Comparison of patient characteristics and in-hospital mortality between patients with COVID-19 in 2020 and those with influenza in 2017−2020: a multicenter, retrospective cohort study in Japan

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Summary

Background COVID-19 has worse mortality than influenza in American and European studies, but evidence from the Western Pacific region is scarce.

Methods Using a large-scale multicenter inpatient claims data in Japan, we identified individuals hospitalised with COVID-19 in 2020 or influenza in 2017−2020. We compared patient characteristics, supportive care, and in-hospital mortality, with multivariable logistic regression analyses for in-hospital mortality overall, by age group, and among patients with mechanical ventilation.

Findings We identified 16,790 COVID-19 patients and 27,870 influenza patients, with the different age distribution (peak at 70−89 years in COVID-19 vs. bimodal peaks at 0−9 and 80−89 years in influenza). On admission, the use of mechanical ventilation was similar in both groups (1·4% vs. 1·4%) but higher in the COVID-19 group (3·3% vs. 2·5%; p<0·0001) during the entire hospitalisation. The crude in-hospital mortality was 5·1% (856/16,790) for COVID-19 and 2·8% (791/27,870) for influenza. Adjusted for potential confounders, the in-hospital mortality was higher for COVID-19 than for influenza (adjusted odds ratio [aOR] 1·83, 95% confidence interval [CI] 1·64−2·04). In age-stratified analyses, the aOR (95%CI) were 0·78 (0·56−1·08) and 2·05 (1·83−2·30) in patients aged 20−69 years and ≥70 years, respectively (p-for-interaction<0·0001). Among patients with mechanical ventilation, the aOR was 0·79 (0·59−1·05).

Interpretation Patients hospitalised with COVID-19 in Japan were more likely to die than those with influenza. However, this was mainly driven by findings in older people, and there was no difference once mechanical ventilation was started.

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Research in context

Evidence before this study

Similarities and differences in the clinical characteristics of COVID-19 and influenza have previously been described. We searched PubMed on July 26, 2021, with the terms ("influenza" OR "seasonal influenza") AND ("COVID-19"), in any language without restrictions of the start and end dates of the search. We also conducted manual searches of the reference lists of identified previous studies. After excluding studies on COVID-19 and influenza co-infection, we identified 17 observational studies that compared patient characteristics and in-hospital mortality between COVID-19 and influenza. Previous studies were more likely to report adverse outcomes, including higher in-hospital mortality, among COVID-19 patients than influenza patients. However, most previous studies were conducted in North America or Europe, and evidence from the Western Pacific region was scarce.

Added value of this study

To the best of our knowledge, this is the first large-scale study from the Western Pacific region, which investigated the clinical differences between COVID-19 and influenza. Our results showed that in-hospital mortality was higher in patients admitted for COVID-19 in 2020 than in patients admitted for influenza in 2017-2020 in Japan, which was consistent with the direction of the effect, albeit less prominent, in American and EU countries. The higher risk of in-hospital death for COVID-19 than influenza was mainly driven by findings in older people, whereas there was no statistically significant difference in in-hospital mortality between COVID-19 and influenza among younger patients and among those with mechanical ventilation.

Implications of all the available evidence

This study supports the hypothesis that COVID-19 is more lethal than influenza in the Western Pacific region, consistent with evidence from American and European countries. As our stratified analysis by age group showed higher in-hospital mortality of COVID-19 compared to influenza only among older people, it is reasonable to prioritize the vaccination of COVID-19 for older citizens. In addition, since in-hospital mortality did not differ between COVID-19 and influenza once mechanical ventilation was started, improvement of the management and development of treatment options for COVID-19 before the introduction of mechanical ventilation may be important in lowering the in-hospital mortality of COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) has affected people's lives worldwide, with a total casualty of approximately five million by October 2021.[1] To identify its clinical features and effective treatments, much effort is being made to illustrate the similarities and differences in characteristics between COVID-19 and other existing respiratory viral infections, such as influenza. COVID-19 and influenza are both caused by enveloped RNA viruses affecting respiratory organs, and both can cause similar symptoms, such as fever and cough.[2] Nevertheless, previous studies largely reported worse outcomes among patients with COVID-19 than those with influenza, including higher mortality,[3–13] higher morbidity of complications,[3–8,14–17] and more excess use of healthcare resources such as mechanical ventilation,[3,4,6,8,16] intensive care unit,[3–9,11,13,14,16] and increased length of hospital stay.[3–6,9,11,14,17] These disparities may be partly explained by differences in pathogenicity or transmissibility,[2,18] as well as the lack of well-established treatment, vaccines (which started in February 2021 in Japan), and herd immunity for COVID-19.

