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

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).

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See **Online** for appendix 1

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).

	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)

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[9,10,12–16,20–27,29–32,34–37,39,40,43,44,47–50,53,55–58,60–73,75–77,79–81,83–86,88,89] 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%).

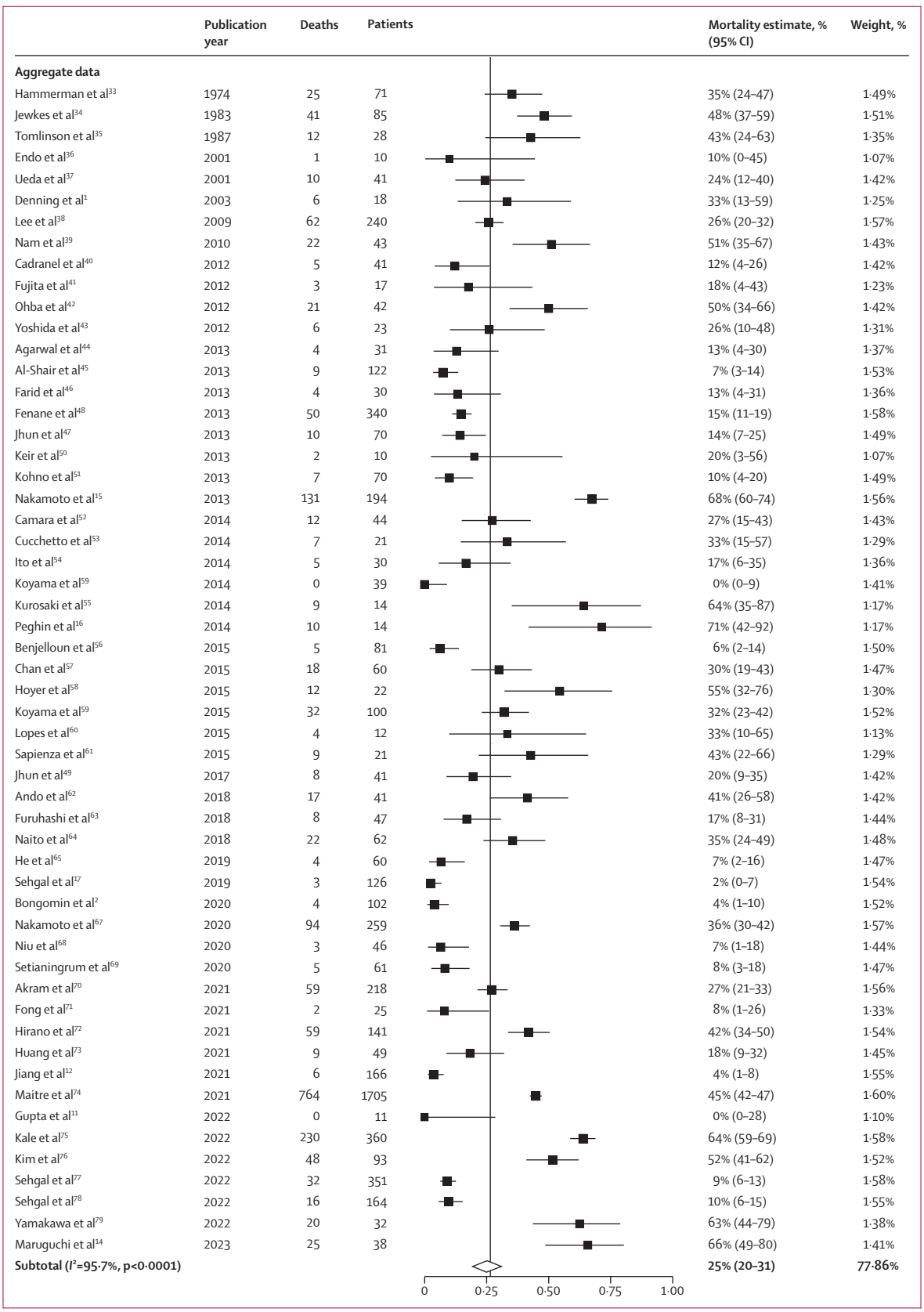
In our IPD cohort, post-tuberculosis lung disease was seen in 676 (37·0%) of 1827 patients, with higher proportions in cohorts from Pakistan (57 [76·0%] of 75) and Brazil (70 [76·9%] of 91). COPD was seen in 586 (32·2%) of 1820. Non-tuberculous mycobacterial lung disease was the underlying lung disease 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.

