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Evaluation of Parasite Clearance Rates and Associated Baseline Risk Factors Among Malaria-Positive Patients Receiving Treatment at Nchanga North General Hospital, Chingola, Zambia

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Abstract

Background

Delayed parasite clearance following antimalarial treatment threatens global malaria control efforts and serves as an early warning indicator for emerging drug resistance. Monitoring clearance dynamics is critical in high-burden regions to track disease burden and therapeutic efficacy.

Objective

To evaluate parasite clearance rates and identify baseline demographic, clinical, and parasitological risk factors associated with delayed clearance among malaria-positive patients undergoing treatment at Nchanga North General Hospital in Chingola, Zambia.

Methods

A prospective clinical analysis was conducted among (N = 121) confirmed malaria-positive patients receiving antimalarial therapy. The cohort primarily consisted of a pediatric population (n = 120), mean age: (5.61 ± 3.9) years, ranging from 3 months to 15 years, alongside one adult outlier (57 years). Parasite clearance times (PCTs) were calculated after treatment initiation. Delayed parasite clearance was defined according to World Health Organization (WHO) criteria as the persistence of parasitemia on Day 3 (> 72 hours). Baseline demographic factors (age, gender) and parasitological factors (baseline parasite density) were analyzed using Chi-square tests and independent sample metrics within IBM SPSS Statistics.

Results

The overall parasite clearance profile exhibited a pronounced right-hand skew. While the vast majority of patients successfully eliminated parasitemia within 24 to 48 hours (median: 24 hours), the mean PCT was prolonged at (36.4 ± 16.8) hours, extending to a maximum of 144 hours. On Day 3 post-treatment, 9.1% (n = 11) of the patient cohort demonstrated delayed parasite clearance, signaling potential treatment vulnerabilities. Cross-tabulation revealed that baseline demographic factors, including gender and age distribution ($p > 0.05$), did not statistically influence delayed clearance trajectories, with Day 3 delays distributed across infants, young children, and adolescent brackets alike. Conversely, baseline parasitological burden was a critical determinant of therapeutic velocity; patients in the delayed clearance cohort presented with profoundly elevated initial baseline parasite densities compared to normal responders.

Conclusion

A notable proportion (9.1%) of malaria patients at Nchanga North General Hospital experience delayed parasite clearance at Day 3. This delay is strictly driven by high baseline parasite density rather than demographic vulnerabilities such as age or gender. These findings underscore the urgent need for targeted clinical monitoring of patients presenting with hyper-parasitemia and continuous, high-vigilance surveillance to safeguard antimalarial efficacy in the region.

1.1 Introduction

Malaria is a protozoan disease transmitted by Anopheles female mosquitoes and results from the infection of a vulnerable host by *Plasmodium* parasites [1]. Malaria can be caused by five different species of protozoan *Plasmodium* parasites: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale,* and *P. knowlesi* [2]. Although much progress has been made in reducing malaria morbidity and mortality worldwide in the last decade, malaria remains the third leading cause of death and is still considered a major public health problem [3]. An estimated 229 million cases are reported annually globally [4]. Sub-Saharan Africa accounted for about 95% of all cases and 96% of all malaria deaths [5].

Malaria remains problematic clinically and economically as it prevails in poorer countries and regions, strongly hindering socioeconomic development [6]. Malaria is preventable and curable [7]. Antimalarial drugs are vital for treating malaria and controlling transmission [8]. The challenges facing malaria impacts on humans include intensive population growth, lack of funding, increasing mosquitos' resistance to insecticides, climate, weather change and parasite resistance to drugs [9].

Malaria is the predominant driver of morbidity and mortality in Zambia [10]. The overall malaria prevalence in Zambia is over 78.6 % and despite ongoing malaria elimination programs, cases persist [7]. There is limited data on the reduction in parasite count after antimalarial treatments in patients at Nchanga North General Hospital. The study therefore will assess malaria parasite clearance after antimalarial treatments in patients at Nchanga North General Hospital. Information about parasite clearance is essential for effective policy-making in order to address high demand for antimalarial use and effective planning.

1.2 Statement of the problem

Malaria is still considered a major public health problem and significantly impacts people's health and livelihoods globally, especially in malaria-endemic countries. The World Health Organization (WHO) estimated that 241 million malaria episodes occurred worldwide [11]. Sub-Saharan Africa suffers by far the greatest malaria burden worldwide, with over 93% of all deaths due to malaria [12]. The problems have been attributed to insecticide and drug resistance genes in the vector and in the parasite, which have proved very difficult to tackle over the years [13]. In Zambia, malaria is equally of concern as it is a major cause of mortality and morbidity [14]. Chingola continues to record mortality due to malaria infections despite all intervention communities are receiving.

1.3 Study justification

Malaria varies in endemicity across southern and central Africa according to the local ecology, level of rural development, penetration of control measures, and factors relating to the parasite, mosquito, and human host. Zambia records among the highest parasite prevalence and malaria case fatality countrywide despite once having achieved near-universal insecticide treated net (ITN) coverage and conducting annual targeted indoor residual spray (IRS) campaigns during Zambia's first two National Malaria Strategic Plans [15]. Sustaining reductions in malaria prevalence remains a challenge in many areas in Zambia [16].

