Comparison of Clinical Features and Outcomes in Critically Ill Patients Hospitalized with COVID-19 versus Influenza

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Abstract

Rationale: No direct comparisons of clinical features, laboratory values, and outcomes between critically ill patients with coronavirus disease (COVID-19) and patients with influenza in the United States have been reported.

Objectives: To evaluate the risk of mortality comparing critically ill patients with COVID-19 with patients with seasonal influenza.

Methods: We retrospectively identified patients admitted to the intensive care units (ICUs) at two academic medical centers with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or influenza A or B infections between January 1, 2019, and April 15, 2020. The clinical data were obtained by medical record review. All patients except one had follow-up to hospital discharge or death. We used relative risk regression adjusting for age, sex, number of comorbidities, and maximum sequential organ failure scores on Day 1 in the ICU to determine the risk of hospital mortality and organ dysfunction in patients with COVID-19 compared with patients with influenza.

Results: We identified 65 critically ill patients with COVID-19 and 74 patients with influenza. The mean (±standard deviation) age in each group was 60.4 ± 15.7 and 56.8 ± 17.6 years, respectively. Patients with COVID-19 were more likely to be male, have a higher body mass index, and have higher rates of chronic kidney disease and diabetes. Of the patients with COVID-19, 37% identified as Hispanic, whereas 10% of the patients with influenza identified as Hispanic. A similar proportion of patients had fevers (∼40%) and lymphopenia (∼80%) on hospital presentation. The rates of acute kidney injury and shock requiring vasopressors were similar between the groups. Although the need for invasive mechanical ventilation was also similar in both groups, patients with COVID-19 had slower improvements in oxygenation, longer durations of mechanical ventilation, and lower rates of extubation than patients with influenza. The hospital mortality was 40% in patients with COVID-19 and 19% in patients with influenza (adjusted relative risk, 2.13; 95% confidence interval, 1.24–3.63; $P = 0.006$).

Conclusions: The need for invasive mechanical ventilation was common in patients in the ICU for COVID-19 and influenza. Compared with those with influenza, patients in the ICU with COVID-19 had worse respiratory outcomes, including longer duration of mechanical ventilation. In addition, patients with COVID-19 were at greater risk for in-hospital mortality, independent of age, sex, comorbidities, and ICU severity of illness.

Keywords: critical care outcomes; severe acute respiratory syndrome coronavirus 2; acute respiratory distress syndrome; mortality

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After severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus that causes coronavirus disease (COVID-19), was first identified in Wuhan, China, in December 2019, the initial reports suggested that hospital mortality among critically ill patients is high and that certain comorbidities are overrepresented in patients with COVID-19 (1–5). However, most of these studies have not included a comparison population of critically ill patients with respiratory viral infections other than COVID-19.

Early in the outbreak, many comparisons were made between COVID-19 and the influenza infection, a common respiratory virus responsible for a significant number of hospitalizations and significant mortality in the United States and globally (6–8). Both COVID-19 and influenza cause a range of clinical disease from mild illness to severe illness, acute respiratory distress syndrome (ARDS), and death (9–12). Yet, there are likely important differences between the two respiratory viral infections, including differences in the proportion of individuals who develop severe disease and the rate of mortality (13–15).

Direct comparisons of the two viruses, particularly with regard to mortality, have been challenging. One reason is that the number of influenza deaths are often based on estimates, whereas for COVID-19, deaths are currently being reported as direct counts rather than as estimates (7, 16, 17). Another limitation is that COVID-19 deaths may have been underreported to surveillance agencies early in the outbreak because of limitations in diagnostic testing (18). One prior observational study from China compared characteristics of patients with ARDS due to COVID-19 with patients with ARDS due to influenza A (H1N1) and demonstrated a lower mortality among those with SARS-CoV-2 infection (19). In contrast, other studies have suggested that mortality rates among persons with COVID-19 are higher than those among persons with seasonal influenza (16, 20).

To further evaluate the risk of mortality between critically ill patients with COVID-19 and patients with seasonal influenza, we identified a cohort of patients admitted to the intensive care unit (ICU) with influenza A or B and compared them with ICU patients with COVID-19 from the same medical system.

Methods

Study Population, Setting, and Data Collection

We performed a cohort study of patients with laboratory-confirmed COVID-19 or influenza who were admitted to the medical ICUs at two hospitals in the University of Washington medical system (University of Washington Medical Center and Montlake and Harborview Medical Center) between January 1, 2019, and April 15, 2020. A confirmed case of COVID-19 was defined as a positive result on a reverse transcriptase–polymerase chain reaction (PCR) assay using specimens collected from nasopharyngeal swabs, from endotracheal aspirates, or on autopsy (21). Influenza A or B infection was confirmed by reverse transcriptase–PCR on a rapid diagnostic test or an extended respiratory-virus PCR panel. All laboratory tests with positive results were completed during the index hospitalization. The cohort search was performed using Leaf, a web-based cohort discovery tool at the University of Washington (22). A total of 142 adults 18 years of age and older were identified from the two hospitals. Three cases (one COVID-19 case and two influenza cases) were excluded from the analysis, as their primary admission diagnosis was determined on chart review to be unrelated to their COVID-19 or influenza infection. The final analysis included 139 cases. From the medical record, we abstracted demographics, clinical symptoms or signs at presentation, comorbidity data, and laboratory and radiologic results during admission by chart review. Data were collected using Research Electronic Data Capture, a secure web-based application hosted at the Institute of Translational Health Sciences (23). The University of Washington Institutional Review Board approved this study.

