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Systematic Review

Efficacy of artemisinin derivatives and kelch13 mutations in *Plasmodium falciparum*: a systematic review and meta-analysis

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Abstract

Artemisinin-based combination therapies (ACTs) remain the cornerstone of treatment for uncomplicated *Plasmodium falciparum* malaria; however, the spread of artemisinin resistance linked to kelch13 (pfk13) mutations poses a major global concern. This study aimed to systematically evaluate ACT efficacy in parallel with the global distribution of pfk13 mutations and to explore the relationship between molecular markers and clinical outcomes.

A systematic review and meta-analysis were conducted using PubMed, Web of Science, and Scopus. Studies reporting 28-day adequate clinical and parasitological response (ACPR) following ACTs and assessing pfk13 mutations were included.

Thirty studies from Asia, Africa, and the Americas were analyzed. ACTs maintained high efficacy, with pooled ACPR rates exceeding 95% and no significant regional differences ($P = .99$). By contrast, pfk13 mutation prevalence was significantly higher in Asia ($P = .001$). Notably, high treatment success rates were maintained despite the increasing prevalence of pfk13 mutations, indicating that the relationship between molecular resistance markers and clinical outcomes remains complex and may be modulated by partner-drug efficacy, host immunity, and local transmission dynamics.

While ACTs remain highly effective, the marked geographical variation and persistence of resistance-associated mutations underscore the need for integrated molecular surveillance and therapeutic efficacy monitoring.

Keywords artemisinin resistance, kelch13, meta-analysis, mutation, *Plasmodium falciparum*

Introduction

Plasmodium spp. remain among the most widespread and neglected parasitic pathogens worldwide and can lead to severe and potentially fatal disease. According to the World Malaria Report 2025, an estimated 282 million malaria cases were recorded across 80 endemic countries in 2024, with ~610 000 deaths attributed to the disease. A noticeable increase has been observed since 2020 in annual malaria case numbers. Several factors are thought to contribute to this trend, including the limited effectiveness of mass screening and treatment campaigns due to the COVID-19 pandemic, the rising prevalence of insecticide-resistant *Anopheles* mosquitoes, and the geographic expansion of artemisinin-resistant parasite clones, among other emerging challenges.[1]

The development of artemisinin derivatives by Chinese scientists and the subsequent recognition of their antiplasmodial properties represent a major milestone in modern medical science.[2,3] During hemoglobin digestion, the release of heme and ferrous iron facilitates the biochemical activation of artemisinin, yielding highly reactive radical species. These radicals cause widespread molecular damage by modifying vital parasite constituents such as proteins, membrane lipids, and nucleic acids, ultimately compromising essential cellular pathways and leading to parasite death.[3] Following the widespread emergence of chloroquine- and sulfadoxine–pyrimethamine-resistant parasite strains, the WHO endorsed the use of artemisinin derivatives for the treatment of uncomplicated *Plasmodium falciparum* malaria in 2001 as a critical strategy to reduce malaria-related morbidity and mortality. Artemisinin-based combination therapies (ACTs) pair a rapidly acting artemisinin compound with a longer-acting partner drug to ensure complete clearance of residual parasitemia and to delay the development of resistance. The ACT regimens currently recommended include artemether–lumefantrine, artesunate–amodiaquine, artesunate–sulfadoxine/pyrimethamine, artesunate–mefloquine, dihydroartemisinin–piperaquine, and artesunate–pyronaridine.[4]

Following nearly a decade of successful implementation of ACTs, evidence of delayed parasite clearance—indicative of reduced susceptibility to artemisinin derivatives and/or their partner drugs—was first documented in 2007 in Western Cambodia.[5,6] A prolonged parasite clearance half-life exceeding 5 hours, as well as the persistence of parasitemia on day 3 after

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treatment initiation, are considered markers of delayed artemisinin response.[4] Progression from reduced susceptibility to clinically significant resistance generally requires concurrent resistance to the partner drug used in the ACT regimen. Artemisinin resistance has been strongly associated with mutations or polymorphisms in the propeller domain of the kelch13 (pfk13) gene, which diminish hemoglobin endocytosis and thereby reduce hemoglobin catabolism and artemisinin activation. These mutations also enhance the parasite's capacity to limit protein damage and improve DNA repair, collectively contributing to reduced drug susceptibility.[3,7] Although artemisinin resistance and pfk13 mutations were initially concentrated in Southeast Asia, recent reports have demonstrated the emergence of similar mutations in several African countries.[8] However, the extent to which geographical variation in pfk13 mutations correlates with contemporary ACT efficacy has not been systematically quantified across endemic regions.

The WHO recommends that therapeutic efficacy studies be conducted every 2 years and that first-line treatment policies be modified when drug efficacy falls below 90%. Drug performance may be assessed through day-3 parasitemia measurements or by evaluating the adequate clinical and parasitological response (ACPR) at day 28 or day 42.[4]

The aim of the present study is to undertake a rigorously designed meta-analysis to systematically evaluate the therapeutic efficacy of artemisinin-based combination therapies and to characterize the prevalence and geographical distribution of pfk13 mutations reported in published studies.

Materials and methods

Search strategies and data resources

A systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.[9] Relevant studies were identified through comprehensive searches of the PubMed, Web of Science, and Scopus databases conducted in October and November 2025. No language or time restrictions were applied. The following Boolean search terms were used: "*Plasmodium falciparum*" AND ("artemisinin resistance" OR "artemisinin-resistant" OR "artemisinin resistance-associated") AND ("K13" OR "kelch13" OR "kelch propeller") AND ("mutation" OR "polymorphism" OR "variant").