However, most of these comparative studies of COVID-19 and influenza focused on populations in North America[3,7–11,16] or Europe,[4–6,12,14] except for a few studies from China with smaller study populations.[13,15,17] Thus, evidence from the Western Pacific region remains scarce. Between the Western Pacific region and American or European countries, some different clinical manifestations of COVID-19 patients have been reported, such as relatively low mortality and fewer morbidities in Japan.[19] Therefore, it is necessary to confirm whether the comparative evaluation results from Europe or the Americas on COVID-19 and influenza are also applicable to the Western Pacific region.

Thus, in this study, we aimed to compare patient characteristics, supportive care, and in-hospital mortality between patients admitted for COVID-19 and influenza in Japan using large-scale multicenter administrative claims data.

Methods

Data source

We conducted a retrospective cohort study using both inpatient and outpatient administrative data and discharge summaries of inpatients at Japanese acute care hospitals under the Diagnosis Procedure Combination (DPC) payment system. In brief, the DPC payment system is a Japanese classification method for inpatients in the acute phase and includes demographic and clinical

information such as diagnoses, pre-existing comorbidities, treatment, admission date, and discharge date.[20] The number of hospitals covered by the DPC payment system increased since its introduction in 2003 and were almost constant at about 1,700 hospitals in 2017–2020.[20] The current database, built by Medical Data Vision Co., Ltd. (Tokyo Japan) (MDV), consists of over 350 acute care hospitals (around 20% of the DPC hospitals).[21] The MDV database consists of hospitals that used the business support system by the MDV Co., Ltd., and provided consent for secondary data uses for research purposes. The MDV database has been widely used in previous studies.[22–25] The age distribution of inpatients in the MDV database is roughly similar to that of all DPC hospitals, whereas the hospital volume (i.e., the number of beds) tends to be larger (Supplementary Table 1). Laboratory test values were available for approximately 10% of participating hospitals that agreed to provide the data. The study was approved by the Ethics Committee of the University of Tsukuba (approval no. 1624). Because the claims data were anonymized before the researchers received the data, individual participants' consent was waived, according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects.[26]

Study population

The study population included patients admitted and discharged for COVID-19 in 2020 or for influenza in 2017–2020 from hospitals which continuously contributed to the MDV database during the study period. For influenza, we included patients admitted not only in 2020 but also between 2017–2019 because the number of influenza cases in 2020 was reported to be very low in most countries including Japan,[27,28] and also because the 3-year data from 2017 to 2019 was more likely to reflect the average characteristics of patients with influenza, given the well-known variation in clinical characteristics of influenza in different years. We identified individuals whose primary disease that triggered admission was COVID-19 (10th revision of the International Statistical Classification of Diseases [ICD-10] codes: U071) or influenza (ICD-10: J09, J10, J11). We categorized a few patients admitted for both COVID-19 and influenza (46 individuals) as patients with COVID-19.[3] For those admitted for COVID-19 or influenza several times in the same year, we used only the first hospitalisation record for each year.

Variables

We obtained information on patient characteristics, including sex, age, body mass index (BMI), smoking history, and comorbidities, based on the inpatient or outpatient ICD-10 codes given on the admission day or before (since 2017): cancer (C00–C43, C45–C97), chronic lung disease (J40–J47), ischemic heart disease (I20–I25), heart failure (I50, I110), arrhythmia (I44, I45, I47–I49), hypertension (I10, I11, I12, I13, I15, I674), diabetes mellitus (E10–E14), cerebrovascular disease (I60–I69), chronic kidney disease (N18), end-stage renal disease (N185, N19), dementia (F00–F03, F051, G30), dyslipidaemia (E78), cirrhosis (K703, K717, K743, K744, K745, K746), deficiency anaemia (D50), and peripheral artery disease (I702, I739).

Furthermore, we extracted information on the supportive care (intensive care unit [ICU] admission, oxygen therapy, non-invasive positive pressure ventilation [NPPV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO], renal replacement therapy, blood transfusion, and vasopressor use), and dexamethasone use, based on procedure codes (detailed definitions are shown in Supplementary Table 2), both on the day of admission and at any time during the entire hospitalisation. In addition, in the MDV database, laboratory test values were available from approximately 10% of the participating hospitals and were therefore extracted. The outcome of interest was in-hospital mortality, which is recorded and constantly monitored for accuracy in the DPC system.

Statistical analysis

First, we crudely compared the participants' demographics and health-related characteristics between patients admitted for COVID-19 in 2020 and influenza in 2017–2020. Second, we compared the supportive care between COVID-19 and influenza patients, on the day of admission and during the entire hospitalisation. For patients discharged alive by the end of 2020, we also compared the length of stay (in hospital and in ICU). We used Student's t-test or the Mann-Whitney U test for continuous variables and the χ^2 test for categorical variables. We also compared laboratory test values between the groups of patients admitted to hospitals with available laboratory results, by calculating the standardized mean difference. We then compared in-hospital mortality between COVID-19 and influenza groups and plotted these by ten-year age groups.

