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### ► To cite this version:

Diane Naouri, Tàì I. Pham, Martin Dres, Albert C. Vuagnat, Gaëtan Beduneau, et al.. Differences in clinical characteristics and outcomes between COVID-19 and influenza in critically ill adult patients: A national database study. *Journal of Infection*, 2023, 87 (2), pp.120-127. 10.1016/j.jinf.2023.05.011 . hal-04190830

**HAL Id: hal-04190830**

**<https://hal.science/hal-04190830v1>**

Submitted on 4 Sep 2024

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Contents lists available at ScienceDirect

Journal of Infection

journal homepage: [www.elsevier.com/locate/jinf](http://www.elsevier.com/locate/jinf)

## Differences in clinical characteristics and outcomes between COVID-19 and influenza in critically ill adult patients: A national database study



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### ARTICLE INFO

#### Article history:

Accepted 11 May 2023

Available online 16 May 2023

#### Keywords:

Intensive care unit

COVID-19

Influenzae

Nationwide study

### SUMMARY

**Objective:** Prior to the coronavirus disease 2019 (COVID-19) pandemic, influenza was the most frequent cause of viral respiratory pneumonia requiring intensive care unit (ICU) admission. Few studies have compared the characteristics and outcomes of critically ill patients with COVID-19 and influenza.

**Methods:** This was a French nationwide study comparing COVID-19 (March 1, 2020–June 30, 2021) and influenza patients (January 1, 2014–December 31, 2019) admitted to an ICU during pre-vaccination era. Primary outcome was in-hospital death. Secondary outcome was need for mechanical ventilation.

**Results:** 105,979 COVID-19 patients were compared to 18,763 influenza patients. Critically ill patients with COVID-19 were more likely to be men with more comorbidities. Patients with influenza required more invasive mechanical ventilation (47 vs. 34%,  $p < 0.001$ ), vasopressors (40% vs. 27%,  $p < 0.001$ ) and renal-replacement therapy (22 vs. 7%,  $p < 0.001$ ). Hospital mortality was 25% and 21% ( $p < 0.001$ ) in patients with COVID-19 and influenza, respectively. In the subgroup of patients receiving invasive mechanical ventilation, ICU length of stay was significantly longer in patients with COVID-19 (18 [10–32] vs. 15 [8–26] days,  $p < 0.001$ ). Adjusting for age, gender, comorbidities, and modified SAPS II score, in-hospital death was higher in COVID-19 patients (adjusted sub-distribution hazard ratio [aSHR]=1.69; 95%CI=1.63–1.75) compared with influenza patients. COVID-19 was also associated with less invasive mechanical ventilation (aSHR=0.87; 95%CI=0.85–0.89) and a higher likelihood of death without invasive mechanical ventilation (aSHR=2.40; 95%CI=2.24–2.57).

**Conclusion:** Despite younger age and lower SAPS II score, critically ill COVID-19 patients had a longer hospital stay and higher mortality than patients with influenza.

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### Introduction

After the first cases were diagnosed in December, 2019, coronavirus disease 2019 (COVID-19) rapidly emerged worldwide. It was recognized as a pandemic by the World Health Organization (WHO) on March 11, 2020.<sup>1</sup> Although most patients with COVID-19 remained asymptomatic or presented with a mild-course form,

about 5% of symptomatic patients required admission to the intensive care unit (ICU) for acute respiratory failure (ARF) and received supportive care.<sup>2,3</sup> Among all hospital admissions for COVID-19, 18% of patients had been admitted in ICU in France during the first (between March 1 and June 30, 2020) and second (between July 1 and December 31, 2020) surges<sup>4</sup> and 23% during the third surge (between January 1 to June 30, 2021).<sup>5</sup> COVID-19 became one of the main reasons for admission to an ICU in France between March, 2020 and June, 2021.<sup>6,7</sup>

Before COVID-19, influenza was the most frequent viral etiology of ARF in the ICU. As such, a previous influenza pandemic was used for modeling and preparing plans for future epidemics.<sup>8,9</sup> Person-to-person transmission by droplets and severe forms of ARF leading to acute respiratory disease syndrome (ARDS) are characteristics common to both influenza and COVID-19.<sup>10,11</sup> However, some discrepancies, such as baseline characteristics and outcomes, have been recorded in monocenter studies of patients displaying heterogeneous severity of wild-type SARS CoV-2.<sup>12–21</sup>

By using the French administrative health care database, we aimed to compare the clinical characteristics and outcomes of critically ill COVID-19 patients with a historical cohort admitted to an ICU for influenza pneumonia.

