



# Incidence and outcomes of patients with COVID-19 associated pulmonary aspergillosis (CAPA) in intensive care units: a systematic review and meta-analysis of 31 cohort studies

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**Background:** We aimed to identify studies systematically that describe the incidence and outcome of COVID-19-related pulmonary aspergillosis (CAPA).

**Methods:** We searched ScienceDirect, PubMed, CNKI, and MEDLINE (OVID) from December 31, 2019 to November 20, 2021 for all eligible studies. Random-model was used to reported the incidence, all-cause case fatality rate (CFR) and 95% confidence intervals (CIs). The meta-analysis was registered with PROSPERO (CRD42021242179).

**Results:** In all, thirty-one cohort studies were included in this study. A total of 3,441 patients with severe COVID-19 admitted to an intensive care unit (ICU) were investigated and 442 cases of CAPA were reported (30 studies). The pooled incidence rate of CAPA was 0.14 (95% CI: 0.11–0.17,  $I^2=0.0\%$ ). Twenty-eight studies reported 287 deceased patients and 269 surviving patients. The pooled CFR of CAPA was 0.52 (95% CI: 0.47–0.56,  $I^2=3.9\%$ ). Interestingly, patients with COVID19 would develop CAPA at 7.28 days after mechanical ventilation (range, 5.48–9.08 days). No significant publication bias was detected in this meta-analysis.

**Discussion:** Patients with COVID-19 admitted to an ICU might develop CAPA and have high all-cause CFR. We recommend conducting prospective screening for CAPA among patients with severe COVID-19, especially for those who receive mechanical ventilation over 7 days.

**Keywords:** COVID-19-associated pulmonary aspergillosis (CAPA); incidence; case fatality rate (CFR)

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## Introduction

From December 2019, a pandemic of coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread rapidly from Asia to the rest of the world. About 5% of patients with COVID-19 require intensive care unit (ICU) management (1). Clinicians are alert to the possibility of bacterial or fungal infection and prescribe antibiotics to nearly 90% of antibiotic patients with COVID-19 in the ICU setting (2). Respiratory viruses (including SARS-CoV-2) cause direct damage the airway epithelium, facilitating bacterial and fungi invasion. Furthermore, ciliary clearance is hampered by viral infection, resulting in immune dysfunction or dysregulation (3). With severe pulmonary inflammation, long-term exposure to broad-spectrum antibiotics, and receipt of immunosuppressive drugs, patients with severe COVID-19 are at risk for secondary infections (4). It was reported that 14% hospitalized patients with COVID-19 had bacterial co-infections in mixed ward or ICU settings (5). Increasing numbers of studies have drawn attention to the high prevalence of COVID-19-associated pulmonary aspergillosis (CAPA) in patients with severe COVID-19 (1,6-8) admitted to the ICU. A diagnosis of CAPA was made based on specific case definitions or diagnostic algorithms, including the AspICU algorithm, modified AspICU algorithm, influenza-associated pulmonary aspergillosis (IAPA) criteria, the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group, the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG), the European Confederation for Medical Mycology, and the International Society for Human and Animal Mycology (ECMM/ISHAM) consensus criteria. However, the exact incidence of CAPA remains unknown and opinions are polarized (9,10). Currently, reports on the incidence and outcomes of CAPA remain inconclusive. To address this gap in the literature, we conducted this systematic review and meta-analysis of 31 cohort studies, with the aim of identifying studies that describe the incidence and outcome of CAPA. We present the article in accordance with the PRISMA reporting checklist (available at <https://apm.amegroups.com/article/view/10.21037/apm-21-2043/rc>).

## Methods

This systematic review was based on a prospectively

registered protocol (PROSPERO CRD42021242179). The review process is illustrated in a flow diagram (*Figure 1*).

### *Search strategy*

A search string was developed to identify original research studies reporting clinical characteristics and outcomes of patients with CAPA. The search was applied to the following databases: ScienceDirect, PubMed, CNKI, and MEDLINE (OVID). Searches were performed for each database from December 31, 2019 to November 20, 2021. The following key words were used in all database searches: “coronavirus”, “COVID”, “COVID-19”, “severe acute respiratory syndrome”, “coronavirus 2”, “SARS-CoV-2”, “*Aspergillus*”, “pulmonary *Aspergillus*”, “invasive *Aspergillus*”, “invasive pulmonary *Aspergillus*”, “COVID-19-Associated pulmonary Aspergillosis” and “intensive care unit”.

