Risk factors for COVID-19-associated pulmonary aspergillosis: a systematic review and meta-analysis

Francesca Gioia, Laura N Walti*, Ani Orchanian-Cheff, Shahid Husain*

Summary

Background COVID-19-associated pulmonary aspergillosis (CAPA) has been reported to be an emerging and potentially fatal complication of severe COVID-19. However, risk factors for CAPA have not been systematically addressed to date.

Methods In this systematic review and meta-analysis to identify factors associated with CAPA, we comprehensively searched five medical databases: Ovid MEDLINE; Ovid Embase; the Cochrane Database of Systematic Reviews; the Cochrane Central Register of Controlled Trials; and the WHO COVID-19 Database. All case-control and cohort studies in adults (aged >18 years) that described at least six cases of CAPA and evaluated any risk factors for CAPA, published from Dec 1, 2019, to July 27, 2023, were screened and assessed for inclusion. Only studies with a control population of COVID-19-positive individuals without aspergillosis were included. Two reviewers independently screened search results and extracted outcome data as summary estimates from eligible studies. The primary outcome was to identify the factors associated with CAPA. Meta-analysis was done with random-effects models, with use of the Mantel–Haenszel method to assess dichotomous outcomes as potential risk factors, or the inverse variance method to assess continuous variables for potential association with CAPA. Publication bias was assessed with funnel plots for factors associated with CAPA. The study is registered with PROSPERO, CRD42022334405.

Findings Of 3561 records identified, 28 articles were included in the meta-analysis. 8009 patients with COVID-19 were included, of whom 1398 (17·5%) were diagnosed with CAPA. Diagnosis rates of CAPA ranged from 2·5% (14 of 566 patients) to 47·2% (58 of 123). We identified nine risk factors for CAPA. These factors included pre-existing comorbidities of chronic liver disease (odds ratio [OR] 2·56 [95% CI 1·30–5·05], p=0·007; I^2=47%), haematological malignancies (OR 2·47 [1·27–4·83], p=0·008; I^2=50%), chronic obstructive pulmonary disease (OR 1·92 [1·42–2·60], p<0·0001; I^2=22%), cerebrovascular disease (OR 1·31 [1·01–1·71], p=0·05; I^2=46%), and diabetes (OR 1·26 [1·04–1·53], p=0·02; I^2=37%). Use of invasive mechanical ventilation (OR 2·73 [1·89–3·94]; p<0·0001; I^2=69%), use of renal replacement therapy (OR 2·26 [1·76–2·90], p<0·0001; I^2=14%), treatment of COVID-19 with interleukin-6 inhibitors (OR 2·69 [1·47–4·90], p=0·001; I^2=88%), and treatment of COVID-19 with corticosteroids (OR 1·72 [1·10–2·68], p=0·02; I^2=77%) were also associated with CAPA. Patients with CAPA were typically older than those without CAPA (mean age 66·0 years [SD 4·4] *vs* 63·1 years [5·4]; mean difference 2·72 [1·33–4·12], p=0·0001; I^2=86%). The duration of mechanical ventilation in patients with CAPA was longer than in those without CAPA (n=7 studies; mean duration 19·3 days [8·9] vs 13·5 days [6·8]; mean difference 5·53 days [1·30–9·77], p=0·01; I^2=88%). In post-hoc analysis, patients with CAPA had higher all-cause mortality than those without CAPA (n=21 studies; OR 2·63 [2·06–3·34], p<0·0001; I^2=48%).

Interpretation The identified risk factors for CAPA could eventually be addressed with targeted antifungal prophylaxis in patients with severe COVID-19.

Funding None.

Lancet Respir Med 2024; 12: 207–16

Published Online January 4, 2024 https://doi.org/10.1016/S2213-2600(23)00408-3

This online publication has been corrected. The corrected version first appeared at thelancet.com/respiratory on May 21, 2024

See Comment page 183

*Contributed equally to this manuscript

Ajmera Transplant Centre, Division of Infectious Diseases (F Gioia PhD, L N Walti MD, S Husain MD) **and Library and Information Services** (A Orchanian-Cheff MISt), **University Health Network, University of Toronto, Toronto, ON, Canada; Infectious Diseases Department, Hospital Ramón y Cajal, Consorcio Centro de Investigación Biomédica en Red (CB21/13/00084), Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación, Madrid, Spain** (F Gioia)**; Department of Infectious Diseases, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland** (L N Walti)

Correspondence to: Shahid Husain, Ajmera Transplant Centre, Division of Infectious Diseases, University Health Network, University of Toronto, Toronto, ON, M5G 2N2, Canada
shahid.husain@uhn.ca

Introduction

COVID-19, caused by SARS-CoV-2, can result in acute respiratory failure. Severely ill patients with COVID-19 and acute respiratory failure have emerged as a new population at high risk of fungal infections.[1,2] COVID-19-associated pulmonary aspergillosis (CAPA) has been reported in studies worldwide, mainly in patients admitted to intensive care units (ICUs) for respiratory failure.[3,4] However, the reported prevalence of CAPA has been highly variable, ranging from 2% to 39%.[5–8] In patients with severe COVID-19 admitted to the ICU with a need for mechanical ventilation, CAPA seems to be associated with high mortality,[9,10] with a reported mortality of around 50% in a recent meta-analysis.[11]

Risk factors for CAPA need to be better defined. In patients with COVID-19 and respiratory failure, the typical host factor criteria for invasive aspergillosis described by the European Organization for Research and Treatment of Cancer and the Mycosis Study Group Education and Research Consortium (EORTC/MSGERC)[12] are not applicable. Although some studies have identified immunosuppressive conditions typical of

Research in context

Evidence before this study

Before undertaking this analysis, we did a search of PubMed, Cochrane Library, Scopus, and Web of Science for studies published between Jan 1, 2020 and March 29, 2022, containing comparative data on patients diagnosed with COVID-19-associated pulmonary aspergillosis (CAPA) and those without CAPA, using the search terms: ("coronavirus disease 2019" OR "COVID-19" OR "severe acute respiratory syndrome coronavirus 2" OR "SARS-CoV-2") AND ("COVID-19-associated pulmonary aspergillosis" OR "CAPA" OR "fungal infections" OR "Aspergillosis" OR "Aspergillus" OR "invasive pulmonary aspergillosis" OR "IPA") OR ("risk factors" OR "prognostic factors"). Results were limited to studies in adults (aged >18 years) and in English. We identified one previous meta-analysis, which assessed the characteristics and outcomes of CAPA among 729 critically ill patients with COVID-19. However, included studies in that analysis were published before August, 2021, and only reflected the first pandemic period.

