Comparison of Clinical Profiles and Mortality Outcomes Between Influenza and COVID-19 Patients Invasively Ventilated in the ICU: A Retrospective Study From All Paris Public Hospitals From 2016 to 2021

Clemence Marois, Thomas Nedelec, Juliette Pelle, Antoine Rozes, Stanley Durrleman, Carole Dufouil, Alexandre Demoule

HAL Id: hal-03819244
https://hal.science/hal-03819244

Submitted on 18 Oct 2022

Comparison of Clinical Profiles and Mortality Outcomes Between Influenza and COVID-19 Patients Invasively Ventilated in the ICU: A Retrospective Study From All Paris Public Hospitals From 2016 to 2021

Clémence Marois, MD[1,2]

Thomas Nedelec, PhD[3]

Juliette Pelle, MD[1]

Antoine Rozes, MS[4]

Stanley Durrleman, PhD[3]

Carole Dufouil, PhD[5,6]

Alexandre Demoule, MD, PhD[2,7,8]

OBJECTIVES: Studies comparing outcomes of ICU patients admitted for either COVID-19 or seasonal influenza are limited. Our objective was to describe baseline clinical profiles, care procedures, and mortality outcomes by infection status (influenza vs COVID-19) of patients who received invasive mechanical ventilation in the ICU.

DESIGN: Retrospective observational study.

SETTING: Data were extracted from the Assistance Publique–Hopitaux de Paris database from September 1, 2016, to April 20, 2021. It includes data from the 39 university hospitals.

PATIENTS: A total of 752 influenza adult patients and 3,465 COVID-19 adult patients received invasive mechanical ventilation in one of the ICUs of the Paris area university hospitals, France.

INTERVENTION: The characteristics and outcome by infection status were compared. Factors associated with mortality were assessed using Cox proportional hazard models after controlling for potential confounders, including infection status.

MEASUREMENTS AND MAIN RESULTS: The median age at admission to the ICU was 67 (interquartile range [IQR], 57–77) and 63 yr (IQR, 54–71 yr) for influenza and COVID-19 patients, respectively. At ICU admission, COVID-19 patients were more frequently obese, more frequently had diabetes mellitus or high blood pressure, and were less likely to have chronic heart failure, chronic respiratory disease, chronic kidney failure, or active cancer than influenza patients. The overall survival at 90 days was 57% for COVID-19 patients and 66% for influenza patients ($p < 0.001$). In a multivariable Cox model, higher age, organ transplant, severe acute respiratory syndrome coronavirus 2 infection, and chronic kidney failure were associated with shorter survival, whereas obesity and high blood pressure were associated with longer survival after invasive ventilation.

CONCLUSIONS: COVID-19 and influenza patients requiring mechanical ventilation in the ICU differed by many characteristics. COVID-19 patients showed lower survival independently of potential confounders.

KEY WORDS: COVID-19; influenza; intensive care unit; invasive mechanical ventilation; mortality

COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), started in 2019 in China and spread rapidly throughout the world (1). It caused a sudden increase in hospitalizations in ICUs,

mostly for acute respiratory failure, and studies have reported case fatality rates ranging from 25% to 50% for patients with severe COVID-19 who received invasive mechanical ventilation (2).

Many comparisons have been made between COVID-19 and influenza infection. Both are seasonal respiratory diseases but are due to different viruses. Both may cause severe pneumonia, leading to acute respiratory failure and requiring invasive mechanical ventilation.

Large studies using national databases have shown differences in the clinical presentation of patients with COVID-19 and those with influenza requiring hospitalization (3–6). In addition, these studies have highlighted higher mortality among COVID-19 patients. However, these large studies focused on hospitalized patients. Studies comparing COVID-19 and influenza patients admitted to the ICU are scarce and based on small and selected samples (7–11).

The aim of the present study was to compare ICU patients mechanically ventilated for either influenza or COVID-19 using data from a large database of electronic health records from 2016 to 2021 from 39 hospitals in the greater Paris area in France. Our specific objectives were to identify similarities and differences between these two infections in terms of characteristics, management, and outcomes from ICU admission.

MATERIALS AND METHODS

Study Design and Setting

We extracted data from the Assistance Publique—Hopitaux de Paris (AP-HP) database (Entrepôt de données de santé [EDS], http://eds.aphp.fr) from September 1, 2016, to April 20, 2021. The database is prospectively managed and comprehensively describes patient stays at the hospital. It includes data since 2016 from the 39 university hospitals of the AP-HP group, all located in the greater Paris area. Twenty are adult acute hospitals. At admission and during their stay at the hospital, data on patients are collected using standardized forms and stored in a centralized database that includes administrative data, demographic characteristics, medical information, vital status, disease diagnoses classified using the *International Classification of Diseases*, 10th revision (ICD-10-Clinical Modification), and details of all medical procedures performed during hospitalization coded according to the French Common Classification of Medical Procedures.

Ethics Committee Approval

Procedures were followed in accordance with the ethical standards and with the Helsinki Declaration of 1975, and approved by the Institutional Review Board of the AP-HP, *n.* CSE-21-03 COVID-Coco-Neuro-Rea on March 24, 2021, which was authorized by the National Commission on Informatics and Liberty for such noninterventional data-based research with no informed consent.

