Comparison of hospitalized COVID-19 and influenza patients requiring supplemental oxygen in a cohort study: clinical impact and resource consumption.

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Abstract

Background: To compare clinical characteristics, outcomes, and resource consumption of patients with COVID-19 and seasonal influenza requiring supplemental oxygen.

Methods: Retrospective cohort study conducted at a tertiary-care hospital. Patients admitted due to seasonal influenza between 2017 and 2019, or with COVID-19 between March and May 2020 requiring supplemental oxygen were compared. Primary outcome: 30-day mortality. Secondary outcomes: 90-day mortality and hospitalization costs. Attempted sample size to detect an 11% difference in mortality was 187 patients per group.

Results: COVID-19 cases were younger (median years, 67 (IQR 54-78) vs 76 (IQR 64-83); p<0.001) and more frequently overweight whereas influenza cases had more hypertension, immunosuppression, and chronic heart, respiratory and renal disease. Compared to influenza, COVID-19 cases had more pneumonia (98% vs 60%, <0.001), higher MEWS and CURB-65 scores and were more likely to show worse progression on the WHO ordinal scale (33% vs 4%; p<0.001). The 30-day mortality rate was higher for COVID-19 than for influenza: 15% vs 5% (p=0.001). The median age of non-surviving cases was 81 (IQR 74-88) and 77.5 (IQR 65-84) (p=0.385), respectively. COVID-19 was independently associated with 30-day (HR 4.6, 95%CI, 2-10.4) and 90-day (HR 5.2, 95%CI, 2.4-11.4) mortality. Sensitivity and subgroup analyses, including a subgroup considering only patients with pneumonia, did not show different trends. Regarding resource consumption, COVID-19 patients had longer hospital stays and higher critical care, pharmacy, and complementary test costs.

Conclusions: Although influenza patients were older and had more comorbidities, COVID-19 cases requiring supplemental oxygen on admission had worse clinical and economic outcomes.

Key words: COVID-19, flu, pandemic, mortality, resource consumption, hospital costs.

Introduction

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], the coronavirus disease 2019 (COVID-19) has been compared to influenza virus. Both viruses are similar in symptoms, transmission routes, and risk groups.

Clinical presentation ranges from asymptomatic to critical cases, although most infections are not severe [2,3]. Among hospitalized patients however, the proportion of critical disease is higher, ranging from 3% to 20% for influenza, and from 14% to 50% for COVID-19 [4–8].

Both viruses can cause severe illness in otherwise healthy individuals, but elderly or comorbid patients are at highest risk of severe influenza illness [9]. In COVID-19, age plays a major role in outcome [10].

In terms of resource consumption, prior data show that seasonal influenza places a strain on the healthcare system [9]. However, the SARS-CoV-2 pandemic is a historic public health crisis, requiring unprecedented allocations of medical resources to ensure patient care and prevent health system collapse.

We hypothesized that adults with SARS-COV-2 requiring oxygen at admission have worse outcomes and consume more resources than those with influenza. Prior studies [4–8,11–22] have compared characteristics and/or outcomes of both diseases. To our knowledge, this is the first study to assess only patients requiring supplemental oxygen at admission. More relaxed admission criteria due to concerns about the novel SARS-COV-2 may have led to hospitalization of fewer sick people with COVID-19. Thus, considering only admitted patients requiring oxygen may provide a more objective selection criterion.

Furthermore, although some cohorts [4–8,16,18,20] have explored resource consumption, none have detailed the burden of disease on hospitalization costs.

This study aims to compare the clinical characteristics, mortality and resource consumption of patients hospitalized for COVID-19 or influenza requiring supplemental oxygen.

Methods

Study design and participants

A retrospective observational cohort study performed at the Hospital del Mar, a tertiary university hospital in Barcelona (Spain).

Patient selection was from the hospital database. Patients diagnosed with influenza or SARS-COV-2 infection during the study period were retrospectively reviewed. Inclusion criteria were age >18-years, laboratory-confirmed influenza/SARS-COV-2 infection, positive test within 48 hours of admission, hospitalization due to influenza/SARS-COV-2 infection and need for supplemental oxygen at admission.

For the influenza cohort, patients hospitalized during the 2017–19 influenza outbreak periods (from January 1, 2017 through December 1, 2019) meeting the study criteria were included. For the COVID-19 cohort, patients admitted for COVID-19 from March 1, 2020 through May 1, 2020 (‘first wave’) were included. Patients were included consecutively, starting from the initial date of the study period until the required sample size was reached.

Patients were followed for 90 days from the date of the positive test, using the regional electronic healthcare records (integrating hospital, primary care, and long-term facilities). Patients whose mortality could not be assessed due to lack of records during the follow-up period were considered lost to follow-up and excluded. Hospital-acquired infections were excluded to avoid overestimating hospitalization costs and length of stay accounted for before the COVID-19 or influenza episode.

Ethics

The Clinical Research Ethical Committee of Parc Salut Mar approved this study (registration no. 2021/9892). Written informed consent was waived due to its observational and retrospective nature.

Outcomes

The primary endpoint was all-cause 30-day mortality. Secondary endpoints were 90-day mortality and hospitalization costs.

Definitions and data collection

Demographic, clinical, and epidemiological data were collected from electronic records. Influenza and pneumococcal vaccination status was ascertained through primary care records. Patients with no official vaccination record were considered “not vaccinated”. Severity of underlying diseases were assessed by Charlson comorbidity index [23]. Immunosuppression was defined as malignancy, untreated HIV and/or CD4 count <200 cells/µl, pregnancy, inflammatory and autoimmune disorders, transplant or other diseases under immunosuppressive agents, corticosteroid therapy, defined as 10 mg of oral prednisone or equivalent for a month, poorly controlled diabetes mellitus, defined as HbA1c>9% with target organ damage, and/or primary immune deficiency disease.

Also recorded were signs and symptoms at admission, time from symptom onset to hospital admission, laboratory test parameters, baseline chest X-ray findings, treatment received, need for intensive care unit (ICU) admission, and respiratory support. Chest X-rays were classified into 2 groups: those with new radiographic findings consistent with acute pneumonia (ground-glass, linear opacities, or consolidations), and those normal or showing non-acute findings

(chronic changes associated with prior pneumopathy) or not attributable to viral infection (pulmonary edema).

Clinical severity was assessed at admission using Modified Early Warning Score (MEWS) [24], CURB-65 [25], and PaO2/FiO2 ratio. Acute respiratory distress syndrome (ARDS) was defined as PaO2/FiO2 ratio ≤300 [26]. When arterial blood gas data were not available, PaO2/FiO2 ratio was inferred from Spo2/Fio2 [27]. Status on the World Health Organization (WHO) ordinal clinical progression scale [28] at baseline and day 7 was also recorded.

Complications developing during hospitalization (pulmonary embolism, secondary infections, heart failure, atrial fibrillation, acute kidney injury) were recorded.

Variables studied for healthcare resource consumption included: length of stay, days in ICU, days of respiratory support, readmissions, and overall hospitalization, pharmaceutical, laboratory, imaging, and other diagnostic procedure costs.

Statistical analysis

Determination of the sample size (187 patients per group) to detect at least an 11% difference in mortality between groups was based on previous results [4]. Statistical power was set at 0.8, alpha error 0.05, and estimated loss to follow-up 0.3.

Continuous quantitative variables were presented as median and interquartile range (IQR), categorical variables as numbers and percentages. Categorical variables were compared by $\chi 2$ test or Fisher's exact test, and continuous variables by the Student's t-test or Mann–Whitney U-test, as appropriate.