Study Definitions

Comorbidities were ascertained on the basis of physician documentation on admission. If comorbidities were not documented, they were assumed to be absent. A similar approach was used to obtain data on clinical symptoms. Positive sputum culture results were defined by bacterial growth in qualified sputum, excluding normal oropharyngeal flora. Positive blood culture results excluded common contaminants such as coagulase-negative *Staphylococcus* and *S. hominis*. The sputum and blood cultures were defined as early if they were collected within the first 2 days of admission to the study hospital. ARDS was reported according to ICU physician documentation. In instances in which documentation was unclear or missing, the presence of ARDS was determined by study personnel on the basis of the presence of bilateral pulmonary opacities on chest imaging and acute (<7 d) onset of hypoxemia (partial pressure of arterial oxygen [Pa_{O_2}]/fraction of inspired oxygen [FI_{O_2}] ratio < 300) (24). Acute kidney injury was defined as an increase in serum creatinine ⩾0.3 mg/dl and/or ⩾50% during hospitalization compared with the baseline serum creatinine value measured within the year before the time of hospitalization. If no prior serum creatinine value was available, the serum creatinine value at the time of admission was used as the baseline value. Renal replacement therapy was defined as the need for acute hemodialysis, continuous renal replacement therapy, or peritoneal dialysis. The primary outcome was in-hospital mortality. Secondary outcomes included the need for mechanical ventilation, shock requiring vasopressors, or acute renal replacement therapy at any time during hospitalization.

Statistical Analysis

Descriptive statistics were used to summarize the data, and results are reported as medians and interquartile ranges (IQRs) or means and standard deviations, as appropriate. The categorical variables were summarized as counts and percentages. No imputation was made for missing data. We conducted comparisons of baseline characteristics, symptoms, laboratory findings, and ICU therapies between the two groups using a *t* test for continuous variables and a chi-square test or Fisher exact test for binary and categorical variables. We performed relative risk regression using a multivariate generalized linear model to test for associations between our primary and secondary outcomes (dependent variable) and type of respiratory virus: COVID-19 versus influenza (independent variable). We used a Poisson model and robust standard error estimates.

We selected adjustment variables *a priori* on the basis of biologic plausibility and prior literature suggesting that these variables may confound associations between the type of respiratory virus and clinical outcomes (25–30). We performed two models for covariate adjustment. The first adjusted model included age, sex, and

number of the following comorbidities: chronic kidney disease, diabetes, asthma, chronic obstructive pulmonary disease, and obesity. We used the number of comorbidities to account for several chronic diseases and also to limit the number of individual covariates included in the model. The second model included model 1 covariates and the sequential organ failure assessment (SOFA) score, based on the worst variables obtained during the first day of ICU admission (31, 32). At the time of manuscript submission, one patient with COVID-19 was still hospitalized. This case was excluded from the analysis of in-hospital mortality.

Analyses were performed using Stata 16.0 software (StataCorp).

Results

Demographic and Clinical Characteristics in COVID-19 and Influenza Cases

Between January 1, 2019, and April 15, 2020, we identified 65 patients admitted to a medical ICU with COVID-19 infection and 74 patients admitted to a medical ICU with influenza infection. The COVID-19 cases were clustered between March 6, 2020, and April 13, 2020. Of the influenza cases, 30 out of 74 (41%) occurred during the most recent influenza season, between September 2019 and March 2020.

Patient Characteristics

Table 1 compares patient characteristics in critically ill patients with influenza and COVID-19. Among patients with COVID-19, 72% underwent testing for influenza. None had a coinfection with influenza. The average age in both groups was similar, 60.4 years (±15.7) among the COVID-19 cases compared with 56.8 years (±17.6) among the influenza cases. In both groups, the majority of patients were male. Among patients with influenza, 10% identified as Hispanic or Latino; in contrast, among patients with COVID-19, 37% identified as Hispanic or Latino ($P < 0.001$). A similar proportion of patients in both groups were admitted from skilled nursing facilities (8% vs. 11%). Body mass index was greater in patients with COVID-19 (median, 30.4 kg/m^2; IQR, 27.2–36.7) than in patients with influenza (median, 24.9 kg/m^2; IQR, 21.7–33.1). Chronic kidney disease and diabetes mellitus were recorded as comorbidities in more patients with COVID-19 than in patients with influenza, although these differences were not statistically significant. In contrast, patients with influenza had higher rates of chronic obstructive pulmonary disease, cirrhosis, and tobacco use than patients with COVID-19. Among the COVID-19 group, 15 (23%) patients had do-not-resuscitate orders documented at the time of hospital admission, compared with the 10 (14%) patients in the influenza group.

