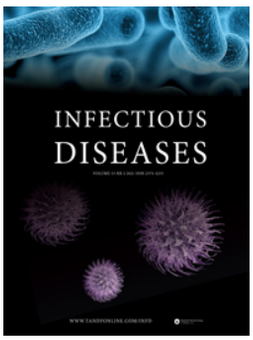

Infectious Diseases

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/infd20

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To cite this article: Raija Auvinen , Hanna Nohynek , Ritva Syrjänen , Jukka Ollgren , Tuija Kerttula , Jarkko Mäntylä , Niina Ikonen , Raisa Loginov , Anu Haveri , Satu Kurkela & Kirsi Skogberg (2021) Comparison of the clinical characteristics and outcomes of hospitalized adult COVID-19 and influenza patients – a prospective observational study, Infectious Diseases, 53:2, 111-121, DOI: 10.1080/23744235.2020.1840623

To link to this article: https://doi.org/10.1080/23744235.2020.1840623

Taylor & Francis
Taylor & Francis Group

INFECTIOUS DISEASES,
2021; VOL. 53,
NO. 2, 111–121

https://doi.org/10.1080/23744235.2020.1840623

ORIGINAL ARTICLE

Comparison of the clinical characteristics and outcomes of hospitalized adult COVID-19 and influenza patients – a prospective observational study

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ABSTRACT

Background: We compared the clinical characteristics, findings, and outcomes of hospitalized patients with coronavirus disease 2019 (COVID-19) or influenza to detect relevant differences.

Methods: From December 2019 to April 2020, we recruited all eligible hospitalized adults with respiratory infection to a prospective observational study at a tertiary care hospital in Finland. Influenza and SARS-CoV-2 infections were confirmed by RT-PCR. Follow-up lasted for 3 months from admission.

Results: We included 61 patients, of whom 28 were COVID-19 and 33 influenza patients with median ages of 53 and 56 years. Majority of both COVID-19 and influenza patients were men (61% vs. 67%) and had at least one comorbidity (68% vs. 85%). Pulmonary diseases and current smoking were less common among COVID-19 than influenza patients (5 [18%] vs. 15 [45%], $p=.03$ and 1 [4%] vs. 10 [30%], $p=.008$). In chest X-ray at admission, ground-glass opacities (GGOs) and consolidations were more frequent among COVID-19 than influenza patients (19 [68%] and 7 [21%], $p<.001$). Severe disease and intensive care unit (ICU) admission occurred more often among COVID-19 than influenza patients (26 [93%] vs. 19 [58%], $p=.003$ and 8 [29%] vs. 2 [6%], $p=.034$). COVID-19 patients were hospitalized longer than influenza patients (six days [IQR 4-21] vs. 3 [2–4], $p<.001$).

Conclusions: Bilateral GGOs and consolidations in chest X-ray may help to differentiate COVID-19 from influenza. Hospitalized COVID-19 patients had more severe disease, required longer hospitalization and were admitted to ICU more often than influenza patients, which has important implications for public health policies.

KEYWORDS
COVID-19
influenza
characteristics
hospitalized
adult
outcome

ARTICLE HISTORY
Received 30 June 2020
Revised 6 October 2020
Accepted 16 October 2020

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Supplemental data for this article can be accessed here.

Introduction

Coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is currently causing such dramatic effects on health, economy and society as a whole that seasonal influenza, disruptive as it is, may seem to pale in comparison. However, several influenza pandemics have swept the globe and pandemic preparedness plans now used for COVID-19 are based on lessons from influenza. Understanding the differences in their epidemiology and clinical course is crucial for planning appropriate control measures for future COVID-19 mitigation.

COVID-19 first emerged in Wuhan, China, in December 2019 and spread to a worldwide pandemic by March 2020 [1–4]. By 27 September 2020, over 32.7 million cases and 991,000 deaths had been reported globally [5]. In comparison, the pandemic A (H1N1) virus caused an estimated 151,700–575,500 respiratory and cardiovascular deaths during the first 12 months of the latest influenza pandemic of 2009–2010 while seasonal influenza is estimated to be responsible for 291,243–645,832 respiratory deaths annually [6,7].

The clinical presentations of COVID-19 and influenza vary from mild respiratory tract infection to severe viral pneumonia leading to acute respiratory distress syndrome (ARDS) and death [3,8–12]. In the largest study on COVID-19 to date, 80.9% of cases were considered mild, 13.8% severe and 4.7% critical [8]. A proportion of SARS-Cov-2 infections appear to be asymptomatic yet contagious [13,14]. Transmission can occur 1–2 days before symptom onset in both influenza and COVID-19 and recent studies suggest that even earlier transmission is possible in COVID-19 [15–17]. Fever and cough are the most common symptoms in both infections while fatigue, myalgia, headache and dyspnoea may be present [3,8–10,12,18,19]. Gastrointestinal (GI) symptoms occur in almost 20% of COVID-19 and 3–31% of influenza patients [20,21]. Olfactory and taste disorders are associated with COVID-19 [22].

Well-known high-risk groups of influenza include elderly, pregnant women, under 2-year-old children and people with pre-existing comorbidities [12,19]. Established risk factors for the development of severe infection, ARDS and death in COVID-19 include older age, male sex and comorbidities [8,10,11,18,23–25]. While 80% of deaths occurred among under 65-year-olds during the 2009 A (H1N1) influenza pandemic, the mortality caused by COVID-19 has been highest among 80+-year-olds [6,8]. In case of seasonal influenza, highest excess respiratory mortality rates occur among people aged 75 years of older [7].

