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Mortality in critically ill patients with coronavirus disease 2019-associated pulmonary aspergillosis: A systematic review and meta-analysis

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Abstract

Reports of COVID-19 associated pulmonary aspergillosis (CAPA) are rising, but the associated mortality and factors affecting it are not well-characterised. We performed a systematic review including 20 peer-reviewed English language studies reporting mortality in CAPA published till 18 February 2021from PubMed, Ovid SP, Web of Science, Embase and CINHAL. The pooled mortality in CAPA was 51.2% (95% CI: 43.1–61.1, I^2 = 38%). The leave one out sensitivity analysis and influential case diagnostics revealed one outlier and its exclusion resulted in a mortality estimate of 54% (95% CI: 45–62). Higher odds of mortality: 2.83 (95% CI: 1.8–4.5) were seen in CAPA compared to controls. No significant difference in various subgroups according to the country of study, the continent of study, income category of country and quality of the included study was seen. None of the host risk factors, mycological test results, therapy for COVID-19 and antifungal therapy affected mortality. Thus, patients with CAPA have a high probability of mortality and early diagnosis with prompt therapy must be ensured to optimally manage these patients. However, more prospective studies with global and multi-centre coordination may help to address CAPA in a better way.

KEYWORDS
COVID-19, meta-analysis, mortality, pulmonary aspergillosis, systematic review

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) virus affects both healthy individuals and those with common co-morbidities.[1] The patients with severe COVID-19 viral pneumonitis may progress to acute respiratory distress syndrome (ARDS), which often requires interventions like mechanical ventilation (MV) and extracorporeal membrane oxygenation (ECMO).[2] Considering the early reports of a low number of bacterial and fungal co-infections in patients with COVID-19, the recognition of COVID-19 associated pulmonary aspergillosis (CAPA) came late in the pandemic.[3] Since the clinical course of COVID-19 shows lymphopenia and systemic pro-inflammatory cytokine responses, it is reasonable to suspect that patients with severe COVID-19 may be susceptible to invasive pulmonary aspergillosis (IPA).[4,5] The use of immunomodulatory therapy and the impact of overburdened critical care services during this pandemic may further exaggerate its impact.

In general, the crude mortality due to the IPA ranges from 30.2% to 99% in critically ill patients.[6,7] The poor outcome is associated with older age, high disease severity scores, use of MV, renal replacement

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therapy (RRT), exposure to a steroid, underlying diabetes and longer length of hospital stay.[7–9] In patients with COVID-19, smoking, renal disease, hypertension, malignancy, diabetes, obesity and elevated laboratory parameters like lactate dehydrogenase (LDH), procalcitonin and D-Dimer ferritin have an unbeneficial impact on mortality.[10-15] However, it is not clear which associated factors adversely affect the outcome in patients with CAPA.

Due to the present gap in knowledge, we present the systematic review and meta-analysis to synthesise the results of primary studies on CAPA and to provide pooled mortality estimators of in-hospital mortality of the disease and the potential predictors of outcome. This would help to predict the prognosis of those groups of patients.

2 | METHODS

2.1 | Data sources and searches

The protocol of this study was registered in the international prospective register of systematic reviews, PROSPERO (Registration number: CRD42021232657), and it was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[16] The population studied was adults (>18 years) with COVID-19, Context/Exposure was Invasive pulmonary aspergillosis, Comparator(s)/controls were patients with COVID without IPA and Outcome was In-hospital mortality.

2.2 | Literature search

The study selection criteria were set and reviewed by three independent investigators (SS, NV and RK), and an electronic search was conducted using databases: PubMed, Embase, Ovid SP, CINHAL and Web of Science in the population of patients with CAPA to include studies published in English literature up to 18 February 2021 for this meta-analysis. The search strategy was performed using Boolean combinations of the MeSH terms of keywords such as Adults AND pulmonary aspergillosis AND COVID-19. An independent librarian supervised the search methodology. The list of references in all original articles and systematic reviews published were also manually searched for any additional studies missed on electronic search.

2.3 | Study inclusion

Studies fulfilling all the following criteria were included:

1. Cohort studies, cross-sectional studies, case-control studies, case series describing ≥4 cases of CAPA.
2. Studies including adults (>18 years age) admitted with the diagnosis of CAPA based on the definition proposed by Koehler et al[17] definitions adapted from the European Organization for Research and Treatment of Cancer and the Mycosis Study Group Education and Research Consortium (EORTC and MSGERC) definitions,[18] and the *Asp*ICU algorithm.[19]
3. Studies describing the mortality among cases with CAPA.

2.4 | Exclusion criteria

1. Studies conducted in paediatric intensive care setups (Age <18 years).
2. Studies describing cases of influenza-associated pulmonary aspergillosis (IAPA).[20]
3. Duplicate publications, insufficient data like abstracts, conference proceedings, posters, case reports, case series with less than four cases etc

2.5 | Data abstraction and synthesis of results

Three reviewers (SS, RK, NV) independently extracted the data, using a predesigned data extraction sheet. For each study, the authors' name, year of publication, country and continent of study origin, number of patients with CAPA/IPA, mean patient age, recruitment strategy etc were documented. The demographic profile, underlying disease, co-morbidities, organ failures, details of antifungal therapy, length of stay etc was noted. Any disparity between the extracted data was re-examined, and a consensus was achieved following discussion. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the included studies took into account the risk of bias within individual studies.[21]

2.6 | Statistical analysis

Subgroup analysis according to the country of study, the continent of study, study design etc was performed according to the available extracted data. The proportion (%), mean ± standard deviation (SD) or median (range) were described as appropriate. All estimates of mortality were pooled using fixed and random effect model with DerSimonian and Laird (DL) method and interpreted from the random-effects model.[22] The variance between estimates was assessed by using the Tau^2, I^2 and Q test. The factors affecting variance were explored by subgroup analysis, meta-regression and outlier assessment. Leave one study out plot and Funnel plot was performed for sensitivity analysis and to assess asymmetry in mortality estimates, respectively. All analyses were performed using the R studio v. 1.2.5033, and a p value of <.05 was considered significant.