The Kaplan-Meier estimator estimated time-until-death. The log-rank test compared the risk of death between study groups. Receiver Operating Characteristic (ROC) curves were used to identify the optimal cutoff age for prediction of 30- and 90-day mortality, and Youden's criterion to determine optimal cutoff points: the sample point maximizing the Youden Index (sensitivity+specificity–1).

Cox proportional hazards was used to perform multivariate survival analyses of 30- and 90-day mortality, with hazard ratios (HR) and 95% confidence intervals (CI). Variables with p value ≤.2 were included in the initial model, together with variables not statistically significant but clinically relevant. Corticosteroid therapy and pneumonia were considered clinically relevant and forced into models. Baseline MEWS score and PaO2/FiO2 ratio were included to adjust for severity. Complications during hospitalization were considered intermediate variables between exposure and death and were not included. Cox models were built using backward stepwise selection. Variance inflation factors were used to detect collinearity between variables in the models. The proportional hazards assumption was tested. Variables with > 25% missing values were not considered.

Sensitivity analyses were performed to investigate the impact of COVID-19 versus influenza on 30- and 90-day mortality in subgroups of interest (age <74 or ≥74-years; including only non-influenza vaccinated patients and those with pneumonia and/or bilateral involvement).

Economic impact was evaluated by median regression to deal with lack of normality of dependent variables (hospitalization costs). Results were expressed as difference of medians. Interpretation of coefficients, as in multiple linear regression, was based on differences of means.

All p-values were 2-tailed and statistical significance was <0.05. Statistical analyses were performed using STATA 15.1. STROBE guidelines were used to report the study (Supplementary Table S1).

Results

Overall, 614 COVID-19 patients and 411 influenza patients were admitted during the study period. Based on the attempted sample size, 187 patients were included per group (Figure 1).

Baseline characteristics and clinical presentation

Differences in baseline characteristics, clinical presentation, complementary tests, complications, and therapeutic management between groups are shown in table 1. The most frequent subtype viruses were influenza A H1N1 (65%) and B (26.74%).

COVID-19 patients were younger than those with influenza and had fewer underlying diseases. Overall, influenza cases had worse abnormal blood count values, excluding ferritin and hepatic enzyme levels. Pneumonia was seen more in COVID-19 than influenza patients (98% vs 59%; p<0.001). Among influenza cases with no pneumonia (n=77), 41 (53%) had radiological changes secondary to chronic pneumopathy and clinical signs of acute exacerbation, 19 (25%) pulmonary edema, and 17 (22%) had normal x-rays but wheezing and/or rales on examination. More than 86% of these 77 patients reported influenza systemic symptoms.

Severity assessment

COVID-19 patients presented higher MEWS and CURB-65 scores at baseline, but mild ARDS was more frequent in influenza cases (66% vs 50%; p=0.022). Evolution of patient status on the WHO ordinal scale during admission is shown in Figure 2.

Therapeutic management and complications

58% of patients received virus-targeting agents. Nearly all influenza cases (98%) received oseltamivir. COVID-19 patients were given lopinavir/ritonavir (17%) and remdesivir (1%). Overall, more than 90% of patients received concomitant antibiotic therapy. The most frequent

regimen in the COVID-19 group was ceftriaxone plus azithromycin (72%) versus amoxicillin/clavulanate (30%) and levofloxacin (21%) in influenza group.

Concomitant bacterial pneumonia at admission was more frequent in influenza than COVID-19 cases (n=39/43, 90.7% vs n=8/27, 29.6%, p<0.001). *Streptococcus pneumoniae* was the leading microorganism (26 and 4 episodes, respectively). Hospital-acquired pneumonia was more seen in COVID-19 (n=19/27, 70.4%) than influenza group (n=4/43, 9.3%) and *Pseudomonas aeruginosa* was the most frequent microorganism (n=8 and n=2 patients, respectively). Patients with COVID-19 were more likely to have hospital-acquired infections other than pneumonia (20% vs 3%, p<0.001) and to develop bacteremia (14% vs 4%, p=0.001).

Clinical outcome: mortality

30-day mortality was 15% (n=29/187) in COVID-19 and 5% (n=10/187) in influenza (HR 3.07, 95%CI, 1.5–6.31). Median age was 81 years (IQR 74-88) in COVID-19 and 77.5 years (IQR 65-84) in influenza (p=0.385). 70% of influenza deaths were caused by influenza A subtype H1N1.

90-day mortality was 19% (n=35/187) in COVID-19 and 6% (n=12/187) in influenza (HR 3.12, 95%CI, 1.62–6.02). Median age was 78 (IQR 72-87) in COVID-19, and 77.5 (IQR 64-84.5) in influenza (p=0.558). Influenza A subtype H1N1 (67%) and influenza B (25%) were the most common subtypes in non-surviving influenza patients.

There were no differences in mortality trends between the three periods of seasonal influenza studied.

Figure 3A shows Kaplan-Meier curves for 30-day mortality by infection group. Based on ROC curve analysis, the optimal cutoff age for predicting mortality was 74 years (Figure S1). When stratified by age, 30-day mortality was markedly higher in COVID-19 patients ≥74-years (HR

5.77, 95%CI, 2.48–13.47; p<0.001) (Figure 3B). In patients under 50-years, only one death, in the COVID-19 group, was observed.

Univariate and multivariate analyses of 30-day mortality are shown in Table 2. COVID-19 was an independent risk factor for 30-day mortality. Data of 90-day mortality are shown in supplementary material (Table S2 and Figure S2). Similarly, COVID-19 was also associated with higher 90-day mortality.

Subgroup and sensitivity analyses of the impact of COVID-19 versus influenza on 30- and 90-day mortality in subgroups of interest are shown in supplementary table S3. COVID-19 was also associated with higher 30- and 90-day mortality considering only patients with pneumonia (Table 3 and supplementary table S4, respectively) and non-vaccinated against influenza (supplementary table S5).

Healthcare resource consumption and costs

COVID-19 patients had longer hospital and ICU stays. Critical care costs for COVID-19 patients were almost twice those associated with influenza patients, with a median difference of 9,268 euros between groups (p<0.001) (Table 4). COVID-19 was independently associated with higher costs of critical care, pharmaceutical treatment, and complementary tests (supplementary Table S6 and S7).

Discussion

The present study details clinical characteristics, outcomes, and resource consumption of patients hospitalized for COVID-19 or influenza requiring supplemental oxygen on admission.

COVID-19 patients were younger and healthier than those with influenza, as previously reported [4,6,16–18,22], with consistent differences in rates of smoking, hypertension, pneumopathy, heart failure, and renal disease. Since many patients with pneumopathy were treated with

corticoid therapy, immunosuppression was especially high in the influenza group. COVID-19 individuals however tended to have higher BMIs [4].

Whereas COVID-19 cases had more general symptoms, dyspnea and ARDS were more seen in influenza patients at baseline. In contrast, COVID-19 cases were more likely to worse during admission. These findings describe the natural history of some COVID-19 cases, who develop respiratory deterioration during the inflammatory stage of the disease [29].

As previously reported, bacterial pulmonary coinfections were uncommon in COVID-19 at baseline [30], which contrasts with previous data from influenza epidemics [31]. Conversely, hospital-acquired infections were more frequent with COVID-19 due to longer hospital and ICU stays.

