

Surgical management of chronic pulmonary aspergillosis in Africa: A systematic review of 891 cases

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Abstract

Chronic pulmonary aspergillosis (CPA) is an emerging fungal infectious disease of public health importance. We conducted a systematic review of studies reporting the outcomes of patients with CPA managed surgically in Africa. A search of Medline, Embase, Web of Science, Google Scholar and African Journals Online was conducted to identify studies indexed from inception to June 2021 that examined surgical management of CPA in Africa. All articles that presented primary data, including case reports and case series, were included. We excluded review articles. A total of 891 cases (557 males (62.5%), mean age 39.3 years) extracted from 27 eligible studies published between 1976 and 2020 from 11 African countries were included. Morocco (524, 59%) and Senegal (99, 11%) contributed the majority of cases. Active or previous pulmonary tuberculosis was reported in 677 (76.0%) cases. Haemoptysis was reported in 682 (76.5%) cases. Lobectomy (either unilateral or bilateral, $n = 493$, 55.3%), pneumonectomy ($n = 154$, 17.3%) and segmentectomy ($n = 117$, 13.1%) were the most frequently performed surgical procedures. Thirty (4.9%) cases from South Africa received bronchial artery embolisation. Empyema ($n = 59$, 27.4%), significant haemorrhage ($n = 38$, 173.7%), incomplete lung expansion ($n = 26$, 12.1%) and prolonged air leak ($n = 24$, 11.2%) were the most frequent complications. Overall, 45 (5.1%) patients died. The causes of death included respiratory failure ($n = 14$), bacterial superinfection/sepsis ($n = 10$), severe haemorrhage ($n = 5$), cardiopulmonary arrest ($n = 3$) and complications of chronic obstructive pulmonary disease ($n = 3$). The cause of death was either unknown or unspecified in 9 cases. We conclude that surgical treatment had very low mortality rates and maybe considered as first-line management option in centres with experience and expertise in Africa.

KEYWORDS

Africa, pulmonary aspergilloma, surgical management

1 | INTRODUCTION

Chronic pulmonary aspergillosis (CPA) is a heterogeneous, debilitating and slowly progressive lung infection that commonly complicates chronic cavitary lung disease, notably pulmonary tuberculosis (PTB).¹ CPA complicates over 1.2 million cases of PTB, with a 15%

annual mortality rate.² However, the true burden of CPA in Africa, a continent with a high burden of PTB, is unknown. Findings from two epidemiological studies from Africa suggest a prevalence of PTB-associated CPA to range between 8.7% and 13.7%.^{3,4} Therefore, PTB may be the most important driver of the burden of CPA in Africa.

The radiological phenotypes of CPA include 1) *Aspergillus* nodule—characterised by a single or multiple nodules which are often found incidentally on chest imaging for other indications, 2) simple aspergilloma, previously termed “surgical aspergilloma”, describes a single, well-circumscribed cavity with a fungal ball (aspergilloma), 3) chronic cavitary pulmonary aspergillosis (CCPA) is characterised by expansion of existing and creation of new cavities with or without an aspergilloma, and 4) chronic fibrosing pulmonary aspergillosis (CFPA) which is a late-stage disease and often a complication of CCPA with extensive pleuro-parenchymal fibrosis.¹

Much as a majority of patients with CPA are managed medically with long-term antifungal therapy, surgical management is indicated for patients with *Aspergillus* nodules and in those with simple aspergilloma with curative intent.⁵⁻⁷ Patients with CCPA or CFPA with life-threatening haemoptysis and those who fail medical treatment due to intolerance or multi-class antifungal resistance may also benefit from surgical interventions.^{5,7}

In the past few decades, several case reports and case series on surgical management of CPA in Africa have been published.⁸⁻¹⁴ Given the limited access to and availability of essential antifungal agents for the management of CPA in Africa, it is important that outcomes of surgically managed CPA patients are evaluated to inform clinicians on the surgical management of CPA and outcomes in Africa. In this study, therefore, we sought to systematically review and summarise outcomes of all published cases of CPA managed surgically in Africa.