### *Study selection and eligibility criteria*

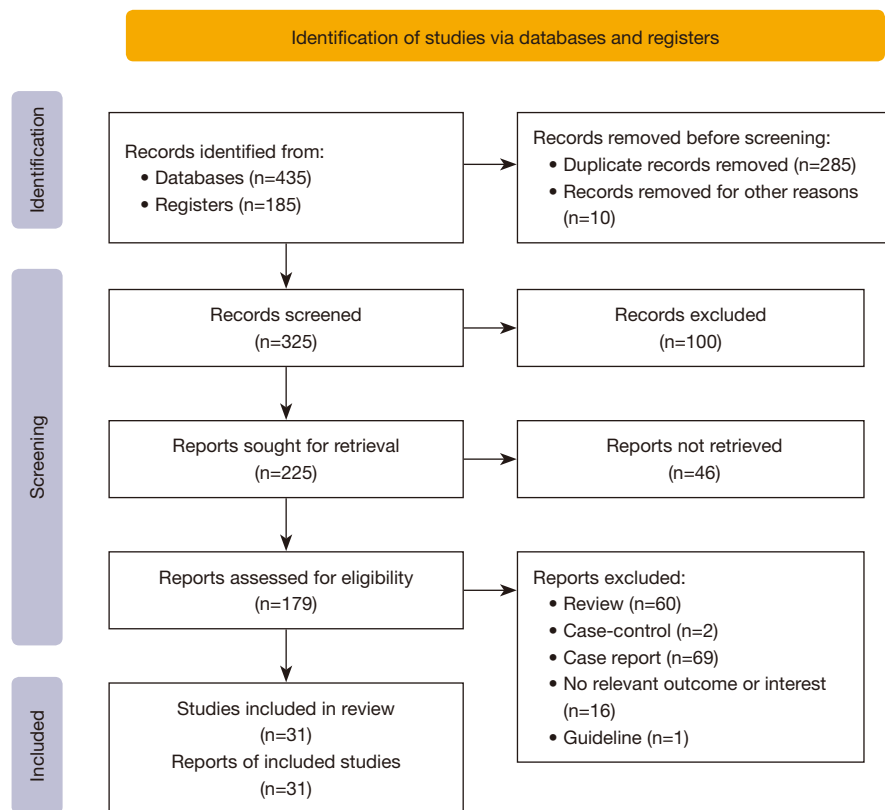
All references were collected and screened independently by two reviewers (W Chen and K Zhang) against a set of predefined eligibility criteria. Potentially eligible studies were selected for full-text analysis. Disagreements were resolved by consensus or by appeal to a third senior reviewer (Y Liu). All observational cohort studies reporting the incidence and outcome of CAPA among patients with COVID-19 admitted to the ICU were included in this meta-analysis. The exclusion criteria included case control studies, case reports, nonhuman research, and meeting abstracts without a full article.

### *Quality assessment*

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) by the two researchers who were involved in the literature search (W Chen and K Zhang), who assessed the quality of all included studies and discussed discrepancies until a consensus was reached with the corresponding author (G Zhuang). The study quality was divided into low quality (0 to 3 stars), moderate quality (4 to 6 stars), and high quality (7 to 9 stars).

### *Data extraction and outcome measures*

Data were extracted for the following variables: study period, study design, location of study, definition of CAPA and outcome. The case fatality rate (CFR) was defined as



**Figure 1** The flow diagram for this systematic reviews and meta-analyses.

the number of CAPA deaths divided by the total number of CAPA cases in the cohort. The primary outcome was all-cause CFR during the ICU.

### Statistical analysis

Random-effects meta-analysis was used to reported the incidence, all-cause CFR and with 95% confidence intervals (CIs) (11). Pooled proportions were computed using the inverse variance method and the variance-stabilizing Freeman-Tukey double arcsine transformation (12). Subgroup analysis was conducted based on the literature design (prospective or retrospective study), the type of research centre (single or multi-centre), and the clinical characteristics of the patients [e.g., acute respiratory distress syndrome (ARDS), mechanical ventilation]. The Mantel-Haenszel estimator was used to calculate the between-study heterogeneity statistic  $Q$ , which was used in the DerSimonian-Laird estimator. The  $I^2$  statistic was used to present between-study heterogeneity, where  $I^2=50\%$  was considered substantial. We assessed publication bias

using Egger's test and by inspecting funnel plots. Statistical analyses were performed using the R software version 3.6.3 (R Foundation for Statistical Computing, 2016), with the package "meta" and Stata Special Edition 15.1 (Stata Corp., College Station, TX, USA). P values less than 0.05 were considered statistically significant.

### Results

A total of 620 references were searched from MEDLINE, OVID, PubMed, and other sources. In all, we identified 31 observational cohort studies that were qualified according to our predefined inclusion and exclusion criteria (Figure 1).

