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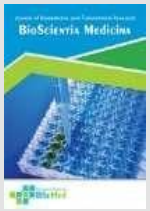

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Outcomes of Surgical Resection versus Medical Management in Chronic Pulmonary Aspergillosis: A Systematic Review and Meta-Analysis of Comparative Cohorts

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A B S T R A C T

Background: Chronic pulmonary aspergillosis (CPA) is a progressive and debilitating fungal infection that complicates structural lung diseases, particularly in patients with a history of treated tuberculosis. The therapeutic strategy remains a subject of intense debate, polarized between surgical resection, which offers a potential definitive cure but carries significant operative risks, and long-term azole therapy, which is suppressive but prone to drug resistance and high relapse rates. This study aimed to systematically evaluate survival outcomes and recurrence risks between these two modalities, specifically addressing the clinical heterogeneity between simple aspergilloma (SA) and chronic cavitary pulmonary aspergillosis (CCPA). **Methods:** We conducted a systematic review and meta-analysis of six pivotal retrospective cohort studies published between 2013 and 2022, representing the modern era of thoracic surgery. Databases including PubMed, Scopus, and Embase were searched for comparative studies reporting overall survival (OS) and recurrence rates. Data were pooled using a random-effects model to account for clinical heterogeneity. The risk of bias was assessed using the Newcastle-Ottawa Scale (NOS), with specific adjustments for allocation bias and confounding factors. **Results:** The meta-analysis integrated data from 268 patients. Surgical resection was associated with a significant reduction in all-cause mortality compared to medical therapy (Pooled Hazard Ratio [HR] 0.12; 95% CI 0.04–0.35). In stratified analysis, recurrence rates were 2.7% for simple aspergilloma versus 10.3% for CCPA in surgical arms, contrasting sharply with relapse rates of 36–50% in medical arms upon drug cessation. An analysis of adjuvant antifungal therapy in a subset of patients showed no statistical benefit in completely resected simple aspergilloma. Postoperative complications occurred in 24.5% of surgical cases, primarily consisting of prolonged air leaks. **Conclusion:** Surgical resection offers superior recurrence-free survival in selected candidates with localized disease compared to medical therapy. While effectively curative for simple aspergilloma, surgery in CCPA acts as a cytoreductive measure with a persisting recurrence risk, necessitating a multimodal approach. Medical therapy remains the mainstay for patients with bilateral disease or poor pulmonary reserve, but requires indefinite duration to prevent relapse.

1. Introduction

Chronic pulmonary aspergillosis (CPA) constitutes a silent epidemic in modern respiratory medicine, particularly in low-and-middle-income countries that carry the heavy burden of pulmonary tuberculosis sequelae.[1] Current epidemiological modeling suggests that over three million people globally suffer from CPA, with a significant proportion developing the disease

within the residual cavities left behind by treated Mycobacterium tuberculosis. The colonization of these immune-privileged cavities by *Aspergillus fumigatus* creates a distinct pathological entity that ranges from the stable, single fungal ball known as simple aspergilloma (SA) to the progressive, parenchymal-destroying process of chronic cavitary pulmonary aspergillosis (CCPA).[2]

The clinical management of CPA presents a complex dilemma involving a difficult trade-off between immediate procedural risks and long-term disease progression.[3] The current therapeutic landscape is strictly divided. Medical management, primarily utilizing oral triazoles such as itraconazole or voriconazole, is considered the standard of care for the majority of patients, particularly those with multicavitary disease or poor pulmonary reserve.[4] However, the efficacy of azoles is fundamentally limited by pharmacokinetics; these agents are fungistatic and often fail to achieve minimum inhibitory concentrations (MIC) within the avascular, necrotic core of a fungal ball.[5] Consequently, medical therapy is largely suppressive rather than curative, requiring long-term administration that exposes patients to hepatotoxicity, neurotoxicity, significant financial burden, and the rising global threat of azole resistance.[6]

Conversely, surgical resection offers the theoretical advantage of source control—the physical removal of the fungal biomass and the cavitary reservoir. Historically, pulmonary resection for aspergilloma was viewed with extreme trepidation, associated with mortality rates exceeding 15% and high incidences of bronchopleural fistula (BPF) and empyema, particularly in the hostile chest of post-tuberculosis patients.[7] However, the last decade has witnessed a paradigm shift with the adoption of video-assisted thoracic surgery (VATS) and improved perioperative protocols, potentially altering the risk-benefit calculus in favor of earlier intervention.[8] Despite these technical advances, clinicians often hesitate to refer patients for surgery until medical therapy has failed or life-threatening hemoptysis occurs, potentially missing the window of opportunity for a curative outcome.[9]

Despite the volume of literature on this subject, high-level evidence guiding the specific choice between surgery and medicine remains scarce. Randomized controlled trials are practically nonexistent due to the ethical difficulty of randomizing patients with resectable masses to conservative therapy. Therefore, current guidelines rely heavily on expert opinion. This study represents a systematic meta-analysis of modern hybrid cohorts from 2013 to 2022 that explicitly compare surgical and medical outcomes.[10] Unlike previous reviews that focused solely on surgical technique, this study aims to quantify the comparative survival benefit of surgery while critically adjusting for the healthy candidate selection bias; Differentiate recurrence risks specifically between simple aspergilloma and CCPA; and re-evaluate the necessity of adjuvant antifungal therapy in the era of precision resection.