We conducted multivariable logistic regression analyses for in-hospital mortality in the whole study population, in line with a previous foreign study.[11] We first adjusted for age group and sex, and then additionally adjusted for smoking history, BMI, and comorbidities. We then further adjusted for treatment on admission day (blood transfusion, mechanical ventilation, vasopressor use, renal replacement therapy, and dexamethasone use; hereafter referred to as the "fully adjusted model"). For missing data on smoking history and BMI, we conducted multiple imputation by chained equations (MICE) using all variables including outcomes.[29] In this study, we generated five complete, filled-in datasets and replaced each missing value with a set of plausible substitutes. For sensitivity analysis, we also conducted complete case analyses, assuming that

missing values for BMI and smoking history were missing not at random.

In addition, we conducted multivariable logistic regression analyses stratified by age group because the relative risk of in-hospital death between COVID-19 and influenza has been suggested to differ by age.[3,4] We stratified the population into two age groups (20–69 years and 70 years or older) after we had plotted the in-hospital death mortality of COVID-19 and influenza by age, finding no fatal COVID-19 case under 20 years old. We also tested the interaction by age, with the multivariable logistic regression model including the interaction term between age and diseases (i.e., COVID-19 or influenza). Furthermore, we conducted a multivariable logistic regression analysis in patients with mechanical ventilation (any time during the entire hospitalisation period) to examine whether the association between COVID-19/influenza and mortality is different when patients are affected by more severe conditions requiring mechanical ventilation.

Statistical significance was set at $p<0.05$. Stata 15 (StataCorp, TX, USA) and Microsoft Excel for Mac 16.56 (Microsoft, WA, USA) were used for all analyses.

Role of the funding source

This work was supported by a grant-in-aid from the Ministry of Health, Labour and Welfare Policy Research Grants, Japan (grant number: 21AA2007). The funder did not play any role in the conception, design, conduct, or reporting of this study.

Results

We identified 16,790 patients admitted for COVID-19 in 2020 and 27,870 patients admitted for influenza in 2017–2020. The number of patients with influenza in 2020 was one-half to one-third of that between 2017–2019 (Table 1). By calendar month, COVID-19 showed two waves in 2020, in line with Japanese national statistics,[1] whereas influenza showed a single peak every year around January (Figure 1). The age distribution was largely different (Figure 2): the number of COVID-19 patients was almost constant among people aged 20–69 years and peaked at 70–89 years, whereas influenza showed a bimodal distribution with peaks at ages 0–9 years and 80–89 years. Patients with COVID-19 were more likely to be men, younger, overweight or obese, have a smoking history, and have comorbidities including cancer, hypertension, diabetes mellitus, chronic kidney disease, end-stage renal disease, dyslipidaemia, cirrhosis, and deficiency anaemia than patients with influenza (Table 1). Among patients with available laboratory test values, whereas most parameters were different with statistical significance (i.e., $p<0.0001$), the standardized mean difference for each parameter, which measures the magnitude of effect,[30] was generally small (Supplementary Table 3).

On admission day, patients with COVID-19 were more likely to enter the ICU and receive a blood transfusion and dexamethasone, whereas patients with influenza received oxygen therapy, NPPV, and vasopressors more often (Table 2). We did not observe statistically significant differences in the proportions of mechanical ventilation, ECMO, and renal replacement therapy on admission between COVID-19 and influenza patients. However, during the entire hospitalisation period, patients with COVID-19 were more likely to receive any of the treatments above, except for oxygen therapy and NPPV, compared to patients with influenza, indicating that patients with COVID-19 were more likely to become severely ill during hospitalisation. For patients discharged alive (15,934 for COVID-19 and 27,079 for influenza), the median length of stay was longer for COVID-19 (10 [IQR, 7–16] days) than for influenza (5 [4–10] days), whereas the median length of stay in ICU for patients with COVID-19 (3 [1–8] days) and patients with influenza (4 [2–8] days) were not statistically different.

Overall, the in-hospital mortality was higher in patients admitted for COVID-19 (856/16,790 [5·1%]) than in patients with influenza (791/27,870 [2·8%] between 2017–2020, consisting of 2·2% [142/6,491] in 2017, 3·4% [272/7,943] in 2018, 3·0% [303/10,170], and 2·3% [74/3,266] in 2020). However, the association between COVID-19 or influenza and in-hospital mortality varied with age (Figure 3). Among people younger than 20 years, the in-hospital mortality was not significantly different between COVID-19 (0/1,092 [0%]) and influenza (6/11,558 [0·05%]). Among individuals aged between 20 and 69 years, it was higher in influenza patients (92/2,957 [3·1%]) than in COVID-19 patients (100/8,443 [1·2%]; $p<0.0001$), whereas in patients 70 years of age or older, it was higher among COVID-19 patients (756/7,255 [10·4%]) than among influenza patients (693/13,355 [5·2%]; $p<0.0001$; Figure 3).

