



# COVID-19 associated pulmonary aspergillosis: a nationwide survey by the Japanese Respiratory Society

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To the Editor:

The pandemic of coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread worldwide and resulted in more than 3.5 million deaths as of June 2021 [1]. Respiratory viruses, such as the influenza virus, cause direct damage to the airway epithelium, enabling *Aspergillus* to invade airway tissues. SARS-CoV-2 infection can also increase the risk of *Aspergillus* superinfection, *i.e.*, the so-called COVID-19 associated pulmonary aspergillosis (CAPA), in severe COVID-19 patients [2]. CAPA has become a serious concern worldwide for the management of severe COVID-19 [2]. Several studies have reported a high incidence of CAPA and associated mortality rates in critical COVID-19 patients [3–12]. However, these reports were from limited facilities in the USA or European countries, and epidemiological data from other regions of the world are limited. Therefore, we conducted a nationwide internet questionnaire surveillance study in Japan to obtain large-scale epidemiological data.

An internet questionnaire survey was conducted with the chief physicians of respiratory disease departments of 715 Japanese Respiratory Society certified hospitals using a Google Form between 28 January 2021 and 28 February 2021. The questionnaire included the total number of COVID-19 cases diagnosed based on reverse transcription-PCR testing and incidence of CAPA in each hospital from the beginning of the COVID-19 pandemic up to 27 January 2021. Information about CAPA patients such as age groups, underlying diseases, the severity of COVID-19 according to the US National Institutes of Health treatment guidelines [13], evidence for the diagnosis of CAPA, treatment, and their outcomes were collected. Informed written consent was not required because the study used de-identified patient data. The study was approved by the Japanese Respiratory Society.

Responses to the questionnaire survey were obtained from 198 of the 715 hospitals (27.6%). About a half of these facilities were tertiary medical centres, and 40 (20.2%) were university hospitals. The hospitals were distributed throughout Japan, with two in Hokkaido, eight in Tohoku, 60 in Kanto, including Tokyo, 43 in Chubu-Hokuriku-Koshinetsu, 25 in Kinki, 19 in Chugoku-Shikoku, and 41 in Kyusyu. The number of moderate/severe and critical COVID-19 patients were 10047 and 1664, respectively, as defined by the National Institutes of Health treatment guidelines. Only 10 cases from seven hospitals were diagnosed with complicating CAPA. The severity of COVID-19 in these 10 cases with CAPA was nine critical and one severe. The age groups of these patients were as follows: one in their 50s, two in their 60s, five in their 70s, and two over 80 years of age. The incidence rate of CAPA in critical patients who needed mechanical ventilation was only 0.54% (9/1664). Respiratory specimens showed *Aspergillus* positive culture in six cases, three being positive for *Aspergillus fumigatus*, and one each for *Aspergillus terreus*, *Aspergillus niger* and *Aspergillus flavus*. Serum  $\beta$ -D-glucan (BDG) and galactomannan (GM) tests were positive in five (50%) and two (20%) patients, respectively. The underlying diseases of the COVID-19 patients with CAPA were hypertension (n=8), COPD (n=5), diabetes mellitus (n=3), cardiac diseases (n=3), and chronic renal failure (n=2). All COVID-19 patients with CAPA had been treated with corticosteroids, two patients had also received tocilizumab. Nine of the patients with CAPA were prescribed voriconazole, and the other patient was administered liposomal amphotericin B and micafungin. Two of the 10 patients with CAPA recovered, five died during their hospital stay, and three were under treatment at the time of the survey.



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An online nationwide questionnaire survey in Japan revealed that the incidence rate of #COVID19 associated pulmonary aspergillosis in critical COVID-19 cases was extremely low (0.54%) compared with those previously reported in the USA and Europe <https://bit.ly/2WdFtPj>

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In this study, we performed an online nationwide questionnaire survey and found that the incidence rate of CAPA in critical COVID-19 cases was extremely low (0.54%) compared with those previously reported, as summarised in table 1. The study subjects in these reports were ICU-managed or critical COVID-19 patients. The incidence rates were 3.3% to 35% in the USA and European countries (table 1).

Obtaining mycological evidence from COVID-19 patients is challenging because diagnostic bronchoscopy could increase the risk of healthcare workers being exposed to dispersed aerosols. Therefore, it was difficult to acquire mycological evidence of *Aspergillus* infection. Serological diagnostic tests, such as *Aspergillus* GM and BDG were useful in this situation. Data from the UK National Mycology Reference Laboratory showed a relatively higher positivity rate (80%) for CAPA through the BDG test than through the GM antigen test (33%) [14].

It is unlikely that many patients with CAPA were overlooked in Japan for the following three reasons. First, data were obtained mostly from tertiary medical centres, including 40 university hospitals. Second, BDG and GM tests are widely available in Japan. Third, the mortality rates per 100 000 population of COVID-19 patients in Japan are similar to those in the USA and lower than those of European countries [15].

Japan has experienced three waves of the COVID-19 pandemic; the second and third waves were much larger than the first one. Use of corticosteroids, mainly dexamethasone, for COVID-19 patients with hypoxia has also been recommended since the second wave hit the country; hence, it is unlikely that the rate of steroid use was lower in Japan than in other countries.

