

# Comparison of critically ill COVID-19 and influenza patients with acute respiratory failure

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**Background:** Coronavirus disease 2019 (COVID-19) is one of the biggest pandemic causing acute respiratory failure (ARF) in the last century. Seasonal influenza carries high mortality, as well. The aim of this study was to compare features and outcomes of critically-ill COVID-19 and influenza patients with ARF.

**Methods:** Patients with COVID-19 and influenza admitted to intensive care unit with ARF were retrospectively analyzed.

**Results:** Fifty-four COVID-19 and 55 influenza patients with ARF were studied. Patients with COVID-19 had 32% of hospital mortality, while those with influenza had 47% (P=0.09). Patients with influenza had higher Eastern Cooperative Oncology Group, Clinical Frailty Scale, Acute Physiology and Chronic Health Evaluation II and admission Sequential Organ Failure Assessment (SOFA) scores than COVID-19 patients (P<0.01). Secondary bacterial infection, admission acute kidney injury, procalcitonin level above 0.2 ng/ml were the independent factors distinguishing influenza from COVID-19 while prone positioning differentiated COVID-19 from influenza. Invasive mechanical ventilation (odds ratio [OR], 42.16; 95% confidence interval [CI], 9.45–187.97), admission SOFA score more than 4 (OR, 5.92; 95% CI, 1.85–18.92), malignancy (OR, 4.95; 95% CI, 1.13–21.60), and age more than 65 years (OR, 3.31; 95% CI, 0.99–11.03) were found to be independent risk factors for hospital mortality.

**Conclusions:** There were few differences in clinical features of critically-ill COVID-19 and influenza patients. Influenza cases had worse performance status and disease severity. There was no significant difference in hospital mortality rates between COVID-19 and influenza patients.

**Key Words:** acute respiratory distress syndrome; coronavirus; intensive care; mortality; outcome; viral pneumonia

## INTRODUCTION

Severe respiratory coronavirus infections have remarkably been encountered over the past decade. While severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) are the two types of coronaviruses which cause severe respiratory failure, the spread of those diseases have been limited compared with coronavirus disease 2019 (COVID-19) which was caused by SARS-coronavirus-2 (SARS-CoV-2) [1]. COVID-19 is a syndrome with variable clinical features ranging from asymptomatic illness to acute

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respiratory distress syndrome (ARDS) [2]. The first case was reported on December 2019 in China [3]. Just 3 months later, the disease extended to all of the continents and in March 11, 2020, World Health Organization declared COVID-19 as a pandemic. Intensive care unit (ICU) mortality rates have been reported to range from 30.9% to 78% [4-6].

Influenza viruses are the most frequent etiological agents of severe viral pneumonia. A retrospective cohort study showed that the incidence of influenza-associated critical-illness to be 12 per 100,000-people per year and influenza was the cause of 3.4% of all intensive care admissions [7]. Recent studies revealed viral pneumonia prevalence between 17% to 53% in the ICU setting [8]. A recent multicenter study found 35.6% hospital mortality due to influenza related severe acute respiratory illness [9]. Being the two-major causes of severe pneumonia, comparison of the clinical characteristics and outcomes of COVID-19 and influenza have not been extensively studied yet. There have been few studies among critically ill patients with COVID-19 and influenza comparing clinical characteristics and outcomes [10-12].

Hereby, our objectives were to compare hospital mortality, clinical characteristics of the patients with COVID-19 and influenza admitted to ICU with acute respiratory failure (ARF) and to reveal independent predictive factors for hospital mortality.

## MATERIALS AND METHODS

The study was approved by the Ethics Committee of Hacettepe University Faculty of Medicine. Due to its retrospective design, informed consent was not obtained.

### Patient Selection

We conducted a retrospective observational study on laboratory confirmed critically ill COVID-19 and influenza patients who were older than 18 years of age, admitted to our ICU due to ARF. We reviewed the records of COVID-19 patients who had been admitted to ICU between March 20, 2020 and August 1, 2020. For the influenza group, we included patients who had been admitted between January 1, 2015 and February 1, 2020. All cases in COVID-19 group had positive results for polymerase chain reaction (PCR) or antibody test and all cases of influenza group were PCR confirmed.