Table 1. Baseline clinical characteristics

Characteristics	COVID-19 (*n* = 65)	Influenza (*n* = 74)	*P* Value*
Age, average (standard deviation), range, yr	60.4 (15.7), 23–97	56.8 (17.6), 20–92	0.20
Sex, *n* (%)			
Male	46 (70.8)	42 (56.8)	0.09
Female	19 (29.2)	32 (43.2)	
Race			
American Indian/Alaska Native	0 (0)	3 (4.1)	0.09
Asian	9 (13.9)	5 (6.8)	
Native Hawaiian or Pacific Islander	3 (4.6)	1 (1.4)	
Black/African American	3 (4.6)	11 (14.9)	
White	47 (72.3)	51 (68.9)	
Unknown	3 (4.6)	3 (4.1)	
Ethnicity	—	—	
Hispanic or Latino	24 (36.9)	7 (9.5)	<0.001
Not Hispanic or Latino	38 (58.5)	56 (75.7)	
Unknown	3 (4.6)	11 (14.9)	
Admission location, *n* (%)			
Home	40 (61.5)	50 (67.6)	0.42
Group home	1 (1.5)	4 (5.4)	
Skilled nursing facility	7 (10.8)	6 (8.1)	
Hospital transfer	17 (26.2)	13 (17.6)	
Unknown	0 (0)	1 (1.4)	
Body mass index, median (IQR), kg/m^2†	30.4 (27.2–36.7)	24.9 (21.7–33.1)	0.006
Coexisting disease, *n* (%)			
Asthma	4 (6.2)	12 (16.2)	0.06
Cancer‡	4 (6.2)	3 (4.1)	0.71
Chronic kidney disease	14 (21.5)	9 (12.2)	0.14
Chronic dialysis	2 (3.1)	2 (2.7)	1.00
Chronic obstructive pulmonary disease	1 (1.5)	17 (23.0)	<0.001
Cirrhosis	0 (0)	6 (8.1)	0.03
Current or former tobacco smoke use, *n*/total *n* (%)	14/47 (29.8)	33/54 (61.1)	0.002
Diabetes mellitus	26 (40.0)	21 (28.4)	0.15
Hemorrhagic or Ischemic stroke	5 (7.7)	7 (9.5)	0.71
HIV	2 (3.1)	2 (2.7)	1.00
Obstructive sleep apnea	10 (15.4)	5 (6.8)	0.10
Immunosuppression§	6 (9.2)	3 (4.1)	0.30
Code status on admission, *n* (%)			
Full code	50 (76.9)	64 (86.5)	0.15
DNR/intubation OK	10 (15.4)	4 (5.4)	
DNR/DNI	5 (7.7)	6 (8.1)	

Definition of abbreviations: COVID-19 = coronavirus disease; DNI = do not intubate; DNR = do not resuscitate; HIV = human immunodeficiency syndrome; IQR = interquartile range.
Data are presented as means (standard deviations) with ranges for continuous variables and as counts with percentages (%) for binary and categorical variables.
*P values were calculated using a t test for continuous variables and a chi-square test or Fisher exact test for binary and categorical variables.
†Body mass index was missing in two patients.
‡Cancer included known lymphoma, leukemia, and metastatic cancer.
§Defined as prednisone over 10 mg daily for more than 1 month or any other immunosuppressant.

Presenting Symptoms and Signs

Patients with COVID-19 had a longer median symptom duration before hospitalization: 7 days (IQR, 5–13) compared with the 3.5 days (IQR, 2–7) for influenza ($P < 0.001$) (Table 2). Although

Table 2. Clinical symptoms and vital signs on admission

Clinical Symptoms and Vitals on Admission	COVID-19 (*n* = 65)	Influenza (*n* = 74)	*P* Value*
Symptom duration before admission, median (IQR), d†	7 (5–13)	3.5 (2–7)	<0.001
Known sick contact, *n*/total *n* (%)	32/55 (58.2)	19/48 (39.6)	0.06
Symptoms on presentation, *n* (%)‡			
Cough	53 (81.5)	50 (67.6)	0.06
Sputum production	18 (27.7)	25 (33.8)	0.44
Shortness of breath	54 (83.1)	51 (68.9)	0.05
Sore throat	10 (15.4)	5 (6.8)	0.10
Nasal congestion	7 (10.8)	11 (14.9)	0.47
Rhinorrhea	9 (13.9)	9 (12.2)	0.77
Subjective fever	41 (63.1)	30 (40.5)	0.008
Chills	22 (33.9)	16 (21.6)	0.11
Headache	13 (20.0)	9 (12.2)	0.21
Myalgias	21 (32.3)	15 (20.3)	0.11
Fatigue	23 (35.4)	35 (47.3)	0.16
Vital signs on ICU admission, *n*/total *n* (%)	—	—	—
Fever, temperature >100.4°F or 38°C, *n*/total *n* (%)	28/64 (43.8)	27/68 (39.7)	0.64
Heart rate >100 beats/min	21/65 (32.3)	46/72 (63.9)	<0.001
Respiratory rate ⩾20 breaths/min	49/65 (75.4)	57/72 (79.2)	0.60
SOFA score on ICU admission, median (IQR)§	6 (3–11)	6.5 (3–10)	0.62