Concerning outcomes, mortality was three times higher for COVID-19 than influenza, which coincides with previous data [4–6,8,20]. Our data suggest that mortality was especially high among older patients (≥74-years) with COVID-19, which reinforces previous evidence [10] identifying age as a key factor in COVID-19 outcomes. Due to the limited number of observations for younger individuals, the burden of influenza and COVID-19 on younger cohorts warrants further investigation.

COVID-19 cases had more frequently pneumonia and bilateral involvement. Prior studies have shown that COVID-19 typically follows a peripheral bilateral pattern, with a predominance of ground-glass, linear opacities or consolidations depending on the stage of the disease [32]. Although bilateral pattern is frequent in influenza, prior series have also found lower rates of bilateral involvement [33].

Most non-surviving cases had pneumonia on chest X-ray. In our cohort, 40% of influenza cases baseline X-rays did not show viral pneumonia. Previous studies [34] show computed tomography (CT) scan is the “gold standard” for detection of pneumonia, since lung opacities

are visible on CT scan when X-rays are normal. In one study [35], the proportion of influenza pneumonia increased from 7% to 72% when CT scan was performed. It can be inferred that a pneumonia diagnosis may be missed using X-rays alone.

Moreover, in clinical practice, clinical and radiographic overlap may make it difficult to differentiate between viral pneumonia and acute exacerbations of chronic pulmonary disease or congestive heart failure [36,37].

To explore the impact of radiological findings on outcome, pneumonia was forced into multivariate models of mortality and subgroup analyses were performed. In all settings, COVID-19 outcomes were worse. Excess mortality may be due to increased intrinsic severity in COVID-19, and not only exacerbation of chronic conditions or presence of pneumonia.

None of the COVID-19 patients were immunized during the study period, which contrasts with 17% of vaccinated influenza patients. Subgroup analysis excluding vaccinated influenza patients did not show different trends.

Therapeutic management may also have affected outcomes. Almost the whole influenza cohort received oseltamivir, whereas remdesivir was administered in just 1% of COVID-19 cases. Furthermore, almost 40% of COVID-19 patients did not receive corticosteroids. While current evidence supports corticosteroid therapy in COVID-19 cases [38], its administration was controversial during the study period [39]. To explore the effect of treatment on outcome, corticosteroids and antiviral treatment were entered as covariates in multivariate analysis. Antiviral treatment was removed from the final model due to the lack of significant differences.

Since we included three seasonal influenza outbreaks (2017-2019), the differences in mortality are unlikely to be the result of an unusually mild influenza season. Of note, it was necessary to review almost three periods of seasonal influenza versus two months of COVID-19 to reach the attempted sample size, reflecting the huge influx of patients in our institution during the first

wave of the COVID-19 pandemic. It may be inferred that the sudden demand for hospital resources may have negatively affected care of COVID-19 cases.

Our findings on resource consumption show that patients with SARS-COV-2 more frequently received respiratory support, were almost three times more likely to be admitted to the ICU and had longer hospital and ICU stays. The costs of critical care, pharmaceutical treatment and complementary tests were also higher in the COVID-19 group. While previous studies [4–6,8,16,18] have found that COVID-19 patients consume more resources in terms of hospital stay and ICU bed occupancy, this is to our knowledge the first to detail those costs.

Our study has the limitations of a retrospective, single-center study. No genotyping studies were conducted due to the timing of study data collection, although it is highly likely that COVID-19 patients were affected by wild-type B.1. These results may not therefore reflect the current scenario, in which multiple SARS-CoV-2 variants are circulating globally. Likewise, the absence of vaccinated COVID-19 patients during the study period may not reflect the current profile of inpatients with COVID-19. Second, patients with COVID-19 and seasonal influenza cannot be compared directly because the cohorts come from different time periods. Third, many influenza cases did not present pneumonia on admission. Even though CT is considered the gold standard for detecting pneumonia, pulmonary X-ray findings could have been considered an additional inclusion criterion. Fourth, antiviral was used for the influenza group, for which studies have shown a decrease in mortality [40]. In contrast, for patients with COVID-19 there was no effective antiviral therapy. Fifth, during the first wave of the pandemic, SARS-CoV-2 detection was occasionally performed alone. Nevertheless, it is unlikely that influenza co-infections were missed in our study because of the study timing. Finally, considerable effort was made to fully adjust for a few covariates; nevertheless, the overall number of events was low, which limits the precision of some estimates, particularly for important subgroups. We did not include interesting laboratory parameters such as ferritin, d-dimer, or interleukin-6 in multivariable models because

of higher proportions of missing values, particularly in the influenza cohort. Several strengths of this study are highlighted. All information was reviewed by trained investigators, which contrasts with studies based on administrative or automated databases where the accuracy of data may not guarantee. Furthermore, the study explores the dimension of resource consumption, a keystone of pandemic management. Finally, we only included patients when infection was the reason for admission, providing an accurate estimation of the true impact of SARS-COV-2 and influenza on hospitalization costs.

In conclusion, COVID-19 was associated with worse clinical and economic outcomes than seasonal influenza in hospitalized patients requiring supplemental oxygen. COVID-19-related hospitalization seems to be more complex and expensive than influenza, either because of greater clinical severity, length of stay, ICU bed occupancy, need for respiratory equipment, or other special measures. Healthcare managers should take this into account to improve healthcare activity and prepare for possible future waves of COVID-19, especially in the current scenario, where the possibility of overlapping influenza and COVID-19 epidemics could mean increased complexity in patient management.

NOTES

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References

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med **2020**; 382:727–733. Available at: http://www.nejm.org/doi/10.1056/NEJMoa2001017.

2. Girard MP, Tam JS, Assossou OM, Kieny MP. The 2009 A (H1N1) influenza virus pandemic: A review. Vaccine **2010**; 28:4895–4902. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0264410X1000719X.

3. Amanat F, Krammer F. SARS-CoV-2 Vaccines: Status Report. Immunity **2020**; 52:583–589. Available at: https://linkinghub.elsevier.com/retrieve/pii/S1074761320301205.

4. Piroth L, Cottenet J, Mariet A-S, 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. Available at: https://linkinghub.elsevier.com/retrieve/pii/S2213260020305270.

5. Ludwig M, Jacob J, Basedow F, Andersohn F, Walker J. Clinical outcomes and characteristics of patients hospitalized for Influenza or COVID-19 in Germany. Int J Infect Dis **2021**; 103:316–322. Available at: https://linkinghub.elsevier.com/retrieve/pii/S1201971220325200.

6. Xie Y, Bowe B, Maddukuri G, Al-Aly Z. Comparative evaluation of clinical manifestations and risk of death in patients admitted to hospital with covid-19 and seasonal influenza: cohort study. BMJ **2020**; :m4677. Available at: https://www.bmj.com/lookup/doi/10.1136/bmj.m4677.

7. Nasir N, Khanum I, Habib K, et al. Comparison of clinical characteristics and outcomes between COVID-19 pneumonia and H1N1 influenza. Adv Respir Med **2021**; 89:254–261.

Available at: https://journals.viamedica.pl/advances_in_respiratory_medicine/article/view/71598.

8. Donnino MW, Moskowitz A, Thompson GS, et al. Comparison between Patients Hospitalized with Influenza and COVID-19 at a Tertiary Care Center. J Gen Intern Med **2021**; 36:1689–1695. Available at: https://link.springer.com/10.1007/s11606-021-06647-2.

