Pneumonia Caused by Severe Acute Respiratory Syndrome Coronavirus 2 and Influenza Virus: A Multicenter Comparative Study

Issei Oi\textsuperscript{1,2}; Isao Ito\textsuperscript{1,2}; Masataka Hirabayashi\textsuperscript{3}; Kazuo Endo\textsuperscript{3}; Masahito Emura\textsuperscript{4}; Toru Kojima\textsuperscript{5}; Hitokazu Tsukao\textsuperscript{5}; Keisuke Tomii\textsuperscript{6}; Atsushi Nakagawa\textsuperscript{6}; Kojiro Otsuka\textsuperscript{7}; Masaya Akai\textsuperscript{7}; Masahiro Oi\textsuperscript{8}; Takakazu Sugita\textsuperscript{9}; Motonari Fukui\textsuperscript{10}; Daiki Inoue\textsuperscript{10}; Yoshinori Hasegawa\textsuperscript{11}; Kenichi Takahashi\textsuperscript{12}; Hiroaki Yasui\textsuperscript{13}; Kohei Fujita\textsuperscript{14}; Tadashi Ishida\textsuperscript{15}; Akihiro Ito\textsuperscript{15}; Hideo Kita\textsuperscript{16}; Yusuke Kaji\textsuperscript{17}; Michiko Tsuchiya\textsuperscript{18}; Hiromi Tomioka\textsuperscript{19}; Takashi Yamada\textsuperscript{20}; Satoru Terada\textsuperscript{1,21}; Hitoshi Nakaji\textsuperscript{22}; Nobuyoshi Hamao\textsuperscript{12}; Masahiro Shirata\textsuperscript{1}; Kensuke Nishioka\textsuperscript{1}; Masatoshi Yamazoe\textsuperscript{1,11}; Yusuke Shiraishi\textsuperscript{1,10}; Tatsuya Ogimoto\textsuperscript{1,12}; Kazutaka Hosoya\textsuperscript{1,12}; Hitomi Ajimizu\textsuperscript{1,18}; Hiroshi Shima\textsuperscript{1,22}; Hisako Matsumoto\textsuperscript{1}; Naoya Tanabe\textsuperscript{1}; Toyohiro Hirai\textsuperscript{1}

\textsuperscript{1} Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Kyoto, 606-8507, Japan

\textsuperscript{2} Department of Internal Medicine, Sugita Genpaku Memorial Obama Municipal Hospital, Obama, 917-8567, Japan

\textsuperscript{3} Department of Respiratory Medicine, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, 660-8550, Japan

\textsuperscript{4} Department of Respiratory Medicine, Kyoto City Hospital, Kyoto, 604-8845, Japan

\textsuperscript{5} Department of Respiratory Medicine, Fukui Prefectural Hospital, Fukui, 910-8526, Japan

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6 Department of Respiratory Medicine, Kobe City Medical Center General Hospital, Kobe, 650-0047, Japan

7 Department of Respiratory Medicine, Shinko Hospital, Kobe, 651-0072, Japan

8 Department of Respiratory Medicine, Japanese Red Cross Fukui Hospital, Fukui, 918-8501, Japan

9 Department of Respiratory Medicine, Japan Red Cross Wakayama Medical Center, Wakayama, 640-8558, Japan

10 Respiratory Disease Center, Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, 530-8480, Japan

11 Department of Respiratory Medicine, Osaka Saiseikai Nakatsu Hospital, Osaka, 530-0012, Japan

12 Department of Respiratory Medicine, Kishiwada City Hospital, Osaka, 596-8501, Japan

13 Department of Internal Medicine, Horikawa Hospital, Kyoto, 602-0056, Japan

14 Division of Respiratory Medicine, Center for Respiratory Disease, National Hospital Organization Kyoto Medical Center, Kyoto, 612-8555, Japan

15 Department of Respiratory Medicine, Ohara Healthcare Foundation, Kurashiki Central Hospital, Kurashiki, 710-8602, Japan

16 Department of Respiratory Medicine, Takatsuki Red Cross Hospital, Takatsuki, 569-1096, Japan

17 Department of Respiratory Medicine, Tenri Hospital, Tenri, 632-8552, Japan

18 Department of Respiratory Medicine, Rakuwakai Otowa Hospital, Kyoto, 607-8062, Japan

19 Department of Respiratory Medicine, Kobe City Medical Center West Hospital, Kobe, 653-0013, Japan

20 Department of Respiratory Medicine, Shizuoka City Shizuoka Hospital, Shizuoka, 420-8630, Japan
Prior Presentations: None

Correspondence to:

Isao Ito

Department of Respiratory Medicine, Graduate School of Medicine
54 Shogoin-kawaharacho, Sakyo, Kyoto 606-8507, Japan

E-mail isaoito@kuhp.kyoto-u.ac.jp

Tel: +81-75-751-3830

Fax: +81-75-751-4643

Alternate corresponding author:

Issei Oi

Department of Respiratory Medicine, Graduate School of Medicine
54 Shogoin-kawaharacho, Sakyo, Kyoto 606-8507, Japan

E-mail isseioi@kuhp.kyoto-u.ac.jp

Tel: +81-75-751-3830

Fax: +81-75-751-4643
**Key points:** The clinical characteristics of hospitalized pneumonia patients with SARS-CoV2 (CP) and influenza (IP) in multicenter cohorts were compared and comprehensive differences between CP and IP were revealed. Our subsequent diagnostic scoring system could effectively differentiate between CP and IP.
ABSTRACT

Background. Detailed differences in clinical information between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pneumonia (CP), which is the main phenotype of SARS-CoV-2 disease, and influenza pneumonia (IP) are still unclear.

Methods. A prospective, multicenter cohort study was conducted by including patients with CP hospitalized between January and June 2020 and a retrospective cohort of patients with IP hospitalized from 2009 to 2020. We compared the clinical presentations and studied the prognostic factors of CP and IP.

Results. Compared with the IP group (n=66), in the multivariate analysis, the CP group (n=362) had a lower percentage of patients with underlying asthma or chronic obstructive pulmonary disease (p<0.01), lower neutrophil-to-lymphocyte ratio (p<0.01), lower systolic blood pressure (p<0.01), higher diastolic blood pressure (p<0.01), lower aspartate aminotransferase levels (p<0.05), higher serum sodium levels (p<0.05), and more frequent multilobar infiltrates (p<0.05). The diagnostic scoring system based on these findings showed excellent differentiation between CP and IP (area under the receiver operating characteristic curve, 0.889). Moreover, the prognostic predictors were different between CP and IP.

