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

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Running Title: COVID-19 Compared to Influenza in Critically Ill Patients

Manuscript Word Count: 3499

Work was performed at the University of Washington, Seattle, Washington

Authors' Contributions: PKB, TEW, and CH contributed to study conception. NLC contributed to data acquisition, analysis, and writing of the manuscript. NAS, KID, KPS, MRT, CCS contributed to data acquisition. All authors contributed to data interpretation and revisions of the manuscript.

Funding: This work was supported by grants from the National Institute of Health (T32 HL007287-41 and UL1 TR002319). PKB was supported by grants from the Digestive and Kidney Diseases (K23DK116967) and the Centers for Disease Control Foundation.

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

This article has an online supplement, which is accessible from this issue's table of contents online at www.atsjournals.org

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

Abstract:

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

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

Methods: We retrospectively identified patients admitted to the intensive care units (ICUs) at two academic medical centers with laboratory confirmed SARS-CoV-2 or influenza A or B infections between January 1, 2019 and April 15, 2020. 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 (SOFA) on ICU day 1 to determine the risk of hospital mortality and organ dysfunction in patients with COVID-19 compared to influenza.

Results: We identified 65 critically ill patients with COVID-19 and 74 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 higher body mass index and higher rates of chronic kidney disease and diabetes. Thirty-seven percent of COVID-19 patients identified as Hispanic, compared to 10% of influenza patients. A similar proportion of patients had fever (~40%) and lymphopenia (~80%) on hospital presentation. Rates of acute kidney injury and shock requiring vasopressors were similar between the groups. While 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 compared to patients with influenza. Hospital mortality was 40% in COVID-

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

19 patients and 19% in influenza patients (adjusted relative risk 2.13, 95% confidence interval 1.24 to 3.63; p = 0.006).

Conclusions: Need for invasive mechanical ventilation was common in ICU patients with COVID-19 or influenza. Compared to those with influenza, ICU patients with COVID-19 had worse respiratory outcomes, including longer duration of mechanical ventilation. Additionally, patients with COVID-19 were at greater risk for in-hospital mortality, independent of age, sex, co-morbidities, and ICU severity of illness.

Abstract Word Count: 348

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

After Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the novel coronavirus that causes COVID-19, was first identified in Wuhan China in December 2019, initial reports suggested that hospital mortality among critically ill patients is high and that certain comorbidities are over-represented 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 influenza infection, a common respiratory virus responsible for a significant number of hospitalizations and mortality in the United States and globally (6-8). Both COVID-19 and influenza cause a range of clinical disease from mild 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 the proportion of individuals that develop severe disease and mortality (13-15).

Direct comparisons of the two viruses, particularly with regards 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 estimates (7, 16, 17). Another limitation is that COVID-19 deaths may have been underreported to surveillance agencies early in the outbreak due to limitations in diagnostic testing (18). One prior observational study from China compared characteristics of patients with ARDS due to COVID-19 versus influenza A H1N1 and demonstrated a lower mortality among those with SARS-CoV2 infection (19). In contrast, other studies have suggested that mortality rates among persons with COVID-19 are higher than compared to seasonal influenza (16, 20).

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

In order to further evaluate the risk of mortality between critically ill patients with COVID-19 or seasonal influenza, we identified a cohort of patients admitted to the intensive care unit (ICU) with influenza A or B and compared them to 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 admitted to the medical ICUs at two hospitals in the UW Medicine system (University of Washington Medical Center-Montlake and Harborview Medical Center) between January 1st, 2019 and April 15th, 2020. A confirmed case of COVID-19 was defined as a positive result on a reverse-transcriptase polymerase chain reaction (RT-PCR) assay collected by nasopharyngeal swab specimen, endotracheal aspirate, or on autopsy (21). Influenza A or B infection was confirmed by RT-PCR on a rapid diagnostic test or extended respiratory virus PCR panel. All positive laboratory tests were completed during the index hospitalization. The cohort search was performed using Leaf, a web-based cohort discovery tool (22). One hundred and forty-two adults ≥ 18 years of age were identified from the two hospitals. Three cases (one COVID-19 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. One hundred thirty-nine cases were included in the final analysis. From the medical record, we abstracted demographics, clinical symptoms or signs at presentation, comorbidity data,

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

laboratory, and radiologic results during admission by chart review. Data was collected using Research Electronic Data Capture (REDCap), a secure web-based application (23). The University of Washington institutional review board approved this study.

