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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Letter to the Editor

Medical features of COVID-19 and influenza infection: A comparative study in Paris, France

Dear Editor,

In this Journal, Zheng et al. have report the symptoms of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection -named coronavirus disease 2019 (COVID-19)- appear very similar to influenza.[1] We would like to share our findings for SARS-CoV-2 and influenza virus infections as virus co-circulation is likely to occur in future.[2] It is important to facilitate differential diagnosis. We therefore conducted a retrospective study to further explore specific features and to better characterize risk factors for severe illness.

This retrospective study included 200 inpatients from the Pitié-Salpêtrière University Hospital (Paris, France) with SARS-CoV-2 ($n=100$, 'COVID-19 group') or influenza ($n=100$, 'influenza group') laboratory-confirmed infections on respiratory specimens between January 1st-March 25th, 2020. Patients with complete baseline clinical and biological available data were consecutively included. The study was approved by the Comité Ethique de la Recherche of Sorbonne University (approval number CER 2020–44). Demographic, biological, treatment, and clinical outcome data were extracted from medical records using a standardized form. We collected date of symptom onset, comorbidities, radiographic findings upon admission, and relevant data concerning hospital courses (overall duration of stay, and transfer in intensive care unit [ICU] and supportive care ward). Clinical outcomes were monitored up to April 11th, final date of follow-up. Overweight/obesity was defined as body mass index (BMI) $>25\ kg/m^2$.

Variables are presented as 'median' (interquartile ranges; IQR) or 'number of' (%). We used the Mann-Whitney U test, $\chi 2$ test, or Fisher's exact test to compare groups, where appropriate. A two-sided $\alpha<0.05$ was considered as statistically significant. Risk factors were analyzed by logistic regression analysis. We excluded variables from univariable analysis if their between-group differences were not statistically significant. Variables for multivariable analysis were chosen if $p<0.20$ in univariable analysis and if the number of events was sufficient to calculate odds ratios (OR). Analyses were performed using GraphPad Prism v.8.

Baseline characteristics of the 200 patients included are shown in the Table 1. Overall, the median age was 60 (IQR=50–73; 42 females) and 61 (48–76; 44 females) in COVID-19 and influenza groups, respectively. Comorbidities were present in the majority of patients (>89%) with diabetes, hypertension, and overweight/obesity as most common comorbidities. However, influenza patients were more likely to have chronic pulmonary diseases ($p=0.01$). Overweight/obesity rate ($p=0.02$) and median BMI ($p=0.04$) were significantly higher in COVID-19. At the time of diagnosis, the most frequent symptoms were fever ($p=0.63$) and cough ($p=1.00$) in both groups. COVID-19 patients complained more significantly about fatigue, faintness, diarrhea, and anosmia/ageusia. Conversely, sputum production ($p=0.0001$) and nasal congestion ($p=0.02$) were reported most frequently in influenza. The frequency of patients presenting with respiratory failure were similar in both groups (around 10.0%). However, secondary respiratory failure were only observed in COVID-19 (21%; $p<0.0001$). COVID-19 patients experienced more often acute kidney failure ($p=0.048$) and pulmonary embolism ($p=0.03$). Heart congestion was more frequent in influenza ($p=0.003$). Notably, ground-glass opacities showed a trend towards higher frequency in COVID-19 patients, although not statistically significant ($p=0.06$). Conversely, pulmonary nodules were much more observed in influenza ($p=0.001$). Influenza patients had statistically higher levels of white blood cells, neutrophils, platelets, sodium, troponin, albumin than COVID-19 patients (Table 1). Both groups exhibited lymphocytopenia (around 80% of patients) (data not shown), however no significant median value difference was observed.