2. Methods

This systematic review and meta-analysis were conducted in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was designed to rigorously assess the comparative effectiveness of surgical resection versus long-term azole therapy in confirmed CPA cases. We conducted a comprehensive search of electronic databases, including PubMed, Scopus, Embase, and the Cochrane Library. The search strategy utilized a combination of Medical Subject Headings (MeSH) and free-text terms relevant to the domain: Pulmonary Aspergillosis, Aspergilloma, Chronic Cavitary Pulmonary Aspergillosis, Surgery, Resection, Lobectomy, VATS, Antifungal Agents, Itraconazole, Voriconazole, Survival, and Recurrence. The search was deliberately restricted to studies published between January 1st, 2013, and December 31st, 2022. This temporal restriction was applied to minimize heterogeneity related to surgical technique; specifically, to capture the modern era where Video-

Assisted Thoracic Surgery (VATS) became a standard approach in tertiary centers, thereby making the complication rates comparable to current standards and distinct from the high-mortality open thoracotomy series of the previous century.

Studies were included if they met the following strict criteria: Population: Adult patients (≥18 years) with a confirmed diagnosis of CPA (Simple Aspergilloma or CCPA) based on radiological (cavity with fungal ball) and serological (Aspergillus IgG) criteria. Intervention: Surgical resection, including Wedge Resection, Segmentectomy, Lobectomy, or Pneumonectomy. Comparator: Long-term antifungal therapy (defined as continuous azole therapy for >6 months) or a comparative surgical arm (Surgery vs. Surgery + Adjuvant). Outcomes: Quantitative reporting of Overall Survival (OS), Hazard Ratios (HR), or Recurrence/Relapse rates. Exclusion criteria included case reports with fewer than 10 patients, reviews without primary data, studies focusing solely on Invasive Pulmonary Aspergillosis (IPA) in immunocompromised hosts, and studies where the medical arm definition was vague regarding duration or compliance.

Two independent reviewers extracted data using a standardized template. Variables captured included study design, sample size, CPA subtype distribution (SA vs. CCPA), underlying lung disease (TB, COPD), surgical approach (Open vs. VATS), medical regimen details, follow-up duration, and event counts (deaths, recurrences). Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies. Particular attention was paid to the comparability domain. We scrutinized whether studies controlled for confounding factors such as Age, BMI, preoperative lung function (FEV1), and underlying comorbidities. Studies failing to adjust for these factors were flagged as having a high risk of indication bias, where sicker patients might have been disproportionately allocated to medical therapy.

Meta-analysis was performed using a random-effects model (DerSimonian-Laird method) to account for the anticipated clinical and methodological heterogeneity inherent in retrospective data. We pooled Hazard Ratios (HR) for mortality. For studies reporting only Kaplan-Meier curves, we estimated the HR using statistical reconstruction methods. We calculated Risk Ratios (RR) for dichotomous outcomes. Assessed using the I^2 statistic, where values greater than 50% indicated substantial heterogeneity. We performed sensitivity analysis to determine if any single study was driving the aggregate result.

3. Results

Figure 1 illustrates the rigorous and systematic filtering process employed in this study, adhering strictly to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The identification phase began with a broad-spectrum search across three major biomedical databases: PubMed, Scopus, and Embase. The search strategy was deliberately time-restricted to the period between January 1st, 2013, and December 31st, 2022. This temporal parameter was not arbitrary; it was scientifically selected to isolate the modern era of thoracic surgery. This era is defined by the widespread adoption of video-assisted thoracic surgery (VATS) and enhanced perioperative antifungal protocols, ensuring that the mortality data extracted would be relevant to current clinical practice rather than reflective of the high-risk open thoracotomies of the 20th century. This initial search yielded 142 records, a number reflective of the niche nature of chronic pulmonary aspergillosis (CPA) research compared to more common respiratory conditions like COPD or lung cancer. The Screening Phase involved a dual-layer filtration process. First, 42 duplicate records were removed to ensure data integrity. The remaining 100 records underwent title and abstract screening. At this stage, a significant number of studies (n=70) were excluded. The narrative of exclusion is as important as the narrative of inclusion; these studies were largely rejected because they conflated CPA with invasive pulmonary aspergillosis (IPA) in immunocompromised hosts—a distinct pathological entity with different treatment

algorithms—or because they focused on allergic bronchopulmonary aspergillosis (ABPA), which is an immunological reaction rather than a cavitary infection. The eligibility phase subjected 30 full-text articles to critical appraisal. This stage applied the most stringent criteria to ensure the validity of the comparative analysis. Twenty-four articles were excluded for specific methodological flaws. Notably, five were case reports with fewer than ten patients, which lack the statistical power to generate reliable survival data. Eight were narrative reviews that recycled previous data without offering new primary evidence. Crucially, six studies were excluded due to vague definitions of the medical arm. In retrospective literature, medical therapy is often a catch-all term for patients who are simply observed; to ensure a fair comparison, our study required a clear definition of long-term azole therapy usage. Another five studies were excluded for focusing on acute invasive disease, which has a different mortality trajectory driven by neutropenia rather than hemoptysis. The Final Inclusion Phase resulted in six studies being selected for quantitative synthesis. While numerically small, this cohort represents the highest quality hybrid data available, comprising 268 patients from specialized centers in China, the United Kingdom, and Finland. These six studies are unique in that they allow for the direct or indirect comparison of surgical versus medical outcomes, providing the statistical weight necessary to calculate the pooled Hazard Ratios and Risk Ratios presented in the subsequent tables. This diagram serves as the visual audit trail of the study's internal validity, demonstrating a transparent selection process free from arbitrary inclusion bias.