3 | RESULTS

The search yielded a total of 195 articles of which 20 were included.[23-42] The search strategy and PRISMA flow chart depicting

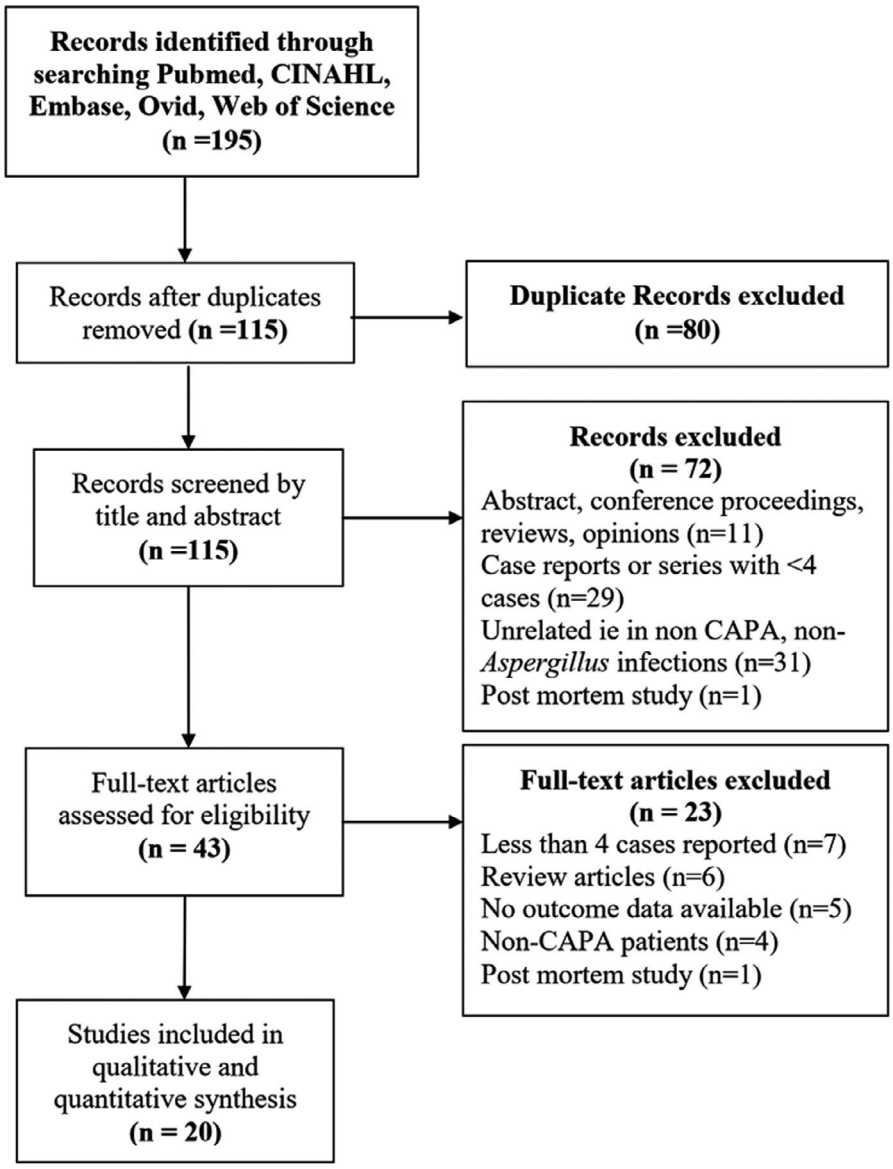

FIGURE 1 Flow chart depicting study selection

the selection of studies is shown in Figure S1 and Figure 1, respectively. The clinical, demographic and mycological characteristics of patients in the 20 included studies (n = 215 patients with CAPA) are detailed in Table 1. The pooled mortality seen in cases of CAPA was 51.2% (95% CI: 43.1–61.1, I^2 = 38%, p =.04) as shown in Figure 2.

The I^2 value (38%) from the pooled mortality estimates indicated moderate heterogeneity between included studies. The funnel plot revealed one study as an outlier, but the Eggers test for plot asymmetry was not significant (p value = .245) (Figure S2). The leave one out sensitivity analysis and influential case diagnostics revealed that the study by Marr et al had a substantial influence on the overall mortality estimates (Figures S3 and S4). The estimate of mortality on the exclusion of this study was 54% (95% CI: 45–62). The pooled mortality was also computed in various subgroups (Table 2), and a significant difference in mortality was seen only in subgroups based on the continent where the study was conducted.

3.1 | META-REGRESSION

The multivariate meta-regression to confirm the association of pooled mortality was performed in various categories and continents where study was found to not significantly affect mortality (p value = .088). The study direction (p value = .3422), proportion of cases with- obesity (p value = .6115), hypertension (p value = .931), diabetes (p value = .5083), chronic obstructive pulmonary disease (COPD) (p value = .6203), malignancy (p value = .370) and chronic steroid use (p value = .377) did not affect mortality estimates. Among factors related to treatment of COVID, the proportion of cases receiving therapy with steroid (p value = .1624), tocilizumab (p value = .4198) and lopinavir-ritonavir (p value = .472) did not influence the mortality in patients with CAPA. Among mycological evidence, the proportion of culture positive cases (p value = .4387), values of serum GM (p value = .3319) and BAL GM (p value = .4845) were not found to correlate with mortality. The use of antifungals therapy among cases did not influence mortality (p value = .4198).