Conclusions. Comprehensive differences between CP and IP were revealed, highlighting the need for early differentiation between these two pneumonias in clinical settings.

Keywords: COVID-19, influenza, pneumonia, multicenter study
INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originated in Wuhan, China in 2019 and has become a global threat with 150 million cases worldwide as of April 30, 2021 [1].

Pneumonia is the most typical and critical presentation of COVID-19 as it occurs even in asymptomatic patients [2] and in almost all severe cases [3]. The World Health Organization has stated that the severity of COVID-19 patients with pneumonia is moderate at the least [4]. In clinical practice, the process of assuming a pathogen after confirming the presence of pneumonia is convincing. Therefore, from a clinical perspective, there is a need to elucidate the differences between pneumonia caused by SARS-CoV-2 (CP) and those caused by other pathogens, especially in situations where SARS-CoV-2 and other pathogens are simultaneously prevalent.

Viruses are among the causative pathogens of community-acquired pneumonia [5]; moreover, before the advent of SARS-CoV-2, the most common causative virus of adult viral pneumonia was influenza virus [6]. It can be anticipated that SARS-CoV-2 and influenza will account for a substantial proportion of viral pneumonia cases.

Therefore, given the differences in the optimal treatment for CP and influenza pneumonia (IP), it is necessary to precisely distinguish them. This is further emphasized by the fact that SARS-CoV-2 could have more potent transmissibility than influenza, as observed in numerous studies on large-scale nosocomial transmissions [7–9]. Rapid diagnostic tools for both pathogens remain suboptimal, with a sensitivity of 60.8–85.0%, a detective rate at first test of 71%, and a false-negative rate of 20–67% for SARS-CoV-2 polymerase chain reaction (PCR) [10–12] and a sensitivity of 62.3–64.0% for the influenza rapid antigen test [13,14]. It is necessary to elucidate differences in the clinical presentations of both viral pneumonias, especially when viral pneumonia by either pathogen
is strongly suspected and the corresponding rapid testing tools do not yield definitive results. Further, sometimes testing cannot be performed promptly, such as at night or on weekends.

Several studies have compared the clinical presentations of SARS-CoV-2 and influenza. However, they are limited in terms of generalizability and clinical implication because of a lack of focus on pneumonia [15–29] and applicability in real-world settings given the use of single-center cohorts [15–20,27,28,30–33] or huge databases [22–25], or focused only on symptoms [19], laboratory data [21,30] or computed tomography (CT) findings [28,31,32]. A multicenter cohort study is required given the diversity of patient characteristics and treatment strategies for viral pneumonia across facilities.

We aimed to establish cohorts for comprehensive comparisons between the clinical characteristics of CP and IP, as well as to develop a scoring system for discriminating between CP and IP.

METHODS

Patients

The study prospectively enrolled patients with CP from 20 teaching hospitals between January 26 and June 28, 2020, which corresponded to the first COVID-19 wave in Japan. CP was defined as pneumonia with SARS-CoV-2 infection at admission, confirmed through PCR or positive results of loop-mediated isothermal amplification assay. IP was defined as pneumonia with influenza virus infection at admission confirmed through positive results on the rapid antigen test or PCR. Patients with IP were retrospectively included from the 2009–2010 to 2019–2020 season from nine hospitals with a pneumonia cohort. Each hospital had an accumulated pneumonia cohort over the different time periods. The presence of pneumonia was radiologically confirmed in each patient. We excluded patients aged <16 years or without infiltration on X-ray or CT scan at admission.
In Japan, all patients with COVID-19 were admitted to the hospital, during the period of the study, even if asymptomatic. However, as hospitalization was elective in influenza, besides comparing all patients, those who presented with hypoxia at admission, were compared separately.

**Patient Consent Statement:**

This study was approved by the institutional review boards at Kyoto University, Japan, and each participating hospital. Informed consent was obtained from patients, or their guardians in case of severely ill patients such as those on mechanical ventilation, and the institutional review boards at Kyoto University waived the need for written informed consent.

**Data Collection**

We collected clinical data regarding age, sex, smoking history, nursing home residence, clinical symptoms, underlying diseases, and vital signs and laboratory/radiographic findings at admission. Data were obtained from registries of participating hospitals. Moreover, chest X-ray and CT images were assessed by two experienced pulmonologists, with discrepancies being resolved through consensus. Concurrent bacterial pneumonia was diagnosed upon identification of causative organisms by sputum cultures, urinary antigen tests, or serological examinations at admission. Further, we recorded treatment drugs, oxygen requirements, need for respiratory support, intensive care unit (ICU) admission, and date of death/discharge. All patients with CP and IP were compared and subsequently, only patients with hypoxia at admission, were compared. Hypoxia at admission was defined as having an oxygen saturation of <90% by pulse oximetry, a partial pressure of oxygen of 60 mmHg, or receiving oxygen therapy at admission. We followed all patients until death/discharge.
Statistical Analysis

Regarding background factors and baseline laboratory data, continuous variables were reported as median values and interquartile ranges. The Mann-Whitney U test was used for between-group comparisons of continuous variables. The Chi-squared test or Fisher’s exact test was used for between-group comparisons of categorical variables, as appropriate. Subsequently, we conducted a multivariate logistic regression analysis using sex, age, and significant variables (p<0.10) from the univariate analysis. We excluded variables that contained missing data in >20% of the patients. Given their subjective nature, symptoms were excluded from the multivariate analysis. We excluded the clinical course after admission from the multivariate analysis in order to compare the clinical presentations at hospitalization. All statistical analyses were conducted using JMP version 14.0.0 (SAS Institute Inc., Cary, NC). All p-values <0.05 were considered statistically significant.

Results

Between-group Differences in Patient Background

We recruited 362 patients with CP and 66 patients with IP, of whom 90 (24.9%) and 44 (66.7%), respectively, had hypoxia at diagnosis (Figure 1). Seasons and types of IP are shown in Supplementary Table 1. The between-group differences in patient background are shown in Table 1. Younger age, lower number of nursing home residents, and lower percentage of underlying bronchial asthma (BA) or chronic obstructive pulmonary disease (COPD) were observed in the CP group compared to the IP group (p<0.001, p=0.016, and p<0.001, respectively). In contrast to the initial comparison, there was no significant difference in age and nursing home residence; however, there was a significant difference in the frequency of BA/COPD between hypoxic CP and hypoxic IP (p<0.001).
Symptomatic Differences Between Types of Pneumonia

The reported symptoms for CP and IP are shown in Supplementary Table 2. Dry cough, sore throat, headache, and diarrhea were more common in patients with CP (p<0.001, p=0.013, p=0.009, and p=0.016, respectively), while dyspnea and wet cough were more common in patients with IP (p<0.001 for both). Seven (1.9%) patients with CP were completely asymptomatic; however, all patients with IP had minimum one symptom. Furthermore, among hypoxic patients, dry cough was more common in patients with CP (p=0.029), whereas wet cough was more common in patients with IP (p<0.001; Supplementary Table 2). There was no significant between-group difference in the other symptoms between hypoxic patients in both groups.