## Material and method

### Study design and participants

This claims study was performed using the French administrative health care database (Système National des Données de Santé, SNDS). The SNDS contains data on outpatient care (medical consultation, paramedical interventions, dispensing of reimbursed drugs) as well as data from the program for the medicalization of the information system (admission date, duration, ICD-10 codes for main and associated diagnosis, medical interventions) collected during hospital stay.<sup>22</sup> All data were linked by means of a unique personal identification number.

We included all adult patients hospitalized in French ICUs from March 1, 2020 to June 30, 2021, for whom a complete hospital course was available. For the comparative group (influenza cohort), we included all adult patients hospitalized in an ICU from January 1, 2014 to December 31, 2019. To be included in one of these two groups, the patient should have had either one ICD-10 diagnosis code of COVID-19 or influenza. The complete list of ICD-10 diagnosis codes is available in [Appendix 1](#).

### Variables

Age, gender, and Simplified Acute Physiology Score (SAPS) II score<sup>23</sup> at admission were collected for each inpatient stay. The SAPS II score is a severity score and mortality estimation tool developed from a large sample of medical and surgical patients in North America and Europe. It includes 17 variables: 12 physiology variables, age, type of admission (scheduled surgical, unscheduled surgical, or medical), and three underlying disease variables.<sup>23</sup>

We calculated the Charlson Comorbidity Index (CCI)<sup>24</sup> based on all ICD-10 diagnoses collected. Several comorbidities were also recorded: arterial hypertension, diabetes mellitus, heart disease, chronic lung disease, cirrhosis, cancer, hematological malignancies, chronic kidney disease, and immunosuppression. Immunocompromised patients were defined as patients with agranulocytosis, medullary aplasia, immunodeficiency, cancer treated by chemotherapy, or solid organ transplants (ICD-10 diagnosis codes used to identify patients are available in [Appendix 1](#)).

We recorded the oxygenation and ventilation procedures used during hospitalization (according to the French Common Classification of Medical Procedures [CCAM]<sup>25</sup>): invasive mechanical

ventilation, non-invasive mechanical ventilation (NIV), and high-flow nasal cannula therapy (HFNC). Some patients received more than one of the three oxygenation techniques, in which case the most invasive was retained for further analyses, assuming invasive mechanical ventilation to be more invasive than NIV and NIV to be more invasive than HFNC. We also recorded patients who received prone position or extracorporeal membrane oxygenation (ECMO).

We additionally documented whether the patients required renal replacement therapy (RRT) or shock-requiring vasopressors, or presented with venous thrombosis events, including pulmonary embolism, acute liver failure, and disseminated intravascular coagulation. The list of CCAM codes used to identify advanced life support therapies is available in [Appendix 2](#). Patient outcomes included mechanical ventilation duration, ICU and hospital length of stay (LOS), and vital status at hospital discharge.

For patients admitted after January 1, 2021, we collected vaccination status. A full vaccination scheme was defined as more than 28 days after a single dose of Ad26. COV2-S vaccine (Covid-19 Vaccine Janssen®) or more than 7 days after the second dose of vaccine other than Ad26. COV2-S vaccine. A partial vaccination was defined as fewer than 28 days after a single dose of Ad26. COV2-S vaccine or fewer than 7 days after the second and/or after the first dose of vaccine other than Ad26. COV2-S. Patients were considered non-vaccinated if they did not receive any dose of any vaccine against Covid-19.

### Ethics

The SNDS database was created by French law n°2016–41 on 26 January, 2016.<sup>26</sup> The purpose of the database is to reuse claims data for research after names and social security numbers have been removed. The condition of use and forms of security that apply to the database are defined by the French government regulation dated 22 March, 2017.<sup>27</sup> As part of its public statistics mission, the Directorate for Research, Studies, Assessment and Statistics (DREES) of the French Ministry of Health, has permanent access to the SNDS database. An internet page has information available to the public about the reuse of data from the database and their rights according to the European General Data Protection Regulation n° UE 2016/679 dated 27 April, 2016.<sup>28</sup>

### Statistical analysis

Characteristics of patients were reported as frequencies and percentages for categorical variables and as medians and interquartile ranges for continuous variables. A Chi-square test and a Wilcoxon test were used, as appropriate, to compare characteristics between COVID-19 patients and influenza patients.

