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Research Article

Therapeutic Efficacy of Artemether-Lumefantrine in Treating Uncomplicated Plasmodium falciparum Malaria in Children at Wad-Medani, Sudan

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Abstract:

Malaria remains a significant public health concern in Sudan, particularly among children, with Plasmodium falciparum as the dominant species. Artemether-Lumefantrine (AL) is the recommended first-line treatment for uncomplicated malaria; however, rising treatment failure rates necessitate further evaluation. This study assessed the therapeutic efficacy of AL in children aged 6 months to 16 years at Wad-Medani Pediatric Teaching Hospital, Gezira State. A prospective single-arm interventional study was conducted, enrolling 80 patients and following 70 through a 28-day treatment regimen. Clinical assessments, parasitological responses, and adherence evaluations were performed. The results showed a cure rate of 91.5%, with significant adherence-related outcomes ($p<0.05$). Early treatment failure (ETF) was observed in 5% of cases, with no late clinical or parasitological failures reported. Clinical pharmacist interventions improved awareness and adherence among healthcare providers and caregivers. The study concluded that AL remains highly effective for treating uncomplicated malaria in Sudan, although targeted interventions to enhance adherence are critical for sustained efficacy.

Keywords: Artemether-Lumefantrine; Therapeutic efficacy; malaria; adherence; plasmodium falciparum.

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1. Introduction

Malaria is a life-threatening disease caused by Plasmodium parasites. *Plasmodium falciparum* is responsible for most severe cases and deaths globally. According to the World Health Organization (WHO), malaria affected approximately 230 million people and caused 430,000 deaths in 2020, with sub-Saharan Africa bearing over 90% of this burden (1). Children under five years old are particularly vulnerable, accounting for 61% of malaria-related deaths (2,3). Sudan is among the countries heavily affected, with nearly 75% of its population at risk, and P. falciparum contributing to 87.6% of reported cases (4). The emergence of drug resistance threatens malaria control efforts globally, necessitating effective case management strategies (5). Artemether-lumefantrine (AL), a fixed-dose artemisinin-based combination therapy (ACT), has been recommended by WHO as the first-line treatment for uncomplicated malaria since 2001 (5,6); However, continuous surveillance of its therapeutic efficacy is essential to inform treatment policies and ensure optimal disease management(7). AL is favored due to its high efficacy, rapid parasite clearance, and low resistance rates when administered

according to protocol (8). However, treatment failure rates in some regions, including Sudan, have raised concerns. In Wad-Medani Pediatric Teaching Hospital, treatment failures increased to 15.7% between 2018 and 2019, highlighting the need for re-evaluation (4). This study aims to evaluate the therapeutic efficacy of AL in treating uncomplicated P. falciparum malaria among children at Wad-Medani Hospital. It seeks to identify factors influencing treatment outcomes, including adherence, dosage accuracy, and patient-specific factors, to guide interventions that improve malaria management in Sudan.

2. Materials and Methods

Study Design: This study employed a prospective, single-arm interventional design conducted at Wad-Medani Pediatric Teaching Hospital, Gezira State, Sudan, between November 2022 and May 2023. The study monitored patients receiving partially supervised artemether-lumefantrine (AL) treatment over a 28-day follow-up period to evaluate therapeutic efficacy and identify factors influencing treatment outcomes.

Study Area: The study was conducted in Wad-Medani Pediatric Teaching Hospital, a referral center for children in Gezira State, Sudan. The hospital provides outpatient and inpatient services and includes 204 beds for patients aged from one day to 16 years. The region has a high prevalence of *P. falciparum* malaria, with climatic conditions conducive to malaria transmission.

Study Population: The study included children aged 6 months to 16 years diagnosed with uncomplicated *P. falciparum* malaria, meeting inclusion criteria based on WHO guidelines.

Inclusion and Exclusion Criteria:

Inclusion Criteria: Febrile children (>37.5°C) or with a history of fever within 24 hours. Microscopically confirmed *P. falciparum* infection. Body weight >5 kg. Patients residing in the Wad-Medani area.

Exclusion Criteria: Mixed infections or severe malaria. Hemoglobin <5.0 g/dL. Known hypersensitivity to AL. Chronic or severe underlying diseases.

Ethical Approval Ethical clearance was obtained from the Ethical Committee of the University of Gezira and the Gezira State Ministry of Health. Written informed consent was obtained from the parents or guardians of all participants.