9. Lina B, Georges A, Burtseva E, et al. Complicated hospitalization due to influenza: results from the Global Hospital Influenza Network for the 2017–2018 season. BMC Infect Dis **2020**; 20:465. Available at: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-020-05167-4.

10. Verity R, Okell LC, Dorigatti I, et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis **2020**; 20:669–677. Available at: https://linkinghub.elsevier.com/retrieve/pii/S1473309920302437.

11. Deng L-S, Yuan J, Ding L, et al. Comparison of patients hospitalized with COVID-19, H7N9 and H1N1. Infect Dis Poverty **2020**; 9:163. Available at: https://idpjournal.biomedcentral.com/articles/10.1186/s40249-020-00781-5.

12. Qu J, Chang LK, Tang X, et al. Clinical characteristics of COVID-19 and its comparison with influenza pneumonia. Acta Clin Belg **2020**; 75:348–356. Available at: https://www.tandfonline.com/doi/full/10.1080/17843286.2020.1798668.

13. Shen C, Tan M, Song X, et al. Comparative Analysis of Early-Stage Clinical Features Between COVID-19 and Influenza A H1N1 Virus Pneumonia. Front Public Heal **2020**; 8. Available at: https://www.frontiersin.org/article/10.3389/fpubh.2020.00206/full.

14. Gjurašin B, Santini M, Krajinović V, et al. A retrospective comparison between influenza

and COVID-19-associated ARDS in a Croatian tertiary care center. Wien Klin Wochenschr **2021**; 133:406–411. Available at: https://link.springer.com/10.1007/s00508-020-01759-x.

15. Zhang J, Ding D, Huang X, et al. Differentiation of COVID-19 from seasonal influenza: A multicenter comparative study. J Med Virol **2021**; 93:1512–1519. Available at: https://onlinelibrary.wiley.com/doi/10.1002/jmv.26469.

16. Serpa Neto A, Burrell AJC, Bailey M, et al. Comparison of Critical Care Occupancy and Outcomes of Critically Ill Patients during the 2020 COVID-19 Winter Surge and 2009 H1N1 Influenza Pandemic in Australia. Ann Am Thorac Soc **2021**; 18:1380–1389. Available at: https://www.atsjournals.org/doi/10.1513/AnnalsATS.202010-1311OC.

17. Burn E, You SC, Sena AG, et al. Deep phenotyping of 34,128 adult patients hospitalised with COVID-19 in an international network study. Nat Commun **2020**; 11:5009. Available at: https://www.nature.com/articles/s41467-020-18849-z.

18. Auvinen R, Nohynek H, Syrjänen R, et al. Comparison of the clinical characteristics and outcomes of hospitalized adult COVID-19 and influenza patients – a prospective observational study. Infect Dis (Auckl) **2021**; 53:111–121. Available at: https://www.tandfonline.com/doi/full/10.1080/23744235.2020.1840623.

19. Chen X, Wang Z, Bromfield SG, DeVries A, Pryor D, Willey V. Identification and Comparison of Patient Characteristics for Those Hospitalized with COVID-19 versus Influenza Using Machine Learning in a Commercially Insured US Population. Pragmatic Obs Res **2021**; Volume 12:9–13. Available at: https://www.dovepress.com/identification-and-comparison-of-patient-characteristics-for-those-hos-peer-reviewed-fulltext-article-POR.

20. 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. Available at: https://www.atsjournals.org/doi/10.1513/AnnalsATS.202007-805OC.

21. Tang X, Du R-H, Wang R, et al. Comparison of Hospitalized Patients With ARDS Caused by COVID-19 and H1N1. Chest **2020**; 158:195–205. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0012369220305584.

22. Zayet S, Kadiane-Oussou NJ, Lepiller Q, et al. Clinical features of COVID-19 and influenza: a comparative study on Nord Franche-Comte cluster. Microbes Infect **2020**; 22:481–488. Available at: https://linkinghub.elsevier.com/retrieve/pii/S1286457920300940.

23. Charlson ME, Pompei P, Ales KL, MacKenzie RC. A New Method of Classifying Prognostic in Longitudinal Studies : Development. J Chronic Dis **1987**; 40:373–383.

24. Subbe CP, Davies RG, Williams E, Rutherford P, Gemmell L. Effect of introducing the Modified Early Warning score on clinical outcomes, cardio-pulmonary arrests and intensive care utilisation in acute medical admissions*. Anaesthesia **2003**; 58:797–802. Available at: http://doi.wiley.com/10.1046/j.1365-2044.2003.03258.x.

25. Lim WS. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax **2003**; 58:377–382. Available at: https://thorax.bmj.com/lookup/doi/10.1136/thorax.58.5.377.

26. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med **1994**; 149:818–824. Available at:

http://www.atsjournals.org/doi/abs/10.1164/ajrccm.149.3.7509706.

27. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB. Comparison of the Sp o 2 /F io 2 Ratio and the Pa o 2 /F io 2 Ratio in Patients With Acute Lung Injury or ARDS. Chest **2007**; 132:410–417. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0012369215374316.

28. Marshall JC, Murthy S, Diaz J, et al. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis **2020**; 20:e192–e197. Available at: https://linkinghub.elsevier.com/retrieve/pii/S1473309920304837.

29. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical–therapeutic staging proposal. J Hear Lung Transplant **2020**; 39:405–407. Available at: https://linkinghub.elsevier.com/retrieve/pii/S105324982031473X.

30. Rawson TM, Moore LSP, Zhu N, et al. Bacterial and Fungal Coinfection in Individuals With Coronavirus: A Rapid Review To Support COVID-19 Antimicrobial Prescribing. Clin Infect Dis **2020**; Available at: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa530/5828058.

31. Morris DE, Cleary DW, Clarke SC. Secondary Bacterial Infections Associated with Influenza Pandemics. Front Microbiol **2017**; 8. Available at: http://journal.frontiersin.org/article/10.3389/fmicb.2017.01041/full.

32. Pan F, Ye T, Sun P, et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology **2020**; 295:715–721.

33. Reyes S, Montull B, Martínez R, et al. Risk factors of A/H1N1 etiology in pneumonia and its impact on mortality. Respir Med **2011**; 105:1404–1411.

34. Self WH, Courtney DM, McNaughton CD, Wunderink RG, Kline JA. High discordance of chest x-ray and computed tomography for detection of pulmonary opacities in ED patients: implications for diagnosing pneumonia. Am J Emerg Med **2013**; 31:401–405. Available at: https://linkinghub.elsevier.com/retrieve/pii/S0735675712004639.

35. Schoen K, Horvat N, Guerreiro NFC, de Castro I, de Giassi KS. Spectrum of clinical and radiographic findings in patients with diagnosis of H1N1 and correlation with clinical severity. BMC Infect Dis **2019**; 19:964. Available at: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-019-4592-0.

36. Black AD. Non-infectious mimics of community-acquired pneumonia. Pneumonia **2016**; 8:2. Available at: http://pneumonia.biomedcentral.com/articles/10.1186/s41479-016-0002-1.

37. Lieberman D, Lieberman D, Gelfer Y, et al. Pneumonic vs Nonpneumonic Acute Exacerbations of COPD. Chest **2002**; 122:1264–1270. Available at: https://linkinghub.elsevier.com/retrieve/pii/S001236921537793X.

38. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med **2021**; 384:693–704. Available at: http://www.nejm.org/doi/10.1056/NEJMoa2021436.

39. Li H, Chen C, Hu F, et al. Impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV, or MERS-CoV infection: a systematic review and meta-analysis. Leukemia **2020**; 34:1503–1511. Available at: http://www.nature.com/articles/s41375-020-0848-3.

40. Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. Lancet Respir Med **2014**; 2:395–404. Available at: https://linkinghub.elsevier.com/retrieve/pii/S2213260014700414.

Table 1. Baseline characteristics, clinical presentation, laboratory and radiological findings, infection severity, complications and therapeutic management of COVID-19 and influenza Inpatients requiring supplemental oxygen.

Variable	2017-2019 Influenza (n=187)	COVID-19 (n=187)	p-value
Demographic information			
Male sex	102 (54.5)	91 (48.7)	0.255
Age (years), m (IQR)	76 (64-83)	67 (54-78)	**<0.001**
Distribution			
18 – 30 years	1 (0.5)	2 (1.1)	0.562
31 – 40 years	4 (2.1)	6 (3.2)	0.521
41 – 50 years	7 (3.7)	27 (14.4)	**<0.001**
51 – 60 years	20 (10.7)	29 (15.5)	0.168
61 – 70 years	38 (20.3)	41 (21.9)	0.704
71 – 80 yeas	58 (31)	47 (25.1)	0.206
81 – 90 years	56 (29.9)	28 (15)	**0.001**
≥ 91 years	3 (1.6)	7 (3.7)	0.200
Ethnic group			
Arab	2 (1.1)	11 (5.9)	**0.010**
Asian	0 (0)	9 (4.9)	**0.002**
Latin American	5 (2.7)	13 (7)	**0.050**
White	178 (95.2)	150 (81.1)	**<0.001**
Other	2 (1.1)	4 (2.2)	0.410
Underlying condition			
Charlson comorbidity index, m (IQR)	2 (1-4)	1 (0-2)	**<0.001**
Dependent for activities of daily living	48 (25.7)	29 (15.5)	**0.015**
Current smoker	55 (29.4)	13 (7)	**<0.001**
Hypertension	134 (71.7)	108 (57.8)	**0.005**
Dyslipidemia	85 (45.5)	72 (38.5)	0.173
Diabetes	58 (31)	43 (23)	0.081
COPD	80 (42.8)	24 (12.8)	**<0.001**
Asthma	19 (10.2)	6 (3.2)	**0.007**
Chronic heart disease	86 (42.2)	28 (15)	**<0.001**
Chronic neurologic disorder	18 (9.6)	30 (16)	0.064
Chronic kidney disease	49 (26.2)	7 (3.7)	**<0.001**
Liver disease	15 (8)	21 (11.2)	0.293
Immunosuppression	119 (63.6)	24 (12.8)	**<0.001**
Malignancy	17 (9.1)	11 (5.9)	0.238
Inflammatory and autoimmune disorders	22 (11.8)	7 (3.7)	**0.004**
Long-term oral corticosteroids	53 (28.3)	3 (1.6)	**<0.001**
Other*	27 (14.4)	3 (1.6)	**<0.001**

HIV chronic infection	7 (3.7)	5 (2.7)	0.557
BMI, m (IQR)	26.3 (23-31.6)	28.4 (25.1-32.5)	**0.008**
Overweight, BMI ≥ 25 kg/m^2	102 (60.7)	136 (76)	**0.002**
Vaccination status (No./No. of patients with indication)			
Influenza vaccination	30 (17.2) (30/174)	31 (22.3) (31/139)	0.503
Pneumococcal vaccination	45 (26.9) (45/167)	23 (19) (23/121)	0.143
Clinical presentation			
Days from illness onset to admission, m (IQR)	4 (2-7)	8 (5-11)	**<0.001**
Fever	111 (59.4)	156 (83.4)	**<0.001**
Malaise	123 (65.8)	142 (75.9)	**0.031**
Headache	5 (2.7)	35 (18.7)	**<0.001**
Altered level of consciousness	16 (8.6)	23 (12.3)	0.236
Gastrointestinal disorders	12 (6.4)	61 (32.6)	**<0.001**
Anosmia and/or dysgeusia	0 (0)	29 (15.5)	**<0.001**
Upper respiratory tract symptoms	40 (21.4)	52 (27.8)	0.150
Cough	154 (82.4)	152 (81.3)	0.789
Dyspnea	156 (83.4)	115 (61.5)	**<0.001**
Laboratory parameter, m (IQR) (No./No. of patients with data)			
Hemoglobin, g/l	12.6 (11.2-14.3) (187/187)	13.4 (12.2-14.5) (187/187)	**0.005**
Leukocyte count, x10^9/L	9.3 (4.1-10.9) (187/187)	6.6 (5.1-9.9) (187/187)	**<0.001**
Neutrophil count, x10^9/L	7.5 (5.1-10.9) (187/187)	5.2 (3.5-8.5) (187/187)	**<0.001**
Lymphocyte count, x10^9/L	0.9 (0.6-10.9) (187/187)	0.9 (0.7-1.3) (187/187)	0.184
Platelet count, x10^9/L	194 (148-263) (187/187)	203 (156-278) (187/187)	0.220
Urea, mg/dl	51 (34.8-80) (187/187)	35 (28-50) (187/187)	**<0.001**
Creatinine, mg/dl	1.1 (0.8-1.6) (187/187)	0.9 (0.7-1.1) (187/187)	**<0.001**
Serum albumin, g/dl	3.4 (2.9-3.7) (130/187)	3.5 (3.2-3.8) (159/187)	**0.005**
Total bilirubin, mg/dl	0.4 (0.3-0.7) (175/187)	0.4 (0.3-0.6) (186/187)	0.626
Alanine aminotransferase, U/L	19 (13-32) (175/187)	25 (16.8-43.2) (185/187)	**0.004**
Aspartate aminotransferase, U/L	25 (18-36) (176/187)	35 (24-51) (186/187)	**<0.001**
Lactate dehydrogenase, U/L	333 (251-428) (34/187)	308 (249-425) (183/187)	0.626
Creatine kinase, U/L	210 (100-477) (37/187)	90 (53-218) (170/187)	**0.001**
C-reactive protein, mg/dl	9.1 (3.5-23.2) (186/187)	9.6 (4-20.9) (185/187)	0.944
Procalcitonin, ng/ml	0.6 (0.2-3.4) (116/187)	0.1 (0.09-0.4) (127/187)	**<0.001**
Ferritin, ng/ml	435 (154-1148) (50/187)	670 (374-1320) (147/187)	**0.011**