Added value of this study

To our knowledge, this is the first systematic review and meta-analysis of risk factors associated with CAPA. Our analysis was updated to include patients from all COVID-19 waves and those who received vaccination. We analysed 25 dichotomous variables as potential risk factors, and found nine risk factors for CAPA. These factors were haematological malignancies, chronic liver disease, chronic obstructive pulmonary disease, cerebrovascular disease, diabetes, invasive mechanical ventilation, renal replacement therapy, and treatment with corticosteroids or anti-interleukin-6 for COVID-19 infection. CAPA also showed an association with age and duration of mechanical ventilation, and, in post-hoc analysis, with length of ICU stay and all-cause mortality. To avoid bias derived from different definitions of CAPA, we did a post-hoc subanalysis of only the studies that used the European Confederation for Medical Mycology and the International Society for Human and Animal Mycology consensus criteria. Results in the subanalysis were mostly unchanged; notably, corticosteroids were no longer a risk factor for CAPA, and asthma and chronic kidney disease became risk factors for CAPA.

Implications of all the available evidence

Most of the studies included in our analysis reported pre-vaccine data, and none of them considered the effect of vaccination on CAPA. As such, the reported estimates might represent an overestimation of effect. Nonetheless, these data could be useful to determine CAPA risk, especially when classical risk factors for invasive aspergillosis are absent. Patients with the risk factors identified in our analysis could potentially be targeted with antifungal prophylaxis. In the absence of antifungal prophylaxis, adequate screening for CAPA and recognising associated factors is essential. Further studies should evaluate the efficacy of prophylaxis in patients with severe COVID-19 presenting with the risk factors identified in this meta-analysis.

invasive aspergillosis, such as haematological tumours and solid organ transplantation, as factors associated with CAPA,[13] most patients with CAPA do not have the usual factors that are associated with invasive aspergillosis in other patients.[14,15]

The high mortality in patients with CAPA highlights the importance of identifying potential risk factors predisposing to CAPA. The identification of risk factors is important to determine adequate surveillance and inform antifungal prophylaxis strategies. Several studies have assessed factors associated with CAPA. However, most studies describing patients with CAPA have been single-centre cohorts with limited sample sizes, and CAPA risk factors have not been assessed in systematic reviews or meta-analyses. Thus, the aim of this study was to conduct a systematic review and meta-analysis of published studies to identify factors associated with CAPA.

For the **Canadian Agency for Drugs and Technologies in Health COVID-19 Evidence Portal** see https://covid.cadth.ca/literature-searching-tools/cadth-covid-19-search-strings/

See **Online** for appendix

Methods

Search strategy and selection criteria

In this systematic review and meta-analysis, a comprehensive search strategy was first developed for Ovid MEDLINE, with use of a combination of database-specific subject headings and text words for the main concepts of COVID-19 and pulmonary aspergillosis. The search string for COVID-19 was based on the COVID-19 filter developed by the Canadian Agency for Drugs and Technologies in Health. The search strategy was then modified for each database. Searches were done on March 29, 2022 (for studies published up to March 28, 2022) and updated on July 28, 2023 (for studies published up to July 27, 2023). The databases searched were Ovid MEDLINE, Ovid Embase, the Cochrane Database of Systematic Reviews (Ovid), the Cochrane Central Register of Controlled Trials (Ovid), and the WHO COVID-19 Database. The search strategies for all databases are provided in the appendix (pp 3–9).

Results were limited to studies in adults (aged >18 years) published from Dec 1, 2019, to July 27, 2023. Conference proceedings and books were excluded. Only reports written in English were included. No other search limits were applied. The reference lists of retrieved publications were also searched. We included only cohort and case-control studies that described at least six cases of CAPA and evaluated any factor associated with CAPA. Additionally, only studies with a control population of COVID-19-positive individuals without CAPA were included, with no restriction on group size. The definition of CAPA varied between studies. Case definition was based on

definitions proposed by proposed by Koehler and colleagues (European Confederation for Medical Mycology and the International Society for Human and Animal Mycology [ECMM/ISHAM] consensus criteria),[16] the EORTC/MSGERC consensus criteria,[12] the AspICU algorithm,[17] and the influenza-associated pulmonary aspergillosis (IAPA) criteria proposed by Verweij and colleagues.[18]

We required COVID-19 to have been diagnosed by RT-PCR in all cases, from respiratory tract specimens that could include nasal and pharyngeal swabs, sputum, tracheal aspirate, and non-directed bronchial lavage.

Two investigators (LNW and FG) independently screened the search results. First, titles and abstracts of the retrieved citations were screened for eligibility on the basis of the inclusion criteria, followed by a detailed analysis of the full texts. The reference lists of all full-text articles assessed for eligibility were hand-searched to identify any relevant studies that were missed in the preliminary searches, and the full texts of any such studies were assessed for eligibility.

Data analysis

The data extraction was done independently and in duplicate (LNW and FG). Any disagreements were resolved by discussion, and, if necessary, a third author (SH) was consulted for arbitration. Duplicate data were removed manually. The data extracted from each eligible study were author name, study location and year, study design, the criteria used to define CAPA, demographic characteristics, comorbidities and risk factors, treatment received, admission to the ICU, and outcome. Outcome data were extracted as summary estimates. All extracted data were entered into a Microsoft 365 Excel spreadsheet.

The primary outcome of our study was to identify the factors associated with CAPA. The difference in length of ICU stay between patients with CAPA and those without CAPA was assessed as a secondary outcome, and the difference in all-cause mortality between patients with CAPA and those without CAPA was assessed as a tertiary outcome. The primary outcome was prespecified in the protocol of the study, and the secondary and tertiary outcomes were added post-hoc.

We did the meta-analysis using a random effects model. Due to the expected heterogeneity across the included studies, we chose a random-effects model over a fixed-effects model. Summary estimates extracted from individual studies manually were combined in the meta-analysis. The Mantel–Haenszel statistical method was used to assess dichotomous outcomes as potential risk factors, providing pooled odds ratios (ORs) and 95% CIs, which were presented in forest plots. Continuous variables were evaluated by the inverse variance method for potential association and reported as mean differences with 95% CIs. For the analysis of specific associated risk factors, we excluded studies with zero events (or where the risk factor was not reported); in case of zero events in one of the groups in a given study, the statistical software adds 0·5 to all cells for that group to be able to calculate effects or standard errors.

The risk of bias in the included studies was assessed independently in duplicate (by LNW and FG) with use of the Risk of Bias In Non-randomized Studies – of Exposures tool (version 20). A traffic light plot was created with the robvis tool (version 20).

The heterogeneity of effect size estimates across the studies was quantified with the Q statistic and I^2 test. I^2 values of 0–40% indicate low heterogeneity, 41–75% indicate moderate heterogeneity, and greater than 75% indicate high heterogeneity, as defined by Cochrane Statistical Methods Group. Variability within studies was not assessed. Publication bias was assessed with funnel plots for factors that were associated with CAPA. In a post-hoc sensitivity analysis, we excluded studies with the largest and smallest effect size estimates. Additionally, a post-hoc subgroup analysis was done only for studies that used unmodified ECMM/ISHAM criteria to define CAPA, to assess whether associations were maintained for risk factors identified in the primary analysis.

Data analysis was done with Review Manager (version 5.4) software from The Cochrane Collaboration (London, UK). A p value less than 0·05 was considered to indicate statistical significance.

The protocol of this study was registered with PROSPERO, CRD42022334405, and the study was reported according to the PRISMA guidelines.[19] The appendix (pp 15–18) provides the PRISMA checklist.

