# Renal Function Changes in Treated and Untreated Malaria Patients at Livy Good Health Hospital in Port Harcourt, Rivers State

**Winifred C. Udeh (Ph.D)**
Department of Medical Biochemistry,
Faculty of Basic Medical Sciences,
College of Health Sciences,
University of Port Harcourt,
Port Harcourt.

**Irene I. Ijeh (Prof)**
Department of biochemistry,
Faculty of Natural sciences,
Michael Okpara University of Agriculture,
Umudike, Umuahia.

**Alexander E. Mene (Ph.D)**
Department of Medical Biochemistry,
Faculty of Basic Medical Sciences,
College of Health Sciences,
University of Port Harcourt,
Port Harcourt.

***Abstract***
*Malaria is an important parasitic infection of man caused by the protozoan parasites* Plasmodium falciparum, P. vivax, P. malariae *or* P. ovale *and transmitted by the bite of a sporozoite-bearing female anopheline mosquito. Acute kidney injury (AKI) is a known complication of malaria, and is reported to occur in up to 40 % of adult patients and about 20% of paediatric patients with a severe* Plasmodium falciparum *infection in endemic regions. This work was done to determine the renal function changes that accompany malaria infection in humans in Port Harcourt, Rivers state in Nigeria and to determine the effects of anti-malaria therapies on the renal function of patients treated. One hundred and eighty patients who presented at Livy Good Health hospital Port Harcourt with symptoms of malaria within 6 months of the study were screened for the presence of malaria parasites in their blood stream via blood tests using rapid diagnostic test films and thick and thin blood smears tested at the microbiology laboratory of the hospital while the microbial loads of the micro-organisms were counted. Positive blood samples of one hundred and twenty patients with high levels of parasitemia were then followed up by the collection of 5milliters of venous blood samples from each patient prior to onset of treatment and after treatment and analyzed chemically. The age distribution of the patients studied were as follows; 0–4years (16 patients; 13.33%), 5 – 9 years (23 patients; 19.17%), 10–14 years (13 patients; 10.83%), 15–19 years (7 patients; 5.83%), 20-24 years (11patients; 9.17%), 25-29 years (9 patients; 7.50%), 30-34 years (5 patients; 4.17%), 35-39years (9 patients; 7.50%), 40-44 years (6 patients; 5.00%), 45-49 years (8 patients; 6.67%), 50-54years (6 patients; 5.00%) 55-59 years (4 patients; 3.33%) while only 3 patients or 2.5% of the total population were 60 years and above. Sex distribution records of the patients*

*revealed that 73 patients or 60.83% were females while 47 patients or 39.17% were males.. Most parasites (82%) seen in almost all patients during microscopic examination of their blood samples were plasmodium falciparum, 13% were P. malaria while 5% were P.ovale; no P. vivax species were seen. Parenteral antimalarial agents did not show any significant (P<0.5) adverse effect on renal functions as they did not increase serum creatinine in treated patients but rather significantly (P>0.5) ameliorated the effects of malaria on renal functions when compared with the oral medications. However, oral medications did not significantly (P< 0.5) improve renal functions in treated patients as evidenced by lower improvement rates in blood serum creatinine levels when compared to parenteral anti-malaria agents.*

## STATEMENT OF THE PROBLEM

Acute kidney injury is a known complication of malaria and is reported to occur in up to 40% of adult population and 20% of paediatric patients with severe *P. falciparum* infection.

## AIM OF THE STUDY

The aim of the study was to determine the renal function changes that accompany malaria infection in humans and to determine the effects of anti-malaria therapies on the renal function of patients treated.

## OBJECTIVES OF THE STUDY

- **i)** To determine if plasmodium species responsible for causing malaria in humans also cause renal damage.
- **ii)** To determine if present, the extent of renal damage or changes in renal functions that accompany malaria infestation.
- **iii)** To determine if anti-malaria therapies commonly used in Nigeria, especially in Port Harcourt for the treatment of malaria, affects the renal status of treated patients.
- **iv)** To compare and contrast the effects of the different antimalarial agents on renal functions of patients treated.

## MATERIALS AND METHODS

### STUDY AREA AND CLINICAL CONCEPT

A total of 180 patients who presented at Livy Good Health hospital Port Harcourt with symptoms of malaria within 6 months of the study, were screened for the presence of malaria parasites in their blood stream via blood tests using rapid diagnostic test films and thick and thin blood smears tested at the microbiology laboratory of the hospital while the microbial loads of the micro-organisms were counted.

**BLOOD COLLECTION:** Positive blood samples of 120 patients with high levels of parasitemia were then followed up by the collection of 5 milliters of venous blood samples from each patient prior to onset of treatment. The 5 milliliters of blood were collected by venipuncture from each participant. 3 mls of each sample were dispensed into sterile plain blood collection tubes (BD Vacutainer®) and allowed to clot and retract at room temperatures of 22-26°C for 1 hour. The sera were then separated, after centrifuging at 3000 rpm for 5 min in clinical bench top centrifuge using Pasteur pipettes.

### SAMPLE STORAGE AND PROCESSING

The sera were stored in a refrigerator at 2-8°C until required for analysis, while the analyses were carried out within 24 hours. The remaining 2mls of each sample were stored in EDTA bottles for hematological and clinical chemistry analysis at the haematological/chemical pathology laboratory of the University of Port Harcourt teaching hospital.

**PATIENT PREPARATIONS**

The patients seen and screened for the research cut across different age limits, tribes and religion while the patients' educational status or those of the parents of children treated were noted.

Duration of the illness were recorded as starting from the time of onset of symptoms till date of presentation at the hospital while serum electrolytes such as sodium, chloride, potassium, urea and creatinine which are altered in renal diseases and sometimes serve as indicators of the renal status of a patient were all measured. Also hematological parameters such as fasting blood sugar, packed cell volume and hemoglobin were assayed for, alongside parasitemia counts from blood films for each patient. Urine samples were collected alongside blood samples and were analyzed for their contents which included glucose, protein, ketones, bilirubin and uric acid. The above screenings were performed prior to commencement of treatment on the patients while their blood pressures were also noted especially for adults.

**3.4 EXPERIMENTAL DESIGN**

The Patients were carefully placed in one of six treatment groups as they presented and the placement was based on the severity or otherwise of the disease in the Patient. Treatment was then commenced for each of the involved patient and their anti-malaria therapy lasted between 3-5 days depending on the severity of the disease per patient.

At the end of 2 weeks post-treatment, 5 mls of venous blood samples were collected from each treated patient and analyzed again for their hematological and serum electrolyte contents. Urine samples were also obtained from them alongside the blood samples. The pre-treatment and post-treatment results alongside the treatment administered for each of the 120 patients were duly recorded and the parameters compared based on age, parasite load/severity, treatment given, presence of co-morbidities before treatment and their pre- and post-treatment renal function test results.

The results were checked for differences in renal function tests pre and post-treatment and compared with normal ranges to determine whether malaria diseases affected renal function. Also the study determined if the antimalarial drugs administered had palliative or deteriorative effects on the renal status of treated patients.

**ORAL DRUGS USED FOR THERAPY IN THE STUDY INCLUDED**

1) Coartem (Artemether /Lumefantrine)
2) Artequin (Artesunate /Mefloquine)
3) Amiodaquine
4) Artesunate

Tablets, syrups and suspension of the above oral drugs were used to cater for the adult and paediatric patients.

**PARENTERAL MEDICATIONS USED FOR THE TREATMENTS INCLUDED**

1) Paluther injection (Artemether suspension administered intramuscularly)
2) Quinine injection. (Administered intravenously)

**GROUPINGS**

Group A Treated with Parenteral Paluther
Group B Treated with Parenteral Quinine
Group C Treated with Oral Coartem
Group D Treated with Oral Artequin
Group E Treated with Oral Artesunate
Group F Treated with Oral Amodiaquine

**PROCEDURE FOR SERUM CREATININE ESTIMATION (2007)**

| **Laboratory** | **Creatinine, mg/Dl (µmol/L)** |
|---|---|
| Method | O'Leary modified Jaffe |
| Instrument | Roche modular P unit (Roche diagnostic) |
| Reference range | Male: 0.68-1.36 (60-120)<br>Female:0.68-1.10 (60-97) |

**STATISTICAL ANALYSIS**

Data was processed using SPSS 13. A one way ANOVA was performed to depict statistical differences and the results were presented as Mean ± Standard deviation (SD) while a *P*-value of <0.05 was considered as significant

**RESULTS AND DISCUSSION**

The analysis carried out with the help of SPSS 13 and the results obtained from descriptive statistics are presented in the following figures and tables.

**POPULATION OF STUDY WITH RESPECT TO GENDER**

The distribution of the patients based on their gender Figure 4.1, reveals that 60.83% that is 73 out of the 120 patients infected were female both young and old while only 39.17% that is 47 out of the 120 patients that were infected were male both young and old. This is an indication that the lower immune status of females as a result of hormonal changes amongst other factors propelled this high margin. Data for this analysis are presented in Appendix A, Table A1.

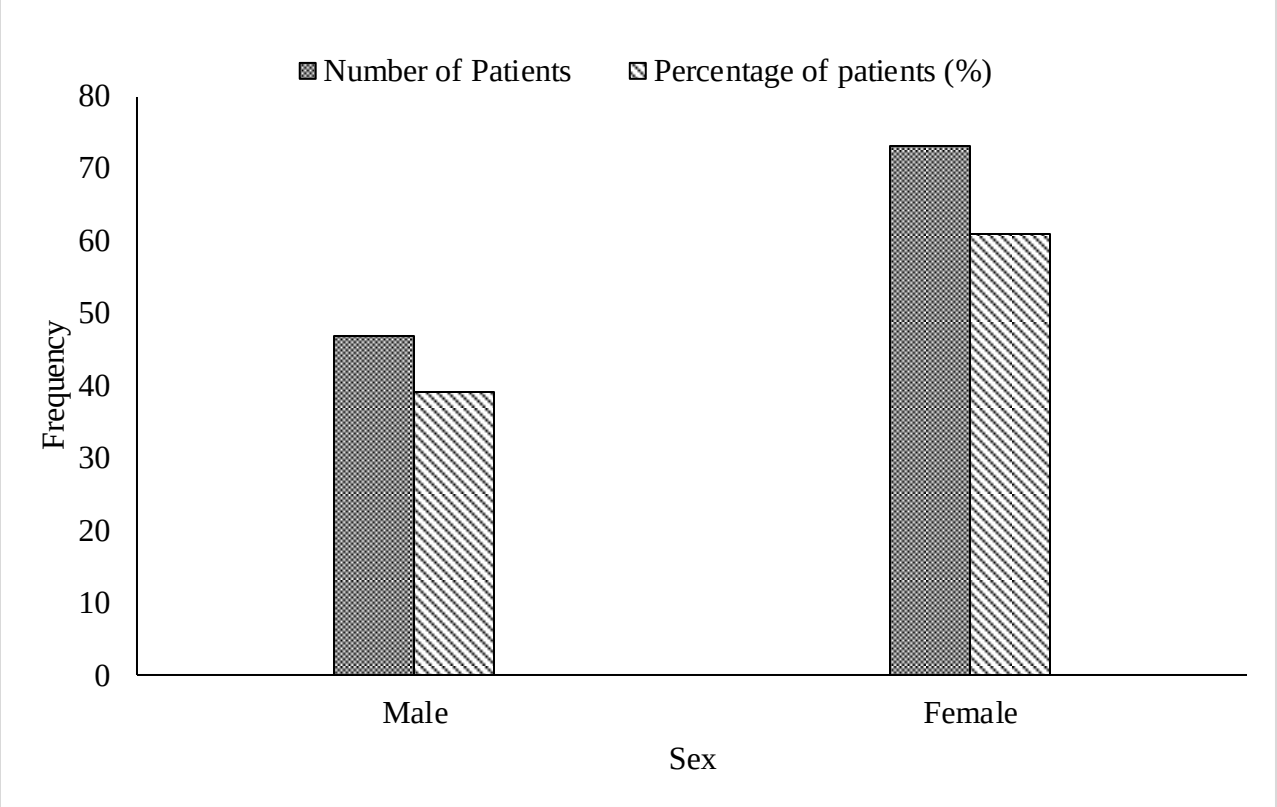


**Figure 4.1 Sex distribution of patients**

**MALARIA INFESTATION IN RELATION TO THE AGE BRACKET OF PATIENTS**

Figure 4.2, also present spread of the distribution of malaria parasites amongst the patients. It is evident that the disease infestation decreased, based on the number of exposure to the malaria parasite and the age of patients. Out of the total 120 patients infested, 19.17% that is 23 patients within the ages of 5–9 years are predominant with the disease. While 2.5%, that is 3 patients from the total numbers of patients considered within the age bracket of 60 and above in this study have a low infection rate. Several researchers attributed this phenomenon to immunity developed in patients because of constant exposure to the disease and age differences. The data for this analysis is presented in Appendix A Table A2.