Interleukin 6, pg/ml	- (0/187)	55.2 (19-107) (153/187)	-
D-dimer, mcg/L	- (0/187)	840 (490-1580) (179/187)	-
Troponin T, ng/L	42.4 (22.6-108.1) (29/187)	14 (13.2-25.2) (169/187)	**<0.001**
NT-proBNP, pg/ml	3960 (1258-9891) (78/187)	192 (95-623) (77/187)	**<0.001**
Radiological findings on chest X-ray at admission (No./No. of patients with pneumonia)			
Pneumonia	110 (58.8)	183 (97.9)	**<0.001**
Ground-glass opacities/consolidation	66 (60) (66/110)	72 (39.3) (72/183)	**0.001**
Linear opacities	45 (40.9) (45/110)	146 (79.8) (146/183)	**<0.001**
Bilateral involvement	53 (48.2) (53/110)	160 (87.4) (160/183)	**<0.001**
Pleural effusion	12 (10.9) (12/110)	2 (1.1) (2/182)	**0.001**
Severity assessment			
Baseline MEWS, m (IQR)	2 (0-3)	3 (2-4)	**<0.001**
Baseline CURB-65, m (IQR)	1 (1-1)	1 (1-2)	**<0.001**
Baseline PaO2/FiO2 ratio, m (IQR)	267 (211-330)	304 (214-372)	0.238
ARDS	123 (65.8)	86 (46)	**<0.001**
Moderate-severe ARDS	42 (22.5)	43 (23)	0.902
Baseline WHO ordinal scale			
Admitted to hospital, receiving supplemental oxygen	140 (74.9)	151 (80.7)	0.171
Admitted to hospital, receiving NIV or HFNC	39 (20.9)	27 (14.4)	0.104
Admitted to hospital, receiving MIV	8 (4.3)	9 (4.8)	0.804
Day 7 WHO ordinal scale			
Not admitted to hospital	35 (18.7)	20 (10.7)	**0.029**
Admitted to hospital, without supplemental oxygen	42 (22.5)	27 (14.4)	**0.046**
Admitted to hospital, receiving supplemental oxygen	91 (48.7)	64 (34.2)	**0.005**
Admitted to hospital, receiving NIV or HFNC	10 (5.3)	18 (9.6)	0.116
Admitted to hospital, receiving MIV, or death	9 (4.8)	58 (31)	**<0.001**
Worsening on WHO ordinal scale	7 (3.74)	62 (33.16)	**<0.001**
ICU admission	26 (13.9)	69 (39.4)	**<0.001**
Complications during admission			
Bacterial pneumonia	43 (23)	27 (14.4)	**0.034**
Non-respiratory bacterial infection	5 (2.7)	38 (20.3)	**<0.001**
Pulmonary embolism	-	17 (9.1)	**0.048**
Heart failure	56 (29.9)	20 (10.7)	**<0.001**
Atrial fibrillation	24 (12.8)	13 (7)	0.057
Acute kidney injury	24 (12.8)	41 (21.9)	**0.020**
Therapeutic management			
Antibiotic	169 (90.4)	180 (96.3)	**0.023**
Antiviral	184 (98.4)	34 (18.2)	**<0.001**
Corticosteroids	180 (80.2)	115 (61.5)	**<0.001**
Interleukin 6 inhibitors	-	48 (25.7)	**<0.001**

Pronation	5 (2.7)	73 (39)	**<0.001**

Data are presented as nos. and % or as medians (m) with interquartile ranges (IQR). Abbreviations: COVID-19 (coronavirus disease 2019), COPD (chronic obstructive pulmonary disease), HIV (human immunodeficiency virus), BMI (body mass index), N-terminal pro-B-type natriuretic peptide (NT-proBNP), Modified Early Warning Score (MEWS), non-invasive ventilation (NIV), high-flow nasal cannula (HFNC), invasive mechanical ventilation (IMV), Intensive care unit (ICU), acute respiratory distress syndrome (ARDS).

*Other: Diabetes mellitus 9, primary immunosuppression 5, immunosuppressive agents 4, renal transplant 5, untreated HIV and/or CD4 count < 200 cells/µl4, immunosuppressive agents 4 in influenza cases. Renal transplant 2 and pregnancy 1 in COVID-19 cases.

Table 2. Cox regression analysis of associations between main variables and mortality at day 30.

	Crude analysis		Adjusted analysis	
Variable	**HR (95%CI)**	**p value**	**HR (95%CI)**	**p value**
COVID-19	3.07 (1.5-6.31)	**0.002**	4.56 (2.01-10.43)	**<0.001**
Demographic information				
Male sex	1.69 (0.88-3.25)	0.117	3.02 (1.44-3.36)	**0.004**
Age (per unit)	1.07 (1.04-1.04)	**<0.001**	1.09 (1.06-1.13)	**<0.001**
Underlying condition				
Charlson comorbidity index (per unit)	1 .7 (1.01-1.36)	**0.038**	1.19 (0.99-1.43)	0.060
Dependent for activities of daily living	3.34 (1.87-5.95)	**<0.001**		
Current smoker	0.51 (0.18-1.41)	0.190		
Hypertension	1.86 (0.89-3.95)	0.098		
Dyslipidemia	1.47 (0.83-2.75)	0.231		
Diabetes	1.07 (0.53-2.14)	0.650		
COPD	1.46 (0.76-2.81)	0.258		
Chronic heart disease	1.28 (0.65-2.46)	0.463		
Chronic neurologic disorder	4.01 (2.06-7.8)	**<0.001**		
Chronic kidney disease	0.82 (0.32-2.09)	0.677		
Malignancy	1.4 (0.5-3.95)	0.521		
Immunosuppression	0.46 (0.22-0.97)	0.043		
HIV/AIDS	0.66 (0.35-1.26)	0.207		
BMI (per unit)	1.01 (0.9-1.01)	0.270		
Severity assessment				
Baseline MEWS (per unit)	1.41 (1.21-1.64)	**<0.001**	1.59 (1.31-1.94)	**<0.001**
Baseline CURB-65 (per unit)	2.24 (1.7-2.93)	**<0.001**		
Baseline PaO2/FiO2 ratio (per unit)	1 (0.99-1)	**0.046**	1 (0.99-1.01)	0.086
Baseline WHO ordinal scale				
Admitted to hospital, receiving supplemental oxygen	Reference			
Admitted to hospital, receiving NIV or HFNC	0.53 (0.19-1.5)	0.233		
Admitted to hospital, receiving MIV	1.59 (0.49-5.21)	0.440		
Day 7 WHO ordinal scale				
Admitted to hospital, receiving supplemental oxygen	Reference			
Admitted to hospital, receiving NIV or HFNC	3.58 (1.3-9.84)	**0.014**		
Admitted to hospital, receiving MIV	2.96 (1.23-7.1)	**0.015**		
Worsening on WHO ordinal scale (per unit)	7.64 (4.03-14.47)	**<0.001**		
Radiological findings in chest X-ray				
Pneumonia	5.38 (1.3-22.34)	**0.020**	1.82 (0.38-8.64)	0.451
Ground-glass opacities/consolidation	1.67 (0.89-3.12)	0.111		
Linear opacities	1.97 (1.01-3.83)	**0.046**		
Bilateral involvement	1.18 (0.56-2.5)	0.666		
Pleural effusion	1.41 (0.34-5.86)	0.634		
Complications during admission				
Bacterial pneumonia	0.77 (0.32-1.83)	0.549		

Non-respiratory bacterial infection	4.1 (2.11-7.99)	**<0.001**		
Pulmonary embolism	0.4 (0.06-2.92)	0.365		
Heart failure	1.35 (0.66-2.77)	0.412		
Atrial fibrillation	2.87 (1.36-6.04)	**0.006**		
Acute kidney injury	4.42 (2.35-8.3)	**<0.001**		
Therapeutic management				
Antibiotic	2.76 (0.38-20.1)	0.317		
Antiviral	0.42 (0.22-0.79)	**0.008**		
Corticosteroids	0.83 (0.45-1.53)	0.548	0.34 (0.16-0.73)	**0.006**
Interleukin 6 inhibitors	0.93 (0.38-2.3)	0.883		
Pronation	0.96 (0.44-2.08)	0.912		

Abbreviations: COVID-19 (coronavirus disease 2019), COPD (chronic obstructive pulmonary disease), HIV/AIDS (human immunodeficiency virus/acquired immune deficiency syndrome), BMI (body mass index), Modified Early Warning Score (MEWS), non-invasive ventilation (NIV), high-flow nasal cannula (HFNC), invasive mechanical ventilation (IMV), intensive care unit (ICU).