Between-Group Differences in Vital Signs

There were between-group differences in all vital signs in the cohort composing all patients (Table 2). Compared to patients with IP, patients with CP showed lower systolic blood pressure (p=0.024), higher diastolic blood pressure (p=0.004), lower heart rate (p<0.001), lower respiratory rate (p<0.001), and lower body temperature (p<0.001). Hypoxia and confusion were less frequent in patients with CP than in patients with IP (both p<0.001). However, hypoxic patients with CP had lower heart rates (p=0.002) than hypoxic patients with IP, and there was no other difference in vital signs between hypoxic patients in both groups.

Between-group Differences in Laboratory Data and Radiographic Findings at Admission

Regarding the laboratory data shown in Table 3, patients with CP had lower white blood cell (WBC) counts and glucose levels (p<0.001); contrarily, patients with IP showed a higher neutrophil-to-lymphocyte ratio (NLR; p<0.001); higher levels of serum aspartate aminotransferase
(AST; p<0.001), creatinine phosphokinase (CK; p<0.001), and C-reactive protein (p<0.001); and lower sodium levels (p<0.001). Between the hypoxic patients with CP and IP, there were significant between-group differences in NLR, platelet, and CK levels (p<0.001, p=0.045, and p=0.048, respectively).

Radiographic findings are shown in Table 3. There were significantly more patients with CP than those with IP with no visible infiltration on chest X-ray (p=0.003), and this difference was not observed between hypoxic patients with CP and IP (p=0.467). Ground-glass opacities and multilobar infiltrates on CT scan were more prevalent in the CP group (p<0.001 for both); however, consolidation was more prevalent in the IP group (p<0.001). These differences were also observed between hypoxic patients with CP and IP. Concurrent bacterial pneumonia was more common in patients with IP (p<0.001).

**Independent Risk Factors for Types of Pneumonia by Multivariate Analysis**

Multivariate analysis revealed significant between-group differences between CP and IP in the frequency of comorbid BA/COPD (p=0.018), systolic blood pressure (p=0.003), diastolic blood pressure (p=0.007), NLR (p=0.001), AST levels (p=0.034), sodium levels (p=0.019), and frequency of multilobar infiltrates (p=0.032; Figure 2A). The diagnostic characteristics of these variables are described in Supplementary Figure 1. Among the five variables, NLR was the best predictor for differentiating between CP and IP with an area under the receiver operating characteristic (ROC) curve (AUROCC) of 0.809. The optimal cutoff value for NLR as determined by Youden’s index was 7.34, with a sensitivity of 80.7% and specificity of 72.3%. Moreover, the AUROCC for CP diagnosis increased to 0.889 by combining a NLR of <7.3 with the absence of BA/COPD, systolic blood pressure of ≤150 mmHg, diastolic blood pressure of >75 mmHg, AST ≤70 U/L, sodium ≥135 mEq/L, and presence of multilobar infiltrates (Figure 3A). Here, the cutoff values were derived from the ROC
curve and Youden’s index for each variable with adjustment for clinical convenience. The scores for differentiating CP from IP, as well as its sensitivities, specificities, and predictive values are shown in Table 4 and Supplementary Table 3A.

In the hypoxic patients, there was an independent association of IP with the presence of underlying BA/COPD (p=0.014), a higher NLR (p=0.001), and lower sodium levels (p=0.004), Figure 2B). The AUROCC of the differentiating score for CP diagnosis, which was determined in the initial comparison, was 0.846 among hypoxic patients (Figure 3B). Its diagnostic powers among hypoxic patients are shown in Supplementary Table 3B.

**Differences in Post-Admission Clinical Course**

Data on the post-admission clinical course are shown in Supplementary Table 4. Antibiotics were used in 36.5% and 92.4% of the patients with CP and IP, respectively (p<0.001). Respiratory failure requiring oxygen supplementation was more common in the IP group (p<0.001); however, among those requiring oxygen supplementation, newly onset respiratory failure after admission was more common in the CP group (p=0.026). This suggests that post-hospitalization deterioration was more common in the CP group than in the IP group. There was no significant between-group difference in the proportion of patients who received tracheal intubation or ICU admission (p=0.191 and 0.169, respectively). Death was observed in 30 (8.3%) and 13 (19.7%) patients with CP and IP, respectively (p=0.005).

In the hypoxic patients, ICU admission was more common in those with CP (p=0.037); however, there was no significant between-group difference in the length of ICU and mortality rate (p=0.854 and p=0.720, respectively; Supplementary Table 4).
Differences between CP and IP excluding patients with bacterial pneumonia

The differences between CP and IP excluding patients with bacterial pneumonia are shown in Supplementary Table 5. The NLR was significantly higher in patients with IP (p<0.001), ground-glass opacity was more common in patients with CP (p<0.001), and air space consolidation was more common in patients with IP (p<0.001). Multilobar infiltrations on CT scan was more common in IP group (p=0.004). Multivariate analysis revealed independent differences between CP and IP without bacterial co-infection in the frequency of comorbid BA/COPD (OR 0.148, 95% CI 0.032-0.679, p=0.014), systolic blood pressure (OR 0.958, 95% CI 0.932-0.984, p=0.002), and NLR (OR 0.860, 95% CI 0.772-0.958, p=0.006).

Differences in post-admission clinical course between CP and IP without bacterial co-infection at admission is shown in Supplementary Table 6. Antibiotics were used in 123 (34.9%) of the 352 patients with CP and 39 (90.7%) of the 43 patients with IP (p<0.001). There was no significant between-group difference in the proportion of patients who received tracheal intubation or ICU admission (p=0.345 and 0.153, respectively). Death was observed in 30 (8.5%) and 9 (20.9%) patients with CP and IP without bacterial superinfection, respectively (p=0.010). In the hypoxic patients, there was no difference in ICU admission (p=0.126) and mortality rate (p=0.396; Supplementary Table 6).

Mortality Risk Factors for Types of Pneumonia

The risk factors for mortality in both groups are shown in Supplementary Tables 7 and 8. Based on univariate analyses, there were significant differences in background characteristics, vital signs, and laboratory/radiological findings between survivors and non-survivors in patients with CP (Supplementary Table 7). In the multivariate analysis, non-surviving patients with CP were older...
(p=0.005) and more frequently resided in nursing homes (p=0.020). Furthermore, non-survivors had higher systolic blood pressure and WBC counts (p=0.045 and p=0.009, respectively).