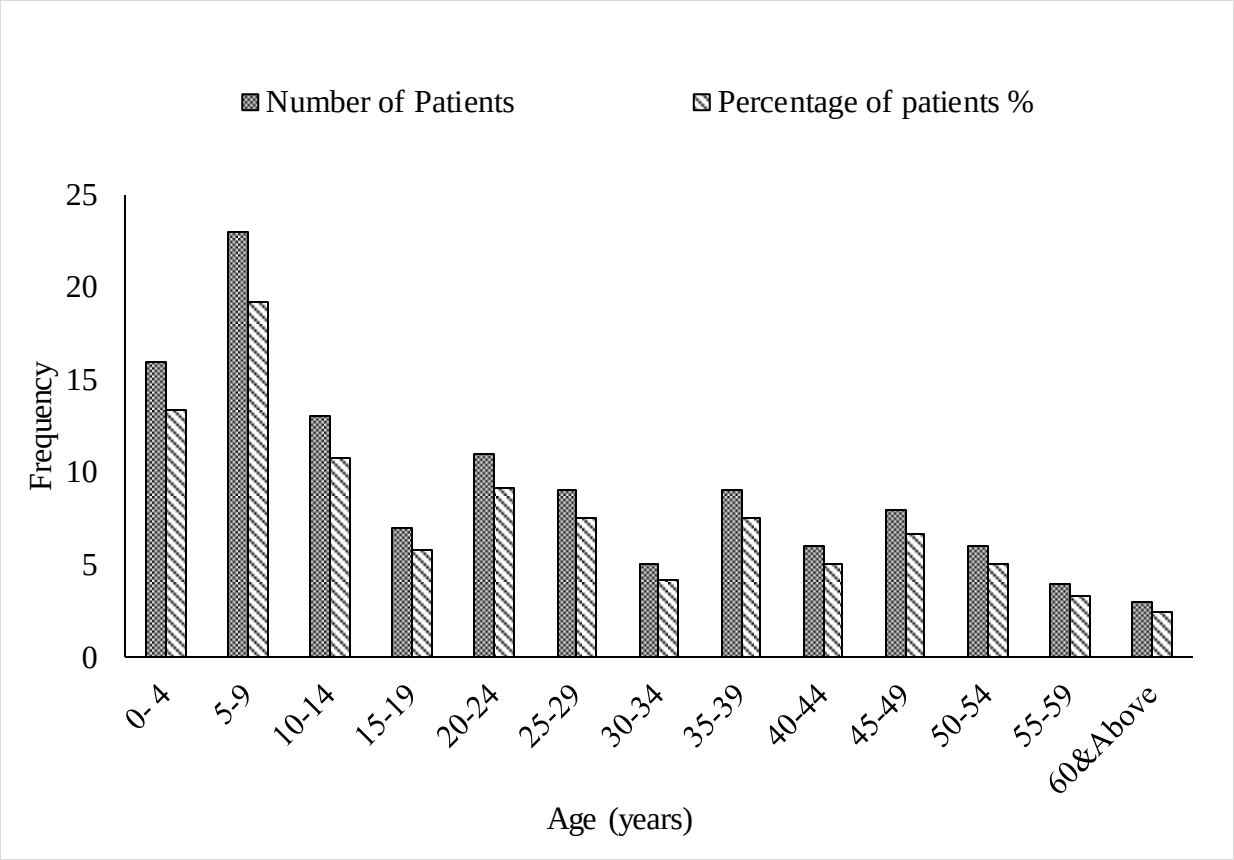


**Figure 4.2: Age distribution of Patients in years and percentage distribution**

**MALARIA PARASITES PRESENT IN PATIENTS**

The results obtained from the microscopic examination of the blood samples are presented in Figure 4.3. A percentage of 98.4 % of the total patients that is 82 patients out of the 120 patients tested were infected by *p. falciparum* parasites, while 15.6% of the patients or 13 patients were infected by P. *malariae* and 6% of the patients or 5 patients were infected by *P. ovale*. Only *P. vivax* species was not seen in any of the patients. This is an indication that the *P. vivax* species is not common in the region considered for this research and at the time of this research.

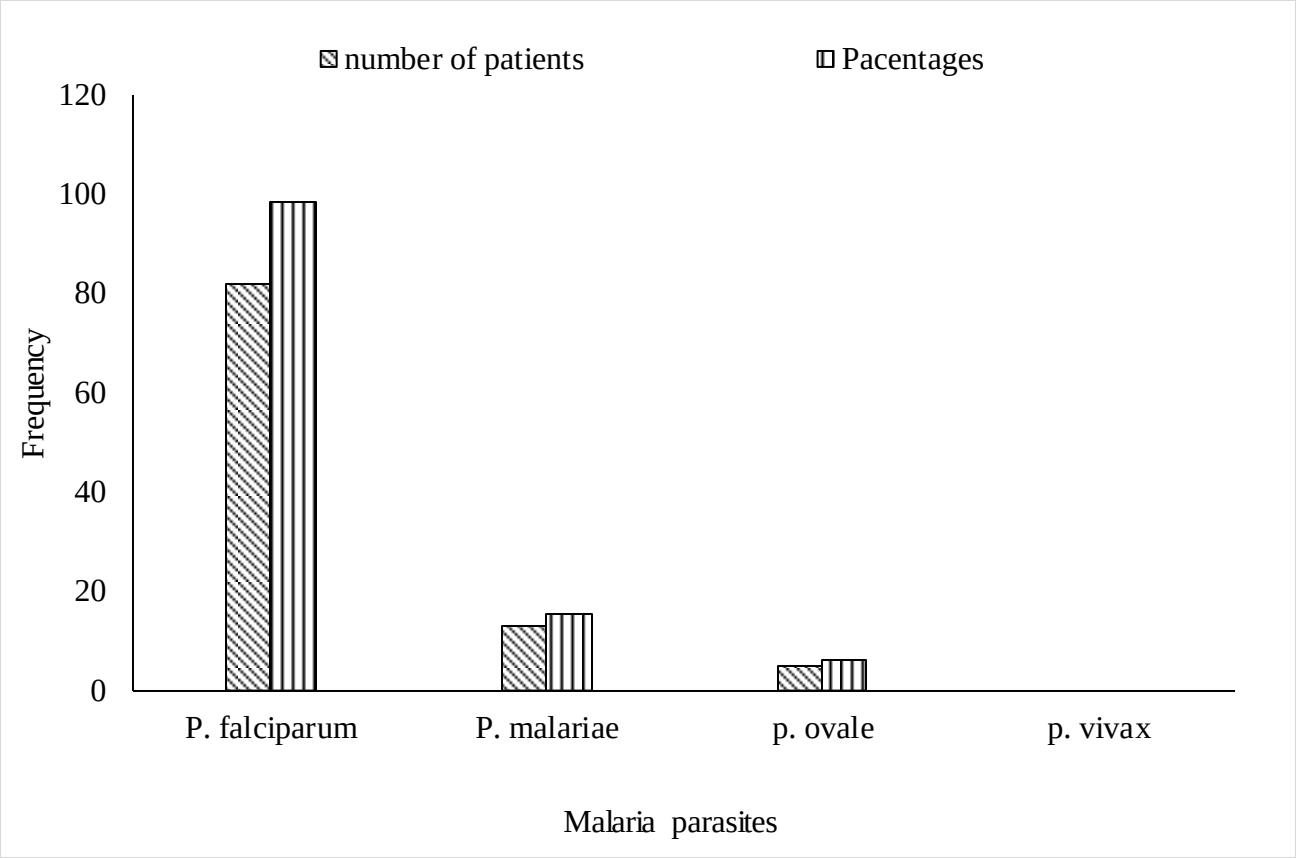


**Figure 4.3: Plasmodium present in patients**

**SEVERITY OF THE PARASITES PRESENT IN PATIENTS**

Ascertaining the severity of the disease, the results obtained were classified into three different categories namely: mild malaria, moderate malaria and severe malaria as at the time of diagnosis. Figure 4.4 showed that 35% of the patients that is 42 patients suffered mild malaria infection, 50.83% of the patients that is 61 patient suffered moderate malaria infection while 14.17% of the patient that is 17 patients suffered severe malaria infection. Conclusively not obvious from this analysis, it is in an affirmation that the severity of the disease is moderate in Port Harcourt region. Table for this analysis is presented in Appendix A Table A3.

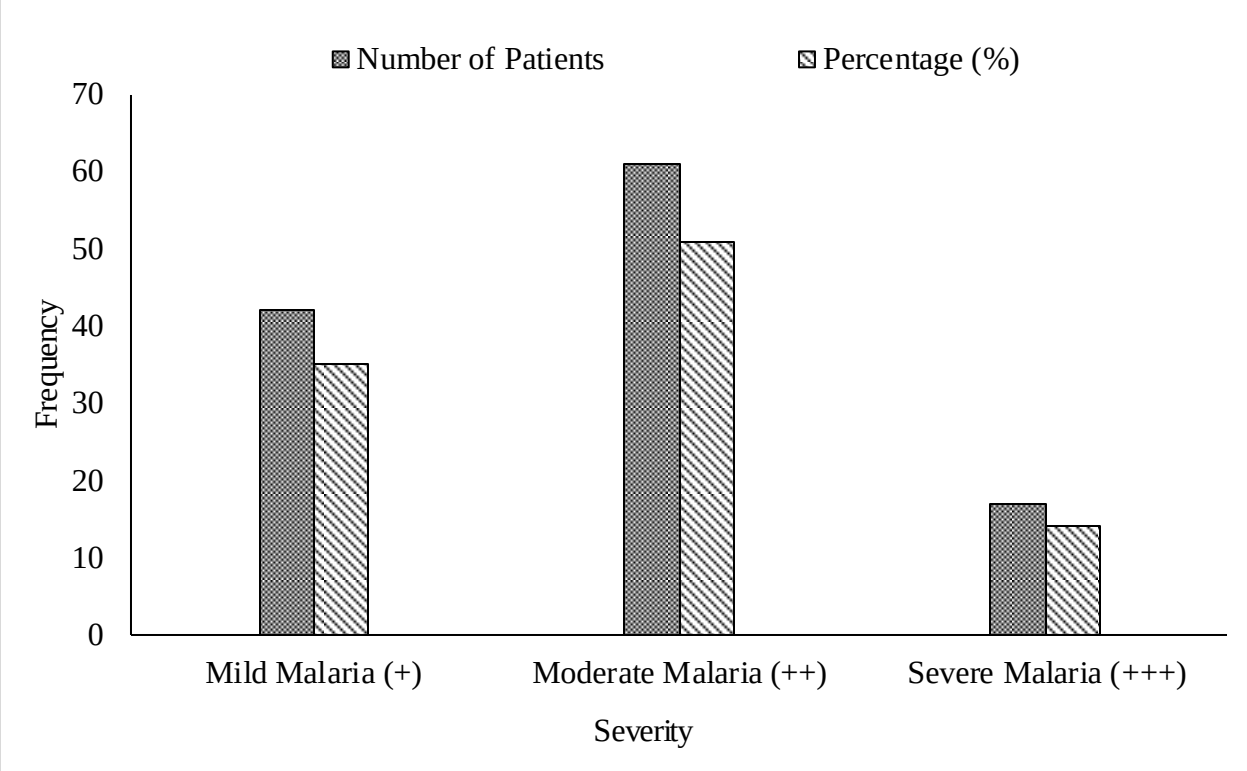


**Figure: 4.4 Parasite count / Severity of Malaria in Patient**

**SEVERITY OF THE PARASITES IN PATIENTS WITH RESPECT TO AGE**

Comparison of the disease with age is presented in Figure 4.5, and Appendix A, Table A4.It is evident that the age range at which malaria infestation produces the dares consequences is between the age bracket of 5-9, 0-4 and 45-49 years. This is also evident from the WHO (2014) report, which explained that reoccurrence of malaria on a victim usually causes mild symptoms in patients who survived an infection not too long that disappears on discontinuing exposure to the disease parasite. This is not common among children of age bracket 5-9, and 0-4 as the rate of their exposure to the disease parasites maybe low compare to adult of age bracket 45-49.