### Data Collection

Data were collected from electronic medical records and pa-

### KEY MESSAGES

- There was no significant difference in hospital mortality between critically ill coronavirus disease 2019 (COVID-19) and influenza patients.
- Critically ill influenza patients had worse performance status and disease severity than patients with COVID-19.
- Secondary bacterial infection, admission acute kidney injury, procalcitonin level above 0.2 ng/ml were the independent factors distinguishing influenza from COVID-19 while prone positioning differentiated COVID-19 from influenza.

tient charts. ARF was defined as respiratory rate greater than 30 breaths per minute, respiratory distress symptoms, PaO<sub>2</sub> lower than 60 mm Hg or SaO<sub>2</sub> lower than 0.90 on room air or a need for ventilatory support [13]. Demographic data, comorbidities, Eastern Cooperative Oncology Group (ECOG) Performance Status, Clinical Frailty Scale (CFS; appropriate permission was obtained), Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score on admission were recorded. Related laboratory results, arterial blood gas analysis and the ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) on ICU admission were noted. The signs and characteristics of infection in chest computed tomography (CT) were examined. The presence of septic shock based on Sepsis-3 definitions [14] and acute kidney injury (AKI) defined by Kidney Disease Improving Global Outcomes criteria [15] on admission were recorded. Type of mechanical ventilation as non-invasive and invasive including prone position were documented. Primary viral infection was considered when respiratory and blood bacterial cultures were negative within first 72 hours during the acute phase of viral ARF. Bacterial co-infection was considered as positive culture results within the first 72 hours in patients with confirmed viral infection. Secondary bacterial infection was considered as positive culture results after 72 hours in patients with confirmed viral infection [16,17]. The features of survivors and non-survivors according to hospital mortality were documented.

### Statistical Analysis

Results are presented as medians with interquartile ranges, percentages, odds ratios (OR) and 95% confidence interval (CI). Comparisons were performed with Mann Whitney U-test and chi-square/exact tests, as appropriate. The one variable

analyses to identify variables discriminating viral cohorts between each other and to figure out associated parameters with hospital mortality for the whole group were studied. Numeric variables were categorized according to their median values. For multivariable analysis, factors identified with one variable analysis ( $P < 0.20$ ) with no interaction in between were further entered into the logistic regression model by Backward Stepwise method to determine independent predictors differentiating COVID-19 from influenza and predictors for hospital mortality. Since the primary outcome in these analyses are hospital mortality, there was no censored case in our study group, we performed Backward Stepwise method. Hosmer-Lemeshow goodness of fit statistical analysis was used to assess fitness of the model. Kaplan-Meier survival analysis and log rank test were performed to assess the effects of COVID-19 and influenza on survival.  $P$ -value  $< 0.05$  was accepted as significant. All analysis was done with IBM SPSS ver. 23 (IBM Corp., Armonk, NY, USA).

## RESULTS

Out of 56 COVID-19 and 64 influenza cases admitted to ICU, 54 COVID-19 and 55 influenza patients with ARF were included in the study. Two of the COVID-19 patients and 6 of the influenza patients who did not have a diagnosis with ARF were excluded. We also excluded three of the influenza patients whose medical records were missing. General characteristics of patients are seen at [Table 1](#). In COVID-19 group the median age of patients was 64 years and 34 (63%) were male, while the median age was 62 years and 29 (53%) were male in influenza group. Cardiac disease was higher in the influenza group ( $P = 0.01$ ). In COVID-19 group median ECOG status ( $P < 0.01$ ), CFS ( $P < 0.01$ ), APACHE II ( $P < 0.01$ ) and SOFA ( $P = 0.01$ ) scores were lower than in influenza patients. In terms of admission laboratory tests, white blood cell counts ( $P < 0.01$ ), median neutrophil lymphocyte ratio (NLR;  $P < 0.01$ ), international normalized ratio ( $P < 0.01$ ) and procalcitonin (PCT) values ( $P < 0.01$ ) were lower in patients with COVID-19 than those with influenza. Evaluation of arterial blood gas analysis on admission revealed that patients with influenza had lower pH ( $P < 0.01$ ) and higher PaCO<sub>2</sub> levels ( $P < 0.01$ ) than those with influenza.

Influenza patients had higher rates of admission septic shock ( $P < 0.01$ ), AKI ( $P < 0.01$ ) and secondary bacterial infection ( $P = 0.02$ ) during ICU stay in comparison with COVID-19 patients. There was no difference in systemic steroid use during ICU stay between COVID-19 and influenza patients (61% vs.

