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Incidence and mortality of COVID-19-associated pulmonary aspergillosis: A systematic review and meta-analysis

Hayato Mitaka[1] | Toshiki Kuno[1] | Hisato Takagi[2] | Paru Patrawalla[3]

[1]Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, New York, NY, USA

[2]Division of Cardiovascular Surgery, Shizuoka Medical Center, Shizuoka, Japan

[3]Division of Pulmonary and Critical Care Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, New York, NY, USA

Correspondence
Toshiki Kuno, Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, 281 First Avenue, New York, NY, 10003, USA.
Email: Toshiki.Kuno@mountsinai.org

Abstract

COVID-19-associated pulmonary aspergillosis (CAPA) has been reported worldwide. However, basic epidemiological characteristics have not been well established. In this systematic review and meta-analysis, we aimed to determine the incidence and mortality of CAPA in critically ill patients with COVID-19 to improve guidance on surveillance and prognostication. Observational studies reporting COVID-19-associated pulmonary aspergillosis were searched with PubMed and Embase databases, followed by an additional manual search in April 2021. We performed a one-group meta-analysis on the incidence and mortality of CAPA using a random-effect model. We identified 28 observational studies with a total of 3148 patients to be included in the meta-analysis. Among the 28 studies, 23 were conducted in Europe, two in Mexico and one each in China, Pakistan and the United States. Routine screening for secondary fungal infection was employed in 13 studies. The modified AspICU algorithm was utilised in 15 studies and was the most commonly used case definition and diagnostic algorithm for pulmonary aspergillosis. The incidence and mortality of CAPA in the ICU were estimated to be 10.2% (95% CI, 8.0–12.5; I^2 = 82.0%) and 54.9% (95% CI, 45.6–64.2; I^2 = 62.7%), respectively. In conclusion, our estimates may be utilised as a basis for surveillance of CAPA and prognostication in the ICU. Large, prospective cohort studies based on the new case definitions of CAPA are warranted to validate our estimates.

KEYWORDS
acute respiratory distress syndrome, COVID-19, pulmonary aspergillosis, SARS-CoV-2

1 | INTRODUCTION

With the emergence of the COVID-19 pandemic, there have been a number of reports worldwide of COVID-19-associated pulmonary aspergillosis (CAPA).[1–3] As observed in influenza-associated pulmonary aspergillosis, patients with CAPA may lack classic host factors for invasive fungal diseases.[4] It is speculated that immune dysregulation associated with acute respiratory distress syndrome (ARDS), disrupted ciliary clearance and lymphopenia due to severe respiratory viral infection may contribute to the development of invasive pulmonary aspergillosis in critically ill patients with COVID-19.[5,6] Multiple prospective cohort studies suggested that CAPA was associated with increased mortality in patients with COVID-19.[7–12] Furthermore, corticosteroids are currently being used to patients with severe COVID-19 more universally than in early 2020 since RECOVERY trial[13] showed mortality benefit, which could lead to a further increase in the incidence of CAPA in the ICU. Galactomannan testing from bronchoalveolar lavage (BAL) fluid is the most sensitive test for pulmonary aspergillosis in ICU patients[4]; however, studies on CAPA have been hindered by diagnostic challenges, primarily as

bronchoscopies are rarely performed in patients with COVID-19 due to the risk of disease transmission.[14] As the majority of studies on CAPA have been case series[15,16] and small observational studies,[1,2,17–19] the true incidence and clinical significance of CAPA in ICU patients is uncertain. In this study, we conducted a systematic review and meta-analysis to determine the incidence and mortality of CAPA in patients with COVID-19 for better guidance on surveillance and prognostication.

2 | PATIENTS AND METHODS

2.1 | Data sources and search

All prospective and retrospective observational studies reporting CAPA were searched using a two-level search strategy. First, we conducted a comprehensive literature search of PubMed and Embase databases through 4 April 2021. The search terms included ("COVID-19" OR "SARS-CoV-2" OR "coronavirus") AND ("aspergillosis" OR "aspergillus"). Second, we performed an additional manual search of secondary sources, including references of initially identified articles, to maximise the completeness of the collection of relevant studies. The search was performed without language restriction.