TABLE 1 Summary of details of individual studies included in the systematic review

S. No.	Author	Country, income group	Study design, direction, centre -multi/ single	CAPA cases *N* (% of studied population)	Gender (Male) *N* (%)	Median age (Mean SD)	MV	Comorbidity *n* (%)	Pao2/Fio2 mean (SD)
1	Alanio et al[23]	France/HI	C/P/S	9 (33.3)	5 (56)	63 ± 9	9 (100)	Obesity – 3 (33.3) HT – 7 (77.7) DM – 3 (33.3) CAD – 2 (22.2) Asthma – 1 (11.1) Steroids – 2 (22.2)	
2	Bartoletti et al[24]	Italy/HI	C/P/M	30 (3.60)	24 (80)	63 ± 3.25	–	Obesity – 10 (33.3) HT – 16 (53.3) DM – 5 (16.67) CAD – 3 (10) CVSD – 3 (10) CKD – 6 (20) COPD – 4 (13.34) Steroids – 5 (16.6)	
3	Benedetti et al[25]	Argentina/ UMIC	C/P/S	5 (NA)	4 (80)	57 ± 11.5	–	Obesity – 2 (40) HT – 2 (40) DM – 3 (60) BTX – 1 (20)	137.4 ± 18.7
4	Delliere et al[26]	France/HI	C/R/M	21 (5.73)	16 (76)	63 ± 7.25	20 (95)	Obesity – 4 (19) HT – 14 (66.6) DM – 9 (42.85) CAD – 2 (9.5) Asthma – 2 (9.5) Steroids – 3 (14.2)	187.7 ± 114.74
5	Dupont et al[27]	France/HI	C/P/S	19 (12.4)	15 (79)	70 ± 10.5	18 (94)	Obesity – 1 (5) HT – 7 (36.8) DM – 7 (36.8) TB – 19 (10.5) Asthma –4 (21) CKD – 2 (10.5) COPD –4 (21) ABPA – 1 (5.2)	
6	Falces et al[28]	Spain/HI	C/R/S	10 (0.17)	8 (80)	69.5 ± 6.25	7 (70)	Obesity – 2 (20) DM – 5 (50) CAD – 1 (10) COPD – 4 (40) Steroids – 1 (10)	
7	Koehler et al[29]	Germany/HI	Se/R/S	5 (NA)	3 (60)	62 ± 4.75	–	Obesity – 1 HT – 3 DM – 1 Smoking – 3 COPD – 2 Steroids – 3	
8	Machado et al[30]	Spain/HI	C/P/S	8 (0.29)	6 (75)	65 ± 3.125	8 (100)	Obesity – 4 (50) HT – 7 (87.5) DM – 1 (12.5) Asthma – 2 (25) CVSD – 1 (12.5) CKD – 3 (37.5) COPD – 1 (12.5)	89 ± 17.25
9	Mitaka et al[31]	USA/HI	Se/P/S	4 (NA)	4 (100)	79 ± 2.75	4 (100)	HT – 1 (25) DM – 1 (25) CAD – 1 (25) CVSD – 1 (25) COPD – 1 (25)	
10	Nasir et al[32]	Pakistan/LMIC	R/S	5 (3.4)	3 (60)	71 ± 8.5	2 (40)	HT – 3 (60) DM – 4 (80) CVSD – 1 (20)	
11	Segrelles et al[33]	Spain/HI	C/R/S	7 (3.25)	5 (71)	59.6 ± 15.2	–		136.4 ± 71