	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**



	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%**

0 0·25 0·50 0·75 1·00

(Figure 1 continues on next page)

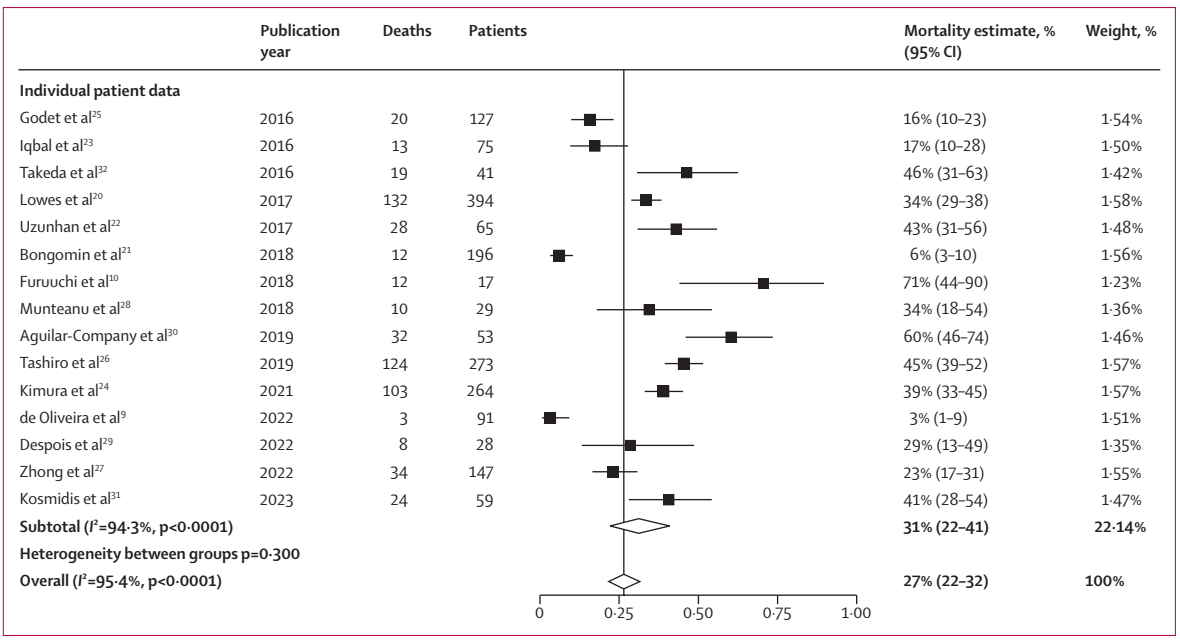


Figure 1: **Overall mortality in chronic pulmonary aspergillosis in included studies (n=70)**