Inclusion criteria

Studies were included if they met the following criteria: patients were diagnosed with *P. falciparum* mono-infection and treated with artemisinin derivatives; the study explicitly reported ACPR; 28-day ACPR outcomes were available; and pfk13 polymorphisms or mutations were analyzed using polymerase chain reaction (PCR) and/or sequencing techniques. Eligibility criteria were restricted to studies reporting 28-day ACPR outcomes. In studies presenting both 28- and 42-day ACPR results, analyses were limited to treatment arms for which 28-day ACPR data were available. Whenever reported, PCR-corrected ACPR was preferentially extracted. In studies in which ACPR was not explicitly defined as PCR-corrected or uncorrected, the reported results were used.

Exclusion criteria

The following publications were excluded: reviews, systematic reviews, meta-analyses, letters to the editor, and commentaries; studies involving infections with more than one *Plasmodium* species; studies in which patient selection was based on artemisinin treatment response; and studies that did not report the term ACPR within the text.

Risk of bias assessment

As all included studies reported both treatment efficacy (ACPR) and pfk13 mutation data, risk of bias was assessed separately for each outcome using outcome-specific appraisal tools. For treatment efficacy outcomes, non-randomized comparative studies were evaluated using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool, whereas single-arm therapeutic efficacy and observational studies, which comprised the majority of included studies, were assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series. For pfk13 mutation prevalence outcomes, risk of bias was assessed using the JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data, as this outcome was analyzed as a prevalence measure rather than an intervention effect.

Assessment of publication bias

Publication bias was assessed by visual inspection of funnel plot asymmetry and statistically evaluated using Egger's regression test. Funnel plot analysis and Egger's test were performed only when at least 10 studies were available for a given outcome. $P < .05$ was considered indicative of potential small-study effects.

Data synthesis and statistical analysis

We conducted a meta-analysis of proportions based on data extracted from individual studies, including the number of events and total sample size. Proportions were stabilized using a logit transformation prior to pooling to account for studies with extreme values. Forest plots were generated using R (version 4.5.2) and the *meta* and *metafor* packages. Each plot displayed individual study proportions with 95% CIs.

Pooled estimates were calculated using both fixed-effects (FE) and random-effects (RE) models. Statistical heterogeneity was evaluated using the I^2 statistic; in accordance with conventional thresholds, a RE model was employed when heterogeneity exceeded 50%, while an FE model was adopted in cases of low heterogeneity ($I^2 \leq 50\%$). Fixed-effect estimates were presented only as a sensitivity analysis to evaluate the robustness of the pooled estimates. Between-study variance (I^2) was estimated using the maximum likelihood method. Wald-type confidence intervals were constructed on the logit scale and subsequently back-transformed to the proportion scale. A continuity correction of 0.5 was applied when necessary to accommodate studies with zero or all events.

Subgroup analyses were performed by continent and country to evaluate geographic differences in *pfk13* propeller mutation prevalence and the treatment efficacy of artemisinin derivatives. This approach enabled comparison of mutation prevalence and

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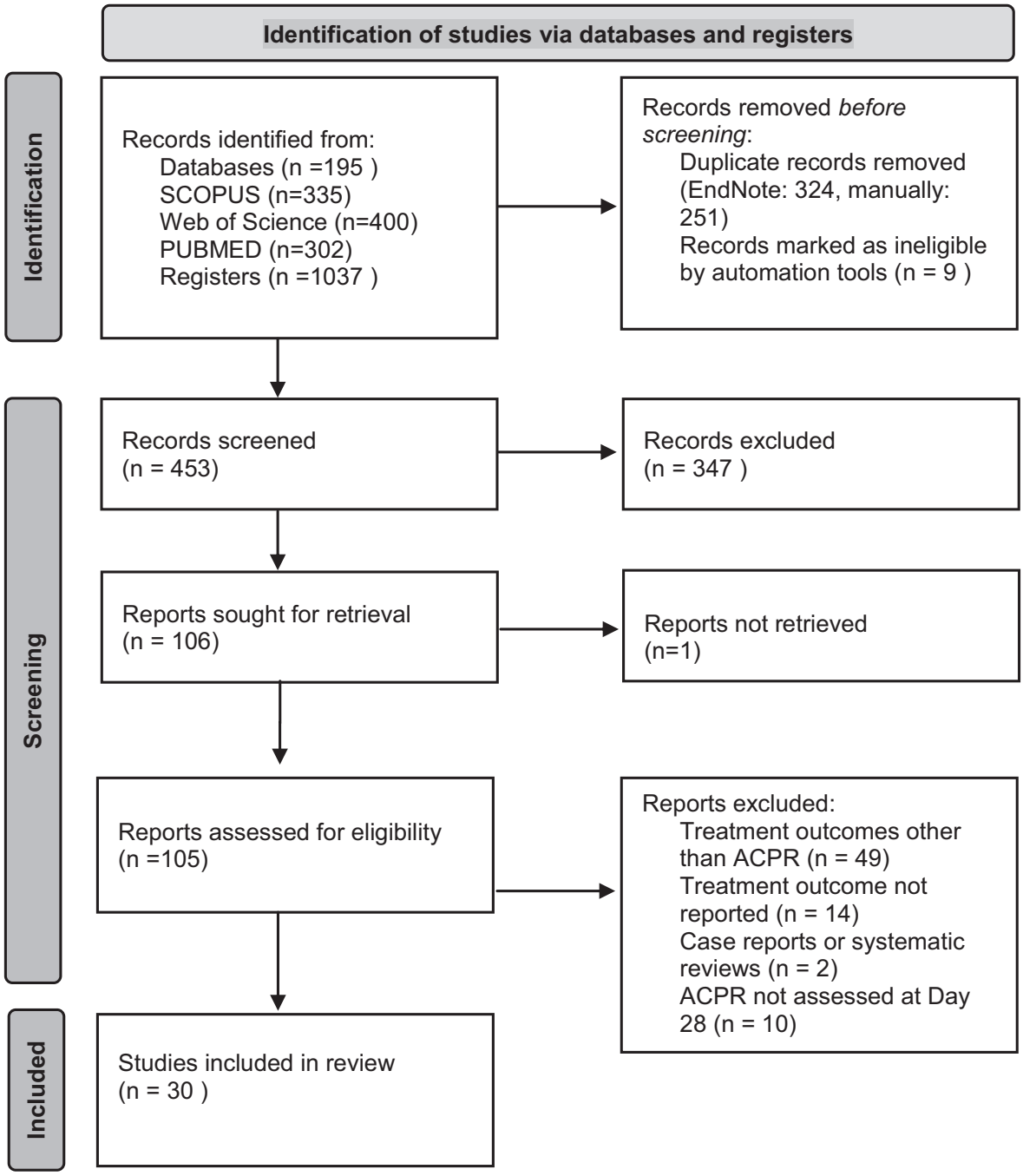