The median time from illness onset to admission was 4 [1–6] and 2 [0–4] days for COVID-19 and influenza, respectively ($p=0.02$, Fig. 1). COVID-19 patients more frequently required hospitalization ($p=0.001$) (data not shown). Noteworthy, the median duration of overall hospital stay was significantly longer for COVID-19 than for influenza (10 [4–17] and 4 [1–11] days, respectively, $p<0.0001$). Overall, COVID-19 patients more frequently required oxygen therapy ($p=0.002$) (Table 1). The median duration between onset of symptoms and aggravation was 7 (5–10) and 4 (2.5–6) days in COVID-19 and influenza groups, respectively ($p<0.0001$) (data not shown). Clinical worsening was linked to a higher ICU rate admission among COVID patients ($p=0.002$). Baseline characteristics, clinical courses, outcome, and duration from illness onset concerning severe infections (31 and 12 severe COVID-19 and influenza, respectively) are shown in Supplementary Tables 1–3/Fig. 1. Noteworthy, no significant difference was evidenced concerning corticosteroid use comparing both severe infection groups ($p=0.84$).

In multivariable analysis, odds of severe COVID-19 were significantly higher in individuals with chronic lung disease (OR=6.45; $p=0.009$), hypertension (3.05; $p=0.02$), and overweight/obesity (3.23; $p=0.02$). Obstructive sleep apnea and overweight/obesity were significantly associated with severe influenza in univariable analysis ($p=0.04$ and $p=0.04$, respectively) (Supplementary Tables 4–5). The mortality rate was significantly higher in COVID-19 group than in influenza group (20% *vs.* 5%; $p=0.002$). Age and diabetes appear as death risk factors in COVID-19 in multivariable analysis (OR=1.06 [95% CI=1.02–1.11]; $p=0.004$ and OR=4.50 [1.48–14.24]; $p=0.009$, respectively) (Supplementary Table 6).

To the best of our knowledge, this study is the largest case series to date comparing COVID-19 and influenza. COVID-19 patients more frequently reported dry cough, asthenia, diarrhea, anosmia/ageusia, and clinical worsening around 7 days after symp-

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Table 1
Overall baseline characteristics of patients with COVID-19 or influenza.

