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

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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 who were 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 ($P < .01$), lower neutrophil-to-lymphocyte ratio ($P < .01$), lower systolic blood pressure ($P < .01$), higher diastolic blood pressure ($P < .01$), lower aspartate aminotransferase level ($P < .05$), higher serum sodium level ($P < .05$), and more frequent multilobar infiltrates ($P < .05$). 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 2 pneumonias in clinical settings.

Keywords. COVID-19; influenza; multicenter study; pneumonia.

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

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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%, 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 rapid antigen test or PCR. Patients with IP were retrospectively included from the 2009–2010 to 2019–2020 season from 9 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 on 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

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 cases 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 2 experienced pulmonologists, with discrepancies resolved through consensus. Concurrent bacterial pneumonia was diagnosed upon identification of causative organisms by sputum cultures, urinary antigen tests, or serological examinations on 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-square test or Fisher 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 ($P < .10$) 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, USA). All *P* values <.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. 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 with the IP group ($P < .001$, $P = .016$, and $P < .001$, 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 ($P < .001$).

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 ($P < .001$, $P = .013$, $P = .009$, and $P = .016$, respectively), while dyspnea and wet cough were more common in patients with IP ($P < .001$ for both). Seven (1.9%) patients with CP were completely asymptomatic; however, all patients with IP had a minimum of 1 symptom. Furthermore, among hypoxic patients, dry cough was more common in patients with CP ($P = .029$), whereas wet cough was more common in patients with IP ($P < .001$) (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 with patients with IP, patients with CP showed lower systolic blood pressure ($P = .024$), higher diastolic blood pressure ($P = .004$), lower heart rate ($P < .001$), lower respiratory rate ($P < .001$), and lower body temperature ($P < .001$). Hypoxia and confusion were less frequent in patients with CP than in patients with IP (both $P < .001$). However, hypoxic patients with CP had lower heart rates ($P = .002$) 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 ($P < .001$); contrarily, patients with IP showed a higher neutrophil-to-lymphocyte ratio (NLR; $P < .001$); higher levels of serum aspartate aminotransferase (AST; $P < .001$), creatinine phosphokinase (CK; $P < .001$), and C-reactive protein ($P < .001$); and lower sodium levels ($P < .001$). Between the hypoxic patients with CP and IP, there were significant between-group differences in NLR, platelet, and CK levels ($P < .001$, $P = .045$, and $P = .048$, 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 ($P = .003$), and this difference was not observed between hypoxic patients with CP and IP ($P = .467$). Ground-glass opacities and multilobar infiltrates on CT scan were more prevalent in the CP group ($P < .001$ for both); however, consolidation was more prevalent in the IP group ($P < .001$). These differences were also observed between hypoxic patients with CP and IP. Concurrent bacterial pneumonia was more common in patients with IP ($P < .001$).

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 ($P = .018$), systolic blood pressure ($P = .003$), diastolic blood pressure ($P = .007$), NLR ($P = .001$), AST levels ($P = .034$), sodium levels ($P = .019$), and frequency of multilobar infiltrates ($P = .032$) (Figure 2A). The diagnostic characteristics of these variables are described in Supplementary Figure 1. Among the 5 variables, NLR was the best predictor for differentiating between CP and IP, with an area under the receiver operating

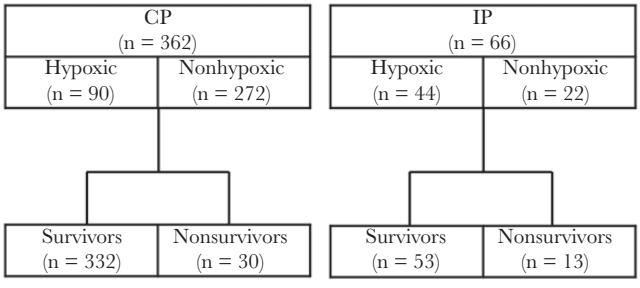

Figure 1. Participant enrollment in the study. We compared the characteristics of 362 patients with CP and 66 patients with IP. Moreover, we compared 90 (24.9%) and 44 (66.7%) hypoxic patients with CP and IP at diagnosis, respectively. There were 30 (8.3%) and 13 (19.7%) patients with CP and IP who did not survive, respectively. Abbreviations: CP, severe acute respiratory syndrome coronavirus 2 pneumonia; IP, influenza virus pneumonia.