Non-surviving patients with IP were also found to be older (p=0.017; Supplementary Table 8). Furthermore, they had significantly lower hematocrit levels (p=0.007), which remained significant after multivariate analysis. Significant predictors for mortality were different between patients with CP and IP, indicating the need for new criteria for predicting CP prognosis.

DISCUSSION

In this study, we compared the clinical characteristics of hospitalized patients with CP and IP by establishing respective multicenter cohorts. Based on multivariate analysis, we revealed that underlying asthma or COPD was less common in patients with CP. Furthermore, patients with CP had lower NLRs, lower systolic blood pressure, higher diastolic blood pressure, lower AST levels, higher sodium levels, and more frequent multilobar infiltrates. The NLR was a useful diagnostic indicator for distinguishing between CP and IP. Subsequently, we developed a diagnostic scoring system with excellent performance in differentiating between CP and IP (AUROCC of 0.889). We were also able to observe differences in the prognostic factors for CP and IP.

COVID-19 is an emerging infectious disease. Although various diagnostic methods have been developed [34,35], the standard diagnosis is still nucleic acid amplification testing like PCR, and given its sensitivity and false negative rate [10,12], repetitive testing might be needed to establish a diagnosis [36]. It may not be possible to perform PCR at times, such as during the night or on holidays; therefore, it is worthwhile to attempt differentiating CP and IP using laboratory data and radiographic imaging.

Tang et al. [18] compared acute respiratory distress syndrome (ARDS) caused by SARS-CoV-2 and H1N1 influenza and found that COVID-19-induced ARDS was associated with lower illness
severity. However, they assessed two independent single-center cohorts and focused on ARDS rather than pneumonia. Qu et al. [33] retrospectively analyzed the differences between CP and IP; however, the influenza patients were derived from a single-center cohort. Patient characteristics and treatment strategies for CP or IP could greatly differ across facilities. Moreover, a multicenter cohort study is required to yield more generalizable findings. This is the first multicenter cohort study utilizing multivariate analysis to examine differences between CP and IP that covered every aspect of clinically relevant features, including patient background, vital signs, laboratory results, and radiographic findings.

Bacterial superinfection at admission was more common in IP group. As the purpose of this study was to compare "clinical features" of CP and IP at admission in real world settings, we did not exclude bacterial superinfection in the aforementioned comparison. In our study, concurrent bacterial pneumonia was defined as pneumonia with causative organisms identified, and 10 (2.8 %) of CP patients and 23 (34.8 %) of IP patients were diagnosed with bacterial superinfection. Microbiological etiology was reportedly determined in 7 % of COVID-19 patients, regardless of the presence/absence of pneumonia [37], and in 19.6 % of influenza-associated community-acquired pneumonia patients [38]. Given that there was a considerable difference in proportion of bacterial superinfection in previous studies as well, this difference is a crucial aspect of the two types of pneumonia. Thus, the higher proportion of bacterial superinfection in IP group may have led to our results on NLR, radiographic findings, and the frequency of antibiotic use. Therefore, we further examined a population in which bacterial co-infection at admission was excluded, and we confirmed that the frequency of BA/COPD, systolic blood pressure, and NLR were independent factors distinguishing the two (p=0.014, 0.002, and 0.006, respectively).

Patients with CP had lower and higher systolic and diastolic blood pressures, respectively. Hypertension is a prognostic factor in viral pneumonia caused by SARS-CoV-2 [39] and other viruses [40]. Additionally, the higher systolic blood pressure in patients with IP could have reflected the
higher disease severity, as evidenced by a higher mortality. This is further supported by the lack of differences in blood pressure and mortality rates between patients with CP and IP when hypoxic patients were compared. Therefore, vital signs cannot solely distinguish between CP and IP in severe cases, indicating the need for laboratory and radiological testing.

A low lymphocyte count is a distinctive characteristic of COVID-19 [41,42]; however, lymphopenia is also common in influenza [43,44]. In this study, the NLR was significantly lower in patients with CP than in patients with IP. Lin et al. [45] reported that an NLR of <3.2 could distinguish COVID-19 from other upper respiratory tract infections; however, the small sample size (n=9) of the study renders its findings inconclusive. In our study, the optimal NLR cutoff value for distinguishing between CP and IP was 7.35 with an AUROCC of 0.809, rendering NLR as the best differentiating indicator for CP. The diagnostic performance was further improved by combining NLR with the absence of BA/COPD, lower systolic blood pressure, higher diastolic blood pressure, lower AST levels, higher sodium levels, and presence of multilobar infiltrates. This scoring system demonstrated utility for severely hypoxic patients. Further studies should verify its diagnostic efficacy in distinguishing between CP and IP, and explore its utility in discriminating between CP and viral pneumonia other than IP.

Furthermore, we studied the risk factors for in-hospital mortality. Among patients with CP, older age, nursing home residence, higher systolic blood pressure, and higher WBC counts were independent risk factors. Contrarily, only the hematocrit level was a prognostic factor among patients with IP. Previous authors have reported numerous prognostic factors, including D-dimer, interleukin-6 [41,46], lactate dehydrogenase, ferritin [46], troponin-T [47], and several mortality-scoring systems [48,49]. However, most of these studies have limited clinical relevance since the measurement of these markers is often unavailable in clinical practice. Conversely, our analysis largely comprised of clinically available information and measurements. In this study, there were only four significant indicators of in-hospital mortality. Based on our findings, CP and IP have
different risk factors for mortality. This further highlights the need for early differential diagnosis between CP and IP in clinical settings, which was the primary objective of our study.

This study has several limitations. First, the data of patients with IP were retrospectively collected. However, this could be considered a strength since influenza is a seasonal infection with some among-season differences in clinical features. By collecting data from patients with IP over 10 years, we minimized the influence of this seasonal fluctuation and improved the generalizability of the findings. Second, the number of patients with IP was small. While most COVID-19 patients were assessed radiologically, those with influenza were radiologically assessed only when pneumonia was suspected due to decrease in SpO$_2$ or worsening general condition. This may have led to selection bias, as infection control procedures and clinical practices were different for influenza and COVID-19. Thus, we first compared real-world clinical presentations and further compared hypoxic patients to minimize the selection bias. Last, patients hospitalized with CP had milder disease than patients hospitalized with IP, as indicated by the difference in the mortality rate. In Japan, all patients with COVID-19, during the study period, were admitted to the hospital, even if asymptomatic. To account for this, we performed comparisons among hypoxic patients, which revealed similar mortality rates among the groups. Furthermore, we tested the performance of the diagnostic scoring method in the hypoxic cohort.