Figure 1 PRISMA flow diagram illustrating the study selection process for the meta-analysis.

treatment outcomes across different geographic regions, providing a quantitative synthesis of available data.

Results

Study selection

The literature search was independently performed by two reviewers (Ö.U.B. and G.A.A.) and repeated twice across the databases, yielding a total of 1037 records. Following the removal of duplicate and inaccessible publications, 453 records remained for screening. Title and abstract screening led to the exclusion of studies unrelated to the research question, as well as reviews, case reports, letters to the editor, and commentaries, resulting in 106 articles eligible for full-text assessment.

Full-text articles were evaluated according to predefined inclusion criteria: reporting day 28 ACPR, inclusion of *P. falciparum* mono-infection, treatment with artemisinin derivatives, and assessment of pfk13 polymorphisms or mutations. Seventy-five studies were excluded following full-text assessment, and one report could not be retrieved. Ultimately, 30 studies fulfilled all eligibility criteria and were included in the meta-analysis. A detailed overview of the study selection process is provided in the PRISMA flow diagram (Fig. 1).

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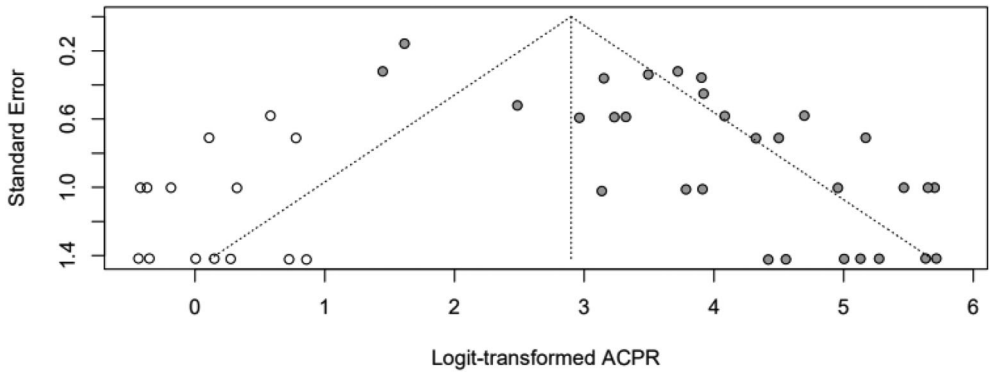

Figure 2 Funnel plot assessing publication bias.

Assessment of publication bias

Publication bias was evaluated using both visual and statistical methods, with results presented in Fig. 2. The funnel plot, in which each point represents an individual study plotted against its standard error, demonstrated evidence of asymmetry upon visual inspection. This asymmetry suggests the presence of potential small-study effects. Consistent with this observation, Egger's regression test showed statistically significant results ($P < .0001$), indicating possible publication bias.

Comparison of day 28 ACPR rates of artemisinin derivatives across continents and countries

Eleven studies were conducted exclusively in Asian countries, 15 in African countries, and three in the Americas; one study included sites in both Asia and Africa. Treatment success rates approached 100% in studies from the Americas, whereas the mean success rate was 98% in both Asian and African countries. Subgroup analysis by continent, as depicted in the forest plot (Fig. 3), did not reveal any statistically significant differences in ACPR rates among continents ($P = .999$), indicating consistent treatment efficacy of artemisinin derivatives across geographical regions.

Comparison of day 28 ACPR rates of different artemisinin-based combination therapies

In the studies included in the meta-analysis, various artemisinin-based treatment regimens were evaluated, including artefenomel–ferroquine, artemether–lumefantrine, artesunate, artesunate–amodiaquine, artesunate/amodiaquine–primaquine, artesunate–primaquine, artesunate–sulfadoxine/pyrimethamine, dihydroartemisinin–piperaquine, and pyronaridine–artesunate. In the forest plot analysis, five treatment combinations that were investigated in at least two studies were included in the comparative evaluation (Fig. 4). A statistically significant difference in ACPR rates was observed among the treatment regimens ($P = .001$). Post-hoc pairwise comparisons demonstrated that artemether–lumefantrine, artesunate–amodiaquine, artesunate–sulfadoxine/pyrimethamine, and dihydroartemisinin–piperaquine were significantly more effective than artefenomel–ferroquine ($P = .032$, $P = .008$, $P = .016$, and $P = .002$, respectively), whereas no statistically significant differences were identified among the remaining four treatment regimens ($P > .05$).