Risk factors of treatment with mechanical ventilation were identified through a competing risk framework (i.e., the Fine and Gray model) with ICU discharge alive or death in the ICU without intubation as competing events.<sup>29,30</sup> The strength of the association between a specific risk factor and the event of interest in the Fine-Gray model was measured by the sub-hazard ratio (SHR), which is the ratio of hazards associated with the cumulative incidence function in the presence and absence of the risk factor. We first computed SHR for invasive mechanical ventilation and 95% confidence intervals (CIs) associated with each of the risk factors in univariate analysis. Then we performed a multivariable analysis to adjust for the following predefined potential confounding factors: type of infection (COVID-19 vs. influenza), age, sex, arterial hypertension, diabetes mellitus, heart disease, chronic lung disease, cirrhosis, cancer, hematological malignancies, chronic kidney disease, immunosuppression, and modified SAPS II score. No pre-selection covariate procedure was performed because of the high number of events limiting the risk of overfitting. In the same way, we

assessed the association between the type of infection (COVID-19 vs. influenza) and in-hospital mortality (considering that being discharged alive was a competing risk). We also performed a sensitivity analysis modeling the likelihood of death only in patients who received invasive mechanical ventilation. And finally, to specifically assess the impact of the vaccination programme, we performed an analysis including only patients admitted after January, 2021, when the vaccine was available to the entire French population.

A *P* value < 0.05 was considered significant. Analyses were computed using the SAS 2017 software (SAS Institute, Cary, NC, USA).

## Results

Between March 1, 2020 and June 30, 2021, 105,979 COVID-19 patients were admitted to an ICU in France. These patients were compared to 18,763 patients with influenza admitted between January 1, 2014, and December 31, 2019.

### Patients' characteristics

The baseline characteristics of the influenza and COVID-19 population are described in [Table 1](#). Most patients with COVID-19 were men (64%, *n* = 67,951) and 30% (*n* = 32,044) were younger than 60 years. Their median SAPS II score at admission was 32<sup>24–41</sup> ([Table 1](#)). Patients with COVID-19 were more frequently men, and had a lower SAPS II score at ICU admission than patients with influenza ([Table 1](#)). The type of comorbidities differed between the two populations. Arterial hypertension, diabetes mellitus, chronic kidney disease, and solid tumors were more frequent in COVID-19 patients, while congestive heart disease, chronic respiratory disease, cirrhosis, and malignancies were more frequent in influenza patients.

### Organ failure and support

The maximal level of respiratory support for patients with COVID-19 was invasive mechanical ventilation for 34% (*n* = 36,185), non-invasive mechanical ventilation for 6% (*n* = 6749), and HFNC therapy for 18% (*n* = 19,024) ([Table 2](#)). Patients with influenza were

**Table 1**  
Main characteristics at intensive care unit (ICU) admission.

	COVID-19 N = 105 979	INFLUENZA N = 18 763	<i>p</i>
<b>Age (years)</b>	67 (57–76)	68 (58–78)	< 0.001
<b>Male gender</b>	67,951 (64.12%)	10,590 (56.44%)	< 0.001
<b>Charlson comorbidity index</b>			
0	69,886 (65.94%)	12,006 (63.99%)	< 0.001
1–2	24,887 (23.48%)	4870 (25.96%)	
3–4	6748 (6.37%)	1197 (6.38%)	
5 and more	4458 (4.21%)	690 (3.68%)	
<b>Comorbidities</b>			
Arterial hypertension	38,608 (36.43%)	4898 (26.10%)	< 0.001
Diabetes mellitus	5139 (4.85%)	818 (4.36%)	0.0038
Congestive heart disease	12,934 (12.20%)	2978 (15.87%)	< 0.001
Chronic respiratory disease	10,766 (10.16%)	3470 (18.49%)	< 0.001
Chronic kidney disease	8685 (8.20%)	348 (1.85%)	< 0.001
Cirrhosis	957 (0.90%)	209 (1.11%)	0.0057
Solid tumor	2431 (2.29%)	317 (1.69%)	< 0.001
Malignancy	1895 (1.79%)	525 (2.80%)	< 0.001
<b>SAPS II score at ICU admission</b>	32 (24–41)	39 (29–52)	< 0.001

SAPS II, Simplified Acute Physiology Score; ICU, intensive care unit.

more frequently treated with invasive mechanical ventilation (47% vs. 34%, *p* < 0.001). After adjustment for age, sex, comorbidities, and modified SAPS II score at admission, the Fine-Gray model revealed that COVID-19 was associated with a lower likelihood of treatment with invasive mechanical ventilation (aSHR = 0.87; 95%CI=0.85–0.89) as well as higher likelihood of death without invasive mechanical ventilation (aSHR = 2.40; 95%CI = 2.24–2.57) ([Table 3](#)).