Radiological finding	Severity scores	Other laboratory parameters	COVID-specific therapy	Fungal culture	BAL Galactomannan – positive cases *n* (%), median (range)	Serum Galactomannan – positive cases *n* (%), median (range)
	APACHE – 16 (8 to 26)		Ribavarin	7 cases	1 (11.1) 0.15 (0.03 to 3.91)	1 (11.1), 0.09 (0.03 to 0.51)
	SOFA – 3± (1.48)	Creatinine mg/dl – 1 (0.94) CRP – 11 (5–18) LDH – 375 (140)	LPV-R (12) DC (2), T (22)	19 cases *A fumigatus (15)*, *A niger (3)*, *A flavus (1)*	30 (100) 3.5 (1.72 to 4.7)	1 (0.3), 0.06 (0.03 to 0.11)
GGO – 3 (60) CPP – 2 (40) Emphysema – 1 (20) Nodules – 1 (20) Bronchiectasis – 1 (20) Air-bronchogram – 1 (20)			–	3 cases *A fumigatus (3)*	2 (40) 3.17 (0.25 to 3.17) – (in TA)	5 (100), 0.92 (0.57 to 1.01)
	SAPS II – 38.1 ± 13.8 SOFA 7.1 ± 4.5	Creatinine mg/dl – 149.8 (132.96) D-dimer – 2515 (1610 to 10 917) LDH – 740.2 (350.52)	LPV-R (6), Eculizumab (2), T (2)	19 cases	3 (14.2)	5 (23.8)
GGO – 13 (86.6) Emphysema – 5 (33.3) Nodules – 2 (13.3) Bronchiectasis – 2 (13.3) Pulmonary embolism – 5 (33.3) Cavitation – 2 (13.3) Secondary infection signs – 5 (33.3)			–	19 cases *A fumigatus (14)*, *A niger (3)*, *A calidoustus (1)*	5 (26.3) 1.5725 (0.076 to 3.483)	
GGO – 5 (50) Interstitial/basal infiltrates – 5 (50) Pleural effusion – 1 (10) Diffuse opacities – 2 (20)			LPV-R (4), T (4)	10 cases *A fumigatus (9)*, *A nidulans (1)*	2 (20) 2.16 (1.11 to 3.87)	1 (10), 0.17 (0.08 to 1.97)
GGO – 5 (100) CPP – 1 (25) Emphysema – 1 (25) Nodules – 5 (100) Cavitation – 1 (25) Air crescent – 1 (25) Consolidation – 1 (25)			Ribavarin (1), LPV-R (1), DC (1)	3 cases *A fumigatus (3)*	3 (60) 2.5 (all more than 2.5)	2 (40)
GGO – 5 (62.5) Cavitation – 1 (20) Pneumothorax – 5 (62.5) Lung fibrosis 1 (20)			LPV-R (8), Interferon-beta (5), T (8)	8 cases *A fumigatus (6)*, *A lentulus (1)*, *A citrinoterreus (1)*, *A terreus (1)*, *A awamori (1)*	2 (40) 4.9 (2.8 to 7)	4 (50), 0.385 (0.05 to 1.94)
Interstitial/basal infiltrates – 1 (25) Cavitation – 1 (25) Consolidation – 1 (25) Diffuse opacity – 1 (25)		Creatinine mg/dl – 2.85 (3.38)	T (1)	4 cases *A fumigatus (4)*		1 (25), 0.71
Pleural effusion – 1 (25) Infiltration- 5 (100) Consolidation – 1 (25)			T (3)	5 cases *A fumigatus (1)*, *A niger (1)*, *A flavus (3)*		0 0.14 (0.126 to 0.272)
			LPV-R (3), Interferon-beta (5), T (5)	7 cases *A fumigatus (3)*, *A niger (2)*, *A flavus (2)*		

(Continues)

TABLE 1 (Continued)

S. No.	Author	Country, income group	Study design, direction, centre -multi/ single	CAPA cases *N* (% of studied population)	Gender (Male) *N* (%)	Median age (Mean SD)	MV	Comorbidity *n* (%)	Pao2/Fio2 mean (SD)
12	VanArkel et al[34]	Netherland/HI	C/P/S	6 (4.44)	6 (100)	62.5 ± 10	–	Asthma – 1 (16.6) COPD – 2 (33.34) Steroids – 3 (50)	
13	Gangneux et al[35]	France/HI	C/P/S	7 (20)	4 (57)	70 ± 3	7 (100)	HT – 3 (33.3) DM – 2 CAD – 2 (22.2) CKD – 1 (11.1)	136 ± 61.02
14	Rutsaert et al[36]	Belgium/HI	C/P/S	4 (11.7)	4 (100)	62.5 ± 10.5	4 (100)	Obesity – 2 (40) HT – 2 (50) DM – 3 (75) CKD – 1 (25)	
15	Fekkar et al[37]	France/HI	C/P/S	6 (0.68)	5 (83.3)	56 ± 7.25	6 (100)	Obesity – 5 (83.3) HT – 5 (83.3) DM – 1 (16.6) Steroids – 1	67.5 ± 66.6
16	Marr et al[38]	The USA and Spain/HI	Se/R/M	20 (100)	9 (45)	65.5 ± 9		Obesity – 2 (10) HT – 12 (60) DM – 6 (30) CAD – 3(15) Asthma – 3 (15) CKD – 3 (15) COPD – 4 (20) Steroids – 1 (5)	
17	White[39]	UK/HI	Co/P/M	18 (13.3)	NA	NA	NA	Obesity – 4 HT – 5 DM – 7 CAD – 1 Asthma – 0 CKD – 2 COPD –8 Steroids – 14 Malignancy-2	
18	Roman-Montes[40]	Mexico/UMIC	Co/P/S	14 (9.72)	11	48.3 ± 11.7	11 (100%)	Obesity – 9 HT –4 DM – 4	
19	Biesen[41]	Netherland/HI	Co/S	9 (21.4)	5	68 ± 9.25	5 (100%)	Obesity – 5 HT –3 DM – 1 Asthma – 2 COPD – 4 Steroids – 1 Malignancy – 0 SOT-1	94 ± 10
20	Meijer[42]	Netherland/HI	Co/R/S	8 (12.1)	6	65 ± 6	6 (100%)	HT –1 DM – 1 CAD – 3 CKD – 1 COPD – 1	

Abbreviations: HI, high-income country; LMIC, low-middle income country; UMIC, upper-middle-income country; C, cohort; Se, case series; P, prospective; R, retrospective; M, multicentre; S, single-centre; NA, Not available; HT, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; CVSD, Cerebrovascular disease; CKD, chronic kidney disease; COPD, Chronic obstructive pulmonary disease; ABPA, allergic bronchopulmonary aspergillosis; TB, tuberculosis; BTX, bone marrow transplant; GGO, ground-glass opacity; CPP, crazy paving pattern; LPV-R, lopinavir-ritonavir; DC, Darunavir-cobicistat; T, Tocilizumab; TA, tracheal aspirate.

