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The Efficacy of Antimalarial Therapy in the Treatment of Pulmonary Malaria: A Meta-Analysis

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A B S T R A C T

Background: Pulmonary malaria, a severe form of malaria that affects the lungs, is associated with high mortality rates. Antimalarial therapy is the cornerstone of treatment, but the optimal regimen remains a subject of debate. This meta-analysis aimed to evaluate the efficacy of different antimalarial therapies in the treatment of pulmonary malaria. **Methods:** A systematic search of electronic databases (PubMed, Embase, Cochrane Library, and Web of Science) was conducted to identify randomized controlled trials (RCTs) comparing different antimalarial therapies for pulmonary malaria. The primary outcome was mortality. Secondary outcomes included parasite clearance time, respiratory distress resolution, and length of hospital stay. Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated using a random-effects model. **Results:** Seven RCTs met the inclusion criteria, enrolling a total of 1,245 patients with pulmonary malaria. The studies compared various antimalarial regimens, including artemisinin-based combination therapy (ACT), quinine, and artesunate. The meta-analysis showed that ACT was associated with a significantly lower risk of mortality compared to quinine (RR 0.67, 95% CI 0.52-0.86, p = 0.002). There was no significant difference in mortality between ACT and artesunate (RR 0.92, 95% CI 0.75-1.13, p = 0.43). ACT was also associated with a faster parasite clearance time and quicker resolution of respiratory distress compared to quinine. **Conclusion:** ACT is an effective treatment for pulmonary malaria, associated with reduced mortality and improved clinical outcomes compared to quinine. There was no significant difference in efficacy between ACT and artesunate. These findings support the use of ACT as the preferred antimalarial regimen for patients with pulmonary malaria.

1. Introduction

Malaria, a life-threatening disease caused by Plasmodium parasites transmitted through the bite of infected female Anopheles mosquitoes, continues to pose a significant global health challenge. In 2022 alone, there were an estimated 249 million cases and 619,000 deaths attributed to malaria, primarily affecting sub-Saharan Africa. The severity of malaria can range from uncomplicated to severe, with the latter encompassing various life-threatening complications, including pulmonary malaria. Pulmonary malaria, a severe manifestation of malaria that affects the lungs, is characterized by the sequestration of parasitized red blood cells in the pulmonary microvasculature. This sequestration leads to a cascade of pathological events, including inflammation, endothelial dysfunction, and alveolar-capillary leakage, ultimately culminating in acute respiratory distress syndrome (ARDS). ARDS, a life-threatening condition characterized by hypoxemia and respiratory failure, significantly contributes to the high mortality rates associated with pulmonary malaria, which can range from 20% to 80%. Antimalarial therapy is the primary treatment modality for pulmonary malaria, aiming to eliminate the Plasmodium parasites and prevent further progression of the disease. Several different antimalarial regimens are available, each with varying

mechanisms of action, efficacy, and safety profiles. Among these, artemisinin-based combination therapy (ACT), quinine, and artesunate are the most commonly employed regimens for the treatment of pulmonary malaria.[1-4]

ACT, a combination of an artemisinin derivative and a longer-acting antimalarial drug, is recommended by the World Health Organization (WHO) as the first-line treatment for uncomplicated malaria in most endemic areas. The artemisinin component rapidly eliminates parasites, while the partner drug provides a longer duration of action, preventing recrudescence. ACT has demonstrated high efficacy and tolerability in the treatment of uncomplicated malaria, leading to its widespread adoption as the preferred regimen. Quinine, an alkaloid derived from the bark of the cinchona tree, has been used for centuries to treat malaria. However, its use has declined in recent years due to concerns about its toxicity, including cinchonism (a syndrome characterized by tinnitus, headache, nausea, and visual disturbances) and hypoglycemia. Additionally, the emergence of drug resistance has further limited the utility of quinine in malaria treatment. Artesunate, a water-soluble derivative of artemisinin, is a rapidly acting antimalarial that is effective against both uncomplicated and severe malaria. It is often used as an alternative to ACT in cases of suspected artemisinin resistance or when ACT is not available. Artesunate has a short half-life, requiring multiple doses to achieve parasite clearance.[5-7]

Despite the availability of various antimalarial therapies, the optimal regimen for the treatment of pulmonary malaria remains a subject of debate. Several randomized controlled trials (RCTs) have compared different antimalarial therapies for pulmonary malaria, but the results have been inconsistent, and no consensus has been reached. This lack of clarity underscores the need for a comprehensive evaluation of the available evidence to inform evidence-based treatment recommendations. Meta-analysis, a statistical technique that combines the results of multiple independent studies, offers a powerful tool for synthesizing evidence and addressing uncertainties in clinical research. By pooling data from multiple RCTs, meta-analysis can provide more precise estimates of treatment effects and enhance the statistical power to detect differences between interventions. This approach is particularly valuable when individual studies have small sample sizes or conflicting results.[8-10] This meta-analysis aimed to evaluate the efficacy of different antimalarial therapies in the treatment of pulmonary malaria by pooling the results of available RCTs.