This is the first multicenter study to reveal comprehensive differences between CP and IP in real-world settings. Despite the overall similarity with viral pneumonia, there were significant differences in vital signs, laboratory data, and radiographic findings. Patients with CP had more frequent multilobar infiltrates, lower NLRs, lower systolic blood pressure, higher diastolic blood pressure, lower AST levels, higher sodium levels, and no history of BA/COPD. A scoring system developed based on these findings could differentiate hypoxic CP from hypoxic IP with >84% sensitivity and 72% specificity.
CONCLUSION

Early differentiation between CP and IP is important because their prognoses and optimal treatments differ. Although CP and IP have similar clinical presentations, we found seven significant differences between them. Moreover, the presentation of the two viral pneumonias was more similar when the patients were hypoxic at diagnosis. Altogether, these distinctive clinical characteristics provide potential means for differentiating CP from IP, even when patients are hypoxic.
Notes

**Author contributions.** IO is the guarantor of the manuscript and takes responsibility for the content (including data and analysis). Study design, literature search: IO, II, NH, MS, KN, and TH. Data collection/interpretation/analysis: IO, II, MH, KE, ME, TK, HT1, KT1, AN, KO, MA, MO, TS, MF, DI, YH, KT2, HY, KF, TI, AI, HK, YK, MT, HT2, TY, ST, HN, NH, MS, KN, MY, YS, TO, KH, HA, HS, HM, NT, and TH. Manuscript writing/revisions and drafting of figures: IO, II, NH, MS, KS, and HT. All authors revised the manuscript for important intellectual content and approved the final version of the manuscript.

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**Potential conflict of interests:**

All no reported conflicts of interest.

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References

1. Johns Hopkins University & Medicine. Coronavirus resource Center. Available at: https://coronavirus.jhu.edu/. Accessed 30 April, 2021.

2. Inui S, Fujikawa A, Jtsu M, et al. Chest CT Findings in Cases from the Cruise Ship Diamond Princess with Coronavirus Disease (COVID-19). Radiol Cardiothorac Imaging 2020; 2:e200110.

3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497–506.

4. Diaz JV, Appiah J, Askie L, et al. COVID-19 Clinical management: living guidance. World Heal Organ. Available at: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1. Accessed 30 April, 2021.

5. Jain S, Self WH, Wunderink RG, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. N Engl J Med 2015; 373:415–27.

6. Alimi Y, Lim WS, Lansbury L, Leonardi-Bee J, Nguyen-Van-Tam JS. Systematic review of respiratory viral pathogens identified in adults with community-acquired pneumonia in Europe. J Clin Virol 2017; 95:26–35.

7. Wang X, Zhou Q, He Y, et al. Nosocomial outbreak of COVID-19 pneumonia in Wuhan, China. Eur Respir J 2020; 55:2000544.

8. Schwierzeck V, König JC, Kühn J, et al. First Reported Nosocomial Outbreak of Severe Acute Respiratory Syndrome Coronavirus 2 in a Pediatric Dialysis Unit. Clin Infect Dis 2021; 72:265–70.

9. Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. N Engl J Med 2020; 382:2081–90.
10. Chan JF-W, Yip CC-Y, To KK-W, et al. Improved Molecular Diagnosis of COVID-19 by the Novel, Highly Sensitive and Specific COVID-19-RdRp/Hel Real-Time Reverse Transcription-PCR Assay Validated In Vitro and with Clinical Specimens. McAdam AJ, editor. J Clin Microbiol 2020; 58:1–10.

11. Fang Y, Zhang H, Xie J, et al. Sensitivity of Chest CT for COVID-19: Comparison to RT-PCR. Radiology 2020; 296:E115–7.

12. 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; 173:262–7.

13. Keitel K, Wagner N, Lacroix L, Manzano S, Gervaix A. Performance characteristics of a rapid immunochromatographic assay for detection of pandemic influenza A (H1N1) virus in children. Eur J Pediatr 2011; 170:511–7.

14. Chartrand C, Leeflang MMG, Minion J, Brewer T, Pai M. Accuracy of Rapid Influenza Diagnostic Tests. Ann Intern Med 2012; 156:500–11.

15. Faury H, Courboulès C, Payen M, et al. Medical features of COVID-19 and influenza infection: A comparative study in Paris, France. J Infect 2021; 82:e36–9.

16. Auvinen R, Nohynek H, Syrjänen R, et al. Comparison of the clinical characteristics and outcomes of hospitalized adult COVID-19 and influenza patients—a prospective observational study. Infect Dis (Auckl) 2021; 53:111–21.

17. Lee J, Lee YH, Chang H-H, et al. Comparison of short-term mortality between mechanically ventilated patients with COVID-19 and influenza in a setting of sustainable healthcare system. J Infect 2020; 81:e76–8.
18. Tang X, Du RH, Wang R, et al. Comparison of Hospitalized Patients With ARDS Caused by COVID-19 and H1N1. Chest 2020; 158:195–205.

19. Zayet S, Kadiane-Oussou NJ, Lepiller Q, et al. Clinical features of COVID-19 and influenza: a comparative study on Nord Franche-Comte cluster. Microbes Infect. 2020; 22:481–8.

20. Zhang J, Ding D, Huang X, et al. Differentiation of COVID-19 from seasonal influenza: A multicenter comparative study. J Med Virol 2021; 93:1512–9.

21. Chen J, Pan Y, Li G, et al. Distinguishing between COVID-19 and influenza during the early stages by measurement of peripheral blood parameters. J Med Virol 2021; 93:1029–37.

22. Cates J, Lucero-Obusan C, Dahl RM, et al. Risk for In-Hospital Complications Associated with COVID-19 and Influenza — Veterans Health Administration, United States, October 1, 2018–May 31, 2020. MMWR Morb Mortal Wkly Rep 2020; 69:1528–34.

23. Piroth L, Cottenet J, Mariet AS, et al. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. Lancet Respir Med 2021; 9:251–259.

24. Niquini RP. Description and comparison of demographic characteristics and comorbidities in SARI from COVID-19, SARI from influenza, and the Brazilian general population. 2020; 36:1–12.

25. Burn E, You SC, Sena AG, et al. Deep phenotyping of 34,128 patients hospitalised with COVID-19 and a comparison with 81,596 influenza patients in America, Europe and Asia: an international network study. MedRxiv 2020.04.22.20074336 [Preprint]. 1 January 2020. Available at: http://medrxiv.org/content/early/2020/04/25/2020.04.22.20074336.abstract.