2.2 | Study selection

A study was included in the meta-analysis if the following criteria were met: (1) the study was published in a peer-reviewed journal, (2) the study design was a prospective or retrospective observational study, (3) the study population included hospitalised adult patients with COVID-19 and (4) the diagnosis of pulmonary aspergillosis was made based on specific case definitions or diagnostic algorithms including the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) definitions,[20] AspICU algorithm,[21] modified AspICU algorithm,[4] case definitions of influenza-associated pulmonary aspergillosis (IAPA),[22] and the European Confederation for Medical Mycology and the International Society for Human and Animal Mycology (ECMM/ISHAM) consensus criteria.[5] We excluded observational studies with diagnostic criteria for CAPA not clearly documented, as well as case reports and case series.

2.3 | Data extraction

Two investigators (HM and TK) reviewed the search results separately to select the studies based on the inclusion and exclusion criteria and assessed the eligibility of each study. The full text of articles was retrieved for eligibility assessment and further analyses after the initial screening with title and abstract. Any discrepancies were resolved by discussion and consensus. The following data were extracted from each eligible study: author name, study location, design, setting and case definition or diagnostic algorithm used to classify CAPA. We also collected the following patient characteristics and outcomes: the number of patients in the ICU during the study period, the number of patients with CAPA, the numbers of patients who received systemic steroids, tocilizumab and antifungal treatment, and the number of deaths among the patients with CAPA. If the patient population in a primary study was not limited to the ICU, we used only patients in the ICU for the analysis.

2.4 | Statistical analysis

The endpoints of this study were the incidence and mortality of CAPA in patients with COVID-19 in the ICU. We conducted a one-group meta-analysis with a random-effects model using the DerSimonian-Laird method. OpenMetaAnalyst version 12.11.14 was used to perform the statistical analysis (available at http://www.cebm.brown.edu/openmeta/).[23] The I^2 statistic was used to quantify heterogeneity among studies, with $I^2 > 50\%$ indicating substantial heterogeneity. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[24]

3 | RESULTS

A total of 302 articles were identified through the initial database search and subsequent manual search. After the removal of duplicated items and screening based on title and abstract, 105 articles were assessed for eligibility. We excluded 77 articles including five case series and 38 case reports. Notably, two retrospective observational studies were excluded because the case definitions or diagnostic algorithms used to classify pulmonary aspergillosis were not documented. Finally, 28 observational studies were included in our meta-analysis (Figure 1).

The study characteristics included in the meta-analysis are summarised in Table 1.[1,2,7–12,17–19,25–41] Among the 28 studies selected, 23 were conducted in European countries, two in Mexico and one each in China, Pakistan and the United States. All studies started during the first wave of the pandemic, or in early 2020, with the exception of four studies that did not specify their study periods. Routine screening for secondary invasive fungal infection (eg aspergillosis and candidiasis) was employed in 13 studies. There was a variation in galactomannan index cut-off values used across studies. For serum galactomannan index, 0.5 was the most common cut-off value, used by 16 studies, followed by 1.0 being used by two studies. For BAL galactomannan index, 1.0 was most commonly used by 16 studies, followed by 0.5 and 0.8 being used by two studies, respectively. Five studies did not document the