In Finland, the first cases of COVID-19 appeared in the Hospital District of Helsinki and Uusimaa in late February and since 17 March 2020 a nationwide lockdown was put in place (Figure 1). Our prospective population-based influenza study was already recruiting

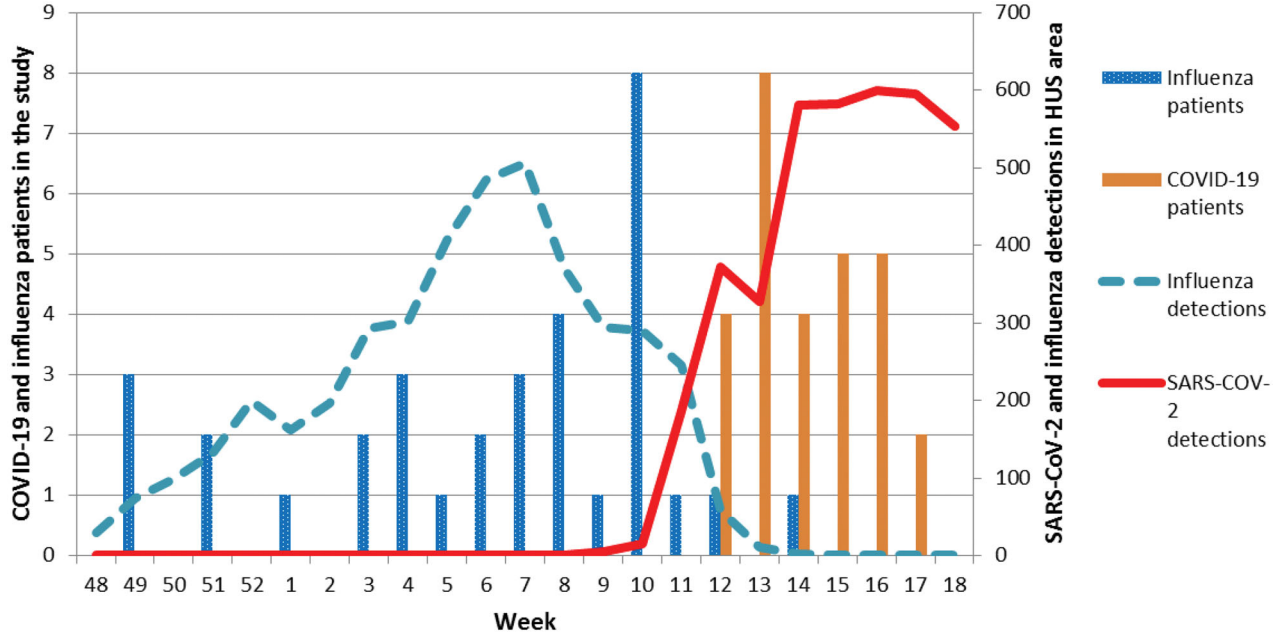

Figure 1. Weekly COVID-19 and influenza cases in the study (bars) and in the whole Hospital District of Helsinki and Uusimaa (lines) between December 2019 and April 2020. Influenza and SARS-CoV-2 detections in the Hospital District of Helsinki and Uusimaa (HUS area) were obtained from the National Infectious Diseases Register (NIDR). Since 17th of March (week 12), nationwide lockdown was in place.

hospitalized adult patients with severe acute respiratory infection (SARI), which gave us the opportunity to enrol COVID-19 patients since the beginning of the outbreak. We compared the clinical characteristics and outcomes of hospitalized adult COVID-19 and influenza patients to provide information for clinical diagnostics and public health strategies used in COVID-19 mitigation.

Materials and methods

Study design

We conducted a prospective observational study at the HUS Helsinki University Hospital, Jorvi Hospital, Espoo, Finland together with the Finnish Institute for Health and Welfare (THL) as a part of the international DRIVE collaboration (www.drive-eu.org). The study was primarily focused on estimating influenza vaccine effectiveness and disease burden but its objectives included collecting data on other respiratory pathogens for the needs of national surveillance.

The study was approved by the Local Ethics Committee of the HUS Helsinki University Hospital. Appropriate study permits were obtained from the University Hospital, THL and the municipalities involved. Informed consent was obtained from the patients or the next of kin of those critically ill.

Study population

Jorvi Hospital, which is a tertiary care hospital of the HUS Helsinki University Hospital, provides specialized care for the 339,000 residents of the cities of Espoo, Kauniainen and Kirkkonummi. All community-dwelling adult (18+-year-old) SARI patients admitted to the hospital were interviewed by a study nurse and recruited to the study if they fulfilled the eligibility criteria listed in the study protocol and gave their informed consent [26]. A SARI patient was defined as a hospitalized person with at least one systemic symptom (fever or feverishness, malaise, headache or myalgia) or deterioration of general condition (asthenia or loss of weight or anorexia or confusion or dizziness) and at least one respiratory symptom (cough, sore throat, shortness of breath) at admission or within 48 h after admission. Initially, only patients with symptom onset within the last seven days were eligible; however, during the COVID-19 epidemic, SARI patients were recruited symptom onset notwithstanding to include all COVID-19 patients. Patients were followed up for 3 months from admission.