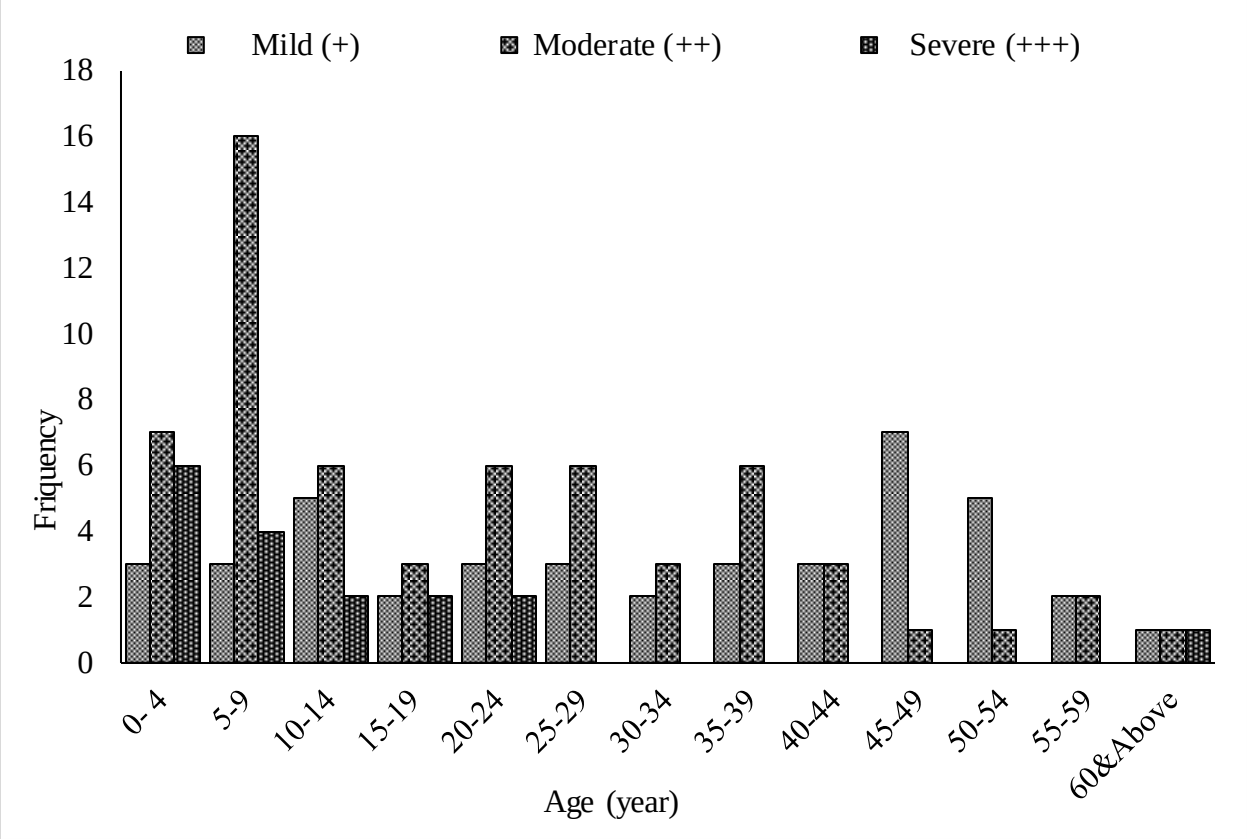


**Figure 4.5 Severity of disease with age**

## CO-MORBIDITIES ALONGSIDE MALARIA

Co-morbidities alongside malaria in the patients were noted at the beginning or prior to commencement of treatment (Table 4.1). Upper respiratory tract infection, typhoid fever, hypertension and diabetes are the highest co-morbidities found in 12.5%, 12.5%, 6.67% and 5.83% of the patients respectively. The Co-morbidities presented in the patients prior to treatment were also compared with their age ranges (Appendix) and this was done to elicit the age limits or ranges at which certain diseases predominantly occur in humans aside malaria. (Appendix 5).

**Table 4.1: Co-Morbidities Present Alongside Malaria**

| Co-Morbidities present | Number of Patients | Percentage of patients (%) |
|---|---|---|
| Upper respiratory tract infection | 15 | 12.50 |
| Lower respiratory tract infection | 4 | 3.33 |
| Sickle cell anaemia | 3 | 2.50 |
| Typhoid fever | 15 | 12.50 |
| Urinary tract infection | 3 | 2.50 |
| Helminthiasis | 2 | 1.67 |
| Hypertension | 8 | 6.67 |
| Diabetes | 7 | 5.83 |

## PRE-TREATMENT AVERAGE SERUM CREATININE

Pre-treatment average serum creatinine values for the patients were compared with those obtained after treatment with the different medications and results obtained are outlined in Table 4.2 The patients were placed in 6 treatment groups of 20 patients each, based majorly on the severity of the disease they were suffering from, with few interloping for comparison. Severely ill patients were given parenteral treatment of either Paluther injections or Quinine injections. Four oral medications namely Coartem, Artequin, Artesunate and Amodiaquine were used for some moderately ill patients and patients with mild diseases as well as in paediatric cases, with the exception of severely ill children.

**Table 4.2: Treatment Administered to Patients**

| Treatment Given | Route of Administration | Total No of Patients Given | Distribution of Patients |
|---|---|---|---|
| Coartem tablets/dissolvable/ dispersible tablets | Oral | 20 | 1 severe malaria<br>10 moderate malaria<br>9 mild malaria |
| Artequin tablets/syrup | Oral | 20 | 12 moderate malaria<br>8 mild malaria |
| Amiodaquine tablets/syrup | Oral | 20 | 11moderate malaria<br>9 mild malaria |
| Artesunate tablets/syrup | Oral | 20 | 12 moderate malaria<br>8 mild malaria |
| Quinine injection only | Intravenous | 20 | 8 severe malaria<br>8 moderate malaria<br>8 mild malaria |
| | Intramuscular | 20 | 8 severe malaria<br>8 moderate malaria<br>4 mild malaria |

## COMPARISON OF PRE-TREATMENT SERUM CREATININE AND POST-TREATMENT SERUM CREATININE WITH AGE

Figure 4.6 and Appendix 6 present the average mean of the pre-treatment serum creatinine and the post (Paluther parenteral) treatment. Patient treated with Paluther parenteral, the serum creatinine level of those within the age ranges of A (0-4) to K (50-54), reduces while those patients within the age ranges of L (55-59) and M (60&above) had less number of patients, with most having mild malaria, a few moderate and only one severe cases of malaria. Yet they had elevated serum creatinine levels prior to treatment that did not respond to parenteral Paluther.

This can be attributed to the presence of co-morbidities such as hypertension and diabetes in these age groups which are diseases known to cause renal impairment, hence their renal dysfunctions were not fully attributed to malaria disease nor to anti-malaria medications.

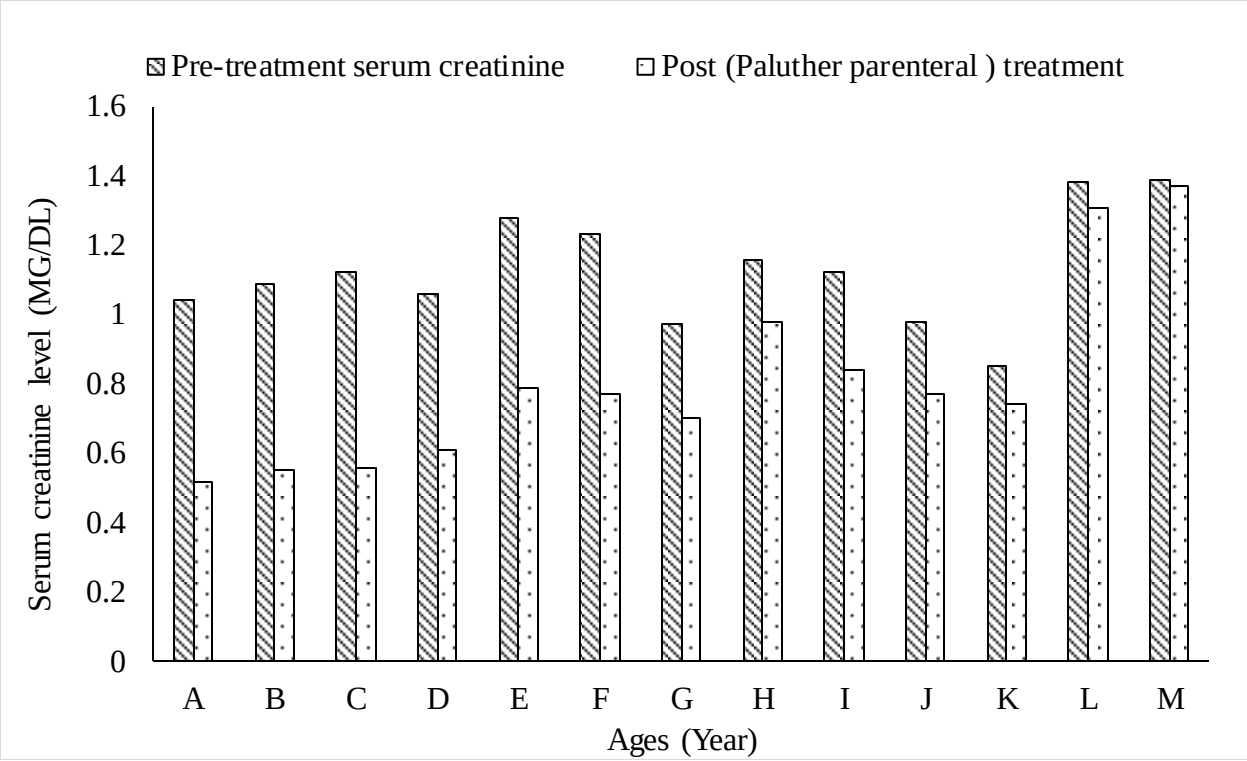


**Figure: 4.6 Pre-treatment serum creatinine, post (Paluther parenteral) treatment and age**

Figure 4.7 and Appendix 7 present the average mean of the pre-treatment serum creatinine and the post (Quinine parenteral) treatment. The serum creatinine level of those within the age ranges of A (0-4) to K (50-54), reduces while those patients within the age ranges of L (55-59) and M (60&above) had elevated serum creatinine levels prior to treatment that did not respond to Quinine parenteral.

The high level of response from quinine corroborate the report of (WHO, 2016) on the use of Quinine in malaria treatment and the low level of response in L and M can be link with co-morbidities.

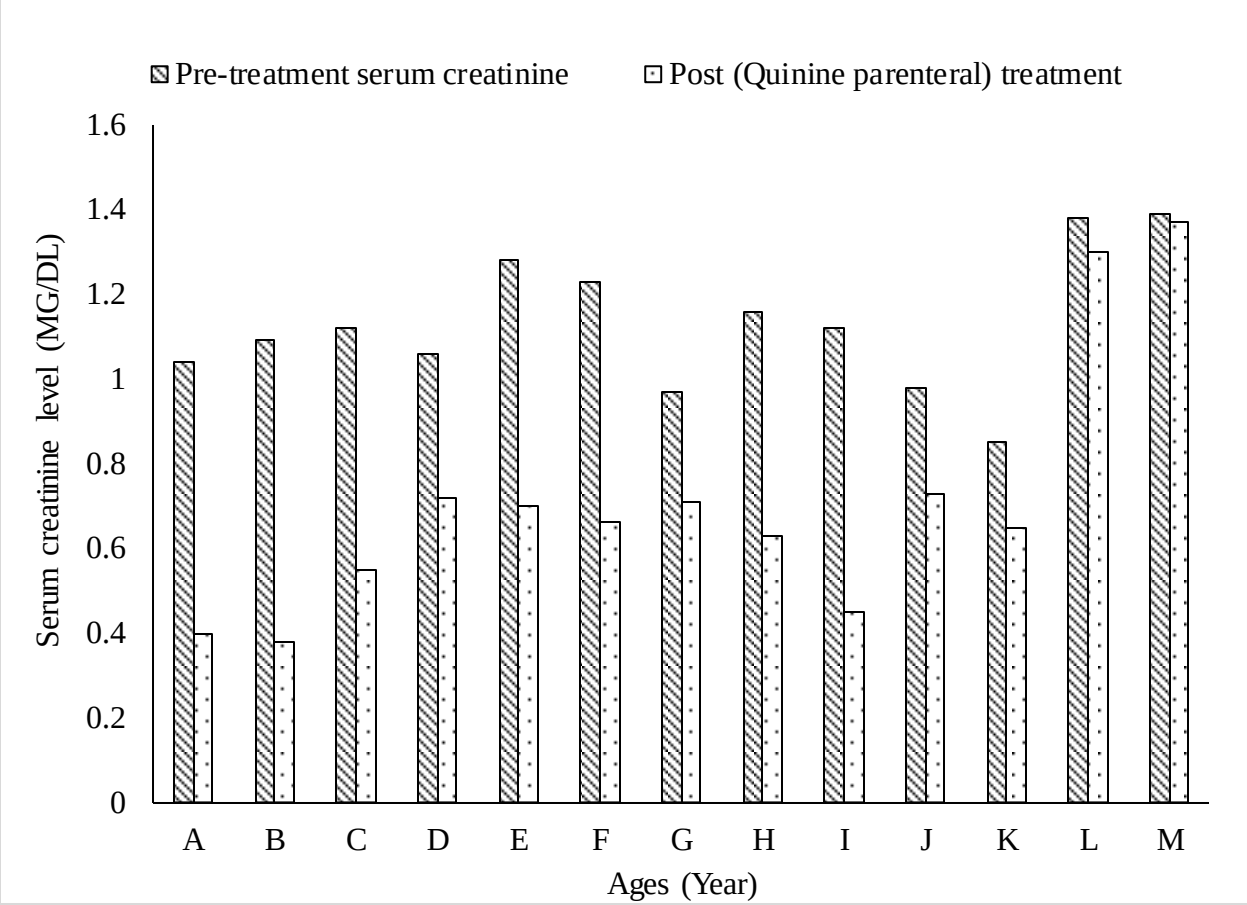


**Figure: 4.7 Pre-treatment serum creatinine, post (Quinine parenteral) treatment and age**

Figure 4.8 and Appendix 8 present the average mean of the pre-treatment serum creatinine and the post (Coartem oral) treatment.

The serum creatinine level of patients within the age ranges of I (40-44) and J (45-49), are higher than the pretreatment creatinine level while those patients within the age ranges of L (55-59) and M (60 & above) had elevated serum creatinine levels prior to treatment that did not respond to Coartem oral.