Study Definitions

Comorbidities were ascertained based on 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 cultures were defined by bacterial growth in qualified sputum, excluding normal oropharyngeal flora. Positive blood cultures excluded common contaminants such as coagulase negative staphylococcus and staphylococcus hominis. Sputum and blood cultures were defined as early if they were collected within the first 2 days of admission to the study hospital. Acute respiratory distress syndrome was reported according to ICU physician documentation. In instances where documentation was unclear or missing, the presence of ARDS was determined by study personnel based on the presence of bilateral pulmonary opacities on chest imaging and acute (< 7 days) onset of hypoxemia (P_aO_2/F_IO_2 ratio < 300) (24). Acute kidney injury (AKI) was defined as an increase in serum creatinine ≥ 0.3 mg/dL and/or ≥ 50% during hospitalization compared to the baseline serum creatinine value measured within the year prior to the time of hospitalization. If no prior serum creatinine was available, the serum creatinine at time of admission was used as the baseline. 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.

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

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 or means and standard deviation, as appropriate. 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 T-test for continuous variables and Chi-square test or Fisher's exact test for binary and categorical variables. We performed relative risk (RR) 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 these variables may confound associations between 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 number of comorbidities to account for several chronic diseases and to also limit the number of individual covariates included in the model. The second model included model 1 covariates and the sequential organ failure score (SOFA), based on the worst variables obtained during the first

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

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, College Station, TX, USA).

Results

Demographic and Clinical Characteristics in COVID-19 and Influenza Cases

Between January 1, 2019 to 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, 30/74 (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 co-infection with influenza. The average age in both groups was similar, 60.4 years (± 15.7) among COVID-19 compared to 56.8 years (± 17.6) among influenza cases. In both groups, the majority of patients were male. Among patients with influenza, 10% identified as Hispanic or Latino; in contrast, among 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) compared to

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

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 compared to influenza, though 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 to 10 (14%) patients in the influenza group.

Presenting Symptoms and Signs

Patients with COVID-19 had a longer median symptom duration prior to hospitalization, 7 days (IQR 5-13) compared to 3.5 days (IQR 2-7) for influenza (*p<0.001*) (Table 2). While 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 sequential organ failure assessment (SOFA) scores on ICU admission were similar in both groups, with a median score of 6 (IQR 3-11) among COVID-19 cases compared to a median of 6.5 (IQR 3-10) among influenza cases (*p=0.62*).

Laboratory, Radiologic and Microbiologic Results

Admission white blood cell count was higher in patients with influenza than with COVID-19 (*p=0.007*) (Table 3). Lymphocyte count was similar between the two populations, with ~80% of patients in both groups having a lymphocyte count less than 1500 per mm^3. In patients with COVID-19, blood inflammatory markers were elevated, including c-reactive protein, lactate

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

dehydrogenase and interleukin-6, but because these were not commonly measured in patients with influenza, no direct comparisons could be made between groups (Table E1 in the Online Supplement). D-dimer was elevated in both the influenza and COVID-19 groups. Other markers of coagulation, specifically INR and PTT, 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 days) in patients with influenza compared to COVID-19 (72% versus 27%; *p=0.005*) (Table 3). Staphylococcus aureus was the most common organism identified in early and late sputum cultures in both groups (Table E3 and E4). 15% of patients with COVID-19 had positive blood cultures during hospitalization compared to 8% among influenza patients (p=*0.28*). Viral co-infection was found in 4/36 (11%) influenza patients versus 1/17 (6%) COVID-19 patients based on testing with an extended panel viral PCR (*p= 1.0*). Almost all patients with COVID-19 had bilateral opacities (92%) on chest radiograph compared to 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 P_aO_2/F_IO_2 ratio on Day 1 of mechanical ventilation was 126 (IQR 73-165) for patients with COVID-19 compared to 101.5 (IQR 83-188) for patients with influenza. Patients with influenza experienced more rapid improvement in the P_aO_2/F_IO_2 ratio during their ICU admission (Table 3). Respiratory system compliance and plateau pressure were similar between