71%, respectively;  $P = 0.47$ ). IMV applied more in influenza group (43% vs. 66%, respectively;  $P = 0.01$ ). Prone positioning was performed in 52% of the COVID-19 and 6% of the influenza patients ( $P < 0.01$ ). Seventy-eight of the whole patients had primary viral infection. Out of 78 patients, 9 (24.3%) in COVID-19 and 19 (46.3%) in the influenza group passed away ( $P = 0.04$ ). There was no difference in hospital mortality between COVID-19 and influenza patients (32% vs. 47%;  $P = 0.09$ , respectively). Multivariable analysis revealed that only prone position discriminates COVID-19 from influenza in favor of COVID-19, while the presence of secondary bacterial infection, admission AKI and PCT level above 0.2 ng/ml differentiate in favor of influenza ([Figure 1](#)).

The characteristics of survivors and non-survivors were depicted at [Table 2](#). After logistic regression analyses; IMV, admission SOFA  $> 4$ , malignancy and age  $> 65$  years were found to be independent variables for predicting hospital mortality when adjusted for cardiac disease, CFS, APACHE II score  $> 16$ , presence of septic shock, secondary bacterial infection, NLR  $\geq 10$  and patient group as COVID versus influenza ([Table 3](#)). In Kaplan-Meier survival analysis, there was no difference between COVID-19 and influenza patients (log-rank  $P = 0.81$ ) ([Figure 2](#)).

## DISCUSSION

The present study revealed that patients with influenza had worse performance status, clinical severity scores and more complications than patients with COVID-19 while there was no significant difference in hospital mortality rates between two groups. Age, disease severity and the existence of comorbidities and their types are one of the main influencing factors for outcomes of respiratory failure due to viruses. In this study, patients with influenza had more cardiac and chronic kidney disease and had higher ECOG, CFS, APACHE II and admission SOFA scores than COVID-19.

The only article focusing on ICU patients comparing COVID-19 and influenza was reported by Tang et al. [10] They investigated 73 COVID-19 and 75 influenza patients with ARDS and found 29% versus 35% hospital mortality rates, respectively, not reaching statistical significance similar to our study. Although they did not report data on patients' performance status, they found higher median SOFA score in patients with influenza. Another recently published study in this field was a retrospective nationwide, population-based study from France by Piroth et al. [12] comparing COVID-19 and 2018-19 season-

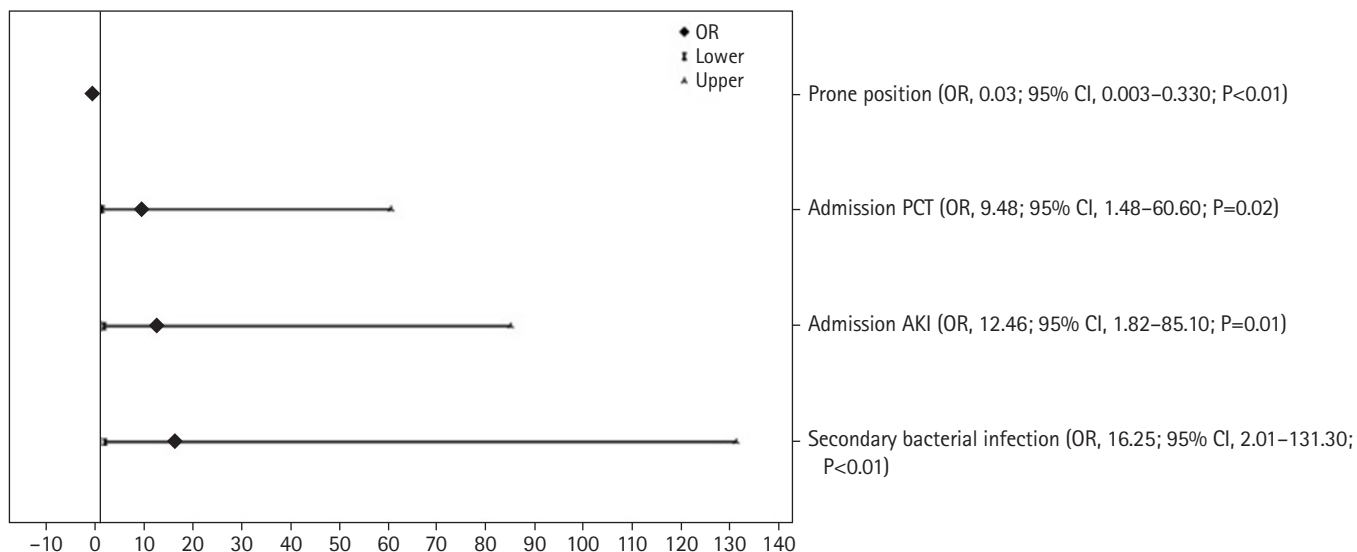
**Table 1.** General characteristics and outcomes of COVID-19 and influenza patients