3.2 | COMPARISON OF STUDIES DESCRIBING CAPA CASES AND CONTROLS

Details regarding the mortality among patients with COVID-19 who did not develop CAPA were available in 12 out of the 20 included studies. The patients with CAPA had higher mortality compared to controls with an odds ratio of 2.83 (95% CI: 1.80–4.46) and relative risk of 1.84 (95% CI: 1.45–2.33) as shown in Figure 3A,B, respectively. The heterogeneity was low (I^2: 0% for OR and I^2: 25% for RR). There was no significant publication bias on the funnel plot (eggers test: −0.033 [95% CI: −1.34 to −1.27], *p* value: .9614), and the leave one out analysis and influence diagnostics did not reveal any substantial influence of individual studies on OR estimate (Figures S5–S7). The odds of mortality in cases vs controls in different subgroups within included studies are summarised in Table 3. There was no significant difference in the OR in any subgroup.

Radiological finding	Severity scores	Other laboratory parameters	COVID-specific therapy	Fungal culture	BAL Galactomannan – positive cases *n* (%), median (range)	Serum Galactomannan – positive cases *n* (%), median (range)
	APACHE 15 (10 to 16)		LPV-R (6)	5 cases *A flavus (5)*	3 (50) 3.8 (1.6 to 4)	0 0.1 (0.1 to 0.4)
	SAPS II – 43 ± 34.8 SOFA – 9 ± 7.40	Creatinine mg/dl – 101 (123.25) CRP – 112 (109–178)	–	6 cases		2 (30)
			–	4 cases *A fumigatus (4)*	4 (100) 2.8 (2 to 2.8)	0 0.15 (0.1 to 0.3)
	SAPS II – 73 ± 22.96			4 Cases *A fumigatus (5)*	3 (75) 1.55 (0.7 to 3.2)	1 (25), 1.19
			Ocrelizumab (1), Rituximab (1), Siltuxmab (1), T (5)	17 cases *A fumigatus (12)*, *A niger (4)*, *A terreus (1)*, *Aspergillus* spp *(2)*		
Nodule – 7 (38.8) Cavity– 5 (44.4) Tree in bud–1 (5.6)				8 cases *A fumigatus (8)*	12 6.2 (0.7–16.6)	11, 0.55 (0.3–4.9)
Diffuse infiltrates –14(100) GGO – 2 (14.3) Consolidation – 1 7.1)			T – 4, Steroid-1, Remedesvir 1	9 cases *A fumigatus (6)*, *A flavus (2)*, *A versicolor (1)*, *Aspergillus* spp *(1)*	11 5.8 (2.3–11.4)	6, 0.8 (0.04–2.39)
	APACHE 19 (12 to 25)		LPV-RIT – 9	7 cases *A fumigatus (5)*, *A flavus (1)*, *A terreus (1)*	9 3.33 (2.67–4)	
Cavity – 1 (12.5) Nodule – 1 (12.5)			Steroid – 6, Remidisvir 1	8 cases *A fumigatus (8)*	2 0.3 (0.1–5.9)	

4 | DISCUSSION

In this systematic review, we report a pooled mortality of 51.2% in patients with CAPA with low heterogeneity among the included studies. No significant difference in mortality estimates was seen in various subgroups according to the country of study, the continent of study, income category of country and quality of the included studies. Other parameters such as host risk factors, mycological investigation results, therapy for COVID-19 and the use of antifungal therapy did not influence the estimate of mortality. Higher odds of mortality (Odds ratio: 2.83) were seen in patients with COVID-19 who had CAPA compared to those who did not.

Despite increasing concern, the real burden of CAPA in patients requiring ICU admission is probably underestimated.[45] Severe