Patient Selection

All patients with a diagnosis of COVID-19 or influenza infection and who had received invasive mechanical ventilation in the ICU were included in the study. To select these patients, a retrospective search was performed from the database according the following codes: patients with COVID-19 (causing hospitalization or hospitalized for another cause) were identified using the ICD-10 codes U07.10, U07.11, U07.12, U07.14, or U07.15. Patients with influenza infection (causing hospitalization or hospitalized for another cause) were identified using the ICD-10 codes J09, J10, or J11. For these analyses, we restricted patient records to those who had received invasive mechanical ventilation during the same ICU stay, identified using the codes GLLD004, GLLD008, or GLLD015 in the French Common Classification of Medical Procedures. Patients under the age of 18 years were excluded. For patients with several ICU admissions, only the first stay was included in the analysis.

Data Collection

For each patient, we extracted the age, sex, and following comorbidities based on ICD-10 diagnostic codes: high blood pressure, obesity, diabetes mellitus, chronic respiratory disease (including chronical bronchitis, chronic obstructive pulmonary disease, and asthma), cancer, organ transplant, cirrhosis, chronic kidney failure, and chronic heart failure. Outcomes, such as shock, cardiac arrest, pulmonary embolism, venous thromboembolism, myocarditis, acute renal failure, stroke, or status epilepticus, were recorded. The occurrence of ICU-acquired bacterial pneumonia, pathogens responsible, and ICU-acquired aspergillosis was also recorded.

The following advanced life support therapies initiated during the ICU stay were extracted: prone

positioning, tracheostomy, extracorporeal membrane oxygenation, inhaled nitric oxide (iNO), use of vasopressors, and renal replacement therapy. Finally, the duration of mechanical ventilation and length of ICU stay and ICU mortality and mortality 90 d (day 90) after ICU admission were computed. The exact date of death was available if it occurred during or after hospitalization and before data extraction was recorded, through a merge between the EDS database and the French Statistics Agency file recording all dead people in France. The precise codes used to define all extracted variables are provided in **Table S1** (http://links.lww. com/CCX/B43).

Statistical Analysis

Continuous variables are described as medians (interquartile ranges) and categorical variables as frequencies (percentages). To study the characteristics at admission, continuous and categorical variables were compared using univariable logistic regression (COVID-19 vs influenza as the outcome). To study outcomes and management in the ICU, time-dependent variables were compared using Cox regression models with COVID-19 versus influenza as the exposure of interest, considering the event as the outcome and the time to the event or death/data extraction as the time variable. For nontime-dependent variables, logistic regression or linear regression with COVID-19 versus influenza as the exposure was performed. We provide raw and adjusted p values, after adjusting for sex and age at admission.

We used Kaplan-Meier curves to compare survival after ICU admission between influenza and COVID-19 patients. To further investigate factors associated with ICU time to death, we performed a multivariable Cox proportions hazards model with death as the outcome and time to death or data extraction in days as the time variable. COVID-19 versus influenza was the exposure of interest; interactions between the exposure of interest and each risk factor or confounding variable in the model were tested, with adjustments for the 10 largest centers. All risk factors analyzed in the univariable Cox model were added to the multivariable Cox model. Estimated hazard ratios (HRs) and 95% CIs were calculated for each variable. All analyses were conducted using StatsModel 0.11.1 (Seabold, Skipper and Perktold, Josef and developer-statsmodel, Nashville, TN) and Lifeline 0.26.3 (Cam Davidson-Pilon, Waterloo, Canada) libraries in Python 3.6

(Python Software Foundation, Wilmington, DE). Values of $p < 0.05$ were considered significant.

RESULTS

The study flowchart is presented in **eFigure 1** (http:// links.lww.com/CCX/B43). Between September 1, 2016, and April 20, 2021, 52,383 patients with either COVID-19 or influenza were admitted to one of the 39 hospitals. Among them, 752 patients with influenza and 3,465 with COVID-19 received invasive mechanical ventilation and were included in the analytical sample.

The temporal distribution of ICU admissions for COVID-19 and influenza over the study period is presented in **Figure 1**. Among patients with influenza, 107 (14%) were hospitalized during the 2016–2017 season, 374 (50%) during the 2017–2018 season, 224 (30%) during the 2018–2019 season, 44 (6%) during the 2019–2020 season, and two during the 2020–2021 season. Among COVID-19 patients, 3,465 were admitted between January 1, 2020, and April 20, 2021 (**Table 1**).

Patient Characteristics and Management

The characteristics of patients admitted to the ICU and mechanically ventilated for either COVID-19 or influenza infection are presented in Table 1. COVID-19 patients were younger and more often male than influenza patients. In terms of comorbidities, COVID-19 patients were less likely to have chronic respiratory disease, active cancer, organ transplant, cirrhosis, chronic kidney failure, or chronic heart failure. Conversely, COVID-19 patients more often had high blood pressure, obesity, and diabetes mellitus.