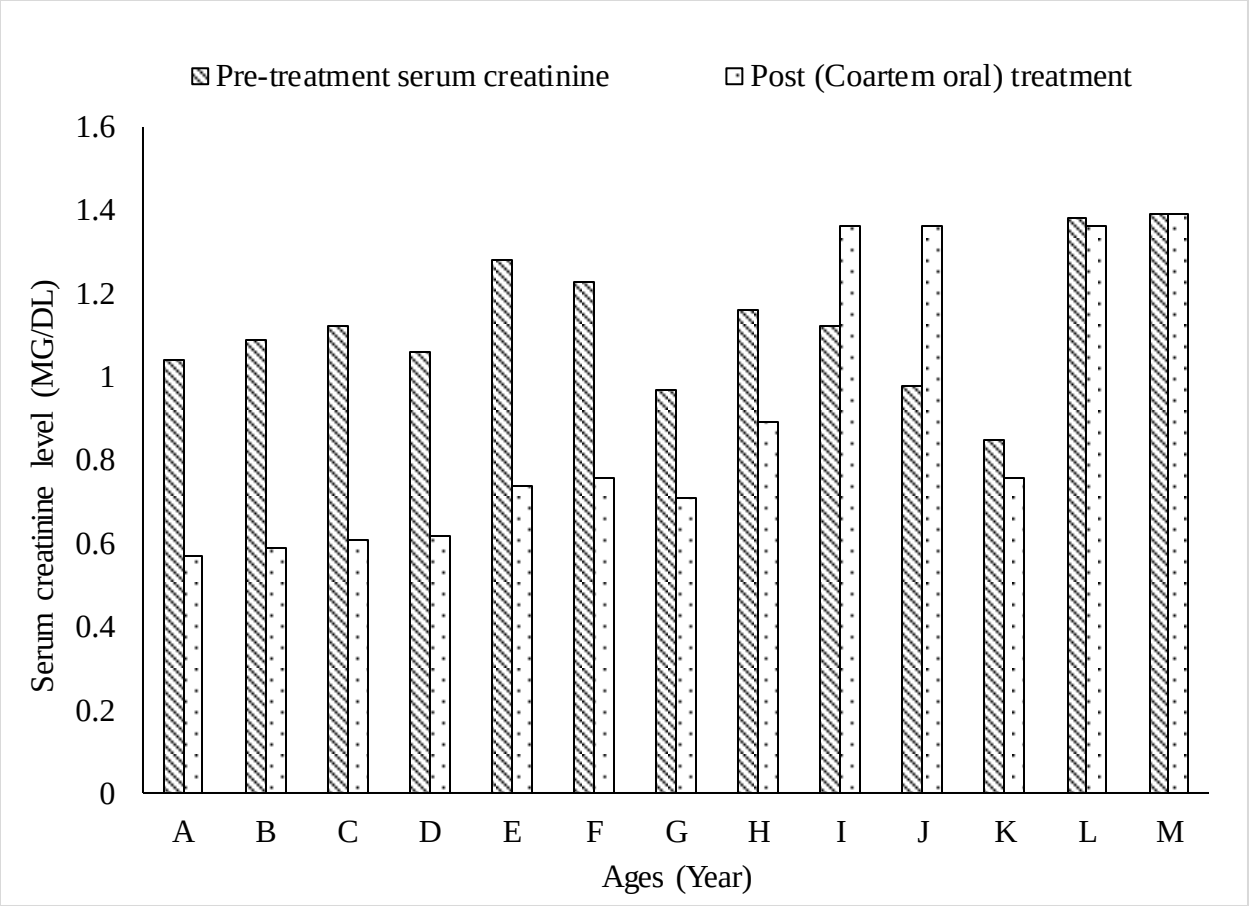


**Figure: 4.8 Pre-treatment serum creatinine, post (Coartem oral) treatment and age**

Figure 4.9 and Appendix 9 present the average mean of the pre-treatment serum creatinine and the post (Artequin oral) treatment.
The serum creatinine level of patients within the age ranges of L (55-59) high compared to the pretreatment creatinine level M (60 & above) had elevated no patient.

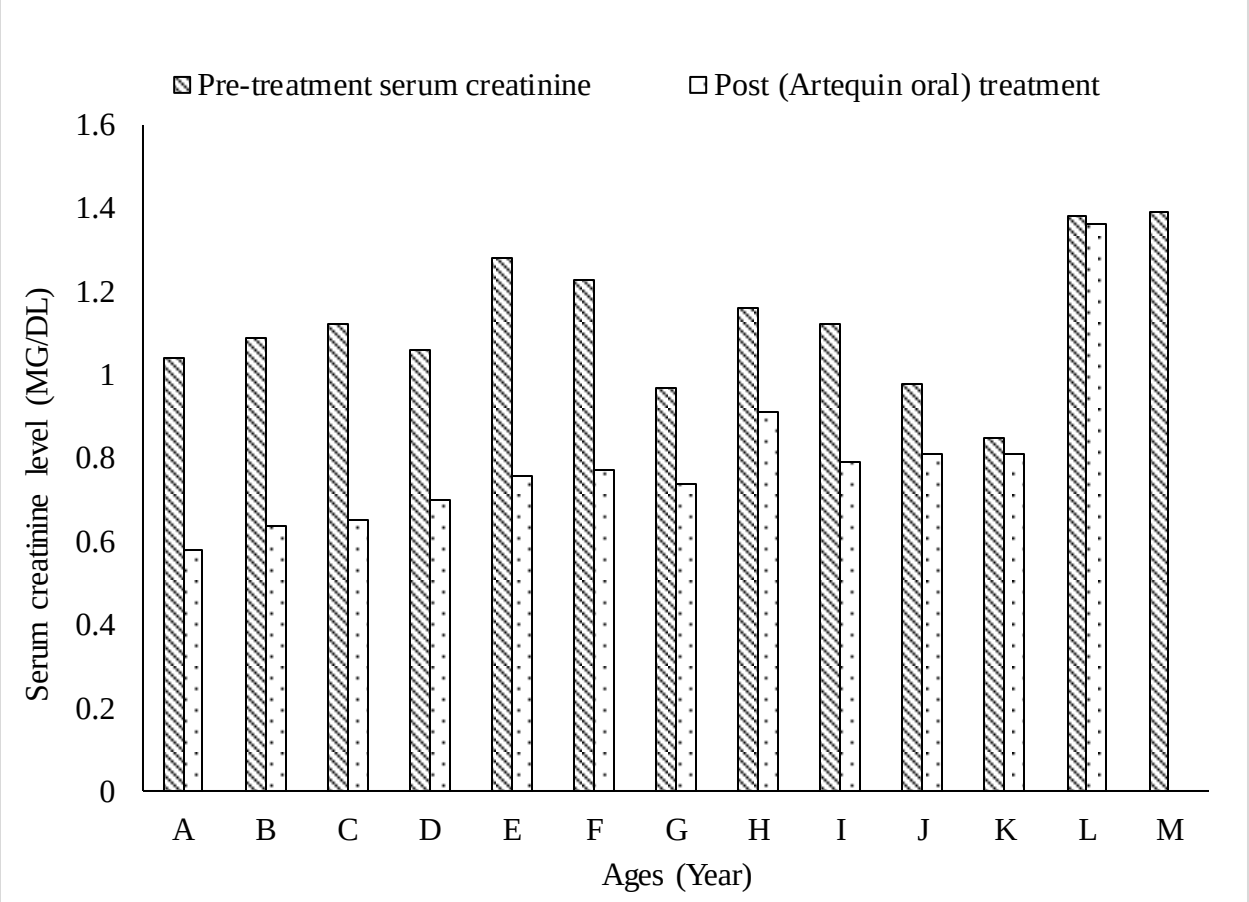


**Figure: 4.9 Pre-treatment serum creatinine, post (Artequin oral) treatment and age**

Figure 4.10 and Appendix 10 present the average mean of the pre-treatment serum creatinine and the post (Artesunate oral) treatment. Patient treated with Artesunate oral, there was only a significant response in their serum creatinine level observed. The respond rate of the patients is very poor. This is not liken to co-morbidity, as the age range for co-morbidity were not considered in this treatment. Malaria affectation on serum creatinine was seen to be slightly high in the age ranges of A(0-4) to K(50-54), with high mean serum creatinine values compared with the normal reference values of 0.5 to 1.0Mg/dL normal for children.

This may be attributed to the severity of the disease within these age groups. Evident by their symptoms of excessive vomiting, diarrhea, loss of appetite, high grade fever and moderate to severe dehydrations; factors which are all known to lead to hypovolemic shock, poor renal perfusion and acute renal failure with increases in serum creatinine.

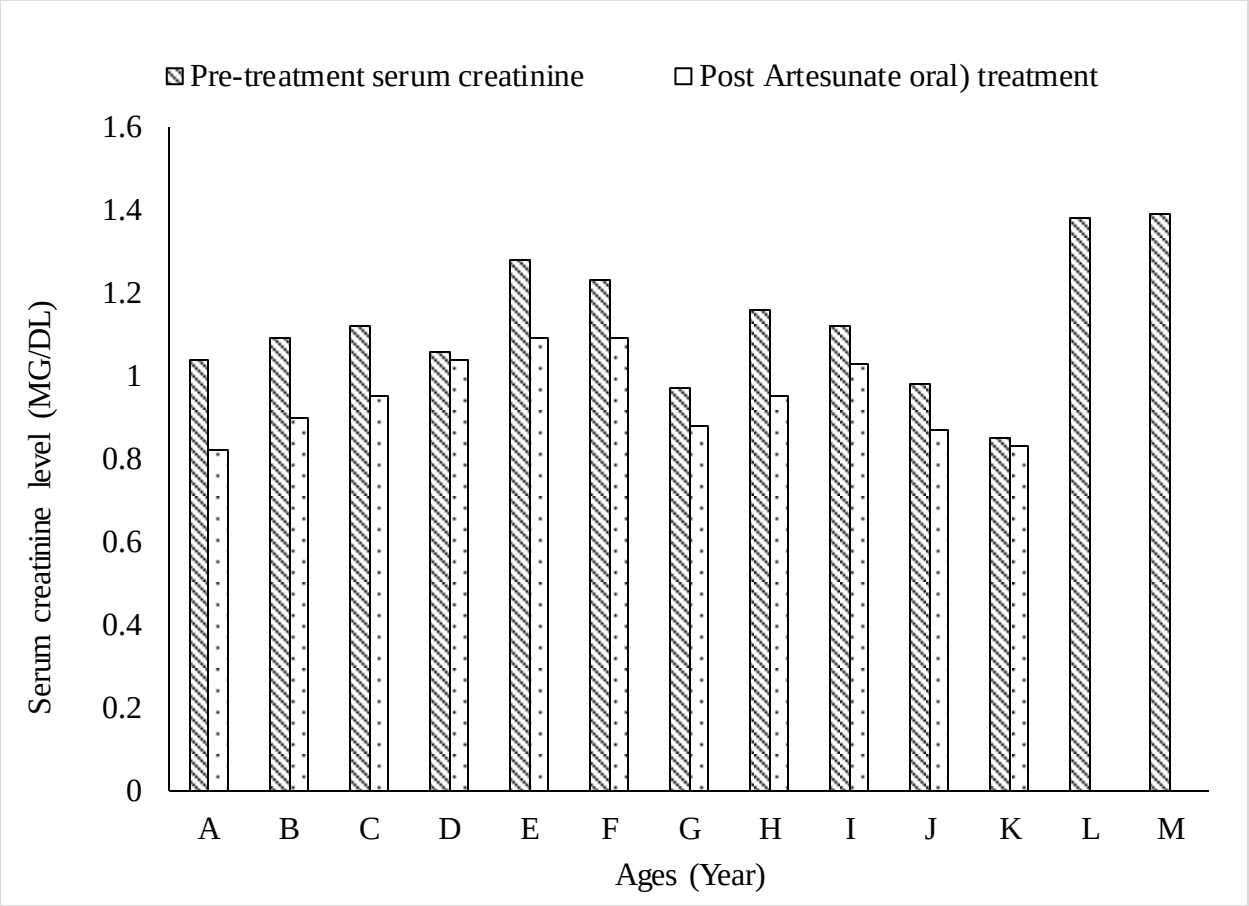


**Figure: 4.10 Pre-treatment serum creatinine, post (Artesunate oral) treatment and age**

In Figure 4.11 and Appendix 11 the serum creatinine level of patients is above normal. Malaria had a negative effect on renal function as evidenced by significant increases in levels of serum creatinine above normal, prior to onset of treatment. Serum creatinine elevation is worse slightly in children than in the adult population as was severity of the disease.