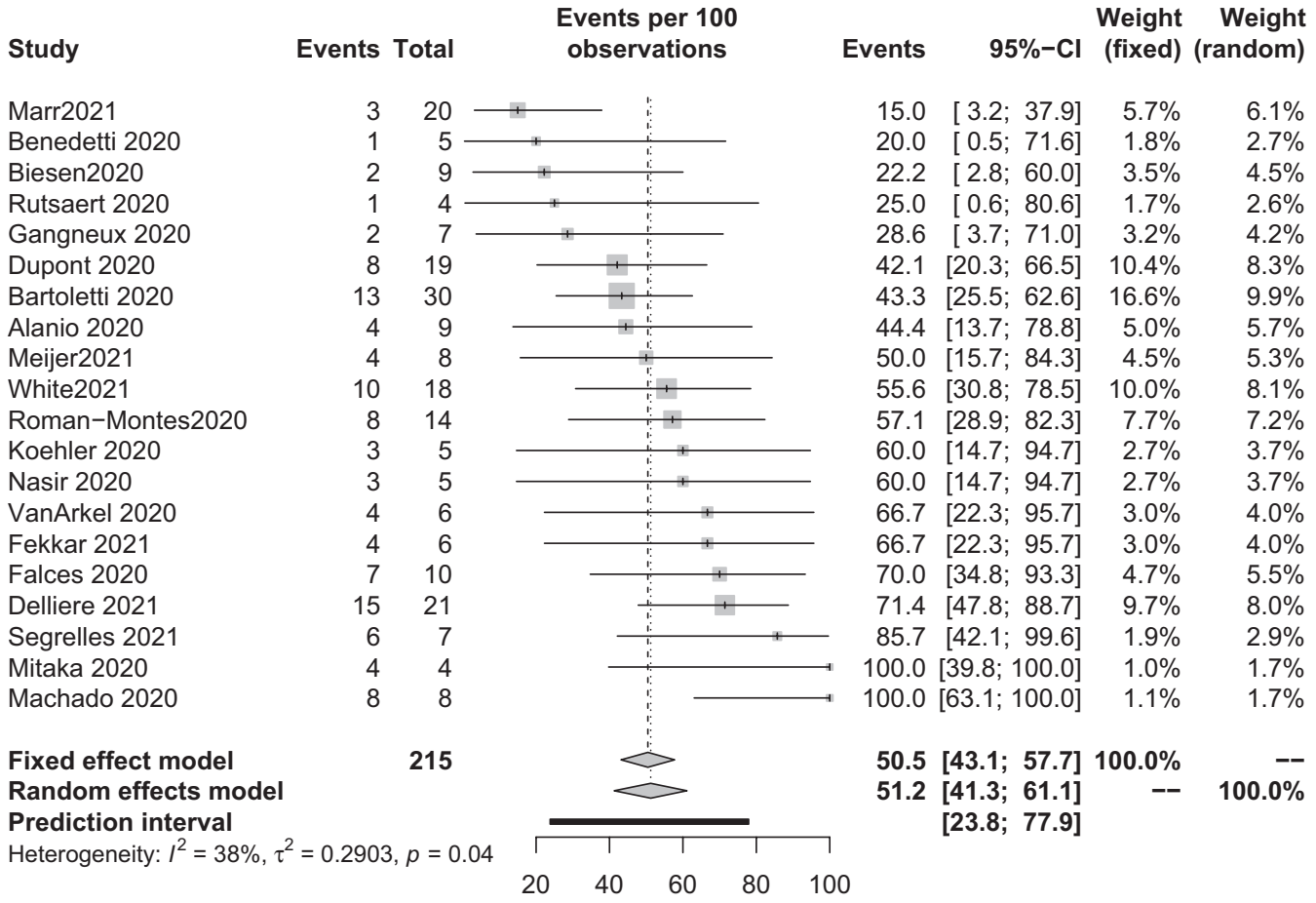

FIGURE 2 Forest plot showing the pooled mortality in patients with COVID-19 associated pulmonary aspergillosis. The mortality in the included studies is represented by the grey square with horizontal bars indicating the 95% confidence interval. The diamond at the end denotes the overall pooled mortality

COVID-19 infection with the need for intensive care or presence of ARDS is a common feature in CAPA, and the possibility of invasive aspergillosis must be kept in mind in such cases to ensure prompt diagnosis.[46] In mild COVID-19, strong activation of the innate immunity, with elevated expression of interferon (IFN)-stimulated genes, is seen while dysfunctional monocytes and neutrophils and reduction in IFN response are noted in severe cases.[47,48] This reduced IFN is opposed by the abundant inflammatory cytokine production resulting in a cytokine storm which contributes to the clinical deterioration.[49]

Mechanisms involved in the immune recognition of *Aspergillus* are relatively well-characterised[50,51]; however, our understanding of the immune signalling pathways for sensing and responding to SARS-CoV-2 are in the nascent stage. Possible mechanisms to explain the development of CAPA in patients with severe COVID-19 are first, the pulmonary epithelial damage secondary to the release of endogenous danger molecules released from damaged or dying cells, secondly, the presence of a permissive inflammatory environment and defective IFN type I response, which favours *Aspergillus* invasion.[52,53] The inhibition of neutrophil recruitment by influenza A mediated signal-transducer and activator of transcription-1 (STAT-1) signalling increases susceptibility IAPA[54] and such mechanisms may also be prevalent in patients with COVID-19.

Autopsy studies show that IPA is among the most commonly missed diagnoses in ICU in-patient deaths from any cause.[55] A systematic review of an autopsy series in decedents with COVID-19 also revealed the presence of CAPA in 11.7%, comprising 54.5% of autopsy-confirmed invasive mould infections.[56] One of the main caveats in the timely diagnosis of CAPA is the lack of specific clinical presentation and radiological signs of COVID-19 pneumonia. In critically ill patients, especially those with ARDS, other factors like co-infections and drug toxicities add to the complexity of diagnosis. Even in patients with IPA, mortality ranging from 47% to 61% has been reported and a delay in diagnosis with subsequently delayed antifungal therapy has been suggested to contribute to poor outcome.[57,58] During the initial stages of this pandemic, there was no generally accepted case definition for patients with CAPA and most studies used the EORTC MSG or *Asp*ICU criteria for the diagnosis of IPA, even in patients with severe COVID-19 infection. However, these criteria cannot adequately classify all critically ill patients due to the absence of required host factors. Thus, the modified *Asp*ICU criteria, based on clinical, radiological and mycological

TABLE 2 Pooled mortality in CAPA in various subgroups from included studies

Subgroup (No. of studies)	Cases	Mortality (%)	95% – CI	Heterogeneity (I^2)	Subgroup difference (*p* value)
Quality of study[b]					
NOS score 5 [25,29–32,36]	31	58.8	30.5–82.3	41%	.21
NOS score 6 [28,42]	18	60.7	37.0–80.2	0%	
NOS score 7 [27,38,39,41]	66	34.1	17.8–55.2	59%	
NOS score 8 [26,35,37,40,43,44]	87	52.8	40.4–65.0	19%	
NOS score 9 [33,34]	13	75.5	45.0–92.0	0%	
Continent of study					
Asia [32]	5	60	20–90	NA	.03
Europe [26–30,33–37,39,41–44]	167	53.5	43.5–63.1	25%	
South America [25,40]	19	43.5	14.1–78.2	45%	
North America [31]	4	90	32.6–99.4	NA	
North America and Europe [38]	20	15	4.9–37.6	NA	
The income of the country where the study was conducted[a]					
High [26–31,33–39,41–44]	191	51.7	40.4–62.8	45%	.86
Upper middle [25,40]	19	43.5	14.1–78.2	45%	
Lower middle [32]	5	60	20.0–90.0	NA	
Direction of study[c]					
Prospective [27,33–37,39,40,43,44]	120	49.4	40.2–58.6	0%	.24
Retrospective [25,26,28–32,38,42]	86	57.2	36.2–75.9	60%	

[a]Classification bases on the World Bank data (2020).