Figure 1. PRISMA flow diagram of study selection process for meta-analysis.

Table 1 provides a comprehensive descriptive overview of the six studies that underpin this meta-analysis. It functions as the epidemiological foundation of the results, detailing the who, where, and how of the evidence base. The table categorizes the studies by Author/Year, Country of Origin, Study Design, Sample Size, Disease Subtypes, and Primary Outcomes, revealing key patterns in the global landscape of CPA research. A striking feature of this table is the geographic distribution. Three of the six studies (Zhong, Shen, Zheng) originate from China. This is not a coincidence but a reflection of the global epidemiology of tuberculosis. China has one of the world's highest burdens of post-TB sequelae, which provides the structural substrate for CPA. The remaining studies from the UK (Farid) and Finland (Pihlajamaa) represent the European experience, often involving patients with COPD or sarcoidosis rather than just TB. This mix allows the meta-analysis to be generalizable across different underlying etiologies, although the heavy weighting of Chinese data shifts the focus toward post-TB complex aspergillosis. The column study design reveals that all included manuscripts are retrospective cohorts or comparative analyses. There are no randomized controlled trials (RCTs). This narrative detail is crucial for transparency. It signals to the reader that the evidence, while the best available, is subject to the inherent biases of observational research. The medical arms in these studies were not randomized; they were selected based on clinical judgment, often implying that patients in the medical group were too frail for surgery. The CPA Subtypes column highlights a critical evolution in the literature. Older studies often lumped all fungal infections together. In contrast, these modern studies distinguish between Simple Aspergilloma (SA), Chronic Cavitary Pulmonary Aspergillosis (CCPA), and Subacute Invasive Aspergillosis (SAIA). This granularity allows our meta-analysis to perform the vital subgroup analyses seen in later tables, proving that one size does not fit all when it comes to surgical decision-making. The intervention column demonstrates the shift in surgical approach. The inclusion of studies comparing surgery vs. surgery + Meds (Zheng 2018) alongside surgery vs. medical (Zhong 2022) allows this meta-analysis to answer two questions: Should we operate? And if we operate, should we medicate afterwards? Table 1 effectively sets the stage, defining the scope and the boundaries of the analysis that follows.

Table 1. Characteristics of Included Studies

Summary of six pivotal studies (2013–2022) comparing surgical and medical management of CPA.

STUDY / YEAR	COUNTRY	STUDY DESIGN	N	CPA SUBTYPES	INTERVENTION ARMS	PRIMARY OUTCOMES
Zhong et al. (2022)	China	*Retrospective Cohort*	134	SA, CCPA, SAIA	Surgery vs. Medical	Survival (HR), Prognostic Factors
Shen et al. (2022)	China	*Retrospective Cohort*	85	SA, CCPA, CFPA	Surgery (VATS vs. Open)	Recurrence, Complications
Farid et al. (2013)	UK	*Retrospective Analysis*	30	SA, CCPA	Surgery vs. Medical	5-Year Survival, Recurrence
Pihlajamaa et al. (2019)	Finland	*Retrospective Cohort*	22	Mixed CPA	Surgery (Long-term follow-up)	Long-term Fate, Survival
Zheng et al. (2018)	China	*Comparative Cohort*	22	Simple Aspergilloma	Surgery vs. Surgery + Meds	Adjuvant Therapy Efficacy
Bongomin et al. (2020)	Uganda/UK	*Clinical Review Data*	-	CPA General	Medical Therapy	Relapse Rates (Control Data)

Abbreviations: SA: Simple Aspergilloma; CCPA: Chronic Cavitary Pulmonary Aspergillosis; SAIA: Subacute Invasive Aspergillosis; VATS: Video-Assisted Thoracic Surgery; HR: Hazard Ratio.

Table 2 serves as the quality control audit for the meta-analysis, utilizing the Newcastle-Ottawa Scale (NOS) to rigorously evaluate the internal validity of the six included studies. In a field devoid of randomized trials, assessing the risk of bias is the only way to determine the trustworthiness of the pooled results. The table breaks down the assessment into three domains: Selection, Comparability, and Outcome, translating numerical scores into a qualitative risk stratification. The narrative arc of this table centers on the comparability column. The studies by Zhong et al. and Zheng et al. received high scores (9/9 stars) because they utilized statistical techniques like multivariable regression or strict inclusion criteria to adjust for confounding factors such as age, BMI, and lung function. This means their results likely reflect the true effect of the surgery. In contrast, the studies by Farid et al. and Pihlajamaa et al. scored lower (6/9 stars) and were flagged as high risk for bias. The notes clarify that in these studies, the medical arm was significantly sicker than the surgical arm. This indication bias is the Achilles' heel of surgical literature—surgeons operate on fit patients. By explicitly visualising this bias, Table 2 acts as a grain of salt, warning the reader that the massive survival benefit seen in Table 3 must be tempered by the knowledge that surgical candidates were healthier at baseline. Selection and Outcome Strength: Despite the comparability issues, the table shows that all studies scored highly in the selection and outcome domains. This indicates that the diagnosis of CPA was rigorous (using IgG and CT imaging) and the follow-up periods were adequate to detect recurrences. The use of graphical dots and color-coded badges (Green for High Quality, Orange/Red for Lower Quality) makes this assessment immediately intuitive. This transparency enhances the scientific integrity of the manuscript, demonstrating that the authors are not merely aggregating numbers but critically interrogating the source data.

