Mortality in chronic pulmonary aspergillosis: a systematic review and individual patient data meta-analysis

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Summary

Background Despite antifungal treatment, chronic pulmonary aspergillosis (CPA) is associated with substantial morbidity and mortality. We conducted a systematic review and meta-analysis to evaluate rates of mortality and its predictors in CPA.

Methods A systematic literature search was conducted across MEDLINE (PubMed), Scopus, Embase, and Web of Science to identify studies in English, reporting mortality in CPA, from database inception to Aug 15, 2023. We included clinical studies, observational studies, controlled trials, and abstracts. Case reports, animal studies, letters, news, and literature reviews were excluded. Authors of studies published since 2016 were also contacted to obtain anonymised individual patient data (IPD); for other studies, summary estimates were extracted. Subgroup analysis was done for differences in overall 1-year and 5-year mortality, data source, study design, risk of bias, country, Human Development Index, age groups, and the underlying lung disease. We used random-effects meta-analyses to estimate pooled mortality rates. Subgroup analyses and meta-regression were done to explore sources of heterogeneity. One-stage meta-analysis with a stratified Cox proportional hazards model was used to estimate the univariable and hazards for mortality, adjusting for age, sex, type of CPA, treatment, and underlying pulmonary comorbidities. This study was registered with PROSPERO (CRD42023453447).

Findings We included 79 studies involving 8778 patients in the overall pooled analysis and 15 studies involving 1859 patients in the IPD meta-analysis. Pooled mortality (from 70 studies) was estimated at 27% overall (95% CI 22–32; I^2=95·4%), 15% at 1 year (11–19; I^2=91·6%), and 32% at 5 years (25–39; I^2=94·3%). Overall mortality in patients with CPA with pulmonary tuberculosis as the predominant predisposing condition was 25% (16–35; I^2=87·5%; 20 studies) and with chronic obstructive pulmonary disease was 35% (22–49; I^2=89·7%; 14 studies). Mortality in cohorts of patients who underwent surgical resection was low at 3% (2–4). In the multivariable analysis, among predisposing respiratory conditions, pulmonary tuberculosis history had the lowest mortality hazard (relative to an absence of the disease at baseline), whereas worse outcomes were seen with underlying malignancy; subacute invasive pulmonary aspergillosis and chronic cavitary pulmonary aspergillosis subtypes of CPA were also significantly associated with increased mortality relative to simple aspergilloma on multivariable analysis. Mortality hazard increased by 25% with each decade of age (adjusted hazard ratio 1·25 [95% CI 1·14–1·36], p<0·0001).

Interpretation CPA is associated with substantial mortality. Advancing age, CPA subtype, and underlying comorbidities are important predictors of mortality. Future studies should focus on identifying appropriate treatment strategies tailored to different risk groups.

Funding None.

Introduction

Chronic pulmonary aspergillosis (CPA) is a constellation of diseases affecting the lungs, caused by ubiquitous fungi of the genus *Aspergillus*.[1] The most common subtype of CPA is chronic cavitary pulmonary aspergillosis (CCPA); chronic fibrosing pulmonary aspergillosis (CFPA) is a severe end-stage. Other subtypes, including simple aspergilloma and *Aspergillus* nodule, are likely to have different clinical trajectories to CCPA.[2] Subacute invasive pulmonary aspergillosis (SAIA) usually occurs in modestly immunocompromised patients, such as those with low-dose systemic corticosteroid dependence, poorly controlled diabetes, or advanced HIV, and is often included in CPA series.[3]

In 2011, the first study to assess the global burden of CPA occurring after pulmonary tuberculosis cure (post-tuberculosis CPA) estimated that 852 000–1 372 000 people were affected, assuming 10–20% annual mortality or surgical resection, in the 5 years following tuberculosis diagnosis.[4] In a more recent estimation of CPA burden in India by Denning and colleagues, among patients with or thought to have pulmonary tuberculosis, the 5-year

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See **Online** for appendix 1

Research in context

Evidence before this study

The clinical course of chronic pulmonary aspergillosis (CPA) is variable, with some patients appearing to have rapidly progressive infections leading to extensive lung fibrosis, haemoptysis, significant fatigue, weight loss, breathlessness, and often death. The early features of CPA are often silent. Many patients die with or of CPA, but the patient and treatment factors linked to death have been incompletely characterised and have varied by study. We did a literature review of all studies published in English describing mortality in patients with CPA up to July, 2024, using the keywords "chronic pulmonary aspergillosis", "death", "survival", and "mortality" in MEDLINE (PubMed), Scopus, Embase, and Web of Science. A 2024 review estimated approximately 1·8 million new cases of CPA globally each year, resulting in over 300 000 deaths, primarily in patients with possible, proven, or previous pulmonary tuberculosis. The review did not detail specific risk factors for mortality, but studies from individual centres did, including some patient characteristics associated with death (such as particular lung conditions), and also summarised data on attributable mortality. Large-scale, multicentre studies with long-term follow-up and diverse patient populations were found to be absent.

Added value of this study

By systematically reviewing the published data, and focusing on the predisposing and associated underlying conditions, we identified key variables linked to higher mortality rates. 1-year mortality of CPA after diagnosis was low in patients with post-tuberculosis lung disease at 7%, contrasting with those with interstitial lung disease (18%), malignancy (17%), chronic obstructive pulmonary disease (16%), and non-tuberculous mycobacterial lung disease (11%). Mortality in subsequent years was much lower in all groups and not very different between the various groups: 8% in year 2, 7% in year 3, 5% in year 4, and 1% in year 5. Age older than 60 years, subacute invasive aspergillosis or chronic cavitary pulmonary aspergillosis subtypes, and underlying malignancy were associated with higher hazards of death.

Implications of all the available evidence

While less lethal than invasive aspergillosis, CPA is a disease linked to considerable morbidity and mortality. Given the high 1-year mortality rates after CPA diagnosis, screening and early detection and appropriate management are likely to be crucial to reducing global deaths related to CPA. Since the treatment modality, intensity, and duration of CPA treatment have been a subject of active research, our study suggests that studies in the future should stratify these patients based on the reported risk factors. This is required to both confirm the mortality rate among patients with different and multiple risk factors, as well as to identify the best therapeutic regimen.

prevalence was found to be 1·5 million, assuming 20% mortality in year 1 and 7·5% in years 2–5.[5,6] Applying the same assumptions globally, the annual incidence of CPA was estimated to be 1·8 million cases, with 304 000 deaths.[7] While these estimates indicate that millions of individuals around the world are affected by this disease, CPA is often unrecognised or unsuspected. Moreover, CPA cases might be misdiagnosed as sputum-negative pulmonary tuberculosis (newly detected or recurrence) in tuberculosis-endemic countries, leading to delayed or missed diagnosis.[8] In contrast to invasive pulmonary aspergillosis, CPA has a slower course, leading to significant burden and morbidity in the patients affected. Despite the relatively slow rate of progression of CPA, mortality is high among patients with the condition, with around 50% dying within 5 years of diagnosis.[6]

However, the mortality reported has varied considerably in different studies,[2,9–17] possibly reflecting the variability in nomenclature, region of publication, demographic background, underlying pulmonary comorbidities, subtypes included, different management protocols, and the inequity of access to health care, among other factors. Since CPA occurs typically in people with pre-existing lung diseases with other comorbidities, it is difficult to estimate the exact contribution of different factors influencing overall mortality. Previous single-centre or country studies have variably reported on the different factors contributing to mortality—such as age, underlying lung disease, CPA subtype, and therapy received—and do not allow a representative summary estimate. A comprehensive understanding of CPA mortality is essential for burden estimation, guiding clinical decision making, shaping treatment strategies, and formulating health policies to tackle this often lethal disease. We aimed to systematically review the literature on CPA mortality, focusing on the individual categories of underlying diseases, antifungal therapy, and year after diagnosis of disease, among other factors. We also analysed the various factors that influence mortality in CPA.

Methods

Overview

We did a systematic review and meta-analysis, in accordance with PRISMA and PRISMA-IPD guidelines.

We systematically searched MEDLINE (PubMed), Embase, Scopus, and Web of Science databases for relevant studies published in English from the inception of the databases until Aug 15, 2023. We used keywords related to CPA, CCPA, CFPA, CNPA, or SAIA, and mortality; keywords used to search each database are provided in full in appendix 1 (p 2).

Details of the methodology are provided in appendix 1 (pp 6–7). Publications were included if they were clinical studies, observational studies, controlled trials, and abstracts. We excluded case reports, animal studies, letters, news, and literature reviews (unless original data were described). Conference papers and abstracts were also included.

Two independent reviewers (AS and ADU) screened the identified citations for potentially relevant articles, after removing duplicate records. All disagreements between the reviewers were resolved mutually after discussion with a third reviewer (AR). Full texts were obtained for all potentially eligible citations and screened for mortality data. Reference lists of included publications were also screened.

Data were extracted into a standardised spreadsheet by AS and ADU (appendix 1 pp 4–6). The corresponding authors of studies published after 2016 (the year of publication of updated guidelines for the diagnosis and management of CPA) were contacted by email to obtain anonymised individual patient data (IPD). For all other studies, we extracted summary estimates only (appendix 1 p 7). For aggregate data, we used WebPlotDigitizer to extract year-wise mortality data from Kaplan–Meier curves where available.[18]

This study was registered with PROSPERO (CRD42023453447).

Data analysis

Detailed methodology is provided in appendix 1 (pp 6–7). The quality assessment was done with the National Heart, Lung, and Blood Institute checklist.[19] Means, SDs, and *t* tests were used for parametric data, and medians, IQRs, and Wilcoxon rank-sum or Kruskal–Wallis tests were used for non-parametric data. These results are expressed as median (IQR) unless otherwise stated. The meta-analysis was undertaken using a random-effects model; a pooled estimate and 95% CI were calculated for all mortality statistics. Heterogeneity was reported using the I^2 statistic. The source of heterogeneity was explored using subgroup analysis and meta-regression. In the IPD dataset, a time-to-event analysis was done using the univariable Cox proportional hazards model, stratified by study. A multivariable stratified Cox regression model was done, adjusting for CPA subtypes (simple aspergilloma, SAIA, CCPA, or CFPA), underlying respiratory condition (pulmonary tuberculosis, chronic obstructive pulmonary disease [COPD], non-tuberculous mycobacterial lung disease, interstitial lung disease, or malignancy), age at diagnosis (per 1-year or 10-year increase), sex (male or female), and type of treatment received (medical, surgical, or both). We did not assess attributable mortality as this has been recently summarised.[7] $p<0·05$ was considered statistically significant. The statistical analysis was done using Stata version 17 and RStudio version 4.3.1.

Role of the funding source

There was no funding source for this study.

Results

We screened 1452 citations from the literature search, from which 72 were included, with an additional seven added from the references of screened studies (appendix 1 p 3). We received anonymised IPD from the authors of 15 studies.[9,10,20–32] We used the aggregate data for the remaining 64 studies.[1,11–17,33–88] The included studies were published between 1974 and 2023, and were from 21 countries (including 25 studies from Japan).[1,10,13–15,24,26,32,36,37,38,41–43,51,54,55,59,62–64,67,72,79,87,88] These studies included one cross-sectional study,[11] two case series,[1,53] and three randomised controlled trials;[44,51,77] the rest were cohort studies (eight were prospective,[17,28,40,41,43,45,73,86] 61 were retrospective[9,10,12–16,20–27,29–32,34–37,39,40,43,44,47–50,53,55–58,60–73,75–77]

	Aggregate data		Individual patient data		Combined	
	Studies, n	CPA mortality estimate (95% CI)	Studies, n	CPA mortality estimate (95% CI)	Studies, n	CPA mortality estimate (95% CI)
Overall mortality	55	25% (20–31)	15	31% (22–41)	70	27% (22–32)
Mortality by year since diagnosis						
First year	24	16% (12–21)	15	13% (9–19)	39	15% (11–19)
Second year	1	8% (2–22)	14	8% (5–11)	15	8% (5–11)
Third year	1	8% (1–27)	14	7% (5–11)	15	7% (5–11)
Fourth year	1	18% (5–40)	13	4% (1–9)	14	5% (1–10)
Fifth year	1	8% (0–36)	13	0% (0–3)	14	1% (0–3)
Overall 5-year mortality	10	34% (24–46)	14	30% (22–39)	24	32% (25–39)
Postoperative mortality	17	2% (0–3)	0	NA	NA	NA
Deaths per 1000 person-years	32	98·0 (64·7–148·5)	15	114·8 (74·0–178·1)	47	104·5 (77·6–140·7)
Mortality by predominant predisposing condition						
Post-tuberculosis lung disease	5	21% (3–48)	15	26% (16–38)	20	25% (16–35)
COPD	0	NA	14	35% (22–49)	NA	NA
NTM lung disease	3	39% (17–65)	11	30% (14–48)	14	33% (20–47)
Bronchiectasis	0	NA	12	21% (10–35)	NA	NA
Interstitial lung disease*	3	51% (26–76)	13	42% (21–63)	16	44% (27–61)
Malignancy	2	54% (45–64)	13	42% (25–60)	15	47% (33–61)
Autoimmune disease	0	NA	13	38% (18–59)	NA	NA
Pneumothorax	0	NA	9	28% (7–53)	NA	NA
Post-thoracic surgery	0	NA	12	21% (8–38)	NA	NA
Overall mortality by age, years						
<40	0	NA	14	1% (0–6)	NA	NA
40–60	0	NA	15	23% (14–32)	NA	NA
>60	0	NA	15	38% (28–49)	NA	NA
Overall mortality by sex						
Male	0	NA	15	34% (24–45)	NA	NA
Female	0	NA	15	25% (15–36)	NA	NA

(Table 1 continues on next page)

	Aggregate data		Individual patient data		Combined	
	Studies, n	CPA mortality estimate (95% CI)	Studies, n	CPA mortality estimate (95% CI)	Studies, n	CPA mortality estimate (95% CI)
(Continued from previous page)						
First-year mortality by predominant predisposing condition						
Post-tuberculosis lung disease	0	NA	15	7% (3–13)	NA	NA
COPD	0	NA	14	16% (9–24)	NA	NA
NTM lung disease	3	12% (3–25)	11	12% (4–22)	14	11% (5–19)
Bronchiectasis	0	NA	12	10% (3–19)	NA	NA
Interstitial lung disease*	1	10% (0–45)	13	19% (4–39)	14	18% (4–36)
Malignancy	1	10% (5–18)	13	18% (7–33)	14	17% (6–30)
Autoimmune disease	0	NA	13	11% (1–26)	NA	NA
Pneumothorax	0	NA	9	9% (1–22)	NA	NA
Post-thoracic surgery	0	NA	12	7% (1–17)	NA	NA
Overall mortality by CPA subtype						
CFPA	0	NA	7	51% (23–79)	NA	NA
CCPA	7	14% (6–25)	13	28% (16–42)	20	23% (14–33)
SAIA	6	29% (17–43)	8	39% (15–65)	14	34% (20–49)
Simple aspergilloma	7	10% (2–21)	8	14% (1–33)	15	11% (4–20)
Overall mortality by treatment received						
Voriconazole only	0	NA	14	38% (25–51)	NA	NA
Itraconazole only	0	NA	15	24% (15–34)	NA	NA
No treatment	0	NA	11	40% (25–57)	NA	NA

CCPA=chronic cavitary pulmonary aspergillosis. CFPA=chronic fibrotic pulmonary aspergillosis. COPD=chronic obstructive pulmonary disease. CPA=chronic pulmonary aspergillosis. NA=not applicable. NTM=non-tuberculous mycobacterial. SAIA=subacute invasive pulmonary aspergillosis. *Including sarcoidosis.

Table 1: **Estimates of CPA mortality as derived from aggregate data and individual patient data meta-analyses (and both combined), listing the underlying disease**

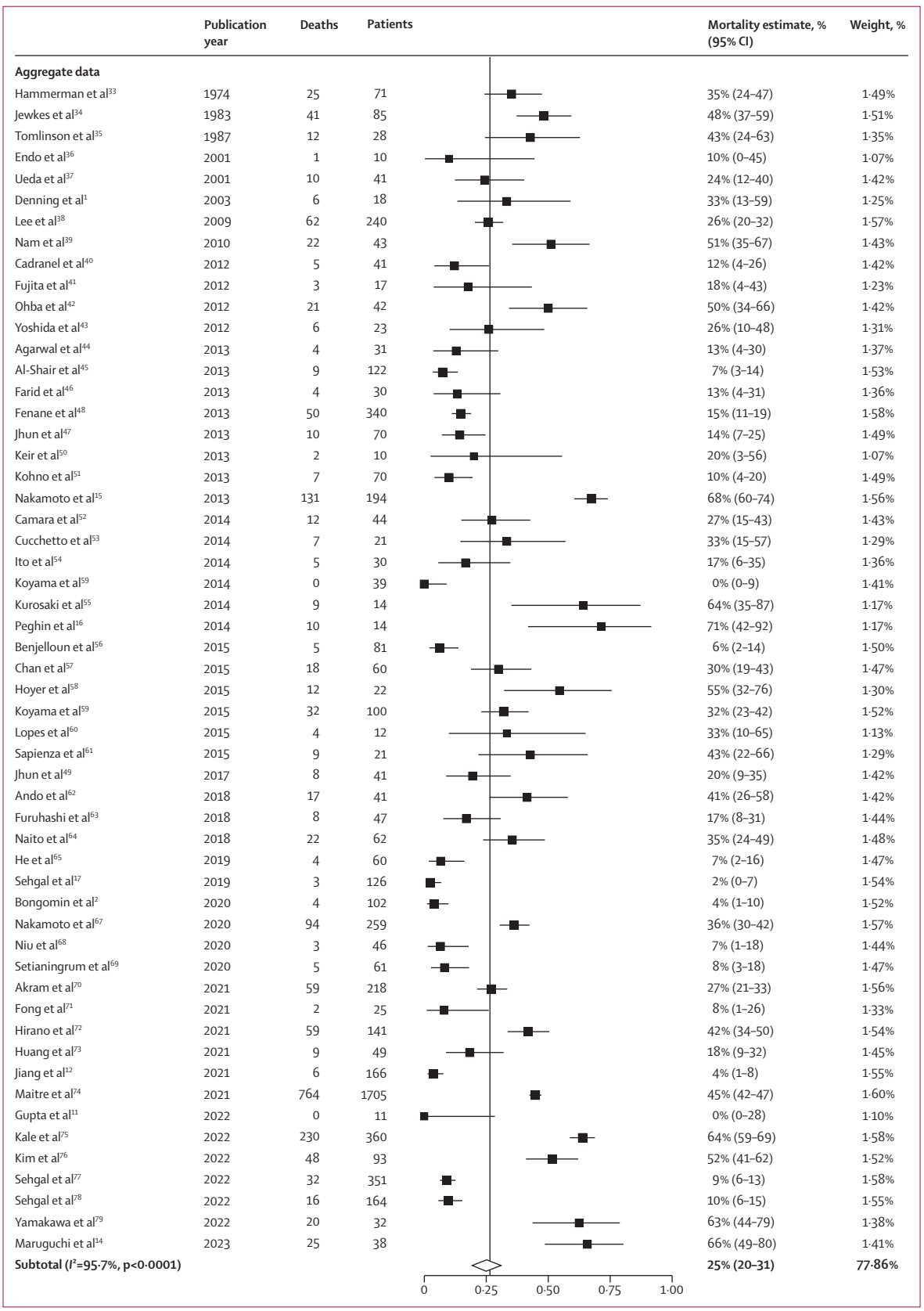
[79–81,83–86,88,89] and in four study type was not reported[33,50,58,81]). 17 studies reported surgical outcomes.[12,16,30,35,36,38,46,48,56,57,65,80,81,83–86] The sample sizes of the studies ranged from ten to 1705, comprising a total of 8778 patients with CPA. The follow-up duration was calculable in 47 studies, totalling 10 972 patient-years (4136 patients). Mean age reported in the studies ranged from 30 years to 79·1 years, with younger patients being reported in the WHO African region (30 years, in a single study) and South-East Asian region (mean 41·1 years [SD 4·0]; five studies) than in the Western Pacific (mean 64·2 years [8·7]; 35 studies). 63 (88·7%) of 71 studies reported a male predominance. Further details of the studies have been tabulated in appendix 1 (pp 8–15).

Post-tuberculosis lung disease was most common in South-East Asian studies with a median of 87·5% (IQR 75·0–92·6) and least frequent in Europe at 21·0% (18·0–38·0). Conversely, COPD was highest in European cohorts at 33·3% (20·0–47·5), followed by Western Pacific cohorts at 29·4% (15·0–45·0). A median of 1·4% (0·7–2·0) of patients in South-East Asian studies had underlying COPD. Non-tuberculous mycobacterial lung disease was most often reported from the Western Pacific region (23·0% [14·3–46·0]), with four studies reporting patients with non-tuberculous mycobacterial lung disease and CPA only. Bronchiectasis was the predominant coexisting lung condition (76 [88·4%] of 86 in one study from the Americas),[9] but was present in only three (5·7%) of 52 patients in one South-East Asian study.[85] Overall, the most frequent underlying lung disease in the South-East Asian and Western Pacific regions was post-tuberculosis lung disease, and COPD was most common in studies from Europe (appendix 1 p 16). A minority of studies reported CPA subtypes, with CCPA being most frequent with a median prevalence of 60·7% (46·7–80) across 29 studies, followed by simple aspergilloma (25·6% [9·9–51·8]; 28 studies), SAIA (18·5% [11·4–41·3]; 20 studies], and CFPA being the rarest (13% [6·7–19·8]; 14 studies; appendix 1 p 17).

