curves were developed to analyze the AUC. The optimal cut-off thresholds, specificity, sensitivity, and predictive values were assessed using the Youden index. The added value of the multi-marker approach was delineated using IDI and Reclassification analyses using NRI; IDI and NRI values were examined with 95% CI. Results: Overall, 1163 inpatients were recruited between January 2017 and January 2021. They were sub-divided into the viral pneumonia (n = 563) and non-viral pneumonia (n = 600) categories. We found that the CT score, blood mononuclear cell count, LDH, and plasma D-dimer were markedly elevated in viral pneumonia patients. At an LDH threshold of 693.595 U/L, an AUC of ROC was 0.805 in differentiating viral pneumonia. The combination of CT score and blood biomarkers had an ROC AUC value of 0.908. Conclusions: Combining elevated biomarkers with CT assessments outperformed the CT score alone in identifying viral pneumonia. It is crucial to better characterize the significance of biomarkers in combination with CT assessments in the diagnosis of viral pneumonia.

**Keywords:** Blood biomarkers, CT score, viral pneumonia, virus, rapid diagnosis

## Introduction

The reported incidence of viral pneumonia has increased over the past decade [1]. Viruses or bacteria are the primary causes of pneumonia, and the symptoms of viral pneumonia are often similar to those of bacterial pneumonia, making accurate diagnosis difficult [2]. Diverse viruses cause viral pneumonia, such as influenza (flu) A and B viruses [3], parainfluenza viruses, respiratory syncytial virus (RSV), coronaviruses, coxsackievirus group B, and adenoviruses [4]. COVID-19 (the ongoing global pandemic that causes pneumonitis) and past influenza pandemics have uncovered that viral infections are potential causes of respiratory failure and coagulopathy with significant mortality risk [5-7]. However, clinicians often neglect the importance of viral pneumonia and only focus on treating bacterial infections, which may lead to viral pneumonia. Worsening viral pneumonia decreases the patient's immunity, which may contribute to bacterial co-infection and other complications that exacerbate symptoms [8, 9]. The best approach is symptom evaluation and applying specific treatment depending on the cause of infection.

In China, routine real-time RT-PCR is the main tool for diagnosing viral infection, whereas virus antigen rapid test (Colloidal gold assay) is the primarily method for rapid detection of viral infection [10]. However, these tests are time-consuming and expensive, making them less

applicable to the diagnosis of pneumonia. Here, we evaluated the diagnostic value of combining CT (computed tomography) results and blood mononuclear cell count, LDH (lactate dehydrogenase), and plasma D-dimer for rapid detection of virus in pneumonia patients.

## Methods

### *Patients*

A total of 1934 consecutive inpatients with pneumonia, who had each undergone virus antigen rapid test (Colloidal gold assay) at The Affiliated Hospital of Chengde Medical University from January 2017 to January 2021, were included in this retrospective study. Patients were divided into the virus IgM antibody-positive group (n = 563) and the virus IgM antibody-negative group (n = 1194) depending on virus antigen rapid test (Colloidal gold assay) results. Major exclusion criteria were pulmonary malignancy, pulmonary embolism, pulmonary tuberculosis, and incomplete data. The study was conducted in accordance with the Helsinki Declaration (as revised in 2013). The study was approved by the institutional review board of The Affiliated Hospital of Chengde Medical University. The approval number for the ethical clearance was LL094.

### *Demographic and clinical data*

The following information was obtained: sex, age, and pneumonia variables like smoking, heart disease, diabetes, and hypertension were collected. Hypertension was defined as diastolic blood pressure ≥90 mmHg and/or systolic blood pressure ≥140 mmHg (1 mmHg = 0.133 kPa) at rest, or a history of hypertension receiving antihypertensive treatment [11]. Diabetes was diagnosed by the following criteria: symptoms of diabetes and random blood glucose levels ≥11.1 mmol/L, or fasting plasma glucose ≥7.0 mmol/L or 2-h oral glucose tolerance test blood glucose level ≥11.1 mmol/L, or no diabetes symptoms and at least twice the blood glucose levels that meet the above-mentioned criteria [12]. Virus antigen rapid test (Colloidal gold assay) results were recorded for all patients. All the virus antigen rapid test results were obtained using a uniform kit: colloidal gold assay kit (Innovita Company, Beijing, China) which was approved by China FDA (No. 20163401649). This test can detect IgM antibodies against: adenovirus, respiratory syncytial virus, parainfluenza virus, influenza B virus, influenza A virus, coxsackievirus group B, mycoplasma, and chlamydia. (Patients positive for mycoplasma and chlamydia were included in the control group).