Table 1. Comparison of Patient Backgrounds Between Pneumonia Caused by CP and IP

	All Cohorts			Hypoxic Cohorts		
	CP (n = 362)	IP (n = 66)	*P* Value	CP (n = 90)	IP (n = 44)	*P* Value
Age, y	57 (46.8–72)	70 (60.8–80.3)	<.001	71 (57–76)	71 (58.5–80.8)	.414
Male, No. (%)	216 (59.7)	44 (66.7)	.284	63 (70.0)	29 (65.9)	.632
Smoker, No. (%)	145/297 (48.8)	37/61 (60.7)	.092	43/77 (55.8)	27/41 (65.9)	.292
Nursing home resident, No. (%)	6/359 (1.7)	5/65 (7.7)	.016	1 (1.1)	2/43 (4.7)	.244
BA/COPD, No. (%)	25 (6.9)	21 (31.8)	<.001	7 (7.8)	15 (34.1)	<.001
DM, No. (%)	60 (16.6)	17 (25.8)	.074	19 (21.1)	12 (27.3)	.427
HT, No. (%)	123 (34.0)	25 (37.9)	.540	44 (48.9)	18 (40.9)	.384
Cardiac diseases, No. (%)	10 (2.8)	7 (10.6)	.008	4 (4.4)	4 (9.1)	.438

Data are presented as median (interquartile range) or percentage of the total number of patients with available data.

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

characteristics (ROC) curve (AUROC) 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 AUROC for CP diagnosis increased to 0.889 by combining an 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 ($P = .014$), a higher NLR ($P = .001$), and lower sodium levels ($P = .004$) (Figure 2B). The AUROC 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 the Postadmission Clinical Course

Data on the postadmission 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 ($P < .001$). Respiratory failure requiring oxygen supplementation was more common in the IP group ($P < .001$); however, among those requiring oxygen supplementation, new-onset respiratory failure after admission was more common in the CP group ($P = .026$). 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 ($P = .191$ and 0.169, respectively). Death was observed in 30 (8.3%) and 13 (19.7%) patients with CP and IP, respectively ($P = .005$).

In the hypoxic patients, ICU admission was more common in those with CP ($P = .037$); however, there was no significant between-group difference in the length of ICU stay and mortality rate ($P = .854$ and $P = .720$, respectively) (Supplementary Table 4).

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)	*P* Value	CP (n = 90)	IP (n = 44)	*P* Value
sBP, mmHg (No.)	126 (115–140) (361)	133.5 (117.3–153)	.024	124 (114–148.3)	130.5 (115.8–149.5)	.557
dBP, mmHg (No.)	80 (69.5–88) (361)	71 (63–82.3)	.004	75.5 (66–83)	70 (60.3–82.5)	.240
HR, /min	87 (77–98)	95.5 (87.8–111.3)	<.001	88 (75.8–102.5)	97.5 (88–112)	.002
RR, /min (No.)	18 (16–22) (245)	24 (20–29.8) (44)	<.001	24 (20–30) (72)	25 (22.3–30) (34)	.179
RR >30/min, No. (%)	24/254 (9.5)	11/46 (23.9)	.005	22/75 (29.3)	10/35 (28.6)	.935
Hypoxia, No. (%)	90 (24.9)	44 (66.7)	<.001			
BT, °C	37.2 (36.6–38.0)	38.1 (37.3–38.6)	<.001	37.6 (36.7–38.5)	38.1 (37.4–38.7)	.082
Confusion, No. (%)	18 (5.0)	14 (21.2)	<.001	16 (17.8)	10 (22.7)	.496

Data are presented as median (interquartile range) or percentage of the total number of patients with available data.