For the **Risk of Bias In Non-randomized Studies – of Exposures tool** see https://www.riskofbias.info/welcome/robins-e-tool

For the **robvis tool** see https://www.riskofbias.info/welcome/robvis-visualization-tool

For the **Cochrane Statistical Methods Group thresholds** see https://training.cochrane.org/handbook/current/chapter-10#section-10-10-2

For more on the **Review Manager software** see https://training.cochrane.org/handbook/current/statistical-methods-revman5

For the **study protocol** see https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42022334405

Role of the funding source

There was no funding source for this study.

Results

A total of 3561 records were identified from the initial database search (figure 1). After removing duplicate records (n=1403) and records removed for other reasons (n=17), 2141 abstracts were independently screened by the two reviewers, and 2084 records were excluded due to irrelevance. Consequently, 57 full-text articles were reviewed. We excluded seven of these articles for including other invasive fungal infections in addition to CAPA, 17 articles for not having a control group, two articles for lacking relevant data (eg, baseline characteristics), and three articles for not reporting on risk factors of CAPA (appendix pp 19–21).

28 observational studies were included in the systematic review and meta-analysis.[6,10,14,15,20–43] The characteristics of the included studies are summarised in the appendix (pp 10–13). Among the 28 observational studies, 17 (60·7%) were retrospective cohort studies, four (14·3%) were prospective cohort studies, three (10·7%) were prospective and retrospective cohort studies, three (10·7%) were retrospective case-control studies, and one (3·6%) was a prospective case-control

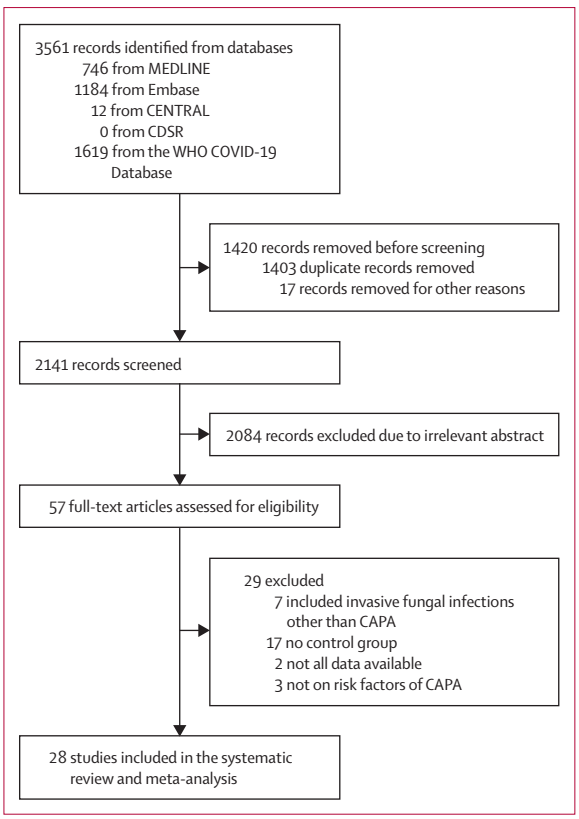

Figure 1: **Study selection**
CAPA=COVID-19-associated pulmonary aspergillosis. CDSR=Cochrane Database of Systematic Reviews. CENTRAL=Cochrane Central Register of Controlled Trials.

study. 16 (57·1%) were single-centre studies and 12 (42·9%) were multicentre studies.

17 (60·7%) of the 28 studies involved European centres; the other studies involved centres in Brazil, China, India, Mexico, Pakistan, South Korea, Taiwan, and the USA (appendix pp 10–13). 12 (42·9%) studies were done during the initial wave of the SARS-CoV-2 pandemic (from January, 2020, to June, 2020[44]). To define CAPA, 20 (71·4%) studies applied the ECMM/ISHAM criteria (three of which used ECMM/ISHAM criteria modified by the investigators), two (7·1%) applied the IAPA criteria, two (7·1%) used both the EORTC/MSGERC and IAPA criteria, two (7·1%) used the AspICU algorithm (one of which used AspICU modified by the investigators), one (3·6%) applied the EORTC/MSGERC criteria, and one (3·6%) used both the AspICU and EORTC/MSGERC criteria. 12 studies had an overall high risk of bias,[6,15,20,34–42] nine studies had an overall moderate risk of bias,[14,22,23,25–27,29,33,43] and seven studies had an overall low risk of bias[10, 21,24, 28,30–32] (appendix p 14).

The total sample size of the included studies was 8009 patients with severe COVID-19, all of whom were included in our meta-analysis (sample size range: 27–1161; 5137 [64·1%] men and 2872 [35·9%] women; appendix pp 10–13). Of these patients, 1398 (17·5%) were diagnosed with CAPA. Across the studies, the proportion of patients diagnosed with CAPA ranged from 2·5% (14 of 566 patients) to 47·2% (58 of 123). Most patients in the total population had severe COVID-19 infection with a need for mechanical ventilation (4885 [61·0%] of 8009). Among patients who developed CAPA after ICU admission, the median onset of CAPA ranged from 3 days (IQR 1–4) to 18 days (13–30) from ICU admission.

In the analysis of dichotomous variables, we analysed 25 potential risk factors from across the 28 studies, and found nine risk factors for CAPA. Among the identified factors associated with CAPA were the following pre-existing comorbidities: chronic liver disease (OR 2·56 [1·30–5·05], p=0·007; I^2=47%), haematological malignancies (OR 2·47 [1·27–4·83], p=0·008; I^2=50%), chronic obstructive pulmonary disease (OR 1·92 [1·42–2·60], p<0·0001; I^2=22%), cerebrovascular disease (OR 1·31 [1·01–1·71], p=0·05; I^2=46%), and diabetes (OR 1·26 (1·04–1·53), p=0·02; I^2=37%; appendix pp 22–23). In addition, use of invasive mechanical ventilation (OR 2·73 [1·89–3·94], p<0·0001; I^2=69%), use of renal replacement therapy (OR 2·26 [1·76–2·90], p<0·0001; I^2=14%), treatment of COVID-19 with interleukin-6 (IL-6) inhibitors (OR 2·69 [1·47–4·90], p=0·001; I^2=88%), and treatment of COVID-19 with corticosteroids (OR 1·72 [1·10–2·68], p=0·02; I^2=77%) were associated with CAPA (appendix pp 24–25). In most of the included studies, detailed descriptions were missing on the type, dose, frequency, and duration of corticosteroid administration, and on the duration of IL-6 inhibitor administration; thus, detailed analysis of these factors was not possible. Forest plots of factors that showed no association with CAPA, including sex distribution, are reported in the appendix (pp 26–32).

On comparison of age, we found that patients with CAPA were typically older than those without CAPA (mean age 66·0 years [SD 4·4] *vs* 63·1 years [5·4]; mean difference 2·72 [1·33–4·12], p=0·0001; I^2=86%; appendix p 32). BMI showed no association (appendix p 31).