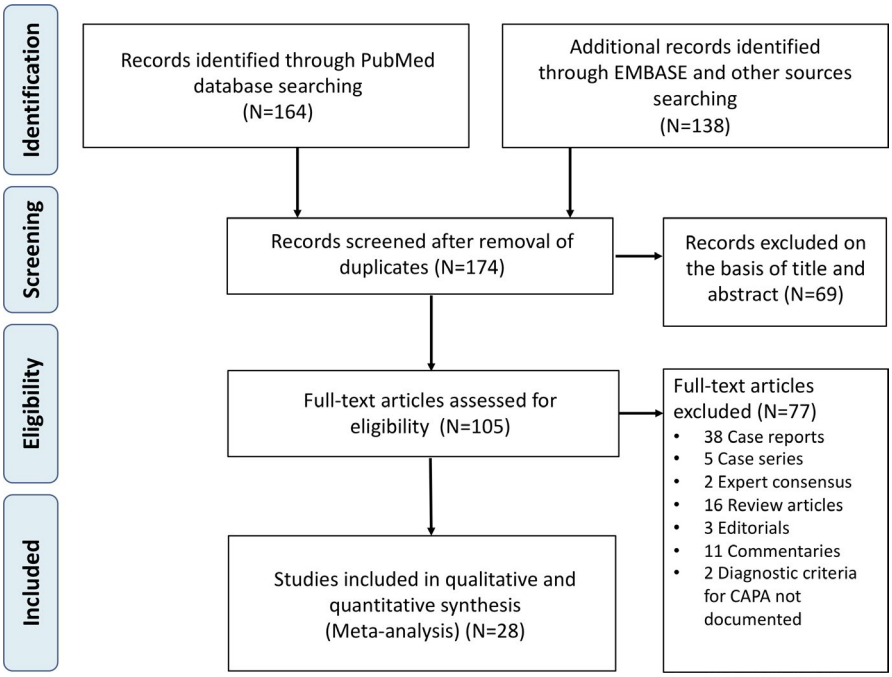

FIGURE 1 Flow diagram of study selection

cut-off values for galactomannan index. The modified AspICU algorithm was used in 15 studies and was the most commonly used case definition and diagnostic algorithm. The median age ranged from 55 to 70. The percentage of males ranged from 60% to 82%. Median time from ICU admission to the diagnosis of CAPA ranged from 3 to 15 days. There was a large variation between studies in the percentages of patients with CAPA receiving systemic steroids and antifungal treatment, ranging from 0% to 100% and 22 to 100%, respectively. A total of 3148 patients with COVID-19 in the ICU were included in the analysis. The incidence and mortality of CAPA in the ICU were estimated to be 10.2% (95% CI, 8.0–12.5; I^2 = 82.0%) and 54.9% (95% CI, 45.6–64.2; I^2 = 62.7%), respectively (Figures 2 and 3).

4 | DISCUSSION

In this meta-analysis, we estimated the incidence and mortality of CAPA in critically ill patients with COVID-19 in the ICU. CAPA occurred in 10.2% of cases in these studies and was associated with high mortality. Since the start of the COVID-19 pandemic, CAPA has been reported as a complication of mechanically ventilated patients with COVID-19 from across the world. However, epidemiological data on incidence and mortality were variable as the reports were mainly based on case series and small observational studies, especially in the early stages of the pandemic.

Early studies and case series from Europe reported that pulmonary aspergillosis occurred in 20%-35% of cases in the ICU.[1–3,18,33] However, several more recent prospective cohort studies reported a lower incidence of 3%.[11,12] Interestingly, studies with larger sample sizes had lower estimates of incidence, potentially suggesting reporting bias in smaller studies. Given that as many as about 10% of mechanically ventilated patients with COVID-19 in the ICU were affected by CAPA as shown in our analysis, routine surveillance with tracheal aspirate and non-bronchoscopic lavage, serum galactomannan and chest CT might be justified.[5] This high incidence, combined with considerable mortality, might also increase the need for clinical trials to determine whether antifungal prophylaxis is beneficial. The high heterogeneity in incidence among each study may be explained by the differences in (1) the routine screening for CAPA, (2) the case definitions used and (3) the pharmacological treatment of critically ill patients with COVID-19. First, there may be a risk of overdiagnosis with routine BAL in mechanically ventilated patients with COVID-19 since positive mycological BAL testing can lead to the classification of CAPA, while progressive radiological and clinical manifestations of COVID-19 itself may fulfil these criteria. Salmanton-García and colleagues also suggested that practice variations in screening for CAPA in COVID-19 patients might have affected detection rates.[3] Second, it is possible that heterogeneous conditions, including colonisation with *Aspergillus*, were reported as CAPA because the definition of CAPA was not clearly determined until recently.[5] It is highly likely that there is underdiagnosis in studies using only EORTC/MSG definitions that are unsuitable for patients in ICU, as a number of patients may not be classifiable due to a lack of host factors and typical radiological features.[20] Underdiagnosis might also be present with the original and modified AspICU criteria since they do not include PCR testing, which is incorporated into the new case definitions and would lead to increased case detection rates. Several studies that examined multiple diagnostic criteria simultaneously found differences in the number of patients classified.[7,8,30] Third, many of the studies included in the meta-analysis were conducted before treatment standardisation where pharmacologic therapies