The previous studies were active surveillance studies, each with specific diagnostic criteria, and could be more accurate compared with our surveillance although the sample sizes were small. Therefore, the reason for the large difference in the incidence rate of CAPA among COVID-19 patients in our study compared with that among those in the USA and European countries might be the difference in study designs. However, a recent meta-analysis of COVID-19 autopsy case studies, mainly from the USA or European countries, showed the very low incidence of CAPA at 8 out of 677 cases (1.18%) [16]. Therefore, there is a possibility that the clinical criteria used in the initial studies might over diagnose cases due to colonisation with *Aspergillus* spp. The other reason for the high incidence rate of CAPA could be due to publication bias.

TABLE 1 Incidence of COVID-19 associated pulmonary aspergillosis (CAPA) patients in different countries

Country	Incidence ratio of CAPA (95% CI) (number of patients/total patients)	Number of facilities	Patient background	Reference
France	0.179 (0.111–0.265) (19/106)	Single centre	Intubated patients	[4]
France	0.333 (0.165–0.539) (9/27)	Single centre	Intubated patients	[5]
Germany	0.263 (0.091–0.512) (5/19)	Single centre	ICU patients	[6]
USA	0.193 (0.074–0.374) (6/31)	Single centre	Intubated patients	[7]
The Netherlands	0.197 (0.109–0.313) (13/66)	Single centre	Intubated patients	[8]
Spain	0.033 (0.014–0.064) (8/239)	Single centre	ICU patients	[9]
France	0.13 (0.049–0.262) (6/46)	Single centre	ICU patients	[10]
Italy	0.277 (0.195–0.372) (30/108)	Single centre	Intubated patients	[11]
Belgium	0.35 (0.153–0.592) (7/20)	Single centre	Intubated patients	[12]
USA	0.098 (0.070–0.132) (39/396)	5 hospitals	Intubated patients	[3]
Japan (this study)	0.0054 (0.0024–0.010) (9/1664)	Nationwide survey by the Japanese Respiratory Society	Intubated patients	This study

ICU: intensive care unit.

The strong point of this study is that we could perform a large-scale, nationwide survey. Our study has some limitations. The available data were limited by the nature of the questionnaire-based study. The diagnosis of CAPA was based on the judgement of each physician, but not based on defined diagnostic criteria. Information such as previous *Aspergillus* infections or colonisation were not collected for the CAPA patients.

In conclusion, our results suggest that the incidence of CAPA in Japan may not be as high as expected from other studies. However, the diagnosis of CAPA is challenging, and large-scale prospective surveillance studies based on international guidelines are warranted to investigate the epidemiology of CAPA.

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## References

- 1 World Health Organization. World Health Organization Coronavirus (COVID-19) Dashboard. <https://covid19.who.int/>
- 2 Koehler P, Bassetti M, Chakrabarti A, *et al.* Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *Lancet Infect Dis* 2020; 21: e149–e162.
- 3 Permpalung N, Chiang TP, Massie AB, *et al.* COVID-19 associated pulmonary aspergillosis in mechanically ventilated patients. *Clin Infect Dis* 2021; in press [<https://doi.org/10.1093/cid/ciab223>].
- 4 Dupont D, Menotti J, Turc J, *et al.* Pulmonary aspergillosis in critically ill patients with Coronavirus Disease 2019 (COVID-19). *Med Mycol* 2021; 59: 110–114.
- 5 Alanio A, Delliere S, Fodil S, *et al.* Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. *Lancet Respir Med* 2020; 8: e48–e49.
- 6 Koehler P, Cornely OA, Bottiger BW, *et al.* COVID-19 associated pulmonary aspergillosis. *Mycoses* 2020; 63: 528–534.
- 7 van Arkel ALE, Rijpsstra TA, Belderbos HNA, *et al.* COVID-19-associated pulmonary aspergillosis. *Am J Respir Crit Care Med* 2020; 202: 132–135.

- 8 Meijer EFJ, Dofferhoff ASM, Hoiting O, *et al.* COVID-19-associated pulmonary aspergillosis: a prospective single-center dual case series. *Mycoses* 2021; 64: 457–464.
- 9 Machado M, Valerio M, Alvarez-Uria A, *et al.* Invasive pulmonary aspergillosis in the COVID-19 era: an expected new entity. *Mycoses* 2021; 64: 132–143.
- 10 Chauvet P, Mallat J, Arumadura C, *et al.* Risk factors for invasive pulmonary aspergillosis in critically ill patients with coronavirus disease 2019-induced acute respiratory distress syndrome. *Crit Care Explor* 2020; 2: e0244.
- 11 Bartoletti M, Pascale R, Cricca M, *et al.* Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. *Clin Infect Dis* 2020; in press [<https://doi.org/10.1093/cid/ciaa1065>].
- 12 Rutsaert L, Steinfort N, Van Hunsel T, *et al.* COVID-19-associated invasive pulmonary aspergillosis. *Ann Intensive Care* 2020; 10: 71.
- 13 US National Institutes of Health. NIH COVID-19 treatment guidelines. [www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/](http://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/) Date last updated: 21 April 2021.
- 14 Borman AM, Palmer MD, Fraser M, *et al.* COVID-19-associated invasive aspergillosis: data from the UK national mycology reference laboratory. *J Clin Microbiol* 2020; 59: e02136-20.
- 15 Johns Hopkins University and Medicine, Coronavirus Resource Center. Mortality Analyses. <https://coronavirus.jhu.edu/data/mortality>
- 16 Kula BE, Clancy CJ, Hong Nguyen M, *et al.* Invasive mould disease in fatal COVID-19: a systematic review of autopsies. *Lancet Microbe* 2021; 2: e405–e414.