Variable	All (n=109)	COVID-19 (n=54)	Influenza (n=55)	P-value
Age (yr)	64 (55–76)	64 (58–76)	62 (51–77)	0.83
Patients >65 yr	50 (46)	24 (44)	26 (47)	0.76
Male sex	63 (58)	34 (63)	29 (53)	0.27
Comorbidity				
Hypertension	51 (47)	25 (46)	26 (47)	0.91
Diabetes mellitus	32 (29)	13 (24)	19 (35)	0.23
Cardiac disease	30 (28)	9 (17)	21 (38)	0.01
Malignancy	24 (22)	8 (15)	16 (29)	0.07
Chronic lung disease	21 (19)	7 (13)	14 (26)	0.09
Chronic kidney disease	6 (6)	0	6 (11)	0.01
Chronic liver disease	5 (5)	4 (7)	1 (2)	0.20
Smoking	37 (34)	17 (32)	20 (36)	0.59
ECOG status	2 (1–3)	1 (0–2)	2 (1–3)	<0.01
CFS	4 (2–6)	3 (1–5)	5 (3–7)	<0.01
APACHE II score	16 (12–24)	13 (10–18)	19 (15–27)	<0.01
SOFA score on admission	4 (3–7)	4 (3–6)	6 (3–10)	0.01
Laboratory values on admission				
WBC ( $\times 10^3$ )	8.1 (5.2–11)	6.1 (4.1–9.3)	9.9 (7.1–13.4)	<0.01
Lymphocyte ( $\times 10^3$ )	0.7 (0.5–1)	0.8 (0.5–1.1)	0.6 (0.4–0.9)	0.19
NLR	9.6 (3.9–16.9)	5.9 (2.6–12.5)	13.4 (6–22.8)	<0.01
Prothrombin time (INR)	1.1 (1–1.2)	1.1 (1–1.1)	1.2 (1.1–1.4) <sup>a</sup>	<0.01
Procalcitonin (ng/ml)	0.2 (0.08–0.77)	0.13 (0.07–0.2)	1.9 (0.2–7.5) <sup>b</sup>	<0.01
pH (mm Hg)	7.42 (7.36–7.46)	7.44 (7.41–7.49)	7.40 (7.33–7.44) <sup>c</sup>	<0.01
PaCO <sub>2</sub> (mm Hg)	36 (31–46)	33 (29–36)	45 (35–57) <sup>c</sup>	<0.01
PaO <sub>2</sub> /FiO <sub>2</sub> on admission	167 (124–234)	160 (127–233)	180 (102–250)	0.24
<100	20 (18)	7 (13)	13 (23)	<0.01
100–199	48 (44)	25 (46)	23 (42)	0.92
200–300	32 (30)	19 (35)	13 (23)	0.02
>300	9 (8)	3 (6)	6 (11)	0.06
Thorax CT findings on admission				
Ground glass opacity	71 (79)	48 (92)	23 (61)	<0.01
Consolidation	8 (9)	2 (4)	6 (16)	0.06
Infiltration	2 (2)	0	2 (5)	0.17
Septic shock on admission	55 (51)	20 (37)	35 (64)	<0.01
AKI on admission	52 (48)	16 (30)	36 (66)	<0.01
Mechanical Ventilation				
IMV	59 (54)	23 (43)	36 (66)	0.01
NIMV	66 (61)	26 (48)	40 (73)	0.01
Prone position	31 (28)	28 (52)	3 (6)	<0.01
RRT	27 (25)	7 (13)	20 (36)	<0.01
Primary viral infection	78 (72)	37 (69)	41 (75)	0.48
Bacterial co-infection	34 (31)	13 (24)	21 (38)	0.11
Secondary bacterial infection	56 (51)	22 (41)	34 (62)	0.02
Opportunistic infection	9 (8)	5 (9)	4 (7)	0.50
Outcomes				
Hospital mortality	43 (39)	17 (32)	26 (47)	0.09
ICU LOS (day)	12 (6–24)	12 (5–18)	12 (6–29)	0.22
Hospital LOS (day)	20 (12–36)	18 (11–29)	24 (13–42)	0.09