TABLE 1 Study and patient characteristics[a]

Author	Country	Design	Setting	Study period	Population	Routine screening for aspergillosis
Alanio et al[2]	France	Prospective	Single-centre	–	MV patients in the ICU	Yes
Bartoletti et al[7]	Italy	Prospective	Multicentre	Feb 22–Apr 20, 2020	MV patients in the ICU	Yes
Chauvet et al[25]	France	Retrospective	Single-centre	Mar 24–May 25, 2020	ARDS patients in the ICU	No
Dellière et al[26]	France	Retrospective	Multicentre	Mar 15–May 01, 2020	Patients in the ICU	No
Dupont et al[27]	France	Prospective	Multicentre	Mar 01–Apr 11, 2020	Patients in the ICU	No
Fekkar et al[36]	France	Retrospective	Single-centre	Mar 6–Apr 24, 2020	Patients in the ICU	No
Gangneux et al[9]	France	Prospective	Single-centre	–	MV patients in the ICU	Yes
Gouzien et al[37]	France	Retrospective	Single-centre	Mar 01–Apr 30, 2020	Patients in the ICU	Yes
Koehler et al[1]	Germany	Retrospective	Single-centre	Mar 07–Apr 22, 2020	ARDS patients in the ICU	Yes
Lahmer et al[10]	Germany	Prospective	Single-centre	Mar 01–Apr 30, 2020	MV patients in the ICU	Yes
Lamoth et al[28]	Switzerland	Retrospective	Single-centre	Mar 06–May 11, 2020	MV patients in the ICU	Yes
Machado et al[11]	Spain	Prospective	Single-centre	Mar 01–May 31, 2020	All hospitalised patients	No
Maes et al[29]	UK	Retrospective	Single-centre	Mar 15–Aug 30, 2020	MV patients in the ICU	No
Nasir et al[17]	Pakistan	Retrospective	Single-centre	Feb–Apr, 2020 (Date unspecified)	All hospitalised patients	No
Permpalung et al[38]	USA	Retrospective	Multicentre	Mar–Aug, 2020 (Date unspecified)	MV patients in the ICU	Yes
Razazi et al[30]	France	Retrospective	Single-centre	Oct 01, 2009–Apr 29, 2020	MV patients in the ICU	No
Ripa et al[31]	Italy	Prospective	Single-centre	Feb 25–Apr 06, 2020	All hospitalised patients	No
Roman-Montes et al[32]	Mexico	Retrospective	Single-centre	Apr 13–Jun 01, 2020	MV patients in the ICU	No
Rutsaert et al[33]	Belgium	Retrospective	Single-centre	Mar 12–Apr 25, 2020	MV patients in the ICU	No
Sarrazyn et al[34]	Belgium	Retrospective	Single-centre	Mar 11–Apr 17, 2020	All hospitalised patients	Yes
Segrelles-Calvo et al[12]	Spain	Prospective	Single-centre	Feb 01–Apr 30, 2020	Patients in the ICU	Yes
van Arkel et al[18]	Netherlands	Retrospective	Single-centre	–	MV patients in the ICU	No
Van Biesen et al[35]	Netherlands	Retrospective	Single-centre	Apr, 2020 (Date unspecified)	MV patients in the ICU	Yes
van Grootveld et al[39]	Netherlands	Retrospective	Single-centre	Apr 01–May 11, 2020	Patients in the ICU	Yes
Vélez Pintado et al[40]	Mexico	Retrospective	Single-centre	Mar 15–Jul 10, 2020	Patients in the ICU	No
Versyck et al[41]	France	Retrospective	Single-centre	Mar 15–Apr 30, 2020	MV patients with in the ICU	Yes
Wang et al[19]	China	Retrospective	Single-centre	Jan–Mar, 2020 (Date unspecified)	All hospitalised patients	No
White et al[8]	UK	Prospective	Multicentre	–	Patients in the ICU	No