Continental comparison of pfk13 propeller mutation prevalence

A statistically significant difference was observed in the prevalence of pfk13 propeller mutations among *P. falciparum* isolates across Asia, Africa, and the Americas ($P = .001$). Studies conducted in Asia reported the highest mutation prevalence, with particularly elevated rates documented in Cambodia (100%) and Vietnam (89.5%) (Fig. 5, Table 1).

The pooled prevalence of pfk13 propeller mutations was highest in Asian studies compared with those conducted in Africa and the Americas, reflecting substantial geographical heterogeneity in mutation distribution (Fig. 5, Table 1). An apparent west-to-east gradient was observed, with pooled prevalences increasing from the Americas towards Asia, particularly in Southeast Asia (Fig. 6).

In addition to propeller-domain mutations, a limited number of studies also investigated non-propeller region mutations or polymorphisms using whole-genome sequencing (WGS) approaches (Table 1). However, the number of such studies was small, precluding a separate quantitative synthesis for non-propeller mutations.

Discussion

This systematic review and meta-analysis demonstrate that artemisinin derivatives remain highly effective for the treatment of *P. falciparum* malaria across diverse geographical regions. Pooled analyses of treatment success consistently showed high efficacy, with success proportions exceeding 95% in most studies (Fig. 3). One of the key findings of this analysis is that high ACPR rates were maintained despite the presence of resistance-associated pfk13 mutations, particularly in Asian settings. This finding may reflect the combined influence of partner-drug activity, host immunity, and local transmission dynamics. Resistance-associated pfk13 mutations may not immediately result in reduced ACPR, particularly in settings where partner drugs remain highly effective or where naturally acquired immunity contributes substantially to parasite clearance, as is often observed in high-transmission African settings. These observations highlight that the rela-

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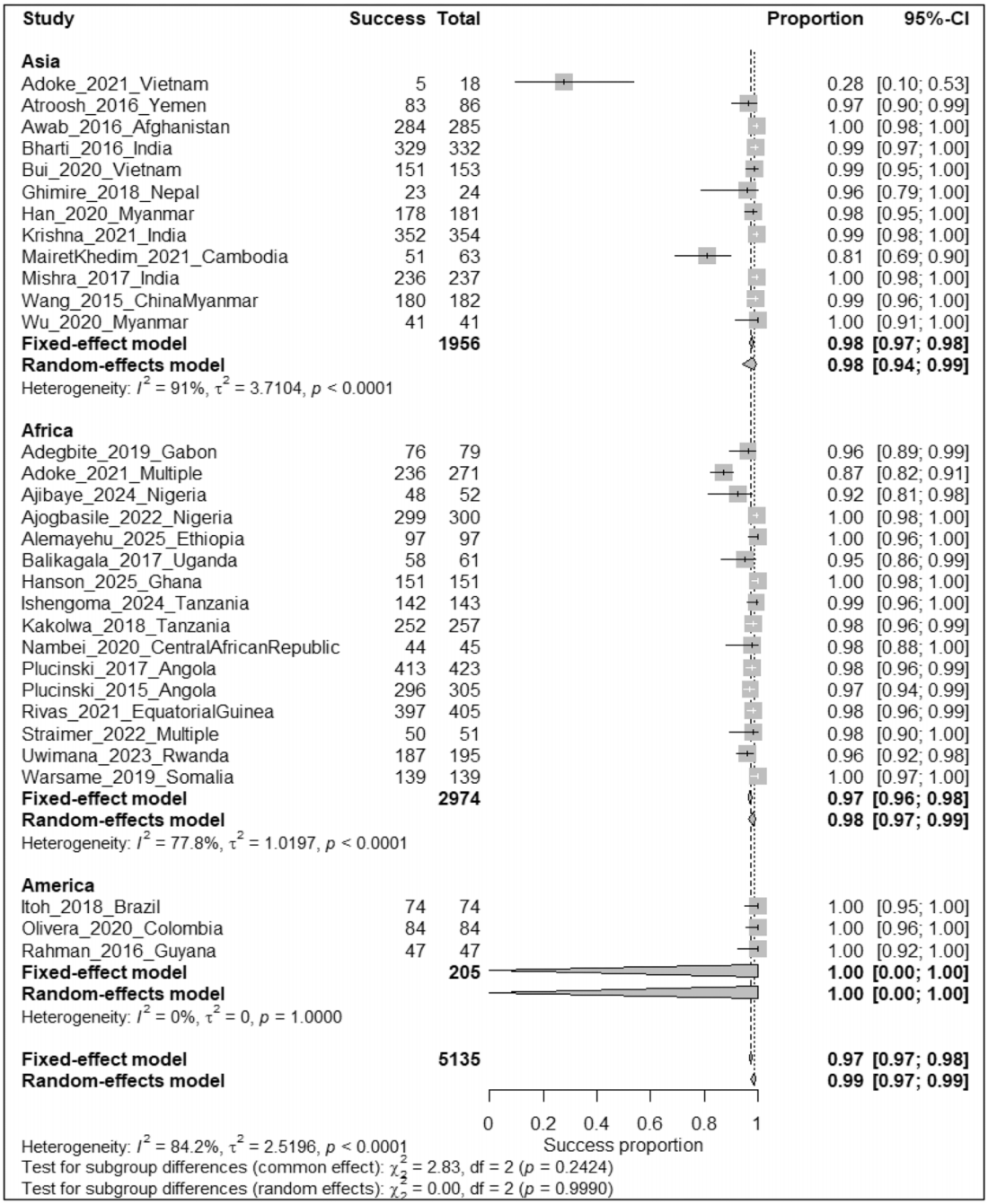

Figure 3 Forest plot comparing the ACPR rates of artemisinin-based treatments on day 28 after completion of therapy for *Plasmodium falciparum* malaria across continents, with countries presented as subgroups (The plot displays pooled ACPR estimates with corresponding 95% confidence intervals for each subgroup).

tionship between molecular markers of resistance and clinical treatment outcomes is complex and may be influenced by several factors beyond the presence of pfk13 mutations alone.