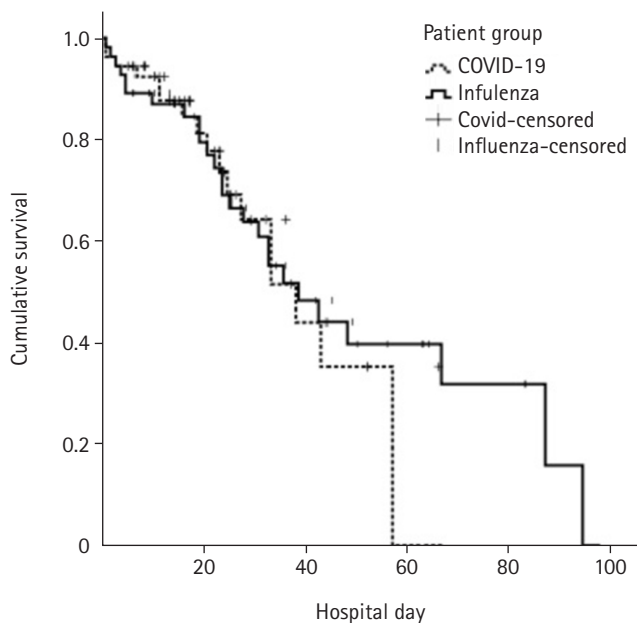
Values are presented as median (interquartile range) or number (%).

COVID-19: coronavirus disease 2019; ECOG: Eastern Cooperative Oncology Group; CFS: Clinical Frailty Scale; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; WBC: white blood cell; NLR: neutrophil lymphocyte ratio; INR: international normalized ratio; PaO<sub>2</sub>/FiO<sub>2</sub>: the ratio of partial pressure arterial oxygen and fraction of inspired oxygen; CT: computerized tomography; AKI: acute kidney injury; IMV: invasive mechanical ventilation; NIMV: non-invasive mechanical ventilation; RRT: renal replacement therapy; ICU: intensive care unit; LOS: length of stay.

<sup>a</sup>n=53; <sup>b</sup>n=23; <sup>c</sup>n=54.



**Figure 1.** Independent parameters differentiating viral agents are schematized by forest plot. Adjusted for the history of cardiac disease, Clinical Frailty Scale, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, presence of septic shock, invasive mechanical ventilation, admission neutrophil/lymphocyte ratio, and admission international normalized ratio. Except prone positioning, admission procalcitonin (PCT), acute kidney injury (AKI) and secondary bacterial infection discriminate influenza patients from coronavirus disease 2019 (COVID-19). OR: odds ratio; CI: confidence interval.



**Figure 2.** Kaplan-Meier survival curve comparing patients with Coronavirus disease 2019 (COVID-19; dotted line) and influenza (straight line) revealing no difference in survival between two groups (log-rank P=0.81).

al influenza patients. This study includes a large ICU cohort (n=14,585 vs. n=4,926, respectively) and demonstrated that patients with COVID-19 had higher hospital mortality than those with influenza (27% vs. 18%, P<0.01). In this study [12], firstly there was no data on disease severity scores, secondarily they used International Classification of Disease codes for predicting comorbidity scores which had some contradictory findings, as patients with influenza had higher mean Elixhauser comorbidity score but lower mean Charlson comorbidity score than in those with COVID-19. In addition, lower disease severity scores in COVID-19 patients may be related to early referral of patients to ICU from wards and emergency department and early diagnosis in pandemic situation.

We determined that PCT levels on admission were higher in influenza patients than in those with COVID-19 and found PCT levels above 0.2 ng/ml as one of the variables that differentiated influenza from COVID-19. Higher PCT levels have been reported as an independent risk factor for predicting ICU mortality [18,19].

In our study regarding with median PaO<sub>2</sub>/FiO<sub>2</sub> on admission, almost half of the patients in each group had a PaO<sub>2</sub>/FiO<sub>2</sub> between 100 and 200. On the other hand, proportion of the patients who had PaO<sub>2</sub>/FiO<sub>2</sub> under 100 was greater in in-