Among Covid-19 patients, prone position and ECMO were used in 20,231 (19%) and 1125 (1%) patients, corresponding to 56% and 3% of patients who received invasive mechanical ventilation, respectively. Among influenza patients, it concerned 2239 (12%) and 282 (1%) patients, respectively.

Compared to influenza patients, COVID-19 patients were less likely to receive vasopressors (27% vs. 40% *p* < 0.001) and RRT (7% vs. 22%, *p* < 0.001). In the subgroup of patients who received invasive mechanical ventilation, COVID-19 patients were still less likely to receive vasopressors (74% vs. 77%, *p* < 0.001) and RRT (18% vs. 22% *p* < 0.001) than the cohort with influenza ([Supplementary Table 1](#)).

Pulmonary embolism was more frequently observed in COVID-19 patients than in influenza patients (7.5% vs. 3%, *p* < 0.001) ([Table 2](#)). This was also the case in patients who received invasive mechanical ventilation (10% vs. 4%, *p* < 0.001) ([Supplementary Table 1](#)).

### Outcome analysis

Of the entire study group, hospital mortality was higher in patients with COVID-19 than in patients with influenza (25% vs. 21%, *p* < 0.001) ([Table 2](#)), both in those who received invasive mechanical ventilation (40% vs. 33%, *p* < 0.001) ([Supplementary Table 1](#)), and in subjects who did not receive invasive mechanical ventilation (17% vs. 11%, *p* < 0.001). Age-specific mortality rates for COVID-19 and influenza are shown in [Fig. 1](#). For patients younger than 60 years, mortality was higher in patients with influenza than in those with COVID-19 (13% vs. 9%, *p* < 0.001). Conversely, mortality rates were higher in COVID-19 patients who were 60 or older (32% vs. 24%, *p* < 0.001).

After adjustment for age, sex, comorbidities, and modified SAPS II score at admission, the Fine-Gray model demonstrated that the likelihood of in-hospital death was higher in patients with COVID-19 (aSHR = 1.69; 95%CI = 1.63–1.75) compared to patients with influenza, especially among patients 65 years and older (aSHR = 1.91; 95%CI = 1.83–1.99) ([Table 4](#)). In the subgroups of patients who required invasive mechanical ventilation, the likelihood of in-hospital death was also higher in patients with COVID-19 (aSHR = 1.46; 95%CI = 1.40–1.53) than in those with influenza ([Supplementary Table 2](#)).

Although the difference between groups was not clinically relevant, ICU length of stay was statistically longer in patients with COVID-19 than in those with influenza (7<sup>3–16</sup> days vs. 7<sup>4–15</sup> days) (*p* < 0.001) ([Table 2](#)). However, in the subgroups of patients receiving invasive ventilation, ICU length of stay was 18<sup>10–32</sup> days for patients with COVID-19 vs. 15<sup>8–26</sup> days for patients with influenza (*p* < 0.001). In the whole population, total hospital LOS was 25<sup>15–40</sup> days vs. 21<sup>12–35</sup> days (*p* < 0.001) in patients with COVID-19 and in patients with influenza, respectively.

### Sars-CoV-2 vaccination

In a sensitivity analysis, we restricted the analysis to patients with COVID-19 admitted after January, 2021 for whom vaccine status was available (*n* = 48,140). Adjusting for age, sex, comorbidities, immunocompromised status, and SAPS-II score at admission, a multivariate model showed that COVID-19 patients had a higher risk of death compared to influenza patients regardless of the vaccination status (COVID-19 non-vaccinated aSHR = 1.73; 95%CI =