### *Chest CT imaging*

Chest CT scores were assigned by 2 independent radiologists, each with >5 years' experience in chest CT diagnosis. Conventionally, the lung is categorized into 5 levels, along the apex-bottom axis, including: the apex of the diaphragm, intermediate bronchus, tracheal carina, aortic arch, and suprasternal notch. We adopted the protocol reported by Feng et al. for ground-glass attenuation and consolidation areas [13]. The Hounsfield Units (HU) of normal attenuation, consolidation areas, frosted glass density, and ground-glass attenuation were quantified. Grading of chest CT density was done as follows: 3 = consolidation; 2 = ground-glass attenuation; 1 = frosted glass density; 0 = normal attenuation (**Figure 1**). For each patient with data from five lung zones, the following scale was adopted based on distribution of affected lung parenchyma using a modified form of the method previously reported by Feng et al: 0 = normal, 1 = 0-25% abnormality, 2 = 25-50% abnormality, 3 = 50-75% abnormality, and 4 = >75% abnormality. The lung parenchyma score was then multiplied by the radiologic scale described, and points from all zones were summed to get a total score ranging from 0-60.

### *Statistical analysis*

Clinical data, including demographic variables like age, gender, and laboratory indexes were collected by our physicians. Data were expressed as numbers and percentages. Group comparisons were performed using an independent sample t-test (Mann-Whitney test and unpaired student's t-test). Optimal cutoff values for CT results and biomarkers were determined using the receivers operating characteristic (ROC) curve (where the sum of false positive and false negative results was the lowest) for viral pneumonia diagnosis. Area under the curve (AUC) values were reported with a 95% confidence interval (CI). ROC curves of CT results, combined biomarkers, and combinations of CT results and biomarkers were gener-

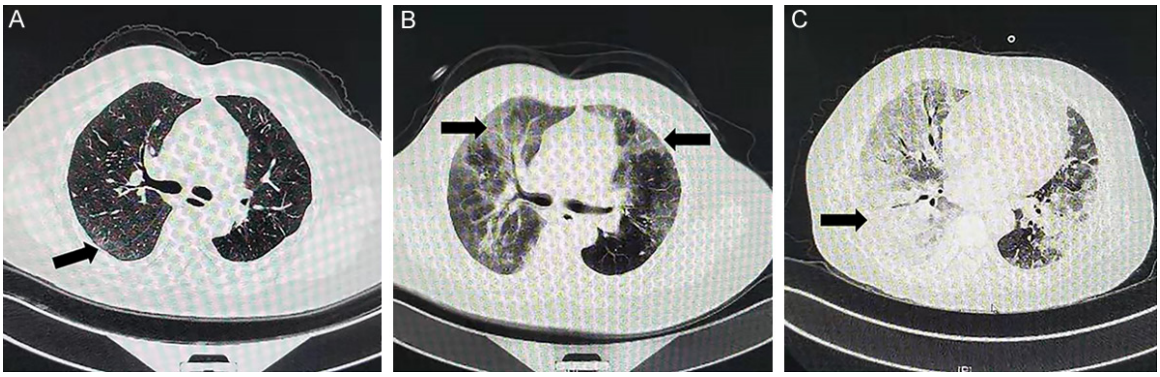


**Figure 1.** Representative lung CT images of patients who had frosted glass density. (A) ground glass opacity (B), and consolidation (C).