Overall, 4885 (61·0%) of the 8009 patients required invasive mechanical ventilation; in patients with CAPA, this proportion was 1069 (76·5%) of 1398. The mean duration of mechanical ventilation was reported in seven studies. The duration of mechanical ventilation in patients with CAPA was longer than in patients without CAPA (mean duration 19·3 days [SD 8·9] *vs* 13·5 days [6·8]; mean difference 5·53 days [1·30–9·77], p=0·01; I^2=88%; figure 2A).

A secondary post-hoc outcome was to compare the length of ICU stays between patients with and without CAPA. Length of ICU stay was reported in 12 studies. The length of ICU stay in patients with CAPA was typically longer than in those without CAPA (mean duration 28·8 days [SD 13·0] *vs* 20·0 days [9·5]; mean difference 7·39 days [95% CI 3·69–11·09], p<0·0001; I^2=87%; figure 2B). A tertiary post-hoc outcome was to compare all-cause mortality between patients with and

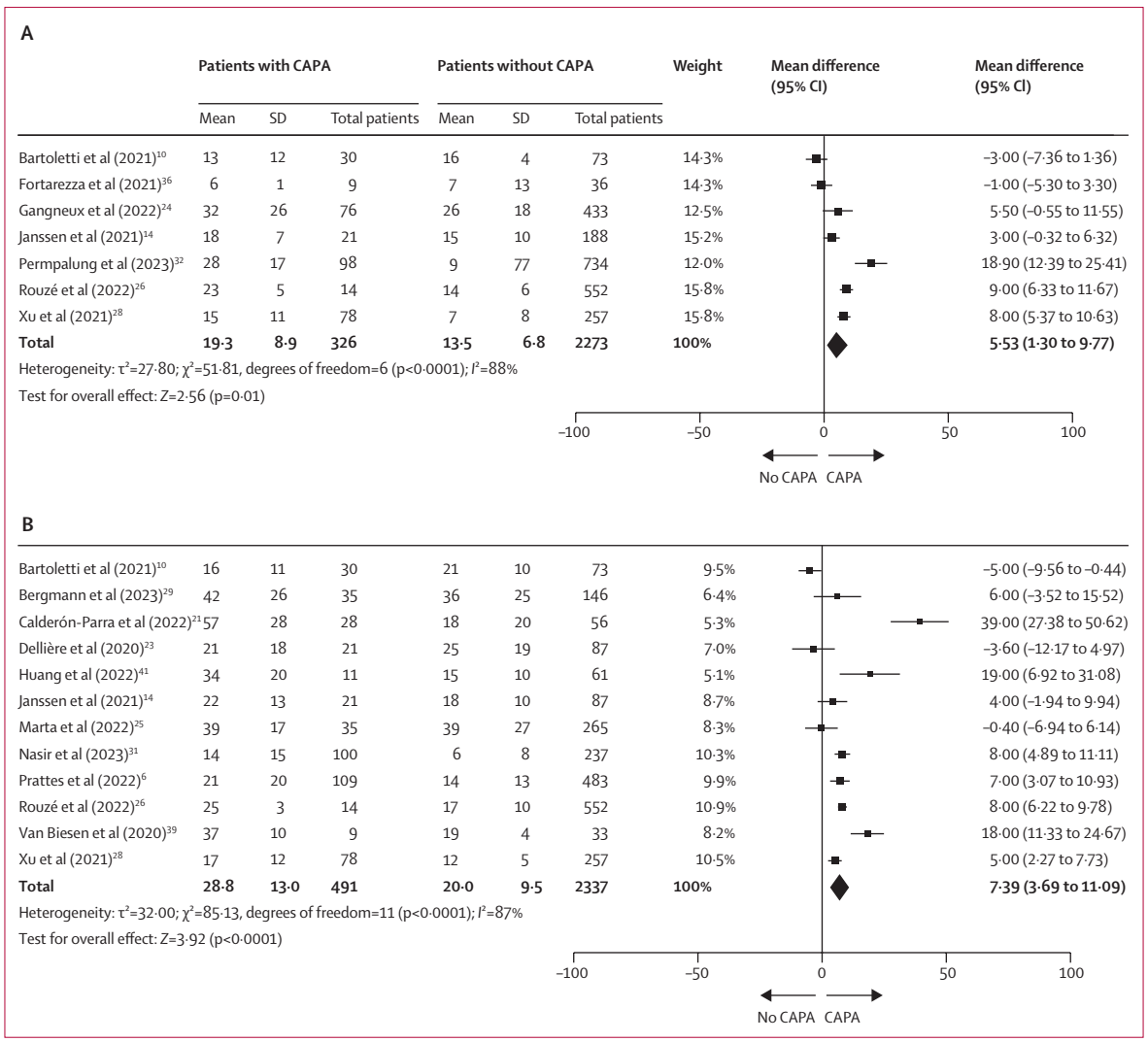

Figure 2: **Forest plot of duration of invasive mechanical ventilation (A) and length of intensive care unit stay*(B) in patients with CAPA versus patients without CAPA**
CAPA=COVID-19-associated pulmonary aspergillosis. *Post-hoc outcome.

without CAPA, reported in 21 studies. Patients with CAPA had higher all-cause mortality than those without CAPA (OR 2·63 [95% CI 2·06–3·34, p<0·0001; I^2=48%; figure 3).

Figure 4 shows the ORs for the CAPA-associated factors. A subgroup analysis was done for 17 studies that used unmodified ECMM/ISHAM criteria to define CAPA (appendix pp 33–37).[6,14,15,21,22,24–27,30,31,34,36,37,41–43] In this analysis, cerebrovascular disease, chronic obstructive pulmonary disease, chronic liver disease, haematological malignancies, invasive mechanical ventilation, renal replacement therapy, and IL-6 treatment remained associated with CAPA, but diabetes and corticosteroids did not. In addition, asthma (OR 1·89 [95% CI 1·04–3·44], p=0·04; I^2=0%) became associated with CAPA in this subgroup analysis, although this association was not apparent in the primary analysis.

A publication bias assessment was done for the nine risk factors for CAPA and for the associated variables of age, length of ICU stay, and duration of invasive mechanical (appendix pp 38–43). The post-hoc sensitivity analysis excluding studies with the largest or smallest effect estimates was robust, with little variation in the overall effect estimates for the factors associated with CAPA, except cerebrovascular disease (OR 1·24 [95% CI 0·97–1·58]; p=0·08; I^2=36%; appendix pp 44–48).