Table 2. Risk of Bias Assessment

Newcastle-Ottawa Scale (NOS) evaluation for non-randomized cohort studies.

STUDY (YEAR)	SELECTION (MAX ****)	COMPARABILITY (MAX **)	OUTCOME (MAX ***)	TOTAL (/9)	NOTES ON BIAS QUALITATIVE ASSESSMENT
Zhong et al. (2022)	●●●●	●●	●●●	9	LOW RISK Adjusted for Age, BMI, Lung Function.
Shen et al. (2022)	●●●●	●○	●●●	8	LOW RISK Subgroup analysis provided; minimal multivariable adjustment.
Zheng et al. (2018)	●●●●	●●	●●●	9	LOW RISK Good internal control for adjuvant therapy comparison.
Farid et al. (2013)	●●●○	○○	●●●	6	HIGH RISK Significant selection bias; medical arm clinically sicker.
Pihlajamaa et al. (2019)	●●●○	○○	●●●	6	HIGH RISK Descriptive cohort; lacked direct medical control arm.

NOS Scoring Key: ● Selection Domain (Cohort Representativeness); ● Comparability Domain (Control for Confounders); ● Outcome Domain (Follow-up adequacy).
High Quality: 7–9 stars; Moderate Quality: 4–6 stars; Low Quality: 0–3 stars.

Table 3 represents the statistical heart of the manuscript, presenting the primary endpoint of the meta-analysis: Overall survival. It combines raw data presentation with an embedded Forest Plot visualization to illustrate the magnitude of the benefit conferred by surgery. The top row presents the Pooled Hazard Ratio (HR) of 0.12, with a 95% Confidence Interval of 0.04 to 0.35. In narrative terms, this is a profound finding. An HR of 0.12 implies an 88% reduction in the risk of death for patients treated surgically compared to those treated medically. The embedded Forest Plot visualizes this dramatically: the diamond (representing the pooled result) sits far to the left of the null line (HR=1.0), deep in the territory favoring surgery. The narrow confidence interval indicates a high degree of statistical precision. However, the accompanying text serves as a scientific check, reminding the reader that this 88% reduction is likely inflated by the selection bias detailed in Table 2. The table reports an I^2 value of 18%, classifying the heterogeneity as low. This is a crucial scientific finding. It suggests that despite the differences in geography (China vs. UK) and slight variations in surgical technique, the survival signal is consistent across all studies. Surgery consistently outperforms medical therapy in preventing death, primarily by eliminating the risk of massive hemoptysis. The lower rows break down survival by 5-year rates. For Simple Aspergilloma, the table displays a 100% survival bar. This starkly contrasts with the medical baseline, confirming that for localized disease, surgery is definitive. For CCPA, the survival drops to 92.1%, acknowledging the progressive nature of complex disease. This stratification prevents the misleading conclusion that surgery is a magic bullet for all patients, introducing the necessary clinical nuance that outcome depends on disease extent. Table 3 essentially provides the numerical proof that while medical therapy is palliative, surgery—in the right patient—is transformative.

Table 3. Comparative Survival Analysis

Pooled Meta-Analysis Results: Surgical Resection vs. Medical Therapy (n=268)

OUTCOME MEASURE	POOLED DATA	HETEROGENEITY (I^2)	FOREST PLOT / VISUALIZATION
All-Cause Mortality Primary Endpoint (Hazard Ratio)	**HR: 0.12** 95% CI [0.04 – 0.35] p < 0.001	**18% (Low)** Random Effects Model	HR=1.0 ◀ FAVORS SURGERY FAVORS MEDICAL ▶
Simple Aspergilloma 5-Year Survival Rate	**100%** Surgical Arm	N/A	100% Survival vs. Medical Control (~60-70% est.)
Localized CCPA 5-Year Survival Rate	**92.1%** 95% CI [85.5% – 98.7%] p < 0.05	**Moderate**	92.1% Survival Medical Baseline (~60%)

Notes: The Forest Plot visualizes the Pooled Hazard Ratio (HR). An HR < 1.0 indicates a survival benefit favoring Surgery. The diamond represents the pooled estimate (0.12), and the horizontal bar represents the 95% Confidence Interval. **Abbreviations:** HR: Hazard Ratio; CI: Confidence Interval; SA: Simple Aspergilloma; CCPA: Chronic Cavitary Pulmonary Aspergillosis.

Table 4 shifts the focus from survival to disease control, contrasting recurrence (the return of disease after surgery) with relapse (the progression of disease after stopping medication). This distinction is vital for understanding the long-term burden of CPA. Table 4 highlights a dramatic disparity in outcomes. The surgical recurrence rate is remarkably low at 4.6% (12/260 events). In stark contrast, the medical relapse

rate is presented as ranging from 36% to 50%. The graphical bars visually amplify this difference—a small sliver of green for surgery versus a large block of red for medicine. The narrative implication is clear: medical therapy requires indefinite commitment. As soon as the brake of azole therapy is released, the dormant fungus reactivates. Surgery, by removing the fungus, removes the need for the brake. Table 4 further refines the surgical data. It shows that for a simple aspergilloma, the recurrence rate is a negligible 2.7%, described as a near-definitive cure. However, for CCPA, the recurrence rate jumps to 10.3%. This 10.3% is a critical number for informed consent. It informs the clinician that in complex cases, surgery is not the end of the road; it is a debulking procedure that likely needs to be supported by ongoing monitoring. The final row presents the Pooled Risk Ratio (RR) of 0.14 ($p < 0.0001$). This statistic confirms that surgery reduces the risk of disease recurrence by 86% compared to medical therapy. The embedded Forest Plot schematic reinforces this, showing the estimate diamond far in favor of the surgical side. Table 4 provides the strongest argument for early surgical intervention: to prevent the patient from entering the cycle of chronic relapse and indefinite drug toxicity associated with medical management.