Data collection

Data were obtained from patient interviews and electronic medical records by the study nurses and physicians. Comorbidities, smoking, influenza vaccinations, SARI symptoms, triage vitals, routine laboratory test results and radiological images, intensive care unit (ICU) admission, invasive mechanical ventilation and outcomes were collected. Overnight hospitalizations during the past 12 months were collected and verified from the Care Register for Health Care (HILMO). The severity of chronic conditions was assessed using the McCabe score (1 = non-fatal, 2 = fatal in 1–4 years and 3 = fatal within a year). National Early Warning Score 2 (NEWS2) at admission was calculated. The severity of infection was classified as in WHO interim guidance for COVID-19 [27]. In short, the categories were mild disease (uncomplicated upper respiratory tract viral infection), pneumonia (no signs of severe pneumonia nor need for supplemental oxygen), severe pneumonia (respiratory rate >30 breaths/min, severe respiratory distress or SpO2 $\leq 93\%$ on room air) and ARDS (as defined by the Berlin Definition). In case of readmission to the hospital for the same reason within three days of hospital discharge, the hospitalization was reported as one episode.

Routine laboratory test results at admission and highest or lowest values during hospitalization and radiological imaging were extracted. Chest X-ray images were interpreted by a radiologist unaware of the microbiologic diagnosis of the patients. Anaemia was defined as haemoglobin <134 g/L for men and <117 g/L for women, leukopenia as white blood cells $<3.4 \times 10^9$/L and lymphopenia as blood lymphocytes $<1.2 \times 10^9$/L and thrombocytopenia as platelet count $<150 \times 10^9$/L.

Laboratory testing for respiratory pathogens

Respiratory samples taken from nasopharynx, oropharynx or trachea for routine diagnostics were tested at the Helsinki University Hospital Laboratory (HUSLAB). Influenza testing was performed using Xpert®Xpress Flu/RSV assay (Cepheid, Sunnyvale, CA). For the detection of SARS-CoV-2 RNA, the specimens were subjected to one the following three methods: (1) the real-time laboratory-developed SARS-CoV-2 RT-PCR based on Corman et al., 2020; (2) Roche Molecular Systems cobas® SARS-Cov-2 assay (Branchburg, NJ, USA); (3) the Amplidiag®COVID-19 assay (Mobidiag, Helsinki, Finland). Influenza virus subtypes or lineages were defined at the THL Expert Unit for Microbiology. If influenza testing

was not done at HUSLAB on clinical grounds, it was performed at THL with the exception of seven COVID-19 patients, whose samples could not be located. Since 13 March 2020, all patients hospitalized with a suspected or diagnosed respiratory infection were tested for SARS-CoV-2 at HUSLAB according to the local testing strategy; before that, testing was conducted based on individual consideration e.g. travel history to an epidemic area or known exposure to COVID-19. However, as a part of this study, all samples tested for influenza at THL were also tested for SARS-CoV-2.

Statistical analysis

Categorical (described as proportions) and continuous (described as medians and interquartile ranges) variables were compared using Fisher's exact test and Mann–Whitney's *U*-test, respectively. Statistical analyses were performed using SPSS version 26.0 (IBM SPSS Statistics®, Armonk, NY) and Stata 16.1 (StataCorp, College Station, TX). To analyse predisposing factors predicting the duration of hospitalization, we did a multivariable Cox regression analysis for the hazard of discharge from the hospital. We entered COVID19, age, sex, BMI and comorbidities (including anaemia, cancer, cardiovascular disease, diabetes, hypertension, immunosuppression, kidney disease, liver cirrhosis, neurological diseases, pulmonary diseases, rheumatic diseases and stroke) into the Cox analysis and used backward selection using Akaike information criterion (AIC) to choose our final model. The predictors chosen in the final model were COVID19, age, BMI and diabetes.

Results

Between 2 December 2019 and 30 April 2020, we recruited altogether 213 eligible SARI patients, of whom those 61 patients positive for either SARS-CoV-2 (28) or influenza (33) by RT-PCR were included in this study. All except two influenza patients were recruited before week 12, whereas all COVID-19 patients were recruited from week 12 onwards (Figure 1). Of the influenza patients, 29 (88%) were positive for influenza A (H1N1) pdm09, two (6%) were positive for influenza A (H3N2) and two (6%) for influenza B/Victoria. All influenza patients were tested for SARS-CoV-2 and 21 (75%) of COVID-19 patients were tested for influenza and no co-infections were found. The median ages of COVID-19 and influenza patients were 53 (range 18–81) and 56 (19–87), and the majority were men (17 [61%] vs. 22 [67%]) (Table 1).

At least one comorbidity was present in 19 (68%) of COVID-19 and 28 (85%) of influenza patients (Table 1). In COVID-19 patients, the most common comorbidities were obesity (11, 41%) and hypertension (8, 29%) whereas in influenza patients hypertension and pulmonary diseases were most prevalent (15, 45%, respectively). Pulmonary diseases and current smoking were significantly less common among COVID-19 than influenza patients (5 [18%] vs. 15 [45%], $p=.03$ and 1 [4%] vs. 10 [30%], $p=.008$). Fatal comorbidities (McCabe score 2 or 3) were slightly less prevalent among COVID-19 than influenza patients (2 [7%] and 7 [21%], $p=.160$). None of the COVID-19 patients had been previously hospitalized during the last 12 months compared with nine (27%) of influenza patients ($p=.003$). No difference was observed in the proportion of influenza vaccinated for 2019–2020 season among COVID-19 and influenza patients (12/26 [46%] vs. 16/33 [48%], $p=1.00$). The vaccination status of two COVID-19 patients remained unknown. The data showed no difference in the duration of hospitalization, need for ICU admission or outcome at 30 days from admission between influenza vaccinated or unvaccinated patients among either COVID-19 or influenza patients (Supplement 1).

