

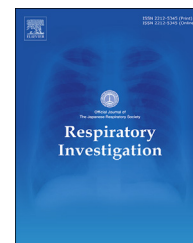


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Rapid Communication

The prevalence of comorbid respiratory disease among COVID-19 patients, and mortality during the first wave in Japan: A nationwide survey by the Japanese Respiratory Society



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ABSTRACT

There is a concern that persons with underlying respiratory disease may have increased susceptibility to COVID-19 and/or increased severity/mortality if infected. However, information regarding such patients during the first wave of the epidemic is lacking in Japan. We surveyed chest physicians nationwide, and collected anonymous data concerning 1444 patients.

Among COVID-19 patients, the prevalence of asthma, chronic obstructive pulmonary disease (COPD), and interstitial lung diseases (ILD) was 3.4%, 4.8%, and 1.5%, respectively. Among COVID-19 patients with these 3 comorbidities, exacerbation of the comorbidity occurred in 12.2%, 18.8%, and 36.4%, respectively, and mortality (6.2% overall) was 4.1%, 13.0%, and 31.8%, respectively.

Abbreviations: COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; ILD, interstitial lung disease; Japanese Respiratory Society, JRS; LPV/r, lopinavir/ritonavir; MV, mechanical ventilation; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2.

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Interstitial lung disease Mortality

The prevalence of asthma among COVID-19 patients was not higher than that for the general population, and mortality in COVID-19 patients with asthma was not higher than mortality in COVID-19 patients without underlying respiratory disease. COVID-19 patients having COPD or ILD had relatively high mortality, especially for ILD.

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), continues to spread worldwide. In Japan, a total of 473,045 cases with 9182 deaths were confirmed as of April 2, 2021 [1] and a fourth wave of the pandemic is in progress. Recently, the prevalence of comorbid respiratory diseases among patients with COVID-19, and the effect of such respiratory comorbidities on the severity of COVID-19, has received increasing attention. Viral infection can trigger exacerbation of underlying respiratory conditions, so the risk of mortality in SARS-CoV-2 infection among people with such comorbidities is likely higher.

The aim of our study was to investigate the prevalence of comorbid respiratory diseases among patients with COVID-19 and mortality during the first wave of pandemic in Japan through a national survey of chest physicians using an online questionnaire.

The study was conducted from 27 May to 17 June 2020, during the first wave of the pandemic in Japan. Japan's number of newly diagnosed COVID-19 patients reached a peak of 708 on April 10, then fell to 22 by June 8. Responsible chest physicians of the country's 904 health institutions certified by the Japanese Respiratory Society (JRS) were asked to participate. The questionnaire concerned patients with COVID-19 and included questions regarding: prevalence and exacerbation of underlying respiratory diseases, including asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), and lung cancer; mortality; the use of selected drugs; mechanical ventilation (MV); and extracorporeal membrane oxygenation (ECMO). Aggregated data responses were fed into an online data collection form. The requirement for ethical approval was waived by the ethical review board of Kobe University, due to the anonymous nature of the data collected.

Of the 171 responding institutions (18.9%), 111 institutions (64.9%) treated COVID-19 patients, accounting for a total of 1444 patients. The Tokyo Metropolitan area accounted for 21.5% of the patients, and Tokyo Metropolitan area plus Kanto and Kinki districts together accounted for 66.0% of the patients (Table 1). At the time, Japan's COVID-19 case count was 17,645 (June 17), and the proportion from Tokyo, Kanto, and Kinki regions was 73.4% [1], so our survey covered 8.2% of the nationwide number of patients and reflected the actual geographic distribution of cases.

According to our data, the prevalence of asthma, COPD, and ILD among COVID-19 patients was 3.4%, 4.8%, and 1.5%, respectively (Table 2). The incidence of physician-reported exacerbation or worsening of comorbid respiratory disease was 12.2% in the case of asthma, and 36.4% in the case of ILD.