In terms of management, COVID-19 patients were less likely to develop shock requiring vasopressors or status epilepticus than influenza patients, nor present more with stroke or develop more acute renal failure or require more frequent renal replacement therapy (**Table 2**; and **eTable 4**, http://links.lww.com/CCX/B43) during ICU stay. In terms of respiratory support, COVID-19 patients were more likely to require prone positioning, tracheostomy, and iNO than influenza patients, but not extracorporeal membrane oxygenation (Table 2). COVID-19 patients were also less likely to develop ICU-acquired pneumonia than influenza patients, but not pulmonary aspergillosis (Table 2).
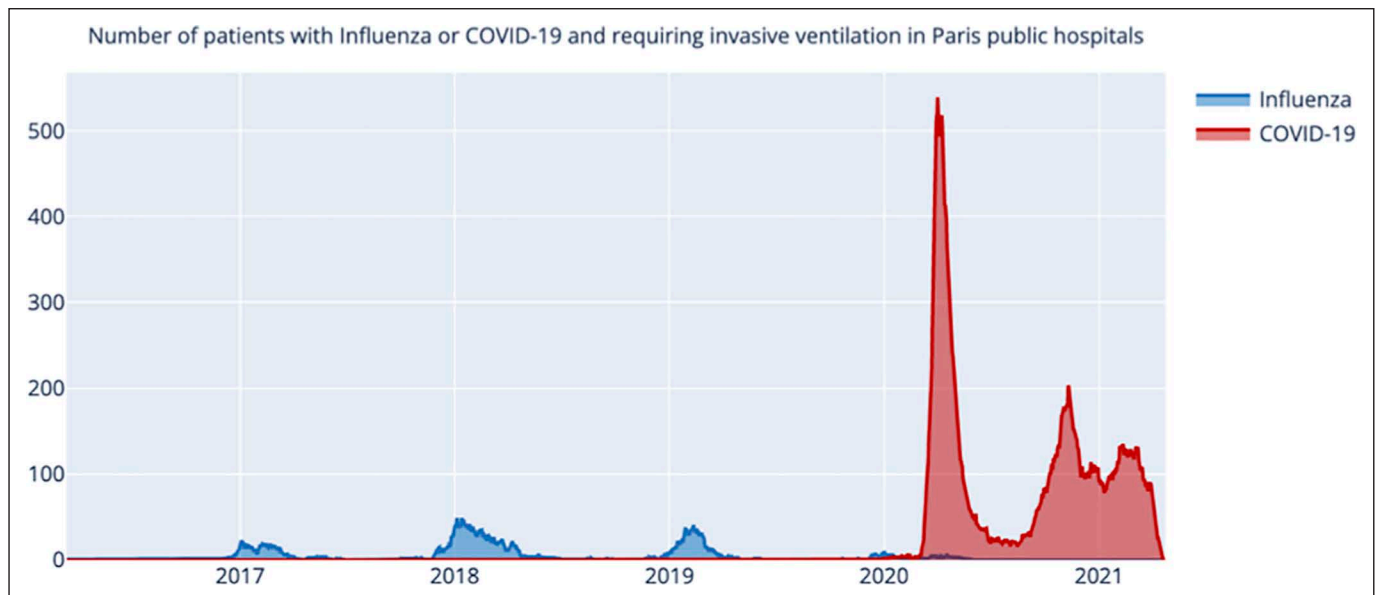
Figure 1. Absolute number of patients with influenza or COVID-19 requiring invasive ventilation in ICUs of the Assistance Publique—Hôpitaux de Paris hospitals between September 1, 2016, and April, 20, 2021.

Outcome Analysis

The duration of invasive ventilation was longer and ICU and 90-day mortality higher for COVID-19 than influenza patients (Table 2 and **Fig. 2***A*). There was no difference in the ICU length of stay for COVID-19 than influenza patients (Table 2).

Factors associated with mortality by univariate analysis in patients ventilated in ICU with either influenza infection or COVID-19 are shown in **Table 3**. COVID-19 infection was individually associated with higher mortality (HR, 1.28; 95% CI, 1.13–1.45; p < 0.001). By multivariate analysis, six variables were independently associated with mortality in patients ventilated in ICU with either influenza infection or COVID-19 (**Fig. 2***B*; see also **eTable 1**, http://links.lww.com/CCX/B43). Obesity was associated with lower mortality (HR, 0.75; 95% CI, 0.68–0.84; p < 0.001). Five variables were associated with higher mortality: age (HR, 2.09; 95% CI, 1.9–2.31; p < 0.001), organ transplant (HR, 1.65; 95% CI, 1.39–1.95; p < 0.001), cirrhosis (HR, 1.34; 95% CI, 1.16–1.55; p = 0.032), active cancer (HR, 1.22; 95% CI, 1.08–1.39; p = 0.002), and COVID-19 infection (HR, 1.28; 95% CI, 1.13–1.45; p < 0.001).

Sensitivity analyses were performed by stratification on COVID-19/influenza (**eTable 2**, http://links.lww.com/CCX/B43). Higher age, organ transplant, and cirrhosis were significantly associated with lower survival of COVID-19 patients, whereas obesity was associated with higher survival. Among influenza patients, higher

age, cirrhosis, and cancer were associated with lower survival (**eTable 3** and **eFig. 2**, http://links.lww.com/CCX/B43).

DISCUSSION

This study compared the characteristics and outcomes for influenza infection or COVID-19 in a large cohort of mechanically ventilated patients. Our major results can be summarized as follows: 1) many more patients were mechanically ventilated for COVID-19 from January 2020 to April 2021 than for influenza during the cumulative 2016–2020 period, 2) comorbidities of COVID-19 and influenza patients were different, and 3) mortality was higher among COVID-19 patients, even after adjustment for confounders.

