Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original Article

A comparative analysis of the outcomes of patients with influenza or COVID-19 in a tertiary hospital in Belgium

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ABSTRACT

Introduction: The COVID-19 pandemic has emerged as a global health problem, associated with high morbidity and mortality rates. The aim of this study was to compare the outcomes of hospitalized patients with COVID-19 or with seasonal influenza in a teaching hospital in Belgium.

Methods: In this retrospective, single-center cohort study, 1384 patients with COVID-19 and 226 patients with influenza were matched using a propensity score with a ratio of 3:1. Primary outcomes included admission to intensive care unit (ICU), intubation rates, hospital length of stay, readmissions within 30 days and in-hospital mortality. Secondary outcomes included pulmonary bacterial superinfection, cardiovascular complications and ECMO.

Results: Based on the analysis of the matched sample, patients with influenza had an increased risk of readmission within 30 days (Risk Difference (RD): 0.07, 95% CI: 0.03 to 0.11) and admission to intensive care unit (RD: 0.09, 95% CI: 0.03 to 0.15) compared with those with COVID-19. Patients with influenza had also more pulmonary bacterial superinfections (46.2% vs 7.4%) and more cardiovascular complications (32% vs 3.9%) than patients with COVID-19.However, a two-fold increased risk of mortality (RD: −0.10, 95% CI: 0.15 to −0.05) was observed in COVID-19 compared to influenza. ECMO was also more required among the COVID-19 patients who died than among influenza patients (5% vs 0%).

Conclusions: COVID-19 is associated with a higher in-hospital mortality compared to influenza infection, despite a high rate of ICU admission in the influenza group. These findings highlighted that the severity of hospitalized patients with influenza should not be underestimated.

ICMJE statement

All authors meet the ICMJE authorship criteria.

1. Introduction

Coronavirus Disease 2019 (COVID-19) is an ongoing infectious illness caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2); the disease primarily affects the respiratory tract, in particular the lungs, with substantial risks of developing severe or critical illness associated with high morbidity and mortality [1–5]. However, studies have shown that case fatality rates for COVID-19 vary significantly worldwide [6].

Seasonal influenza is a useful comparator to assess COVID-19 mortality, given that both are respiratory diseases with similar modes of transmission [7–10]. Comparisons of clinical manifestations and mortality between patients with COVID-19 and with seasonal influenza have been drawn by several reports, public health officials, and the public at

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large. However, most of these comparisons relied on data and mortality statistics obtained by disparate methods and are not based on an "apples with apples" comparison [11,12]. Baseline characteristics of the two populations should be as similar as possible to adequately evaluate the fatality rate of hospitalized patients with COVID-19, compared to influenza hospitalized patients. Indeed, risk factors for developing severe influenza pneumonia have been very well established for decades, but may slightly differ for COVID-19. Several studies have reported a higher Charlson's comorbidity index in the influenza group compared with the COVID-19 group [8,10,13], which highlights that influenza-related mortality could be partly explained by a high-risk population at baseline.

Given the persistence of the COVID-19 pandemic and the advent of seasonal influenza, a prognostic comparison of both diseases is essential to prepare the already weakened health systems for prioritization of care. Based on the analysis of data from cohorts of patients followed in a teaching hospital in Belgium, the current study aimed at making a head-to-head comparison of clinical characteristics and outcomes between hospitalized patients with COVID-19 and those with seasonal influenza.

2. Material and methods

2.1. Study design

This was a retrospective single-center cohort study performed in a large teaching hospital of 1000 beds, Cliniques Universitaires Saint-Luc, Brussels, Belgium.

2.2. Study population, inclusion and exclusion criteria

The study included all adults (>18 years old) who were hospitalized from January 2015 to November 2020 for influenza, or from March 2020 to November 2020 for COVID-19 in our hospital ((COVID-19 dedicated wards, internal medicine wards, geriatric ward, or intensive care units (ICU)).