Author	Patients with COVID-19 in the ICU	Patients with CAPA	Days from COVID-19 diagnosis	Days from ICU admission
Alanio et al	27	9	–	–
Bartoletti et al	108	30	–	–
Chauvet et al	46	6	–	–
Dellière et al	366	21	–	6 (1–15)
Dupont et al	106	19	11 (7–14)	10 (8–14.5)
Fekkar et al	260	6	–	7 (2–56)
Gangneux et al	45	7	–	–
Gouzien et al	53	2	–	–
Koehler et al	19	5	–	–
Lahmer et al	32	11	–	4 (range, 1–7)
Lamoth et al	80	3	8 (7–13)	7 (3–8)

Case definition/diagnostic algorithm	Age	Male (%)	Hypertension (%)	Diabetes (%)	Obesity (%)	CKD (%)	COPD (%)	Immunosuppressive condition (%)
Modified AspICU	63 (56–71)	67	–	–	–	–	–	–
AspICU, IAPA	63 (57–70)	–	63	17	43	12	17	–
EORTC/MSG, AspICU, modified AspICU	–	–	–	41	72	–	13	11
EORTC/MSG, IAPA	62 (56–68)	82	59	37	32	–	2	9
Modified AspICU	–	–	–	–	–	–	–	–
EORTC/MSG	55 (48–64)	72	57	32	68	–	6	14
AspICU, modified AspICU	60 (53–71)	71	33	38	–	9	0	–
EORTC/MSG, AspICU, modified AspICU, IAPA	64 (55–74)	68	43	25	34	–	13	–
AspICU, modified AspICU	–	–	–	–	–	–	–	–
Modified AspICU	70 (range, 27–84)	72	65	25	–	16	10	–
IAPA	–	–	–	–	–	–	–	–
EORTC/MSG, modified AspICU	–	–	–	–	–	–	–	–
Modified AspICU	62 (50–70)	69	33	22	37	12	–	15
Modified AspICU	–	–	–	–	–	–	–	–
Original composite criteria	59 (53–69)	82	66	43	–	16	10	18
AspICU, modified AspICU, IAPA	59 (53–69)	82	66	43	–	16	10	18
Modified AspICU	64 (55–76)	68	47	18	–	11	7	–
Modified AspICU	49 ± 12	72	26	24	57	–	–	–
AspICU	–	–	–	–	–	–	–	–
Modified AspICU	67 (56–79)	60	–	–	–	–	–	–
EORTC/MSG	–	–	–	–	–	–	–	–
IAPA	–	–	–	–	–	–	–	–
AspICU	62 (range, 25–79)	79	31	24	–	–	19	5
ECMM/ISHAM	62 (57–71)	73	–	24	–	–	–	–
ECMM/ISHAM	–	–	31	22	30	–	5	–
Modified AspICU	65 (range, 44–83)	72	–	41	–	7	–	–
EORTC/MSG	53 ± 15	60	37	13	–	2	4	0
AspICU, IAPA	57 (48–64)	–	26	28	20	6	–	–

Patients with CAPA who received systemic steroids	Patients with CAPA who received tocilizumab	Patients with CAPA who received antifungal therapy
6 (67)	–	2 (22)
18 (60)	22 (73)	16 (53)
5 (83)	–	5 (83)
–	2 (10)	–
7 (37)	–	9 (47)
1 (17)	–	5 (83)
–	–	7 (100)
–	–	1 (50)
1 (20)	–	5 (100)
–	–	–
–	3 (100)	3 (100)

(Continues)

TABLE 1 (Continued)

Author	Patients with COVID-19 in the ICU	Patients with CAPA	Days from COVID-19 diagnosis	Days from ICU admission
Machado et al	239	8	–	15 (10–19)
Maes et al	81	3	–	–
Nasir et al	23	5	8 (2–10)	–
Permpalung et al	396	39	15 (9–23)	12 (3–22)
Razazi et al	90	7	–	–
Ripa et al	86	10	–	–
Roman-Montes et al	144	14	–	8.5 (3–13)
Rutsaert et al	34	4	–	–
Sarrazyn et al	131	4	–	–
Segrelles-Calvo et al	215	7	–	–
van Arkel et al	31	6	–	5 (range, 3–28)
Van Biesen et al	53	9	–	3 (1–4)
van Grootveld et al	63	11	–	8 (range, 2–23)
Vélez Pintado et al	83	16	13 (9–20)	6 (4–9)
Versyck et al	54	2	–	–
Wang et al	26	8	–	–
White et al	257	25	–	–