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

Table 3. Comparison of Laboratory Data and Radiographic Findings 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)	*P* Value	CP (n = 90)	IP (n = 44)	*P* Value
Blood sampling test						
WBC, $\times 10^3/\mu L$ (No.)	5.1 (4.0–6.7) (353)	8.1 (4.2–10.2)	<.001	6.6 (4.8–9.2)	8.4 (4.7–10.2)	.272
Neu/Lym (No.)	3.7 (2.2–6.0) (321)	10.8 (6.0–17.7) (65)	<.001	7.5 (4.–10.9) (83)	11.3 (7.6–17.7) (43)	<.001
Ht, % (No.)	40.7 (37.2–43.8) (353)	39.6 (36.1–43.0)	.058	39.5 (36.2–41.4)	39.9 (35.9–42.9)	.829
Plt, $\times 10^4/\mu L$ (No.)	18.7 (15.0–24.4) (352)	17.4 (12.5–21.7)	.022	18.4 (14–23.8)	16.9 (12.1–22.1)	.045
D-dimer, μg/mL (No.)	1.2 (0.9–1.9) (163)	2.1 (1.2–4.5) (34)	<.001	1.9 (1.3–4.2) (43)	2.2 (1.5–4.5) (25)	.854
TP, g/dL (No.)	6.9 (6.5–7.2) (347)	6.8 (6.3–7.3) (64)	.378	6.6 (6.2–6.8) (88)	6.7 (6.2–7.0) (42)	.206
AST, U/L (No.)	31 (23–48) (353)	40.5 (28–90.8)	.001	46.5 (34.8–62.5)	48 (30–100.5)	.684
ALT, U/L (No.)	26 (15.5–43) (353)	25.5 (15.8–51.3)	.686	32 (20–53.5)	25.5 (15.3–51.8)	.396
LDH, U/L (No.)	277 (216–358.5) (353)	324 (246–520.3)	.001	416 (325.8–512.8)	356 (250.3–546.3)	.159
T-bil, mg/dL (No.)	0.56 (0.4–0.7) (338)	0.65 (0.5–0.9) (64)	.003	0.6 (0.5–0.8) (86)	0.7 (0.5–0.9) (43)	.171
CK, U/L (No.)	78 (50–136) (338)	128 (92–556) (63)	<.001	116.5 (64.3–220.3) (88)	161.5 (76.3–668)	.048
BUN, mg/dL (No.)	13.9 (10.5–18.0) (353)	17.1 (13.0–23.2)	<.001	17.3 (14.1–24.7)	19 (14.1–28.3)	.418
Cre, mg/dL (No.)	0.81 (0.63–0.96) (352)	0.8 (0.6–1.0)	.271	0.9 (0.7–1.1)	0.9 (0.7–1.2)	.818
Na, mEq/L (No.)	138 (136–140) (353)	136.5 (133–139)	<.001	137 (135–140)	136 (133–139)	.082
K, mEq/L (No.)	4.0 (3.7–4.3) (352)	4.0 (3.5–4.3)	.380	4.0 (3.6–4.3)	3.9 (3.5–4.3)	.622
Glu, mg/dL (No.)	113 (101–136) (322)	128 (110–155) (59)	.002	124 (109–171) (85)	135.5 (113.8–160.3) (38)	.407
CRP, mg/dL (No.)	3.6 (0.8–8.6) (351)	8.3 (3.6–18.2)	<.001	10.6 (6.1–16.9)	8.4 (3.2–20.1)	.705
PCT, ng/mL (No.)	0.06 (0.03–0.13) (36)	0.53 (0.20–3.01) (22)	<.001	0.11 (0.05–0.32) (11)	1.37 (0.26–4.49) (16)	.001
Radiographic assessment						
X-ray infiltration/image, No. (%)	282/324 (87.0)	65/66 (98.5)	.003	83/84 (98.8)	44/44 (100)	.467
Ground glass opacities, No. (%)	256/282 (90.8)	44/65 (67.6)	<.001	79/83 (95.2)	31 (70.5)	<.001
Air space consolidation, No. (%)	78/282 (27.7)	43/65 (66.2)	<.001	32/83 (38.6)	29 (65.9)	.003
Mixed pattern, No. (%)	52/282 (18.4)	22/65 (33.9)	.006	28/83 (33.7)	16 (36.4)	.767
Bilateral infiltrations, No. (%)	201/282 (71.3)	44/65 (67.7)	.567	83/83 (100)	30 (68.2)	<.001
CT assessment	346 (95.6)	64 (97.0)	.489	83 (92.2)	43 (97.7)	.272
Ground glass opacities, No. (%)	331/346 (95.7)	39/64 (60.9)	<.001	80/83 (96.4)	26/43 (60.5)	<.001
Air space consolidation, No. (%)	77/346 (22.3)	40/64 (62.5)	<.001	26/83 (31.3)	28/43 (34.9)	.406
Mixed pattern, No. (%)	63/346 (18.2)	21/64 (32.8)	.008	23/83 (27.7)	15/43 (34.9)	.406
Multilobar lesions, No. (%)	276/304 (90.8)	46/63 (73.0)	<.001	80/80 (100)	29/42 (69.1)	<.001
Pleural effusion, No. (%)	19 (5.3)	6 (9.1)	.221	13 (14.4)	5 (11.4)	.623
Bacterial pneumonia,[a] No. (%)	10 (2.8)	23 (34.9)	<.001	6 (6.7)	16 (36.4)	<.001