Studies conducted in Africa have consistently reported high treatment success rates and a lower prevalence of resistance-associated mutations, indicating the continued effectiveness of ACTs in high-transmission settings.[10,12,17,29,31,32,34,38] On the other hand, a systematic review conducted by Bohissou *et al*. reported substantial variation in ACT efficacy across Africa from 2015 to 2024, with ACPR rates falling below 90% in certain countries. By contrast, among the African studies included in the present meta-analysis, treatment efficacy exceeded 90% in all but one study.[11,40] However, the persistence and gradual spread of resistance-associated mutations highlight the need for continued vigilance, as high treatment efficacy observed today may not necessarily guarantee sustained effectiveness in the future.

With the further refinement of mutation analyses, it has become evident that not only the presence of mutations, but also their genomic location, is of critical importance. The pfk13 gene comprises both propeller and non-propeller regions. The pfk13 propeller domain, located within the C-terminal region of the gene and spanning approximately codons 440–726, has been widely

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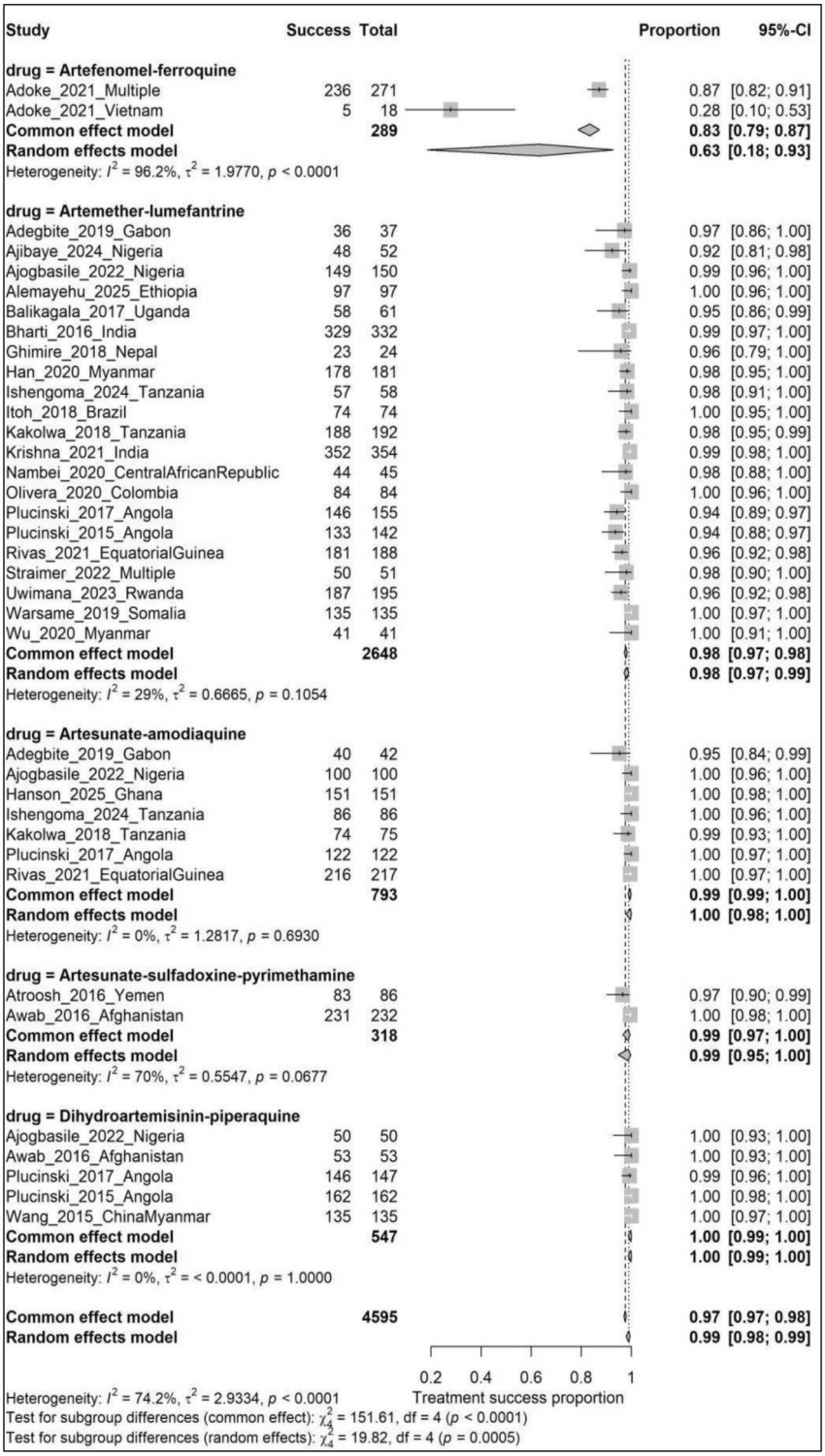

Figure 4 Forest plot comparing the treatment success rates of artemisinin derivatives, expressed as ACPR on day 28 after completion of therapy (Only artemisinin derivatives evaluated in at least two studies were included. The plot presents pooled ACPR estimates with corresponding 95% confidence intervals).

recognized as the principal locus of mutations associated with artemisinin resistance. By contrast, mutations occurring upstream of codon 440 are classified as non-propeller variants and are generally regarded as neutral polymorphisms or of uncertain clinical significance, as most have not demonstrated a consistent association with delayed parasite clearance.[41] From the outset, the primary objective of the WHO has been to identify molecular markers responsible for artemisinin resistance. Accordingly, WHO guidelines report validated, candidate, and potential mutations predominantly within the propeller domain. To date, 14 validated, 6