Discussion

This study aimed to establish the main factors associated with the development of CAPA in patients with severe COVID-19. Our study identified nine risk factors for CAPA: diagnosed chronic obstructive pulmonary disease, cerebrovascular disease, chronic liver disease, diabetes, and haematological malignancy as underlying disease,

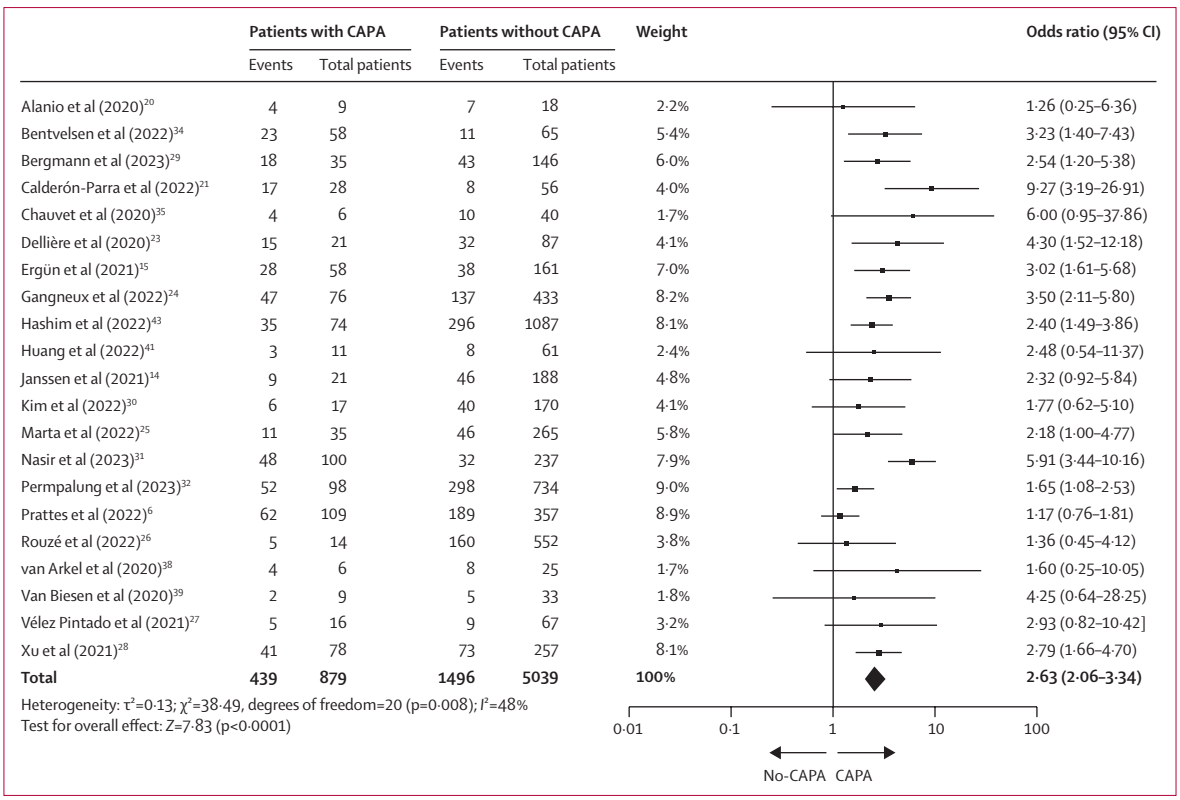

Figure 3: **Forest plot of all-cause mortality in patients with CAPA versus patients without CAPA**
All-cause mortality was assessed as a tertiary post-hoc outcome. CAPA=COVID-19-associated pulmonary aspergillosis.

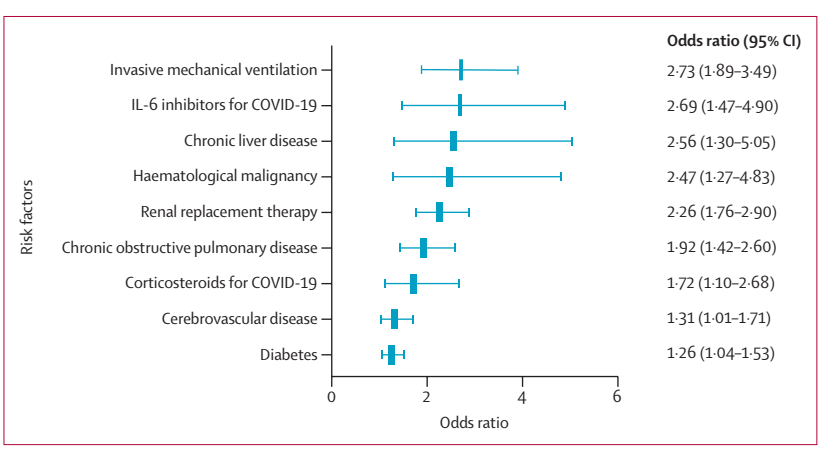

Figure 4: **Risk factors for CAPA**
CAPA=COVID-19-associated pulmonary aspergillosis. IL-6=interleukin-6.

use of invasive mechanical ventilation and renal replacement therapy, and treatment with IL-6 inhibitors and corticosteroids for COVID-19 infection. CAPA also showed an association with age and duration of mechanical ventilation, and, in post-hoc analysis, with length of ICU stay and all-cause mortality.

Across the 28 studies, comprising 8009 patients with severe COVID-19 infections, the prevalence of CAPA varied, ranging from 2·5% to 47·2%. CAPA prevalence has previously been found to vary widely among hospitalised patients with severe COVID-19, from 1% to 39%.[8,45] The variability in CAPA prevalence can be attributed to the different criteria used to define CAPA in different studies (each with a stringent definition), particularly during the initial waves of the COVID-19 pandemic. As a result of the conservative ECMM/ISHAM consensus criteria for CAPA published in late 2020,[16] reported prevalence of CAPA decreased substantially to about half the prevalence reported before publication of the criteria,[5] more closely aligning with the prevalence of CAPA found in autopsy studies.[46] In our review, the majority of studies used ECMM/ISHAM consensus criteria, even if some authors had to adapt these criteria to match their specific local realities. Variations in prevalence might also relate to the difficulty in diagnosing CAPA in patients with COVID-19 associated with acute respiratory distress syndrome, due to similar radiological and clinical findings, making differential diagnosis a challenge. Furthermore, some studies during the first wave of the pandemic avoided the use of bronchoalveolar lavage for diagnosis due to the risk of oxygen deprivation and aerosolisation of SARS-CoV-2.[5,39] Due to the reduced use of bronchoscopy, other non-bronchial lavage specimens have been used, including sputum, bronchial aspirates, and tracheal aspirates,[20,28,39,40] which do not have validated

aspergillus biomarkers, making it difficult to distinguish airway colonisation from invasive infection. These factors are also likely to contribute to variation in CAPA diagnosis across studies and centres.