At admission, the clinical picture of COVID-19 was similar to that of influenza with reported fever and cough being the most common symptoms. Headache was more common among COVID-19 patients (22/25, 85% vs. 16/31, 52%, $p=.004$). COVID-19 patients were hospitalized on average on day 10 of symptoms compared with day 3 for influenza patients (Table 2).

The laboratory results of COVID-19 and influenza patients that differed significantly at admission included leukocyte and platelet counts and alanine aminotransferase (ALAT) (Table 2). CRP values were similar at admission but rose significantly higher in COVID-19 patients during hospitalization. ALAT was higher among COVID-19 patients than influenza patients both at admission and during hospitalization. Blood cultures were taken from 23/28 of COVID-19 and 32/33 of influenza patients and were negative.

In chest X-rays at admission, ground-glass opacities (GGOs) and consolidations were observed significantly more often in the images of COVID-19 than influenza patients (19 [68%] and 7 [21%], $p<.001$), whereas linear opacities were more common among influenza patients (Table 2). Typically, the GGO and consolidations present

Table 1. Characteristics of COVID-19 and influenza patients.

	COVID-19		Influenza		
Characteristics	*N*	%	*N*	%	*p* Value
Total	28	100	33	100	
Age					
Median (IQR) (range)	53 (44–61) (18–81)	N/A	56 (38–73) (19–87)	N/A	.465
18–64	23	82	21	64	.154
65 or over	5	18	12	36	
Sex					
Female	11	39	11	33	.790
Male	17	61	22	67	
Comorbidities					
Anaemia	1	4	4	12	.363
Cancer	2	7	5	15	.437
Cardiovascular disease	4	14	9	27	.347
Coronary artery disease	3	11	3	9	1.000
Congestive heart failure	0	0	4	12	.118
Other	1	4	3	9	N/A
Diabetes	5	18	9	27	.543
Hypertension	8	29	15	45	.197
Immunosuppression	0	0	4	12	.118
Due to medication	0	0	4	12	.118
Kidney disease	1	4	3	9	.618
Liver cirrhosis	0	0	1	3	1.000
Neurological diseases	0	0	4	12	.118
Obesity (BMI $\geq$ 30)	11/27	41	12	36	.793
BMI $\geq$ 35	4/27	15	5	15	1.000
Pulmonary disease (any)	5	18	15	45	**.030**
Asthma	4	14	9	27	.347
Chronic obstructive pulmonary disease	1	4	5	15	.205
Obstructive sleep apnoea	1	4	5	15	.205
Other	0	0	2	6	N/A
Rheumatic disease	0	0	3	9	.243
Stroke	0	0	2	6	.495
No comorbidities	9	32	5	15	.138
McCabe score					
1	26	93	26	79	.269
2 or 3	2	7	7	21	
Smoking					
Never	18	64	15	45	**.011**
Ex-smoker	9	32	8	24	
Current smoker	1	4	10	30	
Hospital admissions in the last 12 months					
Yes	0	0	9	27	**.003**
Influenza vaccination in 2019/2020					
Yes	12/26	46	16	48	1.000

BMI: body mass index.
McCabe score, 1: non-fatal, 2: fatal in 1–4 years and 3: fatal within a year. Data are presented as no. and % or as medians with interquartile ranges (IQR). If data are missing, the proportion of patients with the information available is marked as the denominator.
Values below .05 are shown bolded as that is the standard limit for statistical significance.

in the images of COVID-19 patients were bilateral and peripheral or basal (Figure 2). No findings were observed in five (18%) of COVID-19 and 12 (36%) of influenza patients (p=.154). Three of the five COVID-19 patients with no radiological findings at admission developed consolidations in chest X-ray within one week.

Severe disease (severe pneumonia or ARDS) and ICU admission were significantly more common among COVID-19 patients than influenza patients (26 [93%] vs. 19 [58%], p=.003 and 8 [29%] vs. 2 [6%], p=.034) (Table 3). Notably, all patients admitted to the ICU were men. The median age of the eight COVID-19 patients admitted to the ICU was 60.5 (range 52–61) while the two influenza patients were 38 and 62 years old. All eight COVID-19 patients developed ARDS and were mechanically ventilated compared with one of the two influenza patients and their median stay at the ICU was 20 (range 11–41) compared with 9.5 (3–16) days. Two COVID-19 patients were at the ICU twice and both episodes were included in the total duration of their ICU stay.

As of 5 June 2020, 60 of the 61 patients had been discharged from Jorvi Hospital and one COVID-19 patient had died. COVID-19 patients were hospitalized significantly longer than influenza patients (six days [IQR 4–21] vs. three days [2–4], p<.001) (Table 3, Figure 3). To further examine whether there were other factors predicting the duration of hospitalization besides COVID-19, we did a multivariable Cox regression

Table 2. Characteristics and laboratory and radiological findings of COVID-19 and influenza patients.