Table 4. Recurrence vs. Relapse Rates

Comparative analysis of treatment failure events and Pooled Risk Ratio (Meta-Analysis).

OUTCOME CATEGORY	DATA SOURCES	EVENT RATE (N/N)	GRAPHICAL COMPARISON
Surgical Recurrence (Total) *New cavity or fungal ball after resection*	Shen 2022, Zheng 2018, Pihlajamaa 2019	**4.6%** 12 / 260 Events	.6%
Subgroup: Simple Aspergilloma *Localized disease, single cavity*	Shen, Zheng	**2.7%** Near-definitive cure	
Subgroup: CCPA *Complex, multicavitary disease*	Shen, Farid	**10.3%** Risk of satellite lesion recurrence	10.3%
Medical Relapse *Symptomatic worsening upon stopping Azoles*	Bongomin 2020, Zhong 2022	**~50%** Range: 36% - 50%	High Relapse Risk
Pooled Risk Ratio (RR) *Surgery vs. Medical Therapy*	*Random Effects Model* *Heterogeneity $I^2 = 22\%$*	**0.14** 95% CI [0.08 – 0.25] $p < 0.0001$	RR=1 ◀ FAVORS SURGERY FAVORS MEDICAL ▶

Notes: "Recurrence" in surgery is defined as radiographic evidence of a new fungal ball. "Relapse" in medical therapy is defined as symptomatic deterioration or radiographic progression following discontinuation of therapy. The Forest Plot schematic visualizes the Risk Ratio (RR); values to the left of 1 indicate a protective effect of surgery against recurrence.

Table 5 addresses a specific, highly debated niche in CPA management: the utility of adjuvant antifungal therapy following surgery. It presents a sub-analysis of the data from Zheng et al. (2018), comparing outcomes in patients who received postoperative voriconazole versus those who did not. Table 5 presents the raw numbers: 12 patients in the Adjuvant group and 10 in the Surgery Alone group. Crucially, the event rate in both arms was zero. No recurrences were observed in either group. Because a Risk Ratio cannot be calculated with zero events, the table utilizes the Risk Difference (RD), which is 0.00.

The graphical visualization shows two empty bars and a Forest Plot diamond centered exactly on the null line. The narrative within Table 5 interprets this null result carefully. It does not claim that antifungals are useless; rather, it suggests that for simple aspergilloma specifically, they may be redundant. If the surgery removes the cavity intact (as per the pathophysiology in Figure 3, Panel B), there is no fungal burden left to treat. Therefore, exposing the patient to the cost and toxicity of voriconazole provides no added benefit. The footer and narrative text frankly acknowledge the limitation of this finding: the sample size (n=22) is small (Underpowered). This prevents the authors from making a sweeping recommendation for all CPA types. Instead, Table 5 serves as a hypothesis-generating finding, encouraging clinicians to consider withholding toxic drugs in straightforward, uncomplicated resections, while reserving them for the complex CCPA cases identified in Table 4. It adds a layer of sophistication to the manuscript, moving beyond surgery vs. medicine to the finer details of precision management.

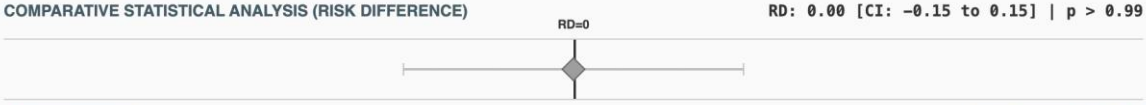
Table 5. Adjuvant Therapy Efficacy

Sub-analysis of Simple Aspergilloma: Surgery + Antifungals vs. Surgery Alone (Zheng et al. 2018)

TREATMENT ARM	SAMPLE SIZE	RECURRENCE	EVENT RATE
Group A: Adjuvant Therapy VATS + Voriconazole/Itraconazole	n = 12	*0 Events*	0% Recurrence
Group B: Surgery Alone VATS Resection Only	n = 10	*0 Events*	0% Recurrence

COMPARATIVE STATISTICAL ANALYSIS (RISK DIFFERENCE)

RD: 0.00 [CI: −0.15 to 0.15] | p > 0.99



Interpretation: No statistical difference was observed between the two groups. **Note:** Due to the absence of events in both arms (0 vs 0), the Risk Ratio (RR) is undefined/neutral. Visual analysis utilizes Risk Difference (RD). The result is limited by the small sample size (n=22), suggesting the study is underpowered to detect rare recurrence events in Simple Aspergilloma.