Data Collection Baseline demographic and clinical data were collected through questionnaires and physical examinations. Finger-prick blood samples were used to prepare thick and thin smears for parasitological confirmation and quantification. Participants were evaluated on Days 0, 3, 7, 14, 21, and 28, with adherence assessed using the Morisky Medication Adherence Scale (MMAS). Treatment and follow-up AL was administered as per WHO-recommended weight-based dosing (20 mg artemether + 120 mg lumefantrine). Doses were given at 0, 8, 24, 36, 48, and 60 hours, with morning doses supervised in the hospital. Patients or caregivers were instructed on the proper administration of evening doses.

Primary and Secondary Endpoints:

Primary Endpoint: Adequate clinical and parasitological response (ACPR) at Day 28. Secondary Endpoints: Parasite and fever clearance rates, treatment adherence, and incidence of treatment failure (early or late).

Statistical Analysis Data were analyzed using SPSS v.20. Descriptive and inferential statistics were performed, with p-values <0.05 considered statistically significant.

3. Results

Patients' Results. General Participation: A total of 2950 children were screened for malaria at Wad-Medani Pediatric Teaching Hospital between November 2022 and May 2023. Of these, 1520 (51.5%) were confirmed positive for *Plasmodium falciparum* malaria. Consent for participation was obtained from 178 parents, and 80 children were enrolled in the study.

A total of 70 participants (40 males and 30 females) completed the 28-day follow-up.

Table 1: Study participation

Total positive patients with simple malaria	Consent given for study	Total enrolled in the study	Completed follow-up (28 days)
1520	178	80	70

Table 2: Participants age ranged from 6 months to 16 years

Age (years)	< 5 (n = 25)	5–10 (n = 36)	11-15 (n=19)	n=80
Male	**11**	**25**	**14**	**50**
Female	**14**	**11**	**5**	**3**
Weight SD	**-2.5**	**+3**	**-1.5**	**2.3**

Weight and age groups were analyzed, showing that most participants were in the 5-10 years range.

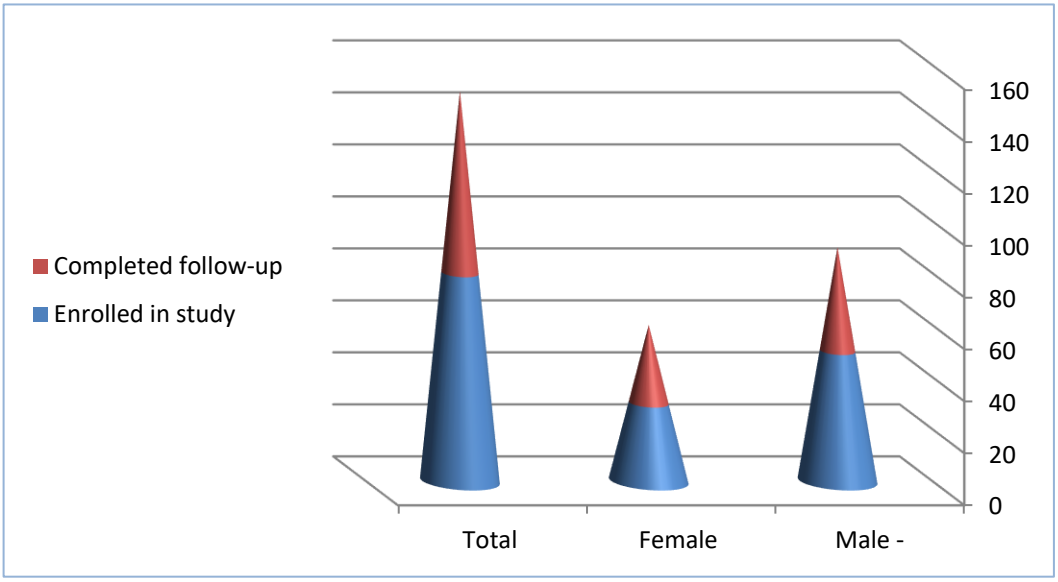

Figure1: study participation by gender

This figure showed that 70 of 80 patients completed follow-up

The statistical analysis displayed shows the follow-up of patient outcomes over 28 days based on four parameters:

1. Clinical Assessment: The percentage of patients completing clinical assessments decreased gradually from 100% on Day 0 to 87.5% on Day 28.