	COVID-19		Influenza		
Characteristics and findings	No.	%	No.	%	*p* Value
Total	28	100	33	100	
Days from symptom onset to hospitalization					
Duration of symptoms at hospitalization, median days (IQR) (range)	10 (7–12) [1–23]	N/A	3 (2–5) [1–8]	N/A	**<.001**
0–3 days	4	14	25	76	
4–7 days	6	21	8	24	
≥8 days	18	64	N/A	N/A	
Reported SARI symptoms					
Fever ≥38	28	100	33	100	N/A
Headache	22/25	88	16/31	52	**.004**
Myalgia	15/25	60	15/31	48	.430
Deterioration of general condition	27	96	32	97	1.000
Cough	27	96	30	91	.618
Sore throat	8/24	33	17/32	53	.179
Dyspnoea	26	93	29	88	.678
Sudden onset	11/23	48	19/31	61	.410
Clinical characteristics at admission, median (IQR)					
Temperature	38.4 (37.5–38.9)	N/A	38.4 (37.6–39.4)	N/A	.482
Fever ≥38	17	61	22	67	.790
Respiratory rate	22 (18–28)	N/A	20 (18–24)	N/A	.401
Oxygen saturation on room air	93 (90–94)	N/A	94 (90–96)	N/A	.616
NEWS2 score (IQR) [range]	5 (3–6)[0–8]	N/A	4 (2–6)[0–10]	N/A	.423
Laboratory results at admission, median (IQR)					
Haemoglobin, g/L (ref. range 134–167 men, 117–155 women)	142 (129–149)	N/A	134 (123–145)	N/A	.078
Anaemia	4	14	10	30	.222
Leukocyte count, $\times 10^9$/L (reference range 3.4–8.2)	5.1 (4.0–6.3)	N/A	6.7 (5.4–10.9)	N/A	**.002**
Leukopenia	3/27	11	1	3	.318
Leukocytosis	3/27	11	13	39	**.019**
Platelet count, $\times 10^9$/L (150–360)	201 (129–269)	N/A	182 (164–218)	N/A	.538
Thrombocytopenia $<150 \times 10^9$/L	11	39	4	12	**.019**
C-reactive protein, mg/L (<4) (IQR) [range]	55 (39–119) [12–186]	N/A	57 (28–117) [7–214]	N/A	.965
Creatinine, μmol/L (60–100 men, 50–90 women) (IQR) [range]	75 (57–87) [42–740]	N/A	77 (66–88) [40–557]	N/A	.406
Alanine aminotransferase, U/L (<50 men, <30 women) (IQR) [range]	42 (30–75) [19–127]	N/A	23 (18–47) [12–123]	N/A	**.011**
Laboratory findings during hospitalization, median (IQR)					
Anaemia	7	25	11	33	.578
Leukopenia	6	21	4	12	.490
Lymphopenia	18/25	72	11/19	58	.357
Thrombocytopenia $< 150 \times 10^9$/L	11	39	9	27	.414
Highest C-reactive protein, mg/L [range]	159 (90–239) [12–410]	N/A	79 (42–171) [8–289]	N/A	**.019**
Highest creatinine, μmol/L [range]	76 (60–89) [45–740]	N/A	80 (66–91) [47–731]	N/A	.482
Highest alanine aminotransferase, U/L [range]	66 (42–190) [19–457]	N/A	23 (18–52) [12–140]	N/A	**<.001**
Radiological findings in chest X-ray at admission					
No findings	5	18	12	36	.154
Linear opacities	4	14	14	42	**.024**
Bilateral basal	3	11	14	42	
Bilateral peripheral	1	4	0	0	
Ground glass opacities/consolidation	19	68	7	21	**<.001**
Unilateral or local	0	0	2	6	
Bilateral basal	8	29	4	12	
Bilateral perihilar	0	0	1	3	
Bilateral peripheral	9	32	0	0	
Bilateral diffuse	2	7	0	0	

SARI: severe acute respiratory infection.
Data are presented no. and % or as medians with interquartile ranges (IQR). If data are missing, the proportion of patients with the information available is marked as the denominator when applicable. Of the SARI symptoms, none of the patients reported malaise and all had fever, thus malaise and feverishness were left out of the table. Leukocyte count was missing from one COVID-19 patient at admission. ALAT was taken only from 25/28 of COVID-19 and 19/33 of influenza patients. Values below .05 are shown bolded as that is the standard limit for statistical significance.

analysis. The predictors associated with a longer duration of hospitalization were COVID-19 (hazard ratio [HR] 0.221, 95% CI 0.118, 0.416, $p<.001$), age (HR 0.972, CI 0.955, 0.990, $p=.002$), BMI (HR 0.950, CI 0.916, 0.986, $p=.006$) and diabetes (HR 0.539, CI 0.272, 1.066, $p=.076$). At 3 months from admission, two (7%) COVID-19 and six (18%) influenza patients had been readmitted to the hospital at least once ($p=.269$). During the three months following admission, one terminally ill influenza patient died whereas no additional COVID-19 patients died.