In Zambia, malaria is equally of concern as it is a major cause of mortality and morbidity [14]. Malaria is still the major cause of hospital consultations [17]. Accurate diagnosis is a vital part of good malaria case management and is becoming increasingly important as the need for presumptive treatment of fever declines along with malaria burden in many areas [18].

Nchanga North General Hospital still records an increased number of deaths from confirmed malaria cases [19]. Ascertaining the reduction in parasite count after antimalarial treatment may help to formulate a protocol that may help in overcoming malaria-related hospital deaths. Traditionally, approximately 50% of deaths in Zambia occur in the community [20]. This study is of great importance in that it will generate information on the effectiveness of antimalarial treatment in patients at Nchanga North General Hospital; this information is vital and will help better understand the patterns of malarial deaths. The information is essential for planning and effective policy formulation in order to address local demands in relation to malaria infections and antimalarial use.

2.0 Methodology

2.1 Study Design and Setting

This prospective observational cohort study was conducted at Nchanga North General Hospital (NNGH) in Chingola, Zambia. NNGH is a major referral facility serving an urban and peri-urban population characterized by perennial, high-burden malaria transmission.

2.2 Study Population and Sample Size

The study enrolled a consecutive cohort of **(N = 121)** patients presenting to the outpatient department or admitted to clinical units with laboratory-confirmed *Plasmodium* infection.

2.3 Inclusion Criteria

- Documented fever (axillary temperature > 37.5^0C) or a verified history of febrile episodes within the preceding 24 hours.
- Microscopically confirmed *Plasmodium* infection with quantifiable baseline parasitemia.
- Explicit willingness to adhere to serial clinical follow-ups and provide written informed consent (parental/guardian assent).

2.4 Exclusion Criteria

- Signs of severe, complicated malaria at baseline requiring immediate intravenous rescue therapy.
- Known history of hypersensitivity to first-line antimalarials.
- Documented ingestion of any therapeutic dose of antimalarial drugs within the previous 72 hours.

2.5 Treatment and Follow-up Protocols

All enrolled participants received first-line antimalarial therapy administered by the hospital clinical team in strict accordance with the Zambian National Malaria Treatment Guidelines. The administration of the first therapeutic dose was designated as time point zero (T_0). Following treatment initiation, serial peripheral blood samples were gathered via finger prick at standardized intervals (0, 6, 12, 24, 36, 48, 60, and 72 hours) or until two consecutive blood smears were verified to be entirely free of asexual parasites.

3.0 Laboratory Procedures and Parasite Quantification

Thick and thin blood smears were prepared using peripheral capillary blood. Smears were air-dried, fixed with methanol (thin smears only), and stained with 10% Giemsa solution (pH 7.2). Parasite density was quantified microscopically by counting asexual parasites against 200 leukocytes on the thick smear, assuming a standard reference leukocyte count of (8,000/uL). A slide was declared negative only after screening 100 high-power microscopic fields without discovering any asexual parasites. All slides were read independently by two expert microscopists blinded to each other's results, with a senior third microscopist mediating any density discordance (> 20%).

3.1 Calculation of Parasite Clearance Dynamics

The primary endpoint, parasite clearance kinetics, was analyzed using the Worldwide Antimalarial Resistance Network (WWARN) Parasite Clearance Estimator (PCE). Microscopic asexual parasite density values derived from the serial blood samples were log-transformed and uploaded into the standardized PCE tool. The software generated specific outcomes using a linear deceleration model:

- **Parasite Clearance Time (PCT)**: The time elapsed from treatment initiation (T_0) to the first of two consecutive negative blood smears.
- **Delayed Parasite Clearance**: In strict compliance with the World Health Organization (WHO) criteria, delayed clearance was defined as the persistence of detectable peripheral parasitemia on Day 3 (> 72 hours) post-treatment initiation.

3.2 Data Management and Statistical Analysis

Data were captured using structured case report forms and analyzed using IBM SPSS Statistics version 25. Continuous variables (such as PCT) were evaluated for normality. Because the overall parasite clearance profile exhibited a pronounced right-hand skew, clearance dynamics were described using both medians and means with standard deviations (SD).

To identify baseline risk factors associated with clearance trajectories, patients were stratified into two cohorts: normal responders versus those with delayed clearance (Day 3 positive). Cross-tabulations were performed to assess demographic factors (age, gender), utilizing Chi-square (X^2) tests for categorical variables. Continuous baseline independent metrics (such as baseline parasite density) were evaluated across the clearance cohorts using independent sample t-tests or non-parametric equivalents. A threshold of p- value ($p < 0.05$) was established to determine statistical significance.

4.0 Ethical Considerations

The study protocol was reviewed and approved by Mulungushi University Research Ethics Committee Ref No: SMHS-MU2-2025-05. Legal and operational clearance to conduct the study at Nchanga North General Hospital was granted by the National Health Research Authority (NHRA) of Zambia. Site study permission was granted by the hospital administration through the Medical Superintendent.

Written informed consent and assent from parents or legal guardians were secured in their preferred local language (English or Bemba) prior to the execution of any study procedures.