Of the 1859 patients in the IPD cohort, most were from the UK (649 [34·9%]), Japan (595 [32·0%]), and France (192 [10·3%]). The mean age in this cohort was 61·4 years (SD 14·6), and 1059 (57·1%) of 1856 patients with available data were male. CPA subtypes were recorded in 1201 cases, with CCPA (851 [70·9%]) being the most frequent, followed by SAIA (179 [14·9%]). *Aspergillus* nodules were infrequent (23 [1·9%] cases). The median duration of follow-up was 616 days (IQR 327–1351). 574 (30·9%) deaths were documented among the 1859 patients, 204 (11·0%) patients were lost to follow-up, and outcome data were missing in seven (0·4%).

In our IPD cohort, post-tuberculosis lung disease was seen in 676 (37·0%) of 1827 patients, with higher proportions in cohorts from Pakistan (57 [76·0%] of 75) and Brazil (70 [76·9%] of 91). COPD was seen in 586 (32·2%) of 1820. Non-tuberculous mycobacterial lung disease was the underlying lung disease in 243 (14·5%) of 1680 patients, predominantly from Japan (153 [63·0%] of 243). Among 676 patients diagnosed with tuberculosis, the age at diagnosis of pulmonary tuberculosis was available in 150 patients, with a mean age of 35·7 years (SD 14·5). In terms of comorbidities (available for 1859 patients), 240 (12·9%) patients had none, 758 (40·8%) had one, 541 (29·1%) had two, and 320 (17·2%) had three or more (appendix 1 p 17). Among the patients with SAIA, the risk factors were diabetes (31 [18·1%] of 171), chronic corticosteroid use (28 [16·5%] of 170), BMI less than 19 kg/m² (31 [23·0%] of 135), radiotherapy (four [4·0%] of 100), HIV infection (four [4·7%] of 86), and chronic alcoholism (26 [31·3%] of 83; appendix 1 p 17).

Treatment data in the IPD cohort were available for 1577 patients, among whom 1281 (81·2%) patients were receiving only oral or intravenous antifungal agents, 170 (10·8%) patients were being managed surgically (with or without antifungals), and 126 (8·0%) patients received no treatment. Various reasons for non-treatment included misdiagnosis, post-mortem diagnosis, or cases that were deemed stable and managed conservatively. Among the patients managed with oral antifungal



	Publication year	Deaths	Patients	Mortality estimate, % (95% CI)	Weight, %
Aggregate data					
Hammerman et al[33]	1974	25	71	35% (24–47)	1·49%
Jewkes et al[34]	1983	41	85	48% (37–59)	1·51%
Tomlinson et al[35]	1987	12	28	43% (24–63)	1·35%
Endo et al[36]	2001	1	10	10% (0–45)	1·07%
Ueda et al[37]	2001	10	41	24% (12–40)	1·42%
Denning et al[1]	2003	6	18	33% (13–59)	1·25%
Lee et al[38]	2009	62	240	26% (20–32)	1·57%
Nam et al[39]	2010	22	43	51% (35–67)	1·43%
Cadranel et al[40]	2012	5	41	12% (4–26)	1·42%
Fujita et al[41]	2012	3	17	18% (4–43)	1·23%
Ohba et al[42]	2012	21	42	50% (34–66)	1·42%
Yoshida et al[43]	2012	6	23	26% (10–48)	1·31%
Agarwal et al[44]	2013	4	31	13% (4–30)	1·37%
Al-Shair et al[45]	2013	9	122	7% (3–14)	1·53%
Farid et al[46]	2013	4	30	13% (4–31)	1·36%
Fenane et al[48]	2013	50	340	15% (11–19)	1·58%
Jhun et al[47]	2013	10	70	14% (7–25)	1·49%
Keir et al[50]	2013	2	10	20% (3–56)	1·07%
Kohno et al[51]	2013	7	70	10% (4–20)	1·49%
Nakamoto et al[15]	2013	131	194	68% (60–74)	1·56%
Camara et al[52]	2014	12	44	27% (15–43)	1·43%
Cucchetto et al[53]	2014	7	21	33% (15–57)	1·29%
Ito et al[54]	2014	5	30	17% (6–35)	1·36%
Koyama et al[59]	2014	0	39	0% (0–9)	1·41%
Kurosaki et al[55]	2014	9	14	64% (35–87)	1·17%
Peghin et al[16]	2014	10	14	71% (42–92)	1·17%
Benjelloun et al[56]	2015	5	81	6% (2–14)	1·50%
Chan et al[57]	2015	18	60	30% (19–43)	1·47%
Hoyer et al[58]	2015	12	22	55% (32–76)	1·30%
Koyama et al[59]	2015	32	100	32% (23–42)	1·52%
Lopes et al[60]	2015	4	12	33% (10–65)	1·13%
Sapienza et al[61]	2015	9	21	43% (22–66)	1·29%
Jhun et al[49]	2017	8	41	20% (9–35)	1·42%
Ando et al[62]	2018	17	41	41% (26–58)	1·42%
Furuhashi et al[63]	2018	8	47	17% (8–31)	1·44%
Naito et al[64]	2018	22	62	35% (24–49)	1·48%
He et al[65]	2019	4	60	7% (2–16)	1·47%
Sehgal et al[17]	2019	3	126	2% (0–7)	1·54%
Bongomin et al[2]	2020	4	102	4% (1–10)	1·52%
Nakamoto et al[67]	2020	94	259	36% (30–42)	1·57%
Niu et al[68]	2020	3	46	7% (1–18)	1·44%
Setianingrum et al[69]	2020	5	61	8% (3–18)	1·47%
Akram et al[70]	2021	59	218	27% (21–33)	1·56%
Fong et al[71]	2021	2	25	8% (1–26)	1·33%
Hirano et al[72]	2021	59	141	42% (34–50)	1·54%
Huang et al[73]	2021	9	49	18% (9–32)	1·45%
Jiang et al[12]	2021	6	166	4% (1–8)	1·55%
Maitre et al[74]	2021	764	1705	45% (42–47)	1·60%
Gupta et al[11]	2022	0	11	0% (0–28)	1·10%
Kale et al[75]	2022	230	360	64% (59–69)	1·58%
Kim et al[76]	2022	48	93	52% (41–62)	1·52%
Sehgal et al[77]	2022	32	351	9% (6–13)	1·58%
Sehgal et al[78]	2022	16	164	10% (6–15)	1·55%
Yamakawa et al[79]	2022	20	32	63% (44–79)	1·38%
Maruguchi et al[14]	2023	25	38	66% (49–80)	1·41%
Subtotal (I^2=95·7%, p<0·0001)				**25% (20–31)**	**77·86%**

(Figure 1 continues on next page)

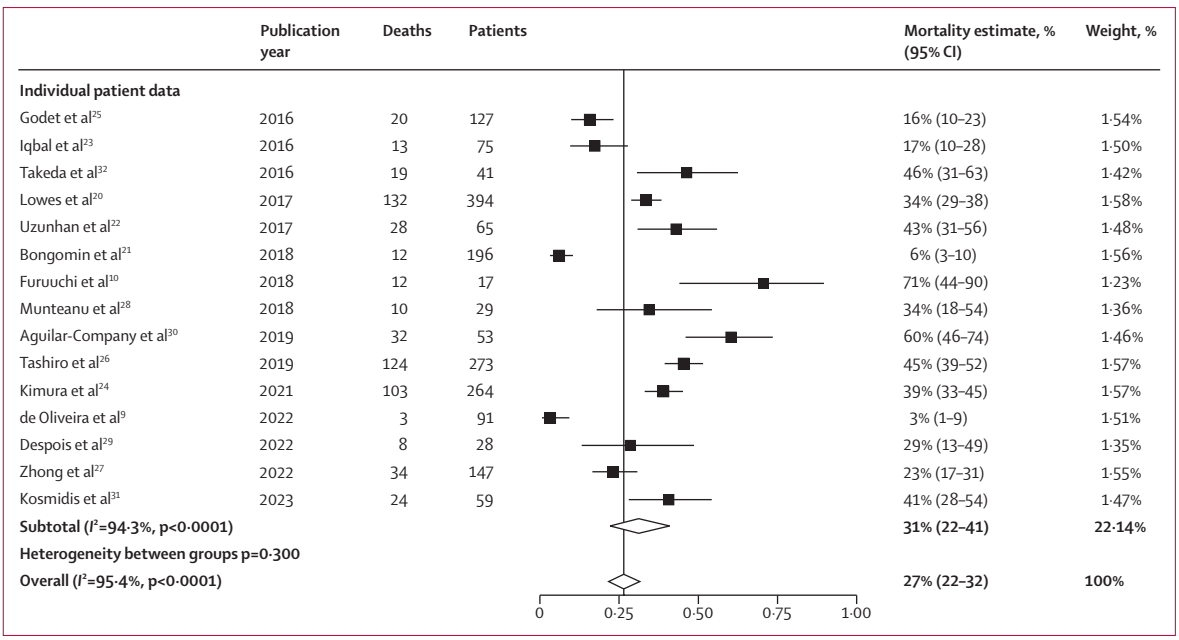


Figure 1: **Overall mortality in chronic pulmonary aspergillosis in included studies (n=70)**

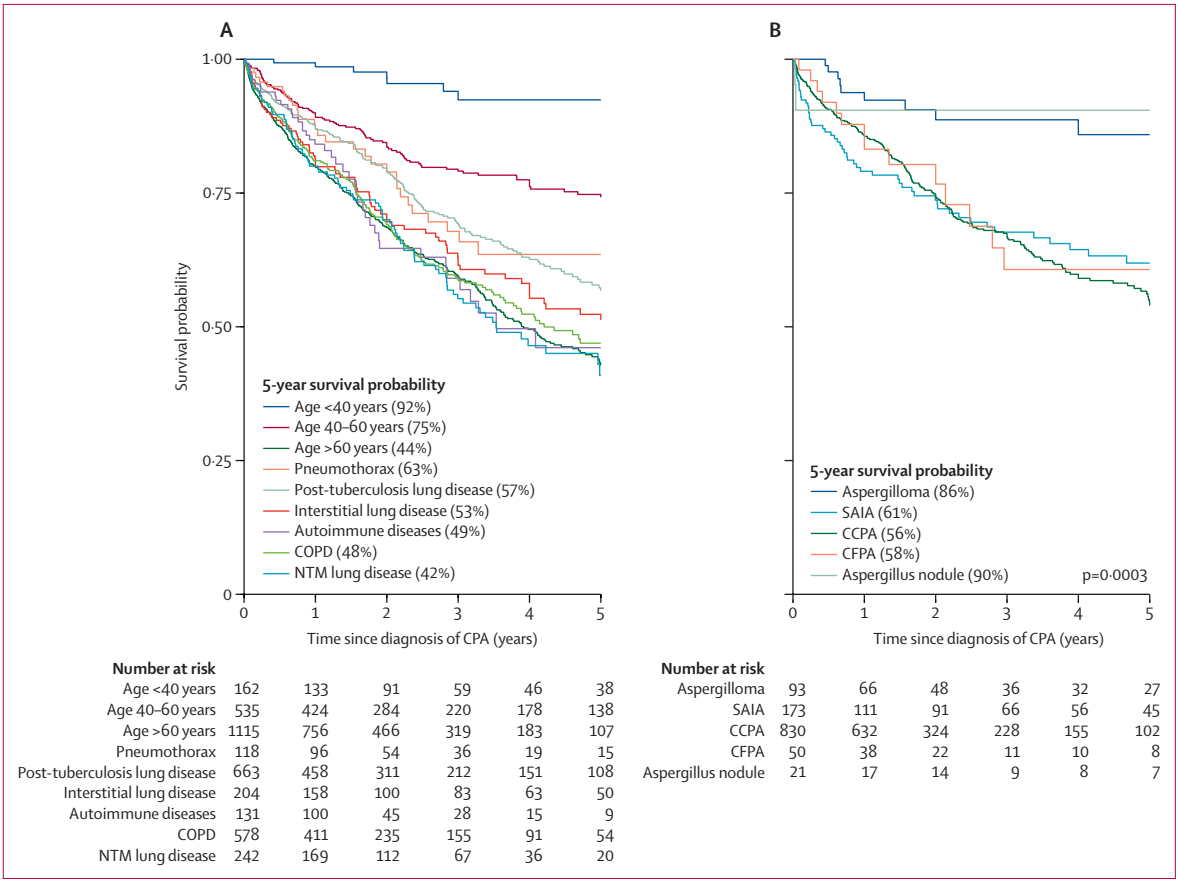


Figure 2: **Kaplan–Meier survival estimates**

(A) Survival by key underlying risk groups; this graph is illustrative only and groups cannot be compared due to overlap of risk categories. (B) Survival by CPA subtype. CCPA=chronic cavitary pulmonary aspergillosis. CFPA=chronic fibrosing pulmonary aspergillosis. COPD=chronic obstructive pulmonary disease. CPA=chronic pulmonary aspergillosis. NTM=non-tuberculous mycobacterial. SAIA=subacute invasive pulmonary aspergillosis.

	Overall mortality in CPA				1-year mortality in CPA				5-year mortality in CPA				Deaths per 1000 person-years in CPA			
	Studies, n	Mortality estimate (95% CI)	I^2	p value	Studies, n	Mortality estimate (95% CI)	I^2	p value	Studies, n	Mortality estimate (95% CI)	I^2	p value	Studies, n	Mortality estimate (95% CI)	I^2	p value
WHO region	..	..	..	0·337	..	..	..	<0·0001	..	..	..	<0·0001	..	..	..	0·005
Western Pacific	35	30% (23–36)	93·0%	<0·0001	22	16% (13–20)	66·3%	<0·0001	11	41% (33–48)	83·4%	<0·0001	24	127·3 (83·5–194·1)	90·7%	<0·0001
Europe	22	27% (18–36)	95·5%	<0·0001	12	14% (6–23)	96·1%	<0·0001	9	29% (19–40)	94·8%	<0·0001	11	91·0 (55·9–147·9)	91·6%	<0·0001
South-East Asia	6	13% (0–39)	98·7%	<0·0001	2	26% (21–31)	NA	NA	0	NA	NA	NA	4	52·9 (31·8–88·1)	49·6%	0·114
Eastern Mediterranean	3	20% (12–29)	NA	NA	1	11% (5–20)	NA	NA	2	15% (12–18)	NA	NA	2	158·3*	97·8%	<0·0001
Americas	4	28% (6–56)	93·7%	<0·0001	2	9% (5–14)	NA	NA	2	7% (3–13)	NA	NA	2	46·0 (0·5–4588·4)	59·8%	0·115
Study type	..	..	..	<0·0001	..	..	..	0·0003	..	..	..	0·749	..	..	..	<0·0001
Randomised controlled trial	3	10% (6–14)	NA	NA	0	NA	NA	NA	0	NA	NA	NA	1	137·9 (51·8–367·5)	NA	NA
Prospective	7	14% (6–24)	82·4%	<0·0001	4	11% (6–17)	24·9%	0·262	1	34% (18–54)	NA	NA	4	75·9 (7·6–757·5)	78·2%	0·010
Retrospective	54	29% (24–35)	95·8%	<0·0001	31	15% (11–20)	92·9%	<0·0001	23	32% (25–39)	94·5%	<0·0001	37	106·9 (77·3–147·8)	93·3%	<0·0001
Case series	2	33% (19–49)	NA	NA	1	33% (15–57)	NA	NA	0	NA	NA	NA	0	NA	NA	NA
Cross-sectional	1	0% (0–28)	NA	NA	1	0% (0–28)	NA	NA	0	NA	NA	NA	0	NA	NA	NA
Human Development Index	..	..	..	0·023	..	..	..	0·0002		..	..	<0·0001	..	..	..	0·0003
Very high	51	31% (26–36)	93·5%	<0·0001	30	17% (12–21)	91·7%	<0·0001	18	36% (30–43)	90·8%	<0·0001	31	126·4 (95·8–166·6)	89·9%	<0·0001
High	9	16% (8–26)	89·5%	<0·0001	6	10% (3–20)	86·8%	<0·0001	4	21% (6–40)	90·5%	<0·0001	6	53·5 (12·7–225·3)	92·1%	<0·0001
Medium	7	13% (1–33)	98·5%	<0·0001	2	26% (21–31)	NA	NA	1	15% (11–19)	NA	NA	4	52·9 (31·8–88·1)	49·6%	0·114
Low	3	23% (16–32)	NA	NA	1	11% (5–20)	NA	NA	1	16% (9–26)	NA	NA	2	158·3*	97·8%	<0·0001
Predominant underlying respiratory condition	..	..	..	<0·001	..	..	..	0·033	..	..	..	0·002	..	..	..	0·687
Post-tuberculosis lung disease	35	23% (17–29)	94·2%	<0·0001	17	17% (13–22)	77·4%	<0·0001	11	27% (18–38)	94·5%	<0·0001	22	94·2 (62·8–141·3)	93·3%	<0·0001
COPD	12	24% (14–36)	96·1%	<0·0001	8	12% (5–23)	96·4%	<0·0001	5	38% (29–48)	88·9%	<0·0001	6	120·1 (86·9–166·0)	55·9%	0·045
NTM lung disease	4	46% (24–69)	87·8%	<0·0001	4	18% (5–35)	82·6%	0·001	3	50% (31–68)	NA	NA	4	149·2 (48·5–458·7)	99·5%	<0·0001
Interstitial lung disease†	1	44% (35–52)	61·7%	0·023	1	3% (0–9)	NA	NA	1	14% (7–25)	NA	NA	1	166·4 (40·3–687·4)	94·4%	<0·0001
Bronchiectasis	5	17% (2–40)	95·9%	<0·0001	3	17% (0–64)	NA	NA	3	29% (0–74)	NA	NA	5	82·7 (9·3–734·9)	96·5%	<0·0001
Malignancy	3	54% (45–63)	NA	NA	1	10% (5–18)	NA	NA	1	38% (28–48)	NA	NA	1	102·4 (77·1–135·8)	NA	NA
Risk of bias	..	..	..	0·807	..	..	..	0·554	..	..	..	0·475	..	..	..	0·211
<7	23	27% (19–36)	96·0%	<0·0001	14	17% (10–24)	93·5%	<0·0001	6	27% (13–44)	97·4%	<0·0001	7	79·3 (49·8–129·0)	70·9%	0·002
≥7	47	26% (20–32)	94·7%	<0·0001	25	14% (10–18)	85·1%	<0·0001	18	34% (26–42)	91·8%	<0·0001	36	110·0 (78·0–155·2)	93·1%	<0·0001
Source of patients	..	..	..	<0·0001	..	..	..	<0·0001	..	..	..	<0·0001	..	..	..	<0·0001
Inpatient	20	29% (23–36)	88·6%	<0·0001	14	15% (10–22)	90·1%	<0·0001	9	31% (22–40)	92·1%	<0·0001	12	110·6 (65·3–187·1)	95·0%	<0·0001
Outpatient	4	8% (4–12)	69·9%	0·019	0	NA	NA	NA	0	NA	NA	NA	2	49·7 (5·8–425·8)	60·8%	0·110
Mixed	3	19% (1–49)	NA	NA	2	2% (0–5)	NA	NA	1	3% (1–9)	NA	NA	1	24·4 (7·9–75·6)	NA	NA
Operated	4	9% (4–15)	78·5%	<0·0001	0	NA	NA	NA	2	13% (10–17)	NA	NA	3	40·0 (0·4–4158·5)	96·0%	<0·0001

(Table 2 continues on next page)

See Online for appendix 2

	Overall mortality in CPA				1-year mortality in CPA				5-year mortality in CPA				Deaths per 1000 person-years in CPA			
	Studies, n	Mortality estimate (95% CI)	I^2	p value	Studies, n	Mortality estimate (95% CI)	I^2	p value	Studies, n	Mortality estimate (95% CI)	I^2	p value	Studies, n	Mortality estimate (95% CI)	I^2	p value
(Continued from previous page)																
Decade of publication	..	..	..	0·013	..	..	..	<0·0001	..	..	..	0·950	..	..	..	0·036
2000 or earlier	3	42% (34–51)	NA	NA	1	35% (24–47)	NA	NA	1	31% (21–42)	NA	NA	1	59·5 (43·8–80·8)	NA	NA
2001–10	5	30% (19–42)	67·6%	0·015	1	37% (23–53)	NA	NA	0	NA	NA	NA	2	98·8*	87·4%	0·005
2011–20	44	25% (19–31)	93·8%	<0·0001	26	14% (11–19)	82·6%	<0·0001	15	33% (24–42)	93·5%	<0·0001	28	112·5 (82·0–154·5)	89·3%	<0·0001
After 2020	18	28% (18–38)	97·5%	<0·0001	11	13% (6–21)	94·8%	<0·0001	8	31% (20–43)	95·0%	<0·0001	12	90·4 (42·1–193·9)	95·4%	<0·0001

I^2 heterogeneity could not be calculated for some subgroups and outcomes as there were too few studies. COPD=chronic obstructive pulmonary disease. CPA=chronic pulmonary aspergillosis. NA=not available. NTM=non-tuberculous mycobacterial. *Due to the small sample size, the 95% CI is very wide, indicating uncertainty in the estimate, and has been omitted. †Including sarcoidosis.