Variables explored in the initial multivariate model were group (COVID-19 or influenza), sex, age, Charlson comorbidity index, current smoker, hypertension, dyslipidemia, immunosuppression, BMI, baseline PaO2/FiO2, baseline MEWS, pneumonia, bilateral involvement, antiviral and corticosteroids therapy.

The adjusted model showed a statistical power of 97.25%.

Table 3. Cox regression analysis of associations between main variables and mortality at day 30 in the subgroup of patients with pneumonia at baseline.

	Crude analysis		Adjusted analysis	
Variable	**HR (95%CI)**	**p value**	**HR (95%CI)**	**p value**
COVID-19	2.39 (1.05-5.02)	**0.038**	5.18 (2.08-12.9)	**<0.001**
Demographic information				
Male sex	1.62 (0.84-3.15)	0.155	2.96 (1.38-6.36)	**0.005**
Age (per unit)	1.08 (1.04-1.11)	**<0.001**	1.1 (1.06-1.14)	**<0.001**
Underlying condition				
Charlson comorbidity index (per unit)	1.21 (1.05-1.39)	**0.007**	1.22 (1.02-1.47)	**0.005**
Dependent for activities of daily living	4.78 (2.5-9.1)	**<0.001**		
Current smoker	0.56 (0.17-1.82)	0.336		
Hypertension	2.32 (1.06-5.08)	**0.035**		
Dyslipidemia	1.56 (0.82-2.98)	0.178		
Diabetes	1.25 (0.62-2.53)	0.537		
COPD	1.86 (0.95-3.66)	0.071		
Chronic heart disease	1.4 (0.71-2.76)	0.324		
Chronic neurologic disorder	3.93 (1.97-7.83)	**<0.001**		
Chronic kidney disease	1.14 (0.46-2.94)	0.780		
Malignancy	1.49 (0.53-4.2)	0.453		
Immunosuppression	0.62 (0.28-1.65)	0.225		
HIV/AIDS	0.78 (0.11-5.72)	0.810		
BMI (per unit)	1.01 (0.99-1.01)	0.360		
Severity assessment				
MEWS (per unit)	1.35 (1.14-1.59)	**<0.001**	1.52 (1.24-1.88)	**<0.001**
CURB-65 (per unit)	2.06 (1.56-2.87)	**<0.001**		
Baseline PaO2/FiO2 ratio (per unit)	1 (0.99-1.01)	0.108	1 (0.99-1.01)	0.061
Baseline WHO ordinal scale				
Admitted to hospital, receiving supplemental oxygen	Reference			
Admitted to hospital, receiving NIV or HFNC	0.37 (0.11-1.21)	0.099		
Admitted to hospital, receiving MIV	1.32 (0.4-4.32)	0.645		
Day 7 WHO ordinal scale				
Admitted to hospital, receiving supplemental oxygen	Reference			
Admitted to hospital, receiving NIV or HFNC	2.61 (0.87-7.79)	0.086		
Admitted to hospital, receiving MIV	2.5 (1.02-6.15)	**0.046**		
Worsening on WHO ordinal scale (per unit)	6.68 (3.43-12.98)	**<0.001**		
ICU admission	1 (0.5-1.99)	0.997		
Radiological findings in chest X-ray				
Ground-glass opacities/consolidation	1.2 (0.63-2.28)	0.586		
Linear opacities	1.29 (0.64-2.61)	0.481		
Bilateral involvement	1.18 (0.56-2.5)	0.666	0.83 (0.36-1.92)	0.663
Pleural effusion	1.24 (0.3-5.17)	0.765		
Complications				
Bacterial pneumonia	0.74 (0.31-1.77)	0.498		

Non-respiratory bacterial infection	3.65 (1.86-7.18)	**<0.001**		
Pulmonary embolism	0.37 (0.05-2.74)	0.332		
Heart failure	1.54 (0.75-3.19)	0.240		
Atrial fibrillation	2.1 (0.96-4.59)	0.064		
Acute kidney injury	4.3 (2.26-8.2)	**<0.001**		
Therapeutic management				
Antibiotic	1.22 (0.17-8.93)	0.842		
Antiviral	0.55 (0.28-1.08)	0.082		
Corticosteroids	0.61 (0.32-1.18)	0.146	0.32 (0.15-0.69)	**0.004**
Interleukin 6 inhibitors	0.75 (0.3-1.86)	0.532		
Pronation	0.79 (0.36-1.72)	0.548		

Abbreviations: COVID-19 (coronavirus disease 2019), COPD (chronic obstructive pulmonary disease), HIV/AIDS (human immunodeficiency virus/acquired immune deficiency syndrome), BMI (body mass index), non-invasive ventilation (NIV), high-flow nasal cannula (HFNC), invasive mechanical ventilation (IMV), intensive care unit (ICU).

Variables explored in the initial multivariate model: group (COVID-19 or influenza), sex, age, Charlson comorbidity index, current smoker, hypertension, dyslipidemia, BMI, baseline PaO2/FiO2, baseline MEWS, bilateral involvement, antiviral and corticosteroid therapy. Bilateral involvement was forced into the model.

The adjusted model showed a statistical power of 98.2%.

Table 4. Univariate analysis of healthcare resource consumption and economic impact for Influenza and COVID-19 patients in the overall cohort and in the pneumonia subgroup.

	2017-2019 Influenza	COVID-19	p-value
Overall cohort			
Healthcare resource consumption			
Length of stay, days	11 (8-17)	14 (8-26)	**<0.001**
Length of stay in ICU, days	10 (7-15)	17 (9-27)	**0.005**
Days of NIV or HFNC	5 (2-8)	4 (2-6)	0.577
Days of IMV	11 (5-15)	15 (10-22)	0.276
Readmissions, 90 days, n (%)	53 (28.3)	5 (2.7)	**<0.001**
Costs, €			
Overall cost of hospitalization	5996 (4049-10955)	6448 (3690-15435)	0.238
Cost of critical care	12082 (6594-22284)	21350 (11309- 42558)	**<0.001**
Cost of pharmacy	132 (53-256)	156 (42-1934)	**0.022**
Cost of laboratory tests, imaging plus other complementary tests	275 (155-571)	925 (628-1560)	**<0.001**
Pneumonia subgroup			
Healthcare resource consumption			
Length of stay, days	11.5 (8-17)	15 (8-26)	**<0.001**
Length of stay in ICU, days	10 (7-15)	17 (9-27)	**0.010**
Days of NIV or HFNC	5 (2.5-8)	4 (2-6.25)	0.532
Days of IMV	11 (6-14)	15 (10-22)	**0.013**
Readmissions, 90 days, n (%)	28 (25.5)	5 (2.7)	**<0.001**
Costs, €			
Overall cost of hospitalization	4370 (7494-12504)	6621 (3723-16164)	**0.008**
Cost of critical care	13258 (8694-23149)	21350 (11309- 42558)	**0.001**
Cost of pharmacy	146 (64-273)	166 (43-1982)	**<0.001**
Cost of laboratory tests, imaging plus other complementary tests	360 (215-921)	930 (637-1569)	**<0.001**

Data are presented as means (m) and interquartile range (IQR) unless otherwise specified. Cost values are shown in euros (€). Abbreviations: COVID-19 (coronavirus disease 2019), non-invasive ventilation (NIV), high-flow nasal cannula (HFNC), invasive mechanical ventilation (IMV), intensive care unit (ICU).