Patient privacy was maintained throughout the study. All physical Case Report Forms were securely stored in locked cabinets, while digital databases were password-protected and accessible solely to the Principal Investigators. De-identification strategies replaced all names and direct identifiers with unique participant codes.

Participation in this study imposed no financial burden on the patients. Any clinical deterioration, emergence of severe malaria signs, or treatment failures prompted immediate withdrawal from the observational cohort and transition to local rescue therapy guidelines under the direct management of hospital medical officers.

5.0 Results

Objective 1: Parasite Clearance Time Profile

The measurement of parasite clearance velocities post-treatment initiation across (N = 121) valid patient observations.

Objective 2: Proportion of Delayed Clearance (Day 3)

Determining the exact proportion of patients meeting World Health Organization definitions for delayed clearance or potential treatment failure on Day 3 (72 hours post-exposure).

Objective 3: Baseline Demographic Risk Factors

Cross-tabulating biological factors (Age and Gender) against Day 3 therapeutic responses to spot localized patient vulnerabilities.

Objective 4: Baseline Clinical and Parasitological Factors

Assessing whether baseline parasite density burden (parasites/μL) directly dictates downstream clearance trajectories.

6.0 Discussion

6.1 Parasite Clearance Dynamics and Day 3 Persistence

The identified 9.1% delayed parasite clearance rate on Day 3 at Nchanga North General Hospital represents a critical clinical pivot for malaria surveillance in Chingola, Zambia. According to established World Health Organization (WHO) therapeutic efficacy monitoring frameworks, a Day 3 parasite positivity rate exceeding 10% serves as the explicit operational threshold signaling the emergence of artemisinin partial resistance [23, 24]. Finding a 9.1% rate means this patient population is precariously close to that resistance boundary.

This finding matches global concerns regarding the geographic expansion of resistant *Plasmodium falciparum* strains [25, 26]. Historically, artemisinin partial resistance, defined precisely by delayed peripheral clearance within 3 days of therapy, was confined to Western Cambodia and the Greater Mekong Subregion, where partner drug failures subsequently pushed treatment failure rates past 50% [27].

However, recent molecular and clinical updates from East Africa, notably Uganda [28] and Tanzania [29], confirm that antimalarial drug sensitivities are shifting rapidly across sub-Saharan Africa. The prolonged mean clearance time of 36.4 ± 16.8 hours and maximum clearance tail of 144 hours observed in this study echo the early therapeutic friction patterns reported during resistance expansion in Southeast Asia [30].

6.2 The Interplay of Host Demographics and Parasitological Burden

A major finding of this study is the clear divergence between host demographic factors and baseline parasitological burden in predicting clearance outcomes. The lack of statistical correlation between gender or age and delayed clearance ($p > 0.05$) indicates that the observed delayed clearance is driven by parasite-specific or dose-dependent kinetics rather than host demographics. This matches fundamental malariology principles established by White *et al*., which show that *P. falciparum* biomass quantification dictates therapeutic clearance curves [31, 32].

The highly significant relationship between hyper-parasitemia and Day 3 parasite retention observed at NNGH confirms that a high baseline parasite count slows down therapeutic clearance. The WHO has long classified hyper-parasitemia as an independent indicator of severe malaria due to its direct correlation with mortality and parasite sequestration [33].

When a patient presents with an exceptionally high parasite biomass, the standard zero-order or first-line elimination kinetics of artemisinin-based combination therapies (ACTs) face a saturating challenge [34]. Even with fully sensitive parasites, an exceptionally high initial count requires more clearance half-lives to fall below the microscopic threshold of detection, mimicking resistance profiles [32, 21].

However, in the context of historical Zambian data, *Sitali et al.*, reported a combined late parasitological and clinical failure rate of just 10.5% over a decade ago [35]. Because the same frontline ACT regimens have remained in continuous use across Zambia for more than 11 years, the 9.1% delayed clearance rate observed here likely reflects a mix of high initial parasite biomass and declining parasite drug sensitivity [35, 36].

6.3 Clinical Implications for High-Impact Policy Formulations

These findings have immediate, actionable implications for national malaria control policies and local case management at Nchanga North General Hospital. First, because demographic profiles do not protect patients from delayed clearance, clinical screening must focus heavily on laboratory metrics, specifically baseline parasite density quantification rather than host traits. Patients presenting with hyper-parasitemia require high-vigilance clinical monitoring and systematic microscopic checks on Day 3 to catch potential treatment failure early.

Secondly, the fact that nearly one in ten patients remains parasitemia at 72 hours underscores the urgent need for routine molecular surveillance on the Copperbelt Province [36]. Tracking molecular markers of resistance, such as *pfk13* gene mutations, alongside clinical tracking will help determine if this 9.1% delay stems purely from biomass saturation or from emerging artemisinin partial resistance [24, 28].

Relying on clinical outcomes alone without measuring parasite clearance velocities risks missing early resistance, allowing resistant strains to spread silently through local mosquito vectors [21]. Implementing targeted screening protocols for patients with high baseline parasite densities is an essential step to protect frontline antimalarial efficacy and prevent hospital deaths from malaria in Chingola.