26. Cobb NL, Sathe NA, Duan KI, et al. Comparison of clinical features and outcomes in critically ill patients hospitalized with COVID-19 versus influenza. Ann Am Thorac Soc 2021; 18:632–40.
27. Yin Z, Kang Z, Yang D, Ding S, Luo H, Xiao E. A Comparison of Clinical and Chest CT Findings in Patients with Influenza A (H1N1) Virus Infection and Coronavirus Disease (COVID-19). Am J Roentgenol 2020; 215:1065–71.

28. Liu M, Zeng W, Wen Y, Zheng Y, Lv F, Xiao K. COVID-19 pneumonia: CT findings of 122 patients and differentiation from influenza pneumonia. Eur Radiol 2020; 30:5463–9.

29. Lin YH, Luo W, Wu DH, et al. Comparison of clinical, laboratory, and radiological characteristics between SARS-CoV-2 infection and community-acquired pneumonia caused by influenza virus: A cross-sectional retrospective study. Medicine 2020; 99:e23064.

30. Luo Y, Yuan X, Xue Y, et al. Using a diagnostic model based on routine laboratory tests to distinguish patients infected with SARS-CoV-2 from those infected with influenza virus. Int J Infect Dis 2020; 95:436–40.

31. Lin L, Fu G, Chen S, et al. CT manifestations of coronavirus disease (COVID-19) pneumonia and influenza virus pneumonia: A comparative study. Am J Roentgenol 2021; 216:71–9.

32. Wang H, Wei R, Rao G, Zhu J, Song B. Characteristic CT findings distinguishing 2019 novel coronavirus disease (COVID-19) from influenza pneumonia. Eur Radiol 2020; 30:4910–7.

33. Qu J, Chang LK, Tang X, et al. Clinical characteristics of COVID-19 and its comparison with influenza pneumonia. Acta Clin Belg 2020; 00:1–9.

34. Lambert-Niclot S, Cuffel A, Pape S Le, et al. Evaluation of a Rapid Diagnostic Assay for Detection of SARS-CoV-2 Antigen in Nasopharyngeal Swabs. J Clin Microbiol 2020; 58:e00977–20.

35. Mertens P, Vos N De, Martiny D, et al. Development and Potential Usefulness of the COVID-19 Ag Respi-Strip Diagnostic Assay in a Pandemic Context. Front Med (Lausanne) 2020; 7:225.
36. Lee TH, Junhao Lin R, Lin RTP, et al. Testing for SARS-CoV-2: Can We Stop at 2? Clin Infect Dis 2020; 71:2246–8.

37. Lansbury L, Lim B, Baskaran V, Lim WS. Co-Infections in People with COVID-19: a systematic review and meta-analysis. J Infect 2020; 81:266–75.

38. Teng F, Liu X, Guo S Bin, et al. Community-acquired bacterial co-infection predicts severity and mortality in influenza-associated pneumonia admitted patients. J Infect Chemother 2019; 25:129–36.

39. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020; 146:110–8.

40. Guo L, Wei D, Zhang X, Wu Y, Li Q, Zhou M, et al. Clinical Features Predicting Mortality Risk in Patients With Viral Pneumonia: The MuLBSTA Score. Front Microbiol 2019; 10:2752.

41. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020; 323:1061–9.

42. Huang C, Wang Y, Li X, et al. Articles Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497–506.

43. Yan X, Li F, Wang X, et al. Neutrophil to lymphocyte ratio as prognostic and predictive factor in patients with coronavirus disease 2019: A retrospective cross-sectional study. J Med Virol 2020; 92:2573–81.

44. Chen L, Han XD, Li YL, Zhang CX, Xing XQ. Comparison of the Clinical Characteristics and Severity of Influenza and Non-influenza Respiratory Virus-Related Pneumonia in China: A Multicenter, Real-World Study. Infect Drug Resist 2020; 13:3513–23.

45. Lin H-A, Lin S-F, Chang H-W, Lee Y-J, Chen R-J, Hou S-K. Clinical impact of monocyte distribution width and neutrophil-to-lymphocyte ratio for distinguishing COVID-19 and
influenza from other upper respiratory tract infections: A pilot study. PLoS One 2020; 15:e0241262.

46. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395:1054–62.

47. Almeida G De, Braga F, Jorge JK, et al. Prognostic Value of Troponin-T and B-Type Natriuretic Peptide in Patients Hospitalized for COVID-19. Arq Bras Cardiol 2020; 115:660–6.

48. Xiao LS, Zhang WF, Gong MC, et al. Development and validation of the HNC-LL score for predicting the severity of coronavirus disease 2019. EBioMedicine 2020; 57:102880.

49. Knight SR, Ho A, Pius R, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: Development and validation of the 4C Mortality Score. BMJ 2020; 370:1–13.
We compared the characteristics of 362 patients with severe acute respiratory syndrome coronavirus 2 pneumonia (CP) and 66 patients with influenza virus pneumonia (IP). Moreover, we compared 90 (24.9%) and 44 (66.7%) hypoxic patients with CP and IP at diagnosis, respectively. There were 30 (8.3%) and 13 (19.7%) patients with CP and IP who did not survive, respectively.

Plots reporting variables independently associated with the risk for CP or IP in the final model, with their 95% CIs. (A) ORs of variables for CP or IP, and (B) ORs of variables for CP with hypoxia or IP with hypoxia.

CP, severe acute respiratory syndrome coronavirus 2 pneumonia; IP, influenza virus pneumonia; OR, odds ratio; CI, confidence interval; BA, bronchial asthma; COPD, chronic obstructive pulmonary disease; sBP, systolic blood pressure; dBP, diastolic blood pressure; Neu, neutrophil; Lym, lymphocyte; AST, aspartate transaminase; Na, sodium.

