



Early View

Research letter

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

Takahiro Takazono, Hiroshi Mukae, Koichi Izumikawa, Naoki Hasegawa, Akihito Yokoyama

Please cite this article as: Takazono T, Mukae H, Izumikawa K, *et al.* COVID-19 associated pulmonary aspergillosis: a nationwide survey by the Japanese Respiratory Society. *ERJ Open Res* 2021; in press (<https://doi.org/10.1183/23120541.00402-2021>).

This manuscript has recently been accepted for publication in the *ERJ Open Research*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

Copyright ©The authors 2021. This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Research letter

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

Takahiro Takazono^{1,2*}, Hiroshi Mukae^{1,3}, Koichi Izumikawa², Naoki Hasegawa⁴, Akihito Yokoyama⁵

¹*Department of Respiratory Medicine, Nagasaki University Hospital, Nagasaki, Japan*

²*Department of Infectious Diseases, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan*

³*Department of Respiratory Medicine, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan*

⁴*Department for Infectious Diseases, Keio University School of Medicine, Tokyo, Japan*

⁵*Department of Respiratory and Allergology Medicine, Kochi Medical School, Kochi University, Kochi, Japan*

***Correspondence:**

Takahiro Takazono, M.D., Ph.D.

Department of Infectious Diseases, Nagasaki University Graduate School of Biomedical Sciences

1-7-1 Sakamoto, Nagasaki 852-8501, Japan

Phone: +81 -95-819-7273

Fax: +81-95-849-7285

E-mail: takahiro-takazono@nagasaki-u.ac.jp

Take home message:

An online nationwide questionnaire survey in Japan revealed that the incidence rate of COVID-19 associated pulmonary aspergillosis in critical COVID-19 cases was

extremely low (0.54%) compared with those previously reported in US and European countries.

Introduction

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 people 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 United States (US) 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.

Materials and Methods

An internet questionnaire survey was conducted with the chief physicians of respiratory disease departments of 715 Japanese Respiratory Society certified hospitals using Google Form between January 28, 2021 and February 28, 2021. The questionnaire included the total number of COVID-19 cases diagnosed based on reverse transcription-polymerase chain reaction testing and incidence of CAPA in each hospital from the beginning of the

COVID-19 pandemic to January 27, 2021. Information of CAPA patients such as age groups, underlying diseases, the severity of COVID-19 according to the National Institute of Health treatment guidelines [13], evidence for the diagnosis of CAPA, treatment, and their outcomes was collected. Informed written consent was not required because the study utilised de-identified data of patients and was approved by the Japanese Respiratory Society.

Results

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 10,047 and 1,664, respectively, as defined by the National Institute 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 one in their 50s, two in their 60s, five in their 70s, and two over 80s. The incidence rate of CAPA in critical patients who needed mechanical ventilation was only 0.54% (9/1,664). 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 β -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),

chronic obstructive pulmonary disease (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 also had received tocilizumab. Nine of the patients with CAPA were prescribed voriconazole, and the other one was administered liposomal amphotericin B and micafungin. Two of the 10 patients with CAPA recovered, five died during the hospital stay, and three were under treatment at the time of the survey.

Discussion

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 US and European countries (Table 1).

Obtaining mycological evidence from COVID-19 patients is challenging because diagnostic bronchoscopy could increase the exposure risk of dispersed aerosols to healthcare workers. 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 National Mycology Reference Laboratory, United Kingdom 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 from mostly tertiary medical centres, including 40 university hospitals. Second, BDG and GM tests are widely available in Japan. Third,

the mortality rates/100,000 population of COVID-19 in Japan are similar to those of the US 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 was also recommended since the second wave had 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 with each specific diagnostic criterion and could be more accurate compared to our surveillance though 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 United States and European countries might be the difference in study designs. However, recent meta-analysis of COVID-19 autopsy cases studies mainly from US or European countries showed the very low incidence of CAPA as 8/677 (1.18%) [16]. Therefore, the possibility that clinical criteria used in initial studies might involve over diagnosis cases due to colonization of *Aspergillus spp.* The other reason for the high incidence rate of CAPA could be due to publication bias.

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 to 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. The information such as previous *Aspergillus* infections or colonization were not collected in 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, a

large-scale prospective surveillance studies based on international guidelines are warranted to investigate the epidemiology of CAPA.

Acknowledgement

We acknowledge the members of the COVID-19 expert opinion working group of the Japanese Respiratory Society for their support in this study.

Funding

This study was not supported by any specific grant.

Conflicts of interest

The authors have no conflicts of interest to declare.