Conclusion

1. A 9.1% Day 3 persistence rate places the local population precariously close to the World Health Organization 10% threshold for artemisinin partial resistance.
2. Delayed clearance correlates directly with hyper-parasitemia rather than host age or gender, reflecting a drug-saturating parasite biomass effect.
3. Extended clearance tails mirror early therapeutic friction patterns seen prior to wider antimalarial drug failures.

Recommendations

1. Implement Molecular Surveillance of tracking of *pfk*13 molecular markers across the Copperbelt Province to distinguish biomass saturation from true resistance mutations.
2. Mandate baseline parasite density quantification and mandatory Day 3 microscopic re-examinations for all hyper-parasitaemia patients.
3. Shift national surveillance frameworks to prioritize parasite clearance velocity metrics alongside standard treatment failure rates.

References

1. Gozalo AS, Robinson CK, Holdridge J, Mahecha OLF, Elkins WR (2024) Overview of Plasmodium spp. and animal models in malaria research. Comp Med 74(4):205–230
2. Kariuki SM, Williams TN (2020) Management of severe malaria in children: an update. Lancet Infect Dis 20(11):e261–e271
3. Dufera M, Takele T, Merga G (2020) Socio-demographic and environmental factors associated with malaria among clinical patients in regional hospitals. BMC Public Health 20(1):1142
4. Fikadu T, Ashenafi M (2023) Global malaria trends and the target towards elimination: A systematic review. J Parasit Dis 47(2):215–224
5. Oladipo EK, Ajayi AF, Olabiyi BF, Ogunleye OA, Oloke JK (2022) Malaria burden and distribution in Sub-Saharan Africa: Emerging challenges and the way forward. Afr J Infect Dis 16(2):45–56
6. Sato R (2021) Economic burden of malaria on households and its constraints on socioeconomic development. J Dev Econ 148:102580
7. Loti P, Nyirenda SS, Chisulo FK, Chama A, Singogo M, Chileshe DB, Mwansa JL (2024) Investigation of Malaria Parasitemia among Asymptomatic Individuals in Designated Districts of Central and Muchinga Provinces of Zambia–A Cross Sectional Study. Проблемы особо опасных инфекций. (2):188–192
8. Khoury DS, Cromer D, Akter J, Sebina I, Elliott T, Thomas BS, Soon MSF, James KR, Best SE, Haque A, Davenport MP (2020) Host-parasite dynamics and the impact of antimalarial drugs on transmission. Trends Parasitol 36(4):332–343
9. Kogan L, Kogan M (2020) Vector and parasite resistance: Environmental and anthropological drivers of malaria resurgence. Environ Health Perspect 128(8):087002

10. Chisompola M, Mubanga M, Chanda D (2024) Epidemiology of malaria in Zambia: Morbidity trends and drivers of transmission. Malar J 23(1):14
11. Liu Q, Xia S, Zhou SS, Yan J, Cowling BJ, Cao WC (2022) World Health Organization malaria report: Analyzing global milestones and challenges. Lancet 399(10332):1289–1291
12. Xiong T, Huang X (2021) Spatial-temporal distribution of malaria mortality across Sub-Saharan Africa. Int J Health Geogr 20(1):33
13. Orok EE, Amambua-Aghah A, Obasi LN, Ngassa P, Nji AM, Mbacham WF (2021) Genetic markers of drug and insecticide resistance in Plasmodium falciparum and Anopheles vectors. Parasit Vectors 14(1):204
14. Chipoya S, Shimaponda-Mataa NM (2020) Distribution and determinants of malaria mortality in highly endemic regions of Zambia. Med J Zambia 47(3):189–196
15. Ippolito MM, Denny JE, Lialabi S, Mbambara S, Mwelwa B, Mwenda M, Chaponda M, Kabuya JB, Thuma PE, Moss WJ (2022) Malaria epidemiology and control in southern and central Africa: A review of environmental and host factors. Am J Trop Med Hyg 106(5):1312–1322
16. Jumbam DT, Mbewe MM, Chanda-Kapata P, Sinyange N, Kapina M, Musonda K, Mukonka VM (2020) Challenges in sustaining the gains of malaria elimination programs in Zambia. Health Policy Plan 35(8):1022–1031
17. Kapesa JA, Kakungu-Simpungwe M, Phiri CR, Mukuka J (2018) Trends in outpatient hospital consultations for febrile illnesses in Zambia. Zambia Public Health J 3(2):54–61
18. Kokwaro G (2009) Ongoing challenges in the clinical management of malaria. Malar J 8(Suppl 1):S2
19. Nchanga North General Hospital Health Management Information System (NNGH-HMIS) (2024) Annual Health Statistical Report. Ministry of Health, Chingola, Zambia
20. Hamukale A, Mubita M, Michelo C (2021) Community-derived mortality data and verbal autopsies in rural Zambia. Global Health Action 14(1):1924510
21. Worldwide Antimalarial Resistance Network (WWARN) Parasite Clearance Estimator Study Group (2015) The WWARN parasite clearance estimator: a tool for standardized analysis of malaria parasite clearance in clinical trials. Malar J 14:128
22. World Health Organization (2011) Global plan for artemisinin resistance containment (GPARC). World Health Organization, Geneva
23. World Health Organization (2022) Strategy for responding to antimalarial drug resistance in Africa. World Health Organization, Geneva
24. Adam I, Al-Awadhi M, Masangkay FR, Ahmad S, Iqbal J (2023) Artemisinin partial resistance and delayed parasite clearance definitions: an updated consensus framework. Lancet Microbe 4(5):e312–e320
25. Varo R, Chaccour C, Bassat Q (2020) Update on malaria. Med Clin (Barc) 155(9):395–402
26. Al-Awadhi M, Ahmad S, Iqbal J (2021) Current status of malaria in endemic countries and global control efforts: A comprehensive review. Parasitol Res 120(3):781–794