Table 2: **Mortality estimates in subgroups of aggregate data and individual patient data**

agents, itraconazole was the most frequent first-line treatment (660 [58·2%] of 1134), followed by voriconazole (474 [41·8%] of 1134). Voriconazole was the most frequent second-line drug (163 [54·7%] of 298).

As shown in table 1, overall mortality was reported in 70 studies, with an estimated mortality of 27% (95% CI 22–32; I^2=95·4%, p<0·0001; figure 1). Overall mortality among the medical (ie, non-surgical) cohorts (63 studies) was estimated at 29% (95% CI 24–34; I^2=95·1%, p<0·0001; appendix 2 p 7). Random-effects meta-analysis yielded estimates of 15% (11–19; I^2=91·6%, p<0·0001; 39 studies; appendix 2 p 14) and 32% (25–39; I^2=94·3%, p<0·0001; 24 studies; appendix 2 p 25) for 1-year and 5-year mortality. After the first year, subsequent years showed a progressive decrease in mortality (figure 2; appendix 2 pp 14, 45–48). The incidence rate of mortality could be calculated in 47 studies, with an estimate of 104·5 deaths per 1000 person-years (77·6–140·7; I^2=92%, p<0·0001; appendix 2 p 36).

20 studies across both aggregate and IPD cohorts reported mortality in patients with post-tuberculosis lung disease, with 25% overall mortality (95% CI 16–35; I^2=87·5%, p<0·0001; appendix 2 p 49). In the IPD cohort, estimated overall mortality was 35% (22–49) in patients with COPD (I^2=89·7%, p<0·0001) and 30% (14–48) in patients with underlying non-tuberculous mycobacterial lung disease (I^2=79·6%, p<0·0001; appendix 2 pp 55, 61). Among predisposing conditions, first-year mortality was lowest in patients with post-tuberculosis CPA at 7% (3–13; I^2=70%, p<0·0001), and was 16% (9–24) in patients with COPD (I^2=78·2%, p<0·0001) and 12% (4–22) in those with non-tuberculous mycobacterial lung disease (I^2=54·4%, p=0·016; figure 2; appendix 2 pp 50, 56, 62). Yearly mortality estimates for CPA patients with different underlying lung diseases can be found in appendix 2 (pp 51–102).

Regarding CPA subtypes, patients with CFPA had the highest mortality at 51% (95% CI 23–79; I^2=41·5%, p=0·11), followed by those with SAIA (34% [20–49]; I^2=67·5%, p=0·0001) and CCPA (23% [14–33]; I^2=90·5%, p<0·0001). Patients with simple aspergilloma had the lowest mortality at 11% (4–20; I^2=66·6%, p<0·0001; appendix 2 pp 121–124). Subsequent-year mortalities were low in all subgroups and decreased progressively. Overall mortality was 24% (15–34) in patients treated with itraconazole (I^2=80·2%, p<0·0001) and 38% (25–51) in those treated with voriconazole (I^2=82·7%, p<0·0001; appendix 2 pp 125, 126). 17 studies reported postoperative mortality, which was low at 2% (0–3; I^2=49·6%, p=0·0108; appendix 2 p 129).

A summary of the subgroup analysis is provided in table 2, and details of significant results have been provided in appendix 1 (p 54).

From the aggregate analysis, univariable meta-regression revealed significantly higher mortality with increasing mean age (β coefficient 0·009 [95% CI 0·005 to 0·013], p<0·0001; appendix 2 p 130), higher

Human Development Index (HDI; 0·460 [0·060 to 0·859], p=0·024; appendix 2 p 130), and higher proportions of patients with underlying malignancy (0·479 [0·211 to 0·743), p=0·0004; appendix 2 p 131) and interstitial lung disease (0·257 [0·001 to 0·514], p=0·049; appendix 2 p 134). Higher proportions of patients with post-tuberculosis lung disease (–0·216 [–0·382 to –0·044], p=0·014; appendix 2 p 133) and being treated surgically (–0·004 [–0·006 to –0·002], p=0·0003; appendix 2 p 135) were associated with lower mortality. A multivariable model made with the above variables showed only the presence of malignancy as an independent predictor (2·390 [0·218 to 5·563], p=0·031), portending poorer prognosis (appendix 1 p 57). We found no significant publication bias by visual evaluation of the funnel plots and Egger's tests for various outcomes evaluated (appendix 2 pp 136–144).

One-stage meta-analysis with a stratified Cox proportional hazards model was done with IPD, with study level clustering, to assess factors affecting mortality. Univariable models revealed that age at diagnosis of CPA (per 10-year increase); SAIA, CCPA, and CFPA subtypes (*vs* simple aspergilloma); receipt of voriconazole therapy (*vs* itraconazole); and the presence of underlying COPD, interstitial lung disease, and malignancy (relative to the absence of these conditions) had significantly increased hazards of mortality (table 3). A multivariable model was made with the age at diagnosis of CPA, sex, antifungal agent received, and underlying predisposing condition. This model showed that age at diagnosis, CPA subtypes of SAIA or CCPA, underlying malignancy, and receipt of voriconazole therapy had higher hazards of mortality, while underlying post-tuberculosis lung disease had lower risks (figure 3). After adjusting for sex, CPA subtypes, antifungal treatments, and underlying comorbidities, there was a 25% increased hazard of mortality (hazard ratio 1·25 [95% CI 1·14–1·36]) with each passing decade of the age of CPA diagnosis (appendix 1 pp 55–56; figure 3) and 3% per year (1·03 [1·01–1·04]; appendix 1 p 55).

	Hazard ratio (95% CI)	p value
Age at diagnosis of CPA (per 1-year increase)	1·04 (1·03–1·05)	<0·0001
Sex		
Female	1 (ref)	..
Male	1·35 (0·97–1·88)	0·078
CPA subtype		
Simple aspergilloma	1 (ref)	..
SAIA	4·21 (2·80–6·34)	<0·0001
CCPA	1·68 (1·23–2·30)	0·001
CFPA	2·95 (1·98–4·41)	<0·0001
Aspergillus nodule	1·03 (0·35–3·04)	0·951
Treatment modality		
No treatment	1 (ref)	..
Medical only	0·98 (0·733–1·31)	0·904
Surgical with or without medical	0·22 (0·09–0·58)	0·002
Antifungal therapy given		
Itraconazole	1 (ref)	..
Voriconazole	1·91 (1·30–2·79)	0·001
Itraconazole then voriconazole	0·94 (0·49–1·82)	0·851
Voriconazole then itraconazole	0·90 (0·55–1·47)	0·670
Antifungal switch*	0·69 (0·42–1·14)	0·150
Predominant underlying respiratory condition†		
Post-tuberculosis lung disease	0·91 (0·75–1·10)	0·324
COPD	1·42 (1·08–1·87)	0·013
NTM lung disease	1·20 (0·84–1·70)	0·310
Interstitial lung disease‡	1·80 (1·25–2·58)	0·001
Malignancy	1·61 (1·23–2·12)	0·001

CCPA=chronic cavitary pulmonary aspergillosis. CFPA=chronic fibrosing pulmonary aspergillosis. COPD=chronic obstructive pulmonary disease. CPA=chronic pulmonary aspergillosis. NTM=non-tuberculous mycobacterial. SAIA=subacute invasive pulmonary aspergillosis. *Any change in antifungal medicine reported. †For each condition, the reference group is the absence of that condition. ‡Including sarcoidosis.

Table 3: **Stratified univariable Cox regression model for risk of mortality in CPA**

Discussion

Our study is the first attempt to systematically review studies from around the world and generate estimates of mortality in patients with CPA. CPA is often perceived to have a relatively benign course, especially compared with invasive pulmonary aspergillosis. Our results show that the diagnosis of CPA in patients is associated with considerable mortality, with only two-thirds of patients surviving 5 years. The overall mortality in CPA across all studies was 27%, while the first-year mortality was 15% and 5-year mortality was 32%. Other work summarises attributable mortality, which varies from as low as 4·8% in advanced fibrocystic pulmonary sarcoidosis to as high as 85·7%.[7]

Early cohorts of patients with CPA had widely differing outcomes. In the UK, from 1956 to 1980, 18 (50·0%) of 36 observed patients had died at 5 years, compared with 15 (37·5%) of 40 of those treated surgically.[34] From a small series in the USA, Tomlinson and Sahn[35] found a 58% mortality in those with sarcoidosis over 18 months, and 38% in patients with post-tuberculosis disease over 5 years. In the 1980s, there was no oral antifungal therapy as itraconazole was first licensed in 1991, voriconazole in 2002, and systemic amphotericin B was rarely used. It might be that corticosteroids were more often used in these early years, but they are detrimental to outcome, increasing mortality by 2·7 times.[89]

As seen in our study, mortality was highest during the first year at 15%, progressively dropping over subsequent years. The reason for this early mortality is not clear, but those admitted to the hospital fared worse, as shown in a nationwide study in France.[74] Underlying disease also appears to affect survival: patients with underlying interstitial lung disease and malignancy had the poorest

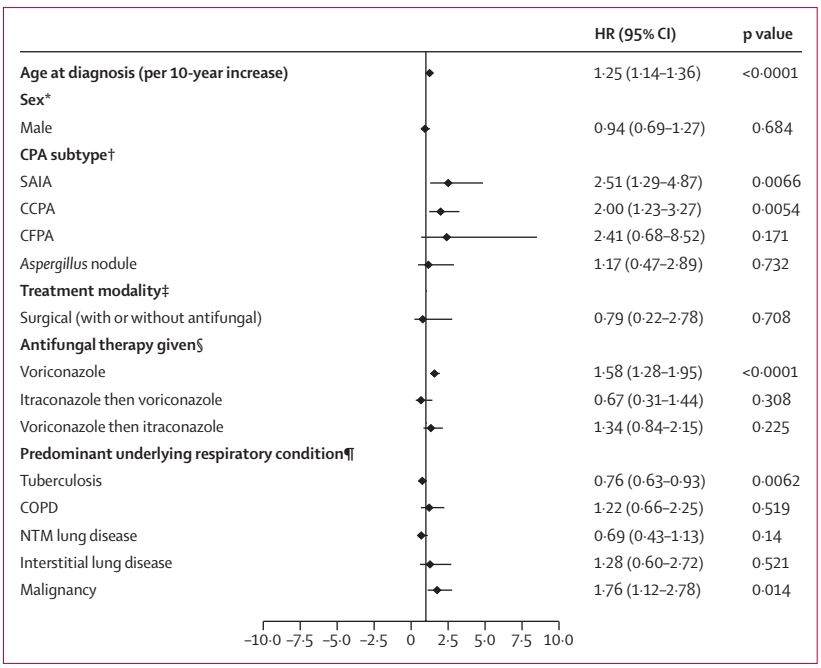


Figure 3: **Stratified multivariable Cox proportional hazards analysis of mortality**
HRs are adjusted for age at diagnosis (per 10-year increase), sex, CPA subtype, treatment modality, antifungal received, and underlying respiratory condition (tuberculosis, COPD, NTM lung disease, interstitial lung disease, and malignancy). CCPA=chronic cavitary pulmonary aspergillosis. CFPA=chronic fibrosing pulmonary aspergillosis. COPD=chronic obstructive pulmonary disease. CPA=chronic pulmonary aspergillosis. HR=hazard ratio. NTM=non-tuberculous mycobacterial. SAIA=subacute invasive pulmonary aspergillosis. *Reference group: female. †Reference group: simple aspergilloma. ‡Reference group: no treatment. §Reference group: itraconazole. ¶Reference groups: absence of specified condition.

survival (42% mortality in both groups), followed by those with autoimmune diseases and COPD (38% and 35%, respectively). Patients with underlying post-tuberculosis lung disease had 25% overall 5-year mortality. Overall mortality seemed to differ numerically between underlying diseases, being highest for malignancy, followed by interstitial lung disease, autoimmune diseases, COPD, non-tuberculous mycobacterial lung disease, pneumothorax, post-tuberculosis, and bronchiectasis, which was as low as for post-thoracic surgery. We could not assess the outcome of CPA misdiagnosed as pulmonary tuberculosis and not treated, or dual CPA and tuberculosis disease. Whether the underlying disorder or the CPA drives the worse survival is not clear, and it is probably a compounding effect. The mortality estimate was lowest for simple aspergilloma (10%) and highest for CFPA (51%), although multivariable analysis did not confirm higher hazards for mortality for the latter. Simple aspergilloma is often treated surgically with resection, but might also be a genuinely milder CPA phenotype.

Subgroup analysis showed that patients from the Western Pacific region and very high HDI countries had low survival (a large proportion [46%] of Western Pacific studies being Japanese). South Asian cohorts had low mortality, as did prospective cohort and randomised studies, and outpatient-only services. Mortality was low in those receiving only itraconazole (24%) compared with voriconazole (38%), possibly linked to the preferential use of voriconazole for SAIA, more ill patients, or those who do not respond to itraconazole treatment. Overall postoperative mortality in the surgical cohorts was low at 2%. Multivariable models using study as the clustering variable showed that age at diagnosis and patients with SAIA or CCPA subtypes had higher adjusted hazards of mortality. A switch in antifungal therapy was not shown to predict mortality in univariable analysis. The underlying respiratory condition could predict mortality, with patients with underlying malignancy having poorer outcomes. Even after adjusting for various factors such as age, sex, and comorbidities, a better prognosis for patients with post-tuberculosis CPA than for patients with other comorbid respiratory conditions was found (24% lower mortality risk), although younger age was almost as important (25% increased mortality risk per 10-year increase in age). The Kaplan–Meier analysis showed post-tuberculosis lung disease to have a 43·1% probability of mortality at 5 years, higher than the overall mortality of patients younger than 60 years with CPA, but we regard the multivariable analysis as more robust. Individual studies have reported variably on the effects of different underlying diseases on mortality in patients with CPA. While Lowes and colleagues[20] found non-tuberculous mycobacterial lung disease and COPD to have significant effects on mortality in their UK cohort of 387 patients, Kimura and colleagues,[24] reporting on 264 patients from Japan, could not find any significant effect due to either non-tuberculous mycobacterial lung disease or COPD. One can speculate that post-pulmonary tuberculosis CPA follows the cure of pulmonary tuberculosis, whereas many other underlying diseases are progressive, accounting for some difference in survival. Age was a significant factor in predicting mortality, even when adjusting for other covariates including subtype of CPA, underlying diseases, and treatment received: a 25% increase in hazard of mortality with every passing decade after CPA diagnosis, as others have previously noted.[15,20,24]

In a previous modelling study on CPA burden[6] related to pulmonary tuberculosis, estimates were based on a first-year death rate of 20% in patients with CPA, followed by an annual death rate of 7·5% (overall 50% at 5 years), but the current study found mortality of 7% in the first year post-tuberculosis, 2% in the second year, and 3% in the third year (~18% at 5 years, adding year-wise mortality data). The previous estimate assumed many patients were undiagnosed. This downward revision of mortality in the most common subgroup of CPA implies a consequent higher prevalence of CPA (by ~12% for 3-year prevalence data), assuming that undiagnosed and untreated CPA has the same mortality trajectory as treated post-tuberculosis CPA. Our results show that patients with SAIA have a worse prognosis than other CPA patients and as such might warrant more intense therapy.

In our IPD analysis, 122 patients were not treated for CPA, of whom 74 were from one study.[24] Many patients who were not treated had more severe underlying disease or were diagnosed retrospectively. The retrospective and observational study design of the included studies prevented us from drawing firm conclusions about the relative efficacy of different treatment modalities. The finding that voriconazole treatment has a significantly higher risk of mortality might reflect the prevalent practice of using voriconazole in sicker and more severely diseased patients, although we could not confirm this.

A notable strength of this study is the large number of patients with CPA in comparison with individual studies on CPA mortality. Our study has a few inherent limitations. First is the inclusion of different types of studies (observational, randomised trials, etc) from different health-care systems (high *vs* low HDI), which might impact mortality. These factors seem likely to be the reason for the significant heterogeneity seen in almost all the estimates (except in the postoperative groups). Second, the IPD analysis did not include all patients studied post-2016, for various reasons (as depicted in the flow diagram). Third, due to the unavailability of data recorded by individual investigators, our meta-analysis could not analyse all the factors reported in individual studies to have a significant effect on CPA mortality (eg, nutritional status, quality of life, or dyspnoea score). Hospitalisation of patients with CPA might reflect disease severity[22,74] or clinical practice, and we could not assess this fully due to the paucity of data in both the aggregate and IPD meta-analysis arms. We also could not usefully address possible differences in outcome based on ethnicity, which could be related to genetic variants yet to be described. Finally, we could not differentiate between deaths attributable to underlying comorbidity vis-a-vis CPA itself as this information was not available in most studies. Patients with CPA might die from haemoptysis, respiratory failure, pneumonia, and other conditions more common with advancing age.

In conclusion, CPA is associated with substantial 1-year mortality of 15% and 5-year mortality of 32%. Mortality in patients with post-tuberculosis CPA tends to be low. Finally, advancing age at diagnosis, CCPA or SAIA subtypes, and underlying malignancy are among the most important identifiable adverse prognostic factors predicting mortality in patients with CPA. Our work highlights the early mortality associated with CPA, which should be a focus of future screening and intensive intervention studies.

Contributors

DWD and AR conceived the study. AS and AR were involved in methodology, investigation, literature searching, most correspondence, formal analysis, writing, reviewing, editing, and visualisation. AS and AR wrote the primary draft of the paper. KI, MT, YK, FB, XS, TM, JC, VFdO, NI, MI, YU, JA-C, OM, JB, KF, TT, AI, and CK contributed patient datasets and corresponded with additional data and commented on the near-final paper draft. ADU undertook most of the statistical analysis and prepared many of the forest plots and other diagrammatic representations of the data. DWD reviewed and commented on multiple drafts and prepared the final draft for submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. AS and AR accessed and verified the data underlying the study.

Declaration of interests

AR has received a grant from Jolly Healthcare. KI has received payments from Pfizer Japan. MT has received grants from the Japan Society for the Promotion of Science and The Rotary Foundation; consulting fees from Asahi Kasei Pharma; and honoraria from Sumitomo Pharma, Kyorin Holdings, Astellas Pharma, Ono Pharmaceutical, Fujifilm Toyama Chemical, Chugai Pharmaceutical, Asahi Kasei Pharma, Janssen Pharmaceutical, and Shionogi Healthcare. TT has received consulting fees or honoraria for speaking from Asahikasei, Insmed, and Shionogi. DWD and family hold founder shares in F2G, a University of Manchester spin-out antifungal discovery company; and hold share options in TFF Pharmaceuticals. DWD acts or has recently acted as a consultant to Pulmocide, Biosergen, TFF Pharmaceuticals, Rostra Therapeutics, Pfizer, Mundipharma, Lifemine, and Cipla; chairs a data review committee for Pulmocide and Biosergen; has (in the past 3 years) been paid for talks on behalf of Hikma, Gilead, Avni, Pfizer, and Knight; and has contributed to multiple guidelines related to aspergillosis and fungal diagnostics. All other authors declare no competing interests.

Data sharing

The anonymised data supporting the findings of this systematic review can be made available from the corresponding author upon reasonable request.

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Supplementary appendix 1

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Sengupta A, Ray A, Upadhyay AD, et al. Mortality in chronic pulmonary aspergillosis: a systematic review and individual patient data meta-analysis. *Lancet Infect Dis* 2024; published online Nov 28. https://doi.org/10.1016/S1473-3099(24)00567-X.