Patients with COVID-19 were enrolled based on a positive SARS-CoV-2 Polymerase Chain Reaction (PCR) test together with clinical and radiological signs suggestive of COVID-19. SARS-CoV-2 PCR was performed on nasopharyngeal swabs and relied on the Genesig® Real-Time PCR assay (Primerdesign Ltd, Chandler's Ford, United Kingdom) which allows detection of viral RNA by targeting the RNA-dependent RNA polymerase (RdRp) gene. The amplification reaction was performed on a LightCycle 480 (Roche Diagnostics, Mannheim, Germany) with a cycle threshold (Ct) < 40 being considered as a positive reaction.

Influenza patients were enrolled based on a positive influenza A and B PCR. The laboratory diagnosis of Influenza A or B infection was confirmed by using the Xpert® Xpress Flu/RSV Real-Time PCR assay (Cepheid, USA) on a nasopharyngeal swab, targeting flu A, flu B, and RSV specific genes.

For both COVID-19 and Influenza, criteria for hospitalization included acute respiratory failure (defined as $SpO2 \leq 92\%$ or $PaO2 \leq$ 105-(age/2)) or any need for hospital care (asthenia, dehydration, acute renal failure, suspected bacterial superinfection, etc.).

Discharge was allowed when patients improved sufficiently. Quarantine was completed at home when the hospital stay was less than 14 days after positive SARS-CoV-2 PCR.

2.3. Data collection

We collected demographics, clinical characteristics, comorbid conditions based on ICD-10 codes, laboratory analyses, clinical symptoms and parameters, and in-hospital medication orders from all patients hospitalized for COVID-19 or seasonal influenza in our hospital using our institutional database for COVID-19 and/or Institutional database Medical explorer V8.

2.4. Outcomes

The primary outcomes of interest were all cause in-hospital mortality, unplanned readmission to any medical unit within 30 days of discharge, admission to ICU, intubation rate, and total hospital length of stay (LOS). A prolonged LOS was defined as more than 14 days.

Secondary outcomes were cardiovascular complications (including acute coronary syndrome, hemodynamic shock and pulmonary embolism), pulmonary bacterial superinfections and the requirement of extracorporeal membrane oxygenation (ECMO). Theses outcomes were analysed in the overall population, matched population and in patients who died.

2.5. Ethical issues

The institutional ethical board of Cliniques Universitaires Saint-Luc and UCLouvain university approved the study (CEHF 2020/06AVR/201). Due to the retrospective design of the study, signing an informed consent was not required according to Belgian and local ethics law.

2.6. Statistical analysis

Analysis was performed with R, version 4.0.2. Influenza cases were matched to COVID-19 patients using a propensity score, with a ratio of 3:1. The matching method used was nearest neighbor and matching was performed without replacement. The following variables were included in the propensity score: age, sex, cardiovascular disease, diabetes, neurocognitive disorders, and obesity. We explored the propensity score by the mean of a histogram and the balance of the matched sample using the love plot. Both the descriptive analysis of the whole sample and the sample after matching were conducted. The difference in outcomes between COVID-19 and influenza patients was obtained using the risk difference (RD) with (their 95% confidence intervals). A p-value lower than 0.05 was considered indicative of a statistically significant difference.

3. Results

3.1. Characteristics of the cohorts

In total, 1384 patients with COVID-19 and 226 patients with influenza were hospitalized during the study periods. The baseline characteristics of patients before and after Propensity-score matching are presented in Table 1. After propensity-score matching, 675 patients with COVID-19 were compared to 225 patients with influenza. The results of the exploration of the propensity score and the matched sample (love plot) are presented in Supplementary Figs. 1–2.

The mean age was 70 years for the matched patients with COVID-19 and 69.8 years for influenza. Overall, unmatched patients with COVID-19 were more frequently obese (26.4% compared to 17.7%) but had less frequently diabetes (22.5% compared to 28.8%), neurocognitive disorders (18.6% compared to 31.4%) than patients with influenza. After matching, there were no more significant differences in these comorbidities as they were used as covariates for matching.