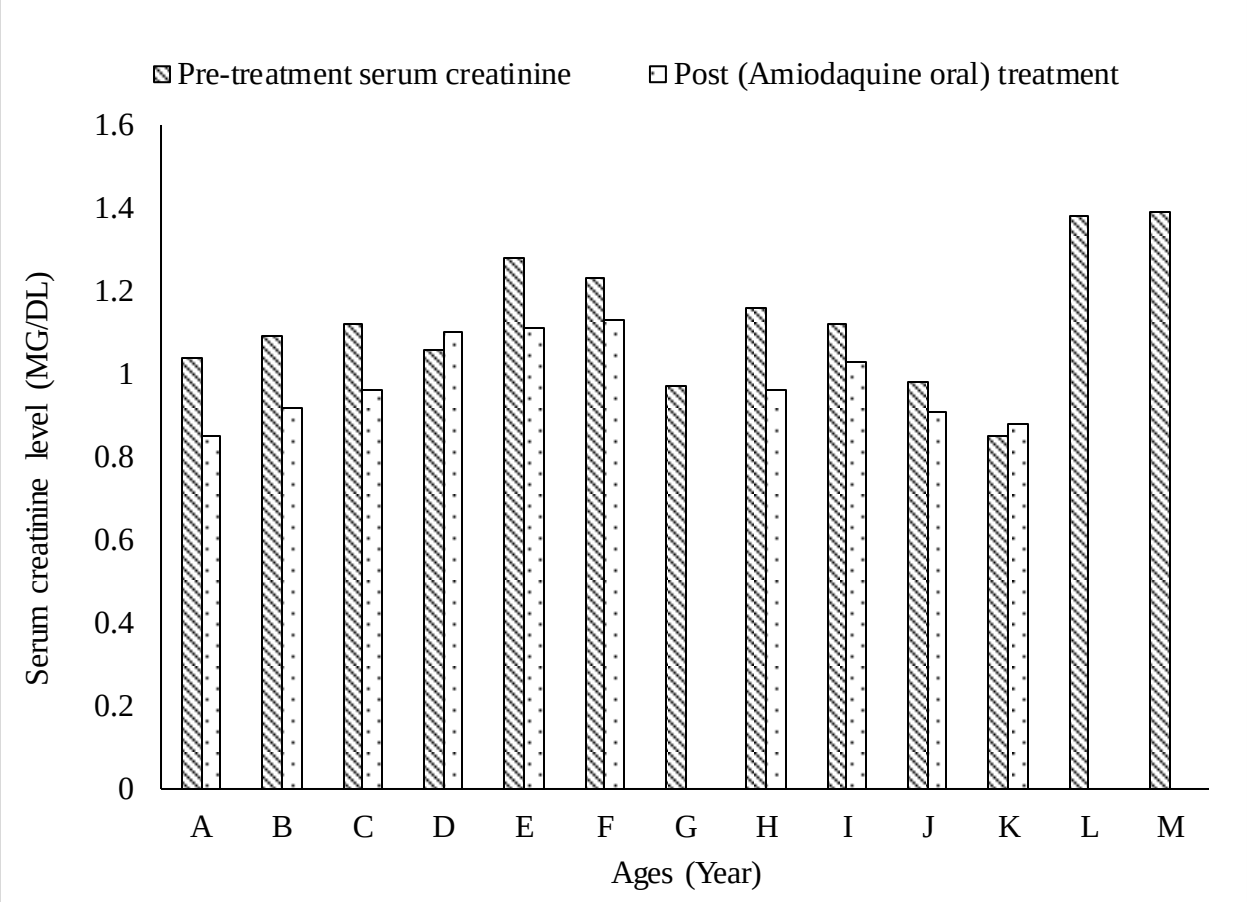


**Figure: 4.11 Pre-treatment serum creatinine, post (Amiodaquine oral) treatment and age**

**COMPARISON OF PRE-TREATMENT SERUM CREATININE AND POST-TREATMENT SERUM CREATININE**

Figures 4.12 to 4.17, present the correlation between the pre-treatment serum creatinine and the post-treatment serum creatinine. The correlation analysis illustrates the direction and strength of the relationship between pre-treatment serum creatinine and the post-treatment serum creatinine. In terms of the relationship strength, the value of the correlation coefficient varies between +1 and -1. A value of ± 1 indicates a perfect degree of association between pre-treatment serum creatinine and the post-treatment serum creatinine.

As the correlation coefficient value goes towards 0, the relationship between pre-treatment serum creatinine and the post-treatment serum creatinine will be weak. The direction of the relationship is indicated by the sign of the coefficient; a + sign means a positive relationship and a – sign indicates a negative relationship.

Figure 4.12 showed that the correlation between pre-treatment serum creatinine and the post-treatment serum creatinine is significant at the 0.01 level of significance (Appendix 12). This is an indication that treatment with intravenous and intramuscular anti-malaria medications with adequate rehydration were noticed to have returned serum creatinine levels to near normal in the younger age groups of A(0-4), B(5-9) and C(10-14) years, which are evident in Figures 4.6 and 4.7.

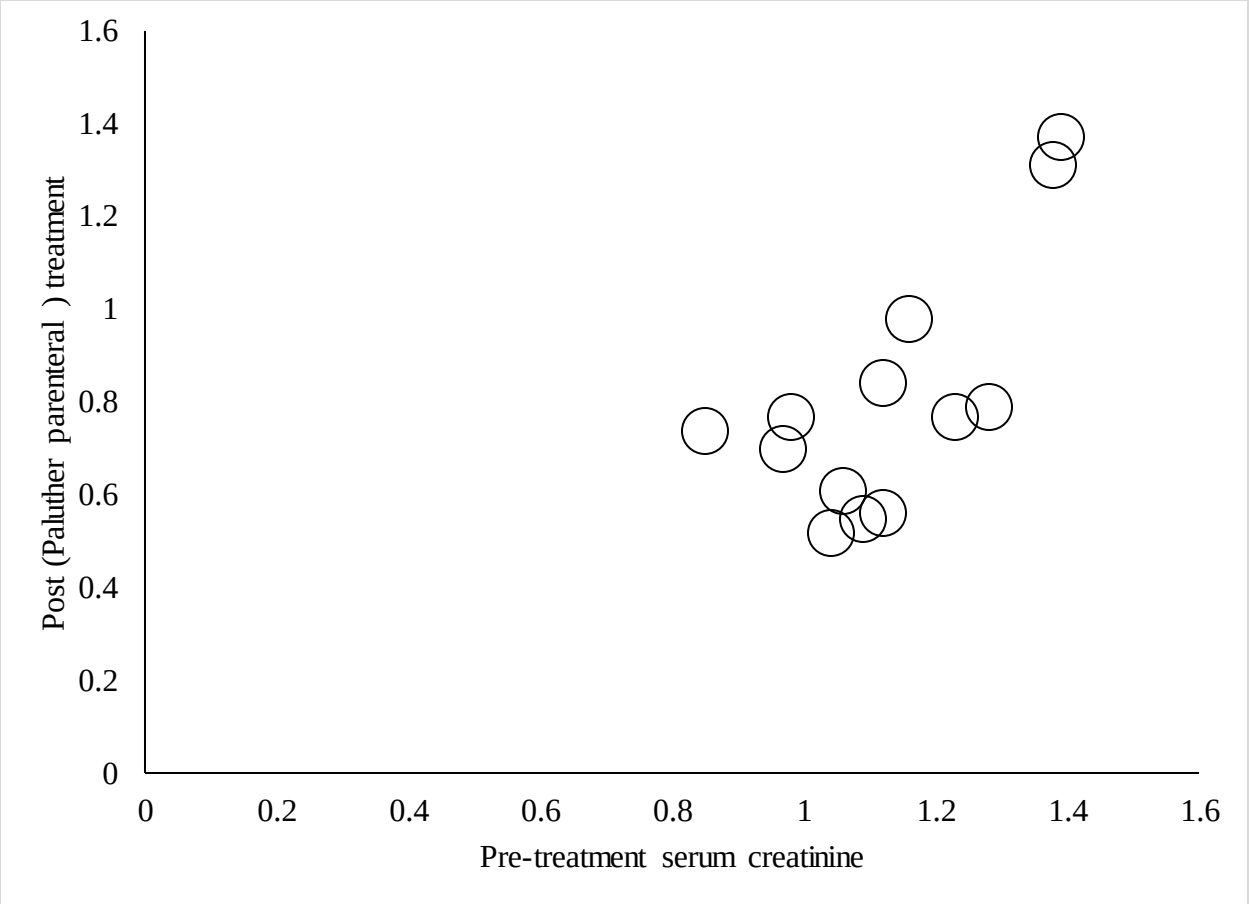


**Figure: 4.12 Pre-treatment serum creatinine and post (Paluther parenteral) treatment**

Also, a similar correlation is seen in Figure 4.13 the correlation between pre-treatment serum creatinine and the post-treatment serum creatinine is significant at the 0.05 level of significance (Appendix 13). This also showed that the use of quinine parenteral on patients reduces their creatinine level to near normal.

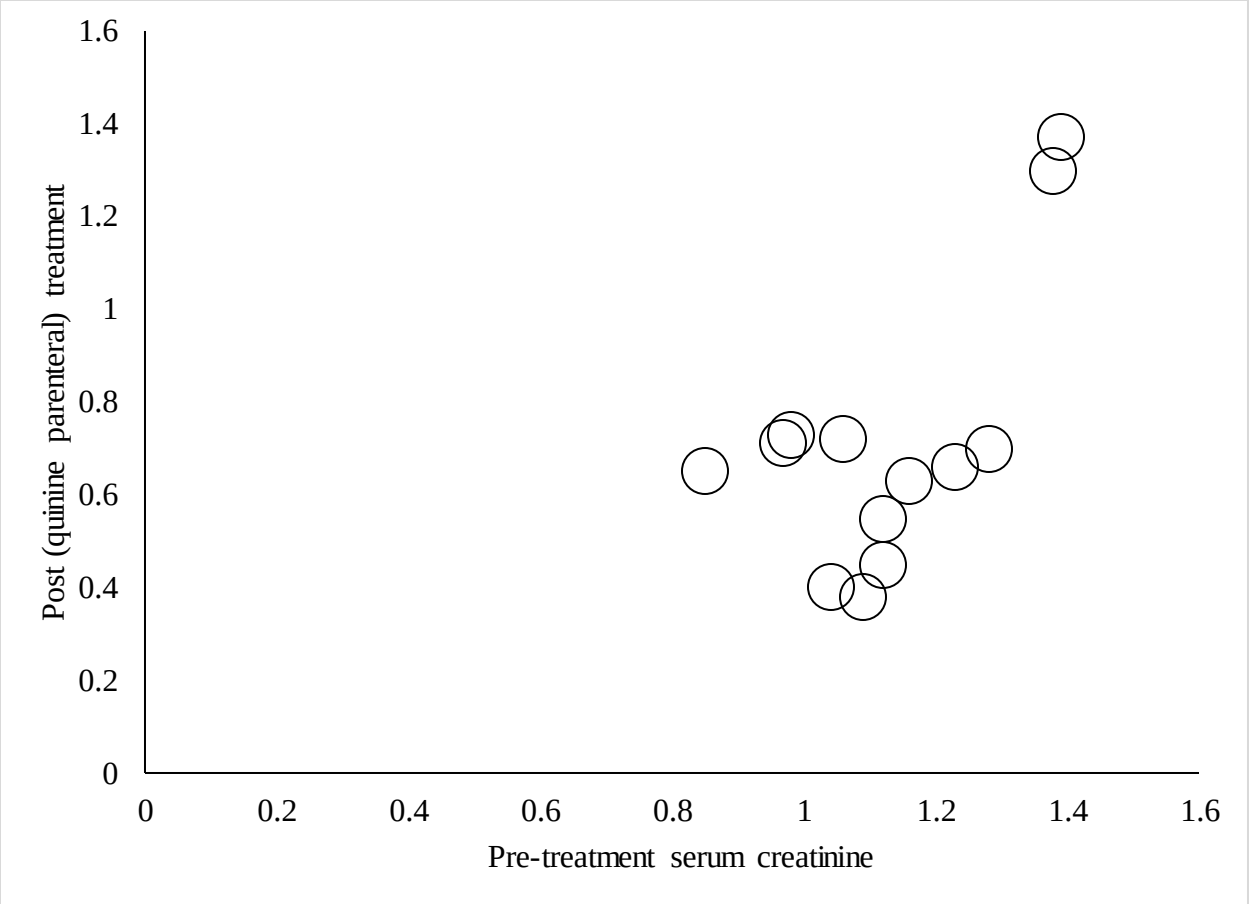


**Figure: 4.13 Pre-treatment serum creatinine and post (Quinine parenteral) treatment**

Figure 4.14 show a weak correlation (Appendix 14) in the creatinine level of the patients. Also evident from Figures 4.8 to 4.10, the elderly patients did not give much response to the drugs (Coartem oral) used for treatment and this necessitated both re-commencement of their routine medications after the anti-malaria treatments as well as referrals to a Consultant Nephrologist for further management.