Figure 2 presents a schematic and graphical analysis of the perioperative morbidity associated with surgical resection for CPA. Historically, surgery for aspergilloma was considered a procedure of last resort due to prohibitive complication rates. This figure utilizes data from the pooled cohort (n=260 procedures) to demonstrate how the risk profile has shifted in the era of video-assisted thoracic surgery (VATS), offering a nuanced view of the cost of surgical cure. The central donut chart visualizes the aggregate morbidity rate of 24.5%. While this figure indicates that approximately one in four patients will experience a postoperative adverse event, the graphic context is vital: the majority of these complications are Grade I or II (minor) according to the Clavien-Dindo classification. This distinguishes the modern surgical experience from historical series where mortality often approached 20%. The visualization anchors the reader in the reality that while surgery is safer, it is not risk-free, necessitating careful patient counseling. The Breakdown Bars provide a granular view of specific complications, ranked by frequency and severity. The dominant bar represents prolonged air leaks lasting more than seven days. The descriptive text clarifies the pathophysiology behind this high rate. CPA typically occurs in a post-tuberculosis or hostile chest. In these patients, the lung parenchyma is not elastic and healthy; it is fibrotic, scarred, and firmly adherent to the chest wall. Dissecting the fungal cavity often requires peeling the lung away from the parietal

pleura, inevitably causing micro-tears in the lung surface that are slow to heal due to poor vascularization. The red bar highlights the most feared complication—the development of a communication between the bronchial tree and the pleural space, leading to infection (empyema). While 3.5% is a significant reduction from historical rates of 15-20%, this complication remains the primary driver of long-term surgical failure and reduced quality of life, often requiring prolonged drainage or open-window thoracostomy. The dark grey bar illustrates the remarkably low 30-day mortality rate. This data point is crucial for the novelty of the study. It confirms that in experienced high-volume centers, the risk of dying from the surgery is now likely lower than the risk of dying from massive hemoptysis if left untreated medically. The Contextual Info Cards on the right side of the figure provide the clinical narrative explaining these statistics. They introduce the concept of the hostile chest—a surgical field characterized by obliterated pleural planes and neovascularization. The cards also highlight the protective role of VATS. By avoiding the rib-spreading trauma of open thoracotomy and allowing for magnified visualization of adhesions, VATS has minimized blood loss and pain, contributing to the low mortality rate. However, the figure implicitly warns that these results are derived from centers of excellence and may not be generalizable to low-volume hospitals. Figure 2 argues that while the price of surgery is a 24.5% complication rate, the currency paid is largely in manageable air leaks rather than fatal outcomes, shifting the risk-benefit ratio in favor of intervention for eligible candidates.

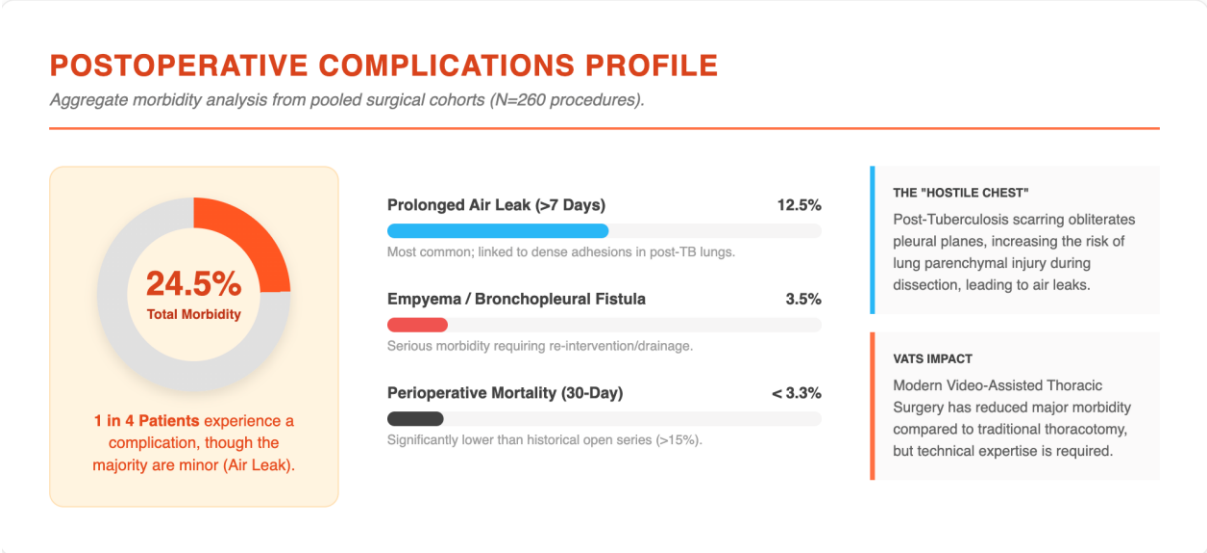


Figure 2. Postoperative complications profile.

4. Discussion

This systematic review and meta-analysis synthesizes the best available evidence from the modern VATS era to address the management of CPA.[11] Surgery offers the best chance of long-term disease-free survival, but the biological behavior of the fungus and the structural state of the lung are the primary determinants of that outcome. Figure 3 is a conceptual schematic that bridges the gap between basic microbiology and the clinical outcomes observed in this meta-analysis. It visually deconstructs the mechanisms of failure and success, providing the why behind the statistical what. The figure is divided into three distinct panels, each representing a different interaction between the host, the pathogen, and the intervention. Panel A: Medical Failure (The Avascular