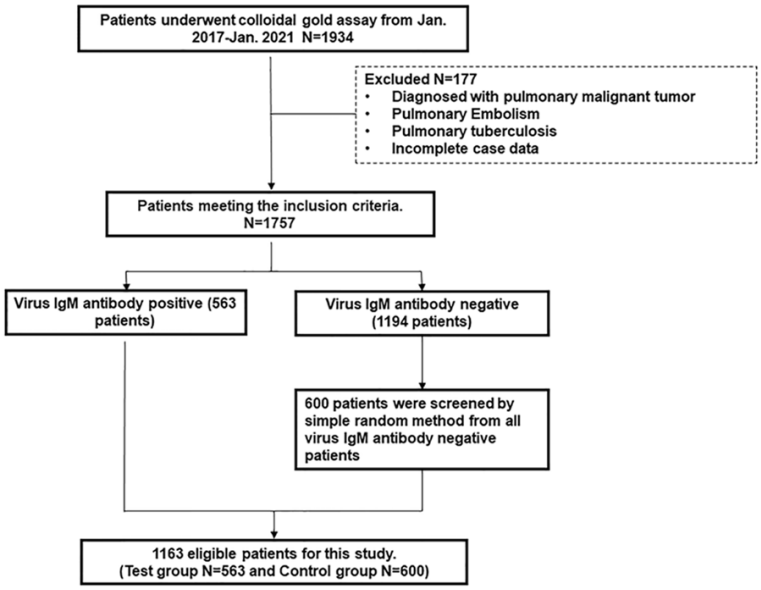


**Figure 2.** A flowchart showing patient selection process.

ated again, and their AUCs were compared to determine the multi-marker diagnostic value. Reclassification analyses using Net Reclassification Index (NRI) and Integrated Discrimination Improvement (IDI) were adopted to examine the value added by the multi-marker approach. NRI and IDI values were analyzed with 95% CI. Statistical analyses were done on SPSS (version 24.0) and R version 3.3.1. $P \leq 0.05$ was considered significant.

## Results

A total of 600 virus IgM antibody-negative participants were identified from 1194 patients using a simple randomized method and 563 patients positive for virus IgM antibodies enrolled in the study (**Figure 2**). The positive test group (test group, 563 patients) and the proportion of patients who were positive for IgM antibodies against various viruses are shown in **Figure 3**. The general conditions and complications, and laboratory indexes are shown in **Table 1**.

Herein, 63.4% of the participants were men with a median age of 56 years. Of note, age and sex were not markedly different between the study groups. Relative to the control group, the ratio of pleural effusion and pericardial effusion in the test group was remarkably higher. CT results showed that the scope of injured pulmonary lobes in the test group exceeded that of the control group. Except PCT concentration, biomarkers, and CT levels were lower in the control group relative to the test group (all $P \leq 0.001$). Chest CT features for all patients are shown in **Table 2**.

ROC curve analysis revealed that the different biomarkers approach of viral pneumonia diagnosis outperformed CT results [monocyte count: AUC = 0.690 (0.660-0.719), D-dimer AUC = 0.791 (0.763-0.818), and LDH AUC = 0.805 (0.780-0.830) vs. CT results AUC = 0.563 (0.529-0.596)]. Their differences in viral pneumonia diagnosis are evidenced by the

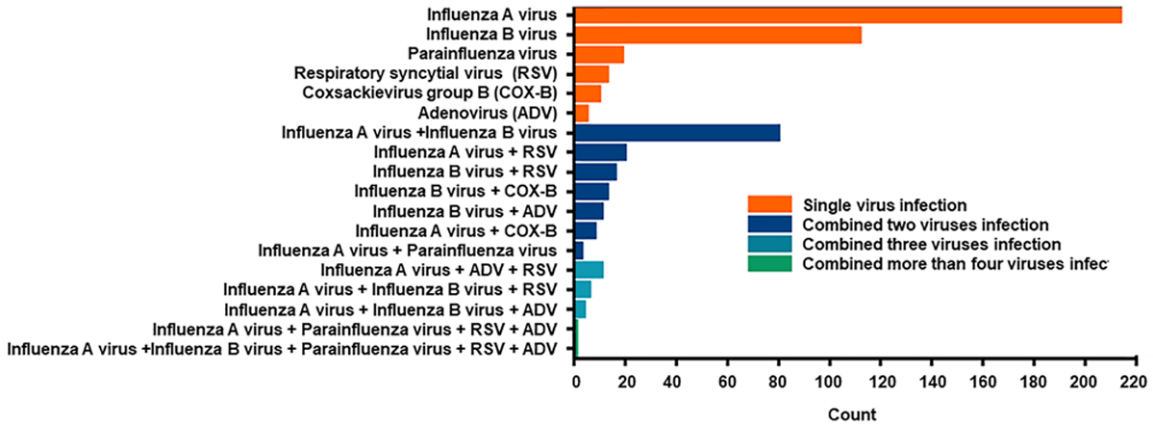


**Figure 3.** Proportion of patients who were positive for IgM antibodies against various viruses in the positive test group (n = 563).