Data are presented as median (interquartile range) or percentage of the total number of patients with available data.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatinine phosphokinase; CP, severe acute respiratory syndrome coronavirus 2 pneumonia; Cre, creatinine; CRP, C-reactive protein; Glu, glucose; Ht, hematocrit; IP, influenza virus pneumonia; K, potassium; LDH, lactate dehydrogenase; Lym, lymphocyte; Na, sodium; Neu, neutrophil; PCT, procalcitonin; Plt, platelet; T-bil, total bilirubin; TP, total protein; WBC, white blood cell.

[a]Bacterial pneumonia was defined as pneumonia in which the pathogen was detected by sputum, urine antigen, or serum test.

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 ($P < .001$), ground-glass opacities were more common in patients with CP ($P < .001$), and air space consolidation was more common in patients with IP ($P < .001$). Multilobar infiltrations on CT scan were more common in the IP group ($P = .004$). Multivariate analysis revealed independent differences between CP and IP without bacterial co-infection in the frequency of comorbid BA/COPD (odds ratio [OR], 0.148; 95% CI, 0.032–0.679; $P = .014$), systolic blood pressure (OR, 0.958; 95% CI, 0.932–0.984; $P = .002$), and NLR (OR, 0.860; 95% CI, 0.772–0.958; $P = .006$).

Differences in postadmission clinical course between CP and IP without bacterial co-infection at admission are 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 ($P < .001$). There was no significant between-group difference in the proportion of patients who received tracheal intubation or ICU admission ($P = .345$ and 0.153, respectively). Death was observed in 30 (8.5%) and 9 (20.9%) patients with CP and IP without bacterial superinfection, respectively ($P = .010$). In the hypoxic patients, there was no difference in ICU admission ($P = .126$) or mortality rate ($P = .396$) (Supplementary Table 6).