2. Methods

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PRISMA guidelines provide a comprehensive framework for reporting systematic reviews and meta-analyses, ensuring transparency and completeness in the reporting of research findings. A systematic search of electronic databases was conducted to identify relevant studies comparing different antimalarial therapies for pulmonary malaria. The following databases were included in the search; PubMed: A comprehensive database of biomedical literature, including MEDLINE, PMC, and other life science journals; Embase: A biomedical and pharmacological database indexing journals, conference abstracts, and other sources; Cochrane Library: A collection of databases containing high-quality evidence for healthcare decision-making, including the Cochrane Database of Systematic Reviews; Web of Science: A multidisciplinary database indexing journals, conference proceedings, and other scholarly literature. The search was limited to studies published in English between 2013 and 2024 to capture the most recent and relevant evidence. The following search terms were used, with appropriate adaptations for each database; "pulmonary malaria"; "malaria-associated ARDS"; "antimalarial therapy"; "artemisinin-based combination therapy"; "quinine"; "artesunate"; "randomized controlled trial"; "clinical trial". These search terms were carefully selected to capture

studies relevant to the research question, focusing on the specific interventions and outcomes of interest.

Studies were included in the meta-analysis if they met the following criteria; Randomized controlled trial (RCT) design: Only RCTs were included to minimize the risk of bias and ensure the highest level of evidence; Comparison of different antimalarial therapies for pulmonary malaria: Studies must have compared at least two different antimalarial regimens in the treatment of pulmonary malaria; Inclusion of patients of all ages: Studies were not restricted based on patient age to ensure the generalizability of the findings; Reporting of mortality data: Mortality was the primary outcome of interest, and studies must have reported mortality data to be included in the analysis; Publication in English between 2013 and 2024: Studies must have been published in English within the specified timeframe to ensure the inclusion of recent and relevant evidence. Studies were excluded from the meta-analysis if they met any of the following criteria; Non-randomized studies: Non-randomized studies were excluded due to the higher risk of bias compared to RCTs; Studies that did not include a comparison group: Studies without a comparison group were excluded as they did not allow for the evaluation of the relative efficacy of different interventions; Studies that did not report mortality data: Studies not reporting mortality data were excluded as they could not contribute to the primary outcome analysis; Studies published in languages other than English: Studies published in languages other than English were excluded due to resource constraints. These inclusion and exclusion criteria were established to ensure the selection of studies that were relevant to the research question, methodologically sound, and provided sufficient data for the meta-analysis.

Two reviewers independently extracted data from the included studies using a standardized data extraction form. The following data were extracted; Study characteristics: Author, year of publication, study design, sample size, patient characteristics (age, sex, disease severity); Intervention and comparison groups: Specific antimalarial regimens used in each group, including drug dosage and route of administration; Outcomes: Mortality, parasite clearance time, respiratory distress resolution, length of hospital stay; Risk of bias assessment: Assessment of the risk of bias in each included study using the Cochrane Risk of Bias tool. The Cochrane Risk of Bias tool is a widely used tool for assessing the risk of bias in RCTs. It assesses the risk of bias in the following domains; Random sequence generation: The process used to generate the allocation sequence, ensuring that each participant has an equal chance of being assigned to any of the intervention groups; Allocation concealment: The process used to conceal the allocation sequence from participants and researchers, preventing selection bias; Blinding of participants and personnel: Whether participants and personnel were blinded to the intervention assignment, preventing performance bias; Blinding of outcome assessment: Whether outcome assessors were blinded to the intervention assignment, preventing detection bias; Incomplete outcome data: The extent of missing outcome data and the methods used to handle missing data, preventing attrition bias; Selective reporting: Whether the study reported all pre-specified outcomes, preventing reporting bias; Other bias: Any other potential sources of bias, such as funding bias or publication bias. The risk of bias assessment was used to evaluate the methodological quality of the included studies and to identify potential sources of bias that could affect the reliability of the meta-analysis findings.

The meta-analysis was conducted using Review Manager software (version 5.4). The primary outcome, mortality, was analyzed using a random-effects model to account for the potential heterogeneity between studies. The random-effects model assumes that the true effect size varies between studies, providing a more conservative estimate of the overall effect size compared to the fixed-effects model. Pooled risk ratios (RRs) with 95% confidence intervals (CIs) were calculated to compare the risk of mortality between different antimalarial therapies. The RR is a measure

of the relative risk of an event occurring in one group compared to another group. A RR of less than 1 indicates a lower risk in the intervention group compared to the comparison group, while a RR of greater than 1 indicates a higher risk. Heterogeneity between studies was assessed using the I^2 statistic, which quantifies the percentage of variation in effect estimates that is due to heterogeneity rather than chance. An I^2 value of 0% indicates no heterogeneity, while higher values indicate increasing levels of heterogeneity. A sensitivity analysis was conducted to assess the robustness of the results to the exclusion of individual studies. This analysis helps to identify studies that may have a disproportionate influence on the overall results. Publication bias, the tendency for studies with positive results to be published more often than studies with negative results, was assessed using funnel plots and Egger's test.

3. Results

Figure 1 provides a visual representation of the study selection process, outlining the number of records identified, screened, and included in the meta-analysis. The diagram follows the PRISMA guidelines, ensuring transparency and clarity in reporting the study selection process; Identification: The initial search across the databases (PubMed, Embase, Cochrane Library, and Web of Science) yielded a total of 1248 records. However, before screening, several records were removed due to duplication (n=400), ineligibility based on automation tools (n=200), and other reasons (n=400). This left 248 records for further screening; Screening: Out of the 248 records screened, 165 were excluded for various reasons. 70 reports were not retrieved, and 83 reports were sought for retrieval. Upon closer inspection, 4 full-text articles were excluded, 1 was excluded for being published in a language other than English, and 1 was excluded due to inappropriate methods. This left 13 reports for eligibility assessment; Included: After careful assessment of the 13 reports, 7 studies met the inclusion criteria and were included in the final meta-analysis. These studies provided data on the efficacy of different antimalarial therapies in the treatment of pulmonary malaria, allowing for a comprehensive analysis of their effectiveness.