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

patients with influenza or 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) for COVID-19 patients versus 27 ml/cm H_2O (IQR 22.1- 28) for influenza patients (Table 4). These findings were similar when comparing COVID-19 and influenza patients with ARDS (Table E5).

Treatment

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

Outcomes

Median hospital and ICU lengths of stay and duration of mechanical ventilation were longer in patients with COVID-19 than influenza (Table 4). Among patients receiving invasive mechanical ventilation, 72% of those with COVID-19 were mechanically ventilated for > 7 days compared to 46% of influenza patients (*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% in COVID-19 versus 19% in influenza (*p=0.006*). Among those with ARDS, hospital mortality was 46% and 37% respectively (Table E10). At the time of manuscript submission one patient was still hospitalized with COVID-19 and was excluded from the survival population for regression

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

analyses. In multivariable analysis, COVID-19 was associated with a two-fold greater risk of hospital mortality compared to influenza, relative risk 2.13 (95% CI 1.24- 3.63), adjusting for age, sex, number of co-morbidities, 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 need for invasive mechanical ventilation, vasopressors, or renal replacement therapy compared to influenza.

Discussion

To our knowledge this is the first study to directly compare outcomes among critically ill patients with influenza to patients with COVID-19 in the United States. Among patients from two U.S. hospitals that are part of the same health care system, we found that critically ill patients with COVID-19 are at twice the risk for hospital mortality compared to 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 to 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 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, while bacterial

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

co-infection early during hospitalization was more common in patients with influenza. Thus, among influenza patients 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 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 compared to 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), though this is controversial (36, 37). One autopsy series described certain histologic features, including alveolar microthrombi and vascular angiogenesis, may be more common among patients with COVID-19 compared to ARDS secondary to influenza (33). However, another series found the histological 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. While shortages of medical resources and ICU beds occurred in a number of hospitals, our

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

center did not experience a limitation of resources, staff, or ICU beds and never approached crisis standards of care. In fact, due to cancellation of elective surgeries and an overall decrease in inpatient census, the ICU bed census at these two hospitals was lower in March and April of 2020 than in previous months and prior years during the same time period (Figure E1 in the Online Supplement). Nonetheless, there were changes in certain practices, such as clustered nursing care, changes in sedation practices and environmental services, which may have affected care and patient outcomes. We would hypothesize that medical systems overwhelmed with a surge of COVID-19 patients may have experienced worse outcomes. Additionally, the literature regarding treatment of COVID-19 has rapidly evolved. While 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 in those with H1N1-induced ARDS compared to COVID-19 induced ARDS (34.7% versus 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 et al. compared COVID-19 cases from a hospital in Hubei province to 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 included only patients diagnosed with ARDS. Given that we found that only a minority of ICU patients with influenza develop ARDS, the study by Tang et al. may have selected for a more severely ill population of influenza patients. Additionally, in the Tang et al. study, approximately 36% of patients with COVID-19 remained hospitalized at the end of the

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

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 COVID-19 patient.

We observed far higher rates of noninvasive positive pressure ventilation among influenza patients compared to 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 COVID-19 patients to minimize the risk of virus transmission. Another reason for the differences in mode of respiratory support may be due to the increased proportion of influenza patients with obstructive lung disease, where the indication for management with noninvasive positive pressure ventilation is well supported by the literature (41). While the use of 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 underlying rates and severity of ARDS, but could also be due to differences in 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 to 10% among the influenza group (30, 44). This may be related to underlying health factors as well as social and economic inequalities (45). Interestingly, while lymphopenia has been commonly described 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

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

influenza and COVID-19 (2, 46). Finally, our findings suggest that the timing of bacterial coinfection may differ between patients with COVID-19 and influenza. Among patients with influenza, sputum cultures with bacterial growth occurred earlier compared to 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 co-infection (47). The longer duration of invasive mechanical ventilation in COVID-19 compared to influenza may explain the higher rate of positive cultures seen later during hospitalization.