Global Findings

Our study highlights the massive influx of patients who required invasive ventilation in the ICU during the COVID-19 pandemic period, 4.5 times more patients from January 2020 to April 2021 than during the cumulative 2016–2020 period. We also confirm the low intensity of the seasonal influenza epidemic in France during the 2019–2020 (12), and 2020–2021 winters in France (13). This result was also reported in other European countries, with a 99.8% reduction in positive sentinel influenza virus detection compared with the previous six seasons

TABLE 1.
Patient Characteristics at ICU Admission

Patient characteristics	Influenza Patients, *n* = 752	COVID-19 Patients, *n* = 3,465	*p*	*p* Corrected for Age and Gender
Admission dates, *n* (%)				
November 2016 to August 2017	107 (14)	0 (0)		
November 2017 to August 2018	374 (50)	0 (0)		
November 2018 to August 2019	224 (30)	0 (0)		
November 2019 to August 2020	44 (6)	1,865 (54)		
November 2020 to August 2021	2 (0)	1,600 (46)		
Gender male, *n* (%)	453 (60)	2,494 (72)	< 0.001	NA
Age at admission, yr, *n* (%)	67 (57–77)	63 (54–71)	< 0.001	NA
18–39	57 (8)	232 (7)		
40–59	182 (24)	1,075 (31)		
60–79	366 (49)	2,023 (58)		
> 80	147 (20)	135 (4)		
Comorbidities at admission, *n* (%)				
High blood pressure	312 (41)	1,679 (48)	< 0.001	< 0.001
Obesity	107 (14)	1,163 (34)	< 0.001	< 0.001
Diabetes mellitus	179 (24)	1,071 (31)	< 0.001	< 0.001
Chronic heart failure	205 (27)	359 (10)	< 0.001	< 0.001
Chronic respiratory disease	170 (23)	326 (9)	< 0.001	< 0.001
Cirrhosis	98 (13)	335 (10)	0.006	< 0.001
Chronic kidney failure	117 (16)	359 (10)	< 0.001	< 0.001
Active cancer	151 (20)	394 (11)	< 0.001	< 0.001
Organ transplant	55 (7)	178 (5)	0.018	0.006

NA = not applicable.
Continuous variables are expressed as medians (interquartile ranges) and categorical variables as absolute values (%).

(14), and the rest of the world (15). This unprecedented result is probably explained by the strict public health and physical distancing measures applied during the COVID-19 pandemic, influenza vaccination, and possible competitive exclusion between these two viruses (16).

Characteristics of the Two Infections

This study confirms that the profile of patients who develop severe COVID-19 and are admitted to the ICU is relatively different from that of patients who develop severe influenza and are admitted to the ICU. COVID-19 patients were more frequently male, more frequently obese, and more frequently had arterial hypertension or diabetes mellitus. Conversely, they were less likely to have chronic respiratory insufficiency, organ transplant, cirrhosis, chronic kidney failure, heart failure, or active cancer than severe influenza patients who required ICU admission (11).

Obesity, arterial hypertension, and diabetes mellitus have already been reported to be frequent comorbidities of severe COVID-19 patients hospitalized in the ICU (17) and as risk factors for ICU admission (11). Although cardiometabolic disorders are not classical risk factors for the development of viral respiratory infections, preexisting arterial hypertension, diabetes, and obesity can cause endothelial dysfunction and increase the risk of endothelial invasion by SARS-CoV-2 via the angiotensin-converting enzyme 2 (ACE2) receptor (18). Furthermore, excessive adipose tissue may serve as a reservoir for ACE2 (19). Finally,

TABLE 2.
Management and Outcomes During the ICU Stay

Management and Outcomes	Influenza Patients, n = 752	COVID-19 Patients, n = 3,465	Hazard Ratio Adjusted for Age and Gender	p
Organ failure during ICU stay, n (%)				
Septic shock	308 (41)	1,336 (39)	0.95 (0.83–1.07)	0.39
Cardiac arrest	34 (5)	128 (4)	1.06 (0.77–1.47)	0.706
Myocarditis	21 (3)	37 (1)	0.34 (0.2–0.59)	< 0.001
Acute renal failure	302 (40)	1,245 (36)	0.87 (0.77–0.99)	0.038
Status epilepticus	16 (2)	31 (1)	0.4 (0.22–0.73)	0.003
Stroke	22 (3)	115 (3)	1.07 (0.68–1.7)	0.766
Pulmonary embolism	39 (5)	405 (12)	2.35 (1.67–3.31)	<0.001
Veinous thromboembolism	21 (3)	148 (4)	1.39 (0.87–2.22)	0.063
Organ support during ICU stay, n (%)				
Prone positioning	155 (21)	1,936 (56)	3.5 (2.97–4.13)	< 0.001
Tracheostomy	33 (4)	245 (7)	1.59 (1.1–2.29)	0.013
Extracorporeal membrane oxygenation	73 (10)	350 (10)	0.93 (0.73–1.2)	0.599
Inhaled nitric oxide	16 (2)	308 (9)	4.3 (2.6–7.13)	< 0.001
Vasopressors	596 (79)	2,852 (82)	1.06 (0.97–1.16)	0.202
Renal replacement therapy	121 (16)	429 (12)	0.72 (0.59–0.88)	0.002
Pneumonia, n (%)				
ICU-acquired pneumonia	465 (62)	1,772 (51)	0.72 (0.65–0.8)	< 0.001
Streptococcus pneumoniae	66 (9)	84 (2)	0.25 (0.18–0.35)	< 0.001
Haemophilus influenzae	46 (6)	108 (3)	0.47 (0.33–0.67)	< 0.001
Pseudomonas aeruginosa	113 (15)	580 (17)	1.11 (0.89–1.38)	0.251
Staphylococcus aureus	85 (11)	406 (12)	1.0 (0.78–1.28)	0.748
Escherichia coli	34 (5)	156 (5)	0.96 (0.65–1.4)	0.982
Other Gram negative bacilli	90 (12)	518 (15)	1.23 (0.97–1.57)	0.035
Other germs	99 (13)	526 (15)	1.14 (0.90–1.43)	0.159
Pulmonary aspergillosis	18 (2)	74 (2)	0.97 (0.58–1.65)	0.922
Outcome variables				
Duration of invasive ventilation, d	12 (4–28)	18 (8–34)	NA	< 0.001
ICU mortality, n (%)	242 (32)	1,447 (42)	NA	< 0.001
ICU length of stay, d	20 (10–37)	21 (11–36)	NA	0.397