Supplement 1

Sengupta A, Ray A et al. **Mortality in chronic pulmonary aspergillosis: a systematic review and individual patient data meta- analysis**

Search strategy

PubMed:

((chronic asper*) OR (chronic pulmonary asper*) OR (chronic pulmonary aspergillosis) OR (chronic necrotizing aspergillosis) OR (chronic necrotising aspergillosis) OR (chronic cavit* pulmonary aspergillosis) OR (chronic progressive pulmonary aspergillosis) OR (chronic fibrosing pulmonary aspergillosis)) AND ((mortality) OR (mortality rate) OR (death rate) OR (death) OR (fatality rate) OR (fatality) OR (survival rate) OR (survival) OR (mortality risk) OR (mortality prediction) OR (outcome) OR (fatal outcome) OR (mortal outcome) OR (terminal event) OR (mortality burden) OR (mortality statistics))

Embase:

('chronic pulmonary aspergillosis'/exp OR 'chronic pulmonary aspergillosis' OR 'chronic necrotising pulmonary aspergillosis' OR 'chronic necrotizing pulmonary aspergillosis'/exp OR 'chronic necrotizing pulmonary aspergillosis' OR 'chronic necrotizing aspergillosis'/exp OR 'chronic necrotizing aspergillosis' OR 'chronic necrotising aspergillosis' OR 'chronic progressive pulmonary aspergillosis'/exp OR 'chronic progressive pulmonary aspergillosis' OR 'chronic fibrosing pulmonary aspergillosis') AND ('mortality'/exp OR 'mortality' OR 'mortality rate'/exp OR 'mortality rate' OR 'death rate'/exp OR 'death rate' OR 'death'/exp OR 'death' OR 'fatality rate'/exp OR 'fatality rate' OR 'fatality'/exp OR 'fatality' OR 'survival rate'/exp OR 'survival rate' OR 'survival'/exp OR 'survival' OR 'mortality risk'/exp OR 'mortality risk' OR 'mortality prediction' OR 'outcome'/exp OR 'outcome' OR 'fatal outcome'/exp OR 'fatal outcome' OR 'mortal outcome' OR 'terminal event' OR 'mortality burden' OR 'mortality statistics'/exp OR 'mortality statistics')

Web of Science:

("chronic pulmonary aspergillosis'" OR "chronic necrotising pulmonary aspergillosis" OR "chronic necrotizing pulmonary aspergillosis" OR (chronic necroti* aspergillosis) OR (chronic cavit* pulmonary aspergillosis) OR "chronic fibrosing pulmonary aspergillosis") AND ("mortality" OR "mortality rate" OR "death rate" OR "death" OR "fatality rate" OR "fatality" OR "survival rate" OR "survival" OR "mortality risk" OR "mortality prediction" OR "outcome" OR "fatal outcome" OR "mortal outcome" OR "terminal event" OR "mortality burden" OR "mortality statistics")

Scopus:

(TITLE-ABS-KEY ("chronic pulmonary aspergillosis") OR TITLE-ABS-KEY ("chronic necrotising pulmonary aspergillosis") OR TITLE-ABS-KEY ("chronic necrotizing pulmonary aspergillosis") OR TITLE-ABS-KEY ("chronic necrotizing aspergillosis") OR TITLE-ABS-KEY ("chronic necrotising aspergillosis") OR TITLE-ABS-KEY ("chronic progressive pulmonary aspergillosis") OR TITLE-ABS-KEY ("chronic fibrosing pulmonary aspergillosis") OR TITLE-ABS-KEY ("chronic cavitary pulmonary aspergillosis") OR TITLE-ABS-KEY ("chronic cavit0ry pulmonary aspergillosis") AND TITLE-ABS-KEY (death) OR TITLE-ABS-KEY (mortality) OR TITLE-ABS-KEY (fatal) OR TITLE-ABS-KEY (survival) OR TITLE-ABS-KEY (outcome) OR TITLE-ABS-KEY (terminal)) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "cp")) AND (LIMIT-TO (SUBJAREA , "MEDI") OR LIMIT-TO (SUBJAREA , "IMMU"))

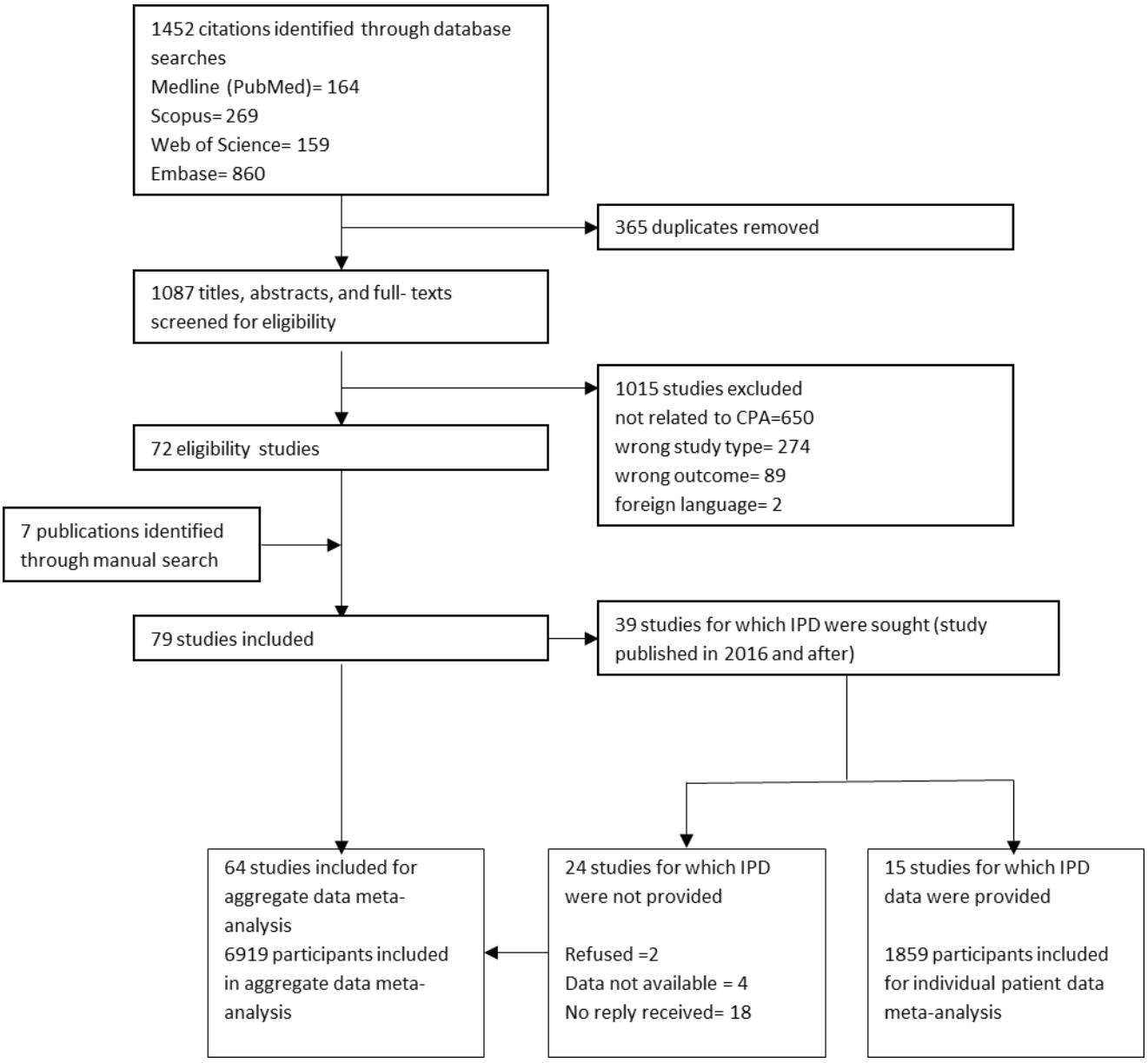

Figure 1: Flow diagram showing IPD and aggregate study selection

Data extraction template for systematic literature review

Variable	
Author	
Year	
Journal	
Country	
WHO Region	
Study period	
Study design	
Source of patients	
Diagnostic criteria	
Inclusion/exclusion criteria	
Human Development Index of country	
Number of patients	
Mean/Median age reported	
Proportion of male patients	
Proportion of smokers	
Proportion of patients with post-TB lung disease	
Proportion of patients with COPD	
Proportion of patients with NTM lung disease	
Proportion of patients with ILD	
Proportion of patients with bronchiectasis	
Proportion of patients with underlying malignancy	
Simple aspergilloma %	
Complex aspergilloma %	
Subacute invasive aspergillosis %	
Chronic cavitary pulmonary aspergillosis %	
Chronic fibrotic pulmonary aspergillosis %	
Mean follow-up of patients	
Overall mortality	
One-year events	
Five-year events	
Post-operative mortality	
Number of patients with post-TB lung disease	
Mortality among patients with post-TB lung disease	
Simple aspergilloma mortality	
SAIA mortality	
CCPA mortality	
CFPA mortality	
Proportion of patients who received medical treatment	
Proportion of patients who received surgical treatment	
Proportion of patients who received no treatment	

Proportion of patients who received voriconazole	
Proportion of patients who received itraconazole	

Data requisition template for anonymized individual patient data

Age of diagnosis of CPA (years)	
Sex	
Subtype of CPA	
Duration of observation (days)	
Reason for censoring (death/loss to follow-up)	
Underlying post-TB lung disease	
Underlying COPD	
Underlying NTM lung disease	
Underlying bronchiectasis	
Underlying autoimmune disease	
Underlying asthma	
Underlying ABPA	
Underlying cancer	
Underlying pneumothorax	
Underlying previous thoracic surgery	
Underlying any other disease	
Age of diagnosis of pulmonary TB	
Antifungal treatment	
Type of antifungal treatment 1	
Type of antifungal treatment 2	
Type of antifungal treatment 3	
Surgical excision for CPA	

Data extraction template for anonymised comorbid disease data among SAIA patients

Sex	
Age of diagnosis of CPA	
Type of CPA	
Observational period	
Reason for censoring	
Underlying disease (Diabetes mellitus)	
Underlying disease (Malnutrition/BMI)	
Underlying disease (Chronic alcoholism)	
Underlying disease (Chronic steroid use)	
Underlying disease (radiation therapy)	
Underlying disease (HIV infection)	

Supplementary statistical methods:

We systematically searched Medline (PubMed), Embase, Scopus, and Web of Science databases for relevant studies in English from the inception of the databases till August 2023 (see Supplement 1 for the detailed search strategy). For the individual patient outcomes, the corresponding authors of studies published after 2016 (the year of publication of updated guidelines for diagnosis and management for CPA)1 were contacted through emails for anonymized individual patient data. This year was selected to get a contemporary picture of mortality from CPA, not clouded by older treatment strategies. In case of no response, other authors of the study were individually contacted. Authors who didn't respond were sent at least

The search strategies were unique to the various databases. In general, the keywords included chronic pulmonary aspergillosis, CCPA, CFPA, CNPA/SAIA, and mortality. Publications were included if they were clinical studies, observational studies, controlled trials, and abstracts. Case reports, animal studies, letters, news, case reports, and literature reviews (unless original data were described) were excluded. Conference papers and abstracts were also included. All citations were exported to Zotero 6.0.26 (citation manager).

Two independent reviewers (AS and AD) screened the identified citations for potentially relevant articles, after removing duplicate records. All disagreements between the reviewers were resolved mutually after discussion with a third reviewer (AR). Full texts were obtained for all potentially eligible citations and screened for mortality data. Only texts available in English were included. In addition to the electronic search, reference lists of included publications were screened and subjected to the same independent selection process.

A qualitative assessment of included studies was performed independently on included studies by AS and AD with the National Heart, Lung, and Blood Institute (NHLBI) checklist, allocating a maximum score of 9 for case series and 14 for both cohort studies and randomized controlled trials.18 The duration of follow-up was divided into short and long, with an arbitrary cut-off of 12 months. Any disagreement was clarified after discussion with AR. Additionally, diagnostic criteria used by the studies were recorded.

All studies in English, reporting outcomes in the form of mortality were included. Studies dealing with other forms of aspergillosis e.g., invasive pulmonary aspergillosis, allergic bronchopulmonary aspergillosis, and non-respiratory aspergillosis were excluded. Data were extracted in a standardized Excel Spreadsheet (2010 v12.0, Microsoft) by AS and AD. Details regarding authors, year of publication, country, journal, study design, and aims; diagnostic criteria for chronic pulmonary aspergillosis, special inclusion and exclusion criteria; sample size, age of patients, gender-wise distribution, subtypes of chronic pulmonary aspergillosis, underlying pulmonary and systemic comorbidities, duration of follow-up, and type of treatment were retrieved. Mortality statistics including all-cause mortality, subtype-specific mortality, and mortality in different background diseases e.g., post-TB/cancer patients, 1-year, and 5-year mortality, etc., were recorded.

All authors were requested to complete a standard MS Excel sheet (2010 v12.0) consisting of demographic details (age, sex), disease-related information (type of CPA, underlying comorbid disease, age at diagnosis of pulmonary tuberculosis), treatment-related (antifungal agents used, duration of antifungal agent/s used in days, surgical treatment), duration of follow-up in days and outcome at the

end of study duration as survived, lost to follow-up and died. Responses were assessed for completeness and correctness of data, and any inconsistency was resolved over email with the responding authors.

An initial descriptive analysis of the studies was undertaken for demographic parameters, underlying comorbidities, and reported mortality rates. Mean, SD, and t-tests were used for parametric data, and median, IQR and Wilcoxon Rank-Sum or Kruskal-Wallis tests were used for non-parametric data. These results are expressed as median with (IQR) in brackets unless otherwise stated. Where individual participant data was available, it was used to enhance the quality and completeness of the data for analysis by recalculating observations to replace or supplement the existing data and subsequently used for analysis. Meta-analysis was undertaken using a random-effects model due to the expected heterogeneity; a pooled estimate and a 95% confidence interval were calculated for all the mortality statistics. Heterogeneity was reported using the I2 statistic, with values above the 50% threshold indicative of significant heterogeneity. Studies reporting all-cause mortality, 1-year mortality, 5-year mortality, CPA mortality as per underlying disease, and postoperative mortality were pooled. Publication bias was estimated using funnel plots and Egger's test.

The source of heterogeneity was explored using subgroup analysis and meta-regression. Subgroup analysis was done for differences in overall, 1-year, and 5-year mortality, with the following categorical variables; the data source, study design, risk of bias, country, Human Development Index, age groups, and the underlying lung disease. The age groups were arbitrarily divided into <40, 40- 60, and >60 years. The studies were also categorized into surgical cohorts which predominantly looked at surgical outcomes, the remainder were categorized as medical cohorts. We used meta-regression to study the effect of continuous variables on mortality rates; publication year, population mean age, proportion of male patients, prevalence of comorbid disease, and proportion treated (antifungal agents/surgery).

For the individual patient data (IPD), the various mortality statistics were recalculated and pooled with the aggregate data, with a subgroup analysis done to look for any significant difference between the aggregate and IPD data. Yearly mortality rates were calculated for the IPD cohort. In the case of the aggregate data, studies with the Kaplan-Meier curve were analyzed by Plot digitizer software (https://automeris.io/WebPlotDigitizer/) to extract year-wise mortality data (possible for the first year only in all except one study). We pooled the data (IPD and WebPlotDigitizer output) together using a random effects model, providing yearly estimates of mortality.19 We assessed publication bias using funnel plots and Egger's test, examining asymmetry to detect potential bias both quantitatively and visually. We divided patients into those receiving no treatment, only medical management, and those receiving surgical treatment with/without antifungal drugs. Those whose antifungals were changed due to any reason (such as non-response/intolerance) were labeled as 'antifungal switched'. The univariable Cox-proportional hazards model stratified by the study was used to calculate hazard ratios for various factors. A multivariable stratified Cox regression model was done using CPA type, underlying comorbidities, age at diagnosis, sex, and type of treatment received to look at various independent factors of mortality. A p-value <0.05 was considered statistically significant. The statistical analysis was done using Stata version 17 and RStudio version 4.3.1, 2023.

Table 1: Characteristics of studies included in the meta-analysis, PS-prospective study, CS-cross-sectional study, RS- retrospective study, Am- Americas, Af- Africa, E- Europe, SEA- South East Asia, WP- Western Pacific, * The number of patients received in the IPD cohort was different from data published, the IPD cohort patients were used for analysis.

Serial no	Author	Region	Study period reported	Type of study:	surgical /medical cohort	Number of patients	HDI Cat
1	Agarwal et al (1)	India (SEA)	Jan 2010- June 2011	RCT	M	31	2
2	Aguilar-Company et al (2)	Spain (E)	Jan 2010 - Dec 2015	RS	M	53	4
3	Akram et al (3)	Pakistan (EM)	Jan 2017-Dec 2019	RS	M	218	1
4	Al-Shair et al (4)	UK (E)	3 years	PS	M	122	4
5	Ando et al (5)	Japan (WP)	Jan 2011- Dec 2016	RS	M	41	4
6	Aydogdu et al (6)	Turkey (E)	Jan 2000- Dec 2013	RS	S	77	4
7	Bongomin et al (7)	UK (E)	Aug 2009- May 2017	RS	M	102	4
8	Benjelloun et al (8)	France (E)	Aug 2003- Sep 2014	RS	S	81	4
9	Bongomin et al (9)	UK (E)	April 2013- Mar 2015	RS	M	196*	4
10	Cadranel et al (10)	France (E)	July 2005- Dec 2008	PS	M	41	4
11	Camara et al (11)	France (E)	2000-2011	RS	M	44	4
12	Chan et al (12)	China (WP)	July 2003- June 2013	RS	M	60	3
13	Chen et al (13)	China (WP)	1975- 2010	RS	S	256	3
14	Cucchetto et al (14)	Italy (E)	Aug 2010- July 2012	Case series	M	21	4
15	Dahmane et al (15)	Tunisia (EM)		RS	S	84	3
16	de Oliveira et al (16)	Brazil (Am)	Jan 2010- Jun 2021	RS	M	91	3
17	Denning et al (17)	UK (E)	Before 2000	Case series	M	18	4
18	Despois et al (18)	Australia (WP)	Jan 2012- dec 2018	RS	M	28	4
19	Endo et al (19)	Japan (WP)	1989-2000	RS	S	10	4
20	Farid et al (20)	UK (E)	Sept 1996- Sept 2011	RS	S	30	4

21	Fenane et al (21)	Morocco (EM)	Jan 1982- Dec 2007	RS	S	350	2
22	Fong et al (22)	Australia (WP)	Jan 2015- Aug 2018	RS	M	25	4
23	Fujita et al (23)	Japan (WP)	Jan 2005- Dec 2007	PS	M	17	4
24	Furuhashi et al (24)	Japan (WP)	2011-2017	RS	M	47	4
25	Furuuchi et al (25)	Japan (WP)	Dec 2005- Jan 2012	RS	M	17*	4
26	Godet et al (26)	France (E)	Jan 2002- Dec 2011	RS	M	127	4
27	Gupta et al (27)	India (SEA)		CS	M	11	2
28	Hammerman et al (28)	USA (Am)		NA	M	71	4
29	Harmouchi et al (29)	Morocco (EM)	Jan 2009-Dec 2018	RS	S	79	2
30	He et al (30)	China (WP)	Jan 2001- Jun 2018	RS	S	60	3
31	Hirano et al (31)	Japan (WP)	April 2013- Mar 2019	RS	M	141	4
32	Hoyer et al (32)	Denmark (E)	Jan 2009- July 2014	NA	M	22	4
33	Huang et al (33)	Taiwan (WP)	May 2018- May 2021	PS	M	49	3
34	Iqbal et al (34)	Pakistan (EM)	Jan 2004 - Dec 2014	RS	M	75*	1
35	Ito et al (35)	Japan (WP)	April 2008- Sep 2013	RS	M	30	4
36	Jewkes et al (36)	UK (E)	1956- 1980	RS	M	85	4
37	Jhun et al (37)	South Korea (WP)	Jan 2008- Jan 2012	RS	M	70	4
38	Jhun et al (38)	South Korea (WP)	Jan 2010- Jun 2015	RS	M	41	4
39	Jiang et al (39)	China (WP)	Jan 2004- Dec 2017	RS	S	166	3
40	Kale et al (40)	India (SEA)	June 2018- June 2020	RS	M	360	2
41	Keir et al (41)	UK (E)	2008-2012		M	10	4
42	Khan et al (42)	India (SEA)	Jan 2000- Oct 2008	RS	S	52	2
43	Kim et al (43)	South Korea (WP)	Jan 2010- Dec 2016	RS	M	93	4

44	Kimura et al (44)	Japan (WP)	Jan 2012-April 2017	RS	M	264	4
45	Kohno et al (45)	Japan (WP)	Aug 2008- July 2010	RCT	M	70	4
46	Kosmidis et al (46)	UK (E)	May 2018- April 2021	RS	M	59	4
47	Koyama et al (47)	Japan (WP)	2007-2013	RS	M	100	4
48	Koyama et al (48)	Japan (WP)	June 2006- June 2012	RS	M	39	4
49	Kurosaki et al (49)	Japan (WP)	April 2006- Aug 2012	RS	M	14	4
50	Lee et al (50)	Japan (WP)	Jan 1990- Dec 2006	RS	M	240	4
51	Lopes et al (51)	Portugal (E)		RS	M	12	1
52	Lowes et al (52)	UK (E)	June 1992- June 2012	RS	M	394*	4
53	Maitre et al (53)	France (E)	2009-2018	RS	M	1705	4
54	Maruguchi et al (54)	Japan (WP)	Jan 2009- Mar 2018	RS	M	38	4
55	Munteanu et al (55)	Moldova (E)	Dec 2009- Dec 2017	PS	M	29*	3
56	Naito et al (56)	Japan (WP)	Jan 2010- dec 2015	RS	M	62	4
57	Nakamoto et al (57)	Japan (WP)	2011-2018	RS	M	259	4
58	Nakamoto et al (58)	Japan (WP)	Jan 1997- mar 2011	RS	M	194	4
59	Nam et al (59)	South Korea (WP)	Jan 1995- Dec 2007	RS	M	43	4
60	Niu et al (60)	China (WP)	Jan 2014- Dec 2017	RS	M	46	3
61	Nonga et al (61)	Cameroon (Af)	Jan 2012- May 2015	PS	S	20	1
62	Ohara et al (62)	Japan (EM)	Jan 2002 -Dec 2011	RS	M	30	4
63	Ohba et al (63)	Japan (WP)	Oct 2001- Sept 2009	RS	M	42	4
64	Peghin et al (64)	Spain (E)	Jan 2008 - Dec 2011	RS	M	14	4
65	Rattananont et al (65)	Thailand (SEA)	Jan 2015- Aug 2019	NA	S	59	1
66	Sapienza et al (66)	Brazil (Am)	Aug 1990- Nov 2002	RS	M	21	3
67	Sehgal et al (67)	India (SEA)	Feb 2019 - Aug 2021	RCT	M	164	2
68	Sehgal et al (68)	India (SEA)		PS	M	126	2
69	Sehgal et al (69)	India (SEA)	Jan 2018- Aug 2022	RS	M	351	2

70	Setianingrum et al (70)	UK (E)	2007- 2018	RS	S	61	4
71	Sugisaki et al (71)	Japan (WP)	2011-2013	RS	M	80	4
72	Takeda et al (72)	Japan (WP)	April 2008- Sept 2013	RS	M	41	4
73	Tashiro et al (73)	Japan (WP)	2011-2013	RS	M	273	4
74	Tomlinson et al (74)	USA(Am)	1975- 1985	RS	M	28	4
75	Ueda et al (75)	Japan (WP)	April 1973- Dec 1999	RS	M	41	4
76	Uzunhan et al (76)	France (E)	1980-2015	RS	M	65	4
77	Yamakawa et al (77)	Japan (WP)	June 2014- May 2021	RS	M	32	4
78	Yoshida et al (78)	Japan (WP)	May 2008- March 2011	PS	M	23	4
79	Zhong et al (79)	China (WP)	Jan 2002- Dec 2020	RS	M	147	3

Table 2: Additional characteristics of studies included in the meta-analysis.