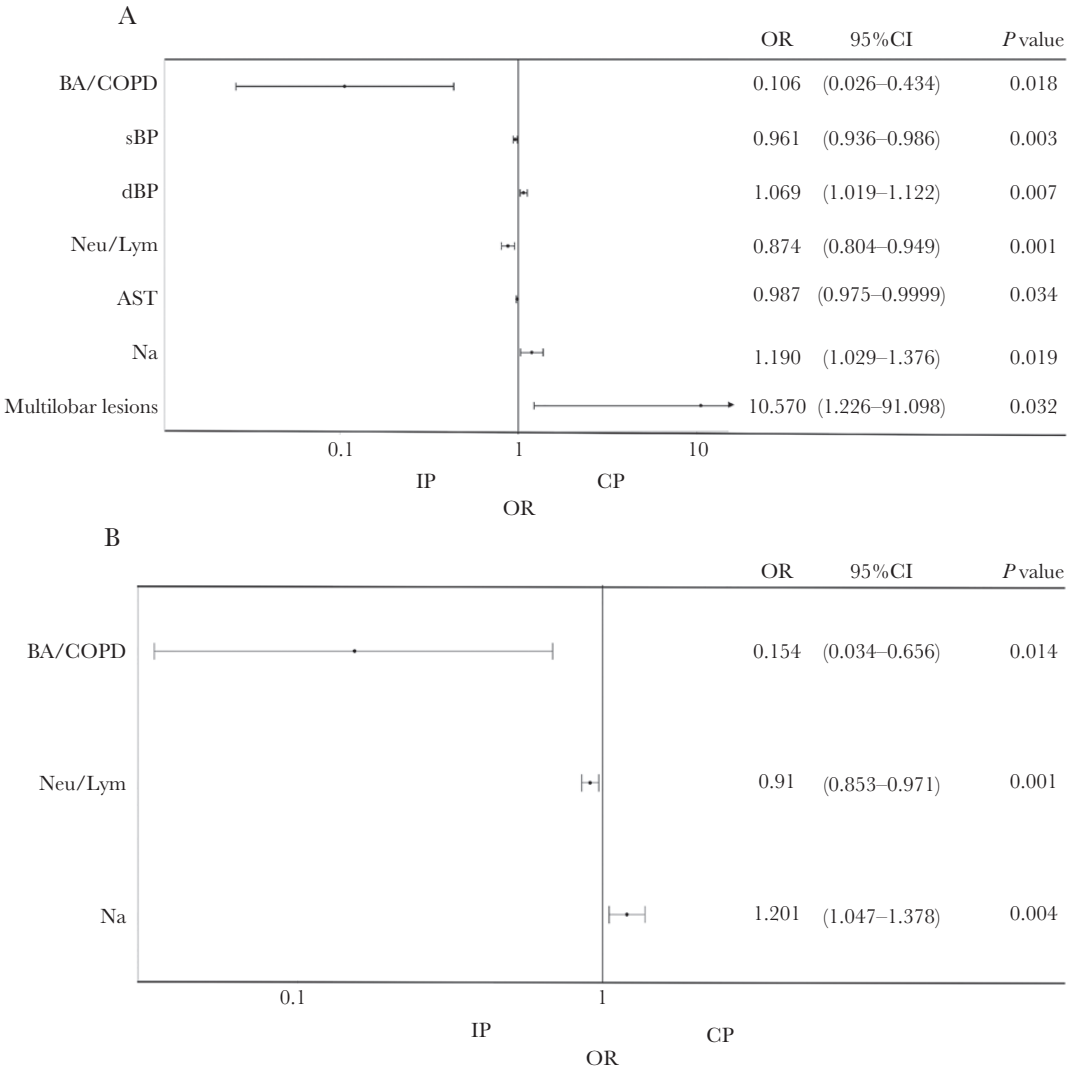

Figure 2. Multivariate models of the specific risk factors for CP or IP. Plots report variables independently associated with the risk for CP or IP in the final model, with their 95% CIs. A, ORs of variables for CP or IP and (B) ORs of variables for CP with hypoxia or IP with hypoxia. Abbreviations: AST, aspartate transaminase; BA, bronchial asthma; COPD, chronic obstructive pulmonary disease; CP, severe acute respiratory syndrome coronavirus 2 pneumonia; dBP, diastolic blood pressure; IP, influenza virus pneumonia; Lym, lymphocyte; Na, sodium Neu, neutrophil; OR, odds ratio; sBP, systolic blood pressure.