NA = not available.
Continuous variables are expressed as medians (interquartile ranges) and categorical variables as absolute values (%). p values are adjusted for age and sex.

obesity results in impairment of the adaptive immune response, cardiometabolic and thrombotic problems, and an increased risk of acute respiratory distress syndrome (ARDS) (20).

The fact that COVID-19 patients were less likely to present chronic respiratory insufficiency than influenza patients may have also been because patients with chronic respiratory insufficiency feared catching a severe COVID-19 illness and adhered better to mitigation measures than other patients (21, 22). Another hypothesis to explain such an association could be the protective effect of nicotine by inhibiting the penetration and propagation of SARS-CoV-2 (23).
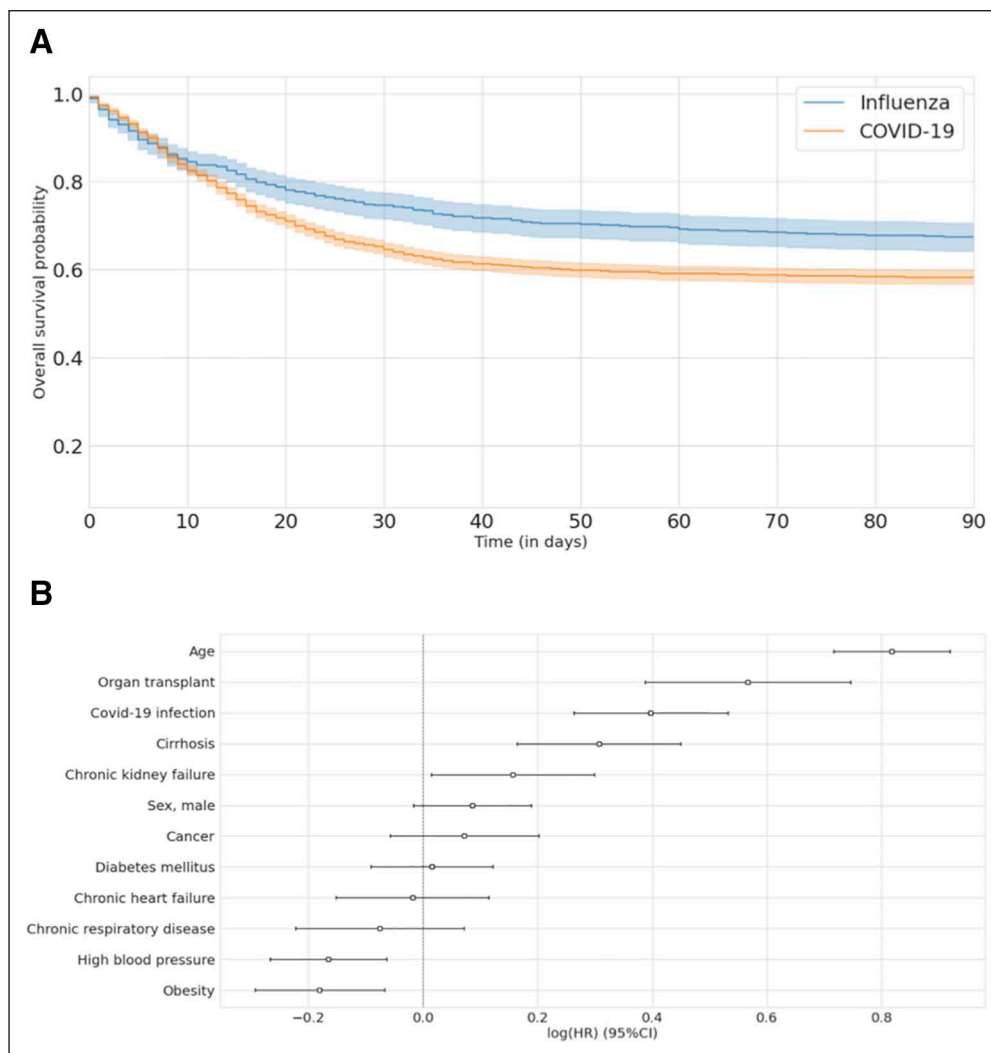
Figure 2. Comparing mortality in COVID-19 and influenza subgroups. Time to death within 90 d following ICU admission for the influenza and COVID-19 cohorts (**A**) and hazard ratios (HRs) and 95% CIs for proportional hazard models assessing the effect of variables associated with survival for all patients by multivariate Cox regression (**B**).

invasive ventilation was longer for COVID-19 than influenza patients, suggesting more severe ARDS. COVID-19 patients had more pulmonary embolism and venous thromboembolism than influenza patients, confirming the remarkably high prevalence of thrombotic complications in ICU patients with COVID-19 (26).