In the multiple logistic regression analyses after multiple imputation, COVID-19 patients had a higher risk of in-hospital death than influenza patients in the age-sex adjusted model (odds ratio [OR] 1·95, 95% confidence interval [CI] 1·76–2·16), in the model further adjusting for smoking history, BMI, and comorbidities (OR 1·86, 95%CI 1·68–2·07), and in the fully adjusted model (OR 1·83, 95%CI 1·64–2·04) (Table 3).

When stratified by age group, in patients aged 70 years or older, the risk of in-hospital death was higher among COVID-19 patients than influenza patients (fully adjusted OR 2·05, 95%CI 1·83–2·30), but there was no statistically significant difference among patients aged 20–69 (fully adjusted OR 0·78, 95%CI 0·56–1·08) (p-for-interaction<0·0001) (Table 3).

Among patients with mechanical ventilation (any time during the entire hospitalisation period), we did not observe a statistically significant difference in the risk of in-hospital death (crude in-hospital mortality

	COVID-19 (n=16,790)	Influenza (n=27,870)	p
Age, median (IQR), year	64 (40–80)	67 (5–84)	<0·0001
Sex (women), n (%)	7,242 (43·1)	13,039 (46·8)	<0·0001
Calendar year, n (%)			
2017	–	6,491 (23·3)	
2018	–	7,943 (28·5)	
2019	–	10,170 (36·5)	
2020	16,790 (100)	3,266 (11·7)	
BMI, n (%), kg/m^2			<0·0001
<25	10,563 (62·9)	19,492 (69·9)	
25 to <30	2,601 (15·5)	2,645 (9·5)	
30≤	910 (5·4)	740 (2·7)	
Missing	2,716 (16·2)	4,993 (17·9)	
Smoking history, n (%)			<0·0001
Yes	4,473 (26·6)	3,665 (13·2)	
No	9,487 (56·5)	21,966 (78·8)	
Missing	2,830 (16·9)	2,239 (8·0)	
Comorbidities, n (%)			
Cancer	2,149 (12·8)	2,385 (8·6)	<0·0001
Chronic lung disease	3,008 (17·9)	8,067 (29·0)	<0·0001
Ischemic heart disease	1,436 (8·6)	6,712 (24·1)	<0·0001
Heart failure	2,517 (15·0)	4,246 (15·2)	0·49
Arrhythmia	1,608 (9·6)	2,831 (10·2)	0·047
Hypertension	5,192 (30·9)	7,965 (28·6)	<0·0001
Diabetes mellitus	3,602 (21·5)	4,804 (17·2)	<0·0001
Cerebrovascular disease	1,739 (10·4)	3,659 (13·1)	<0·0001
Chronic kidney disease	1,048 (6·2)	1,507 (5·4)	<0·0001
End-stage renal disease	690 (4·1)	803 (2·9)	<0·0001
Dementia	1,522 (9·1)	3,064 (11·0)	<0·0001
Dyslipidaemia	2,759 (16·4)	4,052 (14·5)	<0·0001
Cirrhosis	230 (1·4)	252 (0·9)	<0·0001
Deficiency anaemia	1,652 (9·8)	2,165 (7·8)	<0·0001
Peripheral artery disease	233 (1·4)	435 (1·6)	0·14

***Table 1*: Baseline characteristics of participants at admission to a hospital in Japan for COVID-19 or influenza.**
Abbreviations: BMI, body mass index; IQR, interquartile range. Data are reported as number (%) for categorical variables and median (IQR) for continuous variables. We conducted Student's t-test or the Mann-Whitney U test for continuous variables and the χ^2 test for categorical variables.

32·6% [178/546] in COVID-19 patients and 33·1% [229/691] in influenza patients; fully adjusted OR 0·79, 95%CI 0·59–1·05) (Table 3).

The complete case analyses excluding the participants with missing values of BMI and smoking history showed similar results (Supplementary Table 4).

Discussion

In this large Japanese cohort study using administrative claims data in Japan, we compared the characteristics, treatment, and in-hospital mortality between patients with COVID-19 and those with influenza in Japan. We found that overall, patients with COVID-19 were more likely to die in the hospital than patients admitted for influenza. Nevertheless, we did not observe higher in-hospital mortality for COVID-19 than influenza among patients younger than 70 years of age and among patients who received mechanical ventilation during hospitalisation.

To the best of our knowledge, this is the first large-scale study from the Western Pacific region to investigate the clinical differences between COVID-19 and influenza. A few reports from China[13,15,17] compared the characteristics of COVID-19 and influenza, but their results were limited due to the small sample size[13,15,17] or the indirect comparison of separate cohorts at different locations.[13,15] The strength of the current study is that we directly compared data for COVID-19 and influenza patients using a large database of acute care hospitals across Japan.