**Table 2**  
Management and outcomes.

	COVID-19 N = 105 979	INFLUENZA N = 18 763	p
<b>Maximal level of respiratory support</b>			
Invasive mechanical ventilation, n (%)	36,185 (34.14%)	8742 (46.59%)	< 0.001
Non-invasive mechanical ventilation, n (%)	6749 (6.37%)	1578 (8.41%)	
High flow nasal cannula therapy, n (%)	19,024 (17.95%)	1625 (8.66%)	
Other oxygen therapy, n (%)	44,021 (41.54%)	6818 (36.34%)	
<b>Organ failure and support during ICU stay</b>			
Tracheotomy, n (%)	2297 (2.17%)	524 (2.79%)	< 0.001
Prone position, n (%)	20,231 (19.09%)	2239 (11.93%)	< 0.001
Extra-corporeal membrane oxygenation, n (%)	1125 (1.06%)	282 (1.5%)	< 0.001
Vasopressors use, n (%)	28,943 (27.31%)	7448 (39.7%)	< 0.001
Renal replacement therapy, n (%)	7358 (6.94%)	2116 (22.33%)	< 0.001
Acute liver failure, n (%)	1806 (1.70%)	668 (3.56%)	< 0.001
<b>Pulmonary embolism, n (%)</b>	7981 (7.53%)	556 (2.96%)	< 0.001
<b>Venous thrombosis, n (%)</b>	3969 (3.75%)	614 (3.27%)	0.001
<b>In-hospital death, n (%)</b>	26,407 (24.9%)	3966 (21.1%)	< 0.001
<b>Duration of invasive mechanical ventilation (days)</b>			
Survivors only	13 (6–26)	10 (4–19)	< 0.001
<b>ICU length of stay (days)</b>			
Survivors only	13 (6–26)	10 (5–19)	< 0.001
Survivors only	7 (3–16)	7 (4–15)	< 0.001
<b>Hospital length of stay (days)</b>			
Survivors only	7 (3–14)	7 (4–14)	0.007
Survivors only	14 (8–24)	14 (8–25)	< 0.001
Survivors only	14 (8–24)	14 (8–26)	< 0.001
<b>Disseminated intravascular coagulation, n (%)</b>	446 (0.42%)	212 (1.13%)	< 0.001

ICU, intensive care unit.

**Table 3**  
Fine and Gray models of invasive mechanical ventilation.

	Invasive MV		Death without invasive MV	
	aSHR	95%CI	aSHR	95%CI
Age (+10 years)	0.90	0.90–0.91	2.68	2.63–2.74
Male gender	1.21	1.18–1.23	1.06	1.02–1.11
Arterial hypertension	1.25	1.23–1.28	0.72	0.69–0.76
Diabetes mellitus	1.01	0.96–1.05	1.27	1.17–1.38
Heart disease	0.99	0.96–1.02	1.05	0.99–1.11
Lung disease	1.02	0.99–1.04	1.07	1.01–1.14
Cirrhosis	0.92	0.85–1.01	2.12	1.76–2.57
Cancer	0.57	0.53–0.62	2.11	1.91–2.32
Hematological malignancies	0.86	0.81–0.91	1.20	1.07–1.34
Chronic kidney disease	0.69	0.66–0.72	1.21	1.14–1.29
Immunodepression	0.87	0.83–0.90	1.76	1.63–1.91
Modified SAPS II				
≤ 14	Ref		Ref	
15 – 20	2.00	1.93–2.07	1.32	1.25–1.40
21–28	3.41	3.29–3.53	1.53	1.45–1.63
≥ 29	6.95	6.72–7.19	1.70	1.60–1.80
Type of infection				
Influenza	Ref		Ref	
COVID-19	0.87	0.85–0.89	2.40	2.24–2.57

aSHR, adjusted sub distribution hazard ratio; CI, confidence interval; MV, mechanical ventilation; SAPS II, Simplified Acute Physiology Score.

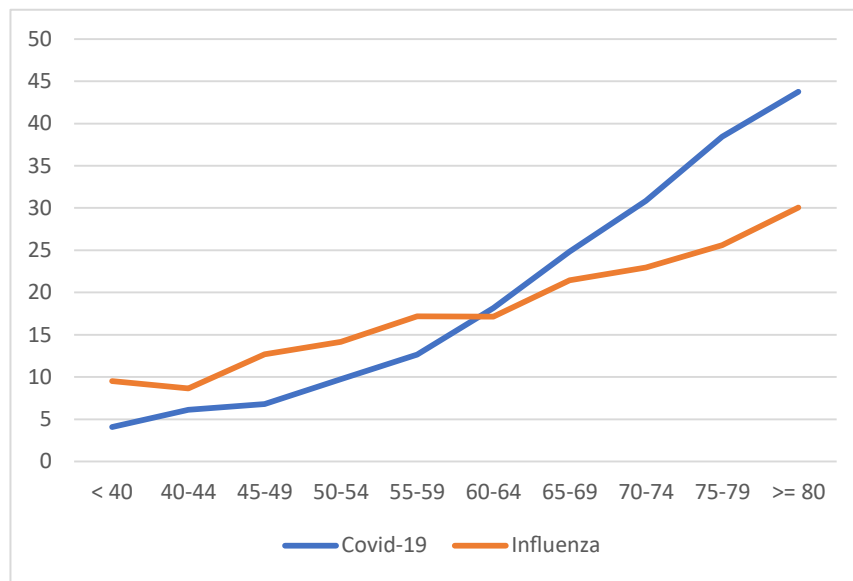
1.66–1.80; COVID-19 partially vaccinated: aSHR = 1.79; 95%CI = 1.67–1.93; COVID-19 fully vaccinated: aSHR = 1.48; 95%CI = 1.26–1.75) (Supplementary Table 3).