Cardiovascular diseases were highly prevalent in both matched groups (50.2% in the influenza group compared to 51.7% in the COVID-19 group). Other most frequent comorbidities in matched groups were neuro-cognitive disorders (31.6% compared to 27.0%), chronic respiratory diseases (40.9% compared to 30.1%), hypertension (60.4% compared to 49.8%), and diabetes (28.9% compared to 28.6%), for the influenza versus COVID-19 populations respectively.

3.2. Treatment

On the basis of international practice guidelines, a majority of patients with COVID-19 received treatment with hydroxychloroquine

Table 1
Characteristics of patients before and after matching.

	Unmatched Patients		Propensity-Score–Matched Patients	
	Influenza (N = 226)	COVID-19 (N = 1384)	Influenza (N = 225)	COVID-19 (N = 675)
Age — mean. (SD)	69.8 (18.4)	65.0 (16.9)	69.8 (18.4)	70.0 (15.7)
Female sex — no. (%)	112 (49.6%)	579 (41.8%)	112 (49.8%)	320 (47.4%)
Neuro-cognitive disorders— no. (%)				
No	155 (68.6%)	1096 (79.2%)	154 (68.4%)	493 (73.0%)
Yes	71 (31.4%)	257 (18.6%)	71 (31.6%)	182 (27.0%)
Missing	0 (0%)	31 (2.2%)	0 (0%)	0 (0%)
Cardiovascular diseases— no. (%)				
No	113 (50.0%)	777 (56.1%)	112 (49.8%)	326 (48.3%)
Yes	113 (50.0%)	563 (40.7%)	113 (50.2%)	349 (51.7%)
Missing	0 (0%)	44 (3.2%)	0 (0%)	0 (0%)
Cancer— no. (%)				
No	180 (79.6%)	1173 (84.8%)	179 (79.6%)	564 (83.6%)
Yes	46 (20.4%)	180 (13.0%)	46 (20.4%)	111 (16.4%)
Missing	0 (0%)	31 (2.2%)	0 (0%)	0 (0%)
Chronic renal failure— no. (%)				
No	178 (78.8%)	1061 (76.7%)	177 (78.7%)	496 (73.5%)
Yes	47 (20.8%)	279 (20.2%)	47 (20.9%)	178 (26.4%)
Missing	1 (0.4%)	44 (3.2%)	1 (0.4%)	1 (0.1%)
Respiratory diseases— no. (%)				
No	133 (58.8%)	990 (71.5%)	133 (59.1%)	472 (69.9%)
Yes	93 (41.2%)	351 (25.4%)	92 (40.9%)	203 (30.1%)
Missing	0 (0%)	43 (3.1%)	0 (0%)	0 (0%)
Immunodepression— no. (%)				
No	157 (69.5%)	1152 (83.2%)	156 (69.3%)	570 (84.4%)
Yes	69 (30.5%)	196 (14.2%)	69 (30.7%)	105 (15.6%)
Missing	0 (0%)	36 (2.6%)	0 (0%)	0 (0%)
Haematological diseases— no. (%)				
No	197 (87.2%)	1308 (94.5%)	196 (87.1%)	655 (97.0%)
Yes	29 (12.8%)	45 (3.3%)	29 (12.9%)	20 (3.0%)