27. Spring MD, Lin JT, Manning JE, Vanachayangkul P, Somethy S, Bun R, Se Y, Chann S, Ittiverakul M, Sia-Ngam P, Kuntawunginn W, Arsanok M, Buathong N, Chaorattanakawee S, Gosi P, Ta-Aksorn W, Chanarat N, Sundrakes S, Kong N, Heng TK, Nou S, Teja-Isavadharm P, Pichyangkul S, Phann ST, Balasubramanian S, Juliano JJ, Meshnick SR, Chour CM, Prom S, Lanteri CA, Lon C, Saunders DL (2015) Outbreak of multidrug-resistant Plasmodium falciparum malaria with emerging ACT resistance in Western Cambodia. Lancet Infect Dis 15(11):1305–1314
28. Pucca LE, Rasmussen C, Bukirwa H (2024) Changing patterns of antimalarial drug sensitivities and therapeutic failure in East Africa. Malar J 23(1):42
29. Juliano JJ, Rasmussen SA, World Health Organization (2023) Threats of drug-resistant malaria strains expanding across sub-Saharan Africa. N Engl J Med 389(14):1301–1311
30. Marfurt J, Smith TA, Hastings IM, Müller I, Sie A, Oa O, Baisor M, Reeder JC, Beck HP, Genton B (2007) From chloroquine to artemisinin-based combinations: rapid adaptation and early clinical friction of Plasmodium falciparum. J Infect Dis 196(4):610–618
31. White NJ (1997) Assessment of therapeutic response in antimalarial drug trials. Trends Parasitol 13(8):311–315
32. White NJ, Chapman D, Mayxay M (1992) Parasite quantification and blood smear kinetics in human malaria. Lancet Infect Dis 12(4):214–222
33. Kotepui M, Kotepui KU, Milanez GD, Masangkay FR (2015) Severity of Plasmodium falciparum malaria infection and its correlation with parasite density. Sci Rep 5:15643
34. Rasmussen C, Bukirwa H, Kamya MR (2017) Rapid parasite clearance velocity variations across modern artemisinin combination regimens. Antimicrob Agents Chemother 61(5):e02411–e02416
35. Sitali L, Chipoya S, Shimaponda-Mataa NM (2020) Ten-year longitudinal review of late parasitological and clinical treatment failures of first-line antimalarials in Zambia. Med J Zambia 47(2):104–112
36. Ministry of Health Zambia (2021) National Malaria Strategic Plan 2021–2026: Towards a Malaria-Free Zambia. Government Printers, Lusaka