**Table 2.** General characteristics of survivors and non-survivors in overall patients

Variable	Survivor (n=66)	Non-survivor (n=43)	P-value
Age (yr)	60 (51–73)	69 (60–79)	0.01 <sup>e</sup>
Patients >65 yr	26 (39)	24 (56)	0.09
Male sex	34 (52)	29 (67)	0.10
Comorbidity			
Hypertension	27 (41)	24 (56)	0.12
Diabetes mellitus	17 (29)	15 (35)	0.30
Chronic lung disease	15 (28)	6 (14)	0.25
Cardiac disease	13 (20)	17 (40)	0.02 <sup>e</sup>
Malignancy	9 (14)	15 (35)	<0.01 <sup>e</sup>
Chronic kidney disease	2 (3)	4 (9)	0.21
Chronic liver disease	0	5 (12)	<0.01 <sup>e</sup>
Smoking	21 (32)	16 (37)	0.56
ECOG status	1 (0–2)	2 (1–3)	0.001 <sup>e</sup>
CFS	3 (2–6)	5 (4–7)	<0.001 <sup>e</sup>
APACHE II score	14 (11–19)	20 (15–31)	<0.001 <sup>e</sup>
SOFA score on admission	4 (2–5)	7 (5–12)	<0.001 <sup>e</sup>
Laboratory values on admission			
WBC ( $\times 10^3$ )	7.5 (5–10)	10 (7–12)	0.01 <sup>e</sup>
Lymphocyte ( $\times 10^3$ )	0.7 (0.5–1)	0.6 (0.4–1)	0.26
NLR	7.6 (3.7–13.5)	13.5 (5–22.5)	0.03
Prothrombin time (INR)	1.06 (1.05–1.16) <sup>a</sup>	1.18 (1.13–1.59) <sup>c</sup>	<0.001 <sup>e</sup>
Procalcitonin (ng/ml)	0.14 (0.07–0.3) <sup>b</sup>	0.6 (0.1–4.7) <sup>d</sup>	<0.01 <sup>e</sup>
pH (mm Hg)	7.43 (7.39–7.47) <sup>a</sup>	7.40 (7.29–7.45)	0.01 <sup>e</sup>
PaCO <sub>2</sub> (mm Hg)	36 (31–44) <sup>a</sup>	35 (30–47)	0.81
PaO <sub>2</sub> /FiO <sub>2</sub> on admission	184 (132–257)	154 (97–206)	0.01 <sup>e</sup>
Prone position	20 (30)	11 (26)	0.60
Septic shock on admission	18 (27)	37 (86)	<0.001 <sup>e</sup>
AKI on admission	19 (29)	33 (77)	<0.001 <sup>e</sup>
Mechanical Ventilation			
IMV	19 (29)	40 (93)	<0.001 <sup>e</sup>
NIMV	39 (59)	27 (63)	0.70
RRT	6 (9)	21 (49)	<0.001 <sup>e</sup>
Primary viral infection	50 (76)	28 (65)	0.23
Bacterial co-infection	18 (27)	16 (37)	0.27
Secondary bacterial infection	27 (41)	29 (67)	<0.01 <sup>e</sup>
Opportunistic infection	3 (5)	6 (14)	0.08
Patient group			
COVID-19	37 (56)	17 (40)	
Influenza	29 (44)	26 (60)	
Outcome			
ICU LOS (day)	11 (6–18)	17 (5–32)	0.23
Hospital LOS (day)	17 (11–34)	24 (13–37)	0.56

Values are presented as median (interquartile range) or number (%).

ECOG: Eastern Cooperative Oncology Group; CFS: Clinical Frailty Scale; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; WBC: white blood cell; NLR: neutrophil lymphocyte ratio; INR: international normalized ratio; PaO<sub>2</sub>/FiO<sub>2</sub>: the ratio of partial pressure arterial oxygen and fraction of inspired oxygen; AKI: acute kidney injury; IMV: invasive mechanical ventilation; NIMV: non-invasive mechanical ventilation; RRT: renal replacement therapy; COVID-19: coronavirus disease 2019; ICU: intensive care unit; LOS: length of stay.

<sup>a</sup>n=65; <sup>b</sup>n=46; <sup>c</sup>n=42; <sup>d</sup>n=31; <sup>e</sup>Indicates statistical significance.

**Table 3.** Multivariable analysis for predicting hospital mortality

Parameter	Odds ratio (95% CI)	P-value
IMV	42.16 (9.45–187.97)	<0.001
SOFA score on admission >4	5.92 (1.85–18.92)	0.01
Malignancy	4.95 (1.13–21.60)	0.03
Age >65 yr	3.31 (0.99–11.03)	0.05

Adjusted for history of cardiac disease, Clinical Frailty Scale, Acute Physiology and Chronic Health Evaluation II score >16, presence of septic shock, secondary bacterial infection, neutrophil lymphocyte ratio  $\geq 10$  and patient group as coronavirus disease 2019 versus influenza.