[b]NOS New Castel Ottawa scale scoring.

[c]In one study by Biesen et al,[41] the direction of the study was unclear and it was excluded from subgroup analysis.

criteria (including serum and BAL galactomannan), were adopted. Recently, the European Confederation for Medical Mycology and the International Society for Human and Animal Mycology instituted a group of experts to propose consensus criteria for a case definition of CAPA.[17] Since the consensus criteria are fairly recent, we included all studies describing the IPA in patients with COVID-19, even those not using this proposed definition.

In a retrospective study by Salmanton-Garcia et al, the analysis if 186 cases of CAPA (including 62 cases from published literature, 45 from the FungiScope registry and 79 from both) revealed an overall mortality of 52.2% which is similar to with our pooled estimate.[59] In other meta-analysis evaluating the factors predicting mortality in patients with COVID-19, patient characteristics like increasing age, male gender; the presence of diabetes or hypertension clinical features like fatigue, expectoration, haemoptysis, dyspnoea, chest tightness and altered laboratory parameters like leukocytosis, lymphopenia, elevated LDH, procalcitonin, CRP and D-dimer have been reported in non-survivors.[11,60] Monitoring these indicators could help in predicting the prognosis of patients with COVID-19. In the present meta-analysis, higher mortality in ICU patients with COVID-19 has seen the patients with CAPA. A higher mortality rate was noted by White et al in ICU admitted COVID-19 patients who developed CAPA compared to overall ICU mortality estimates (55.6% vs 31%).[39] Early and appropriate antifungal therapy is of utmost importance to improve CAPA survival. In a controlled, open-label trial comparing the outcome of patients hospitalised with COVID-19, lower mortality was seen in those receiving dexamethasone vs usual care especially if they were receiving any respiratory support at randomisation.[61] The adverse outcomes in the dexamethasone-treated arm could, potentially, be attributable to CAPA rather than COVID-19, and systematic screening and treatment of CAPA in patients enrolled in such trials may be beneficial.

In a study by Bartoletti et al, CAPA was found to be associated with higher ICU mortality, after adjustment for patient age, RRT and severity scores at ICU admission.[24] Additionally, the authors also reported a 1.41-fold increase in mortality with every point increase in the initial BAL GM index.[24] Impaired host defences due to corticosteroid use, including LC3-associated phagocytosis, have been reported more frequently in patients with CAPA who do not survive.[24] Tocilizumab use may also prevent Th17 responses favouring aspergillosis, and some authors suggest screening/early testing for CAPA in COVID-19 patients being treated with this anti-IL 6 antibody.[53,62] White et al reported mortality in 46.7% of patients with CAPA despite antifungal therapy which could be due to delayed diagnosis.[39] However, in the present study, meta-regression did not reveal an association between any risk factor, COVID-specific therapy or antifungal therapy on mortality in patients with CAPA.

Keeping in view the high mortality associated with CAPA in patients with severe COVID-19, the evaluation of antifungal prophylaxis could be a viable option. Inhalational liposomal amphotericin