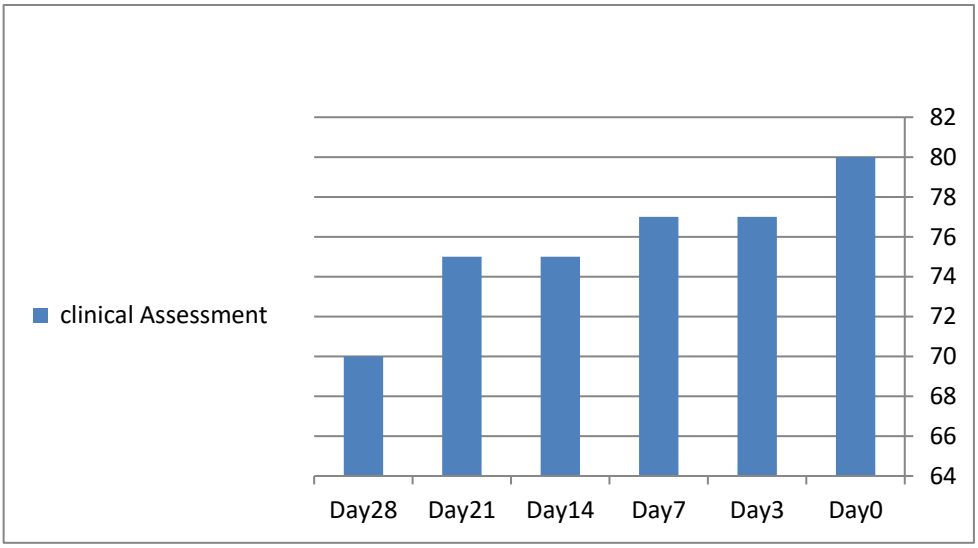

Figure 2: Clinical Assessment of patients who are enrolled

2. Temperature Measurement: Followed a similar downward trend, declining from 100% on Day 0 to 87.5% on Day 28.

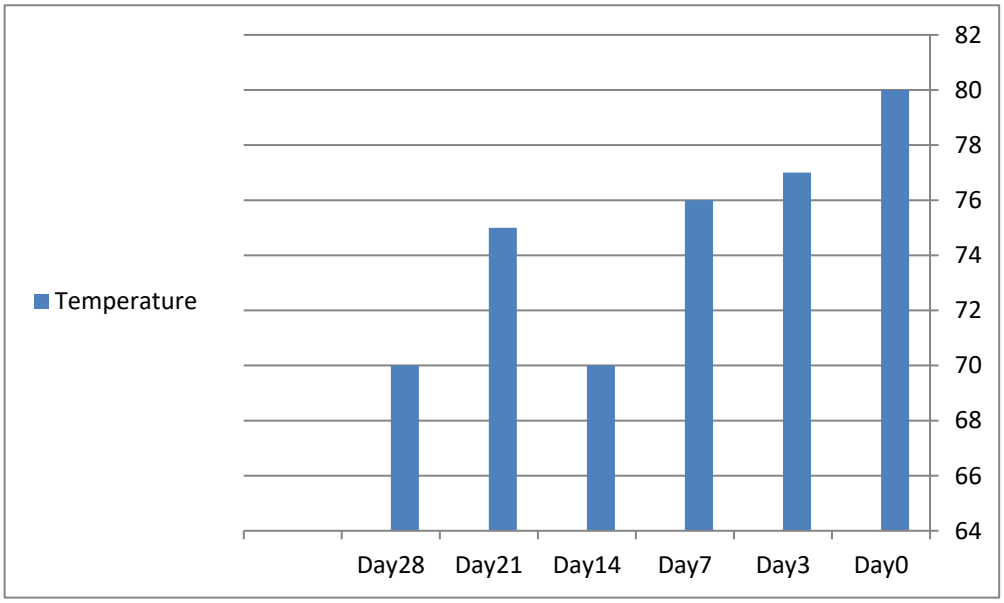

Figure 3: Temperature Assessment of patients who are enrolled

3. Blood Slide for Parasites Count: Also showed a gradual decrease in percentage over time.

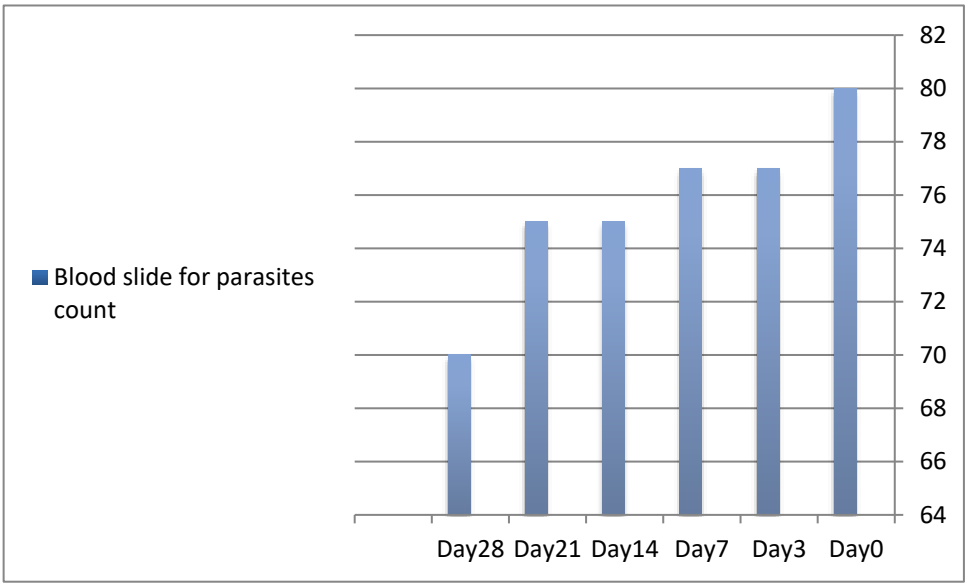

Figure 4:blood slide for parasite counts assessment of patients who are enrolled.

Hemoglobin Measurement: Hemoglobin was not measured on Days 3 and 7, but the percentage declined from 100% on Day 0 to 87.5% on Day 28.