CI: confidence interval; IMV: invasive mechanical ventilation; SOFA: Sequential Organ Failure Assessment.

influenza patients than in those with COVID-19. Tang et al. [10] demonstrated similar findings that there were significantly higher number of patients who had PaO<sub>2</sub>/FiO<sub>2</sub> under 100 in influenza group than COVID-19 (48% vs. 7%, respectively).

It has been recently reported that septic shock was encountered more in COVID-19 patients compared with influenza (31.5% vs. 13.3%) during ICU stay [10]. Similarly, Piroth et al. [12] showed that pulmonary bacterial infection and septic shock were frequently seen in COVID-19 group. Septic shock on admission was found in 51% of our patients and it was more common in those with influenza. Our patients with influenza had worse performance status and more severe illness on admission than those with COVID-19 which could partly explain these different results between our study and previous ones. As known, another confounding factor during ARF is AKI which is associated with mortality among critically ill influenza patients and rates of reported AKI vary between 27 to 61%, consistent with the current study [9,20–22]. In this study, AKI was more common in the influenza group and the presence of AKI on admission draw a distinction with influenza from COVID-19. AKI incidence among critically ill COVID-19 patients was determined to be between 23% to 43% in previous studies [23,24]. In our study, AKI occurrence in COVID-19 cohort on admission was 30%.

Since the beginning of the COVID-19 pandemic, respiratory support practices have varied. At the beginning of the pandemic, IMV was frequently applied to COVID-19 patients with respiratory failure in order to prevent the spread of the disease especially to healthcare workers. Prone positioning has been used as a rescue treatment in severe ARDS patients to improve oxygenation and prevent ventilation induced lung injury [25,26]. In our study prone positioning was performed more commonly in patients with COVID-19 than in those with influenza and it was the only independent parameters that

distinguished COVID-19 from influenza. It has been increasingly utilized in COVID-19 patients with ARDS and many studies showed improvement in oxygenation even during awake prone positioning [27,28].

Bacterial infections developing during the course of viral infections have been frequently reported in recent years, and its association with increased morbidity and mortality has been shown [29,30]. In the current study, secondary bacterial infection was observed in 51% of the whole patients and it was demonstrated to be higher in the influenza group. Furthermore, the presence of secondary bacterial infection stands out as a variable that differentiate influenza from COVID-19.

This study is important because there are limited number of studies comparing COVID-19 with influenza and whether COVID-19 carries poorer prognosis compared to influenza is not well-known yet. However, there are some limitations in this study. First, it was a single-center retrospective study. Therefore, generalization of the results is not quite possible and the study is underpowered to detect a difference in the main outcome. Second, the two groups do not match with each other in terms of disease severity as such clinical severity of influenza was worse than that of the COVID-19 patients. Due to few numbers of patients, it was not possible to do a matched case-control study, however in logistic regression analysis COVID-19 or influenza was not a predictor of mortality when adjusted for other risk factors. Third, COVID-19 group consisted of patients admitted to ICU during the 4 months of the pandemic in our institution, whereas in the influenza group seasonal influenza cases of the last 5 years before the pandemic were included. Therefore, diagnostic and therapeutic options might have been changed during this time period which might have influenced patient outcomes.

This study revealed that there are few differences in clinical features of critically ill COVID-19 and influenza patients and there is no significant difference in hospital mortality between two groups. In fact, influenza cases had worse performance status and disease severity. Therefore, further studies with larger number of critically ill patients matched for clinical severity are needed.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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## AUTHOR CONTRIBUTIONS

Conceptualization: MY, BH, MYP, AT. Data curation: MY, MYP, BE, ITG, GT. Formal analysis: MY, BH, MYP, AT. Methodology: MY, BH, AT. Visualization: MY, BH, EOE. Writing—original draft: MY, BH. Writing—review & editing: BH, AT.