Serial no	Author	Number of patients	Age (mean/median age)	Sex (Male, %)	Proportion of underlying diseases (Post TB/COPD/NTM/ILD/Bronchiectasis/Cancer)-%	SA/CA (surgical)/SAIA/CCPA/CFPA-number	Follow-up duration reported	Overall mortality (%)	Treatment (Medical/Surgical/None, %)	AFA (Itra/Vori %)
1	Agarwal et al (1)	31	35	58	90/NA/NA/NA/NA	NA/NA/NA/31/NA	median 11 (7-16) months	12.9	54.8/NA/45.2	54.8/NA
2	Aguilar-Company et al (2)	53	60	73.6	18.9/47.2/NA/17/49.1/28.3	4/NA/16/32/1	median 5.5 (2- 27) months	60.4	81.1/17/17	24.5/54.7
3	Akram et al (3)	218	45.8	73.4	44/11/NA/4.6/15.1/NA	122/NA/28/68/NA	median 7.5 (IQR 6-8.5) months	27.1	100/8.7/NA	69.7/6.9
4	Al-Shair et al (4)	122	59	55	NA	NA	NA	7.4	89.3/NA/11	39/21.5
5	Ando et al (5)	41	64.6	78	63.4/14.6/12.2/4.9/NA/NA	NA	median 24 months (0-70 months)	42	53.7/NA/NA	NA
6	Aydogdu et al (6)	77	45.5	68.8	48/8/NA/NA/13/NA	40/37/NA/NA/NA	NA	NA	NA/100/NA	NA
7	Bongomin et al (7)	102	63.7	60	21/26/9/3/NA/NA	NA	NA	3.9	42.2/NA/57.8	2/2
8	Benjelloun et al (8)	81	51	59.3	96.3/5/NA/NA/NA/NA	8/NA/NA/NA/NA	NA	6.2	29.6/61.7/8.6	29.6/NA
9	Bongomin et al (7)	196	62	65.8	18/47.5/11.7/11.2/15.8/6.6	NA/NA/NA/196/NA	12 months	6	100/NA/NA	77/22
10	Cadranel et al (10)	41	58	58.5	31.7/43.9/NA/NA/14.6/7.3	NA/NA/18/22/NA	NA	12.2	100/NA/NA	NA/100
11	Camara et al (11)	44	65	57	18/34/7/7/31/9	11/NA/22/11/NA	median 30 (14-55) months	27	95.4/11.9/4.6	32/45
12	Chan et al (12)	60	65	88.3	75/37/NA/NA/35/NA	31/NA/NA/NA/NA	NA	29.4	73.3/NA/NA	NA
13	Chen et al (13)	256	45	57.8	72.3/NA/NA/NA/11.3/0.7	96/160/NA/NA/NA	NA	NA	NA/100/NA	NA
14	Cucchetto et al (14)	21	52.4	71.4	38/33/NA/NA/NA/28.6	NA	12 months of observation	33.3	100/NA/NA	NA/100
15	Dahmane et al (15)	84	51.7	61.9	21.4/NA/NA/NA/10.7/NA	84/NA/NA/NA/NA	NA	NA	NA/100/NA	NA
16	de Oliveira et al (16)	91	50	64	76.9/24.7/8.8/6.6/88.4/4.4	25/NA/11/34/18	12 months of observation	3.3	76.9/47.3/3.3	68.1/17.6
17	Denning et al (17)	18	56.6	72.2	22.2/50/27.8/5.5/5.5/5.5	NA/NA/3/11/4	NA	37.5	100/22.2/NA	NA

18	Despois et al (18)	28	59	60.7	21.4/67.8/14.3/3.6/17.9/10.7	4/NA/3/17/3	12 months of observation	28.6	82.1/14.3/10.7	60.7/42.9
19	Endo et al (19)	10	50	80	30/50/NA/10/NA/NA	NA/NA/NA/10/NA	mean 57.6 (37.2) months	10	90/100/NA	70/NA
20	Farid et al (20)	30	57	50	20/20/NA/3.3/10/1	12/NA/NA/18/NA	NA	13	NA	NA
21	Fenane et al (21)	350	38.3	70.6	78/NA/NA/NA/NA/NA	NA	NA	14.4	NA	NA
22	Fong et al (22)	25	64.3	NA	NA	20/NA/2/NA/NA	NA	8	92/NA/8	80/8
23	Fujita et al (23)	17	73	76.5	53/24/17.6/11.8/NA/5.9	17/NA/NA/NA/NA	NA	17.6	100/NA/NA	NA
24	Furuhashi et al (24)	47	67.9	74.5	NA	NA	mean 35.4 months	17	NA	NA
25	Godet et al(26)	127	54.8	66.7	46.5/13.4/9.5/6.3/7.1/1.6	NA/NA/68/59/NA	mean 33.1 (27.9) months	15.8	100/NA/NA	10.2/74
26	Furuuchi et al (25)	17	76.6	41.2	17.7/23.5/100/11.7/NA/29.4	NA/NA/1/13/3	mean 17.6 (31.3) months	70.6	88.2/NA/NA	35.3/64.7
27	Gupta et al (27)	11	NA	NA	100/NA/NA/NA/NA/NA	NA	4 months	0	100/NA/NA	NA/100
28	Hammerman et al (28)	71	58.6	71.8	61.9/NA/NA/NA/NA/NA	NA	NA	35.20	56.3/NA/43.7	NA
29	Harmouchi et al (29)	79	40.5	72.2	72.2/1/NA/NA/1.3/NA	NA	30 months	NA	NA/100/NA	NA
30	He et al (30)	60	53.3	50	21.7/15/NA/NA/30/1.7	14/NA/9/28/NA	66 months (3 days to 341 months)	6.7	55/100/NA	NA
31	Hirano et al (31)	141	73	83	NA/23/NA/32/NA/NA	NA	NA	42	NA	NA
32	Hoyer et al (32)	22	NA	NA	NA/36/NA/NA/NA/40.9	NA	NA	55.4	NA	NA
33	Huang et al (33)	49	79.1	68.3	34.7/43/NA/NA/NA/34.7	4/NA/19/22/14	3 year survival was seen	18.3	NA	NA
34	Iqbal et al (34)	75	46	64	76/16/1.3/5.3/45.3/2.7	29/NA/1/35/5	NA	22.7	82.7/41.3/5.33	76/16
35	Ito et al (35)	30	NA	NA	NA	NA/NA/6/24/NA	12 months of observation	16.66	NA	NA
36	Jewkes et al (36)	85	45	62.4	28/1/3.5/27/7/NA	85/NA/NA/NA/NA	mean 8.1 years	48.2	38.8/57.6/NA	NA
37	Jhun et al (37)	70	62	65.9	65.9/32/100/7.3/NA/2.4	NA	median 26 (IQR 18-35) months follow-up of all NTM-LD patients	19.5	97.6/NA/NA	92.7/4.9
38	Jhun et al (38)	41	55	73	81/50/46/NA/26/10	NA	median 13 (IQR 9.3-21.0) months	14	100/9/NA	99/1
39	Jiang et al (39)	166	50.4	48.2	27.7/4/NA/NA/32.5/1.8	66/100/NA/NA/NA	mean 71.6 (45.3) months	3.6	100/100/NA	NA/100

40	Kale et al (40)	360	NA	NA	NA	NA	NA	64	NA	NA
41	Keir et al (41)	10	43.9	60	NA/NA/NA/100/NA/NA	NA	NA	20	100/NA/NA	NA
42	Khan et al (42)	52	39.3	61.5	75/NA/NA/NA/5.7/NA	NA	mean 38 (18.6) months	NA	NA/100/NA	NA
43	Kim et al (43)	93	63	61.3	16.1/45/NA/4.3/NA/100	4/NA/19/69/1	median 5.01 yrs	51.6	76.3/NA/23.7	62.4/20.4
44	Kimura et al (44)	264	71	73.9	59/44/32.9/20/17.4/14.4	NA	median 803 days [115.5 days, 1435.5 days]	39	70.8/NA/29.2	64.4/27.3
45	Kohno et al (45)	70	NA	NA	24.3/NA/NA/NA/NA/8.6	NA	NA	10	100/NA/NA	NA
46	Kosmidis et al (46)	59	60.5	41	14/51/8.5/5/NA/12	NA/NA/NA/59/NA	NA	41	100/NA/NA	41/59
47	Koyama et al (47)	100	63.4	93	71/53/NA/NA/NA/2	NA	Median follow-up duration in PT, PE, and CTE groups was 1245 (range; 11-2872), 732 (26-2146), and 831 (34-2601) days, respectively	32	100/2/NA	65/29
48	Koyama et al. (48)	39	59	79	54/54/5/NA/NA/NA	NA	NA	0	NA	NA
49	Kurosaki et al (49)	14	69.2	93.3	NA/NA/NA/100/NA/14.2	NA	mean 21.4 (16.2) months	64.2	100/NA/NA	64.3/50
50	Lee et al (50)	240	51	56.7	63.3/2/NA/NA/12.9/1.3	55/185/NA/NA/NA	NA	25.8	NA/56.2/NA	NA
51	Lopes et al (51)	12	65.5	83.3	50/33.3/NA/NA/NA/16.6	NA/NA/12/NA/NA	6 month	33.3	NA	NA/75
52	Lowes et al (52)	394	58.4	56.4	21/28.3/10.2/NA/16/11.9	NA	mean follow-up in surviving 5.65 years	33.5	29.2/NA/NA	21/18.5
53	Maitre et al (53)	1705	63.7	63.6	5.7/51.4/1.9/5.5/13.8/8.5	NA	NA	44.8	NA	NA
54	Maruguchi et al (54)	38	73.6	76	NA/46/100/27/NA/NA	NA	mean 1,360.4 (1,163.2) days	65.7	44/NA/56	NA
55	Munteanu et al (55)	29	53.6	65.5	37.9/72/NA/3.5/86.2/NA	3/NA/NA/15/9	NA	34.5	65.5/13.8/31	65.5/NA
56	Naito et al (56)	62	69.5	61.3	29/39/100/23/NA/21	NA	median 4.2 yrs	35.4	68/4.8/NA	45/26
57	Nakamoto et al (57)	259	69	72.6	26.3/21/23.9/29.3/NA/NA	NA	NA	36.3	NA	NA
58	Nakamoto et al (58)	194	68.5	80.4	30.4/20/15/16.5/NA/NA	NA	median 2.6 yrs	67.4	61.6/3.6/33.5	28.9/11.3
59	Nam et al (59)	43	60	79	93/9/11.6/2/NA/5	NA	15 months (IQR 2.5–32 months)	51	100/7/NA	91/NA

60	Niu et al (60)	46	52.4	78.3	89.1/11/NA/NA/8.7/NA	7/NA/13/26/NA	1 year	7	62.8/7/11.6	7/55.8
61	Nonga et al (61)	20	30	85	100/NA/NA/NA/NA/NA	NA/20/NA/NA/NA	mean 21.5 months (range 12- 40)	NA	NA/100/NA	NA
62	Ohara et al (62)	30	72	86.7	40/30/10/20/NA/33	NA	NA	NA	NA	NA
63	Ohba et al (63)	42	75.1	73.8	50/14.3/35.7/4.8/7.1/30.9	NA	28.7 ± 26.6 months	50	76.1/NA/NA	69/25
64	Peghin et al (64)	14	60.1	78.6	NA/50/NA/NA/NA/100	NA/NA/14/NA/NA	NA	71.4	100/14.3/NA	14.3/78.6
65	Rattananont et al (65)	59	NA	NA	NA	NA	mean 748 days	NA	NA/100/NA	NA
66	Sapienza et al (66)	21	47	52	100/19/NA/NA/NA/NA	NA	mean 73.5 months, median 25m (1.3-281)	42.9	NA	NA
67	Sehgal et al (69)	351	44.6	53.8	72.4/NA/NA/NA/NA/NA	21/NA/NA/278/52	15.3 (12-30) months	9.1	66.4/NA/NA	66.4/NA
68	Sehgal et al (67)	164	44.3	52.4	92.6/2/NA/NA/NA/NA	NA/NA/NA/141/23	18 months for 6 months group, 12 months for 12 months group	9.8	100/NA/NA	100/NA
69	Sehgal et al (68)	126	42.3	53.2	84.9/0.7/NA/1.4/NA/0.7	3/NA/NA/108/15	mean 1.1 (0.7) years	2.4	100/NA/NA	97.6/2.4
70	Setianingrum et al (70)	61	55.5	45.9	16.4/31.1/NA/NA/23/NA	28/NA/NA/17/NA	mean 36 months	8	66/100/NA	NA
71	Sugisaki et al (71)	80	NA	NA	35/28.8/NA/20/NA/NA	NA	NA	NA	NA	NA
72	Takeda et al (72)	41	67.2	75.6	43.9/46/22/22/7.3/14.6	5/NA/7/29/NA	mean 30.5 (22.2) months	46.3	68.3/NA/31.7	12.2/31.7
73	Tashiro et al (73)	273	70.8	21.6	40.7/23/14.7/8.4/5.9/9.9	NA/NA/NA/273/NA	mean 24.8 (22.7) months	45.4	100/NA/NA	21.6/37
74	Tomlinson et al (74)	28	44.9	46.4	50/NA/NA/50/NA/NA	28/NA/NA/NA/NA	NA	42.9	7.1/35.7/NA	NA
75	Ueda et al (75)	41	60.4	80.5	90.2/NA/NA/NA/NA/NA	NA	NA	24.4	NA	NA
76	Uzunhan et al (76)	65	48.2	66.2	9.2/NA/4.6/100/NA/NA	17/NA/1/41/6	mean 100.5 (27.9) months	43.1	89.2/16.9/4.6	58.8/63
77	Yamakawa et al (77)	32	74.9	75	NA/NA/NA/100/NA/NA	NA	median 18.9 months (range 3.1-54)	62.5	37.5/3.1/NA	NA
78	Yoshida et al (78)	23	64	62.5	26/8.7/26/NA/13/8.7	NA	NA	28	100/NA/NA	100/NA
79	Zhong et al (79)	147	55.5	57.8	33.3/30.6/NA/NA/31.3/10.3	11/NA/71/48/5	mean 61.3 (45.2) months	23.1	83/46.3/1.4	28.6/47.6

SA- Simple aspergilloma, CA- Complex aspergilloma (Belcher Plummer criteria), SAIA- Subacute invasive aspergillosis, CCPA- Chronic cavitary pulmonary aspergillosis, CFPA- Chronic fibrosing pulmonary aspergillosis, HDI cat- Human development index category, AFA- Antifungal agent, Itra- Itraconazole, Vori- Voriconazole

Table 3: Demographic characteristics of patients as per different WHO regions

WHO region	Africas		Americas		Eastern Mediterranean		Europe		South-East Asia		Western Pacific		Overall		p-value
	No. of studies	Median (IQR)	No. of studies	Median (IQR)	No. of studies	Median (IQR)	No. of studies	Median (IQR)	No. of studies	Median (IQR)	No. of studies	Median (IQR)	No. of studies	Median (IQR)	
Age (years)*	1	30	4	50.1(6)	5	44.5(5.2)	22	56.3(6.5)	5	41.1(4)	35	64.2(8.7)	72	57.6(10.9)	<0.0001
Sex (male %)*	1	85%	4	58.6% (11.5)	5	68.4% (5.1)	22	62.8% (10.1)	5	55.8% (3.9)	34	70.1% (15.1)	71	66.3% (13.2)	0.042
Post-TB lung disease	1	100%	4	69.4% (56-88.5%)	5	72.2% (44-76%)	19	21% (18-38%)	6	87.5% (75-92.6%)	31	40.7% (27.7-65.9%)	66	44% (24.3-72.4%)	<0.0001
COPD	0	NA	2	21.9% (19-24.7%)	3	11% (1-16%)	21	33.3% (20-47.5%)	2	1.4% (0.7-2%)	30	29.4% (15-45%)	58	28.6% (14.3-45%)	0.048
NTM-LD	0	NA	1	8.80%	1	1.30%	10	8.8% (4.6-10.2%)	0	NA	18	23% (14.3-46%)	30	13.3% (8.8-27.8%)	0.003
Bronchiectasis	0	NA	1	88.40%	4	12.9% (6-30.2%)	13	14.6% (10-23%)	1	5.70%	15	13% (7.3-30%)	34	14.2% (7.3- 30)	0.183
ILD	0	NA	2	28.3% (6.6-50%)	2	5% (4.6-5.3%)	13	6.3% (5-17%)	1	1.40%	21	16.5% (7.3-23%)	39	10% (4.9-23%)	0.316
Malignancy	0	NA	1	4.40%	1	2.70%	15	9% (5.5-28.3%)	1	0.70%	23	10% (2.4-21%)	41	9% (2.7-16.6%)	0.419

*Mean (SD)

Table 4: Prevalence of different types of CPA in the aggregate studies

Type of CPA	No of studies	Prevalence (median, IQR)
Simple aspergilloma	28	25.6% (9.9 -51.8)
SAIA	20	18.5% (11.4 -41.3)
CCPA	29	60.7% (46.7 -80)
CFPA	14	13% (6.7 -19.8)

Table 5: Distribution of underlying co-morbid diseases in patients of our IPD cohort

Underlying co-morbidity	N	Cases	Percentage (%)
Post-TB lung disease	1827	676	37.0
COPD	1820	586	32.2
NTM-LD	1680	243	14.5
ULD	1318	206	15.6
Malignancy	1825	177	9.7
Bronchiectasis	1746	375	21.5
Autoimmune disease	1827	134	7.3
Pneumothorax	1604	119	7.4
Thoracic surgery	1751	181	10.3

Table 6: Number of co-morbid diseases in our patients of IPD cohort

Number of comorbidities (n= 1859)	N	Percentage (%)
0	240	12.9
1	758	40.8
2	541	29.1
3	242	13.0
4	65	3.5
5	13	0.7

Table 7: Distribution of co-morbid conditions among SAIA patients in our IPD cohort

Underlying comorbid disease	N	Cases	Percentage (%)
Diabetes mellitus	171	31	18.1
Chronic steroid use	170	28	16.5
Malnutrition (BMI< 19)	135	31	23
Thoracic radiation	100	4	4
HIV infection	86	4	4.7
Chronic alcoholism	83	26	31.3

Table 8: Mortality statistics reported in various studies.