Abbreviations: ARDS, Acute Respiratory Distress Syndrome; CAPA, COVID-19-associated Pulmonary Aspergillosis; CKD, Chronic Kidney Disease; COPD, Chronic Obstructive Pulmonary Disease; ECMM/ISHAM, European Confederation for Medical Mycology and International Society for Human and Animal Mycology; EORTC/MSG, European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group; IAPA, Influenza-associated Pulmonary Aspergillosis; ICU, Intensive Care Unit; MV, Mechanically Ventilated; UK, United Kingdom; USA, United States of America.

[a]All studies were conducted in 2020 and focused on adult patients with COVID-19 unless indicated otherwise. Values are mean ± SD or median (interquartile range) unless indicated otherwise. Dashes indicate that data were not available.

such as systemic steroids and tocilizumab were used with varied frequencies, which may have affected a patient's susceptibility to aspergillosis.

Mortality from previous reports also varied between 22%[35] and 100%.[11] Based on our pooled estimate at 55%, the mortality of patients who develop CAPA may be higher than that of average ICU patients with COVID-19 who received mechanical ventilation observed in a large, international, multicentre, prospective cohort study in Europe (28-day mortality: 31%, 90-day mortality: 37%).[42] Two observational studies also reported excess mortality rates compared with patients without CAPA.[7,8] Although it remains unclear whether CAPA directly contributes to death or just unequally affects the most severely ill patients (ie patients with severe ARDS), the presence of CAPA likely represents a higher risk of death. The high heterogeneity in mortality among studies can most likely be explained by the limited number of patients with CAPA and the differences in antifungal treatment strategies. Knowing the mortality with greater certainty based on this meta-analysis may allow us to more accurately prognosticate patients with COVID-19 who develop CAPA in the ICU, which could lead to better goals of care discussions.

Our study has several limitations. First, our meta-analysis included many retrospective observational studies (the ratio of retrospective to prospective studies was approximately 2:1), which could predispose it to reporting bias. Second, the incidence and mortality of CAPA will likely continue to change due to several reasons. Our analysis integrated patients classified as pulmonary aspergillosis by different criteria, as there were no absolute definitions for CAPA. Our pooled estimates were also based on the results mainly from the first wave of the pandemic before the RECOVERY trial[13] was published. With universal administration of systemic steroids to patients with severe COVID-19, overall mortality will likely decrease, but an increase in the incidence of CAPA is possible.[43,44] The incidence and mortality under the current treatment strategy will likely change based on the new case definitions for CAPA.[5] Third, 23 out of 28 studies included were reported from Europe, which may potentially limit its applicability in other regions.[3] Finally, this meta-analysis does not give any insight into whether CAPA contributed to increased mortality compared with critically ill patients with COVID-19 who did not develop CAPA since outcome data for all patients in the ICU were not available.

In conclusion, this meta-analysis provides integrated and refined estimates for the incidence and mortality of CAPA. Our findings can be utilised as a basis for surveillance of CAPA and prognostication in the ICU. Large, prospective cohort studies based on the new case definitions of CAPA are warranted to validate our estimates of incidence and mortality in this important complication of COVID-19.

Patients with CAPA who received systemic steroids	Patients with CAPA who received tocilizumab	Patients with CAPA who received antifungal therapy
8 (100)	8 (100)	5 (63)
0 (0)	–	3 (100)
4 (80)	3 (60)	5 (100)
26 (67)	9 (23)	19 (49)
–	–	–
–	–	–
1 (7)	4 (29)	12 (86)
–	–	4 (100)
–	–	3 (75)
4 (57)	5 (71)	4 (57)
2 (33)	–	6 (100)
1 (11)	–	9 (100)
–	–	6 (55)
2 (13)	12 (75)	–
2 (100)	1 (50)	2 (100)
6 (75)	–	–
16 (64)	–	19 (76)