Definition of abbreviations: COVID-19 = coronavirus disease; ICU = intensive care unit; IQR = interquartile range; SOFA = sequential organ failure assessment.
The total number is given if values are missing.
**P* values were calculated using a *t* test for continuous variables and a chi-square test or Fisher exact test for binary and categorical variables.
†Not reported in 11 patients.
‡Symptoms were assumed to be absent if not reported.
§Highest SOFA score within 24 hours of ICU admission.

patients with COVID-19 had, on average, more symptoms on hospital admission than patients with influenza, no symptoms differentiated the two diseases. In both groups, approximately 40% of patients were febrile at hospital admission. The SOFA scores on ICU admission were similar in both groups, with a median score of 6 (IQR, 3–11) among COVID-19 cases compared with a median score of 6.5 (IQR, 3–10) among influenza cases ($P = 0.62$).

Laboratory, Radiologic, and Microbiologic Results

The admission white blood cell count was higher in patients with influenza than in patients with COVID-19 ($P = 0.007$) (Table 3). The lymphocyte count was similar between the two populations, with approximately 80% of patients in both groups having a lymphocyte count less than 1,500/mm^3. In patients with COVID-19, blood inflammatory markers were elevated, including c-reactive protein, lactate dehydrogenase, and interleukin-6, but because these were not commonly measured in patients with influenza, no direct comparisons could be made between groups (*see* Table E1 in the online supplement). D-dimer was elevated in both the influenza and COVID-19 groups. Other markers of coagulation, specifically international normalized ratio and partial thromboplastin time, did not differ over the first 3 days of hospitalization (Table E2). A higher proportion of sputum cultures with bacterial growth occurred early after hospital admission (within 2 d) in patients with influenza than in patients with COVID-19 (72% vs. 27%; $P = 0.005$) (Table 3). *S. aureus* was the most common organism identified in early and late sputum cultures in both groups (Tables E3 and E4). Out of both groups, 15% of patients with COVID-19 had positive blood cultures during hospitalization compared with 8% among patients with influenza ($P = 0.28$). A viral coinfection was found in 4 out of 36 (11%) patients with influenza versus 1 out of 17 (6%) patients with COVID-19 on the basis of testing with an extended-panel viral PCR ($P = 1.0$). Almost all patients with COVID-19 had bilateral opacities (92%) on chest radiographs compared with only 64% of patients with influenza ($P < 0.001$) (Table 3).

Respiratory Failure and Shock

A similar proportion of patients required invasive mechanical ventilation (59% in COVID-19 vs. 55% in influenza) and vasopressor therapy for shock (55% in COVID-19 vs. 49% in influenza) (Table 4). A diagnosis of ARDS was more common among patients with COVID-19 (63% vs. 26%; $P < 0.001$). The median Pa_{O_2}/FI_{O_2} ratio on Day 1 of mechanical ventilation was 126 (IQR, 73–165) for patients with COVID-19 compared with 101.5 (IQR, 83–188) for patients with influenza. Patients with influenza experienced more rapid improvement in the Pa_{O_2}/FI_{O_2} ratio during their ICU admission (Table 3). Respiratory system compliance and plateau pressure were similar between patients with influenza and patients with COVID-19 during the first 3 days of mechanical ventilation. Respiratory system compliance was low in both groups, with a median of 31.3 ml/cm H_2O (IQR, 25.3–38.3 ml/cm H_2O) for patients with COVID-19 versus 27 ml/cm H_2O (IQR, 22.1–28 ml/cm H_2O) for patients with influenza (Table 4). These findings were similar when comparing patients with COVID-19 and ARDS with patients with influenza and ARDS (Table E5).

Treatment

On the basis of institutional practice guidelines, a majority of patients with COVID-19 received treatment with hydroxychloroquine (Table E6). Over one-third of patients with COVID-19 were enrolled in a placebo-controlled clinical trial (Table E7). Almost all of the patients with influenza received antiviral therapy, most commonly oseltamivir (Table E8). Corticosteroids were more common in the influenza group (51% vs. 20%) (Table E9).