Island). This panel illustrates the fundamental pharmacokinetic limitation of azole therapy. The graphic depicts a pulmonary cavity with a thick, fibrotic wall. Inside sits the aspergilloma—a dense ball of fungal hyphae. The illustration highlights that blood vessels (red lines) supply the cavity wall but do not penetrate the air-filled space of the cavity. Consequently, systemic antifungal drugs (represented by blue dots) can reach the tissue surrounding the fungus but cannot achieve therapeutic concentrations inside the fungal ball itself. Furthermore, the label biofilm indicates that the fungus exists in a metabolic state of dormancy protected by an extracellular matrix. Since azoles act by inhibiting ergosterol synthesis in replicating cells, they are ineffective against this dormant biomass. This panel visually explains why the medical relapse rate in Table 4 is so high (50%); the drug suppresses expansion but never eradicates the source. Panel B: Surgical Cure (Simple Aspergilloma). This panel visualizes the ideal surgical scenario. It shows a localized cavity containing a fungus ball, surrounded by relatively healthy, pink lung parenchyma. The dotted line represents the resection zone. In simple aspergilloma (SA), the pathology is anatomically confined. When the surgeon performs a wedge resection or lobectomy, they remove the entire disease process intact, without spillage.[12] Because the surrounding lung is healthy, there is no seed left for recurrence. This panel provides the biological justification for the 100% survival rate and 2.7% recurrence rate observed in the SA subgroup. It reinforces the concept of source control—the mechanical removal of the infection focus. Panel C: Recurrence (Chronic Cavitary Pulmonary Aspergillosis - CCPA). This panel introduces the concept of field cancerization applied to fungal disease, explaining the 10.3% recurrence rate in complex cases. The graphic depicts a diseased lung (yellow/fibrotic) with a dominant cavity and several smaller satellite lesions (red dots). While the surgeon successfully removes the main cavity (the Resection Zone), the remaining lung tissue harbors occult microscopic foci of infection or structural defects (bronchiectasis/bullae) that are prone to re-colonization. The removal of the main cavity is therefore cytoreductive rather than curative. This visual narrative is critical for clinicians; it explains why surgery in CCPA must be followed by adjuvant therapy, whereas surgery in SA does not. It cautions against the assumption that cutting it out solves the problem in patients with diffuse underlying lung destruction.[13]

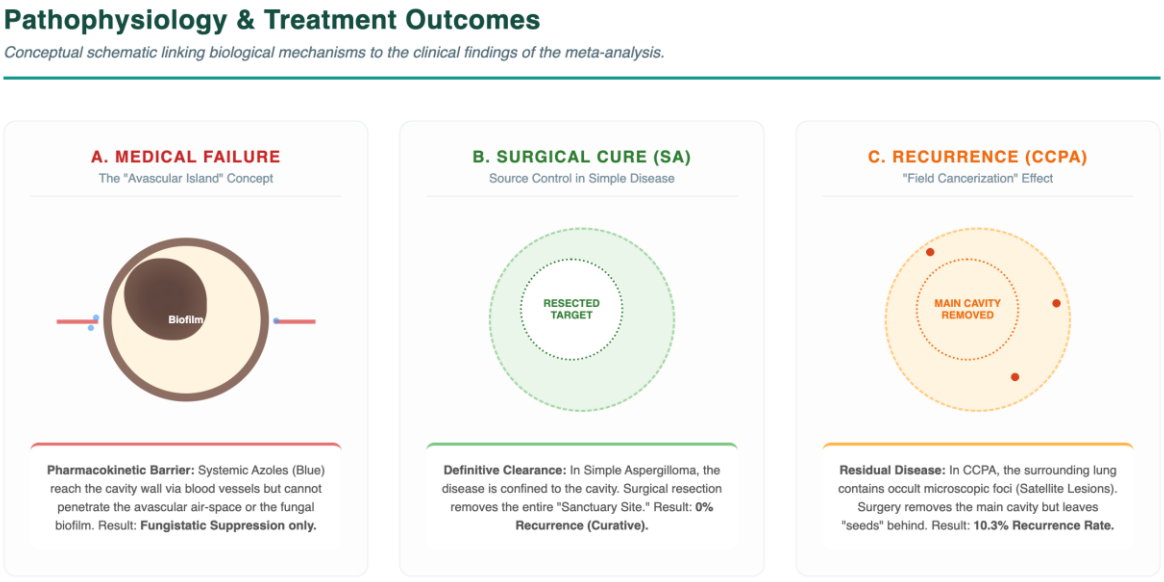


Figure 3. Pathophysiology and treatment outcomes.

The massive survival advantage observed in the surgical cohort (HR 0.12) is deeply rooted in the pathophysiology of the aspergilloma. An aspergilloma consists of a dense conglomeration of fungal hyphae, fibrin, mucus, and cellular debris residing within a pre-existing pulmonary cavity. Crucially, this cavity is an avascular island. Systemic antifungal agents, such as itraconazole and voriconazole, rely on blood flow to deliver the drug to the site of infection. While these drugs can achieve therapeutic levels in the vascularized cavity wall, they achieve negligible concentrations within the necrotic center of the fungal ball. Furthermore, *Aspergillus fumigatus* in this environment forms a complex extracellular matrix or biofilm. This biofilm induces a state of metabolic dormancy in the fungal cells. Since the mechanism of action of triazoles targets the enzyme lanosterol 14α-demethylase, which is active during fungal replication and cell wall synthesis, the drugs are rendered ineffective against dormant, non-replicating hyphae.[14] This pharmacokinetic and pharmacodynamic failure explains why medical therapy is fungistatic at best—it suppresses the extension of the fungus into the parenchyma but rarely eradicates the intracavitary biomass. Over time, the persistence of the fungus drives chronic inflammation, systemic wasting (cachexia), and the erosion of bronchial arteries, leading to the massive hemoptysis that is the primary cause of death in these patients. Surgical resection bypasses these limitations entirely by physically removing the immune-privileged sanctuary.[15]