Missing	0 (0%)	31 (2.2%)	0 (0%)	0 (0%)
Obesity— no. (%)				
No	186 (82.3%)	833 (60.2%)	186 (82.7%)	568 (84.1%)
Yes	40 (17.7%)	366 (26.4%)	39 (17.3%)	107 (15.9%)
Unknown	0 (0%)	185 (13.4%)	0 (0%)	0 (0%)
Hypertension— no. (%)				
No	90 (39.8%)	743 (53.7%)	89 (39.6%)	339 (50.2%)
Yes	136 (60.2%)	598 (43.2%)	136 (60.4%)	336 (49.8%)
Missing	0 (0%)	43 (3.1%)	0 (0%)	0 (0%)
Diabetes— no. (%)				
No	161 (71.2%)	1029 (74.3%)	160 (71.1%)	482 (71.4%)
Yes	65 (28.8%)	312 (22.5%)	65 (28.9%)	193 (28.6%)
Missing	0 (0%)	43 (3.1%)	0 (0%)	0 (0%)
Length of stay (days)				
Mean. (SD)	13.1 (14.7)	12.0 (14.5)	13.1 (14.7)	12.4 (13.2)
Median [Min, Max]	9.00 [1.00, 133]	8.00 [0, 153]	9.00 [1.00, 133]	9.00 [0, 153]
Missing	0 (0%)	30 (2.2%)	0 (0%)	0 (0%)
Lymphocytes				
Median [Min, Max]	0.745 [0, 670]	0.940 [0, 999]	0.750 [0, 670]	0.900 [0, 999]
Missing	0 (0%)	508 (36.7%)	0 (0%)	255 (37.8%)
Eosinophiles				
Median [Min, Max]	0.0100 [0, 0.380]	0.0100 [0, 999]	0.010 [0, 0.380]	0.010 [0, 999]
Missing	0 (0%)	510 (36.8%)	0 (0%)	256 (37.9%)
WBC				
Median [Min, Max]	8.52 [0, 54.6]	6.40 [0, 999]	8.51 [0, 54.6]	6.39 [0, 999]
Missing	0 (0%)	512 (37.0%)	0 (0%)	256 (37.9%)
C-reactive protein — mg/liter				
Median [Min, Max]	106 [2.10, 606]	64.1 [0, 999]	105 [2.10, 606]	63.8 [0, 999]
Missing	0 (0%)	535 (38.7%)	0 (0%)	265 (39.3%)
Lactate dehydrogenase — U/liter				
Median [Min, Max]	286 [90.0, 4280]	321 [0, 2560]	285 [90.0, 4280]	319 [0, 2560]
Missing	1 (0.4%)	539 (38.9%)	1 (0.4%)	274 (40.6%)
Creatinine (mg/dl)				
Median [Min, Max]	1.03 [0.170, 10.6]	0.980 [0, 999]	1.03 [0.170, 10.6]	1.01 [0, 999]
Missing	0 (0%)	511 (36.9%)	0 (0%)	254 (37.6%)
ECMO— no. (%)				
No	224 (99.1%)	1321 (95.4%)	223 (99.1%)	663 (98.2%)
Yes	2 (0.9%)	33 (2.4%)	2 (0.9%)	11 (1.6%)
Missing	0 (0%)	30 (2.2%)	0 (0%)	1 (0.1%)
Cardiovascular Complications — no. (%)				
No	154 (68.1%)	1289 (93.1%)	153 (68.0%)	645 (95.6%)
Yes	72 (31.9%)	57 (4.1%)	72 (32.0%)	26 (3.9%)
Missing	0 (0%)	38 (2.7%)	0 (0%)	4 (0.6%)
Superinfection— no. (%)				
No	122 (54.0%)	1245 (90.0%)	121 (53.8%)	623 (92.3%)
Yes	104 (46.0%)	105 (7.5%)	104 (46.2%)	50 (7.4%)
Missing	0 (0%)	34 (2.5%)	0 (0%)	2 (0.3%)