Overall mortality among COVID-19 patients was 6.2% (Table 2). Compared to patients without respiratory

comorbidity (5.1% mortality), mortality was lower in patients with asthma (4.1%), and higher in patients with COPD (13.0%), ILD (31.8%), and lung cancer (38.5%).

The most frequently prescribed drug was favipiravir (35.5%), followed by ciclesonide (24.1%), whereas only 8.5% of the patients were treated with systemic corticosteroids (Fig. 1). Patients with comorbid respiratory diseases were more frequently treated with favipiravir or ciclesonide than those without respiratory comorbidity (Table 3). The same was true for treatment with systemic corticosteroids, with the exception of patients with asthma, for whom systemic corticosteroids were prescribed less frequently (4.1%) compared to patients without respiratory comorbidity (7.2%).

The proportion of patients placed on MV was higher among patients with COPD or ILD than in patients without respiratory comorbidity (Table 3). ECMO was not used in patients with COPD, ILD, and lung cancer.

In the current study, the mortality in patients without comorbid respiratory disease (5.1%, Table 2) was comparable to the reported overall mortality in Japan (5.3%) at the time of investigation [1]. However, total mortality in patients with respiratory diseases other than asthma was 20.2% (21 deaths from 104 patients), suggesting the paramount importance of prevention of COVID-19 for such patients.

Our data showed a prevalence of asthma among patients with COVID-19 (3.4%) that was lower than the general prevalence of asthma among adults in other countries [2] and in Japan (10.4%) [3], suggesting a lower susceptibility to COVID-19 in persons with asthma. Previous reports have also shown that severity of COVID-19 is not increased by comorbid asthma [4]; the risk was slightly higher for a subgroup of patients with non-allergic phenotype or recent systemic corticosteroid use, but the extent was smaller compared to obesity

Table 1 – Institutions and patients represented, stratified by region.

Region	Institutions (n)	Patients (n)	Patients (%)
Hokkaido	4	62	4.3%
Tohoku	5	64	4.4%
Kanto(other than Tokyo)	27	320	22.2%
Tokyo Metropolitan	18	310	21.5%
Tokai	12	90	6.2%
Hokuriku	5	149	10.3%
Kinki	20	322	22.3%
Chugoku/Shikoku	11	49	3.4%
Kyushu	9	78	5.4%
Total	111	1444	100.0%

Table 2 – Prevalence and exacerbation of comorbid respiratory disease, and mortality among COVID-19 patients.

		Asthma	COPD	ILD	Lung cancer	No respiratory disease	Total
Prevalence of comorbid respiratory disease	N	49	69	22	13	1291	1444
	%	3.4%	4.8%	1.5%	0.9%	89.4%	100%
Exacerbation	N	6	13	8	NA	NA	NA
	%	12.2%	18.8%	36.4%			
Death**	N	2	9	7	5	66	89
	%	4.1%	13.0%	31.8%	38.5%	5.1%	6.2%

**p < 0.01, Pearson's Chi-square test.

COPD, Chronic Obstructive Lung Disease; ILD, Interstitial lung disease; NA, Not analyzed.

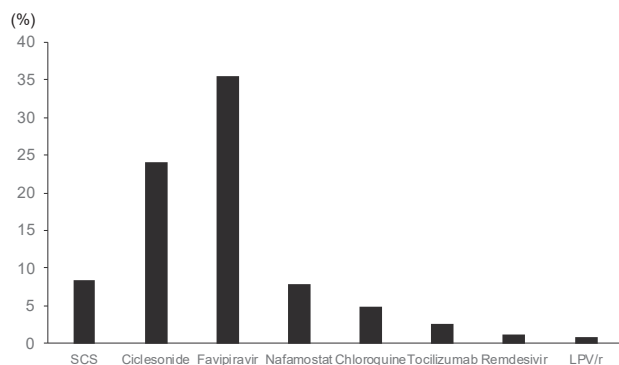


Fig. 1 – The proportion of patients treated with drugs for COVID-19 (n = 1444). SCS, systemic corticosteroid; LPV/r, lopinavir/ritonavir.