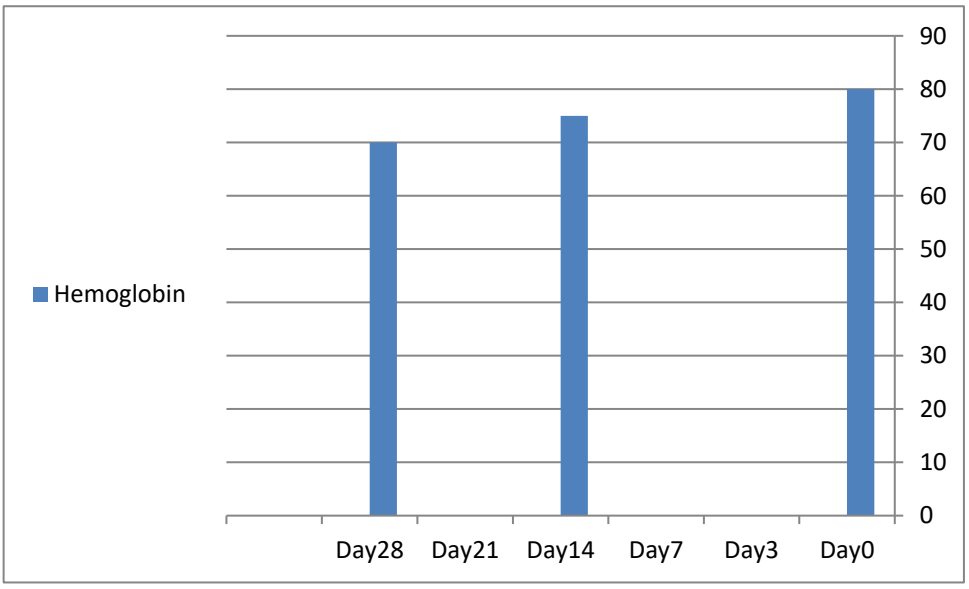

Figure 5: Hemoglobin assessment of patients who are enrolled

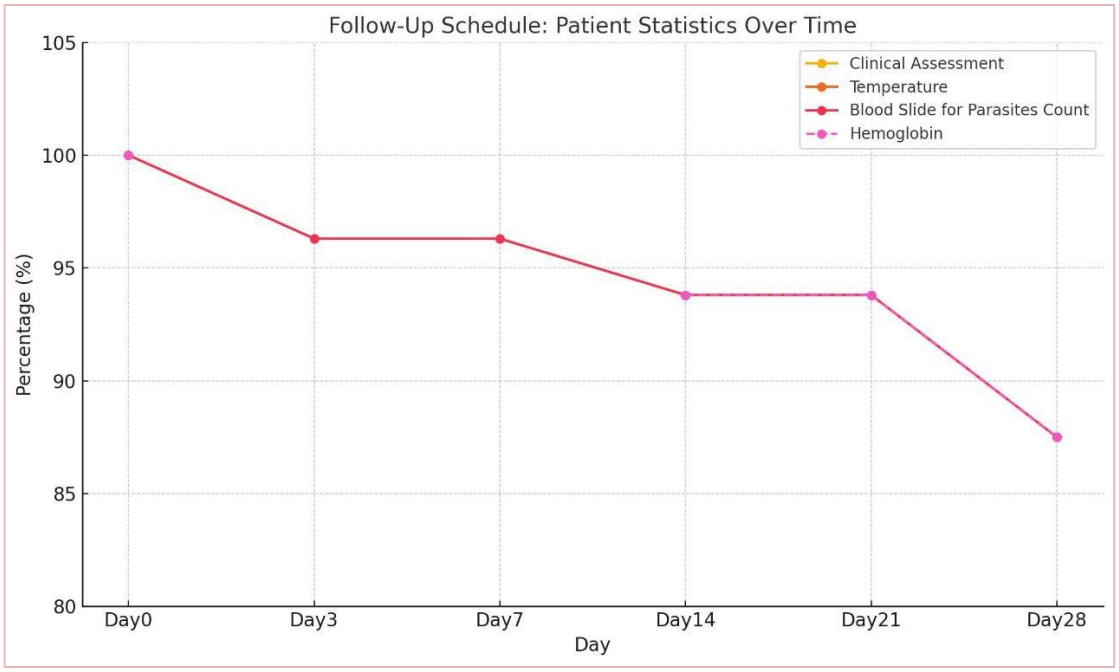

Figure 6: Basic follow-up schedule of patients enrolled in the study

Observations: The data indicates a consistent