Regarding underlying disease, haematological malignancies, chronic liver disease, chronic obstructive pulmonary disease, diabetes, and cerebrovascular disease were associated with CAPA, reflecting that patients with relevant comorbidities seem to have increased susceptibility to CAPA. Similar findings were described in a review article (without meta-analysis) by Hoenigl and colleagues.[45] The association of chronic obstructive pulmonary disease with CAPA in our study, was likely due to the severity of the underlying disease.[47] Patients with chronic obstructive pulmonary disease often have impaired and inflamed ciliary function because of previous episodes of infection, exacerbation, and colonisation, and subsequent destruction of the epithelium. A COVID-19 infection might also impair mucociliary clearance and increase the risk of aspergillosis.[48] Such factors would be amplified in mechanically ventilated patients, given that ventilation causes inflammation of the bronchial mucosa and pulmonary parenchyma that reduces mucociliary clearance and promotes aspergillosis.[48] In chronic liver disease, patients with cirrhosis have an increased likelihood of developing influenza-associated pulmonary aspergillosis, possibly as a result of other comorbid conditions that are associated with cirrhosis or as a consequence of cirrhosis-associated immune dysfunction, in which immunodeficiency is combined with disruption of specific immune cells.[49]

Interestingly, we identified only one conventional risk factor associated with CAPA according to the EORTC/MSGERC criteria,[12] namely, haematological malignancy. Five studies in our review specifically looked for the presence of EORTC/MSGERC host factors without showing association.[14,15,20,33,36] Other typical risk factors, such as being a solid organ transplant recipient, were not associated with CAPA in this meta-analysis; however, the number of solid organ transplants was small in most studies. Similar to individuals who develop influenza-associated pulmonary aspergillosis, most patients with CAPA are not immunocompromised.[50]

It has been reported that virus infection might predispose individuals to CAPA by disrupting the natural lung barrier, resulting in overproduction of cytokines and suppressing cellular immunity.[51] In a review by Kluge and colleagues, severe viral pneumonia, chronic obstructive pulmonary disease, decompensated liver cirrhosis, and sepsis were identified as risk factors for invasive aspergillosis in ICU patients.[52]

Additionally, as described in Chong and colleagues' meta-analysis,[53] patients with CAPA in our study were older than those without CAPA. However, in this analysis, we did not use meta-regression, and so we cannot conclude that older age is a risk factor for CAPA. Interestingly, patients with CAPA and those without CAPA had similar sex distribution and BMI (appendix pp 26, 30). As a result, it might be important to shift focus to patients presenting with the risk factors identified herein for targeted screening, and to consider antifungal prophylaxis in this group.

Use of invasive mechanical ventilation was also a significant risk factor for CAPA, reflecting that the lung damage and severity of COVID-19 in these patients can predispose them to CAPA. Additionally, ICU stays for patients with CAPA were longer than for those without CAPA. In the MYCOVID study, Gangneux and colleagues[24] found a long period of mechanical ventilation (>14 days) to be independently associated with CAPA. Similarly, we found that patients with CAPA received mechanical ventilation for longer durations than those without CAPA.

Renal replacement therapy was another risk factor associated with CAPA. Similarly, renal replacement therapy is a relevant risk factor for invasive fungal infection in patients following solid organ transplantation.[50] A long duration of organ-supportive therapy, such as renal replacement therapy, has also been associated with poor outcomes in critically ill patients with influenza-associated pulmonary aspergillosis.[50,51] As such, there is a need for increased awareness in patients requiring organ-supportive therapy, particularly among chronically ill patients, given the absence of typical risk factors.

The use of corticosteroids as treatment for COVID-19 infection was also a significant risk factor for CAPA, as described in other studies.[24] Per the EORTC/MSGERC and AspICU criteria, prolonged use of corticosteroids in the past 2 months at doses greater than 0·3 mg/kg for 3 weeks or more has been recognised as a host factor predisposing to invasive pulmonary aspergillosis. Systematic administration of glucocorticoids to patients with severe COVID-19 for 10 days has been found to reduce 28-day mortality.[54,55] It is noteworthy that the cumulative dose of dexamethasone used in the RECOVERY trial[56] regimen was not greater than 60 mg (6 mg for 10 days), which is lower than the dose considered a risk factor by EORTC/MSGERC and AspICU guidelines. Among the studies included in our analysis, detailed descriptions were missing on the type, dose, frequency, or duration of corticosteroid administration. Nonetheless, our findings suggest that even a brief course of corticosteroids and a low cumulative dose might predispose to CAPA, and aspergillosis screening should be considered in this population.

Anti-IL-6 treatment also was a significant risk factor for CAPA in our meta-analysis. However, the role of anti-IL-6 in treating COVID-19 infections is yet to be established, as clinical trials have shown conflicting results. Nonetheless, it remains a concern that the use of IL-6 inhibitors is associated with an increased risk of

invasive fungal infections.[4,10] In animal studies, the use of anti-IL-6 predisposed to invasive fungal infections.[57] Anti-IL-6 doses were not detailed in the studies included in this meta-analysis. In the first wave of the pandemic, anti-IL-6 dose and indication were not well defined. However, due to the observational nature of the studies included, we cannot exclude that the association was due to patients with more severe COVID-19, who have potentially higher risk of CAPA and are more likely to receive corticosteroids and anti-IL-6.

A recent review by Hawes and colleagues[58] discussed the results of six studies on the role of antifungal prophylaxis. Some studies showed promising results; however, most of them were retrospective studies, limited by a small sample size and potential bias. In one prospective observational study, antifungal prophylaxis reduced the incidence of CAPA in mechanically ventilated patients with severe COVID-19 and in immunocompromised patients, although an improvement in survival was not found.[59] Prophylaxis should reduce the likelihood of aspergillus colonisation, which reduces the risk of subsequent clinical infection. Before clinical trials are available, antifungal prophylaxis could be considered on the basis of the local prevalence of CAPA, host risk factors, fungal colonisation, and previous fungal infections. Of note, risk factors related to the environment, such as environmental exposure to aspergillus species, were not described in the studies included in our meta-analysis, contrary to other studies.[45]

As a major finding, patients with CAPA had higher all-cause mortality than those without CAPA. This result is important, and probably underestimated, considering that the design of the included studies was not in favour of finding worse survival in patients with CAPA due to immortal time bias.

Our study has several limitations due to the available studies. First, only descriptive studies were available to include; most studies were retrospective, and the majority of studies were from European countries, which might lead to measurement bias. Only eleven studies had a multivariate analysis of risk factors associated with CAPA.[6,15,21,24,25,30–32,41,40,43] In addition, the definition of CAPA was based on various criteria, and in multiple instances the criteria were modified by investigators, which will have introduced bias into our analysis. Therefore, we did a subanalysis of studies that used only unmodified ECMM/ISHAM criteria for diagnosis of CAPA, and the results were mostly unchanged (appendix pp 33–37). Corticosteroid treatment or diabetes were no longer associated with CAPA in this subanalysis. As mentioned, the cumulative dose of dexamethasone used for COVID-19 is not higher than 60 mg,[54] which is lower than the dose considered a risk factor by EORTC/MSGERC and AspICU. Nevertheless, these results should be interpreted cautiously given that dose and duration of corticosteroid therapy are not reported in all studies, and corticosteroid therapy improves overall mortality in critically ill patients with COVID-19.[54] Thus, the use of dexamethasone should be carefully considered in terms of risk–benefit ratio. Further studies are needed to provide insights into the long-term effects of dexamethasone in patients with COVID-19. Finally, 17 (63·0%) of 27 studies included patients from the pre-vaccination era (before January, 2021[60]), and none considered the effect of vaccination on CAPA. Therefore, the results should be interpreted accordingly. Currently, the situation might be different. In addition to providing protection against severe diseases caused by SARS-CoV-2, the vaccine could also prevent subsequent development of CAPA. As a result of several factors, including vaccination uptake and potential differences in the clinical course of omicron variants and ICU admissions, CAPA diagnoses decreased substantially since 2021 in Europe and North America.[61,62] To assess the effect of the vaccine on CAPA incidence and risk factors, further studies are required. Nevertheless, to our knowledge, this is the first systematic review and meta-analysis that has studied factors associated with CAPA.