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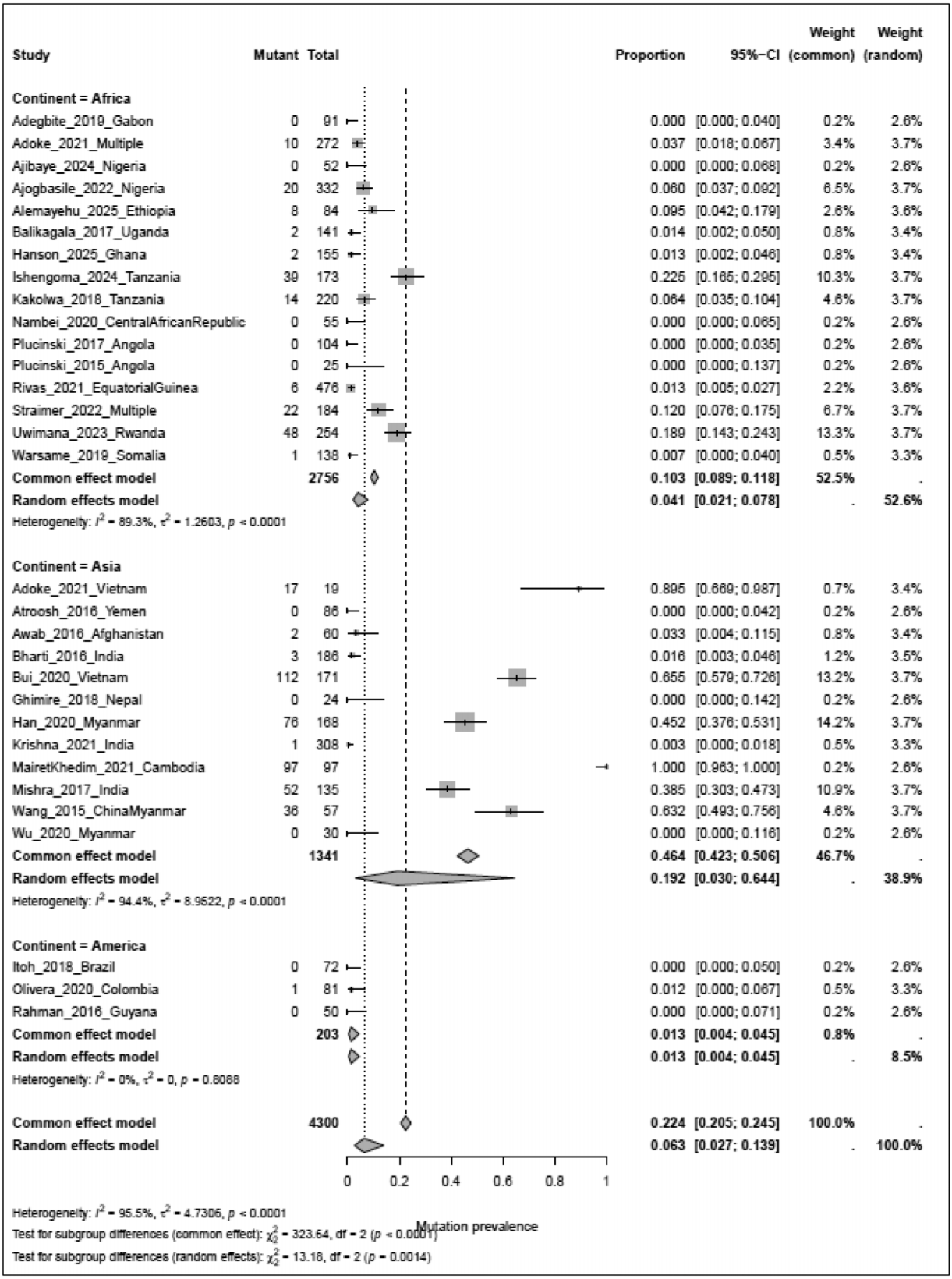

Figure 5 Forest plot showing continent-stratified pooled prevalence estimates of pfk13 propeller mutations in *Plasmodium falciparum* from patients receiving artemisinin-based treatments.

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Table 1 Overview of included studies and distribution of pfk13 mutations by geographic region and protein domain.

First author, publication year, reference	Country	Continent	Time interval	Total isolates (n)	Mutant isolates (n)	Mutation prevalence (%)	Propeller-domain mutations	Propeller mutation prevalence (%)	Non-propeller mutations	Method
Adegbite, 2019[10]	Gabon	Africa	2017–2018	91	0	0	-	0	NA	PCR[a]
Adoke, 2021[11]	Benin, Burkina Faso, Gabon, Kenya, Mozambique, Uganda	Africa	2015–2019	272	10	3.7	L444F, S522C, S550P, A578S, V589I	3.7	NA	PCR and sequencing
Adoke, 2021[11]	Vietnam	Asia	2015–2019	19	17	89.5	**C580Y**	89.5	NA	
Ajibaye, 2024[12]	Nigeria	Africa	2019	52	0	0	-	0	NA	PCR and sequencing[b]
Ajogbasile, 2022[13]	Nigeria	Africa	2018	332	21	6.3	G449S, F451L, C469C, V487E, A557S, A578S, Q613H, A621A, Q661H, N664I, N694K, V692G	6	K438N	PCR and sequencing[c]
Alemayehu, 2025[14]	Ethiopia	Africa	2017–2018	84	8	9.5	V510V, **R622I**	9.5	NA	PCR and sequencing
Atroosh, 2016[15]	Yemen	Asia	2014	86	0	0	-	0	NA	PCR and sequencing[d]
Awab, 2016[16]	Afghanistan	Asia	2007–2014	60	2	3.3	Y493C, S700L	3.3	NA	PCR and sequencing
Balikagala, 2017[17]	Uganda	Africa	2014	141	2	1.4	A578S	1.4	NA	PCR and sequencing
Bharti, 2016[18]	India	Asia	2014–2015	186	3	1.6	M579T	1.6	NA	PCR and sequencing
Quang Bui, 2020[19]	Vietnam	Asia	2017–2018	171	112	65.5	**C580Y**, *C469F*, K503N, **P553L**	65.5	-	PCR and sequencing
Ghimire, 2018[20]	Nepal	Asia	2013–2014	24	0	0	-	0	NA	PCR
Han, 2020[21]	Myanmar	Asia	2014–2015	168	76	45.2	**F446I**, **R561H**, **C580Y**, A676D, V692L	45.2	NA	PCR and sequencing
Hanson, 2025[22]	Ghana	Africa	2018–2019	155	61	39.4	A578S	1.3	F45Y, S97N, G112E, K189N, K189T, R255K, H136_N137insNN	PCR and WGS