SD: Standard deviation; no: number; WBC: white blood cells; ECMO: extracorporeal membrane oxygenation.

during the first months, then with dexamethasone. Almost all of the patients with early influenza infection received antiviral therapy (oseltamivir). Antibiotics were administered accordingly if a bacterial superinfection was suspected or confirmed.

3.3. Primary outcomes

Based on the analysis of the matched sample, patients with influenza had an increased risk of readmission within 30 days (RD: 0.07; 95% CI: 0.03 to 0.11) and admission to ICU (RD: 0.09; 95% CI: 0.03 to 0.15) compared with those with COVID-19. Conversely, patients with COVID-19 had an increased risk of death (RD: −0.10; 95% CI: −0.15 to −0.05) compared with those with influenza (Tables 2–3).

However, the risk of intubation (RD: 0.04; 95% CI: −0.01 to 0.08) and prolonged LOS (RD: −0.01; 95% CI: (−0.08 to 0.06) was not significantly different between the two groups (Tables 2–3).

3.4. Secondary outcomes

Based on the analysis of the matched sample (Table 1), patients with

Table 2
Proportion of patients with the various outcomes, readmission within 30 days, Intubation, admission to ICU, prolonged duration of hospitalization (>14 days) and death in the propensity-score matched sample.

	Matched Patients	
	Influenza	COVID-19
	(N = 225)	(N = 675)
Readmission (30 days)		
No	206 (91.6%)	664 (98.4%)
Yes	19 (8.4%)	11 (1.6%)
Intubation		
No	201 (89.3%)	628 (93.0%)
Yes	24 (10.7%)	47 (7.0%)
Missing	0 (0%)	0 (0%)
Admission to ICU		
No	171 (76.0%)	572 (84.7%)
Yes	54 (24.0%)	103 (15.3%)
Missing	0 (0%)	0 (0%)
Hospital length of stay (day)		
Mean (SD)	13.1 (14.7)	12.4 (13.2)
Median [Min, Max]	9.00 [1.00, 133]	9.00 [0, 153]
Missing	0 (0%)	0 (0%)
Death		
No	203 (90.2%)	540 (80.0%)
Yes	22 (9.8%)	135 (20.0%)

Table 3
Outcome of patients (Risk difference) in the sample matched using the propensity-Score.

	Risk difference (95%CI)
Readmission (30 days)	0.07 (0.03; 0.11)[a]
Intubation	0.04 (−0.01; 0.08)
Admission to ICU	0.09 (0.03; 0.15)[a]
Prolonged length of stay	−0.01 (−0.08; 0.06)
Death	−0.10 (−0.15; −0.05)[a]

ICU: Intensive care unit.CI: confidence interval; In the outcome analysis the reference category (code as 0) was COVID-19.

[a] Significantly different; Prolonged length of stay represented a length of stay >14 days.

influenza had more pulmonary bacterial superinfections (46.2% vs 7.4%) and more cardiovascular complications (32% vs 3.9%) than patients with COVID-19. Requirement for ECMO was similar in both groups (0.9% vs 1.6%).

In the subgroup of dead patients (Supplementary Table 1), pulmonary bacterial superinfections were more frequent among influenza patients (59.1% vs 20.7%) than among COVID-19 patients. Cardiovascular complications were also a lot more frequent (72.7% vs 15%). However, ECMO was more required among the COVID-19 patients than among influenza patients (5% vs 0%).

4. Discussion

The aim of the present study was to compare clinical characteristics, outcomes, and mortality in hospitalized patients with COVID-19 and those with seasonal influenza. The most relevant finding of our study was that COVID-19 was associated with a two-fold increase risk of in-hospital mortality compared to influenza though influenza hospitalized patients were more likely to require intensive care compared to COVID-19 patients.

Fatality rates and requirement of respiratory support in patients with COVID-19 have also been compared with previous severe influenza pandemics in 1918 and 2009 [14,15], and both outcomes were reported to be higher in COVID-19 than in influenza.

To date, most studies comparing the relative severity of COVID-19 with influenza in hospitalized patients showed poorer outcomes for the COVID-19 infections (ICU admissions, intubation rates, hospital LOS) and higher mortality [8,9,13,16]. Whereas, a meta-analysis collecting data of all patients (ambulatory and hospitalized) with COVID-19 and influenza revealed quite similar mortality in both groups [17].

Unlike these previous studies, our study revealed worse outcomes in patients with influenza in terms of higher risk of ICU admission, of hospital readmission rate. This is probably related to higher rates of cardiovascular complications and bacterial superinfections among patients with influenza. However, the requirement of ECMO and the overall mortality were shown to be higher in the COVID-19 group. This suggests that the increased mortality rate in COVID-19 group is not related to secondary complications but probably to a severe pulmonary disease. These findings confirmed that the prognosis of critically ill patients with COVID-19 is primarily poorer, and it should not be only based on a lack of approved treatments. Indeed, even though treatments for influenza such as oseltamivir are available, they are limited to prevent respiratory failure and the management of critically ill patients is mainly supportive. Therefore, the higher mortality in COVID-19 despite the lower rate of ICU admission compared with influenza allows us to underscore the intrinsic severity of COVID-19, especially in critically ill patients.