Serial no	Author	Overall mort (%)	1 year mort (%)	5 yr mort (%)	No of patients managed surgically	Post op mortality (%)	post tb patients	Post-TB mortality (%)	SA	SA mort (%)	SAIA	SAIA mort (%)	CCPA	CCPA mort (%)	CFPA	CFPA mort (%)
1	Agarwal et al (1)	12.9											31	12.9		
2	Aguilar-Company et al (2)	60.4	52.8	60.4	9	22.2	10	20	4	50	16	75	32	53.1	1	100
3	Akram et al (3)	27.1							122	23.7	28	34.1	68	30.9		
4	Al-Shair et al (4)	7.4	7.4													
5	Ando et al (5)	42	4.9	42												
6	Aydogdu et al (6)				77	3.9										
7	Bongomin et al (7)	3.9	3.9													
8	Benjelloun et al (8)	6.2			50	6										
9	Bongomin et al (9)	6	6				36	2.8					196	6.1		
10	Cadranel et al (10)	12.2														
11	Camara et al (11)	27							11	18.2	22	27.3	11	36.4		
12	Chan et al (12)	29.4	23.3						31	19.4						
13	Chen et al (13)				256	1.2										
14	Cucchetto et al (14)	33.3	33.3													
15	Dahmane et al (15)				84	3.6										
16	de Oliveira et al (16)	3.3	0	3.3			70	2.9	25	0	11	0	34	8.8		

17	Denning et al (17)	37.5														
18	Despois et al (18)	28.6	17.9	28.6			6	16.7	4	0	3	33.3	17	41.2	3	0
19	Endo et al (19)	10			10	0							10	10		
20	Farid et al (20)	13			30	0										
21	Fenane et al (21)	14.4		14.4	340	5.9										
22	Fong et al (22)	8							20	0	2	100				
23	Fujita et al (23)	17.6	17.6						17	17.6						
24	Furuhashi et al (24)	17	11.9													
25	Godet et al (26)	15.8	7.8	14.2			59	15.3			68	22.1	59	8.5		
26	Furuuchi et al (25)	70.6	47	70.6			3	66.7			1	100	13	61.5	3	100
27	Gupta et al (27)	0	0													
28	Hammerman et al (28)	35.20	35.2													
29	Harmouchi et al (29)				79	2.5										
30	He et al (30)	6.7			60	3.3			13	0	9	33.3	26	3.8		
31	Hirano et al (31)	42														
32	Hoyer et al (32)	55.4														
33	Huang et al (33)	18.3	12.5													
34	Iqbal et al (34)	22.7	10.7	16			57	14	29	10.3			35	22.9	5	20
35	Ito et al (35)	16.66	16.66								6	33.3	24	12.5		
36	Jewkes et al (36)	48.2		31					85	48.2						
37	Jhun et al (37)	19.5	2.4													
38	Jhun et al (38)	14														
39	Jiang et al (39)	3.6			166	0.6										
40	Kale et al (40)	64	28													
41	Keir et al (41)	20	1													
42	Khan et al (42)				52	1.9										
43	Kim et al (43)	51.6	9.7	37.2												
44	Kimura et al (44)	39	18.5	37.5			156	37.2								
45	Kohno et al (45)	10														
46	Kosmidis et al (46)	41	6.8	41			8	37.5					59	40.7		
47	Koyama et al (47)	32	11				47	8.5								

48	Koyama et al. (48)	0														
49	Kurosaki et al (49)	64.2														
50	Lee et al (50)	25.8			135	4.4										
51	Lopes et al (51)	33.3									12	33.3				
52	Lowes et al (52)	33.5	13.7	29.2			76	27.6								
53	Maitre et al (53)	44.8	32.1	44.8												
54	Maruguchi et al (54)	65.7	18.4	51.2												
55	Munteanu et al (55)	34.5	17.2	34.5			11	45.5	3	33.3			15	26.7	9	55.6
56	Naito et al (56)	35.4	17	35.4												
57	Nakamoto et al (57)	36.3														
58	Nakamoto et al (58)	67.4	17.5	53			59	59.3								
59	Nam et al (59)	51	37.2													
60	Niu et al (60)	7	7						7	0	13	15.4	26	3.8		
61	Nonga et al (61)				20	5	20	5								
62	Ohara et al (62)		36.7													
63	Ohba et al (63)	50	26.2													
64	Peghin et al (64)	71.4			2	50										
65	Rattananont et al (65)				59	3.4										
66	Sapienza et al (66)	42.9		41												
67	Sehgal et al (67)	9.1														
68	Sehgal et al (68)	9.8														
69	Sehgal et al (69)	2.4														
70	Setianingrum et al (70)	8		7												
71	Sugisaki et al (71)						28	10.7								
72	Takeda et al (72)	46.3	14.6	46.3			18	61.1	5	20	7	71.4	29	44.8		
73	Tashiro et al (73)	45.4	21.4	44			111	45.9					273	45.4		
74	Tomlinson et al (74)	42.9			10	20	14	35.7	28	42.9						
75	Ueda et al (75)	24.4														
76	Uzunhan et al (76)	43.1	3.0	13.8			6	50	17	47	1	100	41	39	6	50
77	Yamakawa et al (77)	62.5														
78	Yoshida et al (78)	28														

79	Zhong et al (79)	23.1	11.6	18.4			49	32.7	11	9	71	36.6	48	6.3	5	66.7

SA- Simple aspergilloma, CA- Complex aspergilloma, Belcher Plummer criteria), SAIA- Subacute invasive aspergillosis, CCPA- Chronic cavitary pulmonary aspergillosis, CFPA- Chronic fibrosing pulmonary aspergillosis

Table 9: Risk of bias assessment for cohort studies, 1. Was the research question or objective in this paper clearly stated? 2. Was the study population clearly specified and defined? 3. Was the participation rate of eligible persons at least 50%? 4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? 5. Was a sample size justification, power description, or variance and effect estimates provided? 6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)? 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? 10. Was the exposure(s) assessed more than once over time? 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? 12. Were the outcome assessors blinded to the exposure status of participants? 13. Was loss to follow-up after baseline 20% or less? 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Serial no	Author	Year	Comments	Score	Total	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
												Short 12 months long >12 months		Diagnostic methodology		NA			NA
1	Aguilar-Company et al (2)	2019	patients followed up till 12 months, cancer-related CPA included, workflow chart given, subtype division given, specific mortality	7	14	Y	Y	NA/ NR	Y	N	Y	S	NA	Y	NA	Y	N	Y	NA

			given, TB vs non-TB evaluated															
2	Akram et al (3)	2021	subtype division given, follow-up was short	7	14	Y	Y	NA/ NR	Y	N	Y	S	NA	Y	NA	Y	N	(Y)	NA
3	Ando et al (5)	2018	cohort of CPA patients who underwent BAE chose patients from a BAE cohort, 15 patients discontinued follow-up who were excluded	8	14	Y	Y	(Y)	Y	N	Y	L	NA	Y	NA	Y	N	N	NA
4	Aydogdu et al (6)	2015	surgical cohort, follow-up duration not mentioned, looked at post-op mortality and op-related complications	6	14	Y	Y	NA/ NR	Y	N	Y	NR	NA	Y	NA	(Y)	N	?NR/ NA	NA
5	Benjelloun et al (8)	2015	diagnostic criteria not well mentioned	7	14	Y	Y	NA/ NR	Y	N	Y	L	NA	(Y)	NA	Y	N	7/81 LTFU	NA
6	Bongomin et al (9)	2018	12-month follow-up, no LTFU data	6	14	Y	Y	NA/ NR	Y	N	Y	S	NA	Y	NA	Y	N	NR/ NA	NA
7	Bongomin et al (7)	2020	maximum 12 months follow up, no data to LTFU	6	14	Y	Y	NA/ NR	Y	N	Y	S	NA	Y	NA	Y	N	NR	NA
8	Cadranel et al (10)	2012	maximum follow-up of 6 months, assessed outcome of VCZ, prospective study, no control group, unblinded	8	14	Y	Y	NR	Y	Y	Y	S	NA	Y	NA	Y	N	Y	NA
9	Camara et al (11)	2014	workflow present with reasons for data exclusion, LTFU	8	14	Y	Y	(Y) 18 of	Y	N	Y	L	NA	Y	NA	Y	N	NR	NA

			data NR, subtype-specific mortality given,					62 eligible patients were excluded due to various reasons											
10	Chan et al (12)	2015	LTFU data absent, divided into PA, CPA, IPA	7	14	Y	Y	NA/ NR	Y	N	Y	L	NA	Y	NA	Y	N	NR	NA
11	Dahmane et al (15)	2019	only abstract available	4	14	Y	(N)	NA/ NR	Y	N	Y	NR	NA	CD	NA	Y	N	NR	NA
12	de Oliveira et al (16)	2022	divided into subtypes of CPA, subtype-specific mortality given, 12 months follow-up done	7	14	(Y)	Y	NA/ NR	Y	N	Y	S	NA	Y	NA	Y	N	1 patient lost to follow up	NA
13	Despois et al (18)	2022	CPA subtypes done, subtype-specific mortality given, short follow up, LTFU record based given- included patients with at	7	14	Y	Y	NA/ NR	Y	N	Y	S	NA	Y	NA	Y	N	Y 23/28 had more than 6	NA

			least 6 months follow up															months of follow-up data	
14	Endo et al (19)	2001	surgical cohort, small sample size, only CNPA	8	14	Y	Y	NA/ NR	Y	N	Y	L	NA	(Y)	NA	Y	N	(Y)	NA
15	Fong et al (22)	2021	only abstract available, subtypes of CPA given, treatment data given, type-specific mortality given	3	14	Y	N	NA/ NR	Y	N	Y	NR	NA	CD	NA	CD	N	NR	NA
16	Furuhashi et al (24)	2018	only abstract available	5	14	Y	NR	NA/ NR	Y	N	Y	L	NA	CD	NA	Y	N	NR	NA
17	Furuuchi et al (25)	2018	all NTM-LD, type of CPA, and CPA type specific mortality not mentioned, not mentioned treatment for CPA	7	14	Y	Y	NA/ NR	Y	N	Y	L	NA	Y	NA	Y	N	NR	NA
18	Godet et al (26)	2016	followed-up imaging of patients over 6 months	6	14	Y	Y	NA	Y	N	Y	NR	NA	Y	NA	Y	N	NR	NA
19	Gupta et al (27)	2022	abstract only, no aim, diagnostic criteria, methodological issue? Cross-sectional study reporting follow-up, short follow-up, all patients recorded for	5	14	N	(Y)	NA/ NR	Y	N	Y	S	NA	(Y)	NA	N	N	Y	NA

20	Harmouchi et al (29)	2019	only surgical cohort, no serology in criteria, pathological criteria used, divided into simple and complex aspergilloma	7	14	Y	Y	NA/ NR	Y	N	Y	L	NA	(Y)	NA	Y	N	NR	NA
21	He et al (30)	2019	surgical cohort, used 2016 criteria, gave types of CPA, type-specific mortality present, only post-op mortality	8	14	Y	Y	NA/ NR	Y	N	Y	L	NA	Y	NA	Y	N	Y 5 lost to follo w-up	NA
22	Hirano et al (31)	2021	only abstract available, clear study population not defined reproducibly, diagnostic criteria not available	5	14	Y	(Y)	NA/ NR	Y	N	Y	NR	NA	CD	NA	Y	N	NR	NA
23	Hoyer et al (32)	2015	only abstract available, diagnostic criteria not available	5	14	Y	Y	NA/ NR	Y	N	Y	NR	NA	CD	NA	Y	N	NR	NA
24	Huang et al (33)	2021	prospective study, sample size calculation absent, no blinding, LTFU data absent, divided into types of CPA, no type specific mortality given, no treatment data	7	14	Y	Y	NR	Y	N	Y	L	NA	Y	NA	Y	NR	NR	NA
25	Ito et al (35)	2014	abstract only, short follow-up, type-specific mortality given	6	14	Y	(Y)	NA/ NR	Y	N	Y	S	NA	Y (partial)	NA	Y	N	NR	NA

26	Jhun et al (37)	2013	CPA subtypes were not seen, and no specific mortality	8	14	Y	Y	NA/ NR	Y	N	Y	L	NA	Y	NA	Y	N	Y 4/70	NA
27	Jhun et al (38)	2017	CPA subtypes and subtype-specific mort NA	9	14	Y	Y	(Y)	Y	N	Y	L	NA	Y	NA	Y	N	Y	NA
28	Jiang et al (39)	2021	surgical cohort, Belcher Plummer classification used, CPA subtypes and specific mort absent, LTFU not given	7	14	Y	Y	NA/ NR	Y	N	Y	L	NA	(Y)	NA	Y	N	NR not clarified	NA
29	Khan et al (42)	2011	surgical cohort, criteria to diagnose CPA absent, CPA subtypes absent, subtype-specific mort absent	6	14	Y	Y	NA/ NR	Y	N	Y	L	NA	N	NA	N outcomes not mentioned clearly	N	Y	NA
30	Kim et al (43)	2022	Post lung cancer surgery cohort, LTFU data not recorded	8	14	Y	Y	Y	Y	N	Y	L	NA	Y	NA	Y	N	N	NA
31	Kimura et al (44)	2021	LTFU data not given, CPA subtype not given, underlying cause-specific mortality available	7	14	Y	Y	NA/ NR	Y	N	Y	L	NA	Y	NA	Y	N	NR	NA
32	Koyama et al (47)	2015	LTFU data NA, CPA subtype not mentioned	7	14	Y	Y	NA/ NR	Y	N	Y	L	NA	Y	NA	Y	N	NR	NA
33	Lowes et al (52)	2017		8	14	Y	Y	NA/ NR	Y	N	Y	L	NA	Y	NA	(Y)	N	Y	NA
34	Maitre et al (53)	2021	diagnostic criteria not available, ICD	6	14	Y	Y	NA/ NR	Y	N	Y	L	NA	CD	NA	Y	N	NR	NA

			code-based search of CPA cases															
35	Maruguchi et al (54)	2023	NTM LD population studied, no LTFU data available, CPA types and specific mortality absent, written per 2016 Denning et al diagnostic criteria but but only radiology and serology accounted	8	14	Y	Y	Y same as Kim	Y	N	Y	L	NA	(Y)	NA	Y	N	NR	NA
36	Munteanu et al (55)	2018	Abstract only, diagnostic criteria absent, follow-up data absent	5	14	Y	Y	NA/ NR	Y	N	Y	NR	NA	CD	NA	Y	N	NR	NA
37	Naito et al (56)	2018	CPA subtype and subtype-specific mortality absent, and no LTFU data	7	14	Y	Y	NA/ NR	Y	N	Y	L	NA	Y	NA	Y	N	NR	NA
38	Nakamoto et al (57)	2020	abstract only, diagnostic criteria not mentioned, follow-up NA	5	14	Y	Y	NA/ NR	Y	N	Y	NR	NA	CD	NA	Y	N	NR	NA
39	Nakamoto et al (58)	2013	CNPA only, based on Japanese criteria,	7	14	Y	Y	NA/ NR	Y	N	Y	L	NA	Y	NA	Y	N	NR	NA
40	Nam et al (59)	2010	CNPA cohort, no CPA subtype or subtype-specific mortality	8	14	Y	Y	NA/ NR	Y	N	Y	L	NA	Y	NA	Y	N	Y	NA
41	Niu et al (60)	2020	CPA subtypes and specific mortality given,	7	14	Y	Y	NA/ NR	Y	N	Y	S	NA	Y	NA	Y	N	Y 4/46	NA
42	Ohba et al (63)	2012	LTFU data NA	7	14	Y	Y	NA/ NR	Y	N	Y	L	NA	Y	NA	Y	N	NR	NA

43	Setianingrum et al (70)	2020	Surgical cohort, specific subtype given, LTFU data absent	7	14	Y	Y	NA/ NR	Y	N	Y	L	NA	Y	NA	Y	N	NR	NA
44	Sugisaki et al (71)	2015	only abstract	5	14	Y	Y	NA/ NR	Y	N	Y	NR	NA	CD	NA	Y	N	NR	NA
45	Takeda et al (72)	2016	subclass available, subtype-specific death NA	6	14	Y	Y	NA/ NR	Y	N	Y	NR	NA	Y	NA	Y	N	NR	NA
46	Zhong et al (79)	2022	subtype and specific mort available	8	14	Y	Y	NA/ NR	Y	N	Y	L	NA	Y	NA	Y	N	Y	NA
47	Ohara et al (62)	2015	no follow-up data is available, subtypes are not given, and no treatment data	6	14	Y	Y	NA/ NR	Y	N	Y	NR	NA	Y	NA	Y	N	NR	NA
48	Iqbal et al (34)	2016	no serology for diagnosis, subtype CPA given, no type specific mortality, no follow-up data, no treatment data	6	14	Y	Y	NA/ NR	Y	N	Y	NR	NA	(Y)	NA	Y	N	NR	NA
49	Uzunhan et al (76)	2017	CPA subtype not mentioned, long time frame of data	8	14	Y	Y	NA/ NR	(Y) time frame 35 years	N	Y	L	NA	Y	NA	Y	N	Y	NA
50	Kurosaki et al (49)	2014	only ILD patients had 1 IPA patient also, CPA subtype NA, LTFU NA	7	14	Y	Y	NA/ NR	Y	N	Y	L	NA	Y	NA	Y	N	NR	NA
51	Jewkes et al (36)	1983	old study, long time frame, diagnostic and therapeutic heterogeneity	8	14	Y	Y	NA/ NR	(Y) 1956-	N	Y	L	NA	Y (partial)	NA	Y	N	Y 11/85 loss	NA

									1980								to follow-up	
52	Tomlinson et al (74)	1987		8	14	Y	Y	NA/NR	Y	N	Y	L	NA	Y (partial)	NA	Y	N	3 patients' follow-up data NA 1 in TB 2 in sarcoid	NA
53	Ueda et al (75)	2001		6	14	Y	Y	NA	Y 1973-1999	N	Y	NR	NA	Y (partial)	NA	Y	N	NR	NA
54	Lee et al (50)	2009	the surgical cohort used Belcher Plummer criteria, only pulmonary aspergilloma was mentioned, surgical vs non-surgical	8	14	Y	Y	NA/NR	Y	N	Y	L	NA	Y	NA	Y	N	Y all patients followed up	NA
55	Sapienza et al (66)	2015		7	14	Y	Y	NA/NR	Y	N	Y	L	NA	Y	NA	Y	N	NR	NA
56	Sehgal et al (68)	2019		8	14	Y	Y	NA	Y	N	Y	L	NA	Y	NA	Y	N	(Y)	NA
57	Sehgal et al (69)	2022		7	14	Y	Y	NA	Y	N	Y	L	NA	Y	NA	Y	N	NR	NA
58	Tashiro et al (73)	2019		7	14	Y	Y	NA	Y	N	Y	L	NA	Y	NA	Y	N	NR	NA
59	Al-Shair et al (4)	2013		7	14	Y	Y	NA	Y	N	Y	S	NA	Y	NA	Y	N	Y	NA

60	Koyama et al (47)	2014		7	14	Y	Y	NA	Y	N	Y	S	NA	Y	NA	Y	N	Y none	NA
61	Hammerman et al (28)	1974		6	14	Y	Y	NA	Y	N	Y	S	NA	(Y) the old study mainly imaging and culture-based, serology not used	NA	Y	N	NR	NA
62	Fujita et al (23)	2012		7	14	Y	Y	NA	Y	N	Y	S	NA	Y	NA	Y	N	Y	NA
63	Keir et al (41)	2013	only abstract	7	14	Y	N	NA	Y	N	Y	L	NA	Y	NA	Y	N	(Y) all patient's tabular data were given and followed for 12 months	NA
64	Kosmidis et al (46)	2023		7	14	Y	Y	NA	Y	N	Y	L	NA	Y	NA	Y	V	NR	NA
65	Peghin et al (64)	2014	all patients with malignancy	6	14	Y	Y	NA	Y	N	Y	S	NA	Y	NA	Y	N	NR	NA

66	Rattananon t et al (65)	2021	surgical cohort, only abstract	5	14	Y	Y	NA	Y	N	Y	NR	NA	CD	NA	Y	N	NR	NA
67	Chen et al (13)	2012	surgical cohort	6	14	Y	Y	NA	Y	N	Y	NR	NA	(Y)	NA	Y	N	NR	NA
68	Fenane et al (21)	2013	surgical cohort, only abstract	5	14	Y	Y	NA	Y	N	Y	NR	NA	CD	NA	Y	N	NR	NA
69	Kale et al (40)	2022	all CLD patients, only abstract	5	14	Y	Y	NA	Y	N	Y	NR	NA	CD	NA	Y	N	NR	NA
70	Farid et al (20)	2013	surgical cohort	7	14	Y	Y	NA	Y	N	Y	NR	NA	Y	NA	Y	N	Y	NA
71	Yamakawa et al (77)	2022	ILD patients, excluded aspergilloma, aspergillus nodule	7	14	Y	Y	NA	Y	N	Y	L	NA	Y	NA	Y	N	NR	NA
72	Yoshida et al (78)	2012	CNPA patients	6	14	Y	Y	NA	Y	N	Y	S	NA	Y	NA	Y	N	NR	NA
73	Nonga et al (61)	2018	surgical cohort	7	14	Y	Y	NA	Y	N	Y	L	NA	N	NA	Y	N	Y	NA
74	Lopes et al (51)	2015	abstract only, only SAIA	5		Y	Y	NA	Y	N	Y	S	NA	CD	NA	Y	N	NR	NA

Y- Yes, N- No, CD- Could not be determined, NA- Not Applicable, NR- Not recorded, (Y)- partial yes

Table 10: Risk of bias assessment of case series as per NHLBI tool, 1. Was the study question or objective clearly stated? 2. Was the study population clearly and fully described, including a case definition? 3. Were the cases consecutive? 4. Were the subjects comparable? 5. Was the intervention clearly described? 6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? 7. Was the length of follow-up adequate? 8. Were the statistical methods well-described? 9. Were the results well-described?

Serial no	Case series	Year	Score	Total	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
1	Denning et al (17)	2003	6	9	Y	Y	Y	Y	NA	Y	NR	NA	Y
2	Cucchetto et al (14)	2012	5	9	Y	Y	N	Y	NA	Y	S	NA	Y

Table 11: Risk of bias assessment of randomized controlled trials as per the NHLBI tool. 1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT? 2. Was the method of randomization adequate (i.e., use of randomly generated assignment)? 3. Was

the treatment allocation concealed (so that assignments could not be predicted)? 4. Were study participants and providers blinded to treatment group assignment? 5. Were the people assessing the outcomes blinded to the participants' group assignments? 6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)? 7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment? 8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower? 9. Was there high adherence to the intervention protocols for each treatment group? 10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)? 11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants? 12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power? 13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)? 14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?