Our results were largely compatible with those of previous studies from Europe or North America regarding the higher mortality[3–12] and the longer hospital stay[3–6,9,11,14] among patients with COVID-19 than those with influenza. Differences in the risks of death between COVID-19 and

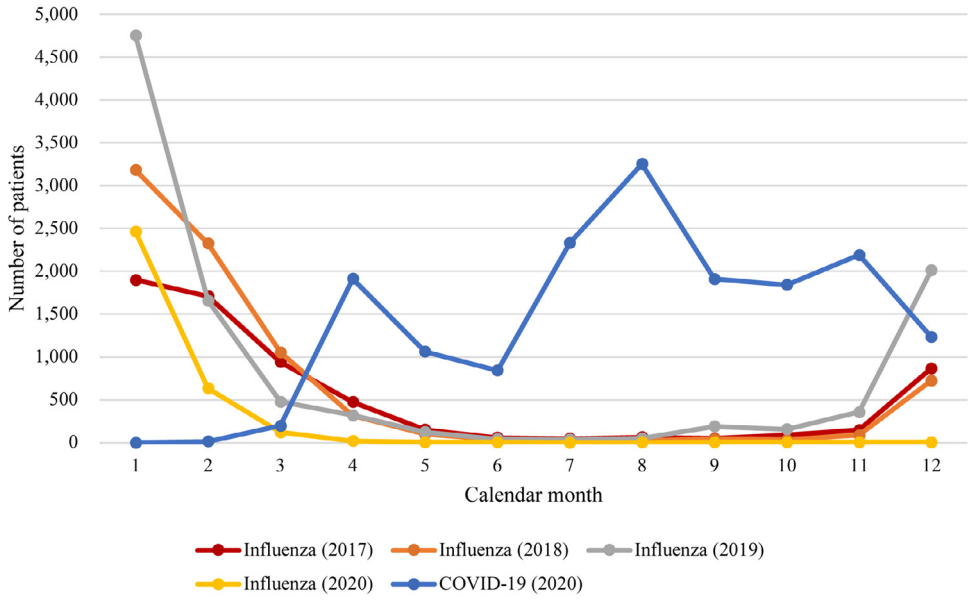

Figure 1. Distribution of patients admitted for COVID-19 in 2020 or influenza in 2017–2020 by calendar month of admission.

influenza might be partly explained by the fact that effective vaccination and appropriate treatments are available for influenza, but not for COVID-19, at least by the end of 2020 in Japan. It should also be noted that, in line with previous studies,[27,28] the number of patients with influenza in 2020 was one-half to one-third of that between 2017–2019, probably because the prevention measures for COVID-19, such as mask and physical distancing, were effective in preventing influenza infection. The influenza vaccination coverage in Japan was almost constant at 48.2% in 2017, 47.9% in 2018, and 50.4% in 2019, among people ≥ 65 and people aged 40–64 with specific conditions (heart, kidney, or respiratory disease, and HIV).[31] Thus, there is seemingly no obvious correlation between in-hospital mortality of patients with influenza (i.e., 2·2% in 2017, 3·4% in 2018, and 3·0% in 2019) and vaccination coverage for influenza between 2017-2019, although the influenza vaccination rate in 2020 is not yet publicly available.

We also identified differences from previous studies in the Americas and Europe. The overall relative risk of in-hospital death for COVID-19 compared to influenza

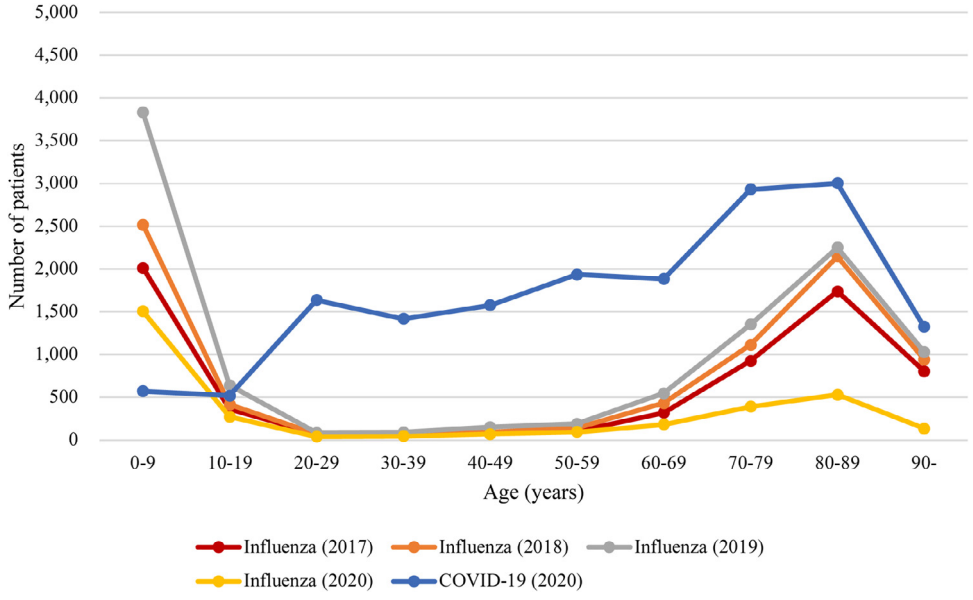

Figure 2. Distribution of patients admitted for COVID-19 in 2020 or influenza in 2017–2020 by age.