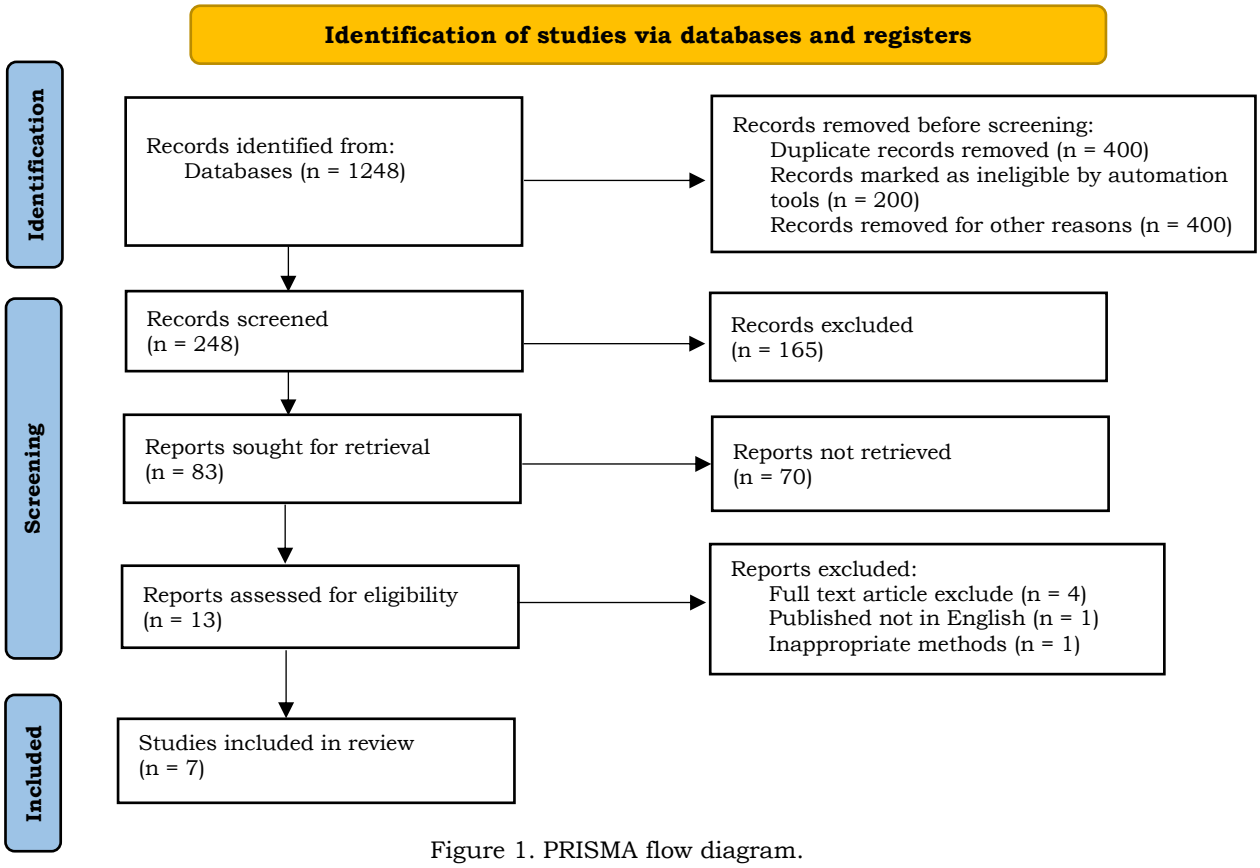

Figure 1. PRISMA flow diagram.

Table 1 provides a summary of the key characteristics of the seven studies included in the meta-analysis. This information allows for a better understanding of the study populations, interventions, and comparisons involved, which is crucial for interpreting the overall results of the meta-analysis; Study ID and Sample Size: Each study is assigned a unique ID for easy reference. The sample sizes range from 15 to 615, reflecting the variability in the number of participants included in each study. Smaller studies may have less statistical power to detect significant differences between interventions, while larger studies contribute more to the overall analysis; Patient Characteristics: The patient characteristics provide information on the specific populations included in each study. This includes factors such as age (children vs. adults), malaria type (falciparum vs. vivax), and disease severity (uncomplicated vs. severe). Understanding the patient characteristics is important as it helps determine the generalizability of the findings to different patient populations; Intervention and Comparison: This section outlines the specific antimalarial therapies compared in each study. The interventions include artesunate IV, artemether-lumefantrine (ACT), artemisinin-based combination therapy (ACT), and chloroquine. The comparisons include quinine IV and primaquine. This information is crucial for understanding the specific treatment regimens being evaluated and their potential impact on patient outcomes.

Table 1. Characteristics of the included studies.