Discussion

Our study is one of the first prospective studies comparing the clinical characteristics and outcomes of hospitalized adult patients with COVID-19 or seasonal influenza

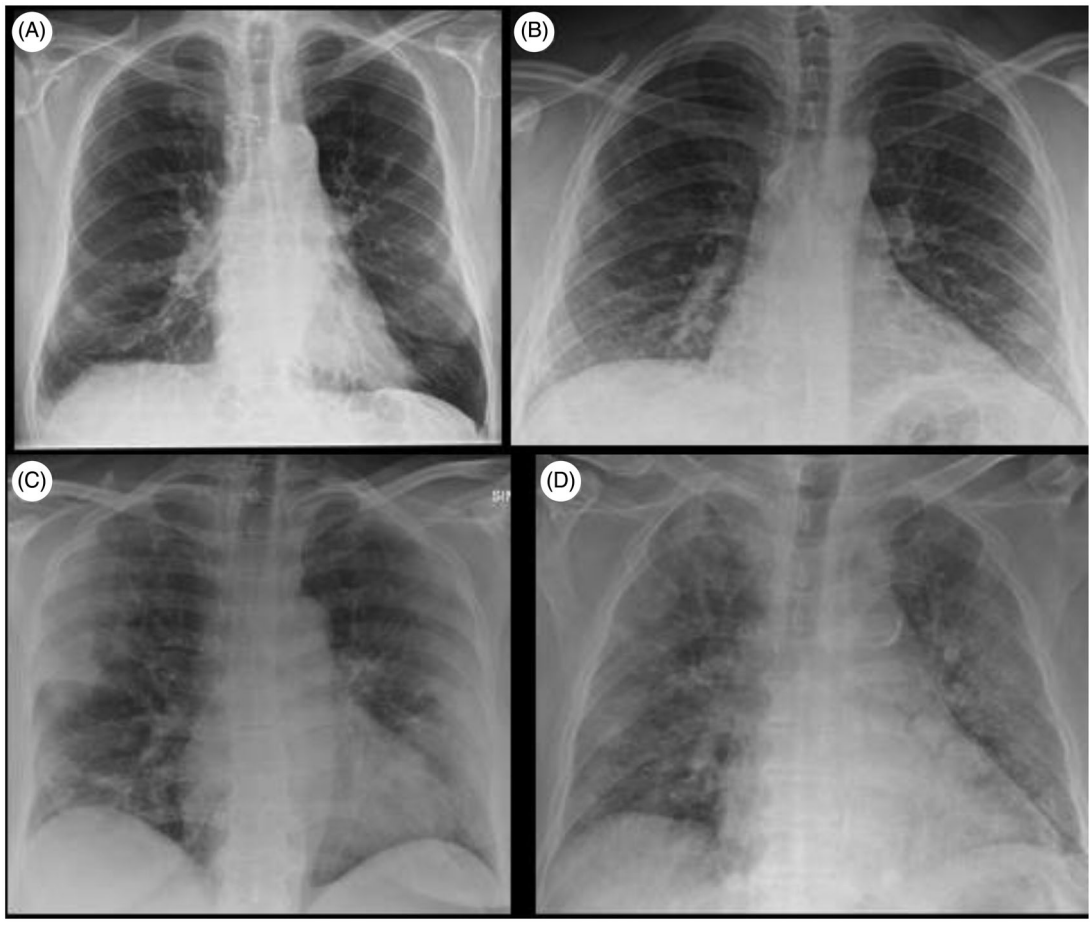

Figure 2. Chest X-rays of COVID-19 and influenza patients at admission. (A) An 88-year-old man, influenza, day 6 of symptoms: bilateral basal linear opacities. (B) A 28-year-old man with COVID-19, day 9 of symptoms, bilateral basal ground-glass opacities (GGOs). (C) A 51-year-old woman with COVID-19, day 13 of symptoms: bilateral peripheral GGO and consolidations. (D) A 68-year-old man with COVID-19, the third day of symptoms: bilateral diffuse GGO and consolidations.

with clinical pictures ranging from mild disease to ARDS. We observed that pulmonary diseases, smoking and previous hospital admissions were less common among COVID-19 than influenza patients. At admission, their symptoms, disease severity and laboratory findings were similar but chest X-ray findings differed. COVID-19 patients developed a more serious disease and required longer hospitalization.

COVID-19 patients had no previous hospitalizations during the past 12 months, 32% had no comorbidities compared with 15% of influenza patients and their comorbidities were less serious based on their McCabe score; however, the latter two findings did not reach statistical significance. Together these findings imply that COVID-19 patients were previously healthier than influenza patients. This is consistent with a recent study by Zayet et al., where they compared adult outpatients and inpatients with COVID-19 or influenza in a French hospital and found that 48.6% of COVID-19 and 23.4% of influenza patients had no comorbidities and the Charlson comorbidity index of COVID-19 patients was lower; however, the numbers are not entirely comparable as their study included outpatients [28].

The lower prevalence of pulmonary diseases among COVID-19 patients was not limited to smoking-related COPD but was also seen for asthma and obstructive sleep apnoea, which were all more prevalent among influenza patients (Table 1). Whether this relates to influenza viruses affecting bronchi more than SARS-CoV-2 for example due to different viral receptors (ACE2 for SARS-CoV-2 and sialic acid-containing molecules for influenza) and viral tropism, remains a subject for further investigation [1,12,29].