Our results are in agreement with those from Cobb et al. [18] which compared outcomes of critically ill patients admitted in ICU with COVID-19 or with influenza. The requirement for mechanical ventilation at admission was the same in both groups but the COVID-19 group needed a longer period of mechanical ventilation, a longer ICU stay, and a longer hospital stay. As in our study, the mortality was also higher in the group of patients with COVID-19.

A possible underlying explanation of the higher mortality rate in our cohort of COVID-19 could be the epidemic context of the first wave. Indeed, the sudden very high influx of patients over a short period created medical structural constraints, and care teams were led to prioritizing patients based on clinical status and prognosis. Moreover, all the COVID-19 patients included were non immune as the vaccination campaign started in January 2021 in Belgium, after the end of the recruitment. This may also explain the severity of COVID-19 compared with influenza for which a vaccine was already available. The potential effect of the different SARS-CoV-2 variants of concern (VOC) was not studied as the first variant alpha was described in December 2020 in Belgium [19]. All COVID-19 cases in this study were due to the wild type virus. Hospital length of stay was very similar in both groups. This underlines the severity of influenza infections. Indeed, most of nursing homes required a negative SARS-CoV-2 PCR before the return of their residents, while droplet precautions in influenza are shorter (7 days). It may have contributed at a small level to prolonged hospital stay of some COVID-19 patients.

In our study, we found an unexpectedly high rate of ICU admission in the influenza group compared to COVID-19. Influenza infections are known to cause high morbidity and mortality rates in the elderly (65 or older) and in young populations with comorbidities. This can be related to the frequency of influenza-associated community-acquired pneumonia (CAP), which can result in severe and fatal complications. In contrast, although hospital-acquired bacterial co-infection is a concern in intubated patients, secondary bacterial CAP at hospital admission appears to be an uncommon complication of COVID-19 [20–22].

Our study has some limitations. First, it was conducted as a single-center, retrospective, and observational study, which, by nature, may translate into a limited and imperfect design. Second, the corresponding diseased group sizes were different. To minimize the potential impact on the power of the analysis, propensity score matching was applied. Third, testing practices for influenza were likely to be not systematic (only based on clinical suspicion), whereas practices for COVID-19 were more standardized (all hospitalized patients required diagnostic testing). This could have reduced the detection of hospitalized influenza patients.

Moreover, as patient enrollment was limited to the first and the second COVID-19 waves in Belgium, outcomes could change in the

following months. Indeed, our understanding of the epidemiology, pathophysiology, and outcomes of COVID-19 continues to evolve. The care of COVID-19 patients has been rapidly improved over time, thanks to the discovery and the use of new therapeutics and vaccines. Finally, our study did not stratified comparison between subtypes Influenza A and Influenza B, in order to ensure sufficient power. In the past, influenza A infection was thought to be more severe than influenza B infection, and some studies comparing COVID-19 with Influenza A and Influenza B find worse outcomes with Influenza A than B [17]. However, a 2014 study [23] in adults with influenza A and influenza B found they both resulted in similar rates of illness and death. That being said, an unusual distribution of Influenza A/B in our study population could possibly contribute to explain our results. Further studies are still needed to compare again the outcomes of these two diseases in light of the progress made.

In conclusion, the higher in-hospital mortality observed in our study population of matched COVID-19 and influenza patients with similar underlying comorbidities confirmed that COVID-19 is intrinsically more severe than influenza, despite a lower rate of ICU admission and intubation. Continuous efforts should still be made to improve the management of critically ill COVID-19 patients.

Furthermore, our findings highlight that the severity of hospitalized patients with influenza should not be underestimated, especially in populations at risk.

Author contribution

All authors contributed to the study conception and design. Material preparation were performed by AS and BK. Data collection were performed by SW and statistical analysis by CD. The first draft of the manuscript was written by SW. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2022.07.012.

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