Outcomes

The median hospital and ICU lengths of stay and duration of mechanical ventilation were longer in patients with COVID-19 than in patients with influenza (Table 4). Among patients receiving invasive mechanical ventilation, 72% of those with COVID-19 were mechanically ventilated for over 7 days compared with the 46% of patients with influenza ($P = 0.21$). Development of acute kidney injury and need for renal replacement therapy did not differ between the two groups. Hospital mortality was 40%

Table 3. Laboratory data on hospital admission and imaging findings

	COVID-19 (*n* = 65)	Influenza (*n* = 74)	*P* Value*
Admission laboratory data†			
White blood cell count			
Median (IQR), per mm^3	7,240 (5,430–11,820)	9,035 (6,590–14,900)	0.007
Distribution, *n*/total *n* (%)			
⩾10,000 per mm^3	22 (33.9)	30 (40.5)	—
⩽4,000 per mm^3	6 (9.2)	3 (4.1)	—
Neutrophil count			
Median (IQR), per mm^3	5,405 (3,880–9,580)	7,210 (4,990–11,890)	0.02
Lymphocyte count			
Median (IQR), per mm^3	910 (550–1,350)	800 (590–1,220)	0.48
Distribution, *n*/total *n* (%)			
⩽1,500/mm^3	50/62 (80.7)	57/71 (80.3)	—
Aspartate aminotransferase >40 U/L, *n*/total *n* (%)	31/59 (52.5)	31/65 (47.7)	0.59
Alanine aminotransferase >40 U/L, *n*/total *n* (%)	21/59 (35.6)	21/65 (32.3)	0.70
Lactate, median (IQR), mmol/L	1.55 (1.2–2.45)	2.15 (1.5–3.4)	0.48
Lactate ⩾1.5 mmol/L, *n*/total *n* (%)	31/52 (59.6)	50/64 (78.1)	—
C-reactive protein, median (IQR), mg/L	148.5 (76.2–219.7)	—	—
Lactate dehydrogenase, median (IQR), U/L	419 (322–513)	—	—
Interleukin-6, median (IQR), pg/ml	160.5 (71–254)	—	—
Laboratory data during first 3 d of ICU admission‡			
Highest serum creatinine, median (IQR), mg/dl	1.13 (0.89–1.92)	1.10 (0.82–1.63)	0.82
Highest troponin ⩾0.06 ng/ml, *n*/total *n* (%)	16/56 (28.6)	21/56 (37.5)	0.32
Lowest platelets, median (IQR), per mm^3	187 (149–230)	168 (118–206)	0.04
Highest bilirubin, median (IQR), mg/dl	0.6 (0.5–0.9)	0.7 (0.4–1.2)	0.15
Creatine kinase ⩾100 U/L, *n*/total *n* (%)	18/27 (66.7)	9/13 (69.2)	1.00
Daily $Pa_{O_2}/F_{I_{O_2}}$ ratio during mechanical ventilation§			
Day 1 lowest $Pa_{O_2}/F_{I_{O_2}}$ ratio, median (IQR)	126 (73–165)	101.5 (83–188)	0.311
Day 2 lowest $Pa_{O_2}/F_{I_{O_2}}$ ratio, median (IQR)	120 (96–167)	167.5 (98–252.5)	0.02
Day 3 lowest $Pa_{O_2}/F_{I_{O_2}}$ ratio, median (IQR)	121 (98–145)	181 (127–216.5)	0.006
Infection analyses, *n*/total *n* (%)‖			
Blood cultures (positive)	7/46 (15.2)	4/49 (8.2)	0.28
Early blood cultures (positive)	1/7 (14.3)	3/4 (75.5)	0.09
Sputum cultures (positive)	22/34 (64.7)	18/34 (52.9)	0.32
Early sputum cultures (positive)	6/22 (27.2)	13/18 (72.2)	0.005
Influenza A	0/47	58 (78.4)	—
Influenza B	0/47	16 (21.6)	—
Extended-spectrum respiratory viruses (positive)	1/17 (5.9)	4/36 (11.1)	1.0
Chest radiographic findings, *n*/total *n* (%)¶			
Clear chest radiograph	1/63 (1.6)	14/73 (19.2)	0.001
Bilateral opacities	57/63 (90.5)	38/73 (52.1)	<0.001
Pleural effusion	7/63 (11.1)	10/73 (13.7)	0.65

Definition of abbreviations: COVID-19 = coronavirus disease; $F_{I_{O_2}}$ = fraction of inspired oxygen; ICU = intensive care unit; IQR = interquartile range; Pa_{O_2} = partial pressure of arterial oxygen; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Data are presented as medians (IQRs) for continuous variables and as counts with frequencies (%) for binary and categorical variables. The total number is given if values are missing.

**P* values were calculated using a *t* test for continuous variables and a chi-square test or Fisher exact test for binary and categorical variables.

†There were 6 missing values for the neutrophil count and lymphocyte count, 15 missing values for aspartate aminotransferase and alanine aminotransferase, and 23 missing values for lactate. Lactate included either arterial or venous lactate. For CRP (c-reactive protein), LDH (lactate dehydrogenase), and IL-6 (interleukin-6), values are presented only for patients with COVID-19 because of the large number of missing values in patients with influenza. For COVID-19, there were 20 missing CRP values, 24 missing LDH values, and 33 missing IL-6 values.