## Discussion

In this French nationwide observational study, we showed major differences between critically ill patients with severe COVID-19 and influenza pneumonia admitted to an ICU. The two categories differed in baseline characteristics, ICU management, and outcomes. Patients with COVID-19 were less likely to receive invasive mechanical ventilation but had a higher likelihood of in-hospital death. Whether or not they received invasive mechanical ventilation, mortality was consistently higher in patients with COVID-19 than in patients with influenza, especially among those who were 65 years and older and independently of the invasive mechanical ventilation status.

Patients with COVID-19 were younger, more frequently male, and had a SAPS II at ICU admission. However, whilst CCI is a useful tool to synthesize comorbid conditions, it does not capture all important chronic diseases, such as arterial hypertension, and one cannot conclude that patients with COVID-19 admitted to the ICU had fewer comorbidities. For instance, patients with COVID-19 presented more often with arterial hypertension, solid tumor, and chronic kidney disease. The higher proportion of arterial hypertension has been already described<sup>31–33</sup> and the potential role of a chronic exposure of renin-angiotensin system (RAS) acting agent on the severity of COVID-19 has been questioned. Indeed, RAS blockers might upregulate the expression of angiotensin-converting enzyme 2 (ACE2) receptor, which acts as a co-receptor for human cell infection by SARS-CoV-2 through the binding with the spike protein. However, several studies, included RCTs concluded to an absence of effect of chronic exposure of RAS blocked and/or RAS blocked discontinuation.<sup>31–33</sup>

Conversely, patients with influenza had higher instances of chronic respiratory disease, congestive heart disease, and malignancy. The greater proportion of male gender and respiratory chronic disease in patients with influenza are common observations reported in observational studies,<sup>13–15,17–19,34</sup> suggesting that the presence of lung damage from a preexisting condition might be necessary for ICU admission in the case of influenza but not in the case of COVID-19. The role of age in these infections remains debated, especially in studies focusing on ICU patients.<sup>35</sup> Indeed, there has been intense research into the management of patients with ARDS over the last decade, leading to improved outcomes and, consequently, a broadening of the criteria for admission to intensive care for older patients.<sup>36–39</sup> Concerning the others comorbidities, we observed that our study is distinguished by a lower proportion of many comorbidities as diabetes, chronic lung disease, congestive heart failure, chronic kidney disease and solid tumor.<sup>14–18,20,39</sup> There are several reason for this. First, we previously published, in a study comparing the management and outcome of COVID-19 patients admitted of ICU according time (March 2020 and June 2021), a significant decreasing of all patient's comorbidities. Majority of studies comparing COVID-19 and influenza have been limited to the first wave of COVID-19 patients, which were exposed to a higher proportion of comorbidities. Second, comorbidities were identified in our study according to coding diagnosis registered in the French nationwide administrative health care database. This could limit the



**Fig. 1.** In-hospital mortality rate according to age and type of infection. Blue line represented COVID-19 patients. Orange line represents Influenzae patients. X-axis correspond to age. Y-axis correspond to in-hospital mortality rate.

comparison with others studies, especially monocentric observational cohorts, which do not use ICD-10 classification and collected data from medical reports or medication. Third, there are already reported some discrepancies between characteristics COVID-19 populations depending on the origin of study suggested the importance of ethnic origin in incidence and severity of the disease.