#### Characteristics of included studies

Of the 31 studies, 9 (29.03%) were from France, 4 (12.90%) were from the Netherlands, 2 (6.45%) were multi-national cohort study (1,6,10,13-20). Fourteen studies dealt with patients who received mechanical ventilation, eight studies were of patients with ARDS, one study was on

**Table 1** The incidence and CFR of CAPA in this meta-analysis

Variables	Incidence of CAPA					References	CFR of CAPA			
	No. of studies	Patients with CAPA/total	Effect	95% CI	I <sup>2</sup> (%)		Deceased/patients with CAPA	Effect	95% CI	I <sup>2</sup> (%)
Overall	30	442/3,441	0.14	0.11–0.17	0.0	28	287/556	0.52	0.47–0.56	3.9
Study design										
Prospective	9	115/816	0.16	0.09–0.24	19.8	10	58/115	0.52	0.43–0.62	0.0
Retrospective	21	327/2,625	0.13	0.10–0.17	0.0	18	229/441	0.56	0.46–0.58	15.3
Study centre										
Single-centre	25	200/1,675	0.13	0.09–0.18	0.0	22	82/160	0.49	0.42–0.57	0.0
Multi-centre	5	242/1,766	0.16	0.09–0.23	50.9	6	205/396	0.54	0.46–0.62	52.7
Category of the patients with COVID										
MV	14	117/895	0.14	0.08–0.21	0.0	14	49/93	0.51	0.42–0.60	0.0
ARDS	8	96/482	0.20	0.12–0.28	0.0	7	35/77	0.45	0.34–0.56	0.0
ECMO	1	2/8	0.25	–0.35 to 0.85	0.0	–	–	–	–	–
Others	7	227/2,056	0.11	0.06–0.17	33.4	7	122/245	0.55	0.47–0.63	45.1

CFR, case fatality rate; CAPA, COVID-19-associated pulmonary aspergillosis; CI, confidence interval; MV, mechanical ventilation; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation.

extracorporeal membrane oxygenation (ECMO), and seven studies included other patients with severe COVID-19 (21-40) (Table S1).

### Quality control of included studies

The risk of bias included in the cohort studies was assessed using the NOS as presented in Table S2. A proportion of 93.55% (29/31) studies were over 7 stars, which is considered to high quality. All studies assessed the outcomes of interest based on medical record linkage (Table S3).

### Incidence of CAPA

In the studies, 3,441 patients with severe COVID-19 admitted to an ICU were investigated and 442 cases of CAPA were reported. The incidence of CAPA was calculated as 0.14 (95% CI: 0.11–0.17, I<sup>2</sup>=0.0%). In the subgroup analysis by study design, the incidence of CAPA was calculated at 0.16 (95% CI: 0.09–0.24, I<sup>2</sup>=19.8%) in the prospective studies and 0.13 (95% CI: 0.10–0.17, I<sup>2</sup>=0.0%) in the retrospective studies (Table 1). When stratified analysis was undertaken by research centre (multi-centre or single centre), the CAPA incidence was 0.13 (95% CI: 0.09–0.18, I<sup>2</sup>=0.0%) for the single centre studies and 0.16 (95%

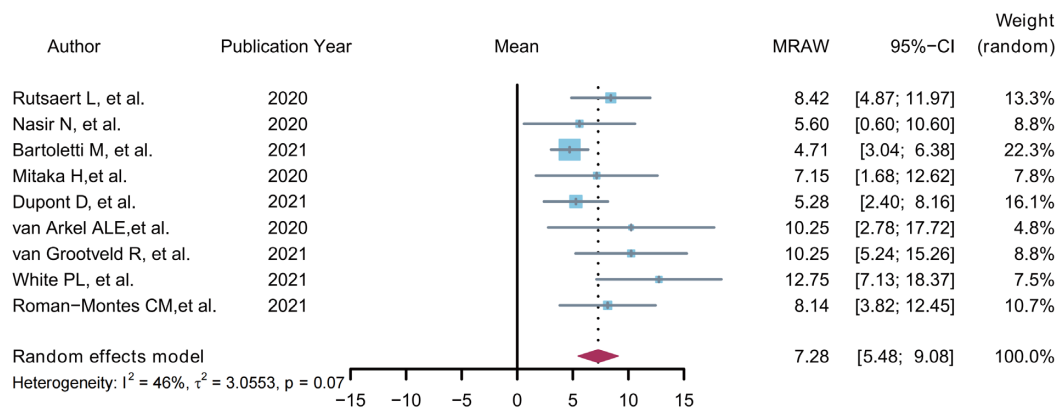
CI: 0.09–0.23, I<sup>2</sup>=50.9%) for the multi-centre studies. We found no significantly heterogeneity for calculation of the incidence of CAPA and significant publication bias according to Egger's regression test. Remarkably, we found that patients with COVID-19 admitted to an ICU would develop CAPA after approximately 7.28 days of mechanical ventilation (nine studies, 95% CI: 5.48–9.08, I<sup>2</sup>=46%) (Figure 2).