2 | METHODS

2.1 | Study design

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁵ We registered the protocol on PROSPERO (CRD42021238648) as part of a large systematic review to evaluate underlying risk factors and comorbidities in patients with CPA.

2.2 | Data sources and search strategy

Using the following Medical Subject Headings (MeSH) terms: “chronic pulmonary aspergillosis,” “CPA,” “simple aspergilloma,” “pulmonary aspergilloma,” “lung aspergilloma,” “pulmonary mycetoma,” “lung mycetoma,” “simple aspergilloma,” “complex aspergilloma,” and “Africa”, we searched all studies published from inception to June 2021 in Embase, Medline, Google Scholar and African Journals Online databases. In addition, manual literature search of all the references of the included articles was performed to find relevant studies. The search was limited to human studies, and no language restriction was applied.

2.3 | Inclusion and exclusion criteria

We included all primary data from cross-sectional studies, cohort studies, case-control studies, retrospective studies, single case reports and case series. Review articles were excluded.

2.4 | Data extraction

The studies found through databases that were duplicates were removed using the Healthcare Database Advanced Search (HDAS) programme (National Institute of Clinical Excellence). Records were initially screened by title and abstract by two independent reviewers (R. O and F.B) to exclude those not related to the current study. The full text of potentially eligible records was retrieved and examined. Any discrepancies were resolved by consensus by RK and JBB.

We extracted data on study location (country), study period, clinical presentation, demographics, surgical procedure, underlying conditions, outcomes and follow-up. We used Excel spreadsheet to summarise the extracted data. In reports where patients had both medical and surgical interventions presented, only details of patients managed surgically were extracted.

2.5 | Risk of bias assessment

With regard to risk of bias assessment, we did not judge the study quality given the number of case reports and small case series.

3 | RESULTS

3.1 | Study selection

The database search retrieved 376 citations. We then removed duplicates and remained with 108 citations from which relevant studies were selected for the review. Their potential relevance was examined using a title and abstract screening to remove studies that were clearly not related to the topic. Sixty-one citations were excluded as irrelevant to the subject. The full papers of the remaining 48 citations were assessed to select those that included data about the surgical management of CPA in Africa. These criteria excluded 21 studies and left 27 studies that were included in the final analysis (Figure 1).

3.2 | Characteristics of studies reviewed

A summary of all the 27 eligible studies published between 1976 and 2020 from 11 countries that were included in the systematic review is provided in Table 1. Of these, seven studies (25.9%) were from

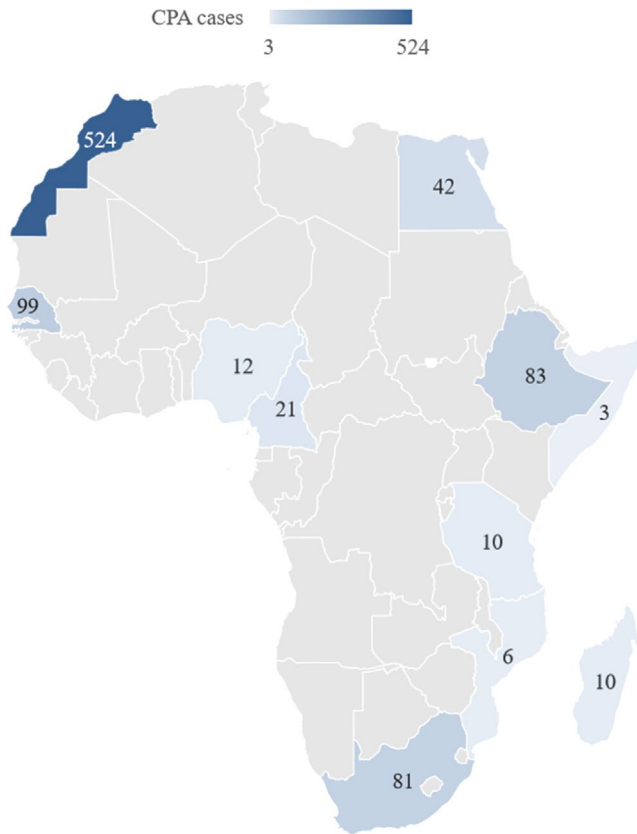


FIGURE 1 Distribution of chronic pulmonary aspergillosis cases managed surgically in Africa. (Grey—no data available)