However, it surprisingly appears that COVID-19 patients did not have more infectious complications or renal, hemodynamic, or neurologic failure than severe influenza patients. These results are similar to previous comparative studies in critically ill patients (6–8, 10), suggesting that extrarespiratory complications are not specific to SARS-CoV-2 invasion but are more likely secondary to nonspecific causes associated with severe ARDS and critical care (sedative drugs, invasive mechanical ventilation, systemic inflammatory response, and hemodynamic failure).

We also confirmed that ICU mortality was higher for COVID-19 than influenza for invasively ventilated patients. This result can be explained by differences in the type and severity of ARDS associated with COVID-19 than that associated with influenza, requiring more respiratory support and a longer duration of invasive ventilation. We were unable to compare ARDS severity between the two groups of patients in this study due to the absence of certain individual data (especially the arterial oxygen [Pao_2]/Fio_2 ratio or the Sequential Organ Failure Assessment score at admission). Although previous studies appear to confirm this hypothesis (8, 27–29), further studies are needed to precisely understand this difference in mortality.

We also highlight that the proportion of elderly patients was higher among ventilated patients with influenza than those with COVID-19. Along with chronic respiratory failure patients, it is likely that older patients better respected physical distancing measures during COVID-19 pandemic. Another possible explanation could be that elderly patients with severe COVID-19 would not be mechanically ventilated due to the shortage of ICU beds during the pandemic period (24, 25).

Outcomes and Mortality Analysis

Prone positioning, tracheostomy, and iNO administration were more frequently used, and the length of

TABLE 3.
Factors Associated With Mortality After ICU Admission With Either Influenza or COVID-19: Hazard Ratio and 95% CI for Univariate Proportional Hazard Models Assessing the Effect of Variables Associated With Survival

Factors Associated With Mortality	ICU Survivors, n = 2,528	Nonsurvivors, n = 1,689	Hazard Ratio	p
Patients characteristics				
Age, yr	61 (51–69)	68 (60–74)	2.09 (1.9–2.31)[a]	< 0.001
Sex, male, n (%)	1,719 (68)	1,228 (73)	1.11 (1.01–1.23)	0.04
Comorbidities, n (%)				
High blood pressure	1,199 (47)	792 (47)	1.02 (0.93–1.12)	0.706
Obesity	833 (33)	437 (26)	0.75 (0.68–0.84)	< 0.001
Diabetes mellitus	724 (29)	526 (31)	1.1 (1.0–1.22)	0.051
Chronic heart failure	331 (13)	233 (14)	1.07 (0.94–1.21)	0.323
Chronic respiratory disease	322 (13)	174 (10)	0.9 (0.78–1.04)	0.142
Cirrhosis	215 (9)	218 (13)	1.34 (1.16–1.55)	< 0.001
Chronic kidney failure	255 (10)	221 (13)	1.37 (1.21–1.57)	< 0.001
Active cancer	299 (12)	246 (15)	1.22 (1.08–1.39)	0.002
Organ transplant	94 (4)	139 (8)	1.65 (1.39–1.95)	< 0.001
Diagnosis				
COVID-19	2,018 (80)	1,447 (86)	1.28 (1.13–1.45)	< 0.001
Organ failure during ICU stay, n (%)				
Septic shock	578 (23)	818 (48)	1.99 (1.81–2.19)	< 0.001
Cardiac arrest	88 (3)	183 (11)	2.17 (1.86–2.53)	< 0.001
Acute renal failure	681 (27)	866 (51)	2.09 (1.9–2.29)	< 0.001
Status epilepticus	31 (1)	16 (1)	0.69 (0.43–1.12)	0.133
Stroke	67 (3)	70 (4)	1.29 (1.02–1.63)	0.032
Myocarditis	47 (2)	11 (1)	0.35 (0.18–0.67)	0.002
Pulmonary embolism	225 (9)	219 (13)	1.52 (1.25–1.86)	< 0.001
Veinous thromboembolism	118 (5)	51 (3)	0.64 (0.46–0.89)	0.008
Organ support during ICU stay, n (%)				
Prone positioning	1,066 (42)	1,025 (61)	1.61 (1.47–1.78)	< 0.001
Tracheostomy	219 (9)	59 (3)	0.43 (0.34–0.56)	< 0.001
Extracorporeal membrane oxygenation	198 (8)	225 (13)	1.55 (1.3–1.83)	< 0.001
Inhaled nitric oxide	100 (4)	224 (13)	2.21 (1.91–2.55)	< 0.001
Vasopressors	1,878 (74)	1,570 (93)	2.81 (2.39–3.31)	< 0.001
Renal replacement therapy	250 (10)	300 (18)	1.44 (1.27–1.63)	< 0.001
Pneumonia, n (%)				
ICU-acquired pneumonia	1,360 (54)	877 (52)	0.85 (0.78–0.93)	< 0.001
Pulmonary aspergillosis	27 (1)	65 (4)	1.97 (1.54–2.51)	< 0.001

[a]Versus patients < 65 years old.