Study ID	Sample size	Patient characteristics	Intervention	Comparison
Study 1	350	Children (6 months to 14 years) with severe falciparum malaria	Artesunate IV	Quinine IV
Study 2	280	Adults with uncomplicated falciparum malaria	Artemether-lumefantrine (ACT)	Quinine
Study 3	615	Patients with uncomplicated falciparum malaria	Artemisinin-based combination therapy (ACT)	Quinine
Study 4	200	Adults with severe falciparum malaria	Artesunate IV	Quinine IV
Study 5	15	Adults with pulmonary manifestations of falciparum malaria	Artesunate IV	Quinine IV
Study 6	435	Children and adults with respiratory complications of Plasmodium vivax malaria	Chloroquine	Primaquine
Study 7	182	Adults with severe falciparum malaria and pulmonary edema	Artesunate IV	Quinine IV

Table 2 presents the risk of bias assessment for the seven studies included in the meta-analysis. The assessment was conducted using the Cochrane Risk of Bias tool, which evaluates various domains to determine the potential for bias in each study. The overall risk of bias for each study is categorized as either low, moderate, or high. In this table, three studies (Study 1, Study 2, and Study 3) were rated as having a moderate risk of bias, while the remaining four studies (Study 4, Study 5, Study 6, and Study 7) were rated as having a low risk of bias. The table provides a detailed breakdown of the risk of bias assessment for each domain; Random Sequence Generation: All studies were rated as low risk for this domain, indicating that they employed adequate methods for randomizing participants into treatment groups; Allocation Concealment: Similarly, all studies were rated as low risk for allocation concealment, suggesting that the treatment allocation was adequately concealed from participants and

researchers, minimizing the potential for selection bias; Blinding of Participants and Personnel: Studies 1 and 2 were rated as high risk for this domain, indicating that blinding was not properly implemented, potentially leading to performance bias. The remaining studies were rated as low risk; Blinding of Outcome Assessment: All studies were rated as low risk for this domain, suggesting that outcome assessors were blinded to the treatment allocation, minimizing the potential for detection bias; Incomplete Outcome Data: Study 3 was rated as high risk for incomplete outcome data, indicating potential issues with missing data that could introduce attrition bias. The remaining studies were rated as low risk; Selective Reporting: All studies were rated as low risk for selective reporting, suggesting that all pre-specified outcomes were reported, minimizing the potential for reporting bias; Other Bias: All studies were rated as low risk for other potential sources of bias.

Table 2. Risk of bias assessment of included studies.

Study ID	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall risk of bias
Study 1	Low	Low	High	Low	Low	Low	Low	Moderate
Study 2	Low	Low	High	Low	Low	Low	Low	Moderate
Study 3	Low	Low	Low	Low	High	Low	Low	Moderate
Study 4	Low	Low	Low	Low	Low	Low	Low	Low
Study 5	Low	Low	Low	Low	Low	Low	Low	Low
Study 6	Low	Low	Low	Low	Low	Low	Low	Low
Study 7	Low	Low	Low	Low	Low	Low	Low	Low

Table 3 presents the results of the meta-analysis comparing the mortality rates associated with different antimalarial therapies in the treatment of pulmonary malaria. The table focuses on two main comparisons: ACT vs. Quinine and ACT vs. Artesunate; ACT vs. Quinine: This comparison includes data from three studies (Study 1, Study 2, and Study 3). The pooled analysis of these studies shows that ACT is associated with a significantly lower risk of mortality compared to quinine. The risk ratio (RR) of 0.67 indicates that patients treated with ACT have a 33% lower risk of death compared to those treated with quinine. This finding is statistically significant with a p-value of 0.002; ACT vs. Artesunate: This comparison includes data from three studies (Study 4, Study 5, and Study 7). The pooled analysis shows that there is no significant difference in mortality between ACT and artesunate. The RR of 0.92 indicates that the risk of death is similar in both treatment groups. This finding is not statistically significant with a p-value of 0.43. The meta-analysis provides strong evidence that ACT is superior to quinine in reducing mortality in patients with pulmonary malaria. This finding supports the use of ACT as the preferred treatment option for this condition. The results suggest that ACT and artesunate have similar efficacy in terms of mortality. This indicates that both therapies are viable options for treating pulmonary malaria, and the choice between them may depend on other factors such as drug availability, cost, and patient preferences. The I^2 statistic is 0% for both comparisons, indicating low heterogeneity between the included studies. This suggests that the results are consistent across different study populations and settings.

Table 3. Meta-analysis of mortality.

Comparison	Study ID	Deaths (Intervention)	Total (Intervention)	Deaths (Comparison)	Total (Comparison)	Risk ratio (95% CI)	P-value	I^2
ACT vs. Quinine	Study 1	15	175	25	175	0.60 (0.35-1.03)	0.06	0%
	Study 2	8	140	15	140	0.53 (0.24-1.17)	0.12	0%
	Study 3	25	308	40	307	0.63 (0.40-0.99)	0.04	0%
	Pooled	**48**	**623**	**80**	**622**	**0.67 (0.52-0.86)**	**0.002**	**0%**
ACT vs. Artesunate	Study 4	10	100	12	100	0.83 (0.40-1.73)	0.62	0%
	Study 5	1	8	1	7	0.88 (0.06-12.98)	0.93	0%
	Study 7	8	91	10	91	0.80 (0.35-1.83)	0.60	0%
	Pooled	**19**	**199**	**23**	**198**	**0.92 (0.75-1.13)**	**0.43**	**0%**

ACT = Artemisinin-based combination therapy; IV = Intravenous; RR = Risk ratio; CI = Confidence interval.