	COVID-19# ($n = 100$)	Influenza[#] ($n = 100$)	p value
Demographic characteristics			
Age, median (IQR) – years	60 (50–73)	61 (48–76)	0.88
Sex – no. (%)			
Female	42 (42.0)	44 (44.0)	0.89
Male	58 (58.0)	56 (56.0)	0.89
Occupation – no. (%)			
Active	44/96 (45.8)	32/85 (37.6)	0.29
Health worker	4/96 (4.2)	4/85 (4.7)	1.00
Unemployed	16/96 (16.7)	13/85 (15.3)	0.84
Retired	35/96 (36.5)	38/85 (44.7)	0.29
Comorbidity – no./total no. (%)			
None	10 (10.0)	11 (11.0)	1.00
Chronic lung disease	12 (12.0)	27 (27.0)	0.01
Cardiovascular disease	28 (28.0)	30 (30.0)	0.88
Chronic renal disease	11 (11.0)	7 (7.0)	0.46
Solid cancer	7 (7.0)	14 (14.0)	0.17
Organ transplant	5 (5.0)	5 (5.0)	1.00
HIV infection	1 (1.0)	1 (1.0)	1.00
HBV infection	1 (1.0)	1 (1.0)	1.00
Pregnancy	1 (1.0)	1 (1.0)	1.00
Hemopathy	10 (10.0)	13 (13.0)	0.66
Neurodegenerative disease	3 (3.0)	5 (5.0)	0.72
Splenectomy	2 (2.0)	2 (2.0)	1.00
Autoimmune and system disease	7 (7.0)	8 (8.0)	1.00
CV risk factors – no./total no. (%)			
Presence of CV risk factors	75/98 (76.5)	66 (66.0)	0.12
Diabetes	24/98 (24.5)	16 (16.0)	0.16
Dyslipidemia	15/98 (15.3)	8 (8.0)	0.12
Hypertension	37/98 (37.8)	38 (38.0)	1.00
Overweight/obesity	40/98 (40.8)	25 (25.0)	0.02
Obstructive sleep apnea	8/98 (8.2)	13 (13.0)	0.36
Current smoker	10/98 (10.2)	11 (11.0)	1.00
Former smoker	15/98 (15.3)	18 (18.0)	0.70
Chronic alcoholism	4/98 (4.1)	5 (5.0)	1.00
BMI[‡]			
Median (IQR)	27.3 (23.8–32.4)	24.8 (21.7–28.6)	0.04
Symptoms – no./total no. (%)			
Fever	92 (92.0)	89 (89.0)	0.63
Fatigue	63/99 (63.6)	39 (39.0)	0.0006
Myalgia	36/99 (36.4)	24 (24.0)	0.06
Dyspnea	45 (45.0)	51 (51.0)	0.48
Cough	81 (81.0)	80 (80.0)	1.00
Productive sputum	12 (12.0)	36 (36.0)	0.0001
Nasal congestion	8/96 (8.3)	21 (21.0)	0.02
Acute respiratory failure	31 (31.0)	9 (9.0)	0.0002
On admission	10 (10.0)	9 (9.0)	1.00
Secondary failure	21 (21.0)	0	<0.0001
Headache	25/99 (25.3)	20 (20.0)	0.40
Nausea	19/97 (19.6)	10 (10.0)	0.07
Vomiting	21/97 (21.6)	11 (11.0)	0.053
Diarrhea	25/97 (25.8)	13 (13.0)	0.03
Anosmia/ageusia	7 (7.0)	0	0.01
Faintness	12/99 (12.1)	3 (3.0)	0.02
Chest pain	21 (21.0)	16 (16.0)	0.47
Chest x-rays and CT-findings – no./total no. (%)			
Abnormalities on chest radiograph	26/36 (72.2)	24/49 (49.0)	0.04
Bronchial syndrome	1/36 (2.8)	6/49 (12.2)	0.23
Interstitial syndrome	11/36 (30.6)	2/49 (4.1)	0.001
Alveolar syndrome	5/36 (13.9)	5/49 (10.2)	0.74
Lobar consolidation	5/36 (13.9)	11/49 (22.4)	0.41
Abnormalities on CT chest	34/34 (100.0)	21/22 (95.0)	0.39
Ground-glass opacities	29/34 (85.3)	13/22 (59.1)	0.06
Pulmonary nodules	3/34 (8.8)	11/22 (50.0)	0.001
Lobar consolidation	16/34 (47.1)	11/22 (50.0)	1.00
Laboratory findings [¤] (unity; normal range) – Median (IQR)[§]			
White-cell count (G/L; 4.00 – 10.00)	5.88 (4.41–7.68)	6.72 (5.15–9.42)	0.01
Neutrophils (G/L; 2.00– 7.50)	4.11 (2.99–5.65)	5.06 (3.43–7.25)	0.02
Lymphocytes (G/L; 1.50–4.00)	1.08 (0.68–1.41)	0.89 (0.66–1.35)	0.41
Hemoglobin (g/dL; 13.0–17.5)	13.6 (12.2–14.5)	13.2 (11.6–14.3)	0.29
Platelets (G/L; 150–400)	179 (145–225)	199 (168–239)	0.04
Fibrinogen (g/L; 2–4)	5.5 (4.2–6.7)	5.4 (4.5–6.4)	0.92
Activated partial thromboplastin time (s; <1.20)	1.16 (1.10–1.30)	1.14 (1.04–1.29)	0.44
Prothrombin time (%; 70–120)	98 (86–100)	91 (76–100)	0.08

(*continued on next page*)

Table 1 (*continued*)