Influenza patients were hospitalized earlier after symptom onset than patients with COVID-19 as in previous publications [28,30]. Fever, cough and dyspnoea were the most common symptoms in both groups. Headache was significantly more common among COVID-19 than influenza patients as also previously reported [28]. Differences in laboratory findings at admission were not remarkable enough to enable differential diagnostics based on laboratory findings alone. As

Table 3. Outcomes of COVID-19 and influenza patients.<.001 .03

	COVID-19		Influenza		
Outcomes	*N*	%	*N*	%	*p* Value
Total	28	100	33	100	
Severity of disease					
Mild illness	1	4	1	3	.906
Pneumonia	1	4	13	39	**<.001**
Severe pneumonia	18	64	18	55	.441
ARDS	8	29	1	3	**.005**
Outcomes during hospitalization					
Duration of hospitalization at HUS, median (IQR) [range]	6 (4–21) [1–64]	N/A	3 (2–4) [1–24]	N/A	**<.001**
Admission to close observation	2	7	3	9	1.000
Admission to ICU	8	29	2	6	**.034**
Median stay at ICU (range)	20 (11–41)	N/A	9.5 (3–16)	N/A	.267
Supplemental oxygen required	26	93	19	58	**.003**
Invasive ventilation	8	29	1	3	**.009**
Death	1	4	0	0	.459
Outcome at 30 days from admission					
Discharged	24	86	31	94	.282
Hospitalized at HUS	3	11	0	0	.054
Hospitalized at rehabilitation hospital	0	0	2	6	.185
Dead	1	4	0	0	.274
Readmission to HUS within 30 days from admission	0	0	2	6	.495
Outcome at 3 months from admission					
Readmitted to HUS within 3 months from admission	2	7	6	18	.269
Dead	1	4	1	3	1.000

ARDS: acute respiratory distress syndrome; ICU: intensive care unit; HUS: Helsinki University Hospital.
Data are presented no. and % or as medians with interquartile ranges (IQR). If data is missing, the proportion of patients with the information available is marked as the denominator.
Values below .05 are shown bolded as that is the standard limit for statistical significance.

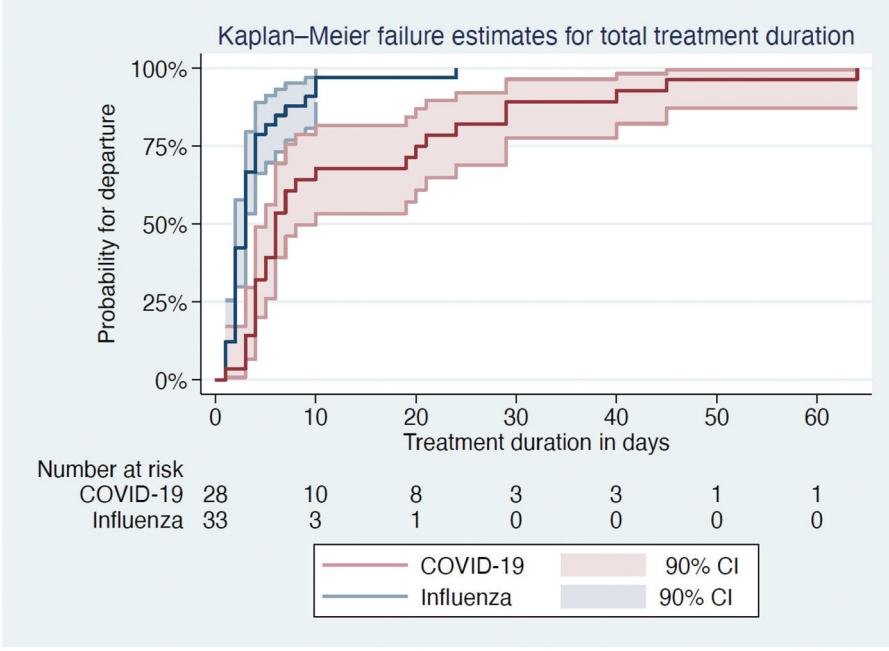

Figure 3. Kaplan–Meier curves for the duration of hospitalization among COVID-19 and influenza patients.

in previous studies, laboratory findings associated with COVID-19 included lymphocytopenia, thrombocytopenia and elevated liver enzymes [9,10,18,24]. During hospitalization, CRP values rose significantly higher among COVID-19 patients especially in patients admitted to ICU, which is consistent with previous finding of elevated CRP being a risk factor for COVID-19 disease progression [25].

Of the COVID-19 patients, 18% had no radiological abnormalities in chest X-ray at admission compared with 41% in a previous study, which is likely explained by the bigger proportion of severe disease in our study [10]. In line with previous CT findings, bilateral basal or peripheral GGOs and consolidations were typically seen in the chest X-rays of COVID-19 patients, which may help in differential diagnostics. In chest CTs of COVID-19

patients, initially unilateral and multifocal GGO evolving to diffuse bilateral GGO and later consolidations in the course of the infection have been described [31]. Rounded opacities, interlobular septal thickening and peripheral distribution and GGO in the CTs of ARDS patients have been more common among COVID-19 than influenza patients [32,33].

Despite similar clinical presentation at admission, COVID-19 patients developed a more severe disease during hospitalization and required longer hospitalization than influenza patients. In multivariable Cox regression analysis, also increasing age, higher BMI and diabetes were associated with longer hospitalization. In previous studies, along with age and other comorbidities, obesity has been a risk factor for severe disease and ICU admission in both COVID-19 and influenza, which supports our findings [34,35]. In the comparison between COVID-19 and influenza by Zayet et al., no difference in the duration of hospitalization or ICU admissions was found, however in a larger preprint study by Donnino et al. hospitalized COVID-19 patients were hospitalized longer and more likely to require mechanical ventilation or die than hospitalized influenza patients, which is in line with our observations [28,36].