‡There was 1 missing creatinine value, and there were 11 missing bilirubin values.

§Among 80 patients who were mechanically ventilated, the $Pa_{O_2}/F_{I_{O_2}}$ ratio is missing for five patients on Day 1, 28 patients on Day 2, and 35 patients on Day 3.

‖Viral testing was performed on nasopharyngeal swab, endotracheal aspirate, or bronchoalveolar lavage samples. Extended-spectrum testing included metapneumovirus, parainfluenza, respiratory syncytial virus, (non–SARS-CoV-2) coronavirus, rhinovirus, adenovirus, or bocavirus.

¶Reported only for chest radiograph within first 3 days of hospitalization.

in patients with COVID-19 versus 19% in patients with influenza ($P = 0.006$). Among those with ARDS, hospital mortality was 46% and 37%, respectively (Table E10). At the time of the manuscript submission, one patient was still hospitalized with COVID-19 and was excluded from the survival population for regression analyses. In multivariable analysis, COVID-19 was associated with a twofold greater risk of hospital mortality than influenza with a relative risk of 2.13 (95% confidence interval, 1.24–3.63), adjusting for age, sex, number of comorbidities, and SOFA score at the time of ICU admission (Table 5). In contrast, multivariable analyses demonstrated that COVID-19 was not associated with higher risk of organ dysfunction, including the need for invasive mechanical ventilation, vasopressors, or renal replacement therapy, than influenza.

Discussion

Strengths and Limitations

To our knowledge this is the first study to directly compare outcomes among critically ill patients with influenza with patients with COVID-19 in the United States. Among patients from two United States hospitals that are part of the same healthcare system, we found that critically ill patients with COVID-19 are at twice the risk for hospital mortality compared with those with influenza, even after adjusting for physiologic illness severity on ICU admission. We also identified key differences in clinical characteristics and laboratory values between patients with COVID-19 and influenza. Our study results build on those from prior case series and provide further evidence of the added risk for worse outcomes and increased mortality in COVID-19 compared with seasonal influenza (16, 20).

Despite similar rates of invasive mechanical ventilation, shock, and need for renal replacement therapy, the risk of hospital mortality was higher in COVID-19 than in influenza. One reason for the higher risk of mortality in COVID-19 may be differences in the etiology of critical illness. Specifically, there were higher rates of ARDS in patients with COVID-19, whereas bacterial coinfection early during hospitalization was more common in patients with influenza. Thus, among patients with influenza, the cause of ICU admission may have been more responsive to antibiotic treatment. In contrast, patients with COVID-19 not only had higher rates of ARDS but also had a different trajectory of respiratory failure with longer durations of mechanical ventilation. Even though respiratory system compliance was similar between both groups during the first 3 days of mechanical ventilation, patients with influenza had more rapid improvements in oxygenation than the patients with COVID-19. Certainly, there is evidence for the prolonged need for invasive mechanical ventilation in COVID-19 (1–3, 5, 10). In our study, patients with COVID-19 were hospitalized later after symptom onset, consistent with prior reports of ARDS occurring 8–12 days after onset (2, 5, 10). Finally, some have suggested that there may be differences in the type of ARDS in COVID-19 (33–35), although this is controversial (36, 37). One autopsy series described certain histologic features, including alveolar microthrombi and vascular angiogenesis, which may be more common among patients with COVID-19 than in patients with ARDS secondary to influenza (33). However, another series found the histologic features of COVID-19 to be indistinguishable from other causes of diffuse alveolar damage, commonly seen in ARDS (38). When comparing hospital mortality among patients with ARDS, we found a 10% higher mortality in COVID-19. However, our number of patients with ARDS is small, and these results were not statistically different. Further research is needed to understand the mechanisms underlying differences in mortality.

It is important to note that several other factors may have impacted outcomes in this study, including altered care processes and treatment protocols early during the pandemic. Although shortages of medical resources and ICU beds occurred in a number of hospitals, our center did not experience a limitation of resources, staff, or ICU beds and never approached crisis standards of care. In fact, because of the cancellation of elective surgeries and an overall decrease in the in-patient census, the ICU bed census at these two hospitals was lower in March and April of 2020 than in previous years during the same time period (Figure E1). Nonetheless, there were changes in certain practices, such as clustered nursing care, changes in sedation practices, and environmental services that may have affected care and patient outcomes. We would hypothesize that medical systems overwhelmed with a surge of patients with COVID-19 may have experienced worse outcomes. In addition, the literature regarding treatment of COVID-19 has rapidly evolved. Although hydroxychloroquine was widely used during the period of data collection in this study, dexamethasone, which has since been shown to improve outcomes in certain patients, was not used on a routine basis (39, 40).