There were several limitations to our study including the small sample size, which may have limited the ability of our analysis to detect smaller differences between the two groups. Additionally, 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 that may bias the results. Another limitation in analyzing outcomes in COVID-19 patients compared to influenza are differences in practice patterns regarding laboratory testing, respiratory support, sedation practices and medical therapy occurring in the COVID-19 pandemic. The inclusion of critically ill influenza patients contemporaneous with COVID-19 patients 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.

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

COVID-19 has often been compared to influenza, as both respiratory viruses lead to 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 to influenza. These findings underscore the importance of efforts for limiting transmission as well as ongoing investigations for effective therapies and vaccines.

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

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ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

Table 1. Baseline Clinical Characteristics

Characteristics	**COVID-19 (n=65)**	**Influenza (n=74)**	**p-value***
Age, average (standard deviation), range –	60.4 (15.7), 23-97	56.8 (17.6), 20-92	0.20
Sex – no. (%)			0.09
Male	46 (70.8)	42 (56.8)	
Female	19 (29.2)	32 (43.2)	
Race			0.09
American Indian/Alaska Native	0 (0)	3 (4.1)	
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			**<0.001**
Hispanic or Latino	24 (36.9)	7 (9.5)	
Not Hispanic or Latino	38 (58.5)	56 (75.7)	
Unknown	3 (4.6)	11 (14.9)	
Admission Location – no. (%)			0.42
Home	40 (61.5)	50 (67.6)	
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– no. (%)			
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, no/total no. (%)	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
Human immunodeficiency syndrome	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 – no. (%)			0.15
Full Code	50 (76.9)	64 (86.5)	

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

DNR/ Intubation OK	10 (15.4)	4 (5.4)	
DNR/ DNI	5 (7.7)	6 (8.1)	

Data presented as mean (standard deviation) with range for continuous variables, and count with (%) for binary and categorical variables

*P-values were calculated using T-test for continuous variables and Chi-square test or Fisher's exact test for binary and categorical variables

† Body mass index was missing in 2 patients

‡ Cancer included known lymphoma, leukemia and metastatic cancer

§ Defined as prednisone > 10 mg daily for more than one month or any other immunosuppressant

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

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 prior to admission † median (IQR)- days	7 (5-13)	3.5 (2- 7)	**<0.001**
Known sick contact – no./total (%)	32/55 (58.2)	19/48 (39.6)	0.06
Symptoms on presentation ‡- no. (%)			
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 – no./total no.			
Fever, Temperature >100.4 °F or 38 °C, no./total no. (%)	28/64 (43.8)	27/68 (39.7)	0.64
Heart rate > 100 beats per minute	21/65 (32.3)	46/72 (63.9)	**<0.001**
Respiratory Rate ≥ 20 breaths per	49/65 (75.4)	57/72 (79.2)	0.60
SOFA score on ICU admission § – median	6 (3-11)	6.5 (3-10)	0.62

Total number is given if values are missing.

*P-values were calculated using T-test for continuous variables and Chi-square test or Fisher's 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