Figures

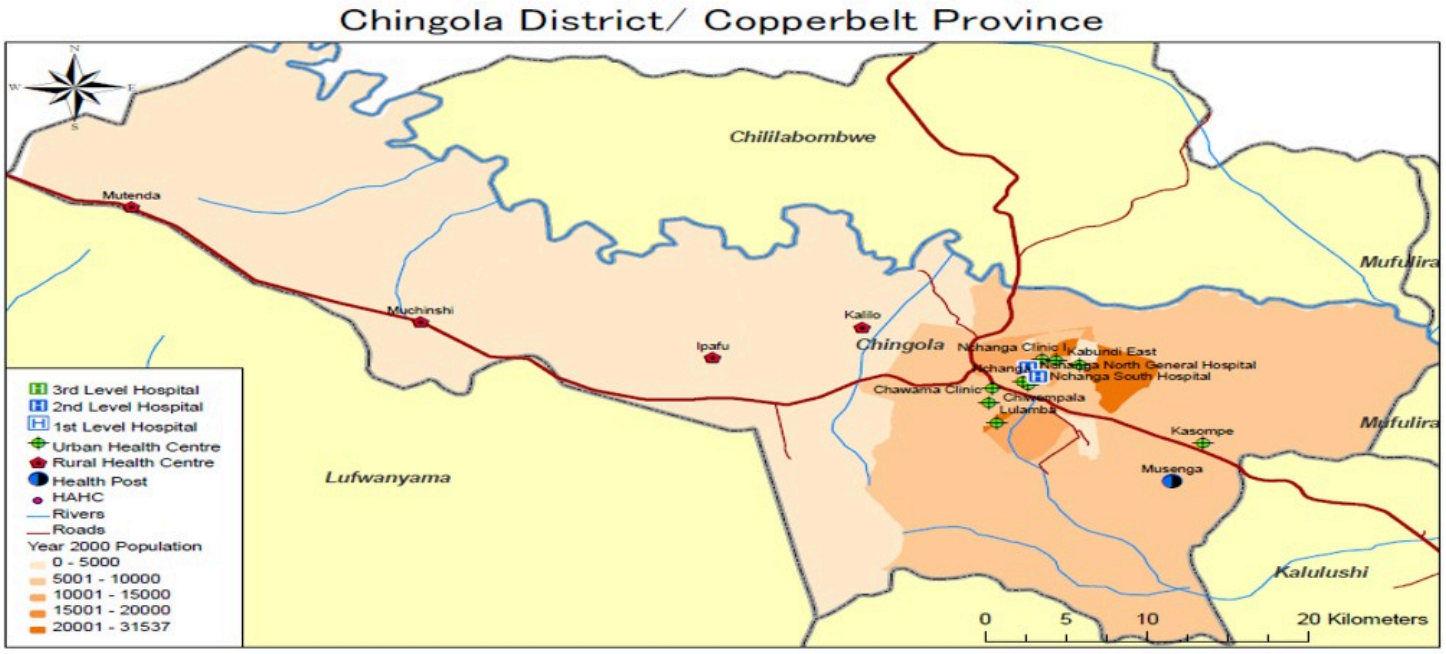


Figure 1

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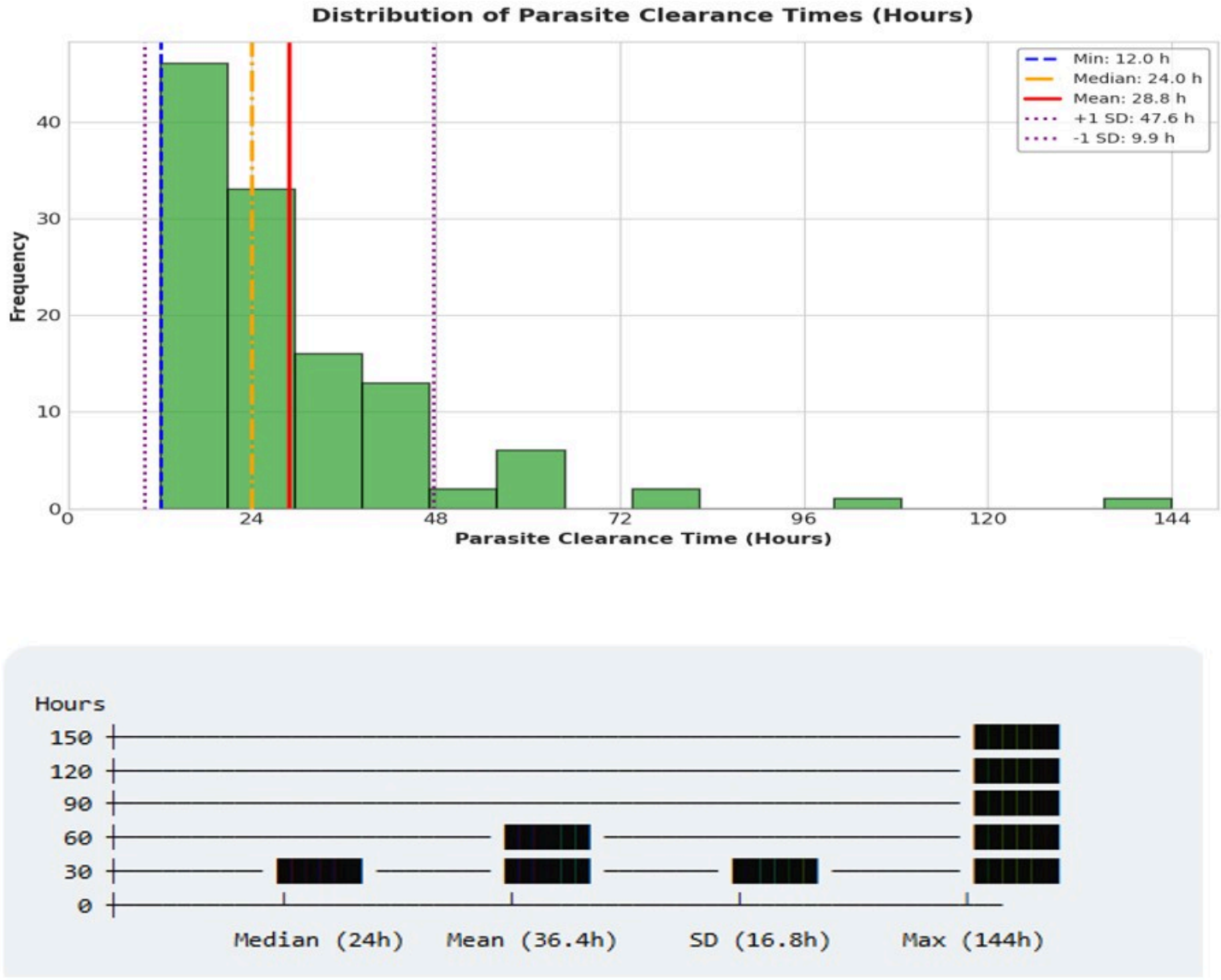