Figure Legends:

Figure 1. Flowchart of patients included in the study.

Abbreviations: COVID-19 (coronavirus disease 2019).

Figure 2. Progression of influenza and COVID-19 patients on WHO ordinal scale during admission. Status on the WHO ordinal scale at baseline (A) and at day 7 (B).

Abbreviations: COVID-19 (coronavirus disease 2019), non-invasive ventilation (NIV), high flow nasal cannula (HFNC), invasive mechanical ventilation (IMV).

Figure 3. Cumulative Kaplan-Meier estimates of (A) probability of overall survival at day 30 in influenza and SARS-CoV-2 virus groups and (B) stratified by age ≥ 74 years.
Abbreviations: COVID-19 (coronavirus disease 2019).

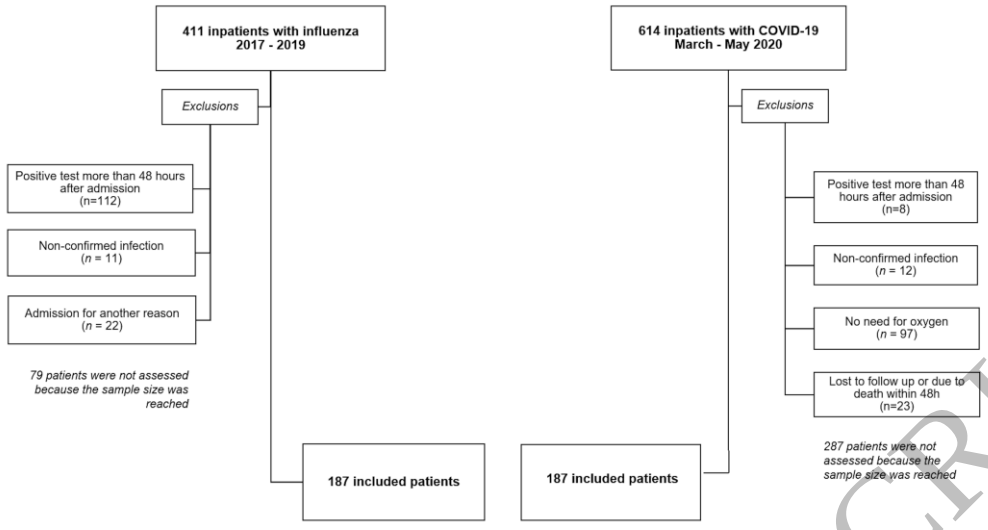

Figure 1
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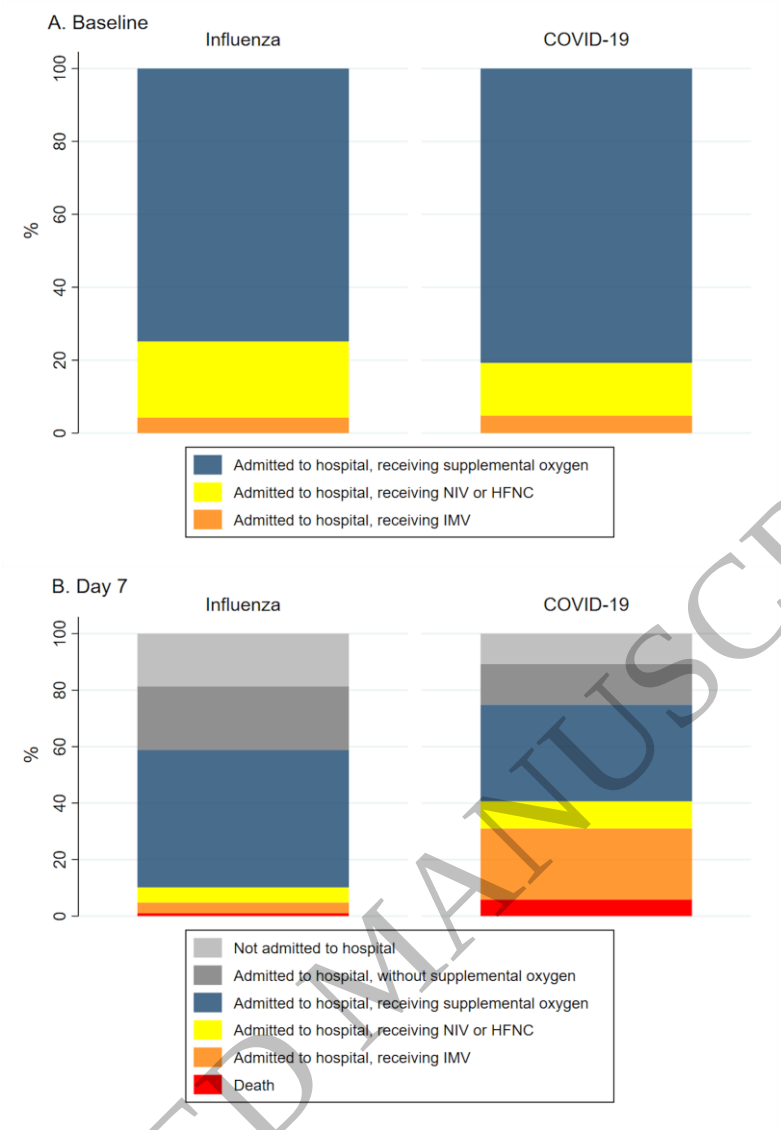

Figure 2
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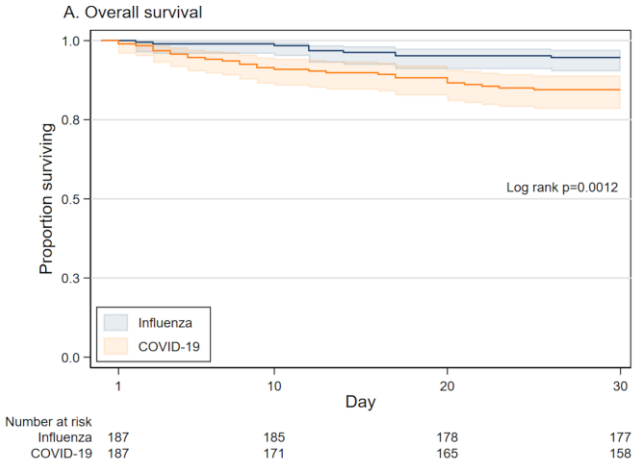

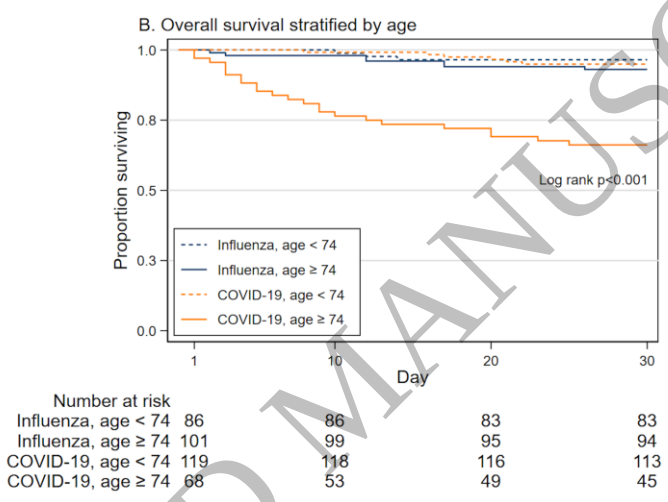

Figure 3
102x149 mm (x DPI)