Continuous variables are expressed as medians (interquartile ranges) and categorical variables as absolute values (%).

Risk Factors and the Obesity Paradox

In the COVID-19 cohort, higher age, organ transplant, and cirrhosis were significantly associated with a lower time of survival, whereas obesity was associated with a higher time of survival. This "obesity paradox" (30) is a subject of debate, illustrated by multiple studies defined by a relationship between body mass index and lower mortality among ICU patients, in which obesity appears to be a protective factor. Our observation that obesity was protective against mortality in the ICU is likely explained by a collider bias (31), but it may only be a partial explanation of this observation, and potential physiologic mechanisms of this association are still unknown.

Strengths and Limitations

A major strength of our study was its large sample size, its multicentric design, and its time coverage, which was sufficient to compare at least four seasonal influenza outbreaks. We also attempted to minimize the effects of confounding variables by using multiple multivariable Cox regression models with all observed confounding variables, enabling separation of the specific role of each comorbidity in the mortality of these two respiratory infectious diseases. This study also had several limitations. First, we cannot exclude that data collection was not strictly identical between centers and periods, especially during the pandemic, during which all hospital units during the first COVID-19 wave were overwhelmed. This may have resulted in inaccuracies in electronic health records in this context. However, our results and baseline characteristics are similar to those of other large studies (17, 32, 33). Second, we cannot exclude that some included patients received invasive ventilation for another cause and received the diagnosis of COVID-19 or influenza during the ICU stay. Certain comorbidities and outcomes may have also been underdetected or misclassified because some of the codes we mentioned in the analysis can also be related to some preexisting active comorbidities. However, such a potential bias is likely nondifferential for most comorbidities. We also lacked information on certain important variables, such as the severity score, treatments used, biological findings, or whether the patient received noninvasive ventilation or high-flow oxygen before being invasively ventilated. Finally, the management of ARDS has evolved in recent years, with

the systematization of prone positioning and the more extensive use of high-flow oxygen, which may have led to different practices between the selected periods and explain some of the differences when comparing patients with influenza and COVID-19.

CONCLUSIONS

This study provides an extensive comparison between patients with influenza infection and COVID-19 in the ICU, confirming known differences between patients admitted to the ICU due to one of these infections. It constitutes an initial attempt to separate the specific impact of the main known comorbidities on the probability of dying in the ICU, providing new insights on the management of severe respiratory infectious diseases in the ICU.

ACKNOWLEDGMENTS

1   AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Service de Neurologie, Unité de de Médecine Intensive et Réanimation à Orientation Neurologique, Paris, France.

2   Sorbonne Université, Assistance Publique - Groupe de Recherche Clinique en REanimation et Soins intensifs du Patient en Insuffisance Respiratoire aiguE (GRC-RESPIRE), Paris, France.

3   Paris Brain Institute, ICM, Inserm U 1127, CNRS UMR 7225, Sorbonne Université, INRIA, Aramis Project-Team, Paris, France.

4   AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Centre de Pharmacoépidémiologie (Cephepi), INSERM, CIC-1901, Paris, France.

5   Univ. Bordeaux, Inserm, UMR Bordeaux Population Health, PHARes Team, CIC1401-EC, Bordeaux, France.

6   Pôle de Santé Publique Centre Hospitalier Universitaire (CHU) de Bordeaux, Bordeaux, France.

7   AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Service de Médecine Intensive - Réanimation (Département R3S), Paris, France.

8   Sorbonne Université, INSERM, UMRS1158 Neurophysiologie Respiratoire Expérimentale et Clinique, Paris, France.

REFERENCES

1. 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; 323:1239–1242

2. Lim ZJ, Subramaniam A, Ponnapa Reddy M, et al: Case fatality rates for patients with COVID-19 requiring invasive mechanical ventilation. A meta-analysis. *Am J Respir Crit Care Med* 2021; 203:54–66

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

4. Ludwig M, Jacob J, Basedow F, et al: Clinical outcomes and characteristics of patients hospitalized for Influenza or COVID-19 in Germany. *Int J Infect Dis* 2021; 103:316–322

5. Faust JS, Del Rio C: Assessment of deaths from COVID-19 and from seasonal influenza. *JAMA Intern Med* 2020; 180:1045–1046

6. Fröhlich GM, De Kraker MEA, Abbas M, et al: Hospital outcomes of community-acquired COVID-19 versus influenza: Insights from the Swiss hospital-based surveillance of influenza and COVID-19. *Euro Surveill* 2022; 27:2001848

7. Herbstreit F, Overbeck M, Berger MM, et al: Characteristics of critically ill patients with COVID-19 compared to patients with influenza-a single center experience. *J Clin Med* 2021; 10:2056

8. Cobb NL, Sathe NA, Duan KI, et al: Comparison of clinical features and outcomes in critically ill patients hospitalized with COVID-19 versus influenza. *Ann Am Thorac Soc* 2021; 18:632–640