Of the COVID-19 patients included in our study, 29% were admitted to the ICU and 4% died compared with 6% and 0% of influenza patients. In a recent large study from the USA, 14.2% of hospitalized COVID-19 patients were admitted to ICU and 21% died [37]. These differences may be explained by the exclusion of institutionalized and elderly patients with poor prognosis from our study and by other differences in patient populations and treatment strategies. Our findings are aligned with the figures from the whole HUS Helsinki University Hospital, where 629 COVID-19 patients had been hospitalized by 11 June 2020, 139 (22%) of them had been admitted to ICU and 38 (6%) had died (personal communication).

In a previous study, COVID-19 patients with ARDS were older, had lower severity of illness scores at presentation and lower Sequential Organ Failure Assessment (SOFA) score-adjusted mortality than H1N1 patients with ARDS [33]. In our study, there were too few ARDS patients for similar comparisons but ARDS developed more often among COVID-19 patients (29% vs. 3%). This is consistent with the study by Donnino et al., who found that hospitalized COVID-19 patients required mechanical ventilation significantly more often than hospitalized influenza patients and in 94% of COVID-19 cases the reason was ARDS [36].

Our study setting offered several advantages. We included COVID-19 patients since the beginning of the outbreak in Finland. All SARI-patients were systematically interviewed and recruited usually before their COVID-19 or influenza test results were available, minimizing selection bias. Data were verified from several sources. Patients had known outcomes as the follow-up lasted until the last patient was discharged. The community-dwelling working-age population of Espoo, the second largest city of Finland, is well represented as Jorvi Hospital provides their specialized care. All patients were recruited during the same influenza season and 88% had influenza A (H1N1) pdm09, the offspring of the pandemic A (H1N1) of 2009 currently circulating as seasonal influenza. Thus, the variation in the clinical course of influenza due to different circulating influenza strains or different composition of seasonal influenza vaccination was minimized.

Our study had several limitations. The sample size was small, which should be taken into account when interpreting the results. All patients admitted to Jorvi Hospital with COVID-19 or influenza were not eligible; for example, they lived outside of the Jorvi Hospital catchment area or did not consent to participate. Elderly patients were underrepresented as patients with pre-existing treatment limitations or not requiring specialized care were admitted to the secondary care Espoo Hospital. The time from symptom onset to hospitalization may not be completely comparable between COVID-19 and influenza patients because, until March, only patients with symptom onset within the last seven days were included. Furthermore, this study is based on clinical data and no extra laboratory testing or radiological imaging was done in addition to the detection of influenza and SARS-CoV-2 RNA. Consequently, CT scans, coagulation markers, cardiac biomarkers or blood gas analyses were mostly not available and thus were not included here. During the COVID-19 epidemic, occasionally SARS-CoV-2 detection alone was conducted without influenza testing on clinical grounds, however, of the COVID-19 patients included in this study, 21 (75%) were tested for influenza and no co-infections were found.

In conclusion, COVID-19 requiring hospitalization had a more severe clinical course than influenza. As SARS-CoV-2 and influenza may continue to circulate simultaneously and influenza already strains health care capacity every influenza season, this has important implications for public health policies for COVID-19 mitigation. Larger

studies are needed to further examine the differences between COVID-19 and influenza.

Acknowledgements

Thank you to our study nurses Outi Debnam and Eija Mikkola for their important work in recruiting the patients to this study and to all patients who participated. We are also very thankful to the DRIVE collaboration for providing the funding and support on which to build our study. We gratefully thank Riitta Santanen, Päivi Hirttiö-Tallbacka, Alena Kaijalainen, Minna Haanpää and Johanna Mustajoki for their expert technical assistance and Esa Ruokokoski for data management.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Local Ethics Committee of the Helsinki University Hospital (3 October 2019, case number: HUS/2517/2018).

Consent to participate

Informed consent was obtained from all study participants or, in the case of the critically ill patients unable to give their consent personally, from their next of kin.

Consent for publication

Informed consent included consent to publish study data. Additional consent for the publication of chest X-rays was obtained.

Code availability

Not applicable.

Disclosure statement

Raija Auvinen, Kirsi Skogberg, Hanna Nohynek, Ritva Syrjänen and Niina Ikonen report an institutional grant to HUS and THL from the DRIVE project funded by IMI under grant agreement no. 777363 during the conduct of the study. Currently, Raija Auvinen is working at THL as a part-time safety physician of a clinical trial on influenza vaccine effectiveness (FinFluHD study), for which THL has received research support from Sanofi Pasteur Inc. FinFluHD study is not related to the current study. Hanna Nohynek is an investigator at THL and coordinates the THL DRIVE project which has received funding from Innovative Medicines Initiative. Ritva Syrjänen is a co-investigator in pneumococcal studies for which THL has received research support from GlaxoSmithKline Biologicals. Currently, Ritva Syrjänen is a co-investigator in the FinFluHD study for which THL has received research support from Sanofi Pasteur Inc. Neither of these studies is related to the current study. Other authors declare no competing interests.

Funding

This study was funded by the DRIVE Project, which receives funding from the Innovative Medicines Initiative (IMI) 2 Joint Undertaking under grant agreement No. 777363. This Joint Undertaking receives support from the European Union's Horizon 2020 Research and Innovation and EFPIA.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request respecting GDPR and with permission from HUS and THL.

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