In contrast to our results, a previous observational study from China found a higher mortality rate in those with H1N1-induced ARDS than in COVID-19–induced ARDS (34.7% vs. 28.8%) (19). There are, however, several important distinctions between this study and ours. In our study, cases of COVID-19 and influenza were from a single medical system, whereas the study by Tang and colleagues (19) compared COVID-19 cases from a hospital in the Hubei province with influenza cases from a hospital in Beijing. Including patients from two different hospital systems may not account for differences in local practice patterns and other factors. In addition, the study from China only included patients with diagnosed ARDS. Given that we found that only a minority of ICU patients with influenza develop ARDS, the study by Tang and colleagues may have selected for a more severely ill population of patients with influenza. In addition, in Tang and colleagues' study, approximately 36% of patients with COVID-19 remained hospitalized at the end of the study, which may have resulted in an underestimate of hospital mortality in the COVID-19 population. In our study, we were able to observe a final outcome of either hospital discharge or death for all except one patient with COVID-19.

We observed far higher rates of noninvasive positive-pressure ventilation among patients with influenza and patients with COVID-19. This may reflect differences in disease severity between the two groups but may also relate to local practice conditions during the pandemic that encouraged invasive mechanical ventilation among patients with COVID-19 to minimize the risk of virus transmission. Another reason for the differences in mode of respiratory support may be owed to the increased proportion of patients with influenza and an obstructive lung disease, in which the indication for management with noninvasive positive-pressure ventilation is well supported by the literature (41). Although the use of a high-flow nasal cannula was similar between the groups, prone mechanical ventilation was employed more often among those with COVID-19. This may reflect the difference in the underlying rates and severity of ARDS, but could also be due to differences in the clinical practice during the pandemic, as earlier studies have suggested that ventilation in the prone position may be underutilized in ARDS (42, 43).

Our findings support prior reports that racial and ethnic minorities may be disproportionately affected, with 37% of patients among the COVID-19 group reporting Hispanic ethnicity compared with 10% among the influenza group (30, 44). This may be related to underlying health factors as well as social and economic inequalities (45). Interestingly, although lymphopenia has been commonly described

Table 4. ICU-level therapies and clinical outcomes

ICU Therapies and Outcomes	COVID-19 (*n* = 65)	Influenza (*n* = 74)	*P* Value*
ICU indication, *n*/total *n* (%)			
Mechanical ventilation on ICU admission	27 (41.5)	32 (43.2)	0.21
Hypoxemic respiratory failure (without mechanical ventilation on ICU admission)	28 (43.1)	24 (32.4)	
Shock requiring vasopressors on ICU admission	5 (7.7)	4 (5.4)	
Other	5 (7.7)	14 (18.9)	
ICU therapies, *n*/total *n* (%)†			
High-flow nasal cannula	20 (30.8)	26 (35.1)	0.59
Bilevel noninvasive positive pressure	1 (1.5)	29 (39.2)	<0.001
Invasive mechanical ventilation	39 (60.0)	41 (55.4)	0.58
Ventilation in the prone position	18/39 (46.2)	6/41 (14.6)	0.002
Neuromuscular blockade	15/39 (38.5)	11/41 (26.8)	0.27
Inhaled epoprostenol	4/39 (10.3)	6/41 (14.6)	0.74
Characteristics of mechanical ventilation‡			
Plateau pressure Day 1, median (IQR), cm H_2O	25 (22–29)	24 (21–27)	0.36
Driving pressure Day 1, median (IQR), cm H_2O§	13 (11–17)	16 (13–18)	0.09
Highest Day 1 $F_{I_{O_2}}$, median (IQR), 0–1	0.9 (0.6–1.0)	0.9 (0.5–1.0)	0.72
Compliance Day 1, median (IQR), ml/cm H_2O	31.3 (25.3–38.3)	27 (22.1–38)	0.40
Plateau pressure Day 2, median (IQR), cm H_2O	26 (20–30)	22 (19–24)	0.06
Driving pressure Day 2, median (IQR), cm H_2O§	13 (10–15)	15 (13–17)	0.15
Highest Day 2, $F_{I_{O_2}}$, median (IQR), 0–1	0.6 (0.5–0.9)	0.4 (0.4–0.65)	0.03
Compliance Day 2, median (IQR), ml/cm H_2O	30 (23–38)	28.2 (22.4–36.3)	0.28
Plateau pressure Day 3, median (IQR), cm H_2O	26 (23–30)	22 (19–26)	0.06
Driving pressure Day 3, median (IQR), cm H_2O§	14 (11–16)	15 (14–18)	0.06
Highest day 3, $F_{I_{O_2}}$, median (IQR), 0–1	0.6 (0.4–0.9)	0.4 (0.3–0.6)	<0.001
Compliance Day 3, median (IQR), ml/cm H_2O	28 (23.8–42)	26.1 (22.7–36.4)	0.29
Outcomes			
Length of hospital stay, median (IQR), d	14 (8–22)	8 (5–23)	0.80
Length of ICU stay, median (IQR), d	9 (3–16)	4 (2–14)	0.22
Acute respiratory distress syndrome	41 (63.1)	19 (25.7)	<0.001
Mechanical ventilation for >7 d, *n*/total *n* (%)	28/39 (71.8)	19/41 (46.3)	0.021
Extubated, *n*/total *n*‖	19/39 (48.7)	26/41 (63.4)	0.19
Duration of mechanical ventilation in extubated patients, median (IQR), d‖	16 (9–34)	3.5 (2–14)	0.49
Vasopressors	36 (55.4)	36 (48.7)	0.43
Acute kidney injury	28 (43.1)	30 (40.5)	0.76
Renal replacement therapy	7 (10.8)	9 (12.2)	0.80
Hospital mortality	26 (40.0)	14 (18.9)	0.006