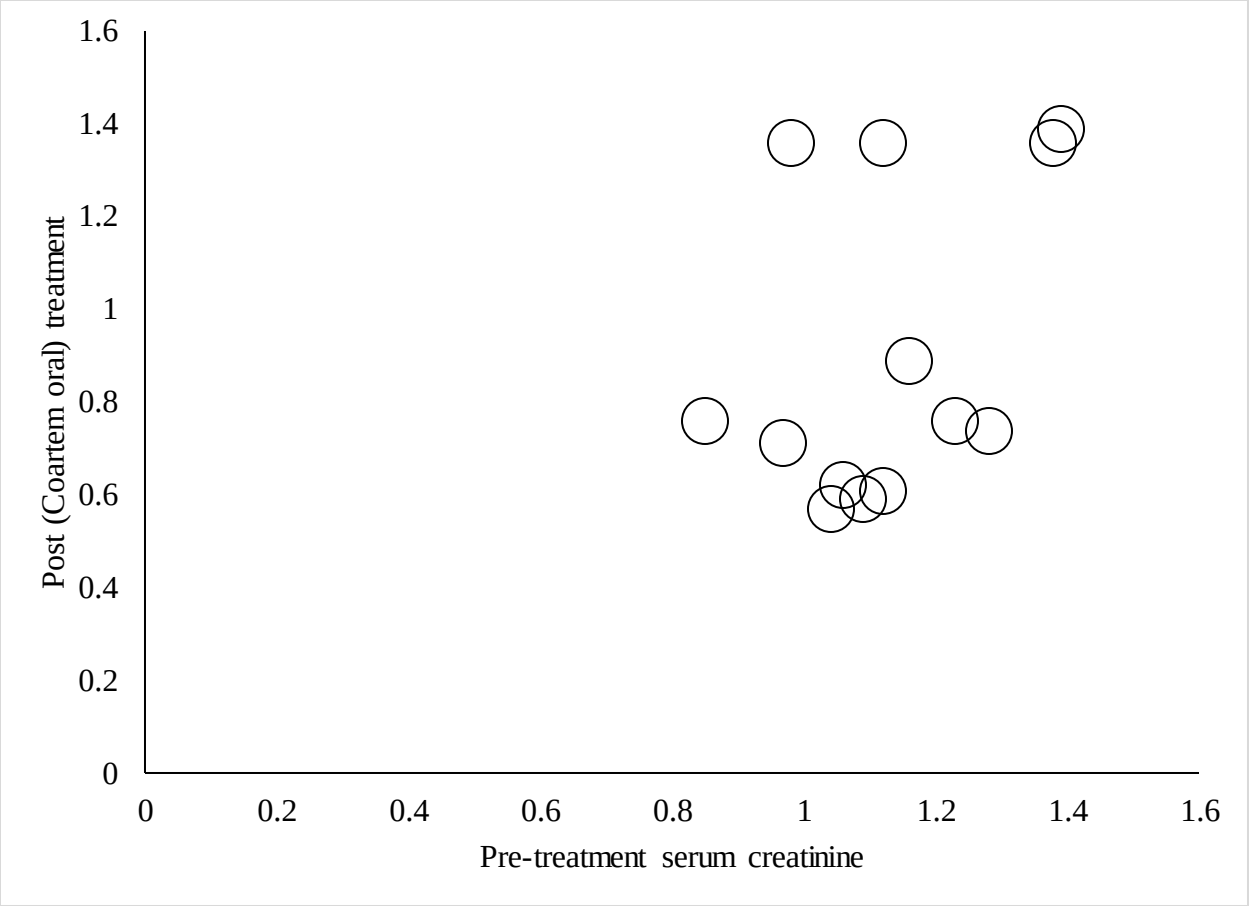


**Figure: 4.14 Pre-treatment serum creatinine and post (Coartem oral) treatment**

The correlation coefficient of Figure 4.15 is shown Appendix 15 compared with those that received only oral medications within the same age groups and in the older age groups. The correlation coefficient has no significance value.

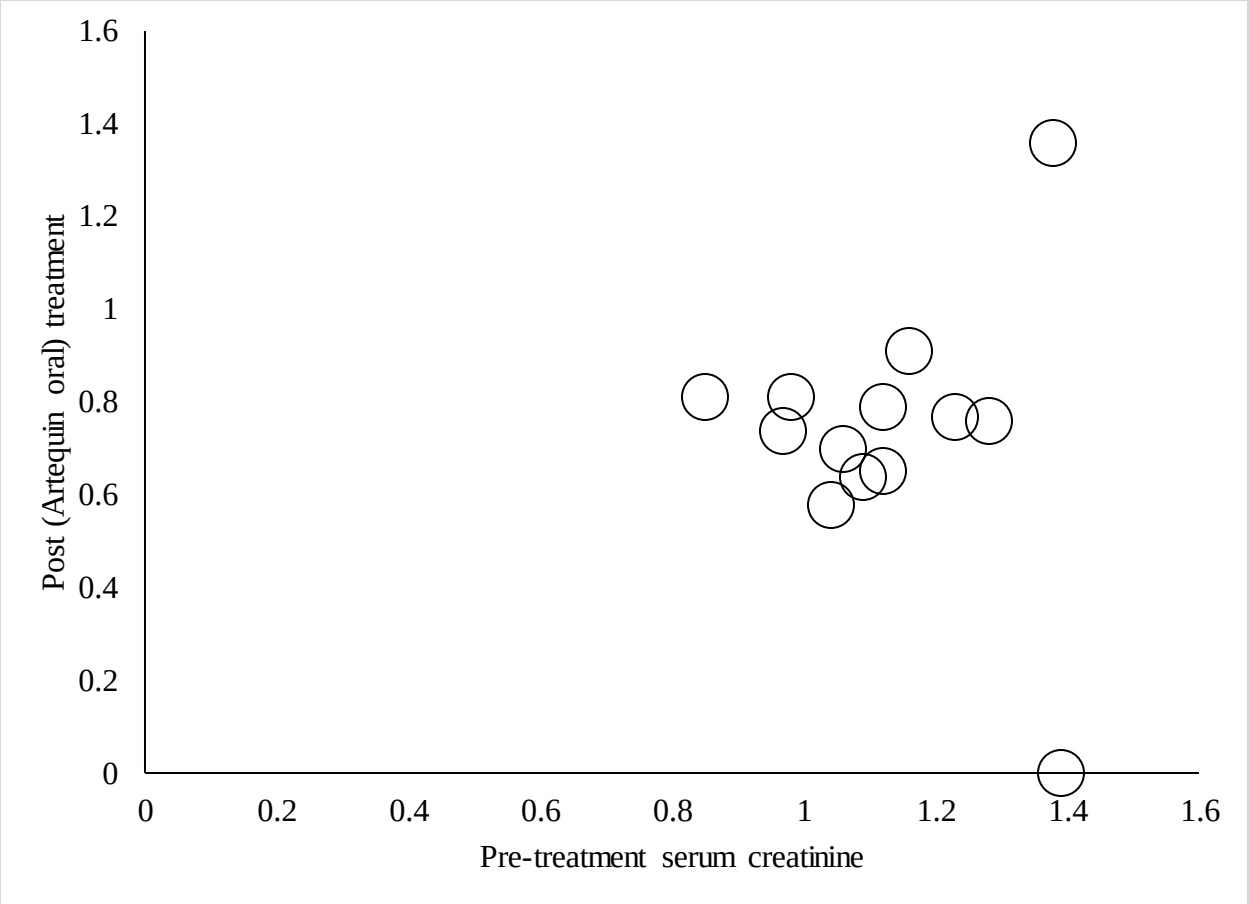


**Figure: 4.15 Pre-treatment serum creatinine and post (Artequin oral) treatment**

The correlation coefficient of Figure 4.16 is shown Appendix 16 of compared with those that received only oral medications within the same age groups and in the older age groups. The correlation coefficient has no significance value.

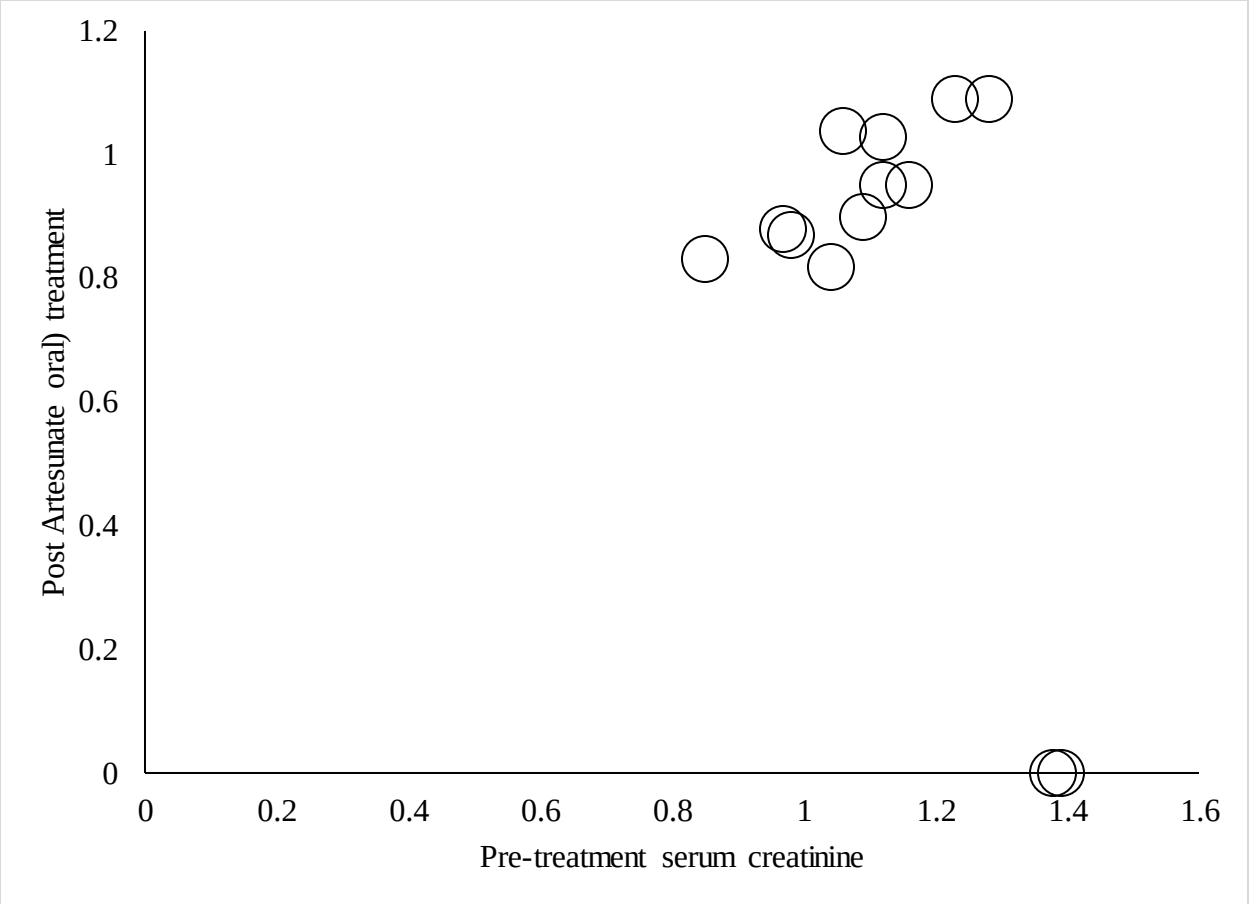


**Figure: 4.16 Pre-treatment serum creatinine and post (Artesunate oral) treatment**

The correlation coefficient of Figure 4.17 is shown Appendix 17 of compared with those that received only oral medications within the same age groups and in the older age groups. The correlation coefficient has no significance value.

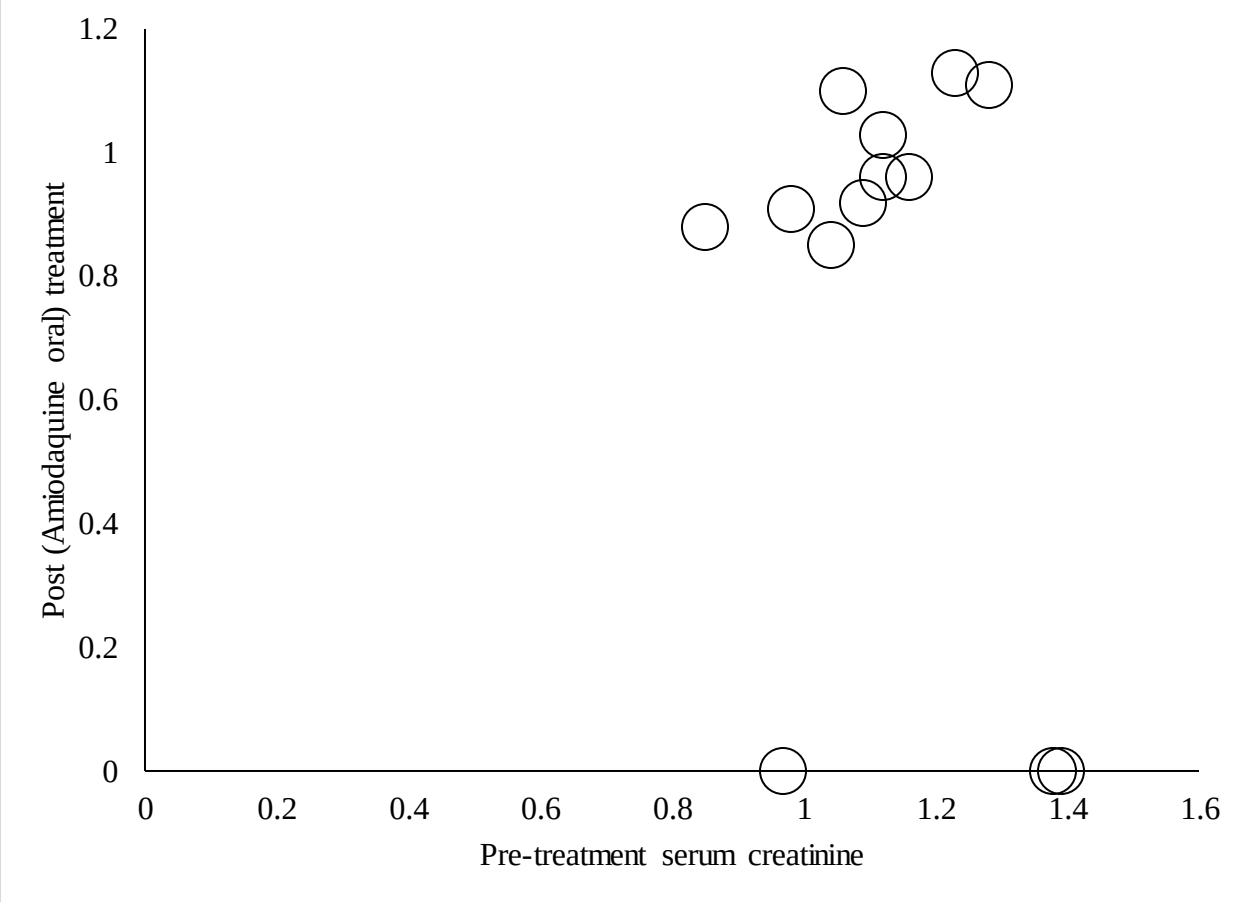


**Figure: 4.17 Pre-treatment serum creatinine and post (Amiodaquine oral) treatment**

## DISCUSSIONS

Malaria infestation amongst the study patients showed that the disease was more predominant in the 5–9 years age range with 23 patients or 19.17% having the disease. Disease occurrence was seen to decrease with age and was lowest within the 60 years and above age group with only 3 patients or 2.5% of cases presenting, which may be attributed to the development of immunity as the patients age, following constant exposure to the disease which is endemic in Port Harcourt.