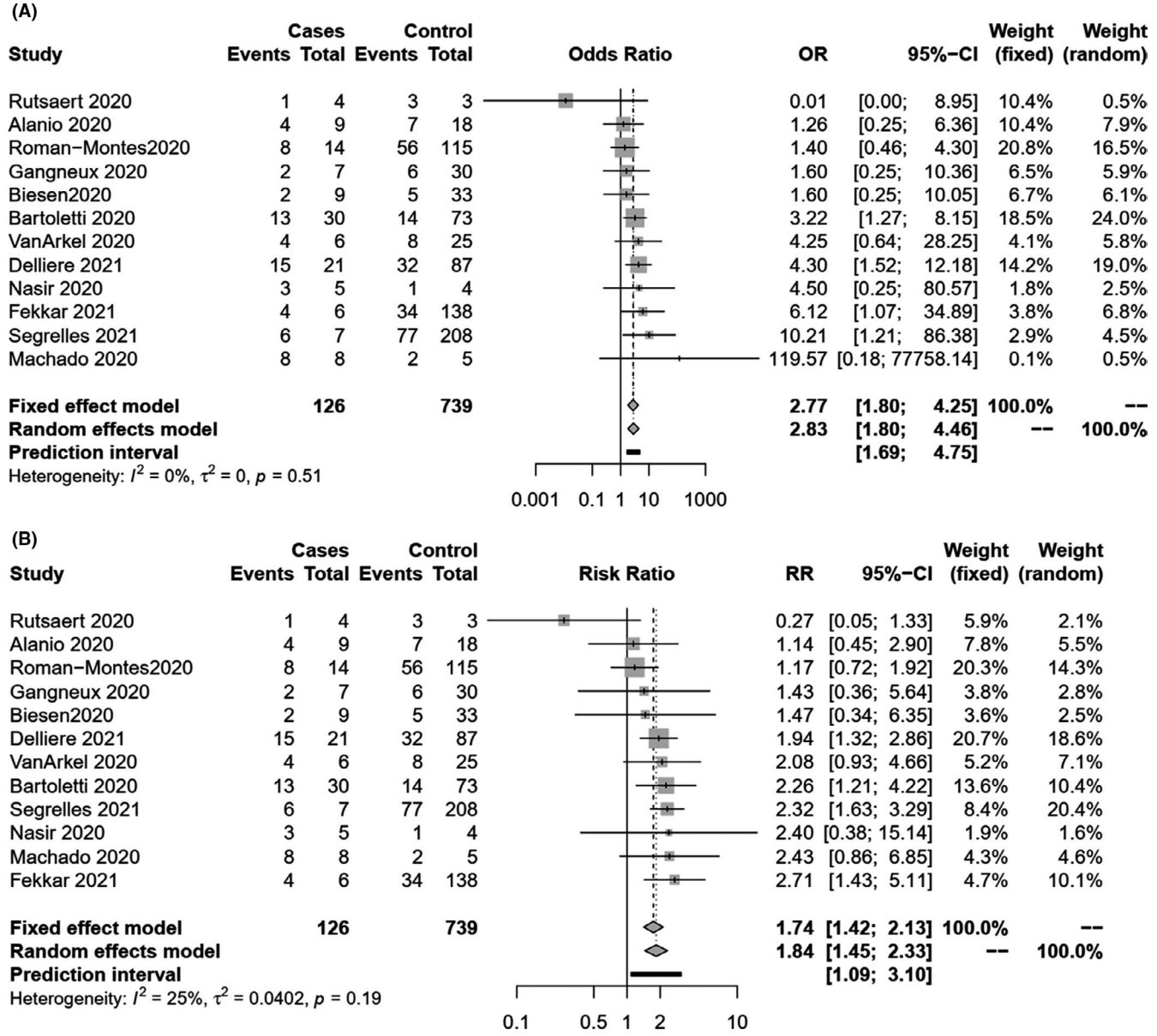

FIGURE 3 Forest plot showing (A) Odds ratio and (B) Relative risk of mortality among cases of CAPA compared to patients without CAPA described in 12 studies. The OR and RR in the included studies are represented by the grey square with horizontal bars indicating the 95% confidence interval. The diamond at the end denotes the overall pooled estimate

B prophylaxis has been evaluated for the prevention of CAPA in a study from Belgium[36] although the use of agents with better safety profile like isavuconazole or posaconazole may be preferable.

5 | LIMITATIONS

Although no difference in the estimates of pooled mortality was noted in any subgroup, one of the main limitations of this study is the lack of a unifying definition of CAPA among all studies and the inclusion of studies with few cases (≥4). Additionally, most studies were conducted in Europe and there is limited representation from other continents. This is important as in different geographic regions the burden of CAPA, inherent characteristics of the patient population, level of hospital care, availability of specific COVID therapy, availability of antifungals etc will be different. All included studies were conducted in ICU patients with severe COVID-19, and it is difficult to attribute the mortality to CAPA. In the absence of uniform severity scores across different studies, we were unable to adjust for disease severity, and thus, only the crude mortality estimates were reported. Nonetheless, given the limited pool of existing information, this study provides a firm base for future studies exploring factors affecting mortality in CAPA.

6 | CONCLUSIONS

CAPA adds insult to injury in critically ill COVID-19 patients resulting in high mortality and must be suspected, diagnosed and treated at

TABLE 3 Subgroup analysis (random-effects model) showing the Odds ratio of mortality in patients with CAPA compared to controls in various subgroups of included studies

Subgroup (No. of studies)	Cases	Controls	OR (95% CI)	Heterogeneity (I^2)	Subgroup difference (*p* value)
Quality of study[b]					
NOS score 5 [30,32,36]	17	12	2.35 (0.03–176.04)	52%	.65
NOS score 7 [41]	9	33	1.60 (0.25–10.05)	NA	
NOS score 8 [26,35,37,40,43,44]	87	461	2.65 (1.60–4.42)	0%	
NOS score 9 (2)	13	233	6.25 (1.52–25.78)	0%	
Continent of study					
Asia [32]	5	4	4.5 (0.25–80.57)	NA	.40
Europe [30,33–37,44]	107	620	3.22 (1.94–5.34)	0%	
South America (1)	14	115	1.40 (0.46–4.30)	NA	
Income of the country where the study was conducted[a]					
High (10)	107	620	3.22 (1.94–5.34)	0%	.40
Upper middle (1)	14	115	1.40 (0.46–4.30)	NA	
Lower middle (1)	5	4	4.50 (0.25–80.57)	NA	
Direction of study[c]					
Prospective (8)	83	610	2.56 (1.43–4.60)	10%	.47
Retrospective (3)	34	96	4.65 (1.77–12.27)	0%	
Comparator					
With *Aspergillus* colonisation (3)	17	12	2.35 (0.03–176.04)	52%	.93
Without IPA (9)	109	727	2.82 (1.78–4.88)	0%	

Abbreviation: CI, confidence interval.

[a]Classification bases on the World Bank data (2020).

[b]NOS New Castel Ottawa scale scoring.

[c]In one study by Biesen et al,[41] the direction of the study was unclear and it was excluded from the subgroup analysis.

the earliest. More multi-centre studies and global prospective registries of cases with CAPA could provide useful information regarding this condition.

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CONFLICT OF INTEREST

There are no conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Shreya Singh: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (equal); Writing-original draft (lead). **Nipun Verma:** Data curation (equal); Formal analysis (lead); Methodology (equal); Writing-review & editing (equal). **Rimjhim Kanaujia:** Data curation (equal); Methodology (equal); Writing-review & editing (equal). **Arunaloke Chakrabarti:** Supervision (equal); Writing-review & editing (equal). **Shivaprakash M Rudramurthy:** Conceptualization (equal); Methodology (supporting); Project administration (equal); Supervision (lead); Writing-review & editing (equal).

DATA AVAILABILITY STATEMENT

All the data are available and will be provided on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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