### Colonisation by *Aspergillus*

In five cohort studies including 365 patients with COVID-19 admitted to an ICU, 21 patients were assessed for *Aspergillus* colonisation. The calculated colonization rate of was 5.75% (21/365), suggesting that clinicians should comprehensively analyse *Aspergillus* colonisation combined with other clinical evidence (such as imaging and inflammatory factors, etc.) to judge whether the patient might develop CAPA and require further anti-fungal treatment.

### CFR of CAPA

Twenty-eight studies were eligible for further analysis of all-cause CFR with 287 deceased patients and 269 surviving patients. We found that the pooled CFR was 0.52 (95% CI:



**Figure 2** Time window of the patients developed CAPA. CAPA, COVID-19-associated pulmonary aspergillosis; CI, confidence interval; MRAW, meta-analysis of single means to calculate an overall mean using untransformed means (Raw).

0.47–0.56,  $I^2=3.9\%$ ). In the subgroup analysis by study design, the calculated CFRs were 0.52 (95% CI: 0.43–0.62,  $I^2=0.0$ ) for the prospective studies, 0.56 (95% CI: 0.46–0.58,  $I^2=15.3\%$ ) for the retrospective studies, 0.49 (95% CI: 0.42–0.57,  $I^2=0.0\%$ ) for the single centre studies, and 0.54 (95% CI: 0.46–0.62,  $I^2=52.7\%$ ) for the multi-centre studies (Table 1).

## Discussion

We conducted this systematic review of 31 cohort studies and observed that 14% of patients with COVID-19 admitted to the ICU developed CAPA. Meanwhile, the median time to develop CAPA among patients with COVID-19 who received mechanical ventilation was 7.28 days. Studies reported that the incidence of CAPA varied from 1.9% to 27.7% (6,34,40). This wide divergence might result an underestimate of the risk of CAPA. Invasive pulmonary aspergillosis is a secondary infection of severe respiratory viral infection (41,42) and these infections have been related with significant morbidity and mortality, even when appropriately diagnosed and treated. CAPA not only occurred in immunosuppressed patients (e.g., those with acute myeloid leukaemia), but also in immunocompetent patients with COVID-19 (43,44). COVID-19 was independently associated with CAPA (31). We recommend that clinicians should be alert to the occurrence of CAPA in patients with COVID-19, especially in those receiving mechanical ventilation more than 7 days.

The occurrence of CAPA would exacerbate the deterioration of respiratory function, thus increasing the risk of death. We pooled 28 cohort studies and found

that the all-cause CFR of patients with CAPA was 52%. Among all included studies, a very high proportion of patients with COVID-19 received mechanical ventilation. The proportion of patients receiving baseline mechanical ventilation and 14 studies were 100% mechanical ventilation. A systematic review has revealed that the CFR of patients with COVID-19 receiving mechanical ventilation was 45% (95% CI: 39–52%) (45). Meijer and others conducted a small-sample cohort study (66 ICU patients with COVID-19) and found that the incidence of CAPA was 19.7% ( $n=13/66$ ), and the fatality rate of a single study was 46.2% (6/13); the author's team listed some of the articles that have been published and analyzed for the CAPA fatality rate. The pooled CFR for CAPA was 47% (62/132) (25).

The NOS was used to evaluate the quality of the included articles. We found that the selected studies were of high quality. However, we observed significant heterogeneity in the pooled analysis of the incidence and CFR of CAPA in the subgroup analysis with multi-centre. Many hospitals do not commonly perform bronchoscopy for CAPA diagnosis or use PCR tests for *Aspergillus* species (46). Non-standardized definitions of CAPA, differences in detection methods (47), and variations among research designs might have contributed to heterogeneity across the studies, which requires further investigation.

Meanwhile, we have some limitation in this study. The included literature did not provide the clear profile of the patients with COVID-19 developed with CAPA. In this case, we only pooled the time window for CAPA in mechanically ventilated patients. On the other hand, there was lack of a unified definition of CAPA and a standard

diagnostic algorithm in the published studies. Although we strictly controlled quality based on the study entry and exclusion criteria, heterogeneity between studies was still unavoidable. We subsequently conducted a subgroup analysis according to different definition and found no significant heterogeneity. Last but not the least, this meta-analysis did not explore the risk factors for mortality in patients with CAPA because of insufficient literature support. Further well-designed research and demonstration would be warranted in the future.

## Conclusions

In this study, the pooled incidence of CAPA was estimated as 14% among patients with COVID-19 admitted to the ICU, with high rate of all cause-mortality and CFR. We recommend that clinicians establish standardized screening methods for CAPA and to identify high risk patients early, especially for patients who have been mechanically ventilated for more than 7 days.

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## Footnote

*Reporting Checklist:* The authors have completed the PRISMA reporting checklist. Available at <https://apm.amegroups.com/article/view/10.21037/apm-21-2043/rc>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://apm.amegroups.com/article/view/10.21037/apm-21-2043/coif>). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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