**Table 1.** General conditions, complications, and laboratory index assessments of 1163 patients

| General conditionand complications n (%) | All patients (n = 1163) | Test group (n = 563) | Control group (n = 600) | *P* value |
|---|---|---|---|---|
| Male sex | 737 (63.4) | 369 (65.5) | 368 (61.3) | 0.151 |
| Age, median years (range) | 62 (18,99) | 64 (18,99) | 61 (18,96) | 0.280 |
| Active smoking | 706 (60.7) | 319 (56.7) | 387 (64.5) | 0.013 |
| Chest pain | 611 (52.5) | 372 (66.1) | 239 (39.8) | <0.001 |
| Heart disease | 386 (33.2) | 207(36.8) | 179 (29.8) | <0.001 |
| Hypertension | 554 (47.6) | 252 (44.8) | 302 (50.3) | 0.103 |
| Diabetes Mellitus | 445 (38.3) | 213 (37.8) | 232 (38.7) | 0.201 |
| C-RP >8 mg/L | 822 (70.7) | 434 (77.1) | 388 (64.7) | <0.001 |
| Mononuclear cell count >0.6*$10^9$/L | 461 (39.6) | 283 (50.3) | 178 (29.7) | <0.001 |
| Leukomonocyte <1.1 & >3.2*$10^9$/L | 423 (36.4) | 223 (39.6) | 200 (33.3) | <0.001 |
| PCT >0.05 ng/ml | 433 (37.2) | 215 (38.2) | 218 (36.3) | 0.658 |
| LDH >620 U/L | 528 (45.4) | 393 (69.8) | 135 (22.5) | <0.001 |
| Fibrinogen >4 g/L | 544 (46.8) | 350 (62.2) | 194 (32.3) | <0.001 |
| D-dimer >0.05 mg/L | 1126 (96.8) | 552 (98.0) | 574 (95.7) | <0.001 |

results of the multi-marker approach (**Figure 4**; **Table 3**).

ROC curves for CT results, combined biomarkers, and CT results and biomarkers showed that combining the 3 biomarkers with CT results increased the diagnostic value relative to the 3 biomarkers combined and CT results, monocyte count, LDH, or D-dimer alone (**Figure 5**; **Table 4**).

During the reclassification analyses of biomarkers and CT results using NRI and IDI, categorical NRI showed that the net reclassification index of the 3 biomarkers combined with CT results was 0.621 higher than that of the 3-biomarker combination alone. Continuous NRI showed a net reclassification index improvement of 1.3246, and IDI showed that the new model improved the comprehensive differential improvement index by 0.4617 relative to the old model (**Table 5**).

## Discussion

As of March 2020, there were eight confirmed COVID-19 cases in Chengde city. Among these patients, it was demonstrated that four of the patients had higher counts of monocytes in peripheral blood, D-dimer levels were elevated in three patients, six patients developed elevated LDH, and the CT score of four patients was

**Table 2.** Chest CT features of patients (n = 1163)

| Chest radiographic feature, Patients, n (%) or median (IQR) | All patients (n = 1163) | Test group (n = 563) | Control group (n = 600) |
|---|---|---|---|
| Frosted glass density | 479 (41.2%) | 233 (41.4%) | 246 (41.0%) |
| Ground glass opacity | 517 (44.5%) | 243 (43.2%) | 274 (45.7%) |
| Consolidation | 164 (14.1%) | 87 (15.5%) | 77 (12.8%) |
| Pleural effusions | 512 (44.0%) | 275 (48.8%) | 237 (39.5%) |
| Pericardial effusion | 148 (12.7%) | 89 (15.8%) | 59 (9.8%) |
| Anatomic sides involved | | | |
| Unilateral | 519 (44.6%) | 102 (18.1%) | 417 (69.5%) |
| Bilateral | 644 (55.4%) | 461 (81.9%) | 183 (30.5%) |
| Involved zone | | | |
| Suprasternal notch | 617 (53.1%) | 323 (57.4%) | 294 (49.0%) |
| Aortic arch | 940 (80.8%) | 439 (78.0%) | 501 (83.5%) |
| Tracheal carina | 1015 (87.3%) | 502 (89.2%) | 513 (85.5%) |
| Intermediate bronchus | 878 (75.5%) | 416 (73.9%) | 462 (77.0%) |
| Apex of diaphragm | 899 (77.3%) | 421 (74.8%) | 478 (79.7%) |
| Radiographic score | 23 (1,58) | 31 (2,58) | 16 (1,45) |

higher than 30 points. During the treatment, the above-described situation raises the research question guiding this study. Due to the low number of cases at that time, we were not able to provide a comprehensive evaluation of the projects that were assessed; however, despite these limitations, our findings are still meaningful for clinical practice.