	COVID-19 (n=16,790)	Influenza (n=27,870)	p
Treatment on admission day, n (%)			
ICU admission	749 (4·5)	207 (0·7)	<0·0001
Oxygen therapy	3,707 (22·1)	7,938 (28·5)	<0·0001
NPPV	34 (0·2)	119 (0·4)	<0·0001
Mechanical ventilation	241 (1·4)	376 (1·4)	0·45
ECMO	6 (0·04)	9 (0·03)	0·85
Renal replacement therapy	108 (0·6)	168 (0·6)	0·60
Blood transfusion	167 (1·0)	67 (0·2)	<0·0001
Vasopressor use	194 (1·2)	436 (1·6)	<0·0001
Dexamethasone use	506 (3·0)	272 (1·0)	<0·0001
Treatment during hospitalisation, n (%)			
ICU admission	937 (5·6)	293 (1·1)	<0·0001
Oxygen therapy	5,573 (33·2)	9,860 (35·4)	<0·0001
NPPV	188 (1·1)	306 (1·1)	0·83
Mechanical ventilation	546 (3·3)	691 (2·5)	<0·0001
ECMO	36 (0·2)	24 (0·1)	<0·0001
Renal replacement therapy	407 (2·4)	395 (1·4)	<0·0001
Blood transfusion	621 (3·7)	400 (1·4)	<0·0001
Vasopressor use	609 (3·6)	891 (3·2)	0·015
Dexamethasone use	1,465 (8·7)	459 (1·7)	<0·0001
Length of stay, median (IQR), days*	10 (7—16)	5 (4—10)	<0·0001
Length of stay in ICU, median (IQR), days‡	3 (1—8)	4 (2—8)	0·089

***Table 2*: Treatment of patients admitted to a hospital in Japan for COVID-19 or influenza, as well as their length of stay.**
Abbreviations: NPPV, Non-invasive Positive Pressure Ventilation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range. Data are reported as number (%) for categorical variables and median (IQR) for continuous variables. We conducted the Mann-Whitney U test for continuous variables and the χ^2 test for categorical variables.
* Length of stay was calculated for patients discharged alive (15,934 for COVID-19 and 27,079 for influenza).
‡ Length of stay in ICU was calculated for patients who stayed in ICU and discharged alive (658 for COVID-19 and 180 for influenza)

(adjusted OR of 1·8) was lower in the current study than in previous studies; four large cohort studies from the United States,[3,11] France,[4] and Canada[9] reported the relative risk of in-hospital death ranging from 2·9 to 19·8. While the in-hospital mortality of influenza in our study (2·8%) was comparable with reported rates

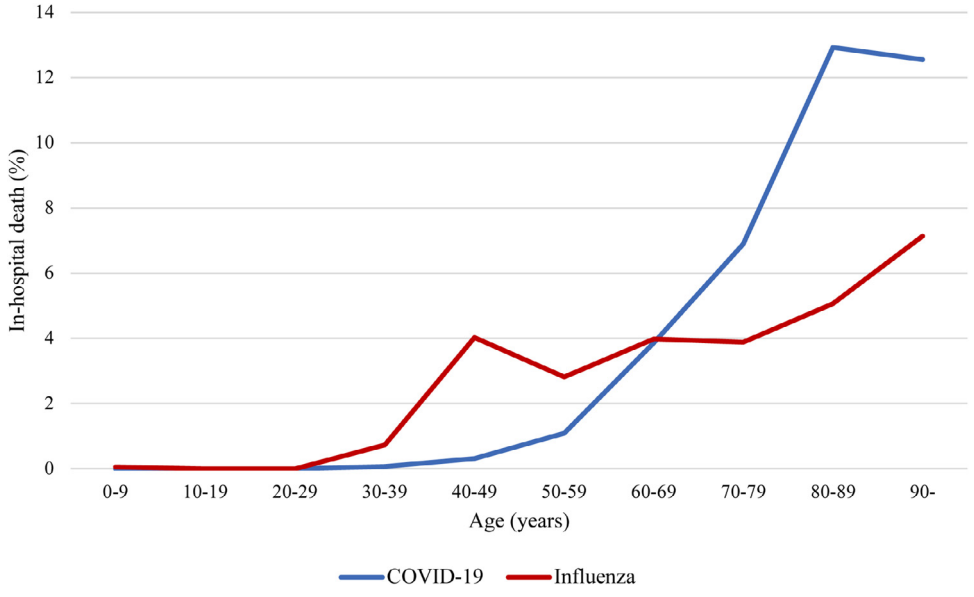

Figure 3. In-hospital death of patients admitted for COVID-19 in 2020 or influenza in 2017—2020 by age.