decline in follow-up rates over time. Hemoglobin measurements were the least consistent, with missing data on specific days.

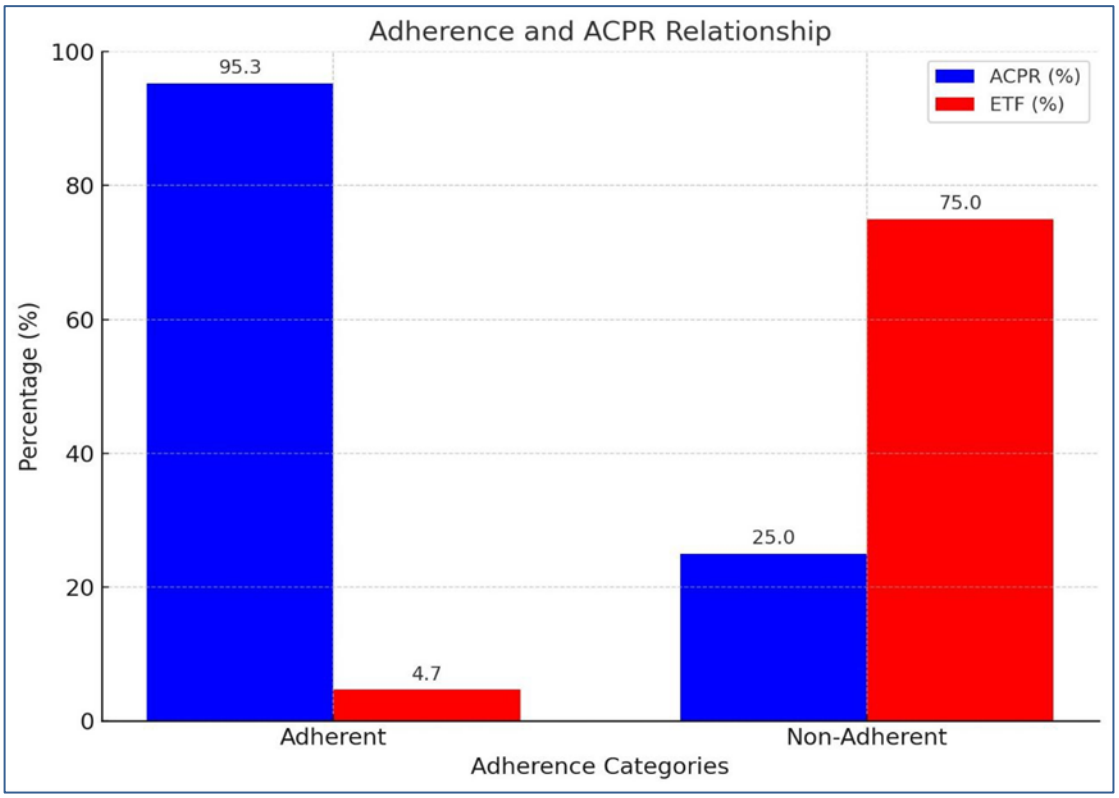

Figure 7: Association between ACPR and adherence to treatment protocol using chi-square