Serial no	RCT	Year	Column3	Column4	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
1	Agarwal et al (1)	2013	12	14	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
2	Kohno et al PPS analysis (45)	2013	11	14	Y	Y	CD	Y	Y	Y	Y 4 patients didn't complete therapy	Y	Y	Y	Y	N	Y	(N) PPS
3	Sehgal et al (67)	2022	11	14	Y	Y	Y	N	N	(Y) more cavities in 12-month grp, no p values	Y	Y	(Y) 20% of patients had to be switched to voriconazole due to unfavorable response	Y	Y	Y	Y	Y

PPS- per protocol set

Table 12: Diagnostic criteria used in the various studies

Serial no	Author	Diagnostic Criteria	Clinical symptoms	Duration of symptoms (3 months)	Imaging	Xray	CT	culture	Antigen	Antibody	HPE	Others	Inclusion	Exclusion
1	Agarwal et al (1)	NA	Y	> 1.5 months	Y	NA	NA	Y	NA	Y	NA	NA	NA	CNPA, uncontrolled DM, and immunosuppressive meds excluded. raised inflammatory markers, invasive aspergillosis, ABPA, active PTB, malignancy, pregnancy
2	Aguilar-Company et al (2)	Denning 2016	NA	NA	NA	NA	NA	NA	Y	Y	NA	NA	NA	Bilateral lung transplant, unilateral lung transplant with aspergillosis affecting infected lung, neutropenia, HSCT, CPA after invasive fungal infection
3	Akram et al (3)	Denning 2016	Y	Y	Y	NA	NA	Y	NA	Y	NA	NA	NA	alternate diagnosis
4	Al-Shair et al (4)	Denning 2003, Kohno 2011	Y	NA	Y	NA	NA	NA	NA	Y	NA	laboratory findings	NA	NA

5	Ando et al (5)	Denning 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	operable patients with simple aspergilloma or CPA
6	Aydogdu et al (6)	NA	Y	NA	Y	Y	Y	NA	NA	NA	NA	NA	NA	NA
7	Benjelloun et al (8)	IDSA 2008	Y	NA	Y	NA	NA	(Y)	NA	(Y)	(Y)	NA	NA	HIV
8	Bongomin et al (9)	Denning 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
9	Bongomin et al (7)	Denning 2016	Y	Y	Y	NA	NA	Y	NA	Y	NA	NA	NA	alternate diagnosis
10	Cadranel et al (10)	NA	NA	NA	NA	Y	NA	Y	Y	NA	Y	NA	NA	NA	Pregnancy, aspergilloma, ABPA, invasive aspergillosis, immunosuppressed
11	Camara et al (11)	NA	Y	Y	Y	NA	Y	Y	NA	Y	NA	NA	NA	exclusion of alternate infection, absence of systemic immunosuppression, raised inflammatory markers
12	Chan et al (12)	Denning 2003	Y	Y	Y	NA	Y	Y	NA	Y	NA	NA	NA	exclusion of alternate infection, absence of systemic immunosuppression, raised inflammatory markers

13	Chen et al (13)	Belcher and Plummer	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
14	Cucchetto et al (14)	NA	Y	Y, >3 months	Y	NA	NA	Y	Y	Y	Y	NA	NA	exclusion of severe immunosuppression, neutropenia, hematological malignancy, AIDS, HSCT, SOT, steroids
15	Dahmane et al (15)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
16	de Oliveira et al (16)	Denning 2016	Y	Y	Y	NA	Y	Y	Y	Y	Y	NA	NA	exclusion of alternative diagnosis
17	Denning et al (17)	NA	Y	Y, >3 months	Y	NA	NA	NA	NA	Y	NA	NA	increased inflammatory markers	immunocompromised patients except in CNPA
18	Despois et al (18)	Denning 2016	Y	Y	Y	NA	NA	Y	NA	Y	NA	NA	at least one marker of inflammation	exclusion of alternate infection, absence of systemic immunosuppression, raised inflammatory markers
19	Endo et al (19)	NA	NA	30 days	Y	NA	NA	NA	NA	NA	NA	NA	ineffective antifungal therapy	exclusion of alternative diagnosis
20	Fenane et al (21)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

21	Farid et al (20)	Belcher and Plummer	Y	NA	Y	NA	NA	Y	NA	NA	Y	NA	NA	NA
22	Fong et al (22)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
23	Fujita et al (23)	NA	Y	NA	Y	NA	NA	Y	Y	Y	NA	PCR used, immunosuppression excluded-CKD, CLD, uncontrolled diabetics, immunosuppressive agents	NA	NA
24	Furuhashi et al (24)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
25	Furuuchi et al (25)	Denning 2016	Y	NA	Y	NA	NA	Y	NA	Y	NA	NA	NA	NA
26	Godet et al (26)	Denning 2003	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	simple aspergilloma
27	Gupta et al (27)	Denning 2016	Y	Y>3 months	Y	NA	NA	NA	Y	Y	NA	NA	NA	NA
28	Hammerman et al (28)	NA	NA	NA	Y	NA	NA	Y	NA	NA	NA	NA	NA	no eosinophilia
29	Harmouchi et al (29)	Belcher and Pulmmer criteria	NA	NA	Y	NA	NA	NA	NA	Y	Y	endoscopic appearance	NA	NA
30	He et al (30)	Denning 2016	NA	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	NA
31	Hirano et al (31)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
32	Hoyer et al (32)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
33	Huang et al (33)	Denning 2016	NA	NA	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA

34	Iqbal et al (34)	Denning 2016	NA	Y	Y	NA	NA	Y	NA	Y	Y	NA	>18 years	NA
35	Ito et al (35)	NA	Y	Y	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA
36	Jewkes et al (36)	NA	NA	NA	Y	NA	NA	NA	NA	Y	NA	NA	NA	NA
37	Jhun et al (37)	Denning 2003, Zmeili 2007	Y	Y	Y	NA	NA	Y	Y	Y	NA	NA	no overt immunosuppression, no dissemination, elevated inflammatory markers	NA
38	Jhun et al (38)	Denning 2016	Y	NA	Y	Y	Y	Y	NA	Y	NA	NA	NA	NA
39	Jiang et al (39)	Belcher and Plummer	Y	NA	Y	NA	Y	Y	NA	Y	Y	NA	NA	NA
40	Kale et al (40)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
41	Keir et al (41)	Denning 2010	Y	Y	Y	NA	NA	Y	NA	Y	Y	NA	increased inflammatory markers	exclusion of other causes
42	Khan et al (42)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
43	Kim et al (43)	Denning 2016	Y	NA	Y	NA	NA	Y	NA	Y	NA	NA	NA	exclusion of alternate diagnosis
44	Kimura et al (44)	Denning 2016	Y	Y	Y	NA	NA	NA	NA	Y	NA	NA	NA	excluded aspergilloma, aspergillus nodule, possible risk of SAIA, immunosuppressing condition
45	Kohno et al PPS	NA	Y	NA	Y	NA	NA	NA	Y	Y	NA	NA	NA	NA

	analysis (45)													
46	Kosmidis et al (46)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
47	Koyama et al (47)	Kohno 2010, Denning 2011	Y	NA	Y	NA	NA	Y	NA	Y	NA	NA	NA	excluded other diagnosis
48	Koyama et al (48)	NA	NA	NA	Y	NA	NA	Y	Y	Y	Y	NA	underlying lung disease	NA
49	Kurosaki et al (49)	NA	Y	> 1 month	Y	NA	Y	Y	Y	Y	NA	NA	CRP, TLC	ABPA, IPA, simple aspergilloma
50	Lee et al (50)	Belcher and Plummer	Y	NA	Y	NA	NA	NA	NA	NA	NA	NA	NA	NA
51	Lopes et al (51)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
52	Lowes et al (52)	Denning 2003,2016	NA	Y > 3 months	Y	NA	NA	NA	NA	Y	NA	NA	NA	NA
53	Maitre et al (53)	Denning 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
54	Maruguchi et al (54)	Denning 2016	NA	Y > 3 months	Y	NA	NA	NA	NA	Y	NA	NA	NA	NA
55	Munteanu et al (55)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
56	Naito et al (56)	Denning 2016	Y	NA	Y	NA	NA	Y	Y	Y	NA	NA	NA	NA
57	Nakamoto et al (57)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
58	Nakamoto et al (58)	Kohno 2004-CNPA	Y	Y> 1 month	Y	NA	NA	Y	NA	Y	NA	NA	NA	NA

		terminology used												
59	Nam et al (59)	Denning 2003	Y	Y > 1 month	Y	NA	NA	Y	NA	Y	NA	CNPA terminology used	NA	Other pulmonary
60	Niu et al (60)	Denning 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	immunosuppression, IPA, other differentials-active TB, NTM LD, CA lung
61	Nonga et al (61)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
62	Ohara et al (62)	NA	Y	NA	Y	NA	NA	Y	NA	NA	NA	NA	NA	NA
63	Ohba et al (63)	NA	Y	1-6 months	Y	NA	NA	Y	NA	NA	NA	NA	NA	IPA, simple aspergilloma other cavitary diseases of lung
64	Peghin et al (64)	Denning 2011	NA	NA	NA	NA	NA	NA	NA	NA	NA	all patients with malignancy	NA	NA
65	Rattanaont et al (65)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
66	Sapienza et al (66)	CNPA terminology used	Y	NA	Y	NA	NA	Y	NA	Y	NA	mentioned as cnpa	NA	NA
67	Sehgal et al (68)	Denning 2016	Y	Y > 3 months	Y	NA	NA	Y	Y	Y	NA	NA	NA	HIV, IPA, IPA, and pregnancy excluded
68	Sehgal et al (69)	Denning 2016	Y	Y > 3 months	Y	NA	NA	Y	Y	Y	NA	NA	NA	Steroid treatment, AIDS, and other active infections excluded SAIA
69	Sehgal et al (67)	NA	Y	Y > 3 months	Y	NA	NA	Y	Y	Y	NA	NA	NA	systemic corticosteroids,

														other cavitary lung diseases
70	Setianingrum et al (70)	Denning 2016	Y	Y > 3 months	Y	NA	NA	Y	NA	Y	Y	NA	NA	NA
71	Sugisaki et al (71)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
72	Takeda et al (72)	Denning 2003	Y	NA	Y	NA	NA	Y	NA	NA	Y	NA	NA	NA
73	Tashiro et al (73)	Denning 2003	Y	6 months	Y	NA	NA	Y	Y	Y	Y	NA	molecular diagnostics, increased inflammatory markers, lack of improvement with 3 days of antibiotics	NA
74	Tomlinson et al (74)	NA	NA	NA	Y	NA	NA	Y	NA	Y	Y	NA	NA	NA
75	Ueda et al (75)	NA	NA	NA	Y	NA	NA	Y	NA	NA	NA	NA	NA	NA
76	Uzunhan et al (76)	Denning 2016	NA	NA	Y	NA	NA	Y	NA	Y	NA	NA	NA	NA
77	Yamakawa et al (77)	Denning 2016	NA	NA	NA	NA	NA	NA	NA	NA	NA	excluded simple aspergilloma, aspergillus nodule	NA	NA
78	Yoshida et al (78)	Japanese 2007-CNPA terminology used	Y	NA	Y	NA	NA	Y	Y	Y	Y	cnpa defined	NA	NA
79	Zhong et al (79)	Denning 2016	Y	Y	Y	NA	NA	Y	Y	Y	NA	NA	NA	NA

Table 13: Yearly mortality estimated from aggregate and IPD datasets among CPA patients

Author	Data source	1-year mortality (n)	1-year at risk (N)	Second-year mortality (n)	Second-year at-risk (N)	Third-year mortality (n)	Third-year at risk (N)	Fourth-year mortality (n)	Fourth-year at risk (N)	Fifth-year mortality (n)	Fifth-year at risk (N)
Furuuchi et al	IPD	8	17	2	8	1	5	1	3	0	1
Iqbal et al	IPD	8	75	2	44	3	40	1	35	0	33
Aguilar-company et al	IPD	28	53	3	21	0	16	1	9	0	5
Kimura et al	IPD	49	264	17	163	17	137	8	105	8	66
Kosmidis et al	IPD	4	59	9	55	5	46	4	29	2	20
Lowes et al	IPD	53	394	25	299	16	218	16	156	5	98
Munteanu et al	IPD	5	29	1	24	4	23	0	0	0	0
Su et al	IPD	17	147	3	122	3	112	1	95	3	87
Takeda et al	IPD	6	41	6	32	5	21	2	13	0	7
Tashiro et al	IPD	59	273	28	169	14	115	13	80	6	49
Bongomin et al	IPD	12	196	0	0	0	0	0	0	0	0
de Oliveira et al	IPD	0	91	3	61	0	15	0	4	0	4
Despois et al	IPD	5	28	1	11	2	7	0	5	0	1
Godet et al	IPD	10	127	3	89	4	73	1	55	0	39
Uzunhan et al	IPD	2	65	2	57	4	55	0	51	4	51
Ando et al	AGG	2	41	3	37	2	24	4	22	1	13

Chan et al	AGG	14	60	NA	NA	NA	NA	NA	NA	NA	NA
Jhun et al	AGG	2	41	NA	NA	NA	NA	NA	NA	NA	NA
Kim et al	AGG	8	93	NA	NA	NA	NA	NA	NA	NA	NA
Maitre et al	AGG	570	1706	NA	NA	NA	NA	NA	NA	NA	NA
Maruguchi et al	AGG	7	38	NA	NA	NA	NA	NA	NA	NA	NA
Naito et al	AGG	10	62	NA	NA	NA	NA	NA	NA	NA	NA
Nakamoto et al	AGG	39	194	NA	NA	NA	NA	NA	NA	NA	NA
Nam et al	AGG	16	43	NA	NA	NA	NA	NA	NA	NA	NA
Ohba et al	AGG	11	42	NA	NA	NA	NA	NA	NA	NA	NA
Ohara et al	AGG	10	30	NA	NA	NA	NA	NA	NA	NA	NA
Koyama	AGG	12	100	NA	NA	NA	NA	NA	NA	NA	NA
Huang et al	AGG	6	48	NA	NA	NA	NA	NA	NA	NA	NA

Table 14: Yearly mortality estimated from the IPD dataset in patients with CPA and post-TB lung disease

CPA with post-TB lung disease	Overall mortality	First-year mortality (n)	First-year at risk (N)	Second-year mortality (n)	Second-year at risk (N)	Third-year mortality (n)	Third-year at risk (N)	Fourth-year mortality (n)	Fourth-year at risk (N)	Fifth-year mortality (n)	Fifth-year at risk (N)
Furuuchi et al	2	1	3	0	2	1	2	0	1	0	1
Iqbal et al	8	3	57	2	34	1	30	1	27	0	26
Aguilar-company et al	2	1	10	1	7	0	5	0	3	0	2
Kimura et al	58	26	156	7	93	11	81	6	61	5	39
Kosmidis et al	3	0	8	1	8	2	7	0	2	0	2

Lowes et al	21	7	76	5	59	4	42	3	29	1	21
Munteanu et al	5	2	11	0	9	3	9	0	0	0	0
Su et al	16	4	49	1	45	2	43	1	35	3	33
Takeda et al	11	4	18	4	13	2	8	1	4	0	1
Tashiro et al	51	23	111	9	67	8	48	6	32	3	21
Bongomin et al	1	1	36	0	0	0	0	0	0	0	0
de Oliveira et al	2	0	70	2	42	0	9	0	3	0	3
Despois et al	1	1	6	0	1	0	1	0	1	0	0
Godet et al	9	5	59	1	39	1	31	0	22	0	15
Uzunhan et al	3	0	6	0	5	0	5	0	5	1	5

Table 15: Yearly mortality estimated from the IPD dataset in patients with CPA and COPD (chronic obstructive pulmonary disease)

CPA with COPD	Overall mortality	First-year mortality (n)	First-year at risk (N)	Second-year mortality (n)	Second-year at risk (N)	Third-year mortality (n)	Third-year at risk (N)	Fourth-year mortality (n)	Fourth-year at risk (N)	Fifth-year mortality (n)	Fifth-year at risk (N)
Furuuchi et al	4	3	4	1	1	0	0	0	0	0	0
Iqbal et al	3	1	12	1	6	0	5	1	5	0	4
Aguilar-company et al	17	13	25	3	11	0	8	1	5	0	3
Kimura et al	44	19	115	9	74	8	59	3	45	4	25
Kosmidis et al	13	2	30	4	28	3	24	3	14	1	10
Lowes et al	40	18	102	8	73	7	53	3	38	2	22

Munteanu et al	7	4	21	1	17	2	16	0	0	0	0
Su et al	20	12	45	1	31	2	28	0	24	1	21
Takeda et al	8	1	19	3	16	3	10	1	7	0	5
Tashiro et al	39	21	63	10	34	5	20	2	14	0	7
Bongomin et al	5	5	93	0	0	0	0	0	0	0	0
de Oliveira et al	0	0	21	0	17	0	5	0	0	0	0
Despois et al	5	3	19	1	9	1	6	0	5	0	1
Godet et al	3	1	17	1	11	1	8	0	6	0	3
Uzunhan et al	0	0	0	0	0	0	0	0	0	0	0

Table 16: Yearly mortality estimated from the IPD dataset and patients with CPA and NTM- lung disease

CPA with NTM-LD	Overall mortality	First-year mortality (n)	First-year at risk (N)	Second-year mortality (n)	Second-year at risk (N)	Third-year mortality (n)	Third-year at risk (N)	Fourth-year mortality (n)	Fourth-year at risk (N)	Fifth-year mortality (n)	Fifth-year at risk (N)
Furuuchi et al	12	8	17	2	8	1	5	1	3	0	1
Iqbal et al	0	0	1	0	1	0	1	0	1	0	1
Aguilar-company et al	0	0	0	0	0	0	0	0	0	0	0
Kimura et al	35	14	87	6	56	10	47	2	31	2	21
Kosmidis et al	1	0	5	1	5	0	4	0	2	0	2

Lowes et al	20	10	37	4	25	4	19	2	9	0	1
Muntean u et al	0	0	0	0	0	0	0	0	0	0	0
Su et al	0	0	0	0	0	0	0	0	0	0	0
Takeda et al	5	2	9	0	7	3	5	0	2	0	0
Tashiro et al	21	9	40	3	26	3	20	3	11	2	7
Bongomin et al	1	1	23	0	0	0	0	0	0	0	0
de Oliveira et al	1	0	8	1	8	0	2	0	0	0	0
Despois et al	1	1	4	0	1	0	0	0	0	0	0
Godet et al	0	0	12	0	10	0	10	0	9	0	7
Uzunhan et al	0	0	0	0	0	0	0	0	0	0	0

Table 17: Yearly mortality estimated from the IPD dataset and patients with CPA and bronchiectasis

CPA with bronchiectasis	Overall mortality	First-year mortality (n)	First-year at risk (N)	Second-year mortality (n)	Second-year at risk (N)	Third-year mortality (n)	Third-year at risk (N)	Fourth-year mortality (n)	Fourth-year at risk (N)	Fifth-year mortality (n)	Fifth-year at risk (N)
Furuuchi et al	0	0	0	0	0	0	0	0	0	0	0
Iqbal et al	5	3	34	0	22	0	22	1	19	0	17
Aguilar-company et al	16	13	26	3	10	0	6	0	4	0	2
Kimura et al	15	5	46	3	32	2	29	2	24	2	15

Kosmidis et al	0	0	0	0	0	0	0	0	0	0	0
Lowes et al	14	7	58	3	46	0	31	2	27	1	16
Munteanu et al	9	4	25	1	21	4	20	0	0	0	0
Su et al	11	5	46	1	39	0	34	0	30	1	28
Takeda et al	2	1	3	1	2	0	1	0	1	0	1
Tashiro et al	7	3	16	0	11	1	11	2	8	1	5
Bongomin et al	0	0	31	0	0	0	0	0	0	0	0
de Oliveira et al	3	0	76	3	52	0	14	0	4	0	4
Despois et al	0	0	5	0	2	0	0	0	0	0	0
Godet et al	1	1	9	0	5	0	3	0	3	0	2
Uzunhan et al	0	0	0	0	0	0	0	0	0	0	0

Table 18: Yearly mortality estimated from the IPD dataset and patients with CPA and ILD (interstitial lung disease)

CPA with ILD	Overall mortality	First-year mortality (n)	First-year at risk (N)	Second-year mortality (n)	Second-year at risk (N)	Third-year mortality (n)	Third-year at risk (N)	Fourth-year mortality (n)	Fourth-year at risk (N)	Fifth-year mortality (n)	Fifth-year at risk (N)
Furuuchi et al	2	1	2	1	1	0	0	0	0	0	0
Iqbal et al	4	4	4	0	0	0	0	0	0	0	0
Aguilar-company et al	5	5	9	0	4	0	3	0	2	0	1
Kimura et al	34	16	53	6	31	6	22	2	14	3	7
Kosmidis et al	0	0	3	0	3	0	3	0	3	0	3

Lowes et al	0	0	0	0	0	0	0	0	0	0	0
Muntean u et al	0	0	1	0	1	0	1	0	0	0	0
Su et al	0	0	0	0	0	0	0	0	0	0	0
Takeda et al	4	1	9	1	8	2	4	0	2	0	1
Tashiro et al	15	8	23	5	14	1	7	1	5	0	1
Bongomin et al	1	1	22	0	0	0	0	0	0	0	0
de Oliveira et al	0	0	6	0	6	0	0	0	0	0	0
Despois et al	1	1	1	0	0	0	0	0	0	0	0
Godet et al	2	1	8	0	5	0	5	1	4	0	1
Uzunhan et al	28	2	65	2	57	2	55	0	51	4	51

Table 19: Yearly mortality estimated from the IPD dataset and patients with CPA and malignancy

Malignancy associated CPA	Overall mortality	First-year mortality (n)	First-year at risk (N)	Second-year mortality (n)	Second-year at risk (N)	Third-year mortality (n)	Third-year at risk (N)	Fourth-year mortality (n)	Fourth-year at risk (N)	Fifth-year mortality (n)	Fifth-year at risk (N)
Furuuchi et al	4	2	5	1	3	1	1	0	0	0	0
Iqbal et al	1	0	2	1	2	0	1	0	1	0	1
Aguilar-company et al	13	12	15	0	2	0	2	1	2	0	1
Kimura et al	17	8	38	2	25	4	20	2	12	1	6