Plain radiography and chest CT scans are important imaging modalities that can identify typical patterns of viral pneumonia. Multifocal ground-glass changes are common CT features of viral pneumonia [14]. However, due to lack of specificity, it is also possible that a similar observation would be made in bacterial or other pneumonia types. The virus antigen rapid test (Colloidal gold assay) is widely used for viral detection in >300 Chinese hospitals. While the average cost (about 9 dollars) of the colloidal gold test is lower than the real-time RT-PCR test (which costs at least 24 dollars) [10], both tests pose an economic burden to patients. Additionally, single examination methods may not be sufficient for comprehensive and accurate detection of all virus types. Thus, rapid evaluation of multi-biomarkers is needed as an auxiliary diagnosis approach for viral pneumonia that combines CT scanning and blood biomarkers to differentiate viral pneumonia from other types of pneumonia in patients.

Here, we investigated the utility of CT scans and serum biomarkers for differentiating definite viral pneumonia from other pneumonia types using clinical data of 1163 patients. Several differences exist in patients with viral and non-viral pneumonia. Blood mononuclear cell count, LDH, and plasma D-dimer were higher in the viral pneumonia group and had significant benefit in differentiating viral from other types of pneumonia. Combining CT scans and multi-biomarkers increased specificity and sensitivity, suggesting that this approach has great diagnostic significance.

Effective application of antivirals or antibiotics in the treatment of pneumonia depends largely on early diagnosis. Herein, we found that patients with viral pneumonia and other types of pneumonia have overlapping symptoms, making it difficult to distinguish them. Similarly, a number of previous studies have shown that viral pneumonia can be associated with smoking history, chest pain, pleural effusion, and pericardial effusion [15-18] . Based on specific radiographic features, differences in CT features were compared between viral pneumonia patients and non-viral pneumonia patients. The results indicated that viral pneumonia exhibited an elevated CT score. However, some scholars did not find any radiographic feature with the potential to differentiate viral cases from non-viral pneumonia.

Lactate dehydrogenase catalyzes the reversible oxidation of lactate to pyruvate, and as a systemic inflammation indicator, has attracted