South Africa, five (18.5%) from Morocco, four (14.8%) from Senegal, with Cameroon, Ethiopia and Nigeria having two studies each (7.7%). The study designs were retrospective in 16 studies (59.3%) and prospective cohort in 5 studies (18.5%) with the rest being case series ($n = 4$, 14.8%) or case reports ($n = 2$, 7.4%).

3.3 | Clinical features of cases of CPA managed surgically in Africa

A total of 891 cases of CPA were managed surgically in Africa between 1976 and 2019. Most of the patients were male ($n = 557$, 62.5%), and the mean age was 39.3 years. The distribution of the total number of cases of CPA managed surgically in Africa is shown in Figure 2. Notably, 434 (54%) and 99 (12%) of the total cases were from Morocco and Senegal, respectively.

The main presenting complaint was haemoptysis that was either severe or recurrent in 682 cases (76.5%), Figure 2. Cough without haemoptysis (20.0%), difficulty in breathing (14.7%) and chest pain (13.1%) were also frequent (Figure 3). The documented underlying comorbidities/risk factors were active or healed PTB in 677 patients (76.0%), cigarette smoking ($n = 57$, 6.4%), diabetes mellitus ($n = 18$, 2.0%), bronchiectasis ($n = 47$, 5.3%), human immunodeficiency virus infection ($n = 8$, 0.9%), chronic obstructive pulmonary disease

(COPD) ($n = 4$, 0.4%), lung abscess ($n = 9$, 1.0%), air cyst ($n = 4$, 0.4%) and pyopneumothorax ($n = 2$, 0.2%). Malignancy and pulmonary fibrosis were documented in one patient (0.1%) each.

The diagnosis of CPA was made either radiologically in 27 studies (100%) and/or histopathological ($n = 10$, 37.0%) and/or microbiologically/serologically ($n = 7$, 25.9%)

3.4 | Surgical procedures performed for CPA cases in Africa

Lobectomy (either unilateral or bilateral, $n = 493$, 55.3%), pneumonectomy ($n = 154$, 17.3%) and segmentectomy ($n = 117$, 13.1%) were the most frequently performed surgical procedures. All bronchial artery embolisation (BAE) procedures (30, 4.9%) were performed in studies from South Africa alone. Other modalities performed included wedge resection, cavernostomy, decortication, endobronchial valve placement and thoracoplasty, either as a single procedure or combined depending on the patients' condition (Table 2).

3.5 | Outcomes of CPA cases surgically managed in Africa

A total of 215 complications were reported. Empyema ($n = 59$, 27.4%), significant haemorrhage ($n = 38$, 17.7%), incomplete lung expansion ($n = 26$, 12.1%) and prolonged air leak ($n = 24$, 11.2%) were the most frequent complications. Other infectious complications reported included pneumonia, suppuration and wound infections. Rare complications that were observed included wound dehiscence, bronchopleural fistula, chylothorax, haemothorax, profuse pleurisy, pulmonary effusion and acute lung oedema (Table 2).

Overall, 45 (5.1%) patients died during or following surgery. The causes of death included respiratory failure ($n = 14$), bacterial superinfection/sepsis ($n = 10$), severe haemorrhage ($n = 5$), cardiopulmonary arrest ($n = 3$) and complications of COPD ($n = 3$). The cause of death was either unknown or unspecified in 9 cases. On follow-up, haemostasis was reportedly achieved in most of the patients. Recurrence of haemoptysis was reported in 4 patients in Morocco¹⁶ and a high but unspecified rate of recurrence in patients who underwent BAE in South Africa.¹⁷ Significant recovery was achieved in the rest of the other studies during medium-term follow-up of up to four years.^{11,12,16}