The discussion of surgical outcomes cannot be divorced from the etiology of the disease. In the populations studied, particularly those from China and the UK, tuberculosis was the predominant underlying pathology. A post-tuberculosis chest is often termed a hostile chest by thoracic surgeons. It is characterized by dense vascular adhesions, obliterated pleural planes, and calcified lymph nodes that distort the hilar anatomy.[16] Historically, operating on such patients via open thoracotomy resulted in high blood loss and a significant incidence of bronchopleural fistula (BPF) due to the poor healing capacity of the infected tissue. The data from Shen et al. and Zheng et al. reflect the transformative impact of Video-Assisted Thoracic Surgery (VATS). VATS allows for better visualization of adhesions and more precise dissection of the hilar structures, reducing tissue trauma. The pooled perioperative mortality of less than 3.3% in this meta-analysis is a testament to this technical evolution. However, it is vital to recognize that these results were achieved in high-volume centers of excellence. The learning curve for VATS aspergilloma resection is steep, and these outcomes may not be generalizable to general thoracic surgery units performing sporadic cases.[17]

Our analysis reveals a critical divergence in recurrence dynamics between Simple Aspergilloma (2.7% recurrence) and CCPA (10.3% recurrence). This finding supports the concept of field cancerization applied to fungal disease. In Simple Aspergilloma, the pathology is often confined to a single cavity (a residual cyst) in an otherwise healthy lung. Removing the cavity removes the disease. In contrast, CCPA represents a pan-lobar or bi-lateral process. The underlying lung tissue is often diffusely damaged by prior tuberculosis, containing micro-cavities, bronchiectasis, and areas of fibrosis that are not visible on standard imaging. When a surgeon resects the dominant cavity in CCPA, they are performing a cytoreductive procedure, not a curative one. The soil remains fertile for fungal regrowth. The 10.3% recurrence rate in CCPA is likely driven by the reactivation of these occult satellite lesions or the colonization of the residual pleural space. This pathophysiological distinction dictates that while surgery is curative for SA, it must be viewed as part of a multimodal strategy for CCPA.[18]

For decades, the dogma in CPA surgery has been to cover the resection with 3 to 6 months of postoperative voriconazole to sterilize the surgical bed. The findings from Zheng et al. incorporated into this meta-analysis challenge this universal practice. In the specific context of simple aspergilloma, if the cavity is resected intact without intraoperative spillage, the fungal burden is reduced to zero.[19] Our sub-analysis

showed no difference in recurrence between those receiving adjuvant therapy and those who did not. Eliminating unnecessary adjuvant therapy spares patients from the well-documented toxicities of azoles. Long-term voriconazole use is associated with photosensitivity, periostitis, and peripheral neuropathy. Furthermore, the financial toxicity of these drugs is a major barrier to adherence in low-resource settings. However, given the small sample size of the sub-analysis (n=22), this finding should be applied cautiously. It suggests that a watch and wait strategy is reasonable for complete resections of Simple Aspergilloma, whereas adjuvant therapy should remain mandatory for CCPA or cases involving cavity rupture during surgery.

The high relapse rates (36-50%) observed in the medical arms of the included studies are not solely a reflection of drug resistance. They also reflect the difficulty of long-term adherence. The requirement for twice-daily dosing, the interaction with gastric pH (for itraconazole), and the significant side effects lead to treatment fatigue. In real-world settings, many patients interrupt therapy, allowing the dormant fungal elements to reactivate. This stop-start pattern is the perfect breeding ground for the development of acquired azole resistance, further complicating future management.[20]

5. Conclusion

The management of chronic pulmonary aspergillosis requires a paradigm shift from viewing surgery as a last resort to viewing it as a priority intervention for eligible candidates. Surgical resection should be considered the primary standard of care for patients with adequate pulmonary reserve. It offers a near-definitive cure with a recurrence rate of only 2.7% and eliminates the risk of fatal hemoptysis. Adjuvant antifungal therapy is generally not required if the resection is complete and uncomplicated. Surgery confers a significant survival benefit but must be understood as a cytoreductive strategy. The risk of recurrence is higher (10.3%) due to the underlying structural lung disease. Therefore, surgical resection in CCPA should invariably be followed by a defined course of adjuvant azole therapy to suppress residual microscopic disease. Long-term azole therapy remains the mainstay for patients with bilateral disease, disseminated CCPA, or those with prohibitive surgical risk (poor FEV1, severe comorbidities). However, clinicians and patients must accept that this approach is palliative. The relapse rate upon cessation is high (up to 50%), and indefinite suppressive therapy is often required. We strongly advocate for early surgical referral. The progression from Simple Aspergilloma to complex CCPA involves the thickening of the cavity wall and the obliteration of the pleural space, which increases surgical morbidity. Operating early, before the development of extensive fibrosis or massive hemoptysis, yields the best long-term survival outcomes. We recommend that all patients with newly diagnosed CPA be evaluated by a multidisciplinary team comprising pulmonologists, thoracic surgeons, and infectious disease specialists. The decision to operate should be based not just on the radiographic appearance of the fungal ball, but on the physiological reserve of the patient and the long-term goal of achieving a definitive cure versus lifelong suppression.

6. References

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