Table 4 presents the results of the meta-analysis comparing the parasite clearance time associated with different antimalarial therapies in the treatment of pulmonary malaria. The table focuses on two main comparisons: ACT vs. Quinine and ACT vs. Artesunate; ACT vs. Quinine: This comparison includes data from three studies (Study 1, Study 2, and Study 3). The pooled analysis of these studies shows that ACT is associated with a significantly faster parasite clearance time compared to quinine. The mean difference of -12.5 hours indicates that, on average, it takes 12.5 hours less for parasites to be cleared from the bloodstream in patients treated with ACT compared to those treated with quinine. This finding is statistically significant with a p-value of <0.0001; ACT vs. Artesunate: This comparison includes data from three studies (Study 4, Study 5, and Study 7). The pooled analysis shows that there is no significant difference in parasite clearance time between ACT and artesunate. The mean difference of -1.2 hours is not statistically significant with a p-value of 0.51. The meta-analysis provides strong evidence that ACT clears parasites from the bloodstream significantly faster than quinine. This rapid parasite clearance may contribute to the improved clinical outcomes observed with ACT, such as reduced mortality and faster resolution of respiratory distress. The results suggest that ACT and artesunate have similar parasite clearance times. This finding is consistent with the observation that both therapies have comparable efficacy in terms of mortality. The I^2 statistic is 0% for both comparisons, indicating low heterogeneity between the included studies. This suggests that the results are consistent across different study populations and settings.

Table 4. Meta-analysis of parasite clearance time.

Comparison	Study ID	Mean difference (Hours)	95% CI	P-value	I^2
ACT vs. Quinine	Study 1	-14.2	-19.8 to -8.6	< 0.0001	0%
	Study 2	-10.8	-16.4 to -5.2	0.0002	0%
	Study 3	-12.5	-17.2 to -7.8	< 0.0001	0%
	Pooled	**-12.5**	**-18.2 to -6.8**	**< 0.0001**	**0%**
ACT vs. Artesunate	Study 4	-1.5	-5.1 to 2.1	0.41	0%
	Study 5	-0.8	-4.4 to 2.8	0.66	0%
	Study 7	-1.2	-4.8 to 2.4	0.51	0%
	Pooled	**-1.2**	**-4.8 to 2.4**	**0.51**	**0%**

Table 5 presents the results of the meta-analysis comparing the time to respiratory distress resolution associated with different antimalarial therapies in the treatment of pulmonary malaria. The table focuses on two main comparisons: ACT vs. Quinine and ACT vs. Artesunate; ACT vs. Quinine: This comparison includes data from three studies (Study 1, Study 2, and Study 3). The pooled analysis of these studies shows that ACT is associated with a significantly faster resolution of respiratory distress compared to quinine. The mean difference of -2.3 days indicates that, on average, it takes 2.3 days less for patients treated with ACT to experience resolution of respiratory distress compared to those treated with quinine. This finding is statistically significant with a p-value of <0.0001; ACT vs. Artesunate: This comparison includes data from three studies (Study 4, Study 5, and Study 7). The pooled analysis shows that there is no significant difference in respiratory distress resolution time between ACT and artesunate. The mean difference of -0.4 days is not statistically significant with a p-value of 0.32. The meta-analysis provides strong evidence that ACT leads to a faster resolution of respiratory distress compared to quinine. This finding is consistent with the faster parasite clearance time observed with ACT and may contribute to the reduced mortality associated with this therapy. The results suggest that ACT and artesunate have similar times to resolution of respiratory distress. This finding further supports the observation that both therapies have comparable efficacy in treating pulmonary malaria. The I^2 statistic is 0% for both comparisons, indicating low heterogeneity between the included studies. This suggests that the results are consistent across different study populations and settings.

Table 5. Meta-analysis of respiratory distress resolution.

Comparison	Study ID	Mean Difference (Days)	95% CI	P-value	I^2
ACT vs. Quinine	Study 1	-2.5	-3.3 to -1.7	< 0.0001	0%
	Study 2	-2.1	-2.9 to -1.3	0.0001	0%
	Study 3	-2.3	-3.1 to -1.5	< 0.0001	0%
	Pooled	**-2.3**	**-3.1 to -1.5**	**< 0.0001**	**0%**
ACT vs. Artesunate	Study 4	-0.5	-1.3 to 0.3	0.22	0%
	Study 5	-0.3	-1.1 to 0.5	0.45	0%
	Study 7	-0.4	-1.2 to 0.4	0.32	0%
	Pooled	**-0.4**	**-1.2 to 0.4**	**0.32**	**0%**

Table 6 presents the results of the meta-analysis comparing the length of hospital stay associated with different antimalarial therapies in the treatment of pulmonary malaria. The table focuses on two main comparisons: ACT vs. Quinine and ACT vs. Artesunate; ACT vs. Quinine: This comparison includes data from three studies (Study 1, Study 2, and Study 3). The pooled analysis of these studies shows that ACT is associated with a significantly shorter length of hospital stay compared to quinine. The mean difference of -3.1 days indicates that, on average, patients treated with ACT are hospitalized for 3.1 days less than those treated with quinine. This finding is statistically significant with a p-value of <0.0001; ACT vs. Artesunate: This comparison includes data from three studies (Study 4, Study 5, and Study 7). The pooled analysis shows that there is no significant difference in the length of hospital stay between ACT and artesunate. The mean difference of -0.8 days is not statistically significant with a p-value of 0.12. The meta-analysis provides strong evidence that ACT leads to a significantly shorter hospital stay compared to quinine. This finding is consistent with the faster parasite clearance time and quicker resolution of respiratory distress observed with ACT, potentially leading to earlier discharge from the hospital. The results suggest that ACT and artesunate have similar lengths of hospital stay. This finding further supports the observation that both therapies have comparable efficacy in treating pulmonary malaria. The I^2 statistic is 0% for both comparisons, indicating low heterogeneity between the included studies. This suggests that the results are consistent across different study populations and settings.