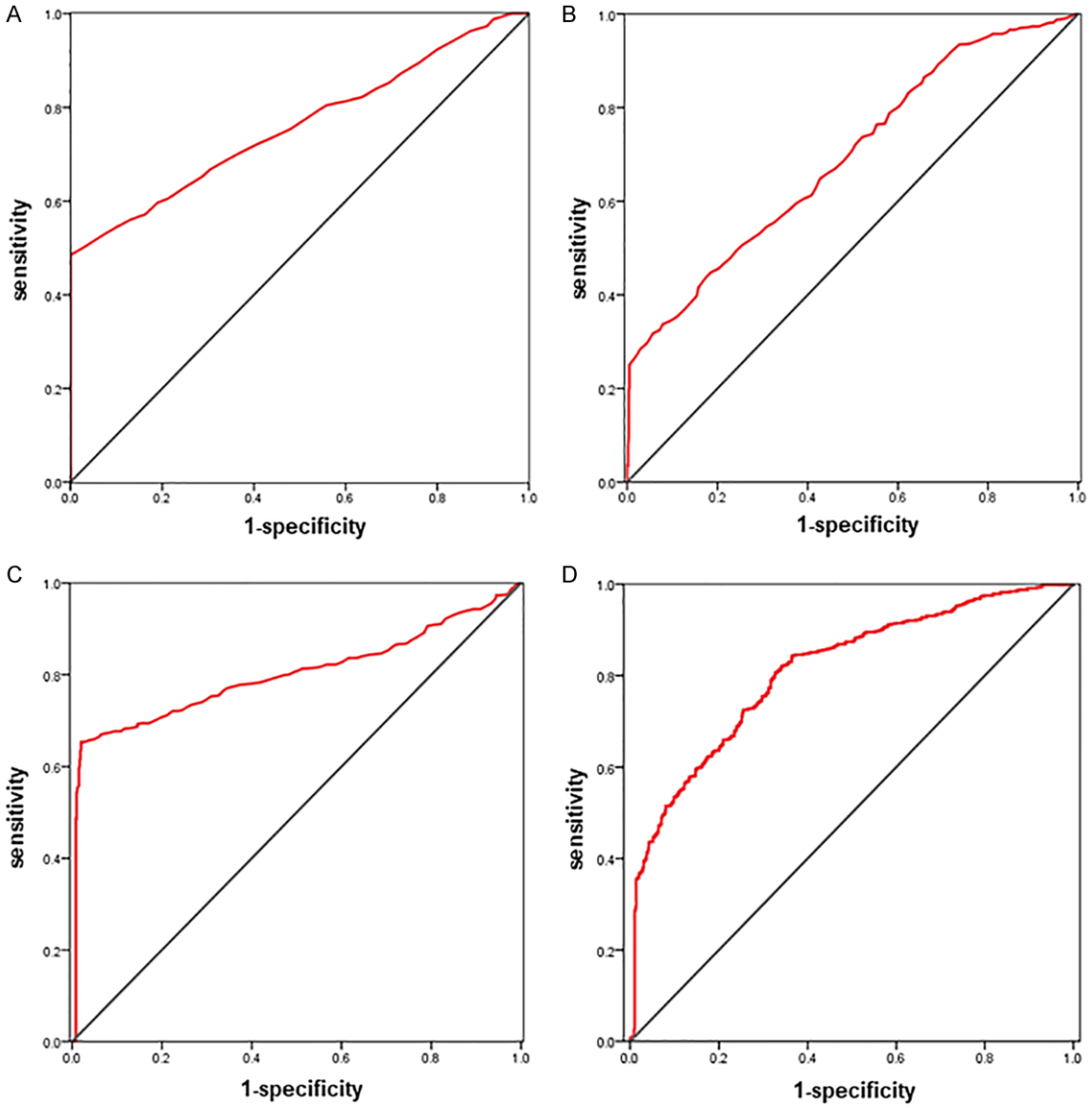


**Figure 4.** Nomogram for prediction of viral infection. Multiple marker approach using cutoff values of CT results (A) and each biomarker ((B) monocyte count; (C) D-dimer; (D) LDH) showed differences in viral pneumonia diagnosis.

**Table 3.** AUC and optimal cutoff values to diagnose viral pneumonia for each biomarker and CT score

| Variable | AUC (95% CI) | Optimal cut-off value | Sensitivity of op mal cut-off value | Specificity of op mal cut-off value |
|---|---|---|---|---|
| CT score | 0.761 (0.733-0.789) | 31.50 | 0.602 | 1.000 |
| Monocyte count | 0.690 (0.660-0.719) | $0.745*10^9$/L | 0.353 | 0.930 |
| D-dimer | 0.791 (0.763-0.818) | 0.885 ug/ml | 0.656 | 0.978 |
| LDH | 0.805 (0.780-0.830) | 693.595 U/L | 0.544 | 0.926 |

attention [19, 20]. Past studies indicate that high LDH is a poor prognostic factor for viral infection, especially in COVID-19 and influenza A patients [21, 22]. Shibata et.al found that patients with HIV infection had increased blood mononuclear cell counts [23]. In a recent COVID-19 study, Lombardi et.al found an altered immune profile in the early phase of