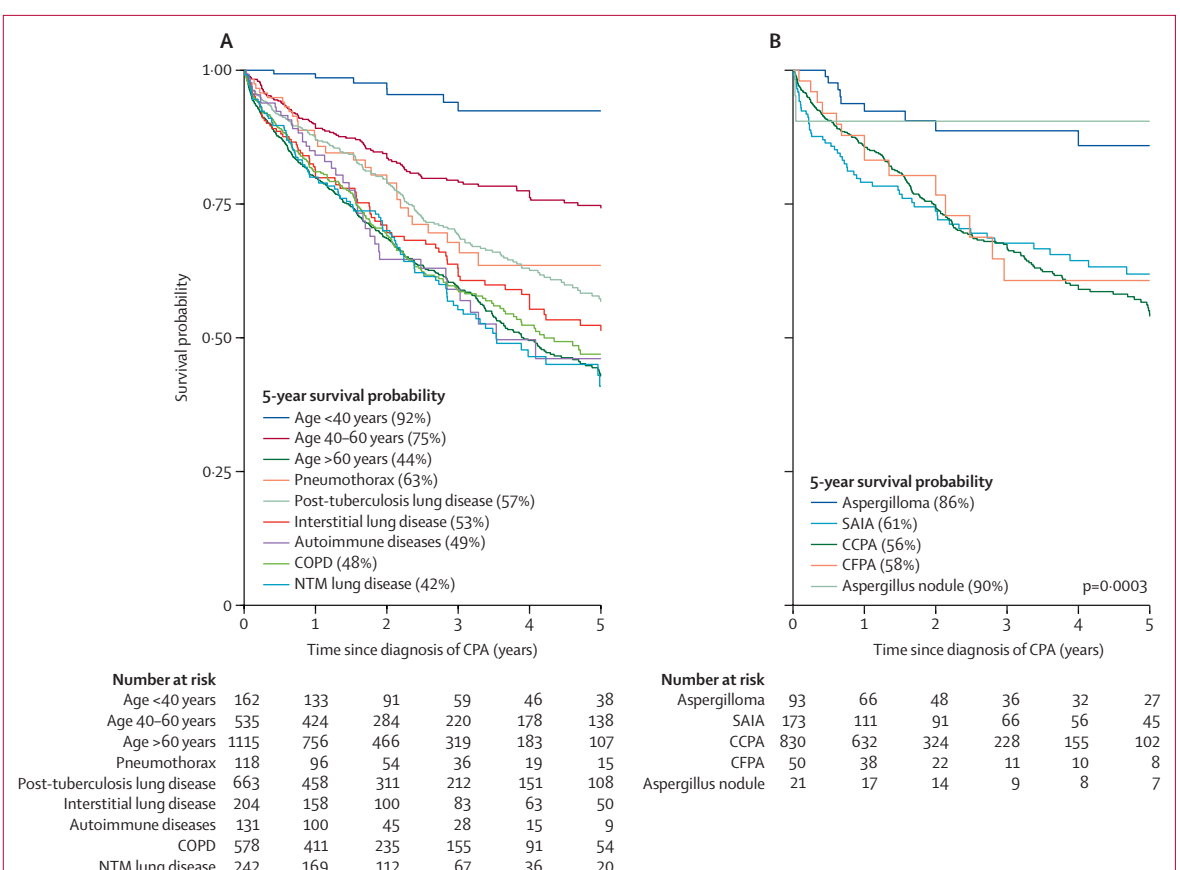


Figure 2: **Kaplan–Meier survival estimates**

(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)	89·5%	<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)

	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**

Among the patients managed with oral antifungal 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).

See Online for appendix 2

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

	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**

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 (–0·213 [–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).

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 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

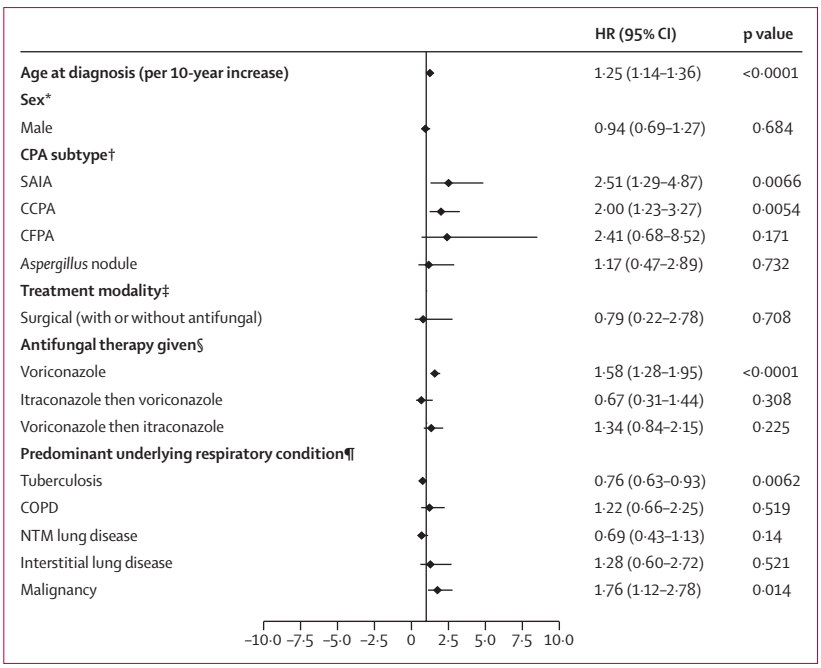


Figure 3: **Stratified multivariable Cox proportional hazards analysis of mortality**
HRs are adjusted for age at diagnosis (per 10-year increase), sex, CPA subtype, treatment modality, antifungal received, and underlying respiratory condition (tuberculosis, COPD, NTM lung disease, interstitial lung 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.

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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