4 | DISCUSSION

The frequency of CPA in Africa is increasing, mainly secondary to active or healed PTB and mostly reported in case reports or series.³⁷ Oral itraconazole (400mg daily for at least 6 months) is the first-line therapy. However, a comprehensive management approach requires a combination of close monitoring, as well as medical (usually oral antifungals), radiological and surgical

TABLE 1 Summary of studies included

Study /reference	Study Type	Country	Study Period	Mean Age (Years)	Cases	Male	Female	Radiology	Histopathology	Serology	Died
Alemu et al (2020) ¹⁰	Retrospective	Ethiopia	2014 - 2019	35.2	72	46	26	Yes	No	No	3 (4.2%)
Harmouchi et al (2019) ¹⁸	Retrospective	Morocco	2009 - 2018	40.5	79	57	22	Yes	Yes	Yes	2 (2.5%)
Nonga et al (2018) ¹⁹	Case Report	Cameroon	-	47.0	1	1	0	Yes	No	No	0 (0%)
Nonga et al (2018) ⁹	Prospective	Cameroon	2012 - 2015	30.0	20	17	3	Yes	Yes	No	1 (5%)
Salami et al (2018) ²⁰	Retrospective	Nigeria	2014 - 2017	32.0	2	1	1	Yes	No	No	0 (0%)
Masoud et al (2017) ²¹	Retrospective	South Africa	2013 - 2015	46.6	23	15	8	Yes	Yes	No	0 (0%)
Issoufoua et al (2016) ²²	Case Series	Morocco	2009 - 2014	38.8	6	-	-	Yes	No	No	NS
El Hammoumi et al (2015) ²³	Retrospective	Morocco	2006 - 2014	37.8	111	93	18	Yes	No	No	2 (1.8%)
Ba et al (2015) ⁸	Retrospective	Senegal	2004 - 2008	43.4	35	28	7	Yes	Yes	Yes	3 (8.6%)
Benjelloun et al (2015) ¹⁶	Retrospective	Morocco	2003 - 2014	51.0	50	30	20	Yes	Yes	Yes	3 (6%)
Koegelenberg et al (2014) ²⁴	Case report	South Africa	-	30.0	1	1	0	Yes	No	No	0 (0%)
Ade et al (2011) ¹¹	Retrospective	Senegal	2004 - 2008	43.4	35	28	7	Yes	Yes	Yes	0 (0%)
Rakoton et al (2011) ²⁵	Prospective	Madagascar	2006 - 2010	-	10	-	-	Yes	No	Yes	0 (0%)
Gross et al (2009) ²⁶	Prospective	South Africa	-	41.4	5	-	-	Yes	No	No	NS
Bekele et al (2009) ²⁷	Retrospective	Ethiopia	2005 - 2008	38.9	11	9	2	Yes	Yes	No	1 (9.1%)
Brik et al (2008) ¹⁴	Retrospective	Egypt	2001 - 2008	44.0	42	28	14	Yes	Yes	No	1 (2.4%)
van den Heuvel et al (2007) ¹⁷	Retrospective	South Africa	2001 - 2003	-	13	-	-	Yes	No	No	0 (0%)
Hassan et al (2004) ²⁸	Case Series	Somalia	2000 - 2003	-	1	-	-	Yes	No	No	0 (0%)
Caidi et al (2006) ²⁹	Retrospective	Morocco	1982 - 2004	32.0	278	161	117	Yes	Yes	Yes	16 (5.6%)
Corr (2006) ³⁰	Prospective	South Africa	2002 - 2003	36.0	12	9	3	Yes	No	No	0 (0%)
Hassan et al (2004) ³¹	Case Series	Mozambique/ Somalia	-	30.0	8	6	2	Yes	No	No	1 (12.5%)
Falkson et al (2002) ³²	Prospective	South Africa	1989 - 1994	45.0	5	5	0	Yes	No	No	0 (0%)
Mbembati et al (2001) ³³	Retrospective	Tanzania	1986 - 2000	-	10	8	2	Yes	No	No	3 (30%)
Ba et al (2000) ³⁴	Retrospective	Senegal	1991 - 1998	-	24	-	-	Yes	No	No	4 (16.7%)
Conlan et al (1987) ³⁵	Retrospective	South Africa	1982 - 1984	-	22	7	15	Yes	Yes	No	1 (4.5%)
Adebayo et al (1984) ¹²	Retrospective	Nigeria	1977 - 1983	42.2	10	7	4	Yes	No	No	2 (20%)
Kane et al (1976) ³⁶	Case series	Senegal	-	-	5	-	-	Yes	No	Yes	2 (40%)
Overall Summary			1976 - 2019	39.3	891	557 (62.5%)	271 (30.4%)	27 (100%)	10 (37.0%)	7 (25.9%)	45 (5.1%)