In conclusion, in this meta-analysis we found that important predictors of CAPA were haematological malignancies, chronic liver disease, chronic obstructive pulmonary disease, cerebrovascular disease, diabetes, invasive mechanical ventilation, renal replacement therapy, and treatment with corticosteroids or IL-6 inhibitors for COVID-19 infection. These data could aid in determining CAPA risk, especially when typical risk factors for invasive aspergillosis are absent. In the absence of antifungal prophylaxis, adequate screening for CAPA and recognising its risk factors are essential. However, it is important to consider that most of the data from studies in this meta-analysis were from the pre-vaccine era, and so the results obtained should be interpreted accordingly.

Contributors

All authors contributed to the development of the research question, to the screening and selection criteria, and to selection of an appropriate quality assessment tool. AO-C and FG developed the search strategies. LNW and FG created and edited the data extraction forms. LNW, FG, and SH selected and assessed the quality of the included studies. LNW and FG provided statistical expertise in data analysis. FG and LNW performed the data synthesis, including the meta-analysis, under the supervision of SH. LNW and FG accessed and verified the data. SH provided expertise on clinical aspects. LNW and FG drafted the manuscript. All authors read the manuscript, provided feedback, and approved the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

All data will be made available by email upon request to the corresponding author.

References

1 Baddley JW, Thompson GR 3rd, Chen SC, et al. Coronavirus disease 2019-associated invasive fungal infection. *Open Forum Infect Dis* 2021; **8:** ofab510.

2 Bassetti M, Kollef MH, Timsit JF. Bacterial and fungal superinfections in critically ill patients with COVID-19. *Intensive Care Med* 2020; **46:** 2071–74.

3 Lai CC, Yu WL. COVID-19 associated with pulmonary aspergillosis: a literature review. *J Microbiol Immunol Infect* 2021; **54:** 46–53.

4 Permpalung N, Chiang TP, Massie AB, et al. Coronavirus disease 2019-associated pulmonary aspergillosis in mechanically ventilated patients. *Clin Infect Dis* 2022; **74:** 83–91.

5 Feys S, Almyroudi MP, Braspenning R, et al. A visual and comprehensive review on COVID-19-associated pulmonary aspergillosis (CAPA). *J Fungi (Basel)* 2021; **7:** 1067.

6 Prattes J, Wauters J, Giacobbe DR, et al. Risk factors and outcome of pulmonary aspergillosis in critically ill coronavirus disease 2019 patients—a multinational observational study by the European Confederation of Medical Mycology. *Clin Microbiol Infect* 2022; **28:** 580–87.

7 Fekkar A, Neofytos D, Nguyen MH, Clancy CJ, Kontoyiannis DP, Lamoth F. COVID-19-associated pulmonary aspergillosis (CAPA): how big a problem is it? *Clin Microbiol Infect* 2021; **27:** 1376–78.

8 Salmanton-García J, Sprute R, Stemler J, et al. COVID-19-associated pulmonary aspergillosis, March–August 2020. *Emerg Infect Dis* 2021; **27:** 1077–86.

9 Schmidt M, Hajage D, Demoule A, et al. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. *Intensive Care Med* 2021; **47:** 60–73.

10 Bartoletti M, Pascale R, Cricca M, et al. Epidemiology of invasive pulmonary aspergillosis among intubated patients with COVID-19: a prospective study. *Clin Infect Dis* 2021; **73:** e3606–14.

11 Mitaka H, Kuno T, Takagi H, Patrawalla P. Incidence and mortality of COVID-19-associated pulmonary aspergillosis: a systematic review and meta-analysis. *Mycoses* 2021; **64:** 993–1001.

12 Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. *Clin Infect Dis* 2020; **71:** 1367–76.

13 Fekkar A, Lampros A, Mayaux J, et al. Occurrence of invasive pulmonary fungal infections in patients with severe COVID-19 admitted to the ICU. *Am J Respir Crit Care Med* 2021; **203:** 307–17.

14 Janssen NAF, Nyga R, Vanderbeke L, et al. Multinational observational cohort study of COVID-19-associated pulmonary aspergillosis. *Emerg Infect Dis* 2021; **27:** 2892–98.

15 Ergün M, Brüggemann RJM, Alanio A, et al. Aspergillus test profiles and mortality in critically ill COVID-19 patients. *J Clin Microbiol* 2021; **59:** e0122921.

16 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* 2021; **21:** e149–62.

17 Blot SI, Taccone FS, Van den Abeele AM, et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. *Am J Respir Crit Care Med* 2012; **186:** 56–64.

18 Verweij PE, Rijnders BJA, Brüggemann RJM, et al. Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion. *Intensive Care Med* 2020; **46:** 1524–35.

19 Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339:** b2700.

20 Alanio A, Dellière S, Fodil S, Bretagne S, Mégarbane B. Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19. *Lancet Respir Med* 2020; **8:** e48–49.

21 Calderón-Parra J, Mills-Sanchez P, Moreno-Torres V, et al. COVID-19-associated pulmonary aspergillosis (CAPA): risk factors and development of a predictive score for critically ill COVID-19 patients. *Mycoses* 2022; **65:** 541–50.

22 de Almeida JN Jr, Doi AM, Watanabe MJL, et al. COVID-19-associated aspergillosis in a Brazilian referral centre: diagnosis, risk factors and outcomes. *Mycoses* 2022; **65:** 449–57.

23 Dellière S, Dudoignon E, Fodil S, et al. Risk factors associated with COVID-19-associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective cohort. *Clin Microbiol Infect* 2020; **27:** 790.e1–5.

24 Gangneux JP, Dannaoui E, Fekkar A, et al. Fungal infections in mechanically ventilated patients with COVID-19 during the first wave: the French multicentre MYCOVID study. *Lancet Respir Med* 2022; **10:** 180–90.

25 Marta GC, Lorena FE, Laura MV, et al. COVID-19-associated pulmonary aspergillosis in a tertiary hospital. *J Fungi (Basel)* 2022; **8:** 97.

26 Rouzé A, Lemaitre E, Martin-Loeches I, et al. Invasive pulmonary aspergillosis among intubated patients with SARS-CoV-2 or influenza pneumonia: a European multicenter comparative cohort study. *Crit Care* 2022; **26:** 11.

27 Vélez Pintado M, Camiro-Zúñiga A, Aguilar Soto M, Cuenca D, Mercado M, Crabtree-Ramirez B. COVID-19-associated invasive pulmonary aspergillosis in a tertiary care center in Mexico City. *Med Mycol* 2021; **59:** 828–33.