## REFERENCES

- Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: are they closely related? *Clin Microbiol Infect* 2020;26:729-34.
- Halacli B, Kaya A, Topeli A. Critically-ill COVID-19 patient. *Turk J Med Sci* 2020;50(SI-1):585-91.
- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020;323:1239-42.
- Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8:475-81.
- Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med* 2020;180:1345-55.
- Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA* 2020;323:2052-9.
- Ortiz JR, Neuzil KM, Shay DK, Rue TC, Neradilek MB, Zhou H, et al. The burden of influenza-associated critical illness hospitalizations. *Crit Care Med* 2014;42:2325-32.
- Arabi YM, Fowler R, Hayden FG. Critical care management of adults with community-acquired severe respiratory viral infection. *Intensive Care Med* 2020;46:315-28.
- Ortac Ersoy E, Er B, Ciftci F, Gulleroglu A, Suner K, Arpinar B, et al. Outcome of patients admitted to intensive care units due to influenza-related severe acute respiratory illness in 2017-2018 flu season: a multicenter study from Turkey. *Respiration* 2020;99:954-60.
- Tang X, Du RH, Wang R, Cao TZ, Guan LL, Yang CQ, et al. Comparison of hospitalized patients with ARDS caused by COVID-19 and H1N1. *Chest* 2020;158:195-205.
- Zayet S, Kadiane-Oussou NJ, Lepiller Q, Zahra H, Royer PY, Toko L, et al. Clinical features of COVID-19 and influenza: a comparative study on Nord Franche-Comte cluster. *Microbes Infect* 2020;22:481-8.
- Piroth L, Cottenet J, Mariet AS, Bonniaud P, Blot M, Tubert-Bitter P, et al. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. *Lancet Respir Med* 2021;9:251-9.
- Schnell D, Gits-Muselli M, Canet E, Lemiale V, Schlemmer B, Simon F, et al. Burden of respiratory viruses in patients with acute respiratory failure. *J Med Virol* 2014;86:1198-202.
- Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:801-10.
- KDIGO Clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012;2(Suppl 1):1-138.
- Martín-Loeches I, Sanchez-Corral A, Diaz E, Granada RM, Zaragoza R, Villavicencio C, et al. Community-acquired respiratory coinfection in critically ill patients with pandemic 2009 influenza A(H1N1) virus. *Chest* 2011;139:555-62.
- MacIntyre CR, Chughtai AA, Barnes M, Ridda I, Seale H, Toms R, et al. The role of pneumonia and secondary bacterial infection in fatal and serious outcomes of pandemic influenza a(H1N1) pdm09. *BMC Infect Dis* 2018;18:637.
- Zhao Z, Chen A, Hou W, Graham JM, Li H, Richman PS, et al. Prediction model and risk scores of ICU admission and mortality in COVID-19. *PLoS One* 2020;15:e0236618.
- Meng FS, Su L, Tang YQ, Wen Q, Liu YS, Liu ZF. Serum procalcitonin at the time of admission to the ICU as a predictor of short-term mortality. *Clin Biochem* 2009;42:1025-31.
- Demirjian SG, Raina R, Bhimraj A, Navaneethan SD, Gordon SM, Schreiber MJ Jr, et al. 2009 influenza A infection and acute kidney injury: incidence, risk factors, and complications. *Am J Nephrol* 2011;34:1-8.



21. Bagshaw SM, Sood MM, Long J, Fowler RA, Adhikari NK; Canadian Critical Care Trials Group H1N1 Collaborative. Acute kidney injury among critically ill patients with pandemic H1N1 influenza A in Canada: cohort study. *BMC Nephrol* 2013;14:123.
22. Beumer MC, Koch RM, van Beuningen D, OudeLashof AM, van de Veerdonk FL, Kolwijck E, et al. Influenza virus and factors that are associated with ICU admission, pulmonary co-infections and ICU mortality. *J Crit Care* 2019;50:59-65.
23. Pei G, Zhang Z, Peng J, Liu L, Zhang C, Yu C, et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. *J Am Soc Nephrol* 2020;31:1157-65.
24. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497-506.
25. Valenza F, Guglielmi M, Maffioletti M, Tedesco C, Maccagni P, Fossali T, et al. Prone position delays the progression of ventilator-induced lung injury in rats: does lung strain distribution play a role? *Crit Care Med* 2005;33:361-7.
26. Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017;195:1253-63.
27. Elharrar X, Trigui Y, Dols AM, Touchon F, Martinez S, Prud'homme E, et al. Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. *JAMA* 2020;323:2336-8.
28. Weatherald J, Solverson K, Zuege DJ, Loroff N, Fiest KM, Parhar KK. Awake prone positioning for COVID-19 hypoxemic respiratory failure: a rapid review. *J Crit Care* 2021;61:63-70.
29. Halaçlı B, Hancı P, Ortaç Ersoy E, Öcal S, Tanrıöver MD, Topeli A. Influenza or other respiratory viruses: does it matter as the cause of acute respiratory failure in the critically-ill patients? *Tuberk Toraks* 2020;68:388-98.
30. Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al. Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis. *Clin Microbiol Infect* 2020;26:1622-9.