Definition of abbreviations: COVID-19 = coronavirus disease; $F_{I_{O_2}}$ = fraction of inspired oxygen; ICU = intensive care unit; IQR = interquartile range.
The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group.
**P* values were calculated using a *t* test for continuous variables and a chi-square test or Fisher exact test for binary and categorical variables.
†Prone position, neuromuscular blockade, and inhaled pulmonary vasodilators are reported for the first 7 days of mechanical ventilation.
‡Plateau pressure, driving pressure, and compliance are missing for 2 patients on Day 1, 10 patients on Day 2, and 21 patients on Day 3. $F_{I_{O_2}}$ is missing for 1 patient on Day 1, 7 on Day 2, and 16 on Day 3.
§Driving pressure = plateau pressure − positive end-expiratory pressure.
‖Extubation does not include patients who were extubated for comfort measures.

in COVID-19, it does not appear to be a unique marker of this viral infection and may not be useful in distinguishing the two causes of viral pneumonia. Nonetheless, lymphopenia appears to be associated with illness severity for both influenza and COVID-19 (2, 46). Finally, our findings suggest that the timing of bacterial coinfection may differ between patients with COVID-19 and patients with influenza. Among patients with influenza, sputum cultures with bacterial growth occurred earlier than in patients with COVID-19. The lack of bacterial growth on sputum cultures early during COVID-19 hospitalization is consistent with prior research demonstrating low rates of bacterial coinfection (47). The longer duration of invasive mechanical ventilation in COVID-19 than in influenza may explain the higher rate of positive culture results seen later during hospitalization.

There were several limitations to our study, including the small sample size that may have limited the ability of our analysis to detect smaller differences between the two groups. In addition, there was incomplete documentation among patients, including limited documentation of clinical symptoms. All laboratory testing was conducted at the discretion of the treating provider, which resulted in missing values, particularly for arterial blood gases, which may have biased the results. Another limitation in analyzing outcomes in patients with COVID-19 compared with patients with influenza are the differences in practice patterns regarding laboratory testing, respiratory support, sedation practices, and medical therapy occurring in the COVID-19 pandemic. The contemporaneous inclusion of critically ill patients with influenza and patients with COVID-19 mitigates, though does not eliminate, this concern. Lastly, the mortality rate observed in patients with COVID-19 early in the pandemic in Washington state may have been higher than current rates as a result of several outbreaks that occurred among vulnerable populations in senior-living and long-term acute care facilities (48, 49). Nonetheless, in our study, the number of patients admitted from a skilled nursing facility was similar between COVID-19 and influenza.

Conclusions

COVID-19 has often been compared with influenza, as both respiratory viruses lead to

Table 5. Association between ICU outcomes and COVID-19 status

	Unadjusted RR (95% CI)	*P* Value	Model 1* RR (95% CI)	*P* Value	Model 2† RR (95% CI)	*P* Value
Renal replacement therapy	0.89 (0.35–2.25)	0.80	0.87 (0.37–2.02)	0.74	1.11 (0.44–2.81)	0.83
Shock requiring vasopressors	1.14 (0.83–1.57)	0.43	1.07 (0.78–1.47)	0.69	1.16 (0.88–1.53)	0.28
Mechanical ventilation	1.06 (0.79–1.41)	0.72	1.06 (0.79–1.42)	0.72	1.18 (0.91–1.53)	0.22
Hospital mortality‡	2.15 (1.23–3.76)	0.007	1.96 (1.13–3.41)	0.017	2.13 (1.24–3.63)	0.006

Definition of abbreviations: CI = confidence interval; COVID-19 = coronavirus disease; ICU = intensive care unit; RR = relative risk.
*Model 1 is adjusted for age, sex, and number of the following comorbidities: asthma, chronic obstructive lung disease, chronic kidney disease, diabetes, and obesity.
†Model 2 is adjusted for model 1 and the highest sequential organ failure assessment score on Day 1 of ICU admission.
‡Excludes one patient with COVID-19 who was not observed until a final outcome of hospital discharge or death.

a wide range of presentations from mild illness to severe respiratory failure and death. Our study highlights important similarities as well as key differences between these two infections. Most notably, our findings suggest an increased risk of hospital mortality among critically ill patients with COVID-19 infection compared with influenza. These findings underscore the importance of efforts for limiting transmission as well as ongoing investigations for effective therapies and vaccines. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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