The highest number of severe cases occurred within the 0–4 age range with 6 patients or 5% of the total study patients recorded and treated for severe malaria while the group in the 5 – 9 years age range recorded the highest number of moderately ill patients with a number of 16 patients or 13.33% of the total cases.

More females were affected (73 patients; 60.83%) than males (47 patients; 39.17), a case which may be attributed to lower immune status of females caused by female hormonal changes amongst other factors. Moderately ill patients were the highest numbers of presenters (61 patients; 50.83%), followed by those with mild afflictations (42 patients; 35%). Severity of disease occurred in only 17 patients or 14.17 of the total population, with children between the ages of 0 – 4 years having the highest presentation of 6 patients or 5%of the population.

Malaria affectation on serum creatinine was seen to be slightly high in the age ranges of 10-14, 20 – 24, 25 – 29 and 35 - 39 years, with mean serum creatinine values of 1.12, 1.28, 1.23 and 1.16Mg/dL respectively as compared with the normal reference values of 0.5 to 1.0Mg/dL normal for children. This may be attributed to the severity of the disease within these age groups,

as evidenced by their symptoms of excessive vomiting, diarrhea, loss of appetite, high grade fever and moderate to severe dehydrations; factors which are all known to lead to hypovolemic shock, poor renal perfusion and acute renal failure with increases in serum creatinine.

The age ranges of 55-59 and above 60 years had less number of patients, with most having mild malaria, a few moderate and only one severe cases of malaria. Yet they had elevated serum creatinine levels prior to treatment, which did not respond much to any of the medications used. This was attributed to the presence of co-morbidities such as hypertension and diabetes in these age groups which are diseases known to cause renal impairment, hence their renal dysfunctions were not fully attributed to malaria disease nor to anti-malaria medications.

Treatment with intravenous and intramuscular anti-malaria medications with adequate rehydration were noticed to have returned serum creatinine levels to near normal in the younger age groups of 0-4, 5-9 and 10-14 years when compared with those that received only oral medications within the same age groups and in the older age groups.

The elderly patients did not give much response to the drugs used for treatment and this necessitated both re-commencement of their routine medications after the anti-malaria treatments as well as referrals to a Consultant Nephrologist for further management.

## CONCLUSION

Malaria had a negative effect on renal function as evidenced by significant increases in levels of serum creatinine above normal, prior to onset of treatment. Serum creatinine elevation was worse slightly in children than in the adult population as was severity of the disease.

Parenteral antimalarial agents did not show any significant ($P<0.5$) adverse effect on renal functions but rather significantly ($P>0.5$) ameliorated the effects of malaria on renal functions when compared with the oral medications. However, oral medications did not significantly ($P< 0.5$) improve renal functions in treated patients as evidenced by lower improvement rates in blood serum creatinine levels when compared to parenteral anti-malaria agents.

Amongst the parenteral drugs used, Paluther which is an Artemether suspension, had a better clinical outcome than Quinine injection while amongst the oral drugs used, Coartem which is a combination of Artemether and Lumefantrine, had better clinical outcomes followed by Artequin which is a combination of Artesunate and Mefloquine. Both combination therapies were seen to have better clinical outcomes than Artesunate and Amodiaquine, both single drug therapies.From the study above, it could be concluded that Artermether-containing drugs performed better than Artesunate and Quinine-based drugs in terms of malaria treatment. We could also conclude that Anti-malaria agents used in Port Harcourt, Rivers State, Nigeria were able to cure malarial infestations in humans with little or no adverse effects on renal functions.

## REFERENCES

Adjuik M, Agnamey P, Babiker A, et al. (2002) Amodiaquine-artesunate versus amodiaquine for uncomplicated Plasmodium falciparum malaria in African children: a randomised, multicentre trial. Lancet 2002; 359:1365.

Andersen S, Pruden L.E, Tietz N. (1996). Tietz Fundamentals of Clinical Chemistry. 2nd ed WB Saunders Company: USA, pp.: 721– 738.

Antony H.A, Parija S.C. (2016). "Antimalarial drug resistance: An overview". Tropical Parasitology. 6 (1): 30–41. doi:10.4103/2229-5070.175081. PMC 4778180.PMID 26998432.

Ayoola O.O, Fawole O.I, Omotade O.O. (2005). Calcium and phosphate levels in Nigerian children with malaria. Ann Trop Paediatr. 2005 Dec; 25 (4): 303– 306.

Baiden R, Oduro A, Halidou T, et al. (2015) Prospective observational study to evaluate the clinical safety of the fixed-dose artemisinin-based combination Eurartesim® (dihydroartemisinin/piperaquine), in public health facilities in Burkina Faso, Mozambique, Ghana, and Tanzania. Malar J 2015; 14:160.

Baloch S, Memon S.A, Gachal G.S, Baloch M. (2011). Determination of trace metals abnormalities in patients with vivax malaria. Iran J Parasitol, 20:3:59-65.

Bartoloni A, Zammarchi L (2012). "Clinical aspects of uncomplicated and severe malaria".Mediterranean Journal of Hematology and Infectious Diseases. 4 (1): e2012026. doi:10.4084/MJHID.2012.026. PMC 3375727 .PMID 22708041.

Brooks D.R, Wang P, Read M, Watkins W.M, Sims P.F, and Hyde J.E (1994) Sequence variation of the hydroxymethyldihydropterinpyrophosphokinase: dihydropteroate synthase gene in lines of the human malaria parasite, Plasmodium falciparum, with differing resistance to sulfadoxine. *Eur J Biochem* **224:** 397-405.

Bukirwa H, Garner P, and Critchley J (2004) Chlorproguanil-dapsone for treating uncomplicated malaria.*Cochrane Database Syst Rev* **4:** CD004387.

Bunnag D, Harinasuta T, Pinichpongse S, and Suntharasami P (1980) Effect of primaquine on gametocytes of Plasmodium falciparuminThailand. *Lancet* **2:** 91.

Burchard G.D, Ehrhardt S, Mockenhaupt F.P. (2003) Renal dysfunction in children with uncomplicated, Plasmodium falciparum malaria in Tamale, Ghana. hbAnn Trop Med Parasitol 2003; 97: 345–350. PubMed

Burgess R.W and Young M.D (1959). The development of pyrimethamine resistance by Plasmodium falciparum.*BullW H O* **20:** 37-46.

Bzik D.J, Li W.B, Horii T, and Inselburg J (1987) Molecular cloning and sequence analysis of the Plasmodium falciparum dihydrofolate reductase-thymidylate synthase gene. *Proc Natl AcadSci USA* **84:** 8360-8364.

Campbell C.C, Chin W, Collins W.E, Teutsch S.M, and Moss D.M (1979) Chloroquine-resistant Plasmodium falciparum from East Africa: cultivation and drug sensitivity of the Tanzanian I/CDC strain from an American tourist. *Lancet* **2:** 1151-1154.

Caraballo H (2014). "Emergency department management of mosquito-borne illness: Malaria, dengue, and west nile virus". Emergency Medicine Practice.16 (5).Archived from the original on 2016-08-01.

Charles E.O, Ejovi O, Innocent O. (2013). Levels of iron and magnesium in serum of Plasmodium falciparum malarial infected children in Abraka, Delta State, Nigeria. J Invest Biochem, 2 ( 1): 62– 64.

Chertow G.M, Burdick E, Honour M. (2005). Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005; 16: 3365–3370.

Conway D.J. (2007). Molecular epidemiology of malaria.Clin Micro biol. Rev, 20: 188–204.PubMed

Day N, Dondorp A, Nosten F, Stepniewska K, White N. (2005). Artesunate versus quinine for treatment of severe falciparum malaria: a randomized trial. Lancet, 366: 717–725.PubMed

Deen J.L, von Seidlein L, Dondorp A. (2008) Therapy of uncomplicated malaria in children: a review of treatment principles, essential drugs and current recommendations. Trop Med Int Health 2008; 13:1111.

Djimdé A, Doumbo O.K, Cortese J.F, et al. (2001) A molecular marker for chloroquine-resistant falciparum malaria. N Engl J Med 2001; 344:257.

Ekpechi O.L, Okoro A.N. (1964) A pattern of pruritus due to chloroquine. Arch dermatol 1964; 89:631.

Fairhurst R.M, Wellems T.E. (2009). Plasmodium species (Malaria). In: Mandell GL, Bennett JE, Dolin R, editors. , Eds. Principles and Practice of Infectious Diseases. 7th ed Elsevier Churchill Livingstone: Philadelphia, chap 275.

Ferdig M.T, Cooper R.A, Mu J, (2004) Dissecting the loci of low-level quinine resistance in malaria parasites. MolMicrobiol 2004; 52:985.

Ferone R (1977) Folate metabolism in malaria. *Bull World Health Organ* **55:** 291-298.

Fidock D.A, Nomura T, Talley A.K, (2000) Mutations in the P. falciparum digestive vacuole transmembrane protein PfCRT and evidence for their role in chloroquine resistance. Mol Cell 2000; 6:861.

Garba I.H, Ubom G.A. (2006). Potential role of serum magnesium measurement as a biomarker of acute falciparum malaria infection in adult patients. Biol Trace Elem Res, 114 (1–3): 115– 120. [PubMed]

Gollin D, Zimmermann C (August 2007). Malaria: Disease Impacts and Long-Run Income Differences (PDF) (Report). Institute for the Study of Labor. Archived (PDF) from the original on 2016-03-18.

Golvan Y.J. (1983). Elements of medical parasitology. 4th ed Paris, pp.: 275– 319.

Greenwood B.M, Bojang K, Whitty C.J, Targett G.A (2005)."Malaria".Lancet. 365 (9469): 1487 98. doi:10.1016/S0140-6736(05)66420-3. PMID 15850634.

Gunther A, Burchard G.D, Slevogt H et al. Renal dysfunction in falciparum--malaria is detected more often when assessed by serum concentration of cystatin C instead of creatinine. Trop Med Int Health 2002; 7: 931–934.

Hatton C.S, Peto T.E, Bunch C, (1986). Frequency of severe neutropenia associated with amodiaquine prophylaxis against malaria. Lancet 1986; 1:411.

Hawke M.T, Conroy A.L, Opoka R.O et al. (2015) Inhaled nitric oxide as adjunctive therapy for severe malaria: a randomized controlled trial. Malar J 2015; 14: 421. PubMed

Hung T.Y, Davis T.M, Ilett K.F, (2004). .Population pharmacokinetics of piperaquine in adults and children with uncomplicated falciparum or vivax malaria. Br J ClinPharmacol 2004; 57:253.

Ikekpeazu E.J, Neboh E.E, Aguchime N.C, Maduka I.C, Anyanwu E.G. (2010). A study on malaria parasitemia:-effect on the sodium and potassium levels. J Biol Med, 2 ( 2): 20–25.

Imani P.D, Odiit A, Hingorani S.R. (2013). Acute kidney injury and its association with in-hospital mortality among children with acute infections. PediatrNephrol 2013; 28: 2199–2206.

Inker L.A, Schmid C.H, Tighiouart H. (2012).Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012; 367: 20–29.

Jasani J.H, Sancheti S.M, Gheewala B.S, Bhuva K.V, Doctor V.S, Vacchani A.B, Patel V.R, Dharya L. (2012). Association of the Electrolyte Disturbances (Na+, K+) with Type and Severity of Malarial Parasitic Infection. J ClinDiagn Res, 6 ( 4): 678– 681.

Josh H, Amir H, Prakaykaew C, Mahtab Uddin H, Timothy M.E. (2009) Hyponatremia in severe

malaria: evidence for an appropriate anti-diuretic hormone response to hypovolemia. Am J Trop Med Hyg, 2009 Jan; 80 (1): 141– 145.

Kapoor K, Gupta S. (2012) Malarial acute kidney injury in a paediatric intensive care unit. Trop Doct 2012; 42: 203–205. PubMed

KDIGO. (2012). Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int. 2012; Supplement 2:1–138.

Keating G.M. Dihydroartemisinin/Piperaquine: a review of its use in the treatment of uncomplicated Plasmodium falciparum malaria. Drugs 2012; 72:937.

Khattak A.A, Venkatesan M, Nadeem M.F, Satti H.S, Yaqoob A, Strauss K, Khatoon L, Malik S.A, Plowe C.V. (2013). Prevalence and distribution of human Plasmodium infection in Pakistan. Malar J, 12 (1): 297.