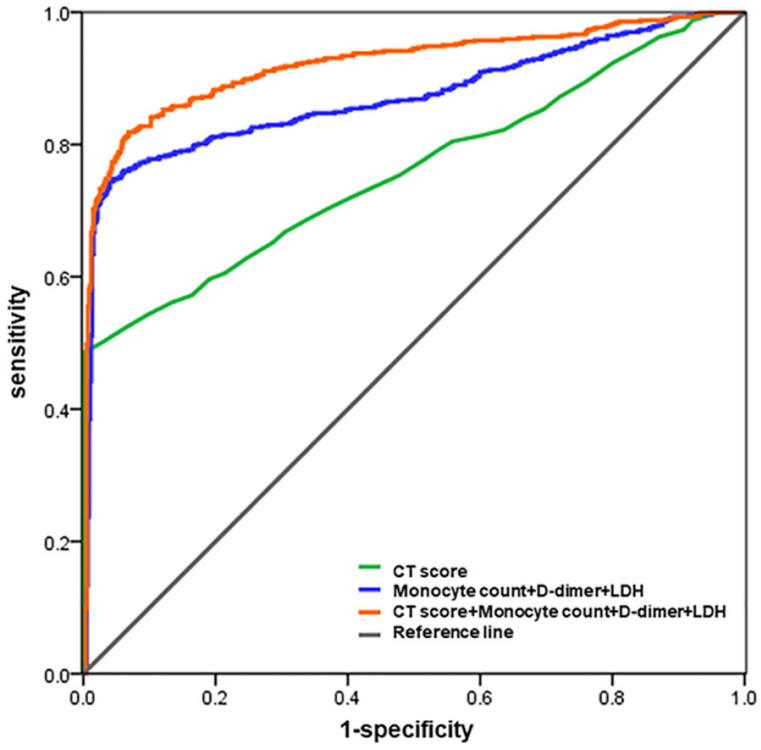


**Figure 5.** Multiple-marker approach using multivariate ROC curve analysis for viral pneumonia diagnosis.

**Table 4.** AUC of multi-marker approach for the diagnosis of viral pneumonia

| Variable | AUC (95% CI) |
|---|---|
| CT score | 0.761 (0.733-0.789) |
| Monocyte count + D-dimer + LDH | 0.872 (0.849-0.894) |
| CT score + Monocyte count + D-dimer + LDH | 0.922 (0.905-0.938) |

**Table 5.** Reclassification analyses of biomarkers and CT level using NRI and IDI

| Variable | Estimated value [95% CI] | *P*-value |
|---|---|---|
| IDI | 0.4617 [0.4342-0.4892] | <0.001 |
| NRI (Continuous) | 1.3246 [1.2389-1.4103] | <0.001 |
| NRI (Categorical) | 0.621 [0.5759-0.6661] | <0.001 |

COVID-19, which includes atypical mononuclear cells [24]. Asghar et al. found that an increased monocyte count in ICU patients indicates that this index may be a reliable biomarker for severe COVID-19 [25]. Numerous studies have confirmed that the formation of thrombi in COVID-19 and severe influenza patients elevates D-dimer level [26-29]. Here, we found that the level of D-dimer in viral pneumonia patients was significantly higher than in patients with non-viral pneumonia.

So far, no studies have combined biomarkers with CT assessment to differentiate viral from non-viral pneumonia. This study established that combining multiple biomarkers with CT assessment improved specificity and sensitivity, hence increasing the accuracy of diagnosis unlike CT applied alone.

Clinicians often neglect the importance of respiratory viruses in pneumonia patients, instead mainly focus on bacterial infections, and this may cause viral pneumonia to remain untreated. Furthermore, in the absence of bacteria, the general consensus is that pleural effusions are of bacterial origin. Currently, pneumonia is treated with antibiotics applied empirically due to the lack of point-of-care diagnostic tools to distinguish viral from non-viral pneumonia. The use of antibiotics has limited efficacy in viral pneumonia patients. Thus, it is necessary to design a diagnostic tool for early identification of viral pneumonia that will minimize the usage of antibiotics which are ineffective when treating viral pneumonia patients. Despite not identifying a clinical feature or biomarker with the potential to differentiate viral from non-viral pneumonia, this study points to the possibility of using sophisticated algorithms based on several radiologic, inflammatory, microbiologic, and clinical biomarkers for accurate diagnoses and treatment of viral pneumonia.

The following limitations should be noted. Although there is a clear distinction between viral and non-viral pneumonia patients, there could be mixed infections or bacterial pneumo-

nia in viral pneumonia patients. In addition, some respiratory bacteria were found in patients' sputum. Nearly, 50% of patients had used antivirals or antibiotics at the time of recruitment, which might have influenced the natural progression of biomarkers, signs, and symptoms, as well as virus-detection sensitivity.

## Conclusion

The combination of CT score and blood biomarkers (blood mononuclear cell count, LDH and plasma D-dimer) may improve diagnostic differentiation of viral pneumonia from other pneumonia types. This method is less costly and hence suitable for inpatient settings with mid-level specificity and sensitivity. In our future work, we will design a prospective study to analyze the significance of the CT score and multiple blood biomarkers using large clinical samples.

## Disclosure of conflict of interest

None.

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