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

Table 3. Laboratory Data on Hospital Admission and Imaging Findings

Admission Laboratory Data †	**COVID-19 (n=65)**	**Influenza (n=74)**	**p-**
White blood cell count			
Median (IQR) – per mm^3	7,240 (5,430-11,820)	9,035 (6,590-14,900)	**0.007**
Distribution – no./total no. (%)			
≥ 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) – mm^3	5,405 (3,880- 9,580)	7,210 (4,990-11,890)	**0.02**
Lymphocyte count			
Median (IQR) – mm^3	910 (550-1,350)	800 (590-1,220)	0.48
Distribution – no./total no. (%)			
≤ 1,500 per mm^3	50/62 (80.7)	57/71 (80.3)	
Aspartate aminotransferase > 40 U/liter, no./total no. (%)	31/59 (52.5)	31/65 (47.7)	0.59
Alanine aminotransferase > 40 U/Liter, no./total on. (%)	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, no./total no. (%)	31/52 (59.6)	50/64 (78.1)	
C-reactive protein, median (IQR), mg/L	148.5 (76.2-	-	
Lactate dehydrogenase, median (IQR), U/L	419 (322-513)	-	
Interleukin-6, median (IQR), pg/mL	160.5 (71- 254)	-	
Laboratory Data during first 3 days 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, no./total no. (%)	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/liter, no./total no.	18/27 (66.7)	9/13 (69.2)	1.00
Daily P_aO_2/F_IO_2 Ratio during mechanical ventilation §			
Day 1 Lowest P_aO_2/F_IO_2 ratio, median	126 (73-165)	101.5 (83-188)	0.311
Day 2 Lowest P_aO_2/F_IO_2 ratio, median	120 (96-167)	167.5 (98– 252.5)	**0.02**

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

Day 3 Lowest P_aO_2/F_IO_2 ratio, median	121 (98– 145)	181 (127– 216.5)	**0.006**
Infection Analyses, no./total no. (%)[‖]			
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	1/17 (5.9)	4/36 (11.1)	1.0
Chest Radiography Findings – no/total no. (%)[¶]			
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

Data presented as median (interquartile range) for continuous variables, and count with frequencies (%) for binary and categorical variables. Total number is given if values are missing. F_iO_2 the fraction of inspired oxygen, P_aO_2 partial pressure of arterial oxygen.
*p-values were calculated using T-test for continuous variables and Chi-square test or Fisher's exact test for binary and categorical variables

[†] There were 6 missing values for neutrophil count and lymphocyte count, fifteen missing values for aspartate aminotransferase and alanine aminotransferase, twenty-three missing values for lactate. Lactate included either arterial or venous. For c-reactive protein (CRP), lactate dehydrogenase (LDH) and interlukin-6 (IL-6), values are presented only for COVID-19 patients due to the large number of missing values in influenza patients. For COVID-19, there were twenty missing CRP values, twenty-four missing LDH, and thirty-three missing IL-6.
[‡] There was one missing creatinine value and eleven missing bilirubin values.
[§] Among 80 mechanically ventilated patients, P_aO_2/F_IO_2 is missing for five patients on day 1, twenty-eight patients on day 2, and thirty-five patients on day 3.
[‖] Viral testing was performed on nasopharyngeal swab, endotracheal aspirate, or bronchoalveolar lavage sample. Extended spectrum testing includes: metapneumovirus, parainfluenza, respiratory syncytial virus, (non-SARS CoV2) coronavirus, rhinovirus, adenovirus or bocavirus.
[¶] Reported only for chest radiograph within first 3 days of hospitalization.

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

Table 4. ICU Level Therapies and Clinical Outcomes

ICU Therapies and Outcomes	COVID-19 (n=65)	Influenza (n=74)	*p-value*
ICU Indication, no./total no. (%)			0.21
Mechanical ventilation on ICU admission	27 (41.5)	32 (43.2)	
Hypoxemic respiratory failure (without mechanical	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, no./total no. (%)[†]			
High flow nasal cannula	20 (30.8)	26 (35.1)	0.59
Bi-level non-invasive 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_IO_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/cmH_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_IO_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/cmH_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_IO_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/cmH_2O	28 (23.8- 42)	26.1 (22.7- 36.4)	0.29
Outcomes			
Length of hospital stay, median (IQR) - days	14 (8-22)	8 (5-23)	0.80
Length of intensive care unit stay, median (IQR)-	9 (3-16)	4 (2-14)	0.22
Acute respiratory distress syndrome	41 (63.1)	19 (25.7)	**<0.001**
Mechanical ventilation > 7 days, no./total no. (%)	28/39 (71.8)	19/41 (46.3)	**0.021**
Extubated, no./total no. (%)[§]	19/39 (48.7)	26/41 (63.4)	0.19
Duration of mechanical ventilation in extubated patients, median (IQR) -days [§]	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**

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group.
FiO_2 the fraction of inspired oxygen, PaO_2 partial pressure of arterial oxygen, Driving pressure=plateau pressure-positive end-expiratory pressure (PEEP).
*p-values were calculated using T-test for continuous variables and Chi-square test or Fisher's 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 two patients on day 1, ten on day 2, and twenty-one on day 3. FiO_2 is missing for one patient on day 1, seven on day 2, and sixteen on day 3.
§ Extubation does not include patients who were extubated to comfort measures.