*Krungkrai J, Webster H.K, and Yuthavong Y (*1989*) De novo and salvage biosynthesis of pteroylpentaglutamates in the human malaria parasite, Plasmodium falciparum*. *MolBiochemParasitol* **32:**25-*37*.

Lesi A, Meremikwu M. (2004) High first dose quinine regimen for treating severe malaria. Cochrane Database Syst Rev 2004; :CD003341.

Lim P; Alker A.P; Khim N; et al. (2009). "Pfmdr1 copy number and arteminisin derivatives combination therapy failure in falciparum malaria in Cambodia". Malar. J. 8: 11. doi:10.1186/1475-2875-8-11. PMC 2627910 .PMID 19138391.

Maitland K, Pamba A, Fegan G, Njuguna P, Nadel S, Newton C.R, Lowe B. (2005). Perturbations in electrolyte levels in Kenyan children with severe malaria complicated by acidosis. Clin Infect Dis, 40 (1): 9– 16. [PubMed]

Maitland K, Pamba A, Newton C.R, Lowe R, Levin M. Hypokalemia in children with severe falciparum malaria. Pediatr Crit Care Med. 2004 Jan; 5 (1): 81-85

Maitland K, Pamba A, Newton CR, Lowe B, Levin M. (2004).Hypokalemia in children with severe falciparum malaria. Pediatr Crit Care Med, 5 ( 1): 81– 85.

Mangou F, Platel D.F, Tribouley-Duret J. (1999).Role of glutathione in the detoxification of erriprotoporphyrin IX in chloroquine resistant Plasmodium berghei.MolBiochemParasitol, 98 (2): 215– 223.

Manning J, Vanachayangkul P, Lon C, et al. Randomized, double-blind, placebo-controlled clinical trial of a two-day regimen of dihydroartemisinin-piperaquine for malaria prevention halted for concern over prolonged corrected QT interval. Antimicrob Agents Chemother 2014; 58:6056.

Markus, M.B (2018). "Biological Concepts in Recurrent Plasmodium vivax Malaria".Parasitology.doi:10.1017/S003118201800032X. PMID 29564998.

Massaga JJ, Lusingu JP, Makunde R, et al.(2008) Biological and haematological safety profile of oral amodiaquine and chloroquine in healthy volunteers with or without Plasmodium falciparum infection in northeast Tanzania. Tanzan J Health Res 2008; 10:144.

Maurois P, Gueux E, Rayssiguier Y. (1993). Magnesium deficiency affects malaria susceptibility in mice. J Am CollNutr, 12 (1): 21– 25. [PubMed]

National Institute of Health, U.S. (2014). MedlinePlus Fluid and Electrolyte Balance. Department of Health and Human Services, Available from: http://www.nlm.nih.gov/medlineplus/fluidelectrolytebalance.html.

Nadjm B, Behrens RH (2012). "Malaria: An update for physicians". Infectious Disease Clinics of North America. 26 (2): 243–59. doi:10.1016/j.idc.2012.03.010. PMID 22632637.

National Kidney Foundation (NKF) 2011. Report of National Kidney Foundation on renal diseases and transplant. 2011

National Kidney Foundation (NKF) 2017. Report of National Kidney Foundation on renal diseases and transplant. 2017

Neftel KA, Woodtly W, Schmid M, et al. Amodiaquine induced agranulocytosis and liver damage. Br Med J (Clin Res Ed) 1986; 292:721.

Olaniyan M.F. (2005). The Pattern of Packed Cell Volume, Plasma Electrolytes and Glucose Levels In Patients Infected With Plasmodium falciparum. Afr J ClinExpMicrobiol, 6 (2): 87– 90.

Olliaro P, Mussano P. Amodiaquine for treating malaria. Cochrane Database Syst Rev 2003; :CD000016.

Olliaro P, Nevill C, LeBras J, et al. Systematic review of amodiaquine treatment in uncomplicated malaria. Lancet 1996; 348:1196.

Petersen E (1987) In vitro susceptibility of Plasmodium falciparum malaria to pyrimethamine, sulfadoxine, trimethoprim and sulfamethoxazole, singly and in combination. *Trans R Soc Trop Med Hyg* **81:** 238-241.

Peterson DS, Di Santi SM, Povoa M, Calvosa VS, Do Rosario VE, and Wellems TE (1991) Prevalence of the dihydrofolate reductase asn-108 mutation as the basis for pyrimethamine-resistant falciparum malaria in the Brazilian amazon. *Am J Trop Med Hyg* **45:** 492-497.

Peterson DS, Milhous WK, and Wellems TE (1990) Molecular basis of differential resistance to cycloguanil and pyrimethamine in Plasmodium falciparum malaria. *Proc Natl AcadSci USA* **87:** 3018-3022.

Peterson DS, Walliker D, and Wellems TE (1988) Evidence that a point mutation in dihydrofolate reductase-thymidylate synthase confers resistance to pyrimethamine in falciparum malaria. *Proc Natl AcadSci USA* **85:**9114-9118.

Phillips RE, Looareesuwan S, Karbwang J, Warrell DA, White NJ, Kasemsarn P, and Warhurst DC (1984) Failure of chloroquine-erythromycin and chloroquine-tetracycline combinations in treatment of chloroquine-resistant falciparum malaria in eastern Thailand. *Lancet* **1:** 300-302.

Phillips-Howard PA, West LJ.Serious adverse drug reactions to pyrimethamine-sulphadoxine, pyrimethamine-dapsone and to amodiaquine in Britain. J R Soc Med 1990; 83:82.

Premji Z, Ume h R.E, Owusu-Agyei S, et al. (2009). "Chlorproguanil-dapsone-artesunate versus artemether-lumefantrine: a randomized, double-blind phase III trial in African children and adolescents with uncomplicated Plasmodium falciparum malaria". PLoS ONE. 4 (8): e6682. Bibcode:2009 PLoSO...4.6682P. doi:10.1371/journal.pone.000668

Pukrittayakamee S, Supanaranond W, Looareesuwan S, et al. Quinine in severe falciparum

malaria: evidence of declining efficacy in Thailand. Trans R Soc Trop Med Hyg 1994; 88:324.

Sauerwein R and Janse C. J. "Rectal artemisinins rapidly eliminate malarial parasites". EurekAlert!. 2008-03-27. Archived from the original on 3 April 2008. Retrieved 2008-03-28.

Schellenberg D, Kahigwa E, Drakeley C, Malende A, Wigayi J, Msokame C, Aponte J.J, Tanner M, Mshinda H, Menendez C, et al. (2002) The safety and efficacy of sulfadoxine-pyrimethamine, amodiaquine and their combination in the treatment of uncomplicated Plasmodium falciparum malaria. *Am J Trop Med Hyg* **67:** 17-23.

Schellenberg K.A and Coatney G.R (1961) The influence of antimalarial drugs on nucleic acid synthesis in Plasmodium gallinaceum and Plasmodium berghei. *BiochemPharmacol* **6:** 143-152.

SCOTT V. Single intravenous injections of chloroquine in the treatment of falciparum malaria: toxic and immediate therapeutic effects in 110 cases. Am J Trop Med Hyg 1950; 30:503.

World Health Organization Malaria ActionProgramme.Severe and complicated malaria. Trans R Soc Trop Med Hyg 1986; 80 Suppl:3.

Shephard M.D. (2011) Point-of-care testing and creatinine measurement. Clin Biochem Rev 2011; 32:109–114.

Sidhu A.B, Verdier-Pinard D, Fidock D.A. (2002).Chloroquine resistance in Plasmodium falciparum malaria parasites conferred by pfcrt mutations. Science 2002; 298:210.

Sitprija V. (2008).Altered fluid, electrolyte and mineral status in tropical disease, with an emphasis on malaria and leptospirosis. Nat Clin Pract Nephrol, 4 (2): 91– 101.

The Economist. 2014-01-25. "Malaria eradication: Cure all?".Retrieved 2014-02-16.

Triglia T and Cowman A.F (1994) Primary structure and expression of the dihydropteroatesynthetase gene of Plasmodium falciparum. *Proc Natl AcadSci USA* **91:** 7149-7153.

Triglia T and Cowman A.F (1999) The mechanism of resistance to sulfa drugs in Plasmodium falciparum. *Drug Resist Updat* **2:** 15-19.

Triglia T, Menting JG, Wilson C, and Cowman AF (1997) Mutations in dihydropteroate synthase are responsible for sulfone and sulfonamide resistance in Plasmodium falciparum. *Proc Natl AcadSci USA* **94:** 13944-13949.

Trouiller P, Olliaro P, Torreele E, Orbinski J, Laing R, and Ford N (2002) Drug development for neglected diseases: a deficient market and a public-health policy failure. *Lancet* **359:** 2188-2194.

Valderramos S.G, Fidock D.A. (2006). Transporters involved in resistance to antimalarial drugs. Trends PharmacolSci 2006; 27:594.

van Vugt M, Brockman A, Gemperli B, Luxemburger C, Gathmann I, Royce C, Slight T, Looareesuwan S, White N.J, Nosten F (1998). "Randomized comparison of artemether-benflumetol and artesunate-mefloquine in treatment of multidrug-resistant falciparum malaria".Antimicrobial Agents and Chemotherapy. 42 (1): 135–9. PMC 105468 .PMID 9449273.

Venkatesan M, Gadalla NB, Stepniewska K, et al. Polymorphisms in Plasmodium falciparum chloroquine resistance transporter and multidrug resistance 1 genes: parasite risk factors that affect treatment outcomes for P. falciparum malaria after artemether-lumefantrine and artesunate-amodiaquine. Am J Trop Med Hyg 2014; 91:833.

Vinge E, Lindergard B, Nilsson-Ehle P, Grubb A. (1999). Relationships among serum cystatin C, serum creatinine, lean tissue mass and glomerular filtration rate in healthy adults. Scand J Clin Lab Invest 1999; 59: 587–592. PubMed

Volpon L.C, Sugo E.K, Carlotti A.P. (2015). Diagnostic and prognostic value of serum cystatin C in critically ill children with acute kidney injury. Pediatr Crit Care Med 2015; 16:e 125-131.

vonSeidlein L, Olaosebikan R, Hendriksen I.C (2012). Predicting the clinical outcome of severe falciparum malaria in African children: findings from a large randomized trial.Clin Infect Dis 2012; 54:1080– 90

Waller D, Krishna S, Crawley J. (1995). Clinical features and outcome of severe malaria in Gambian children. Clin Infect Dis 1995; 21:577–587.

Warhurst D.C, Steele J.C, Adagu I.S.(2003). Hydroxychloroquine is much less active than chloroquine against chloroquine-resistant Plasmodium falciparum, in agreement with its physicochemical properties. J AntimicrobChemother 2003; 52:188.

Wellems T.E, Plowe C.V. (2001).Chloroquine-resistant malaria. J Infect Dis 2001; 184:770.

White N.J (2004). "Antimalarial drug resistance". J. Clin. Invest. 113 (8): 1084–92. doi: 10.1172/JCI21682. PMC 385418.PMID 15085184.

White N.J. (1996).The treatment of malaria. N Engl J Med 1996; 335:800.

World Health Organization (2009).WHO List of Prequalified Medicinal Products. http://www.who.int/prequal/query/ProductRegistry.aspx (Accessed on February 13, 2009).

WHO (2010) "Malaria Fact sheet No 62" Archived from the original on 7 September 2010

WHO (2010). Guidelines for the treatment of malaria, second edition Authors: WHO. Number of pages: 194. Publication date: 2010. Languages: English. ISBN 978-92-4-154792-5

WHO (2014)."Malaria Fact sheet N°94".Archived from the original on 3 September 2014.Retrieved 2 February 2016.

WHO (2014).World Malaria Report 2014. Geneva, Switzerland: World Health Organization. pp. 32–42. ISBN 978-92-4-156483-0.

WHO (2017) "Malaria Fact sheet N° 125".WHO. March 2017. Archived from the original on 3 September 2017.Retrieved 29 November 2017.

Wootton J.C, Feng X, Ferdig M.T. (2002).Genetic diversity and chloroquine selective sweeps in Plasmodium falciparum. Nature 2002; 418:320.

World Health Organisation (2010). Guidelines for the treatment of malaria (2nd ed.). Geneva: World Health Organization. p. ix. ISBN 978-92-4-154792-5.

World Health Organization (2014). Available from: http://www.who.int/malaria/publications/world_malaria_report_2014/en/. World Malaria Report 2017 (PDF).WHO. 2017. ISBN 978-92-4-156552-3.

Worrall E, Basu S, Hanson K (2005). "Is malaria a disease of poverty? A review of the literature".Tropical Health and Medicine. 10 (10): 1047–59. doi:10.1111/j.1365-3156.2005.01476.x. PMID 16185240.

Yoel C. (2007). Clinical symptoms and electrolytes description of children with malaria an outpatient setting in kabupatenmandailing natal.M K N, 40 (1). March 2007.

Zhang Z, Lu B, Sheng X, Jin N. (2011). Cystatin C in prediction of acute kidney injury: a systemic

review and meta-analysis. Am J Kidney Dis 2011; 58: 356–365.

Zwang J, Ndiaye J.L, Djimdé A. (2012). Comparing changes in haematologic parameters occurring in patients included in randomized controlled trials of artesunate-amodiaquine vs single and combination treatments of uncomplicated falciparum in sub-Saharan Africa. Malar J 2012; 11:25.