FIGURE 2 Presenting complaints among the patients

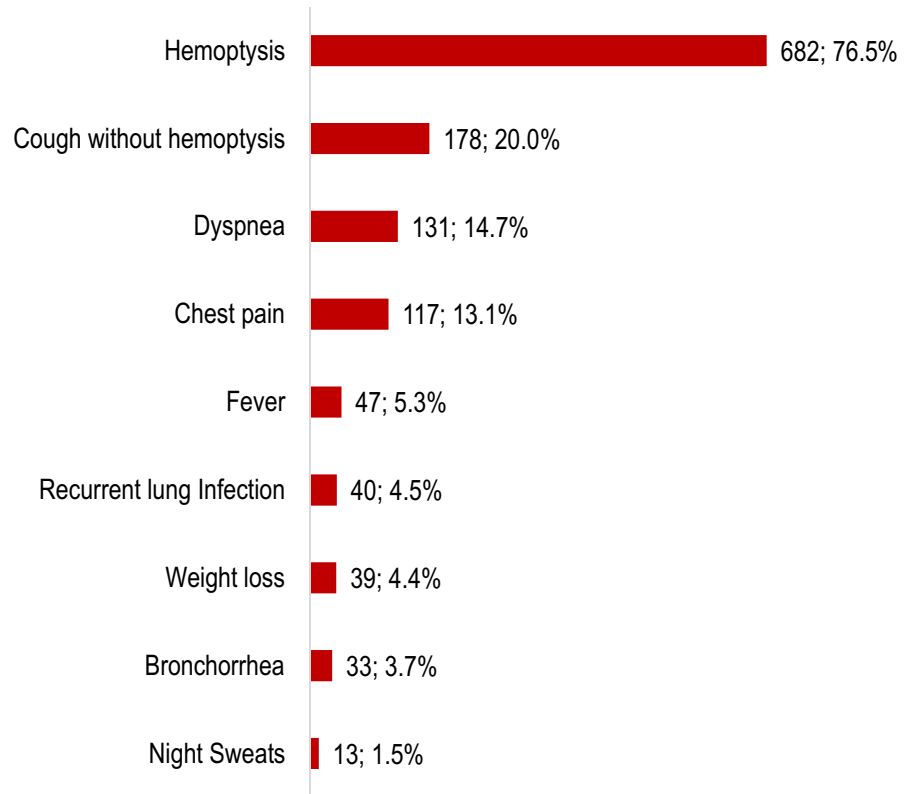
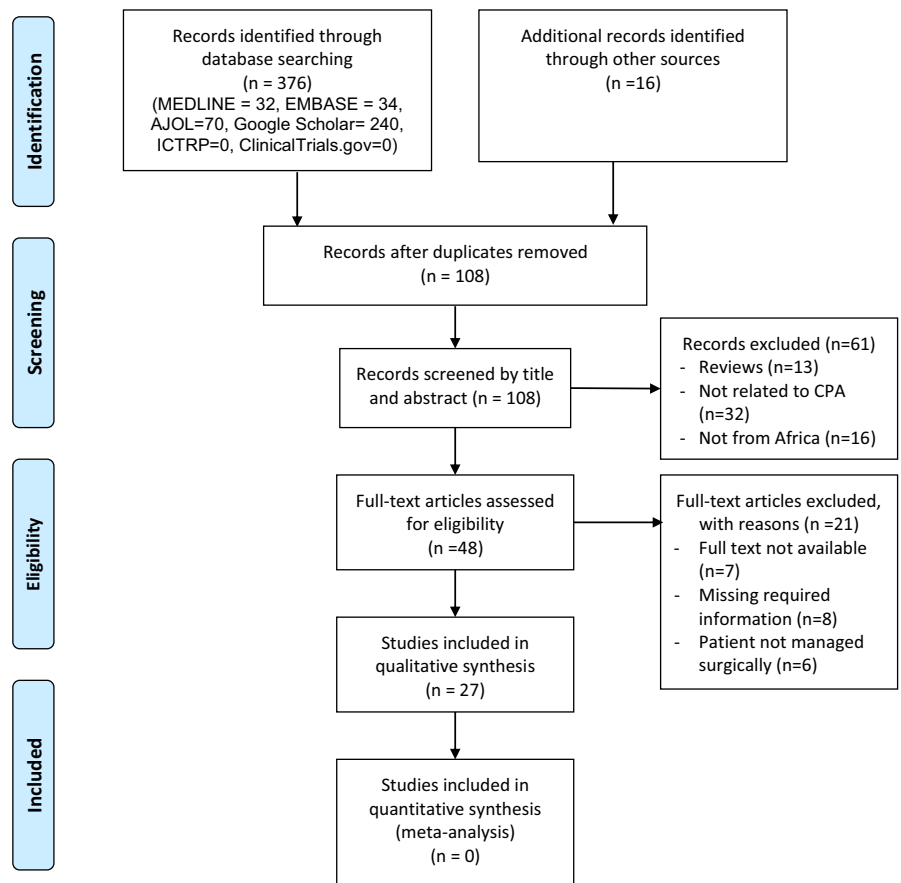