Chi-square value: 15.22, p-value 0.000096; since the p-value is less than 0.05, the result is statistically significant. Including a strong association between adherence to treatment protocol and Adequate clinical and parasitological response

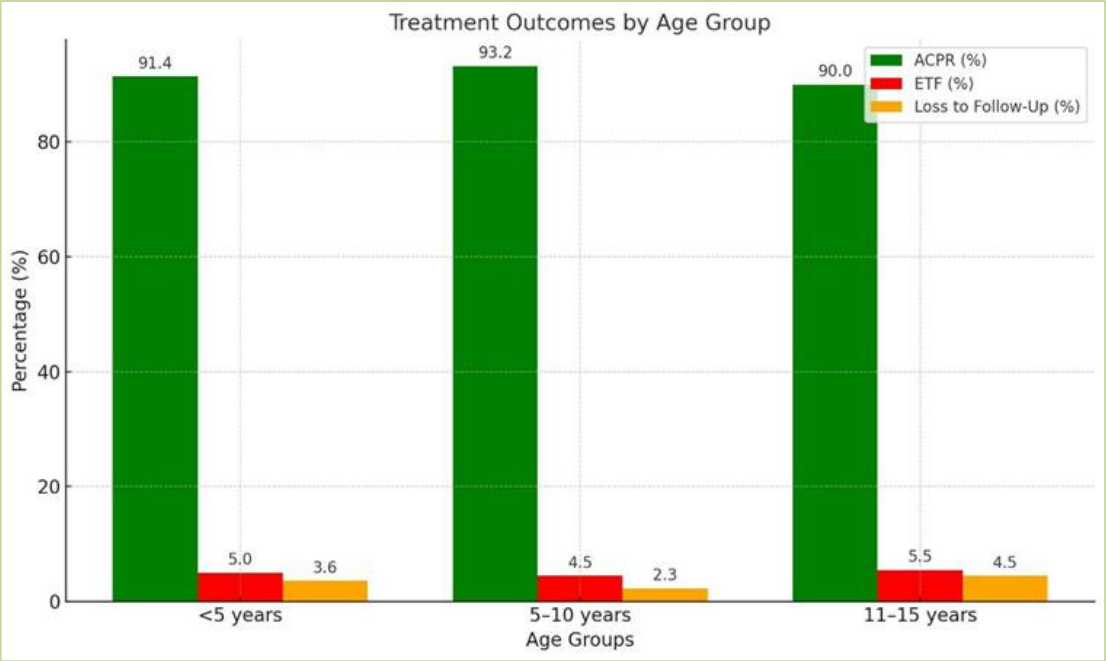

Figure 8: This bar chart represents the treatment outcomes by age group.

ACPR (%): The highest ACPR percentage is observed in the 5–10 years age group (93.2%). The lowest ACPR percentage is seen in the 11–15 years age group (90.0%), though the difference across age groups is minimal.

ETF (%): Early Treatment Failure rates are slightly higher in the 11–15 years age group (5.5%) compared to the other groups. The ETF rates are lowest in the 5–10 years group (4.5%).

Loss to Follow-Up (%): The loss to follow-up rate is highest in the 11–15 years age group (4.5%). The lowest loss to follow-up rate is in the 5–10 years age group (2.3%).

ACPR is consistently high across all age groups, above 90%, indicating effective treatment overall. ETF and Loss to Follow-Up rates remain low, with values below 6% across all groups. The middle age group (5–10 years) shows the most favorable outcomes with the highest ACPR and the lowest ETF and Loss to Follow-Up percentages.