While most studies comparing COVID-19 to influenza have reported greater use of invasive respiratory, hemodynamic and renal supportive care in patients with COVID-19,<sup>14,19,34,40</sup> these studies looked at all patients admitted to hospital and did not focus on patients specifically admitted to the ICU, thus exposing statistical bias due to censoring. Once focused on ICU patients, this difference is either attenuated<sup>15,34</sup> or reversed.<sup>18</sup>

Most epidemiological studies of COVID-19 were performed within the first surge, which may have differed from the subsequent waves regarding treatment, ventilation management, and ICU admission capacity. In our study, although invasive mechanical

ventilation during the first surge remained lower in patients with COVID-19 than in those with influenza, this difference was much smaller and might not have been highlighted in a smaller cohort. Because initial recommendations warned of the potential risk of aerosolisation that, in the case of HFNC or NIV, could have increased the risk of contamination for healthcare workers,<sup>41</sup> studies performed during the first surge of COVID-19 reported that only 19% of patients received HFNC in the ICU.<sup>6</sup> Thereafter, it has been shown that the risk of aerosolisation with HFNC was similar to that with standard oxygen therapy.<sup>42</sup> Moreover, it has been suggested that HFNC use might be associated with a lower intubation rate during the first pandemic wave.<sup>43,44</sup> All combined, international guidelines recommended the use of HFNC and NIV as first-line therapy in COVID-19 patients with ARF for the subsequent pandemic surges.<sup>45</sup> Later, the results of the RECOVERY-RS study found no significant association between initial strategy of HFNC and the risk of tracheal intubation.<sup>46</sup> The main consequence of the first data concerning

**Table 4**  
Fine and Gray models of in-hospital death.

In-hospital death	All patients		Patients < 65 years		Patients ≥ 65 years	
	aSHR	95%CI	aSHR	95%CI	aSHR	95%CI
Age (+ 10 years)	1.69	1.67–1.71	1.57	1.51–1.62	1.65	1.62–1.68
Male gender	1.19	1.16–1.22	1.07	1.01–1.13	1.23	1.20–1.27
Arterial hypertension	0.79	0.77–0.81	0.82	0.77–0.87	0.79	0.77–0.81
Diabetes mellitus	1.17	1.11–1.24	1.10	0.97–1.25	1.17	1.11–1.24
Heart disease	0.99	0.95–1.02	1.15	1.05–1.26	0.97	0.93–1.00
Lung disease	0.99	0.95–1.03	0.90	0.83–0.98	1.00	0.96–1.05
Cirrhosis	1.83	1.64–2.04	2.04	1.75–2.38	1.59	1.37–1.85
Cancer	1.37	1.27–1.47	1.98	1.76–2.27	1.22	1.12–1.32
Hematological malignancies	1.16	1.08–1.24	1.30	1.13–1.51	1.11	1.02–1.20
Chronic kidney disease	1.04	0.99–1.08	1.17	1.05–1.30	1.00	0.96–1.05
Immunodepression	1.45	1.38–1.53	1.61	1.46–1.77	1.33	1.25–1.41
Modified SAPS II						
≤ 14	Ref		Ref		Ref	
15 – 20	1.56	1.50–1.63	2.00	1.79–2.23	1.50	1.44–1.58
21–28	2.20	2.11–2.29	3.09	2.77–3.43	2.05	1.95–2.14
≥ 29	4.09	3.93–4.25	7.12	6.45–7.87	3.54	3.39–3.69
Type of infection						
Influenza	Ref		Ref		Ref	
COVI-19	1.69	1.63–1.75	1.16	1.09–1.25	1.91	1.83–1.99

aSHR, adjusted sub distribution hazard ratio; CI, confidence interval; SAPS II, Simplified Acute Physiology Score.

HFNC was the decreasing rate of intubation in COVID-19 patients over time as reported in our previous study, with a decrease of 10% associated with a lower use of vasopressor therapy and lower rate of renal failure.<sup>47</sup>

The use of prone positioning was doubled during COVID-19 compared to influenza. This might not only be because of more severe hypoxemia in patients with COVID but also because, pre-pandemic, ventilation management trends in the ICU prone position were already being more frequently used following the PROSEVA study published in 2013.<sup>37</sup> In a previous international study, only 13.7% of patients with ARDS had at least one session in the prone position, and the most prevalent reason for not using prone positioning was that hypoxemia was not considered sufficiently severe.<sup>48</sup> Though the severity of the ARDS (PaO<sub>2</sub>/FiO<sub>2</sub> ratio) was not available in our database, many reports on COVID-19-related ARDS showed that these patients were highly hypoxemic.<sup>49</sup> Patients with COVID-19 had a median duration of invasive mechanical ventilation longer than patients with influenza. As ARDS is known to be associated with a higher risk of prolonged duration of invasive mechanical ventilation, it might explain a higher use of the prone position in COVID-19 patients.<sup>50</sup> Finally, prone positioning in non-ventilated patients has been demonstrated to reduce the need for intubation, supporting the use of this procedure, including in less severe patients.<sup>51–53</sup>