ANNALSATS Articles in Press. Published November 13, 2020 as 10.1513/AnnalsATS.202007-805OC

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

	Unadjusted RR (95% CI)	*p*	Model 1* RR (95% CI)	*p*	Model 2[†] RR (95% CI)	*p*
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**

*Model 1 is adjusted for age, sex, and number of the following co-morbidities: asthma, chronic obstructive lung disease, chronic kidney disease, diabetes, and obesity.

[†]Model 2 is adjusted for Model 1 and highest sequential organ failure assessment (SOFA) score on day 1 of ICU admission.

[‡] Excludes 1 COVID-19 patient who was not observed to final outcome of hospital discharge or death

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ONLINE SUPPLEMENT

Comparison of clinical features and outcomes in critically ill patients hospitalized with COVID-19 versus influenza

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Table E1: Inflammatory markers among patients with COVID-19 and influenza at hospital admission

Inflammatory Markers	COVID-19	Influenza
C-reactive protein, median (IQR), total no., mg/L	148.5 (76.2- 219.7), n= 45	33.5 (18.6- 101), n=5
Lactate dehydrogenase – median (IQR), total no., U/L	419 (322-513), n= 41	357 (213- 601), n = 4
Interleukin-6 ⁻ median (IQR), total no.,	160.5 (71- 254), n= 32	-, n= 0

Table E2: Coagulation parameters among patients with COVID-19 and influenza during the first 3 days of hospitalization

Coagulation Tests	COVID-19	Influenza
Highest d-dimer – median (IQR), n	1.5 (0.9- 3.6), n=45	3.8 (1.4- 10.3), n= 11
Highest INR – median (IQR), n	1.1 (1.1-1.2), n= 63	1.2 (1.1- 1.5), n= 47
Highest PTT – median (IQR), n	38 (34- 48), n= 62	38.5 (34- 52.5), n=44

Table E3: Bacterial pathogens in positive early sputum cultures (≤ 48 hours from admission)* among patients with COVID-19 and influenza

Bacteria in Early Sputum Cultures	COVID-19 (n= 6), n (%)	Influenza (n= 13), n (%)
Staphylococcus aureus	4 (66.7)	9 (69.2)
Streptococcus pneumoniae	2 (33.3)	0 (0)
Beta-hemolytic streptococcus	0 (0)	2 (15.4)
Haemophilus influenza	0 (0)	2 (15.4)
Klebsiella species	2 (33.3)	0 (0)
Pseudomonas aeruginosa	0 (0)	1 (7.7)

*Includes 4 COVID-19 and 2 influenza patients transferred from outside hospitals

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Table E4: Bacterial pathogens in positive late sputum cultures (> 48 hours from admission) among patients with COVID-19 and influenza

Bacteria in Late Sputum Cultures	**COVID-19 (n= 16), n (%)**	**Influenza (n= 5), n (%)**
Staphylococcus aureus	6 (37.5)	2 (40.0)
Streptococcus pseudopneumoniae	1 (6.3)	0 (0)
Klebsiella species*	5 (31.3)	1 (20.0)
Pseudomonas aeruginosa	2 (12.5)	0 (0)
Enterobacter cloacae	2 (12.5)	1 (20.0)
Enterococcus faecalis	1 (6.3)	0 (0)
Acinetobacter baumannii	0 (0)	1 (20.0)
Citrobacter koseri	1 (6.3)	0 (0)

*Includes *klebsiella aerogenes*, previously known as *enterobacter aerogenes*.