	COVID-19 In-hospital death, n (%)	Influenza	Model 1 Adjusted odds ratio (95% CI)	Model 2 Adjusted odds ratio (95% CI)	Model 3 Adjusted odds ratio (95% CI)
Full cohort, n (%)	856/16,790 (5·1)	791/27,870 (2·8)	1·95 (1·76-2·16)	1·86 (1·68-2·07)	1·83 (1·64−2·04)
Patients aged 20−69 years old, n (%)	100/8,443 (1·2)	92/2,957 (3·1)	0·58 (0·43−0·79)	0·72 (0·53−0·99)	0·78 (0·56−1·08)
Patients aged 70 or older, n (%)	756/7,255 (10·4)	693/13,355 (5·2)	2·24 (2·01−2·49)	2·10 (1·88−2·35)	2·05 (1·83−2·30)
Mechanical ventilation cohort, n (%)	178/546 (32·6)	229/691 (33·1)	0·81 (0·63−1·05)	0·80 (0·61−1·06)	0·79 (0·59−1·05)

***Table 3*: Risk of in-hospital death of patients hospitalized for COVID-19 or influenza**

Abbreviations: CI, confidence interval. Influenza was treated as reference. Model 1 adjusted for sex and age. Model 2 additionally adjusted for smoking history, body mass index, and comorbidities (cancer, chronic lung disease, ischemic heart disease, heart failure, arrhythmia, hypertension, diabetes mellitus, cerebrovascular disease, chronic kidney disease, dementia, dyslipidaemia, cirrhosis, deficiency anaemia, and peripheral artery disease). Model 3 additionally adjusted for treatment on admission day (blood transfusion, mechanical ventilation, vasopressor use, renal replacement therapy, and dexamethasone use).

overseas (1·4−6·1%),[3,4,9,11] the in-hospital mortality of COVID-19 in our study (5·1%) was lower than that reported in previous foreign studies (13·7−19·9%),[3,4,9,11] which can be the main reason for the lower relative risk in our study. Second, the difference in in-hospital COVID-19 deaths between Japan and American or EU countries may be due to the difference in the capacity of medical care services. The number of COVID-19 cases in Japan was much lower than those in the United States and France (with total numbers per million people by the end of 2020: 1,800 in Japan, 59,000 in the United States, and 38,000 in France).[1] Thus, Japan could maintain access to health care (as suggested by the bed occupancy rate <100% in each prefecture) for patients with COVID-19 during 2020, during the first wave (February−May, 2020), the second wave (June −September, 2020) and the third wave (October 2020 −February 2021).[32] Japan may have been able to preserve the quality of medical care services, leading to lower mortality of COVID-19. In the early phase of the COVID-19 pandemic, the Ministry of Health, Labour and Welfare of Japan initially requested all patients with COVID-19 to be hospitalised, regardless of severity, as of February 2020. However, since March 2020, in response to the rapid increase in the number of patients, the government suggested only patients with moderate to severe symptoms and patients at higher risk (such as pregnant women and individuals aged 65 or older) be eligible for admission, whereas the others (i.e., asymptomatic, or mild cases) should stay at designated facilities (such as hotels) and their home.[33,34] Therefore, we do not believe that the change in hospitalisation indication at the early stage had much effect on our results because the number of cases before March 2020 was very small (at less than 1%) in our data set.

As for the supportive care, the necessity of mechanical ventilation, ECMO, and renal replacement therapy did not differ between COVID-19 and influenza patients on the admission day, but COVID-19 patients were more likely to require these treatments during the entire hospitalisation period. Patients with COVID-19 tended to experience a deterioration of their condition after hospitalisation compared to those with influenza, which seemingly led to a higher risk of in-hospital death. Notably, when mechanical ventilation was started, the in-hospital mortality (both crude and adjusted) did not differ between the study groups. To reduce the overall in-hospital mortality of COVID-19 and bring it closer to that of influenza infection, improvement in the management or development of treatment options for patients with COVID-19 before initiating mechanical ventilation may be important.

The stratified analysis by age group showed that people aged 70 years or older with COVID-19 had a higher risk of in-hospital death than those with influenza. Our results were largely compatible with those of previous studies reporting that in-hospital mortality was higher in the COVID-19 group than in the influenza group, especially among older individuals.[3,4,11] Among people aged 20−69, we did not find a statistically significant difference in in-hospital mortality, which was in line with a report from France.[4] Our results suggest that it is reasonable to prioritize the vaccination of COVID-19 for older people. A French study reported that COVID-19 patients younger than 18 years had a higher risk of in-hospital death,[4] which we could not confirm because the death of COVID-19 patients younger than 20 years was not observed in our study population.