	COVID-19# ($n=100$)	Influenza[#] ($n=100$)	p value
Sodium (U/L; 136–155)	137 (135–139)	138 (136–140)	0.006
Potassium (U/L; 3.4–5.1)	4.1 (3.8–4.6)	4.0 (3.7–4.4)	0.09
Chloride (U/L; 98–107)	99 (97–102)	100 (97–103)	0.35
Bicarbonates (mmol/L; 22 – 26)	24 (22–26)	25 (23–27)	0.07
Troponin (ng/L; <0.60)	9.2 (6.5–22.4)	34.4 (8.8–72.2)	0.007
Albumin (g/L; 35–52)	30 (27–33)	37 (33–39)	0.04
C-reactive protein (mg/L; <5.0)	47.37 (15.42–87.46)	41.44 (15.25–82.05)	0.55
Serum creatinine (µmol/L; 62–106)	86 (70–117)	87 (70–108)	0.75
Total bilirubin (µmol/L; 2–17)	8 (5–12)	8 (5–12)	0.99
Aspartate aminotransferase (U/L; 20–32)	45 (34–76)	34 (29–49)	0.02
Alanine aminotransferase (U/L; 16– 35)	31 (22–59)	26 (20–42)	0.21
γ -glutamyltransferase (U/L; 12–55)	44 (26–101)	32 (21–54)	0.08
Creatine kinase (U/L; <190)	178 (109–473)	117 (65–378)	0.42
Lactate dehydrogenase (U/L; 135–215)	397 (305–544)	298 (248–383)	0.04
Arterial lactates (mmol/L; 0.5–1.8)	1.0 (0.7–1.4)	1.2 (0.9–1.4)	0.09
Procalcitonin (µg/L; <0.10)	0.12 (0.08–0.27)	0.13 (0.07–0.36)	0.74
Arterial blood pH (7.35–7.45)	7.45 (7.42–7.48)	7.43 (7.40–7.78)	0.33
Treatments – no./total no. (%)			
Oseltamivir	11/95 (11.6)	45/97 (46.4)	<0.0001
Any antibiotics	77/98 (78.6)	58/97 (59.8)	0.005
Amoxicillin/Clavulanic acid	40/98 (40.8)	33/97 (34.0)	0.37
Cephalosporin	48/98 (49.0)	21/97 (21.6)	<0.0001
Oxygen therapy	65 (65.0)	42/99 (42.4)	0.002
Complications – no./total no. (%)			
Pulmonary embolism	6 (6.0)	0	0.03
Acute kidney failure	17 (17.0)	7 (7.0)	0.048
Myocarditis	0	2 (2.0)	0.50
Heart congestion	2 (2.0)	14 (14.0)	0.003
Heart rhythm disorder	7 (7.0)	2 (2.0)	0.17
Clinical outcomes at data cutoff no./total no. (%)			
Admitted in ICU	31 (31.0)	12 (12.0)	0.002
Discharged	75 (80.0)	94 (94.0)	0.0003
Death	20 (20.0)	5 (5.0)	0.002
Remained in hospital	5 (5.0)	1 (1.0)	0.21

[#] Denominators of patients included in this analysis are shown if they differed from the overall numbers in the respective group.
[‡] Data regarding BMI medians were available for 56 and 48 patients in COVID-19 and influenza groups, respectively.
[¤] For each biological variable, the number of digits after decimal point depends on technical precision.
[§] Biological data from patients with COVID-19 and Influenza infection were available for hematological values in 100 patients, fibrinogen in 44 and 46 patients, sodium and potassium in 96 and 98 patients, chloride in 96 and 95 patients, bicarbonates in 79 and 85 patients, troponin in 32 and 35 patients, albumin in 7 and 24 patients, C-reactive protein in 64 and 73 patients, serum creatinine in 98 and 98 patients, total bilirubin in 44 and 65 patients, aspartate aminotransferase in 51 and 70 patients, alanine aminotransferase in 51 and 71 patients, γ-glutamyltransferase in 48 and 69 patients, creatine kinase in 23 and 34 patients, lactate dehydrogenase in 21 and 34 patients, arterial lactates in 51 and 36 patients, procalcitonin in 60 and 74 patients, arterial blood pH in 48 and 35 patients, respectively.BMI: body mass index; COVID-19: coronavirus disease 2019; CT: computed tomography; CV: cardiovascular; HBV: hepatitis B virus; HIV: human immunodeficiency virus; ICU: intensive care unit; IQR: interquartile range; no.: number of. $p<0.05$ was considered to be statistically significant.