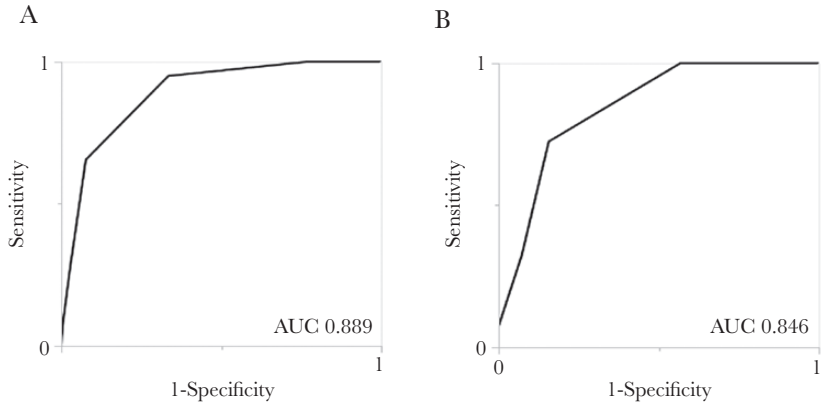

Figure 3. Receiver operating characteristic curves of the differentiating score for CP. A, ROC curves of scores for differentiating CP from IP and (B) hypoxic CP from hypoxic IP (B). The differentiating score is shown in Table 4. Abbreviations: AUC, area under the curve; CP, severe acute respiratory syndrome coronavirus 2 pneumonia; IP, influenza virus pneumonia; ROC, receiver operating characteristic.

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 on radiographic examination	+1
Total	Max 7 points

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.

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

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 nonsurvivors in patients with CP (Supplementary Table 7). In the multivariate analysis, nonsurviving patients with CP were older (P = .005) and more frequently resided in nursing homes (P = .020). Furthermore, nonsurvivors had higher systolic blood pressure and WBC counts (P = .045 and P = .009, respectively).

Nonsurviving patients with IP were also found to be older (P = .017) (Supplementary Table 8). Furthermore, they had significantly lower hematocrit levels (P = .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 (AUROC, 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 PCR's sensitivity and false-negative rate [10, 12], repeat 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 2 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 the 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%) CP patients and 23 (34.8%) 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 the proportion of bacterial superinfection in previous studies as well, this difference is a crucial aspect of the 2 types of pneumonia. Thus, the higher proportion of bacterial superinfection in the 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 2 (P = .014, .002, and .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 higher disease severity, as evidenced by 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 AUROC of 0.809, rendering NLR 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 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 as the measurement of these markers is often unavailable in clinical practice. Conversely, our analysis was largely comprised of clinically available information and measurements. In this study, there were only 4 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 as 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 a 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 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.

CONCLUSIONS

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 7 significant differences between them. Moreover, the presentation of the 2 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.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. I.O. is the guarantor of the manuscript and takes responsibility for the content (including data and analysis). Study design, literature search: I.O., I.I., N.H., M.S., K.N., and T.H. Data collection/interpretation/analysis: I.O., I.I., M.H., K.E., M.E., T.K., H.Ts., K.To., A.N., K.O., M.A., M.O., T.S., M.F., D.I., Y.H., K.Ta., H.Y., K.F., T.I., A.I., H.K., Y.K., M.T., H.To., T.Y., S.T., H.N., N.H., M.S., K.N., M.Y., Y.S., T.O., K.H., H.A., H.S., H.M., N.T., and T.H. Manuscript writing/revisions and drafting of figures: I.O., I.I., N.H., M.S., K.S., and H.T. All authors revised the manuscript for important intellectual content and approved the final version of the manuscript.

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