Table 6. Meta-analysis of length of hospital stay.

Comparison	Study ID	Mean difference (Days)	95% CI	P-value	I^2
ACT vs. Quinine	Study 1	-3.3	-4.5 to -2.1	< 0.0001	0%
	Study 2	-2.9	-4.1 to -1.7	< 0.0001	0%
	Study 3	-3.1	-4.2 to -2.0	< 0.0001	0%
	Pooled	**-3.1**	**-4.2 to -2.0**	**< 0.0001**	**0%**
ACT vs. Artesunate	Study 4	-0.9	-2.1 to 0.3	0.14	0%
	Study 5	-0.7	-1.9 to 0.5	0.26	0%
	Study 7	-0.8	-1.8 to 0.2	0.12	0%
	Pooled	**-0.8**	**-1.8 to 0.2**	**0.12**	**0%**

4. Discussion

This meta-analysis revealed a critical finding in the treatment of pulmonary malaria the significant advantage of artemisinin-based combination therapy (ACT) over quinine in reducing mortality. This section delves deeper into this finding, exploring the evidence, the potential mechanisms behind ACT's superiority, and the broader implications for clinical practice. The pooled analysis of three randomized controlled trials (RCTs) directly comparing ACT to quinine demonstrated a substantial reduction in mortality associated with ACT. Patients receiving ACT had a 33% lower risk of death compared to those treated with quinine. This result was statistically significant, indicating that the observed difference is unlikely due to chance. This finding aligns with a growing body of evidence that supports the use of ACT as the preferred treatment for malaria, particularly in severe cases, including those with pulmonary involvement. Several factors may contribute to the superior outcomes observed with ACT in the treatment of pulmonary malaria. ACT has been shown to clear parasites from the bloodstream more rapidly than quinine. This rapid parasite clearance may be crucial in preventing the progression of pulmonary complications. By quickly reducing the parasite burden, ACT may help to mitigate the inflammatory response and prevent the development of acute respiratory distress syndrome (ARDS), a major cause of death in patients with pulmonary malaria. ACT is generally associated with

fewer adverse effects compared to quinine. Quinine can cause a range of side effects, including cinchonism (a syndrome characterized by tinnitus, headache, nausea, and visual disturbances) and hypoglycemia (low blood sugar). These side effects can be severe and may contribute to poor outcomes in patients with pulmonary malaria. ACT, on the other hand, is generally well-tolerated, with fewer serious side effects. Some studies suggest that ACT may improve endothelial function, which is critical for maintaining the integrity of the pulmonary vasculature. Endothelial dysfunction is a hallmark of pulmonary malaria and can lead to increased vascular permeability, fluid leakage into the lungs, and ultimately, ARDS. By improving endothelial function, ACT may help to prevent these complications and improve patient outcomes. ACT may also have immunomodulatory effects that contribute to its efficacy in pulmonary malaria. The inflammatory response plays a crucial role in the pathogenesis of pulmonary malaria, and excessive inflammation can lead to lung injury and ARDS. ACT may help to regulate the inflammatory response, reducing the severity of lung injury and improving patient outcomes. The findings of this meta-analysis have important implications for clinical practice in the management of pulmonary malaria. The evidence supporting the superiority of ACT over quinine reinforces the World Health Organization (WHO) recommendation of ACT as the first-line treatment for malaria, including severe cases with pulmonary involvement. In settings where both ACT and quinine are available, the choice should generally favor ACT, particularly in patients with severe malaria or those at high risk of developing pulmonary complications. The rapid parasite clearance, reduced adverse effects, and potential benefits on endothelial function and immune response make ACT a more favorable option for these patients.[11-13]

This meta-analysis examined the comparative efficacy of two leading antimalarial treatments, artemisinin-based combination therapy (ACT) and artesunate, in the context of pulmonary malaria. The results revealed no significant difference in mortality between the two therapies, suggesting that both are effective options for this severe condition. This section further explores this finding, discussing the evidence base, potential explanations for the comparable efficacy, and the implications for clinical decision-making. The pooled analysis of three randomized controlled trials (RCTs) directly comparing ACT to artesunate did not demonstrate a statistically significant difference in mortality rates. This indicates that the risk of death is similar for patients treated with either ACT or artesunate. This finding is supported by several individual studies that have also reported comparable efficacy between these two therapies in treating severe malaria, including cases with pulmonary involvement. Several factors may contribute to the comparable efficacy observed between ACT and artesunate in the treatment of pulmonary malaria. Both ACT and artesunate contain artemisinin derivatives as their core active component. These derivatives share a similar mechanism of action, targeting the parasite's mitochondria and disrupting its growth. This shared mechanism likely explains the comparable efficacy observed in clinical trials. Both ACT and artesunate are known for their rapid parasite clearance properties. This rapid reduction in parasite burden is crucial in preventing the progression of pulmonary complications and improving patient outcomes. The comparable speed of parasite clearance with both therapies may contribute to their similar efficacy in reducing mortality. Both ACT and artesunate generally have favorable safety profiles compared to older antimalarial drugs like quinine. This reduces the risk of adverse events that could complicate the clinical course of pulmonary malaria and potentially contribute to mortality. While there are some differences in the pharmacokinetic and pharmacodynamic properties of ACT and artesunate, these differences may not be clinically significant in the context of pulmonary malaria. Both therapies achieve adequate drug concentrations in the lungs to effectively clear parasites and resolve the infection. The finding of comparable efficacy between ACT and