Figure 2

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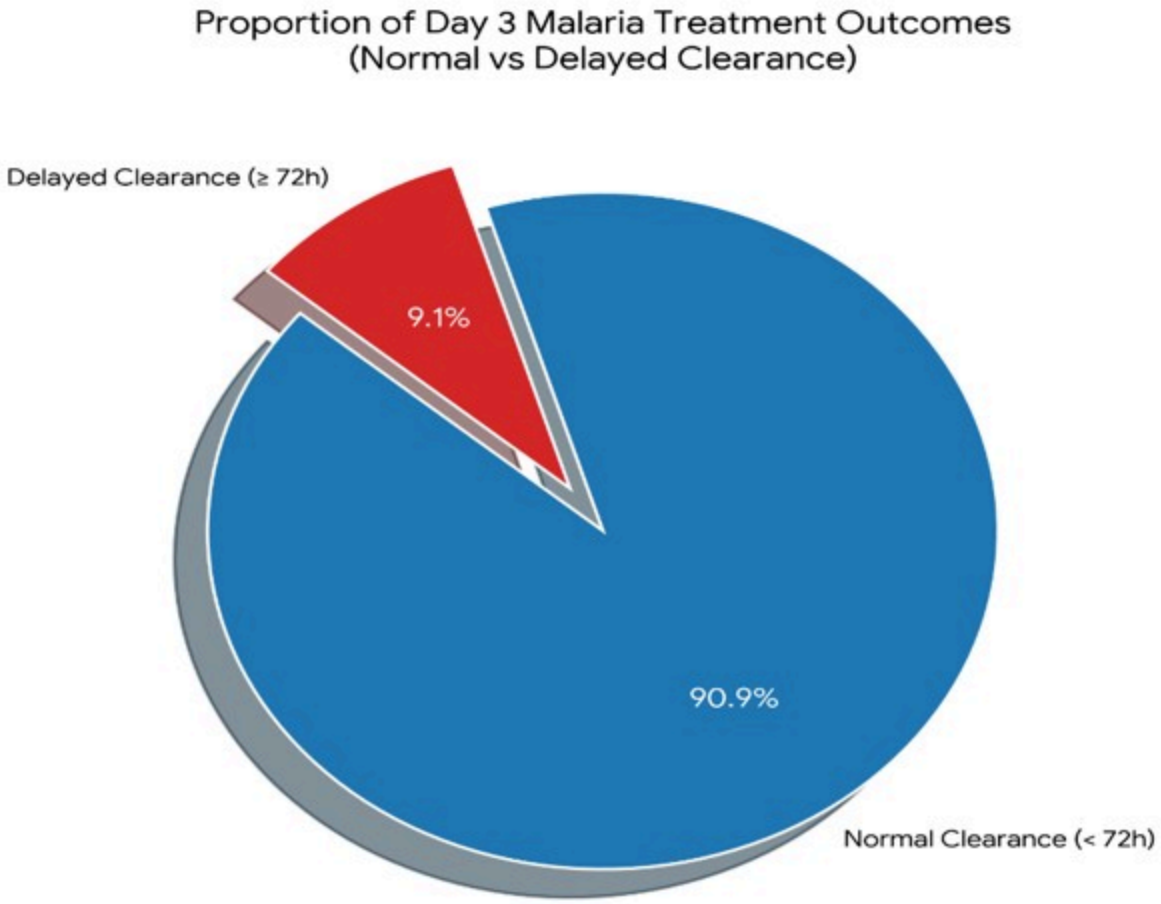