Table E5: Characteristics of mechanical ventilation among intubated patients with ARDS

Characteristics of Mechanical Ventilation	**COVID-19 (n= 34)**	**Influenza (n= 19)**
Plateau Pressure Day 1, median (IQR) – cm H_2O	26 (22-29), n=33	26 (22-32), n=19
Driving Pressure Day 1, median (IQR) – cm H_2O	14 (11-17), n=33	16 (13-20), n=19
Highest Day 1 F_IO_2, median (IQR) – 0 - 1	0.9 (0.6-1.0), n=34	1.0 (0.8-1.0), n=19
Compliance Day 1, median (IQR) – mL/cmH_2O	29.3 (25-35.4),	27.3 (21-30), n=19
Plateau Pressure Day 2, median (IQR) - cm H_2O	27 (23-30), n=31	22.5 (20.5-24.5), n=16
Driving Pressure Day 2, median (IQR) – cm H_2O	14 (12-16), n=31	14 (13.5-15.5), n=16
Highest Day 2 F_IO_2, median (IQR) – 0 - 1	0.7 (0.5-0.9), n=33	0.6 (0.4-0.8), n=17
Compliance Day 2 median (IQR) – mL/cmH_2O	28.7 (20.7-35),	28.4 (21.7-33.2), n=16
Plateau Pressure Day 3, median (IQR) - cm H_2O	26 (23-30), n=29	21 (19-25), n=14
Driving Pressure Day 3, median (IQR) – cm H_2O	14 (11-16), n=29	14 (11-16), n=14
Highest Day 3 F_IO_2, median (IQR) – 0 - 1	0.6 (0.4- 0.9), n=32	0.45 (0.4- 0.6), n= 14
Compliance Day 3 median (IQR) – mL/cmH_2O	27.5 (23.8- 42),	29 (23.6-34.5), n=14
Extubated, no./total no. (%)*	17/34 (50.0)	8/19 (42.1)
Duration of mechanical ventilation in extubated patients, median (IQR) -days *	16 (10-34)	10 (2.5-23)

* Extubation does not include patients who were extubated to comfort measures.

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Table E6: Targeted therapies among patients with COVID-19 infection

COVID-19 Therapies	COVID-19 (n= 65), n (%)
Any COVID-19 therapy	48 (73.9)
Hydroxychloroquine	48 (73.9)
Remdesivir	0 (0)
Convalescent Plasma	2 (3.1)
Tocilizumab	22 (33.9)

Table E7: COVID-19 patients enrolled in placebo-controlled clinical trials

COVID-19 Clinical Trial	COVID-19 (n= 65), n (%)
Any clinical trial	23 (35.4)
Remdesivir versus placebo	20/23 (87.0)
Hydroxychloroquine versus placebo	1/23 (4.4)
Sarilumab versus placebo	2/23 (8.7)

Table E8: Antivirals among patients with influenza infection

Influenza Antivirals	Influenza (n= 74), n (%)
Any antiviral	73 (98.7)
Oseltamivir	71 (96.0)
Baloxavir	3 (4.05)
Zanamivir	0 (0)
Peramivir	3 (4.05)

Table E9: Corticosteroids among patients with COVID-19 and influenza

Corticosteroid	COVID-19 (n= 65), n (%)	Influenza (n= 74), n (%)
Any steroid	13 (20.0)	38 (51.4)
Prednisone	3 (4.6)	22 (29.7)
Hydrocortisone	6 (9.2)	15 (20.3)
Methylprednisolone	1 (1.5)	12 (16.2)
Dexamethasone	3 (4.6)	5 (6.8)
Prednisone $\geq$ 40 mg or equivalent*	8 (12.3)	37 (50.0)

*Defined as: Methylprednisolone 32 mg or above, Hydrocortisone 160 mg or above, Dexamethasone 6 mg or above

Table E10: Hospital mortality among patients with ARDS in COVID-19 and influenza

Outcome	COVID-19, n (%)	Influenza, n (%)	*p-value*
Hospital mortality	26/65 (40.0)	14/74 (18.9)	**0.006**
Hospital mortality in ARDS	19/41 (46.3)	7/19 (36.8)	0.49