FIGURE 3 PRISMA flow diagram



interventions. Gerstl and colleagues reported the first successful surgical management of CPA in a 33-year-old housewife who presented with recurrent haemoptysis at the Uncas-on-Thames

Sanatorium, Norwich, Connecticut on 3 November 1943.³⁸ Since then, several cases series and large studies have been published on the surgical management of CPA.^{5,9,10,39-41} In this study, reviewing

TABLE 2 Surgical procedures performed in patients with aspergilloma and complications

Surgical procedure* (N = 891)	Frequency	%
Lobectomy	493	55.3
Pneumonectomy	154	17.3
Segmentectomy	117	13.1
Wedge resection	78	8.8
Bronchial artery embolisation	30	3.4
Cavernostomy	27	3.0
Thoracoplasty	4	0.4
Decortication	1	0.1
Endobronchial valves	1	0.1
Complications (N = 215)		
Empyema	59	27.4
Bleeding	38	17.7
Incomplete lung expansion	26	12.1
Prolonged air leak	24	11.2
Pneumonia	18	8.4
Wound infection	16	7.4
Respiratory failure	11	5.1
Suppuration	8	3.7
Bronchial fistula	7	3.3
Pleural effusion	3	1.4
Profuse pleurisy	3	1.4
Haemothorax	1	0.5
Acute lung oedema	1	0.5

*Patients were treated with either a single or a combination of multiple surgical procedures.

891 cases of CPA managed surgically in Africa, post-operative mortality rate was about 5%. However, long-term follow-up data are generally lacking. Nevertheless, this is the largest review of cases of CPA managed surgically in the literature.