artesunate offers clinicians valuable flexibility in tailoring treatment decisions for individual patients with pulmonary malaria. The availability of specific ACT formulations or artesunate may vary depending on the region and local healthcare resources. Clinicians should choose the therapy that is most readily accessible to ensure timely and effective treatment. The cost of ACT and artesunate can vary significantly depending on the specific formulation and local market conditions. Cost-effectiveness analysis may be necessary to guide treatment decisions, particularly in resource-limited settings. Patient preferences and individual factors, such as the risk of adverse events or drug interactions, may also influence the choice between ACT and artesunate. Shared decision-making between clinicians and patients is essential to ensure optimal treatment adherence and satisfaction.[14-16]

The findings of this meta-analysis have substantial clinical implications for healthcare professionals involved in the management of malaria, particularly cases complicated by pulmonary involvement. The evidence underscores the importance of adhering to current treatment guidelines while also highlighting the need for individualized patient care and ongoing research to further refine treatment strategies. The meta-analysis strongly supports the World Health Organization's (WHO) recommendation of artemisinin-based combination therapy (ACT) as the first-line treatment for malaria, including severe cases with pulmonary manifestations. The significant reduction in mortality observed with ACT compared to quinine emphasizes the critical role of ACT in improving patient outcomes. This finding should encourage healthcare providers to prioritize ACT as the preferred treatment option for all patients with malaria, especially those at risk of developing pulmonary complications. While ACT is the recommended first-line treatment, the meta-analysis also highlights the comparable efficacy of ACT and artesunate in treating pulmonary malaria. This finding provides clinicians with valuable flexibility in tailoring treatment decisions to individual patient needs and circumstances. Factors such as drug availability, cost considerations, patient preferences, and potential drug interactions should be carefully considered when choosing between ACT and artesunate. For instance, in areas where access to specific ACT formulations is limited, artesunate may be a suitable alternative, especially in severe cases requiring rapid parasite clearance. Conversely, in uncomplicated cases where the risk of recrudescence is a concern, ACT's longer duration of action may be more advantageous. The findings of this meta-analysis emphasize the importance of adhering to established treatment guidelines for malaria. Early diagnosis and prompt initiation of appropriate antimalarial therapy are crucial for preventing severe complications, including pulmonary involvement. Healthcare providers should be vigilant in identifying patients at risk of developing severe malaria and ensure timely access to effective treatment. Furthermore, adherence to the full course of antimalarial treatment is essential to prevent recrudescence and the development of drug resistance. Patient education and counseling play a critical role in promoting treatment adherence and minimizing the risk of treatment failure. The emergence and spread of antimalarial drug resistance pose a significant threat to malaria control efforts. The meta-analysis findings underscore the need for continuous monitoring of parasite resistance to both ACT and artesunate to ensure the long-term effectiveness of these therapies. Healthcare providers should be aware of local resistance patterns and adjust treatment strategies accordingly. In areas where resistance to ACT or artesunate is prevalent, alternative treatment options or combination therapies may be necessary. Ongoing research is crucial to develop new antimalarial drugs and strategies to combat drug resistance and maintain effective malaria control. While antimalarial therapy is the cornerstone of managing pulmonary malaria, supportive care plays a vital role in improving patient outcomes. This includes measures such as respiratory support, fluid management, and treatment of complications such as ARDS and sepsis. Healthcare

providers should be equipped to provide comprehensive supportive care to patients with pulmonary malaria, in addition to appropriate antimalarial therapy. The findings of this meta-analysis have broader public health implications for malaria control programs. The evidence supporting the efficacy of ACT reinforces the need for widespread access to this life-saving therapy, particularly in malaria-endemic regions. Public health initiatives should focus on strengthening healthcare systems, ensuring adequate drug supplies, and promoting early diagnosis and treatment of malaria. Furthermore, efforts to prevent malaria transmission, such as vector control measures and the development of effective vaccines, are crucial for reducing the burden of malaria and preventing severe complications like pulmonary malaria.[17-20]

5. Conclusion

This meta-analysis has demonstrated the significant advantage of ACT over quinine in reducing mortality in patients with pulmonary malaria. The rapid parasite clearance, reduced adverse effects, and potential benefits on endothelial function and immune response make ACT a more favorable option for these patients. The findings of this meta-analysis have important implications for clinical practice in the management of pulmonary malaria. The evidence supporting the superiority of ACT over quinine reinforces the World Health Organization (WHO) recommendation of ACT as the first-line treatment for malaria, including severe cases with pulmonary involvement. This meta-analysis also examined the comparative efficacy of two leading antimalarial treatments, artemisinin-based combination therapy (ACT) and artesunate, in the context of pulmonary malaria. The results revealed no significant difference in mortality between the two therapies, suggesting that both are effective options for this severe condition. The findings of this meta-analysis have substantial clinical implications for healthcare professionals involved in the management of malaria, particularly cases complicated by pulmonary involvement. The evidence underscores the importance of adhering to current treatment guidelines while also highlighting the need for individualized patient care and ongoing research to further refine treatment strategies.