This study has several limitations. First, although our database covered a large number of cases admitted to more than 350 acute care hospitals across Japan, the results may not represent the entire population in Japan. The hospital volume of the MDV database tends to be larger than that of all DPC hospitals. We could not evaluate the representativeness of hospitals in the MDV database in terms of hospital ownership (i.e., public or private) and socio-economic status of hospitalised patients due to lack of information. However, in the Japanese healthcare system, all acute care hospitals are eligible for reimbursement by the national health insurance, and people can be hospitalised for any acute care hospitals regardless of socio-economic status. In addition, we found that the age distribution of inpatients in the MDV database was roughly similar to that

of all DPC hospitals, although information on the sex distribution was unavailable. More importantly, the crude in-hospital mortality for COVID-19 (5·1%) and influenza (2·8%) in our cohort were similar to those reported in previous Japanese studies.[35–37] Second, when we defined comorbidities based on inpatient or outpatient ICD-10 codes recorded in the database, we may have missed some comorbidities if patients received routine health care in medical institutions other than the hospitals to which the patients were admitted. In addition, miscoding of diagnoses and procedures may be possible in claims data, although a previous study reported that the diagnoses and procedure records of DPC data had a high validity in general.[38] For example, although the proportion of patients with oxygen therapy in our data is roughly similar to other Japanese statistics of COVID-19 and influenza,[19,37,39] we might have failed to detect some use of oxygen therapy in case a temporal use of a small amount of oxygen was not recorded or reimbursed by the hospitals. If such misclassification bias existed, it is likely to be non-differential and, therefore, diluting the relative risk between COVID-19 and influenza (meaning that the true relative risk would be even larger than our estimate). These issues may be also true to blood transfusion, although the proportion of blood transfusion in the current study (3.7%) was compatible with the reported value (4.8%) in a previous large-scale Japanese study on COVID-19.[19] Third, as we used data from administrative claims data, we could not acquire information including vital signs, the severity of comorbidities, or socioeconomic status. Thus, we could neither compare these characteristics between COVID-19 and influenza nor consider these factors as potential confounders or mediators in our analysis. Fourth, laboratory test values were available for only 10% of the hospitals that agreed to provide the data in the MDV database; therefore, laboratory test results were unadjusted in our multivariable analysis. Fifth, we conducted the MICE for missing values of BMI and smoking history based on the assumption that these variables were missing at random; however, we could not deny the possibility that they were missing not at random. Thus, we also conducted the complete case analyses to confirm similar results. Sixth, our study did not include patients staying in hospital at the end of 2020. Thus, the length of stay for all COVID-19 patients hospitalised in 2020 could have been even longer than that observed in this study (which was longer than that for influenza patients). Seventh, similar to previous studies in the United States,[3,11] France,[4] and Canada,[9] this study compared patients hospitalised for COVID-19 and influenza, and therefore may suffer from selection or collider bias due to different threshold of admission for each disease. However, our analysis demonstrated that patients admitted for COVID-19 had a higher risk of in-hospital death than those admitted for influenza, even after adjusting for comorbidities and treatment on admission day. Finally, it should be noted that the latest characteristics of COVID-19 in 2021 may be different from our results on COVID-19 cases in 2020. The rapid development of treatments and vaccines may have lessened the outcome differences between COVID-19 and influenza in 2021 compared to 2020. At the same time, it is also possible that the emergence of more transmissible variants, such as the Delta variant,[40,41] first detected in late 2020 in India, has recently worsened health outcomes.

In conclusion, we showed that in-hospital mortality was higher in patients admitted for COVID-19 in 2020 than in patients admitted for influenza in 2017–2020 in Japan, which was consistent with the direction of the effect, albeit less prominent, in American and EU countries. However, this was mainly driven by findings in older people, whereas we did not observe higher mortality for COVID-19 than influenza among younger patients and among those with mechanical ventilation.

Authors' contributions

YT designed the study, conducted data processing, analysed the data, and wrote the initial draft. MAI contributed to conception, acquisition of data, study design, interpretation, and revision of the manuscript. TK contributed to conception, study design, interpretation, and revision of the manuscript. JK, MA and TS accessed and verified the data, and were involved in data processing, interpretation, and revision of the manuscript. TA, MII, AM, MS, HO, YM, SI, TK and NT substantially contributed to study design, interpretation of the data, and revision of the manuscript. All authors approved the final version and had final responsibility for the decision to submit for publication.

Declaration of Competing Interest

Atsushi Miyawaki has a joint research project with Medical Data Vision Co., Ltd. outside of this study and received labour contributions in the financial year 2020.

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Data sharing

We obtained data from the Medical Data Vision Co., Ltd. (MDV), and we are not allowed to share these data with other parties. Researchers who meet the criteria for

access can acquire de-identified participant data from the MDV (https://en.mdv.co.jp).

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanwpc.2021.100365.

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