Data from a global centre of excellence for the management of CPA suggest that about 5% of patients with CPA, especially those with simple aspergilloma require a surgical intervention for definitive management of CPA, obviating the need for long-term antifungal treatment.⁴² About half of patients who fail antifungal therapy may also require surgical interventions.⁵ In a cross-sectional study by Oladele and colleagues in Nigeria, 77.8% (14 of 18) of patients who had CPA had aspergilloma.⁴ Meanwhile in Uganda, a community-based study by Page and colleagues showed that 15 (3.8%) of the 398 patients with healed tuberculosis had a fungal ball.³ In this study, 9 (64.3%) of the 14 patients with a confirmed diagnosis of CPA had a fungal ball. Therefore, aspergilloma is a common presentation of CPA in African populations.

CPA presents with prominent respiratory and systemic symptoms, including chronic productive cough, haemoptysis, chest pain and weight loss.¹ Haemoptysis is a life-threatening symptom, resulting from rupture of bronchial vessels due to enlarging cavities

or oscillating aspergillomas. In the current study, over two-third of patients presented with haemoptysis which were recurrent or massive in most instances. Therefore, most patients with CPA in Africa, a continent with limited access to essential antifungals, may benefit from surgical interventions as first-line management option. Haemoptysis and chronic productive cough are very important features of CPA. In fact, among a cohort of patients with CPA in Uganda, the combination of raised *Aspergillus*-specific IgG, chronic cough or haemoptysis and chest radiography cavitation had sensitivity and specificity of 85.7% and 99.6%, respectively, for the diagnosis of CPA.³

In the present study, 3.4% of the patients benefited from BAE. This rate is comparable to a previous report among CPA patients in the United Kingdom where 4.4% of patients with CPA required BAE.⁴² In the UK study, 22% (2 of 9) patients who had BAE also required surgery for uncontrolled haemoptysis. Therefore, BAE alone may be inadequate in the management of torrential bronchial haemoptysis. BAE is indicated in CPA patients with haemoptysis who are not suitable for surgery.⁴³ Particularly, those with poor lung functions or unfit for surgery.

From the current study, the most commonly performed surgical procedures were lobectomy (in 55.3% of cases), pneumonectomy (17.3%) and segmentectomy (13.1%). Our findings are consistent with experience reported by Farid and colleagues (2013)⁷ at the National Aspergillosis Centre (NAC), Manchester, UK. The procedures included lobectomy (50%), pneumonectomy (10%), sublobar resection (27%), decortication (7%), segmentectomy (3%), thoracoplasty (3%), bullectomy and pleurectomy (3%), and lung transplantation (6%) for associated disease. In the same centre (NAC), a follow-up study by Setianingrum and colleagues (2020),⁵ the most commonly performed surgical procedures were lobectomy (64%), wedge resection (28%), segmentectomy (4.9%), pneumonectomy (4.9%) and decortication (3.3%).

Post-operative complications are common following surgical resections of CPA.⁷ The main complications include prolonged air leak, respiratory failure and infectious complications.⁷ Relapse of CPA occurs in 25%–40% of patients following surgical interventions.^{5,7} Compared to patients with simple aspergilloma, those with complex aspergilloma (CCPA) have higher rates of post-operative recurrence—in one study, this was 75%.⁷ Peri-operative antifungal therapy with agents such as amphotericin B and the oral triazoles and pleural decontamination with taurididine 2% during surgery significantly reduces post-operative complications and relapse.^{5,7}

5 | CONCLUSIONS

We report the first comprehensive review of CPA cases managed surgically in Africa. In the selected studies, surgical treatment had excellent outcomes with very low mortality rates. Post-operative complications were observed in 17% of the patients. Therefore, surgical management may be considered as first-line management option for CPA patients in Africa in centres with experience and

expertise. However, combining both surgical and antifungal treatment may further improve treatment outcomes/ success.

6 | ETHICS

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as the research in this article relates to review of the literature.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Felix Bongomin: Conceptualization (lead); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (lead); Writing-review & editing (lead). **Ronald Olum:** Conceptualization (supporting); Data curation (equal); Formal analysis (lead); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (lead); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Richard Kwizera:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal). **Joseph Baluku:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Project administration (equal); Resources (equal); Software (equal); Supervision (equal); Validation (equal); Visualization (equal); Writing-original draft (equal); Writing-review & editing (equal).

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