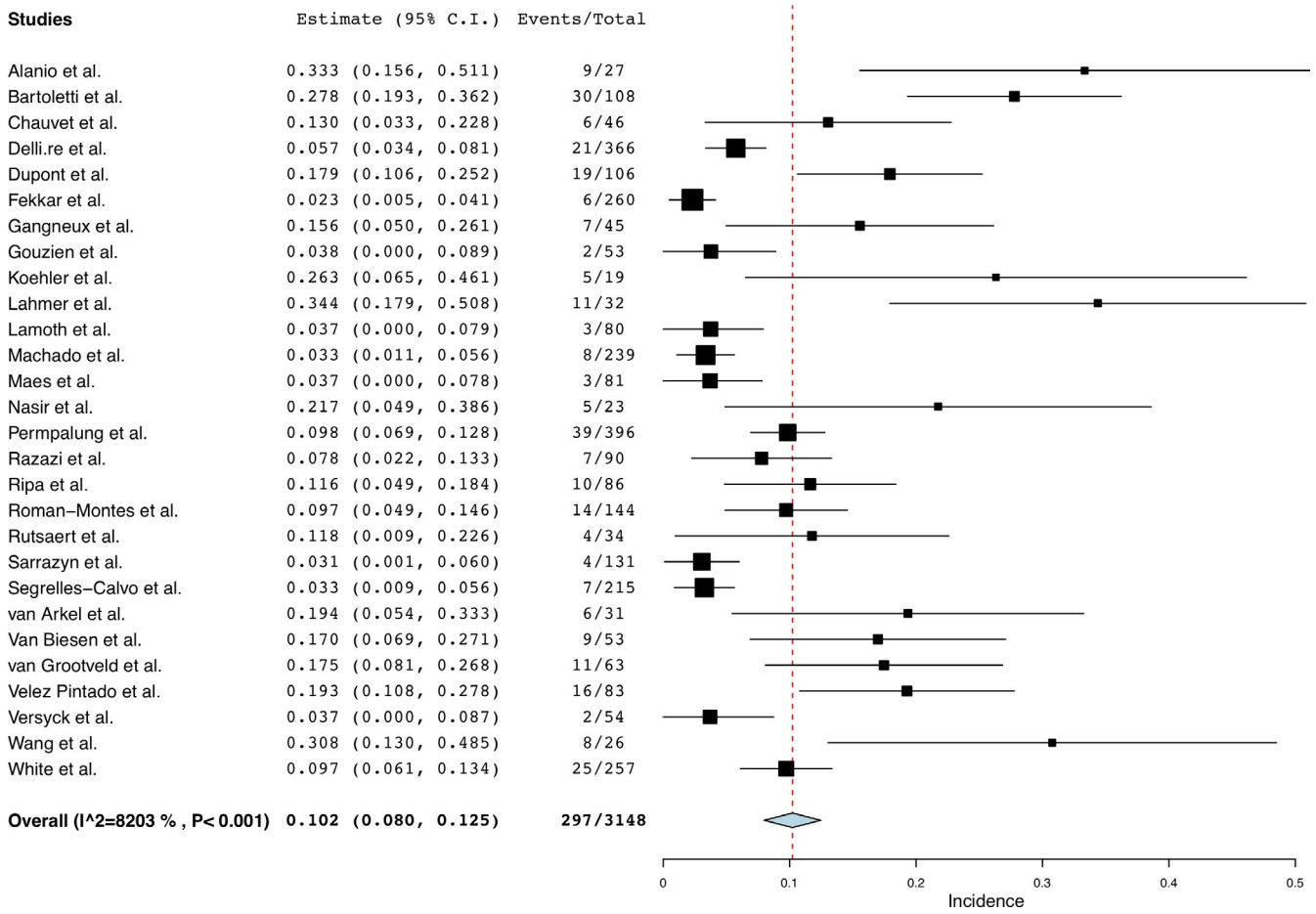

FIGURE 2 Forrest plot showing the pooled estimate of the incidence of COVID-19-associated pulmonary aspergillosis in the ICU