(A) ROC curves of scores for differentiating CP from influenza pneumonia (IP) and (B) hypoxic CP from hypoxic IP (B). ROC, receiver operating characteristic; CP, severe acute respiratory syndrome coronavirus 2 pneumonia; IP, influenza virus pneumonia; AUC, area under the curve. The differentiating score is shown in Table 4.
Table 1. Comparison of patient background between pneumonia caused by severe acute respiratory syndrome coronavirus 2 (CP) and influenza virus (IP)

|                  | All cohorts |                     |                     | Hypoxic cohorts |                     |                     |
|------------------|-------------|---------------------|---------------------|-----------------|---------------------|---------------------|
|                  | CP (n=362)  | IP (n=66)           | P-value             | CP (n=90)       | IP (n=44)           | P-value             |
| Age, years       | 57 (46.8, 72)| 70 (60.8, 80.3)     | <0.001              | 71 (57, 76)     | 71 (58.5, 80.8)     | 0.414               |
| Male, n (%)      | 216 (59.7)  | 44 (66.7)           | 0.284               | 63 (70.0)       | 29 (65.9)           | 0.632               |
| Smoker, n (%)    | 145/297 (48.8)| 37/61 (60.7)       | 0.092               | 43/77 (55.8)    | 27/41 (65.9)        | 0.292               |
| Nursing Home resident, n (%) | 6/359 (1.7)   | 5/65 (7.7)         | 0.016               | 1 (1.1)         | 2/43 (4.7)          | 0.244               |
| BA/COPD, n (%)   | 25 (6.9)    | 21 (31.8)           | <0.001              | 7 (7.8)         | 15 (34.1)           | <0.001              |
| DM, n (%)        | 60 (16.6)   | 17 (25.8)           | 0.074               | 19 (21.1)       | 12 (27.3)           | 0.427               |
| Condition              | n (%)  | 123 (34.0) | 25 (37.9) | 0.540 | 44 (48.9) | 18 (40.9) | 0.384 |
|------------------------|--------|------------|-----------|-------|-----------|-----------|-------|
| **HT, n (%)**          |        |            |           |       |           |           |       |
| **Cardiac diseases, n (%)** | 10 (2.8) | 7 (10.6) | 0.008 | 4 (4.4) | 4 (9.1) | 0.438 |

CP, severe acute respiratory syndrome coronavirus 2 pneumonia; IP, influenza virus pneumonia; BA, bronchial asthma; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HT, hypertension.

Data are presented as medians (interquartile ranges) or percentages of the total number of patients with available data.
Table 2. Comparison of vital signs at admission between pneumonia caused by severe acute respiratory syndrome coronavirus 2 and influenza virus

|                      | All cohorts                  | Hypoxic cohorts               |
|----------------------|------------------------------|-------------------------------|
|                      | CP (n=362)                   | IP (n=66)                     | CP (n=90) | IP (n=44) | P-value | CP (n=90) | IP (n=44) | P-value |
| sBP, mmHg (n)        | 126 (115, 140) (361)         | 133.5 (117.3, 153)            | 0.024     | 124 (114, 148.3) | 130.5 (115.8, 149.5) | 0.557 |
| dBP, mmHg (n)        | 80 (69.5, 88) (361)          | 71 (63, 82.3)                 | 0.004     | 75.5 (66, 83) | 70 (60.3, 82.5) | 0.240 |
| HR, /min             | 87 (77, 98)                  | 95.5 (87.8, 111.3)            | <0.001    | 88 (75.8, 102.5) | 97.5 (88, 112) | 0.002 |
| RR, /min (n)         | 18 (16, 22) (245)            | 24 (20, 29.8) (44)            | <0.001    | 24 (20, 30) (72) | 25 (22.3, 30) (34) | 0.179 |
| RR >30/min, n (%)    | 24/254 (9.5)                 | 11/46 (23.9)                 | 0.005     | 22/75 (29.3) | 10/35 (28.6) | 0.935 |
| Hypoxia, n (%)       | 90 (24.9)                    | 44 (66.7)                     | <0.001    |                     |                    |       |
| BT, °C               | 37.2 (36.6, 38.0)            | 38.1 (37.3, 38.6)            | <0.001    | 37.6 (36.7, 38.5) | 38.1 (37.4, 38.7) | 0.082 |
Confusion, n (%)  18 (5.0)  14 (21.2)  <0.001  16 (17.8)  10 (22.7)  0.496

CP, severe acute respiratory syndrome coronavirus 2 pneumonia; IP, influenza virus pneumonia; sBP, systolic blood pressure; dBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; BT, body temperature.

Data are presented as medians (interquartile ranges) or percentages of the total number of patients with available data.
Table 3. Comparison of laboratory data and radiographic findings at admission between pneumonia caused by severe acute respiratory syndrome coronavirus 2 and influenza virus

| Blood sampling test | All cohorts | Hypoxic cohorts |
|---------------------|-------------|-----------------|
|                     | CP (n=362)  | IP (n=66)       | CP (n=90)  | IP (n=44) |
| WBC, ×10^3/µL (n)   | 5.1 (4.0, 6.7) (353) | 8.1 (4.2, 10.2) | 6.6 (4.8, 9.2) | 8.4 (4.7, 10.2) | <0.001 | 0.272 |
| Neu/Lym (n)         | 3.7 (2.2, 6.0) (321) | 10.8 (6.0, 17.7) (65) | 7.5 (4. , 10.9) (83) | 11.3 (7.6, 17.7) (43) | <0.001 |
| Parameter          | Mean (95% CI) | Std. Dev. | Median (95% CI) | p-value |
|--------------------|--------------|-----------|----------------|---------|
| Ht, % (n)          | 40.7 (37.2, 43.8) (353) | 0.058     | 39.6 (36.1, 43.0) | 0.829   |
| Plt, ×10^9/µL (n)  | 18.7 (15.0, 24.4) (352) | 0.022     | 17.4 (12.5, 21.7) | 0.045   |
| D-dimer, (µg/mL) (n)| 1.2 (0.9, 1.9) (163) | <0.001    | 2.1 (1.2, 4.5) (34) | 0.854   |
| TP, g/dL (n)       | 6.9 (6.5, 7.2) (347) | 0.378     | 6.8 (6.3, 7.3) (64) | 0.206   |
| AST, U/L (n)       | 31 (23, 48) (353) | 0.001     | 40.5 (28, 90.8) | 0.684   |
| ALT, U/L (n)       | 26 (15.5, 43) (353) | 0.686     | 25.5 (15.8, 51.3) | 0.396   |
| LDH, U/L (n)       | 277 (216, 358.5) (353) | 0.001     | 324 (246, 520.3) | 0.159   |
| T-bil, mg/dL (n)   | 0.56 (0.4, 0.7) (338) | 0.003     | 0.65 (0.5, 0.9) (64) | 0.171   |
| CK, U/L (n)        | 78 (50, 136) (338) | <0.001    | 128 (92, 556) (63) | 0.048   |
| BUN, mg/dL (n)     | 13.9 (10.5, 18.0) (353) | <0.001    | 17.1 (13.0, 23.2) | 0.418   |
| Test                  | Mean (Min, Max) (n) | Mean (Min, Max) (n) | p-value | Mean (Min, Max) (n) | Mean (Min, Max) (n) | p-value |
|-----------------------|---------------------|---------------------|---------|---------------------|---------------------|---------|
| Cre, mg/dL (n)        | 0.81 (0.63, 0.96) (352) | 0.8 (0.6, 1.0) | 0.271   | 0.9 (0.7, 1.1) | 0.9 (0.7, 1.2) | 0.818   |
| Na, mEq/L (n)         | 138 (136, 140) (353) | 136.5 (133, 139)   | <0.001  | 137 (135, 140) | 136 (133, 139) | 0.082   |
| K, mEq/L (n)          | 4.0 (3.7, 4.3) (352) | 4.0 (3.5, 4.3) | 0.380   | 4.0 (3.6, 4.3) | 3.9 (3.5, 4.3) | 0.622   |
| Glu, mg/dL (n)        | 113 (101, 136) (322) | 128 (110, 155) (59) | 0.002   | 124 (109, 171) (85) | 135.5 (113.8, 160.3) (38) | 0.407   |
| CRP, mg/dL (n)        | 3.6 (0.8, 8.6) (351) | 8.3 (3.6, 18.2) | <0.001  | 10.6 (6.1, 16.9) | 8.4 (3.2, 20.1) | 0.705   |
| PCT, ng/mL (n)        | 0.06 (0.03, 0.13) (36) | 0.53 (0.20, 3.01) (22) | <0.001  | 0.11 (0.05, 0.32) (11) | 1.37 (0.26, 4.49) (16) | 0.001   |