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Table 1 Continued

First author, publication year, reference	Country	Continent	Time interval	Total isolates (n)	Mutant isolates (n)	Mutation prevalence (%)	Propeller-domain mutations	Propeller mutation prevalence (%)	Non-propeller mutations	Method
Ishengoma, 2024[23]	Tanzania	Africa	2022	173	39	22.5	**R561H** [Arg561His]	22.5	-	WGS
Itoh, 2018[24]	Brazil	America	2015–2016	72	0	0	-	0	NA	PCR and sequencing
Kakolwa, 2018[25]	Tanzania	Africa	2011–2015	220	14	6.4	L463S, **M476I**, G496S, V510M, E556K, M562T, E602D	6.4	NA	PCR and sequencing[e]
Krishna, 2021[26]	India	Asia	2017	308	1	3.3	Q613H	3.3	NA	PCR and sequencing
Mairet-Khedim, 2021[27]	Cambodia	Asia	2016–2017	97	97	100	**C580Y**, **Y493H**	100	NA	PCR and sequencing
Mishra, 2017[28]	India	Asia	2012–2014	135	52	39	M579T, N657H	39	NA	PCR and sequencing
Nambei, 2020[29]	Central African Republic	Africa	2017	55	0	0	-	0	NA	PCR-RFLP
Olivera, 2020[30]	Colombia	America	2018–2019	81	1	1.2	A504D	1.2	NA	PCR and sequencing
Plucinski, 2017[31]	Angola	Africa	2015	104	0	0	-	0	NA	PCR and sequencing
Plucinski, 2015[32]	Angola	Africa	2013	25	0	0	-	0	NA	PCR and sequencing
Rahman, 2016[33]	Guyana	America	2014	50	50	100	-	0	D80G, K189T	PCR and sequencing[f]
Riloha Rivas, 2021[34]	Equatorial Guinea	Africa	2017–2018	476	7	1.5	A578S, R471R, T478T	1.2	E433D	PCR and sequencing
Straimer, 2022[35]	Mali, Gabon, Ghana, Uganda, Rwanda	Africa	2018–2019	184	22	12	**R561H**, **P574L**, *C469F*, Q661E, P667S	12	NA	PCR and sequencing

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Table 1 Continued

First author, publication year, reference	Country	Continent	Time interval	Total isolates (n)	Mutant isolates (n)	Mutation prevalence (%)	Propeller-domain mutations	Propeller mutation prevalence (%)	Non-propeller mutations	Method
Uwimana, 2023[36]	Rwanda	Africa	2018	254	48	18.9	**R561H**, **P574L**, *C469F*, *P441L*, G449A, V555A, R575K	18.9	NA	PCR and sequencing
Wang, 2015[37]	China–Myanmar	Asia	2008–2013	57	38	66.7	**F446I**, **N458Y**, **C469Y**, **R539T**, **P574L**, A676D, H719	63.2	*E252Q*, R255K, NN insertion [136–137]	PCR and sequencing
Warsame, 2019[38]	Somalia	Africa	2016–2017	138	1	0.7	**R622I**	0.7	NA	PCR and sequencing
Wu, 2020[39]	Myanmar	Asia	2015	30	20	66.7	-	0	K189T, NN insertion after aa136	PCR and sequencing

[a]M476I, Y493H, R539T, I543T, and C580Y primers were used; [b]P574L/F446I/N458Y/Y493H/I543T/R539T/M476I/P553L/R561H/C580Y primers were used; [c]codons 427–709 were sequenced; [d]codons 364–709 were sequenced; [e]codons 443–666 were sequenced; [f]codons 49–705 were sequenced; NA: not applicable; PCR-RFLP: polymerase chain restriction fragment length polymorphism.
Note: markers written as bold: validated; italic: candidate; underlined: potential.