Table 1. Incidence of COVID-19 associated pulmonary aspergillosis patients in different countries

Country	Incidence ratio of CAPA [95% confidence interval] (number of patients)	Number of facilities	Patient Background	Reference
France	0.179 [0.111 - 0.265] (19/106)	Singe 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)	Singe centre	ICU patients	[6]
US	0.193 [0.074 - 0.374] (6/31)	Single centre	Intubated patients	[7]
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)	Singe centre	ICU patients	[10]
Italy	0.277 [0.195 - 0.372] (30/108)	Singe centre	Intubated patients	[11]
Belgium	0.35 [0.153 - 0.592] (7/20)	Single centre	Intubated patients	[12]
US	0.098 [0.070 - 0.132] (39/396)	5 hospitals	Intubated patients	[3]
Japan (our study)	0.0054 [0.024 - 0.010] (9/1,664)	Nationwide survey by the Japanese Respiratory Society	Intubated patients	Our study

CAPA: COVID-19 associated pulmonary aspergillosis; ICU, Intensive care unit

References

1. World Health Organization Coronavirus (COVID-19) Dashboard
<https://covid19.who.int/>.
2. Koehler P, Bassetti M, Chakrabarti A, Chen SCA, Colombo AL, Hoenigl M, Klimko N, Lass-Flörl C, Oladele RO, Vinh DC, Zhu LP, Boll B, Brüggemann R, Gangneux JP, Perfect JR, Patterson TF, Persigehl T, Meis JF, Ostrosky-Zeichner L, White PL, Verweij PE, Cornely OA, European Confederation of Medical M, International Society for Human Animal M, Asia Fungal Working G, Group ILIW, Group IPAMW, European Society for Clinical M, Infectious Diseases Fungal Infection Study G, Patients ESGfIICI, Interregional Association of Clinical M, Antimicrobial C, Medical Mycology Society of N, Medical Mycology Society of China Medicine Education A, Infectious Diseases Working Party of the German Society for H, Medical O, Association of Medical M, Infectious Disease C. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. *Lancet Infect Dis* 2020.
3. Permpalung N, Chiang TP, Massie AB, Zhang SX, Avery RK, Nematollahi S, Ostrander D, Segev DL, Marr KA. COVID-19 Associated Pulmonary Aspergillosis in Mechanically Ventilated Patients. *Clin Infect Dis* 2021.
4. Dupont D, Menotti J, Turc J, Miossec C, Wallet F, Richard JC, Argaud L, Paulus S, Wallon M, Ader F, Persat F. Pulmonary aspergillosis in critically ill patients with Coronavirus Disease 2019 (COVID-19). *Med Mycol* 2021; 59(1): 110-114.

5. Alanio A, Delliere S, Fodil S, Bretagne S, Megarbane B. Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. *Lancet Respir Med* 2020; 8(6): e48-e49.
6. Koehler P, Cornely OA, Bottiger BW, Dusse F, Eichenauer DA, Fuchs F, Hallek M, Jung N, Klein F, Persigehl T, Rybniker J, Kochanek M, Boll B, Shimabukuro-Vornhagen A. COVID-19 associated pulmonary aspergillosis. *Mycoses* 2020; 63(6): 528-534.
7. van Arkel ALE, Rijpstra TA, Belderbos HNA, van Wijngaarden P, Verweij PE, Bentvelsen RG. COVID-19-associated Pulmonary Aspergillosis. *Am J Respir Crit Care Med* 2020; 202(1): 132-135.
8. Meijer EFJ, Dofferhoff ASM, Hoiting O, Meis JF. COVID-19-associated pulmonary aspergillosis: a prospective single-center dual case series. *Mycoses* 2021; 64(4): 457-464.
9. Machado M, Valerio M, Alvarez-Uria A, Olmedo M, Veintimilla C, Padilla B, De la Villa S, Guinea J, Escribano P, Ruiz-Serrano MJ, Reigadas E, Alonso R, Guerrero JE, Hortal J, Bouza E, Munoz P, Group C-S. Invasive pulmonary aspergillosis in the COVID-19 era: An expected new entity. *Mycoses* 2021; 64(2): 132-143.
10. Chauvet P, Mallat J, Arumadura C, Vangrunderbeek N, Dupre C, Pauquet P, Orfi A, Granier M, Lemyze M. Risk Factors for Invasive Pulmonary Aspergillosis in Critically Ill Patients With Coronavirus Disease 2019-Induced Acute Respiratory Distress Syndrome. *Crit Care Explor* 2020; 2(11): e0244.

11. Bartoletti M, Pascale R, Cricca M, Rinaldi M, Maccaro A, Bussini L, Fornaro G, Tonetti T, Pizzilli G, Francalanci E, Giuntoli L, Rubin A, Moroni A, Ambretti S, Trapani F, Vatamanu O, Ranieri VM, Castelli A, Baiocchi M, Lewis R, Giannella M, Viale P, group Ps. Epidemiology of invasive pulmonary aspergillosis among COVID-19 intubated patients: a prospective study. *Clin Infect Dis* 2020.
12. Rutsaert L, Steinfort N, Van Hunsel T, Bomans P, Naesens R, Mertes H, Dits H, Van Regenmortel N. COVID-19-associated invasive pulmonary aspergillosis. *Ann Intensive Care* 2020; 10(1): 71.
13. NIH COVID-19 treatment guidelines. [cited; Available from: <https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/>]
14. Borman AM, Palmer MD, Fraser M, Patterson Z, Mann C, Oliver D, Linton CJ, Gough M, Brown P, Dzietyczyk A, Hedley M, McLachlan S, King J, Johnson EM. COVID-19-Associated Invasive Aspergillosis: Data from the UK National Mycology Reference Laboratory. *J Clin Microbiol* 2020; 59(1).
15. Johns Hopkins University and Medicine, Coronavirus Resource center. (<https://coronavirus.jhu.edu/data/mortality>)
16. Kula BE, Clancy CJ, Hong Nguyen M, Schwartz IS. Invasive mould disease in fatal COVID-19: a systematic review of autopsies. *Lancet Microbe* 2021; 2(8): e405-e414.