**Radiographic Assessment**

| Radiographic Feature                  | Mean (Min, Max) (n) | Mean (Min, Max) (n) | p-value | Mean (Min, Max) (n) | Mean (Min, Max) (n) | p-value |
|---------------------------------------|---------------------|---------------------|---------|---------------------|---------------------|---------|
| X-ray infiltration/image, n (%)      | 282/324 (87.0)      | 65/66 (98.5)        | 0.003   | 83/84 (98.8)        | 44/44 (100)        | 0.467   |
| Ground glass opacity, n (%)          | 256/282 (90.8)      | 44/65 (67.6)        | <0.001  | 79/83 (95.2)        | 31 (70.5)          | <0.001  |
| Condition                        | Control (n=282) | Case (n=65) | P Value  | Control (n=83) | Case (n=43) | P Value  |
|---------------------------------|-----------------|-------------|----------|----------------|-------------|----------|
| Air space consolidation, n (%)  | 77/282 (27.7)   | 40/64 (62.5)| <0.001   | 26/83 (31.3)   | 15/43 (34.9) | 0.406    |
| Mixed pattern, n (%)            | 63/346 (18.2)   | 21/64 (32.8)| 0.008    | 23/83 (27.7)   | 15/43 (34.9) | 0.406    |
| Bilateral infiltrations, n (%)   | 201/282 (71.3)  | 44/65 (67.7)| 0.567    | 83/83 (100)    | 30 (68.2)   | <0.001   |
| Multilobar lesions, n (%)       | 276/304 (90.8)  | 46/63 (73.0)| <0.001   | 80/80 (100)    | 29/42 (69.1)| <0.001   |
| Pleural effusion, n (%)         | 19 (5.3)        | 6 (9.1)     | 0.221    | 13 (14.4)      | 5 (11.4)    | 0.623    |
| **Bacterial pneumonia**<sup>a</sup>, n (%) | 10 (2.8)        | 23 (34.9)   | <0.001   | 6 (6.7)        | 16 (36.4)   | <0.001   |
| **CT assessment**               | 346 (95.6)      | 64 (97.0)   | 0.489    | 83 (92.2)      | 43 (97.7)   | 0.272    |
| **Ground glass opacity, n (%)** | 331/346 (95.7)  | 39/64 (60.9)| <0.001   | 80/83 (96.4)   | 26/43 (60.5)| <0.001   |
CP, severe acute respiratory syndrome coronavirus 2 pneumonia; IP, influenza virus pneumonia; WBC, white blood cell; Neu, neutrophil; Lym, lymphocyte; Ht, hematocrit; Plt, platelet; TP, total protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; T-bil, total bilirubin; CK, creatinine phosphokinase; BUN, blood urea nitrogen; Cre, creatinine; Na, sodium; K, potassium; Glu, glucose; CRP, C-reactive protein; PCT, procalcitonin.

Data are presented as medians (interquartile ranges) or percentages of the total number of patients with available data.

*Bacterial pneumonia was defined as pneumonia in which the pathogen was detected by sputum, urine antigen, or serum tests.
Table 4. Score for differentiating pneumonia caused by severe acute respiratory syndrome coronavirus 2 and influenza virus

| Variables                                           | Score |
|-----------------------------------------------------|-------|
| Absence of BA or COPD                               | +1    |
| Systolic blood pressure ≤150 mmHg                   | +1    |
| Diastolic blood pressure >75 mmHg                   | +1    |
| Neutrophil-to-lymphocyte ratio ≤7.3                 | +1    |
| AST ≤70 U/L                                         | +1    |
| Na ≥135 mEq/L                                       | +1    |
| Multilobar infiltration in radiographic examination | +1    |

Total Max 7 points

BA, bronchial asthma; COPD, chronic obstructive pulmonary disease; AST, aspartate aminotransferase; Na, sodium.

The total score was 7 points with each item in the table being scored as 1 point. The higher the differentiating score, the more likely it is to be novel coronavirus pneumonia.
Figure 1

| CP          |                | IP          |                |
|-------------|----------------|-------------|----------------|
| (n = 362)   |                | (n = 66)    |                |
| Hypoxic     | Non-hypoxic    | Hypoxic     | Non-hypoxic    |
| (n = 90)    | (n = 272)      | (n = 44)    | (n = 22)       |
| Survivors   | Non-survivors  | Survivors   | Non-survivors  |
| (n = 332)   | (n = 30)       | (n = 53)    | (n = 13)       |
Figure 2

(A)  

| Condition | OR (95%CI) | p-value |
|-----------|------------|---------|
| BAC/CPD  | 0.106 (0.026-0.434) | 0.018 |
| eBP      | 0.061 (0.936-0.966) | 0.003 |
| dBP      | 1.069 (1.019-1.122) | 0.007 |
| Nati/Lyn | 0.874 (0.804-0.949) | 0.001 |
| AST      | 0.987 (0.975-0.999) | 0.034 |
| Na       | 1.190 (1.029-1.376) | 0.019 |
| Multiobar baseline | 10.570 (1.226-91.098) | 0.002 |

(B)  

| Condition | OR (95%CI) | p-value |
|-----------|------------|---------|
| BAC/CPD  | 0.154 (0.034-0.656) | 0.014 |
| Nati/Lyn | 0.91 (0.853-0.971) | 0.001 |
| Na       | 1.201 (1.047-1.378) | 0.004 |