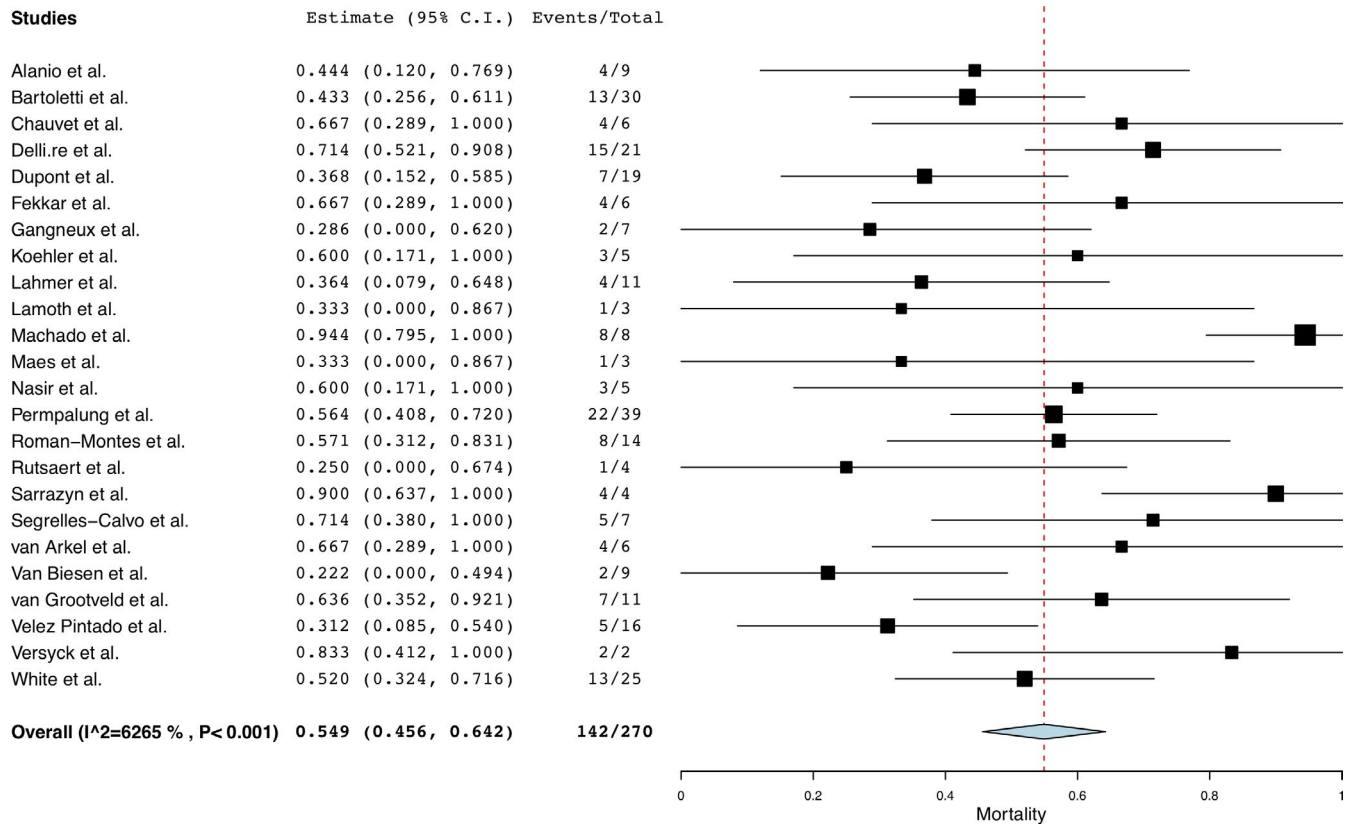

FIGURE 3 Forrest plot showing the pooled estimate of the mortality of COVID-19-associated pulmonary aspergillosis in the ICU

CONFLICT OF INTEREST

There are no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Hayato Mitaka: Conceptualization (lead); Data curation (lead); Formal analysis (equal); Investigation (lead); Methodology (equal); Writing-original draft (lead). **Toshiki Kuno:** Data curation (supporting); Formal analysis (equal); Investigation (supporting); Methodology (lead); Supervision (lead); Writing-original draft (supporting); Writing-review & editing (equal). **Hisato Takagi:** Methodology (supporting); Supervision (supporting); Writing-review & editing (supporting). **Paru Patrawalla:** Conceptualization (supporting); Investigation (supporting); Project administration (supporting); Supervision (equal); Writing-review & editing (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Hayato Mitaka https://orcid.org/0000-0003-0765-3955

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