6. References

1. Abd-Rahman AN, Kaschek D, Kümmel A, Webster R, Potter AJ, Odedra A, et al. Characterizing the pharmacological interaction of the antimalarial combination artefenomel-piperaquine in healthy volunteers with induced blood stage *Plasmodium falciparum*. bioRxiv. 2024.
2. D'Agostino I, Zara S, Carradori S, De Luca V, Capasso C, Kocken CHM, et al. Antimalarial agents targeting *Plasmodium falciparum* carbonic anhydrase: Towards Artesunate hybrid compounds with dual mechanism of action. ChemMedChem. 2023; 18(21): e202300267.
3. WorldWide Antimalarial Resistance Network Methodology Study Group. Temporal distribution of *Plasmodium falciparum* recrudescence following artemisinin-based combination therapy: an individual participant data meta-analysis. Malar J. 2022; 21(1): 106.
4. Pradhan B. Some considerations in antimalarial chemotherapy of severe falciparum malaria. J Evid Based Med Healthc. 2017; 4(13): 743–8.
5. In I, Yb N, Ih N, Yahaya, Timshana, Ibrahim. Antimalarial susceptibility profile of *Plasmodium falciparum* isolated from human population in selected health facilities in Keffi metropolis, Nasarawa state, Nigeria. Asian J Res Biochem. 2025; 15(1): 23–35.
6. K. DS. Pulmonary Complications in Falciparum Malaria in a tertiary care center in costal Andhra Pradesh. IOSR J Dent Med Sci. 2013; 4(3): 82–5.

7. Milner D Jr, Factor R, Whitten R, Carr RA, Kamiza S, Pinkus G, et al. Pulmonary pathology in pediatric cerebral malaria. Hum Pathol. 2013; 44(12): 2719–26.
8. Pantazidou A, Tebruegge M. Pulmonary edema and acute respiratory distress syndrome in a child with *Plasmodium falciparum* malaria. J Pediatr Infect Dis. 2015; 02(04): 231–5.
9. Punsawad C, Viriyavejakul P, Setthapramote C, Palipoch S. Enhanced expression of Fas and FasL modulates apoptosis in the lungs of severe *P. falciparum* malaria patients with pulmonary edema. Int J Clin Exp Pathol. 2015; 8(9): 10002–13.
10. Miller ER, Hunninghake GM. Malaria and the development of pulmonary fibrosis. Eur Respir J. 2017; 50(6): 1702030.
11. Elzein F, Mohammed N, Ali N, Bahloul A, Albadani A, Alsherbeeni N. Pulmonary manifestation of *Plasmodium falciparum* malaria: Case reports and review of the literature. Respir Med Case Rep. 2017; 22: 83–6.
12. Maknitikul S, Luplertlop N, Grau GER, Ampawong S. Dysregulation of pulmonary endothelial protein C receptor and thrombomodulin in severe falciparum malaria-associated ARDS relevant to hemozoin. PLoS One. 2017; 12(7): e0181674.
13. Hage R, Schuurmans M. Malaria-associated pulmonary edema. Eurasian J Pulmonol. 2020; 22(2): 132.
14. Viriyavejakul P, Punsawad C. Overexpression of sphingosine kinase-1 and sphingosine-1-phosphate receptor-3 in severe *Plasmodium falciparum* malaria with pulmonary edema. Biomed Res Int. 2020; 2020: 3932569.
15. Wegener A, Holm A, Gomes L, Lima K, Matos L, Vieira I, et al. B-lines by lung ultrasound is associated with pulmonary symptoms and cardiac function in acute malaria: a prospective cohort study. Eur Heart J. 2021; 42(Suppl_1).
16. Siagian FE. Pulmonary Complication in Severe Malaria. Int J Pathog Res. 2021; 19–27.
17. Pugliese CM, Adegbite BR, Edoa JR, Mombo-Ngoma G, Obone-Atome FA, Heuvelings CC, et al. Point-of-care ultrasound to assess volume status and pulmonary oedema in malaria patients. Infection. 2022; 50(1): 65–82.
18. Ojaimi N, Cifra EM, Mlilo M, Metri A. Severe malaria complicated by noncardiogenic pulmonary edema: When hypoparasitemia provides false reassurance. Chest. 2024; 166(4): A5642–3.
19. Klinkhamhom A, Glaharn S, Srisook C, Ampawong S, Krudsood S, Ward SA, et al. M1 macrophage features in severe *Plasmodium falciparum* malaria patients with pulmonary oedema. Malar J. 2020; 19(1): 182.
20. Ishioka H, Ghose A, Kingston HW, Plewes K, Leopold SJ, Srinamon K, et al. The predictive capacity of biomarkers for clinical pulmonary oedema in patients with severe falciparum malaria is low: a prospective observational study. Malar J. 2024; 23(1): 320.