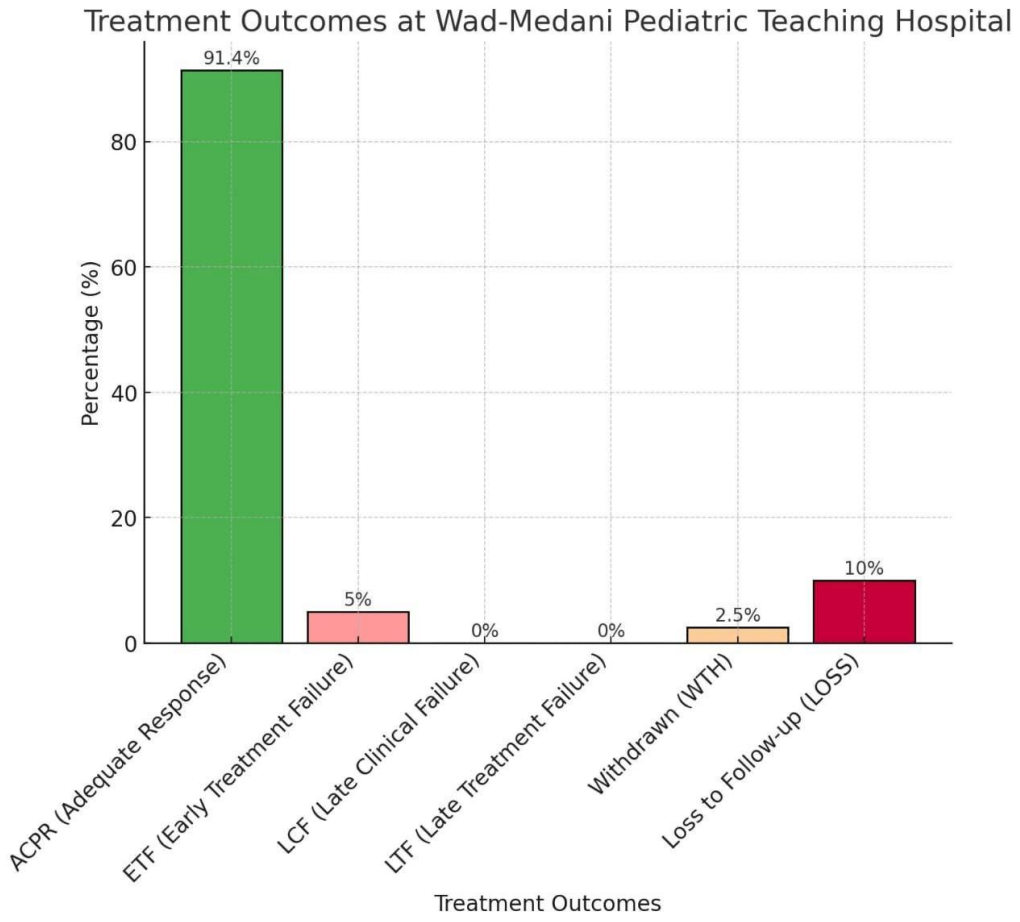

Figure 9: Treatment outcomes based overall assessment on per Protocol analysis among patients treated with AL at Wad-Medani Pediatric Teaching hospital

Incidence of treatment failure 5%

Observations:

- 91.4% of patients showed an adequate clinical and parasitological response (ACPR). 5% experienced early treatment failure (ETF).
- 2.5% were withdrawn (WTH).
- 10% were lost to follow-up (LOSS).
- No cases of late clinical failure (LCF) or late treatment failure (LTF).

4. Discussion

In retrospective assessment, there was an increasing prevalence of treatment failure rate among children treated with AL in uncomplicated P. falciparum malaria in 2018-2019 at Wad-Medani Pediatric Teaching Hospital; 15.7(statically reported from the hospital (4). This highlights the need to evaluate the therapeutic efficacy of AL in the treatment of uncomplicated P. falciparum malaria in children and determine patients' and/or healthcare-related factor/s

that affect the treatment outcome so can be predicted and help in decreasing the incidence of P. falciparum malaria treatment failure.

This study demonstrated an adequate clinical and parasitological response (ACPR) rate of 91.4% (P-value 0.00096) cure rate, which is statically significant, indicating that all participants who strictly adhered to the study protocol achieved successful treatment outcomes. The overall findings of the study indicated that a standard six-dose treatment of AL achieved a 91.5% cure rate for uncomplicated P. falciparum malaria over a 28-day period, without PCR correction. For children treated with artemether-lumefantrine (AL) for uncomplicated *Plasmodium falciparum* malaria. Early treatment failure (ETF) was observed in 5% of cases, with no late clinical or parasitological failures. These results emphasize AL's continued effectiveness as a first-line therapy in Sudan, albeit with notable challenges related to adherence and healthcare delivery; the showed with Similar studies in Sub-Saharan in Africa, In Ethiopia, reported a 100% cure rate for patients who adhered to AL protocols, underscoring the importance of adherence (10). Similarly, a Nigeria study (9) found an ACPR rate of 95% in children under five, demonstrating that AL remains effective when protocols are followed studies on Emerging Resistance.