Despite the lower rate of organ support, we found that COVID-19 was strongly associated with a higher likelihood of in-hospital death after adjustment for age, gender, comorbidities, and severity at ICU admission. Previous reports also found that patients admitted for COVID-19 had higher mortality than those admitted for influenza, whatever the severity.<sup>50,54,55</sup> In our study, the excess of in-hospital deaths of COVID-19 patients compared with influenza was more significant in patients aged 60 years and older. The association between age and the likelihood of in-hospital death is consistent with previous studies.<sup>50,56</sup> Among patients who did not receive invasive mechanical ventilation, mortality was higher in patients with COVID-19 than in patients with influenza. This result suggests that there were probably more patients with COVID-19 admitted to the ICU but for whom life support was more limited (in particular for invasive mechanical ventilation) than in patients with influenza. Indeed, the type of patients who received invasive mechanical ventilation is different between the two groups, as Charlson comorbidity index was lower in patients with COVID-19 than in patients with influenza. It might reflect that selection and therapeutic limitation based on frailty and/or comorbidities was stricter in patients with COVID-19 than in patients with influenza, probably due to epidemic pressure and limited resources.

Finally, anti-virus treatment used in the ICU, and vaccination against influenza before ICU admission, could explain the lower mortality in the influenza cohort compared to those with COVID-19. However, in our study, most of patients have been admitted in ICU during the pre-vaccination era and the current cohort of patients with COVID-19 might have different characteristics to the group studied here. We assessed patients with COVID-19 admitted at the beginning of the French vaccine campaign in those for whom vaccine status was available. We observed that, even though full vaccination decreased the risk of death, patients admitted with COVID-19 still had worse outcomes than those with influenza. However, these data only concerned a few number of patients, at the beginning of the vaccine campaign, and further studies are needed in order to compare vaccinated COVID-19 patients to patients with influenza.

Our study has some limitations. First, clinical data (such as arterial blood pressure), as well as laboratory results (particularly arterial blood gas), were not collected in the SNDS and thus could not be used to describe respiratory and cardiovascular failures at admission. But details regarding SAPS II, as well as respiratory and hemodynamic support, were available from our data and were used

as a surrogate of severity. In the same way, data concerning COVID-19 variants as well as common drugs used (steroids for example) are not available. Indeed, it would have been interesting to compare the risk for each outcomes according to COVID-19 but also influenza variants. It should be noted that in a previous publication, we have analyzed the trends during different surges which could be used here as a proxy for the different variants.<sup>47</sup> Second, we did not collect data on pressures on hospital admission or availability of beds in the ICU. This is critical because it could have led to patient selection and early discharge from the ICU and thus contribute to suboptimal care. Unfortunately, our data did not capture ICU bed occupancy during this period. Thirdly, only patients admitted to ICU were included in our study. Because of epidemic pressure, some patients that would usually be admitted to ICU for NIV or HFNC might have been admitted to another ward (for example infectious disease). This could lead to a selection bias as we do not have data for all severe COVID-19 patients but we assume that it concerns a small number of patients, compared with the large volume of patients in our study.

Our study has some strengths. To the best of our knowledge, our work is the largest study focused on ICU patients comparing COVID-19 with influenza. Indeed, we included all patients with COVID-19 admitted to an ICU between March, 2020 and June, 2021, corresponding to more than 100,000 patients. These patients were compared to all patients with influenza admitted to an ICU over a 5-year period. In addition, because SNDS is a national database, we were able to include all inpatients in the country without center selection. Finally, we were not limited to the first surge but could use patients from successive surges, including the one after the start of the vaccination program.

## Conclusion

In a nationwide observational study, critically ill COVID-19 patients had a higher likelihood of death than patients with influenza despite a lower use of respiratory and hemodynamic invasive supportive care. The excess of in-hospital mortality persisted in COVID vaccinated patients.

## Funding

This study received no support from any funding source.

## CRediT authorship contribution statement

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Naouri Diane. The first draft of the manuscript was written by Naouri Diane and Jamme Matthieu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.jinf.2023.05.011](https://doi.org/10.1016/j.jinf.2023.05.011).

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