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Figure 6 World-map representing country-level pooled prevalence of *P. falciparum* pfk13 propeller mutations (Shading intensity represents the pooled prevalence of mutations, with darker colors indicating higher prevalence. Countries without available data are shown in white).

candidate, and 15 potential mutations or polymorphisms associated with artemisinin resistance have been described.[42]

Studies conducted in Asia predominantly reported mutations located within the propeller domain, including well-established resistance-associated variants such as C580Y, R561H, Y493H, F446I, P553L, R539T, N458Y, C469Y, and P574L (Table 1).[11,19,21,27,37] These mutations have been consistently associated with delayed parasite clearance and are recognized as validated molecular markers of partial artemisinin resistance.[42] Although the frequency of propeller region mutations in Africa is significantly lower than that reported in Asia, the data presented in Table 1 demonstrate that validated mutations are nonetheless present among African isolates.[14,23,25,35,36,38] This observation indicates that, despite the overall lower prevalence, the propeller region is not completely conserved within African parasite populations. For instance, a recent increase in the prevalence of the R622I mutation has been reported. While this mutation may confer a selective advantage under artemisinin drug pressure, its potential impact appears to be mitigated by strong host immunity in regions of high transmission intensity. This may currently limit its impact on population-level treatment outcomes.[14] In addition, another validated mutation, R561H, has been detected at a prevalence of 22.5% and has been associated with delayed parasite clearance and day 3 parasitemia. Notably, however, the continued clinical efficacy of artemisinin derivatives in these settings has largely been attributed to the effectiveness of partner drugs used in artemisinin-based combination therapies. Nevertheless, it should be emphasized that as resistance to partner drugs becomes more widespread and the selection of resistance-associated genes continues, the risk of developing clinically significant artemisinin resistance may increase.[23] Moreover, several studies have demonstrated that reduced artemisinin efficacy associated with pfk13 mutations increases the therapeutic reliance on partner drugs during infection treatment, thereby intensifying selective pressure on these agents and potentially accelerating the development of resistance to partner drugs.[35] The detection of resistance-associated mutations, even at low prevalence and with evidence of temporal increase, underscores the critical importance of sustained molecular surveillance and proactive resistance monitoring to prevent the future emergence or spread of artemisinin resistance.

The genomic context of pfk13 mutations is critical for the accurate interpretation of resistance surveillance data, as not all detected mutations confer the same level of clinical relevance. This highlights the need to integrate domain-specific molecular analyses with therapeutic efficacy studies, rather than relying solely on crude mutation prevalence, to more precisely assess the clinical impact of artemisinin resistance. In this context, although propeller region mutations are more prevalent in Asia, the detection of validated mutations in both Asia and Africa indicates that the risk of artemisinin resistance is not geographically restricted. Furthermore, while mutations outside the propeller domain may also contribute to resistance phenotypes,[13] relatively few studies have systematically investigated non-propeller regions.[22,37,39] This limitation largely stems from the fact that most resistance-focused studies have sequenced only the propeller region, potentially leading to an underestimation of the role of mutations beyond this domain.[13,15,25] Future surveillance efforts should therefore consider full-length pfk13 sequencing to capture the potential contribution of non-propeller variants.

Drug-specific analyses revealed that most artemisinin-based combinations—such as artemether-lumefantrine, artesunate-amodiaquine, dihydroartemisinin-piperaquine, and artesunate-sulfadoxine/pyrimethamine—maintained high efficacy despite regional differences in mutation prevalence. Previous studies have suggested that certain ACTs may exhibit relative advantages over others. Although artemether-lumefantrine remains the most widely used regimen, studies from specific regions have reported lower treatment success rates, potentially reflecting geographic variability in efficacy.[40] In addition, artemether lumefantrine-treated patients have been shown to experience higher rates of recurrence compared with those receiving dihydroartemisinin-piperaquine, likely due to the shorter half-life of lumefantrine.[43,44] However, in the present study, no significant differences were observed in PCR-corrected ACPR rates between the commonly used ACTs.

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Limitations

This review is subject to several limitations. First, studies reported ACPR at different follow-up time points, most commonly at day 28 or day 42. To ensure methodological consistency and avoid direct comparison of outcomes measured at different follow-up durations, only day-28 ACPR data were included in the analysis. Consequently, potentially relevant efficacy data reported exclusively at day 42 were excluded, which may have limited the comprehensiveness of the findings. This limitation is particularly relevant for dihydroartemisinin–piperaquine, for which ACPR outcomes are frequently reported at day 42 because of the longer elimination half-life. Second, while some of the included studies investigated genetic markers associated with partner drug resistance, the primary emphasis was placed on artemisinin and pfk13 mutations, and resistance determinants related to partner drugs were not systematically evaluated. Additionally, most included studies were not powered to detect early clinical resistance phenotypes such as delayed parasite clearance half-life, limiting correlation with molecular markers. Finally, relatively few studies were conducted within the last 3 years, a period during which ACT resistance appears to be emerging and evolving rapidly in parts of East and Central Africa. Consequently, the findings of this review may not fully capture the most recent changes in ACT efficacy and resistance patterns in these regions. These constraints should be considered when interpreting the comparative efficacy of ACTs across different studies and geographic regions.

Conclusions

In conclusion, this meta-analysis underscores that artemisinin derivatives continue to provide excellent clinical outcomes in the treatment of *P. falciparum* malaria. However, the geographical overlap between higher mutation prevalence and increased variability in treatment success—most notably in Asia—as well as the presence of validated pfk13 mutations in both Africa and Asia, highlights the ongoing risk of antimalarial resistance. The sustained high efficacy of current ACTs, coupled with the detection of resistance-associated mutations, underscores a critical window of opportunity for intensified surveillance rather than complacency. These findings reinforce that artemisinin resistance should be interpreted as a dynamic, multilevel phenomenon requiring integrated clinical, molecular, and pharmacological surveillance rather than reliance on single markers.

Author contributions

Özlem Ulusan Bağcı (Conceptualization [lead], Data curation [lead], Investigation [lead], Methodology [lead], Software [lead], Visualization [lead], Writing—original draft [lead]), Atilla Halil Elhan (Formal analysis [lead], Methodology [supporting], Software [supporting], Validation [lead], Writing—review & editing [supporting]), and Gülay Aral Akarsu (Supervision [lead], Validation [supporting], Writing—review & editing [lead])

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Data availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

Code availability

Not applicable.

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