or diabetes [4]. In line with the report, the mortality of patients with asthma (4.1%) did not exceed that of patients without respiratory comorbidity (5.1%) in this study (Table 2). Although the leading cause of asthma exacerbation is infection by viruses, including rhinovirus [3]. As for SARS-CoV-2, the incidence of physician-reported exacerbation of asthma was limited to 12.2% and systemic corticosteroids were prescribed only for 4.1% patients in this study. Findings, both previous and current, concerning low susceptibility or risk for severe COVID-19 in asthma, can be partly explained by the decrease in expression of ACE2 receptor due to inhaled corticosteroids [5] or type 2 cytokines, including IL-13 [6].

Concerning COPD, the susceptibility to COVID-19 is controversial, and it is difficult to infer the extent of susceptibility from our results due to the lack of information regarding age. However, comorbid COPD has been established as a risk factor for severity of COVID-19 [7], and the elevated mortality in our survey (13.0%) is consistent with that. Although 11 patients with COPD were on MV (Table 3), successful weaning was apparently possible in some patients because the number of deaths was 9. Further investigation is required to establish the prediction factor to determine the indication for MV.

Previous reports have revealed high mortality in patients with ILD [8]. The mortality in our study (31.8%) was indeed higher than the reported mortality among COVID-19 patients aged >80 years (28.3%), which is the highest mortality age bracket [1]. Although the number of deaths was 7, only 4 patients were on MV and none of the patients were on ECMO (Table 3), suggesting the estimation of poor prognosis by the physicians involved.

During the first wave in Japan, favipiravir followed by ciclesonide were frequently prescribed, more often to patients with respiratory diseases (Table 3). This might have been due to the higher severity of COVID-19 in patients with respiratory diseases, suggested by high mortality in patients with COPD, ILD, and lung cancer. Since the first wave, there has important progress in treatment for COVID-19, such as the establishment of indication of systemic steroids, the limited efficacy of ciclesonide for mild cases, and the approval of remdesivir in Japan [9]. These advancements may further improve the

Table 3 – Treatment of COVID-19 patients with comorbid respiratory diseases.

		Asthma	COPD	ILD	Lung cancer	No respiratory disease	Total
Patients		49	69	22	13	1291	1444
Systemic Steroids**	N	2	17	7	3	93	122
	%	4.1%	24.6%	31.8%	23.1%	7.2%	8.5%
Ciclesonide**	N	29	30	13	12	264	348
	%	59.2%	43.5%	59.1%	92.3%	20.5%	24.1%
Favipiravir**	N	21	36	11	8	437	513
	%	42.9%	52.2%	50.0%	61.5%	33.9%	35.5%
Mechanical Ventilation**	N	2	11	4	4	94	115
	%	4.1%	15.9%	18.2%	30.8%	7.3%	8.0%
Extracorporeal membrane oxygenation**	N	2	0	0	0	18	20
	%	4.1%				1.4%	1.4%

**p < 0.01, Pearson's Chi-square test.

COPD, Chronic Obstructive Lung Disease; ILD, Interstitial lung disease.

prognosis of patients with COVID-19 and the investigation of mortality in following waves is required.

The limitations of our study include the lack of data about age, gender, baseline treatment, COVID-19 severity, and comorbidities other than respiratory diseases. The above-mentioned data were unavailable due to the data collection approach and reliance on physician responses. The coverage of institution was 18.8%, and the number of COVID-19 patients diagnosed with ILD and lung cancer was limited, which merits further investigation into each specific respiratory disease.

In conclusion, the prevalence of asthma among COVID-19 patients was low compared to the general population, comorbidity with asthma was not related to COVID-19 mortality, and ILD was a comorbid respiratory disease associated with a particularly high COVID-19 mortality. These findings will help to establish an appropriate strategy for prevention and treatment for COVID-19 in patients with comorbid respiratory diseases.

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Conflict of Interest

The authors have no conflicts of interest.

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