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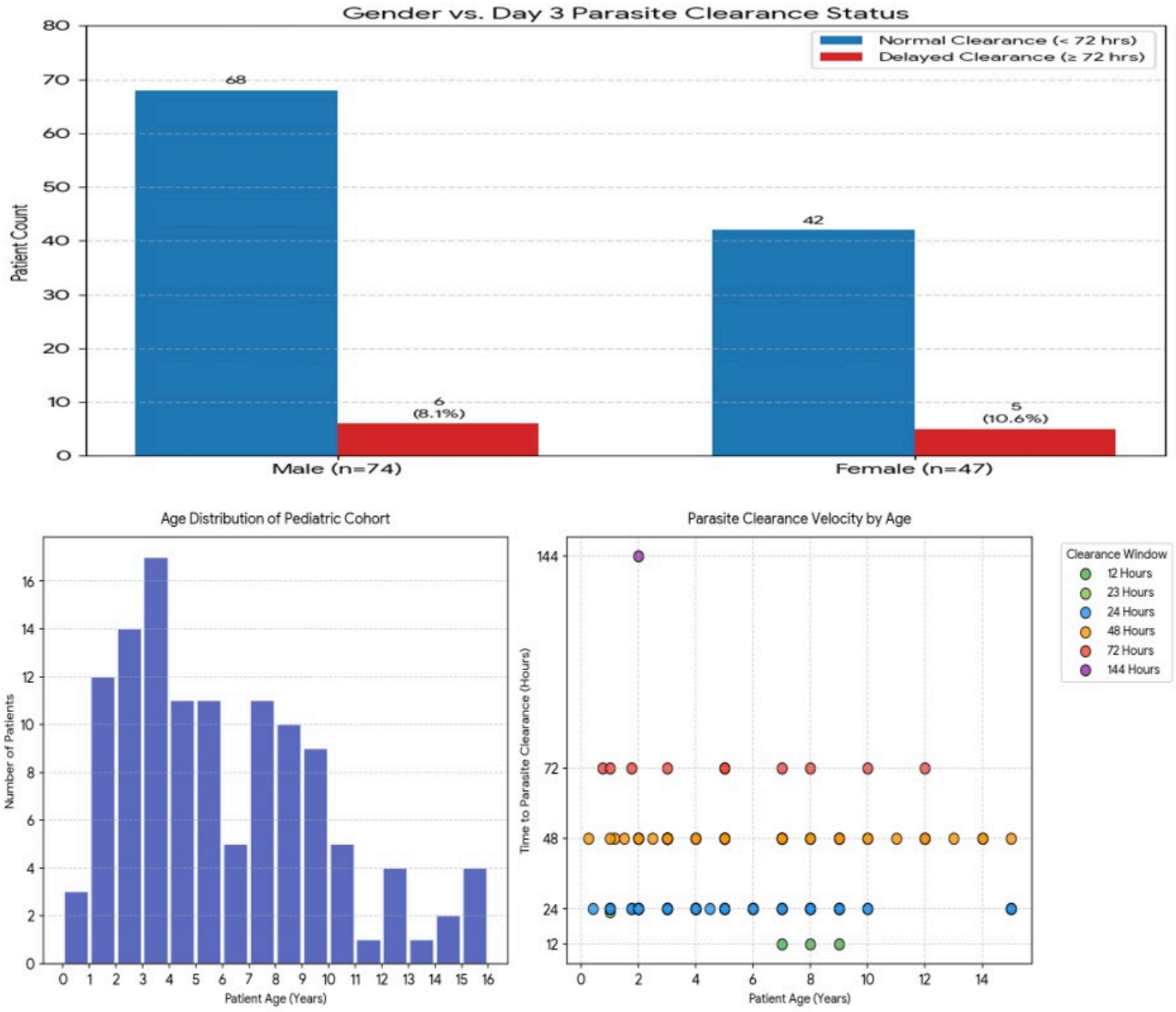


Figure 4

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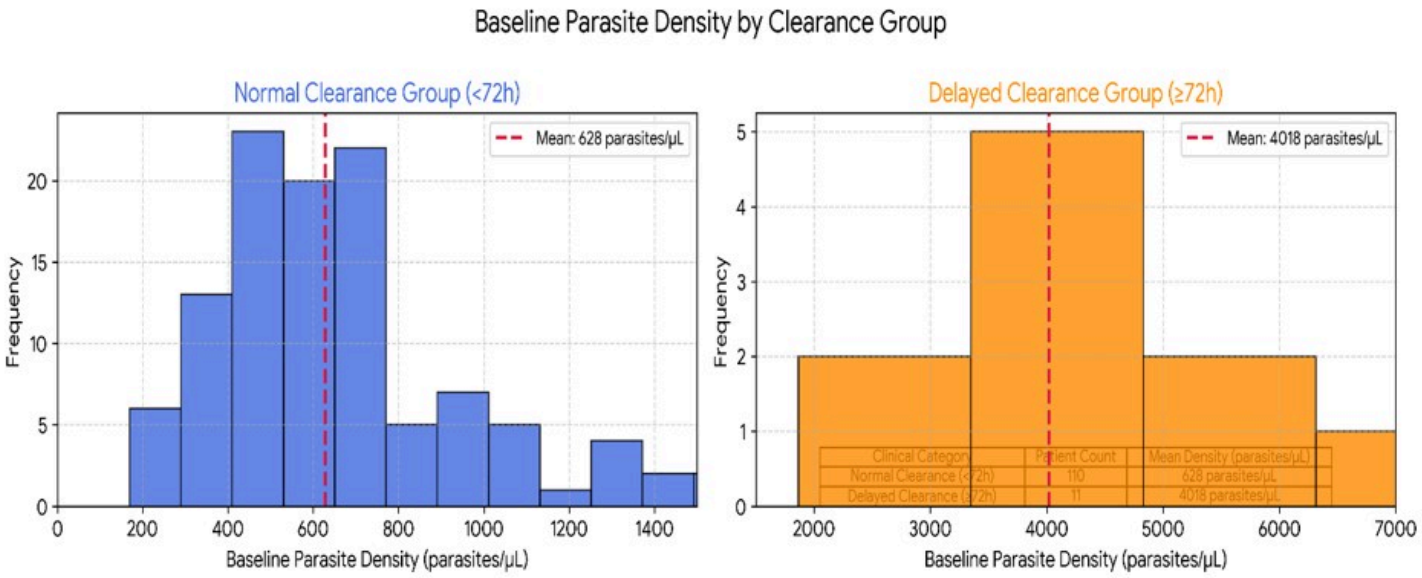


Figure 5

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