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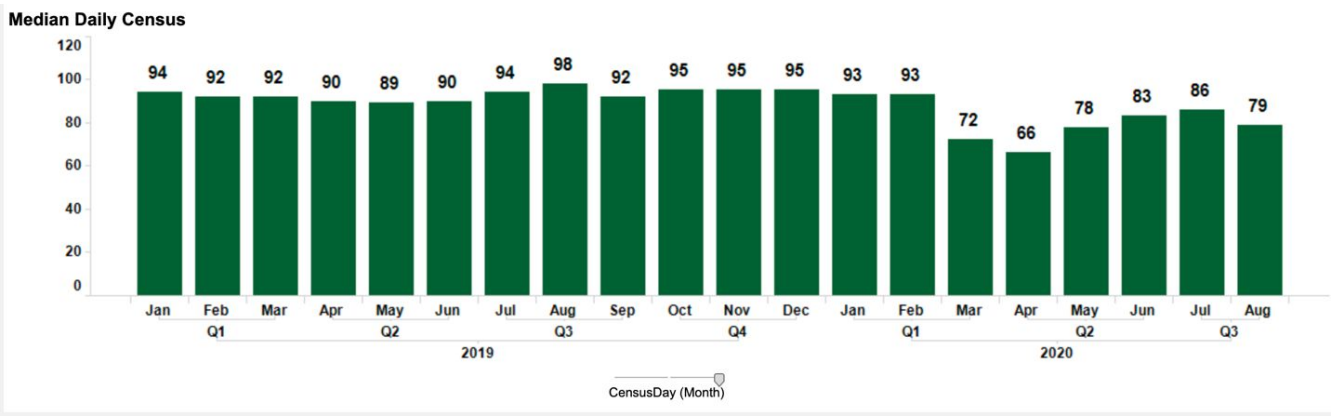
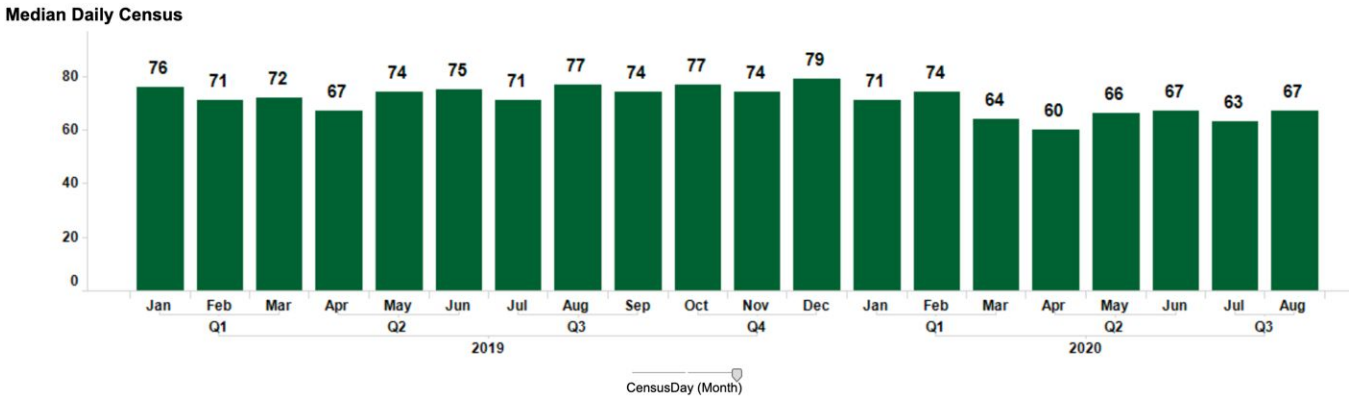
A



B

Figure E1: Median daily ICU census at the University of Washington – Harborview Medical



Center (A) and Montlake (B). The median daily ICU census is shown each month from January 2019 to August 2020. The y-axis includes the number of patients and the x-axis includes the months and year.

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