28 Xu J, Yang X, Lv Z, et al. Risk Factors for invasive aspergillosis in patients admitted to the intensive care unit with coronavirus disease 2019: a multicenter retrospective study. *Front Med (Lausanne)* 2021; **8:** 753659.

29 Bergmann F, Jorda A, Blaschke A, et al. Pulmonary aspergillosis in critically ill COVID-19 patients admitted to the intensive care unit: a retrospective cohort study. *J Fungi (Basel)* 2023; **9:** 315.

30 Kim SH, Hong JY, Bae S, et al. Risk factors for coronavirus disease 2019 (COVID-19)-associated pulmonary aspergillosis in critically ill patients: a nationwide, multicenter, retrospective cohort study. *J Korean Med Sci* 2022; **37:** e134.

31 Nasir N, Farooqi J, Zubair SM, et al. Comparison of risk factors and outcome of patients with and without COVID-19-associated pulmonary aspergillosis from Pakistan: a case-control study. *Mycoses* 2023; **66:** 69–74.

32 Permpalung N, Chiang TP, Avery RK, et al. Coronavirus disease 2019-associated pulmonary aspergillosis: a noninvasive screening model for additional diagnostics. *Open Forum Infect Dis* 2023; **10:** ofad155.

33 van Grootveld R, van der Beek MT, Janssen NAF, et al. Incidence, risk factors and pre-emptive screening for COVID-19 associated pulmonary aspergillosis in an era of immunomodulant therapy. *J Crit Care* 2023; **76:** 154272.

34 Bentvelsen RG, Arkel ALEV, Rijpstra TA, et al. Regional impact of COVID-19-associated pulmonary aspergillosis (CAPA) during the first wave. *J Fungi (Basel)* 2022; **8:** 96.

35 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.

36 Fortarezza F, Boscolo A, Pezzuto F, et al. Proven COVID-19-associated pulmonary aspergillosis in patients with severe respiratory failure. *Mycoses* 2021; **64:** 1223–29.

37 Shadrivova O, Gusev D, Vashukova M, et al. COVID-19-associated pulmonary aspergillosis in Russia. *J Fungi (Basel)* 2021; **7:** 1059.

38 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:** 132–35.

39 Van Biesen S, Kwa D, Bosman RJ, Juffermans NP. Detection of invasive pulmonary aspergillosis in COVID-19 with nondirected BAL. *Am J Respir Crit Care Med* 2020; **202:** 1171–73.

40 Wang J, Yang Q, Zhang P, Sheng J, Zhou J, Qu T. Clinical characteristics of invasive pulmonary aspergillosis in patients with COVID-19 in Zhejiang, China: a retrospective case series. *Crit Care* 2020; **24:** 299.

41 Huang JR, Shen HC, Sun CY, et al. COVID-19-associated pulmonary aspergillosis is associated with increased in-hospital mortality and prolonged SARS-CoV-2 viral shedding. *J Formos Med Assoc* 2022; **121:** 2617–25.

42 Iqbla A, Rauf-Ul-Hassan M, Waseem M, Ashraf MZ, Abaid T, Saleem A. Risk factors for development of covid associated pulmonary aspergillosis in ICU population. An observational study from a large tertiary care hospital. *Pak J Med Sci* 2022; **16:** 321–23.

43 Hashim Z, Nath A, Khan A, et al. New insights into development and mortality of COVID-19-associated pulmonary aspergillosis in a homogenous cohort of 1161 intensive care patients. *Mycoses* 2022; **65:** 1010–23.

44 Working group for the surveillance and control of COVID-19 in Spain. The first wave of the COVID-19 pandemic in Spain: characterisation of cases and risk factors for severe outcomes, as at 27 April 2020. *Euro Surveill* 2020; **25:** 2001431.

45 Hoenigl M, Seidel D, Sprute R, et al. COVID-19-associated fungal infections. *Nat Microbiol* 2022; **7:** 1127–40.

46 Egger M, Bussini L, Hoenigl M, Bartoletti M. Prevalence of COVID-19-associated pulmonary aspergillosis: critical review and conclusions. *J Fungi (Basel)* 2022; **8:** 390.

47 Tutar N, Metan G, Koç AN, et al. Invasive pulmonary aspergillosis in patients with chronic obstructive pulmonary disease. *Multidiscip Respir Med* 2013; **8:** 59.

48 Gangneux JP, Bougnoux ME, Dannaoui E, Cornet M, Zahar JR. Invasive fungal diseases during COVID-19: we should be prepared. *J Mycol Med* 2020; **30:** 100971.

49 Phoompoung P, Herrera S, Pérez Cortés Villalobos A, Foroutan F, Orchanian-Cheff A, Husain S. Risk factors of invasive fungal infections in liver transplant recipients: a systematic review and meta-analysis. *Am J Transplant* 2022; **22:** 1213–29.

50 Vanderbeke L, Spriet I, Breynaert C, Rijnders BJA, Verweij PE, Wauters J. Invasive pulmonary aspergillosis complicating severe influenza: epidemiology, diagnosis and treatment. *Curr Opin Infect Dis* 2018; **31:** 471–80.

51 Feys S, Gonçalves SM, Khan M, et al. Lung epithelial and myeloid innate immunity in influenza-associated or COVID-19-associated pulmonary aspergillosis: an observational study. *Lancet Respir Med* 2022; **10:** 1147–59.

52 Kluge S, Strauß R, Kochanek M, Weigand MA, Rohde H, Lahmer T. Aspergillosis: emerging risk groups in critically ill patients. *Med Mycol* 2021; **60:** myab064.

53 Chong WH, Saha BK, Neu KP. Comparing the clinical characteristics and outcomes of COVID-19-associate pulmonary aspergillosis (CAPA): a systematic review and meta-analysis. *Infection* 2022; **50:** 43–56.

54 Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med* 2021; **384:** 693–704.

55 Sterne JAC, Murthy S, Diaz JV, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020; **324:** 1330–41.

56 Abani O, Abbas A, Abbas F, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397:** 1637–45.

57 Cenci E, Mencacci A, Casagrande A, Mosci P, Bistoni F, Romani L. Impaired antifungal effector activity but not inflammatory cell recruitment in interleukin-6-deficient mice with invasive pulmonary aspergillosis. *J Infect Dis* 2001; **184:** 610–17.

58 Hawes AM, Permpalung N. Diagnosis and antifungal prophylaxis for COVID-19 associated pulmonary aspergillosis. *Antibiotics (Basel)* 2022; **11:** 1704.

59 Hatzl S, Reisinger AC, Posch F, et al. Antifungal prophylaxis for prevention of COVID-19-associated pulmonary aspergillosis in critically ill patients: an observational study. *Crit Care* 2021; **25:** 335.

60 Warren GW, Lofstedt R. COVID-19 vaccine rollout management and communication in Europe: one year on. *J Risk Res* 2022; **25:** 1098–117.

61 Fiolet T, Kherabi Y, MacDonald CJ, Ghosn J, Peiffer-Smadja N. Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: a narrative review. *Clin Microbiol Infect* 2022; **28:** 202–21.

62 Nyberg T, Ferguson NM, Nash SG, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet* 2022; **399:** 1303–12.