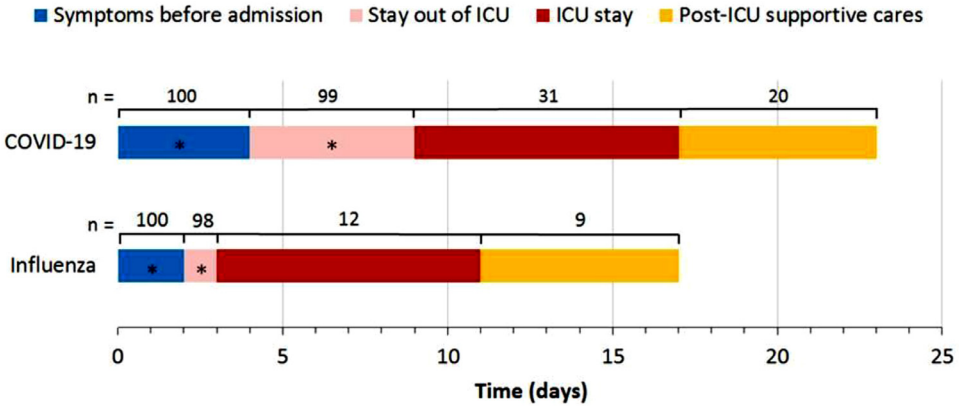

Fig. 1. Duration from illness onset and clinical courses in COVID-19 ($n=100$) and influenza groups ($n=100$)
Histograms represent duration in days of symptoms before admission (blue), stay out of ICU (light pink), stay in ICU for severe cases (red), and in post-ICU supportive care wards (yellow). n represent the number of concerned patients according to type of hospitalization. The median time from illness onset (*i.e.* before admission) to admission was 4 days [IQR: 1–6] and 2 days [IQR: 0–4] for COVID-19 and influenza patients, respectively ($p=0.02$). The median time of hospitalization out of ICU was 5 days [IQR: 1–10] and 1 day [IQR: 0–8] for COVID-19 and influenza patients, respectively ($p=0.0112$). Overall, 20 and 5 patients died in both groups, respectively. Among ICU-hospitalized patients (31 COVID-19 and 12 influenza), 11 and 3 patients died in both groups, respectively. * symbolizes significant differences between COVID-19 and influenza groups. COVID-19: coronavirus disease 2019; ICU: intensive care unit. $p<0.05$ was considered to be statistically significant.

tom onset, as previously described[3–6]. As previously reported, radiologic findings showed that ground-glass opacity was more common in COVID-19,[3] however it could be also observed during influenza.[5,6] We reported more severe cases requiring oxygenation therapy, a higher death rate, and a longer hospital stay in COVID-19 group. Moreover, COVID-19 patients also experienced disease aggravation around 7 days post-symptom onset, as previously reported.[3,6] Both infection may evolve to respiratory failure,[3,5,6] however, COVID-19 patients developed preferentially secondary respiratory failure. Interestingly, inflammation marker levels were significantly higher in severe COVID-19 cases. It is well established that SARS-CoV-2 triggers an excessive harmful proinflammatory response[7] promoting thrombotic events as pulmonary embolism.[8] In our study, pulmonary embolism was only reported during COVID-19 ($p = 0.03$). COVID-19 and influenza patients commonly share overweight/obesity as risk factor for severe infection.[9] As previously reported, pre-existing hypertension and diabetes were additionally associated with a higher risk to develop severe COVID-19. Similarly, our study also confirmed older age and diabetes as major contributing death risk factors in COVID-19.[3,10] To conclude, we described similarities but also differences between COVID-19 and influenza, thereby providing some guidance for healthcare management.

Contributors

HF and MP had the idea for and designed the study. HF, MP, CC, and SB and had full access to the collected data and take responsibility for the integrity of the data and the accuracy of the data analysis. PH, CEL, MD, and VP assessed the accuracy of clinical data. HF, CC, and AJ processed statistical data. HF, CC, MP, DB, and SB drafted the paper. All authors critically revised the manuscript for intellectual content and gave final approval for the submitted version.

Declaration of Competing Interest

We declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2020.08.017.

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