The ETF rate of 5% in this study is consistent with WHO's threshold for detecting potential resistance in high-transmission areas (2). Comparatively, a study in Kenya by . reported ETF rates of 7%, highlighting regional variability in drug efficacy (10). Resistance to artemisinin derivatives, although not confirmed in Sudan, has been documented in Southeast Asia (11), emphasizing the need for regular surveillance .

Adherence and Treatment Outcomes: This study indicates a strong association between adherence to the treatment protocol and achieving an adequate clinical and parasitological response (ACPR). Observations: Adherence leads to higher ACPR (95.3%) compared to non-adherence (4.7%). Non-adherence showed a higher percentage of early treatment failure (ETF). Visual Representation: The bar chart in figure (3) highlights the difference between adherence and non-adherence groups regarding ACPR and ETF. The adherence group consistently outperformed the non-adherence group. Adherence significantly influenced outcomes in this study, with adherent patients achieving a 95.3% cure rate versus 25% in non-adherent patients. Similar findings were reported by in Uganda, where adherence improved efficacy by 20%. Factors affecting adherence, such as forgetting doses and lack of fatty food co-administration, align with global findings that highlight the impact of patient education and counseling (11). Implications of Findings The high ACPR rate and low ETF rate in this study suggest that AL remains effective in Sudan for treating uncomplicated malaria. However, adherence challenges and healthcare delivery gaps indicate areas for improvement. Ongoing surveillance is crucial to detect resistance trends, particularly given the rise of artemisinin resistance in Southeast Asia and parts of Africa.

WHO guidelines emphasize the importance of adherence to ACTs, with a target cure rate exceeding 95%. (12). While the 91.5% in the current study is slightly below this, it indicates efficacy but also highlights areas needing improvement, particularly adherence and education. Resistance Concerns: The presence of parasitemia on Day 3 in 5% of cases aligns with WHO's indicator for artemisinin resistance but remains within acceptable ranges to avoid alarming resistance levels Comparison with Global and Regional Studies, as in WHO Guidelines and Benchmarks: WHO specifies ACT cure rates should exceed 95%, but variations often depend on regional compliance and resistance levels. The study's 91.5% is lower but still supports AL as an effective first-line treatment in Sudan. Efficacy in Sub-Saharan Africa (13): Other regional studies, such as those from Ghana, report similar outcomes, emphasizing ACT efficacy but also noting challenges in patient adherence and treatment protocol implementation. Challenges in Sudan vs. Other Regions: Factors like limited healthcare infrastructure, low provider awareness (especially among less experienced doctors), and patient-related factors like diet and follow-up visits contribute more prominently in Sudan compared to countries with stronger health systems

5. Conclusion

Strengthen adherence programs, particularly targeting education on dose timing and the necessity of administering AL with fatty foods. and Enhance healthcare provider training, ensuring awareness and access to national treatment protocols. Further research to monitor emerging resistance and improve cure rates toward the WHO target of 95% (11,12).

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Author contribution: Conceptualization , investigation, methodology : prof: Imd-Eldeen Mohamed Taj Eldeen, Huda M. Harron, Bakri Y.M. Nour and Ibrahim O.M. Omer. Data curation ,software, formal analysis, writing original draft and visualization Dr. Nehal Ahmed Mohamed Musa. Resources (patients) prof: Huda M. Harron and Dr. Nehal Ahmed Mohamed Musa. Malaria test confirmation by Bakri Y.M. Nour. Role of clinical pharmacist by Ibrahim O.M. Omer and Nehal Ahmed Mohamed Musa. Validation prof: Imd-Eldeen Mohamed Taj Eldeen, Huda M. Harron, Bakri Y.M. Nour and writing editing by Dr. Nehal Ahmed Mohamed Musa

Intuitional Review Board Statement: This study conducted after it had been approved by Ministry of Health Gezria State and Ethical Committee of University of Gezria before Patients had been approached, recruited, and enrolled in the in the study. This article was a part of author study carried out by same authors. So, ethical approvial was taken for the whole study and it possessed the number 6-22 date 23/2/2022 ; however, this article involved no experimental test on humans or animals.

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Conflicts of Interest: authors declare that they have no conflict of interest

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