9. Shih E, Squiers JJ, DiMaio JM, et al: Outcomes of extracorporeal membrane oxygenation in patients with severe acute respiratory distress syndrome caused by COVID-19 versus influenza. *Ann Thorac Surg* 2022; 113:1445–1451

10. Cousin N, Bourel C, Carpentier D, et al; Lille Intensive Care COVID-19 Group: SARS-CoV-2 versus influenza-associated acute respiratory distress syndrome requiring veno-venous extracorporeal membrane oxygenation support. *ASAIO J* 2021; 67:125–131

11. Fayol A, Livrozet M, Pereira H, et al: Cardiometabolic disorders and the risk of critical COVID-19 as compared to influenza pneumonia. *J Clin Med* 2021; 10:4618

12. SPF: Bulletin Épidémiologique Grippe. Bilan de la Surveillance, Saison 2019-2020. 2020. Available at: https://www.sante-publiquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/grippe/documents/bulletin-national/bulletin-epidemiologique-grippe.-bilan-de-la-surveillance-saison-2019-2020. Accessed November 18, 2021

13. SPF: Bulletin Épidémiologique Grippe, Semaine 15. Bilan Préliminaire. Saison 2020-2021. 2021. Available at: https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/grippe/documents/bulletin-national/bulletin-epidemiologique-grippe-semaine/15.-bilan-preliminaire-saison-2020-2021. Accessed November 18, 2021

14. Adlhoch C, Mook P, Lamb F, et al: Very little influenza in the WHO European Region during the 2020/21 season, weeks 40 2020 to 8 2021. *Euro Surveill* 2021; 26:2100221

15. Olsen SJ, Azziz-Baumgartner E, Budd AP, et al: Decreased influenza activity during the COVID-19 pandemic - United States, Australia, Chile, and South Africa, 2020. *MMWR Morb Mortal Wkly Rep* 2020; 69:1305–1309

16. Kiseleva I, Ksenafontov A: COVID-19 shuts doors to flu but keeps them open to rhinoviruses. *Biology (Basel)* 2021; 10:733

17. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators: Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: A prospective cohort study. *Intensive Care Med* 2020; 47:60–73

18. Varga Z, Flammer AJ, Steiger P, et al: Endothelial cell infection and endotheliitis in COVID-19. *Lancet* 2020; 395:1417–1418

19. Huang Y, Lu Y, Huang YM, et al: Obesity in patients with COVID-19: A systematic review and meta-analysis. *Metabolism* 2020;113:154378

20. Gong MN, Bajwa EK, Thompson BT, et al: Body mass index is associated with the development of acute respiratory distress syndrome. *Thorax* 2010; 65:44–50

21. Leung JM, Niikura M, Yang CWT, et al: COVID-19 and COPD. *Eur Respir J* 2020; 56:2002108

22. Jung Y, Wee JH, Kim JH, et al: The effects of previous asthma and COPD on the susceptibility to and severity of COVID-19: A nationwide cohort study in South Korea. *J Clin Med* 2021; 10:4626

23. Labro G, Tubach F, Belin L et al. Nicotine patches in patients on mechanical ventilation for severe COVID-19: a randomized, double-blind, placebo-controlled, multicentre trial. *Intensive Care Med* 2022; 48:876–887

24. Flaatten H, Guidet B, de Lange DW, et al: The importance of revealing data on limitation of life sustaining therapy in critical ill elderly Covid-19 patients. *J Crit Care* 2022; 67:147–148

25. DeJong C, Chen AH, Lo B: An ethical framework for allocating scarce inpatient medications for COVID-19 in the US. *JAMA* 2020; 323:2367–2368

26. Klok FA, Kruip MJHA, van der Meer NJM, et al: Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020; 191:145–147

27. Brault C, Zerbib Y, Kontar L, et al: COVID-19- versus non-COVID-19-related acute respiratory distress syndrome: Differences and similarities. *Am J Respir Crit Care Med* 2020; 202:1301–1304

28. Gattinoni L, Coppola S, Cressoni M, et al: COVID-19 does not lead to a "Typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020; 201:1299–1300

29. Bhaskaran K, Rentsch CT, Hickman G, et al: Overall and cause-specific hospitalisation and death after COVID-19 hospitalisation in England: A cohort study using linked primary care, secondary care, and death registration data in the OpenSAFELY platform. *PLoS Med* 2022; 19:e1003871

30. Decruyenaere A, Steen J, Colpaert K, et al: The obesity paradox in critically ill patients: A causal learning approach to a casual finding. *Crit Care* 2020; 24:485

31. Jose RJ, Manuel A: Does coronavirus disease 2019 disprove the obesity paradox in acute respiratory distress syndrome? *Obesity (Silver Spring)* 2020; 28:1007

32. Fartoukh M, Voiriot G, Guérin L, et al; AP-HP Clinical Data Warehouse; EPIcuFLU_APHP Group: Seasonal burden of severe influenza virus infection in the critically ill patients, using the Assistance Publique-Hôpitaux de Paris clinical data warehouse: A pilot study. *Ann Intensive Care* 2021; 11:117

33. Rouzé A, Lemaitre E, Martin-Loeches I, et al; coVAPid study group: Invasive pulmonary aspergillosis among intubated patients with SARS-CoV-2 or influenza pneumonia: A European multicenter comparative cohort study. *Crit Care* 2022; 26:11