Kosmidis et al	3	0	7	1	7	2	6	0	2	0	1
Lowes et al	17	9	40	2	29	0	22	5	17	0	7
Munteanu et al	0	0	0	0	0	0	0	0	0	0	0
Su et al	10	6	15	1	8	2	7	0	4	1	4
Takeda et al	1	0	6	1	6	0	3	0	3	0	2
Tashiro et al	20	8	27	5	15	2	10	2	7	2	5
Bongomin et al	1	1	13	0	0	0	0	0	0	0	0
de Oliveira et al	0	0	4	0	3	0	2	0	0	0	0
Despois et al	0	0	3	0	0	0	0	0	0	0	0
Godet et al	0	0	2	0	2	0	2	0	1	0	1
Uzunhan et al	0	0	0	0	0	0	0	0	0	0	0

Table 20: Yearly mortality estimated from the IPD dataset and patients with post-thoracic surgery CPA

Post-thoracic surgery CPA	Overall mortality	First-year mortality (n)	First-year at risk (N)	Second-year mortality (n)	Second-year at risk (N)	Third-year mortality (n)	Third-year at risk (N)	Fourth-year mortality (n)	Fourth-year at risk (N)	Fifth-year mortality (n)	Fifth-year at risk (N)
Furuuchi et al	0	0	0	0	0	0	0	0	0	0	0
Iqbal et al	0	0	5	0	4	0	3	0	3	0	3
Aguilar-company et al	4	3	4	1	1	0	0	0	0	0	0

Kimura et al	13	7	33	1	20	4	17	1	9	0	3
Kosmidis et al	0	0	0	0	0	0	0	0	0	0	0
Lowes et al	12	3	54	4	49	1	34	2	28	0	19
Munteanu et al	1	1	5	0	4	0	4	0	0	0	0
Su et al	0	0	3	0	3	0	3	0	3	0	2
Takeda et al	5	1	12	2	9	1	6	1	5	0	3
Tashiro et al	12	6	21	4	14	0	8	1	7	1	4
Bongomin et al	2	2	17	0	0	0	0	0	0	0	0
de Oliveira et al	0	0	11	0	8	0	5	0	1	0	1
Despois et al	0	0	1	0	0	0	0	0	0	0	0
Godet et al	1	0	15	0	11	0	10	0	8	0	6
Uzunhan et al	0	0	0	0	0	0	0	0	0	0	0

Table 21: Yearly mortality estimated from the IPD dataset and patients with CPA and pneumothorax

CPA with pneumothorax	Overall mortality	First-year mortality (n)	First-year at risk (N)	Second-year mortality (n)	Second-year at risk (N)	Third-year mortality (n)	Third-year at risk (N)	Fourth-year mortality (n)	Fourth-year at risk (N)	Fifth-year mortality (n)	Fifth-year at risk (N)
Furuuchi et al	0	0	0	0	0	0	0	0	0	0	0
Iqbal et al	2	1	5	1	3	0	2	0	1	0	1

Aguilar-company et al	0	0	0	0	0	0	0	0	0	0	0
Kimura et al	5	4	9	0	5	0	5	0	3	0	1
Kosmidis et al	0	0	0	0	0	0	0	0	0	0	0
Lowes et al	8	4	51	2	42	0	26	1	21	0	12
Munteanu et al	0	0	2	0	2	0	2	0	0	0	0
Su et al	0	0	0	0	0	0	0	0	0	0	0
Takeda et al	1	0	2	1	2	0	1	0	1	0	1
Tashiro et al	10	4	14	1	9	0	7	1	3	0	2
Bongomin et al	0	0	21	0	0	0	0	0	0	0	0
de Oliveira et al	0	0	0	0	0	0	0	0	0	0	0
Despois et al	1	0	3	0	2	0	2	0	1	0	0
Godet et al	4	2	12	1	10	0	9	0	6	0	3
Uzunhan et al	0	0	0	0	0	0	0	0	0	0	0

Table 22: Yearly mortality estimated from the IPD dataset and patients with CPA and autoimmune disease

CPA with autoimmune disease	Overall mortality	First-year mortality (n)	First-year at risk (N)	Second-year mortality (n)	Second-year at risk (N)	Third-year mortality (n)	Third-year at risk (N)	Fourth-year mortality (n)	Fourth-year at risk (N)	Fifth-year mortality (n)	Fifth-year at risk (N)
Furuuchi et al	2	2	2	0	0	0	0	0	0	0	0

Iqbal et al	0	0	1	0	0	0	0	0	0	0	0
Aguilar-company et al	2	2	2	0	0	0	0	0	0	0	0
Kimura et al	7	2	13	3	9	0	4	1	4	1	1
Kosmidis et al	4	3	9	1	6	0	5	0	2	0	1
Lowes et al	13	4	35	3	27	0	20	3	17	0	8
Munteanu et al	0	0	0	0	0	0	0	0	0	0	0
Su et al	5	2	14	2	12	1	9	0	6	0	6
Takeda et al	2	0	4	0	4	2	3	0	0	0	0
Tashiro et al	5	1	11	4	9	0	5	0	2	0	2
Bongomin et al	3	3	29	0	0	0	0	0	0	0	0
de Oliveira et al	0	0	12	0	9	0	2	0	0	0	0
Despois et al	1	1	1	0	0	0	0	0	0	0	0
Godet et al	1	0	1	1	1	0	0	0	0	0	0
Uzunhan et al	0	0	0	0	0	0	0	0	0	0	0

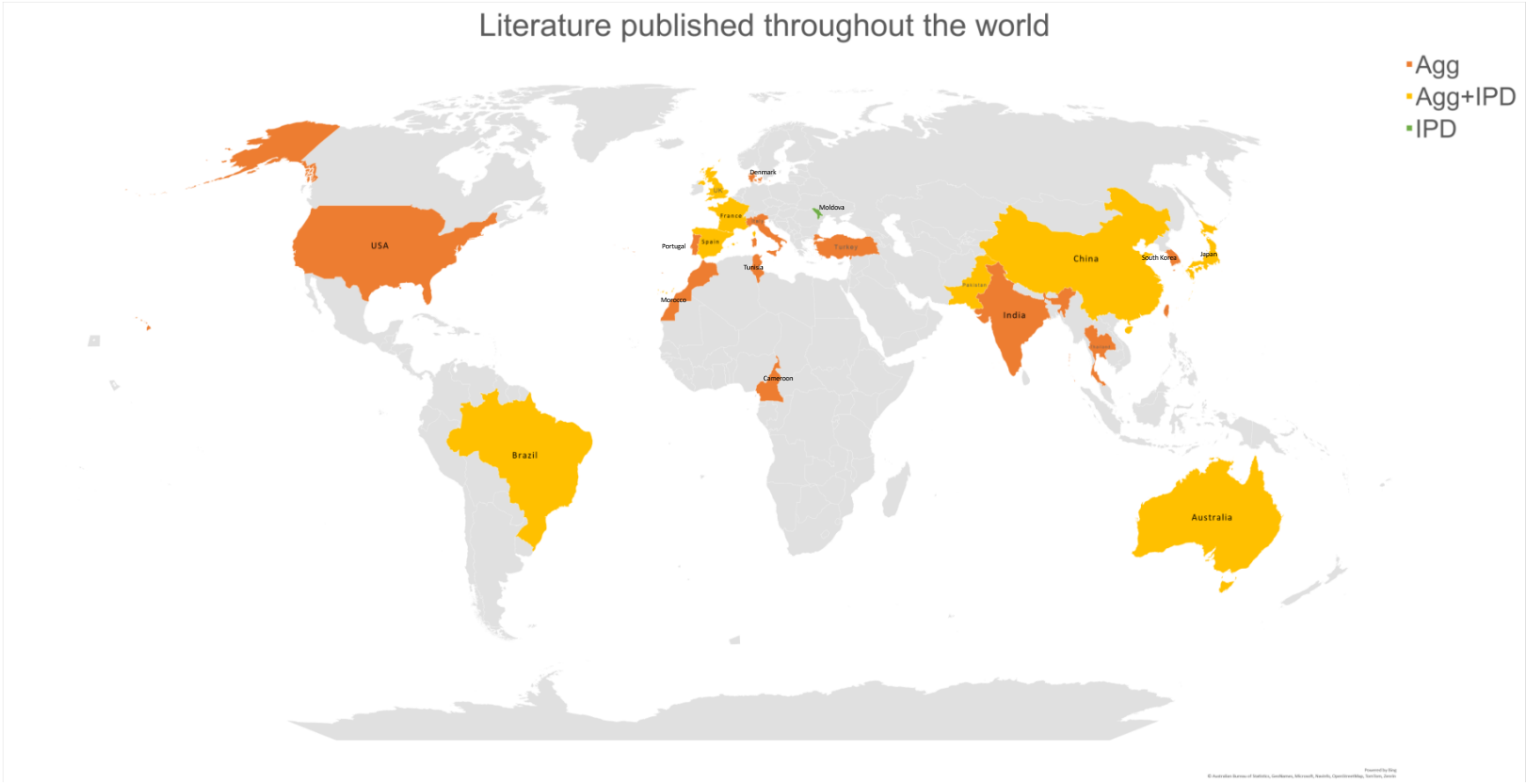

Figure 2: Geographical distribution of literature published on mortality published in patients with chronic pulmonary aspergillosis

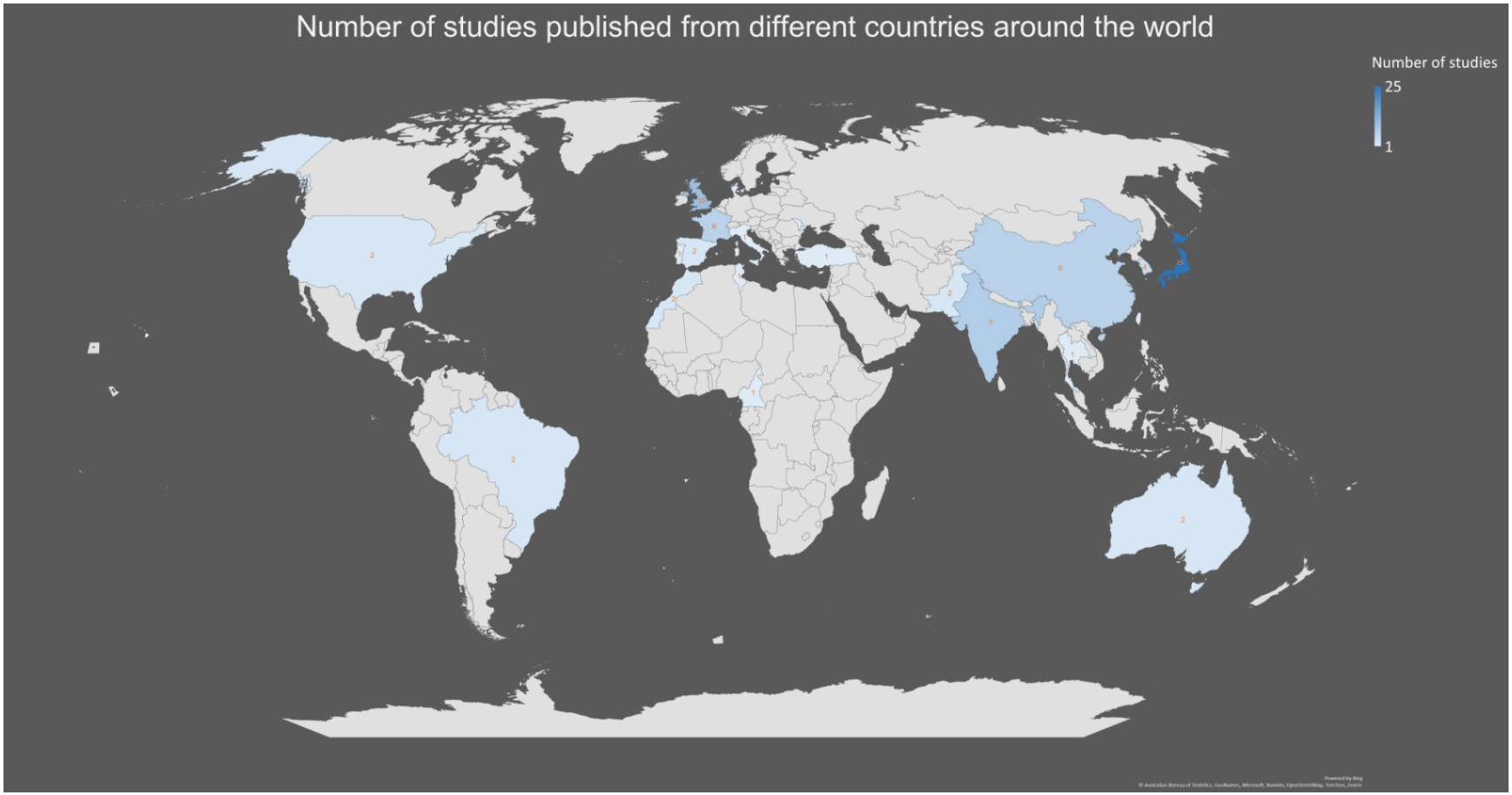

Figure 3: Map showing the number of studies reporting mortality data in CPA published from different countries.

Significant subgroup analysis:

Subgroup analysis was done to investigate heterogeneity. WHO region and Human Development Index (HDI) of the country were used to account for the demographic and socioeconomic factors. Overall mortality was significantly different among patients from different HDI categories. Studies from the Southeast Asian region (13%, 0- 39%. I2= 98.7%, P<0.01, Supplementary 2 figure 3) reported the lowest mortality, predominantly formed by Indian studies. High HDI countries (statistically significant) and studies from Western Pacific, American, and European cohorts reported higher mortality (numerically higher). Medical cohorts (29%, 24- 34%, i2= 95.1%, p<0.01) had significantly higher mortality compared to surgical cohorts (8%, 4- 13%, i2= 69.9%, p<0.01, Supplementary 2 figure 7). There was no difference based on the risk of bias in the studies and source of data. When sub-grouped as per decade of publication, there was highest overall and one-year mortality in the pre-2000 studies with a decreasing trend in the subsequent decades, however, five-year mortality remained similar with passing time.

Subgrouping by study type revealed significantly lower mortality rates in prospective (14%, 6- 24%, i2= 82.4%, p<0.001) and randomized controlled trials (10%, 6- 14%, i2=.), Supplementary 2 Figure 4. The studies which recruited patients only from out-patients clinics reported the least mortality (8%, 4- 12%, i2= 69.9%, p=0.02), while those with only admitted patients – the highest (29%, 23- 36%, i2=88.6%, p<0.001), Supplementary 2 figure 10. Subgrouping by age revealed increasing mortality with increasing age. Grouping of studies by the predominant underlying lung disease found those studies with predominant malignancy had 54% mortality (45- 63%, 12=.), ILD 44% (35- 52%, i2= 61.7%, p=0.02), and NTM-LD 46% (24- 69%, i2=87.8%, p<0.001); higher compared to the other subgroups. Studies with predominant underlying post-TB lung disease had 23% (17- 29%, i2=94.2%, p<0.001) overall mortality (Supplementary 2 Figure 8). However, there was persistent intragroup heterogeneity in most subgroups, making data interpretation uncertain.

The incidence density of mortality (per 1000 patient-years) was not significantly different in studies with various study designs even with differing predominant underlying predisposing conditions. Studies with a higher mean age had a significantly higher incidence of deaths (p= 0.03). Mortality was also significantly higher in studies from very high HDI countries (126.4 per 1000 patient-years, p<0.01) and Western Pacific (127.3 per 1000 patient-years, p<0.01), (Supplementary 2 figure 32).

Risk factors for mortality among patients with CCPA:

We performed a multivariable stratified Cox regression analysis among 545 patients with CCPA, revealing age at diagnosis, use of voriconazole, and underlying malignancy to be significantly associated with mortality. The presence of post-TB lung disease was protective. In this group of CCPA patients, the presence of underlying NTM-LD was also associated with reduced hazards of mortality. (Table 20)

Table 23: Stratified Cox regression model (n=747)

Variable	Haz. ratio	Robust std. err.	z	p-value	[95% conf.	interval]
Age of diagnosis	1.025474	0.0055444	4.65	<0.001	1.014665	1.036399
Male	0.9421799	0.147002	-0.38	0.703	0.6939475	1.279208
Aspergilloma*	1 (ref)					
SAIA	2.519887	0.8392325	2.78	0.006	1.311879	4.840257
CCPA	2.07543	0.5144094	2.95	0.003	1.276827	3.373527
CFPA	2.448145	1.524967	1.44	0.151	0.7221337	8.299589
Aspergillus nodule	1.174004	0.543147	0.35	0.729	0.4740951	2.907191
Surgical +- medical#	0.8000183	0.5150078	-0.35	0.729	0.2265391	2.825249
Itra*	1 (ref)					
Vori	1.560339	0.1688306	4.11	<0.001	1.26217	1.928946
Itra f/b vori	0.6939229	0.2580199	-0.98	0.326	0.3348195	1.438175
Vori f/b itra	1.344795	0.3475456	1.15	0.252	0.8103518	2.231714
Underlying disease tuberculosis	0.7660576	0.0811421	-2.52	0.012	0.6224447	0.9428055
Underlying disease emphysema	1.214141	0.3909552	0.6	0.547	0.6459233	2.282219
Underlying disease NTM LD	0.6790512	0.1662326	-1.58	0.114	0.420269	1.09718
Underlying disease ILD	1.292609	0.5064293	0.66	0.512	0.5997585	2.785853
Underlying disease cancer	1.765673	0.423807	2.37	0.018	1.103062	2.826315

Baseline with HR of 1, # Baseline compared to no treatment

Table 24: Stratified Cox regression model with age as per decades (n= 747)

Variable	Haz. ratio	Robust std. err.	z	P>z	[95% conf.	interval]
Age as per decade	1.247261	0.0556004	4.96	<0.001	1.142912	1.361138
Male	0.9392661	0.1443536	-0.41	0.684	0.6949755	1.269427
Aspergilloma*	1 (ref)					

SAIA	2.506833	0.8483451	2.72	0.007	1.29142	4.866124
CCPA	2.002814	0.5010272	2.78	0.005	1.226599	3.270232
CFPA	2.412481	1.553001	1.37	0.171	0.6831478	8.519479
Aspergillus nodule	1.171468	0.5407197	0.34	0.732	0.4740646	2.894832
Surgical +- medical#	0.7853743	0.5068505	-0.37	0.708	0.2216888	2.782336
Itra*	1 (ref)					
Vori	1.581446	0.1675233	4.33	<.001	1.28495	1.946358
Itra f/b vori	0.6731338	0.2613726	-1.02	0.308	0.3144752	1.440842
Vori f/b itra	1.339095	0.322388	1.21	0.225	0.8353798	2.146539
Underlying disease tuberculosis	0.7627467	0.0755004	-2.74	0.006	0.628238	0.9260544
Underlying disease emphysema	1.222227	0.3805221	0.64	0.519	0.6639621	2.249887
Underlying disease NTM LD	0.6932512	0.1719669	-1.48	0.14	0.426327	1.127297
Underlying disease ILD	1.279671	0.4912731	0.64	0.521	0.6029996	2.715686
Underlying disease cancer	1.763676	0.4087907	2.45	0.014	1.119759	2.777878

* Baseline with HR of 1, # Baseline compared to no treatment

Table 25: Stratified Cox regression model exploring risk factors of mortality in patients with CCPA (n= 575)

Variable	Haz. ratio	Robust std. err.	z	P>z	[95% conf.	interval]
Age of diagnosis	1.027995	0.0070076	4.05	<0.001	1.014352	1.041822
Male	0.9851588	0.1746301	-0.08	0.933	0.6960196	1.394412
Surgical +- medical#	0.6747479	0.6302584	-0.42	0.674	0.1081593	4.209389
Itra*	1 (ref)					
Vori	1.596678	0.2292782	3.26	0.001	1.205001	2.115667
Itra f/b vori	0.8369478	0.3561166	-0.42	0.676	0.3635104	1.926992
Vori f/b itra	0.7608665	0.4057781	-0.51	0.608	0.2675184	2.16403
Underlying disease tuberculosis	0.7627606	0.0975745	-2.12	0.034	0.5936084	0.9801136

Underlying disease emphysema	1.211305	0.4585473	0.51	0.613	0.5768007	2.543791
Underlying disease NTM LD	0.725484	0.0898252	-2.59	0.01	0.5691635	0.9247378
Underlying disease ILD	1.00663	0.5751936	0.01	0.991	0.3284648	3.084969
Underlying disease cancer	1.820652	0.42361	2.58	0.01	1.153927	2.872602

* Baseline with HR of 1, # Baseline compared to no treatment

Table 26: Multivariable meta-regression model

Variable	Coefficient	Std. err.	z	P>z	[95% conf.	interval]
Age of diagnosis	-0.0129975	0.0179934	-0.72	0.47	-0.0482639	0.0222689
HDI	-0.1446007	0.6399894	-0.23	0.821	-1.398957	1.109755
Proportion of patients with underlying malignancy	2.39025	1.108555	2.16	0.031	0.2175226	4.562977
Proportion of patients with ILD	-1.432648	1.308456	-1.09	0.274	-3.997174	1.131879
Proportion of patients with Post-TB lung disease	0.1757002	0.2596022	0.68	0.499	-0.3331107	0.6845111
Proportion of patients treated surgically	-0.0124807	0.0074637	-1.67	0.094	-0.0271092	0.0021479
_cons	1.243825	1.135839	1.1	0.273	-0.9823787	3.470028

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