

CARBONYL STRESS INDUCED PROTEIN MODIFICATION -A PATHOGENESIS LINK IN MALARIAL ACUTE RENAL FAILURE

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INTRODUCTION

Falciparum Malaria is common parasitic infection in Asian countries and potentially fatal when involved multi organs including kidney.

AIMS

- To find out the incidence of acute renal failure in falciparum malaria.
- To correlate between the degree of parasitism at presentation with acute renal failure and its outcome in falciparum malaria.
- To measure the carbonyl and oxidative stress and correlation with outcome

METHOD

All cases of *P. falciparum* malaria, confirmed by antigen and/or in peripheral blood smear were included. Parasite density was calculated. AKI was calculated as per RIFLE criteria. Demographical, clinical and biochemical data were analyzed and they are followed from hospitalization to discharge/death upto six month of admission. Oxidative and carbonyl stress markers [Advanced oxidation protein product (AOPP), Advanced Glycation End product (AGE), Pentosidine, Dityrosine, Thiobarbituric acid reactive substance (TBARS) and Methyl glyoxal (MG)] were measured consecutively in 15 FMAKI patient according to standard protocol. All data were analysed in appropriate statistical tool.

RESULTS

Out of the 174 patients with falciparum malaria admitted in 18 months 50 patients (28.7%) had acute kidney injury (FMAKI). M: F was 2.6:1. Two third were < 40 years. About 72% were oliguric / anuric. 45 had marked reduction in GFR with a mean value of 10.65 ± 3.07 ml/min. Mean Serum urea and creatinine level was 177 mg% (66 – 290) and 7.2 mg% (3.2 - 13.6 mg%). About 29 cases were found to have severe AKI (cr>5mg %) and 21 cases had milder form of AKI (cr<5mg %). Out of the 50 cases of FMAKI 21(42%) had parasite density <5%, 13(26%) had 5-10% and 16(32%) had >10%. Out of 21 cases of mild AKI 12 patients had parasite density<5% and 9 had >5%. Out of 29 cases of severe AKI 9 patients had parasite density<5% and 20 had >5%. Dialysis was required in 31 cases (62%). Mostly in severe form of FMAKI. In six month follow up 34 patients recovered fully with normal serum creatinine within 1 month, 2 patients within 3 month and 13 patients died. out of the 13 pts expired all belong oliguric severe form of AKI.

There is positive correlation between parasite density, renal failure and surrogate outcome. So early measurement of parasite density can prognosticate the renal failure. The Oxidative stress indexes (OSI) of FMAKI patients were 1.89 times higher than normal control. The TBARS, MG level were 6.49 and 5.56 times higher indicating a significant carbonyl stress in these patients. AOPP level the marker of protein modification was also 2.33 times higher than normal control indicating that proteins are highly insulted in FMAKI. Areas under the curves for AOPP and MG were (0.735, p= 0.001), (0.691, p= 0.005) respectively. Mortality and need for dialysis is more in high value of MG and AOPP.

ROC curve for AOPP and MG in FMAKI patients

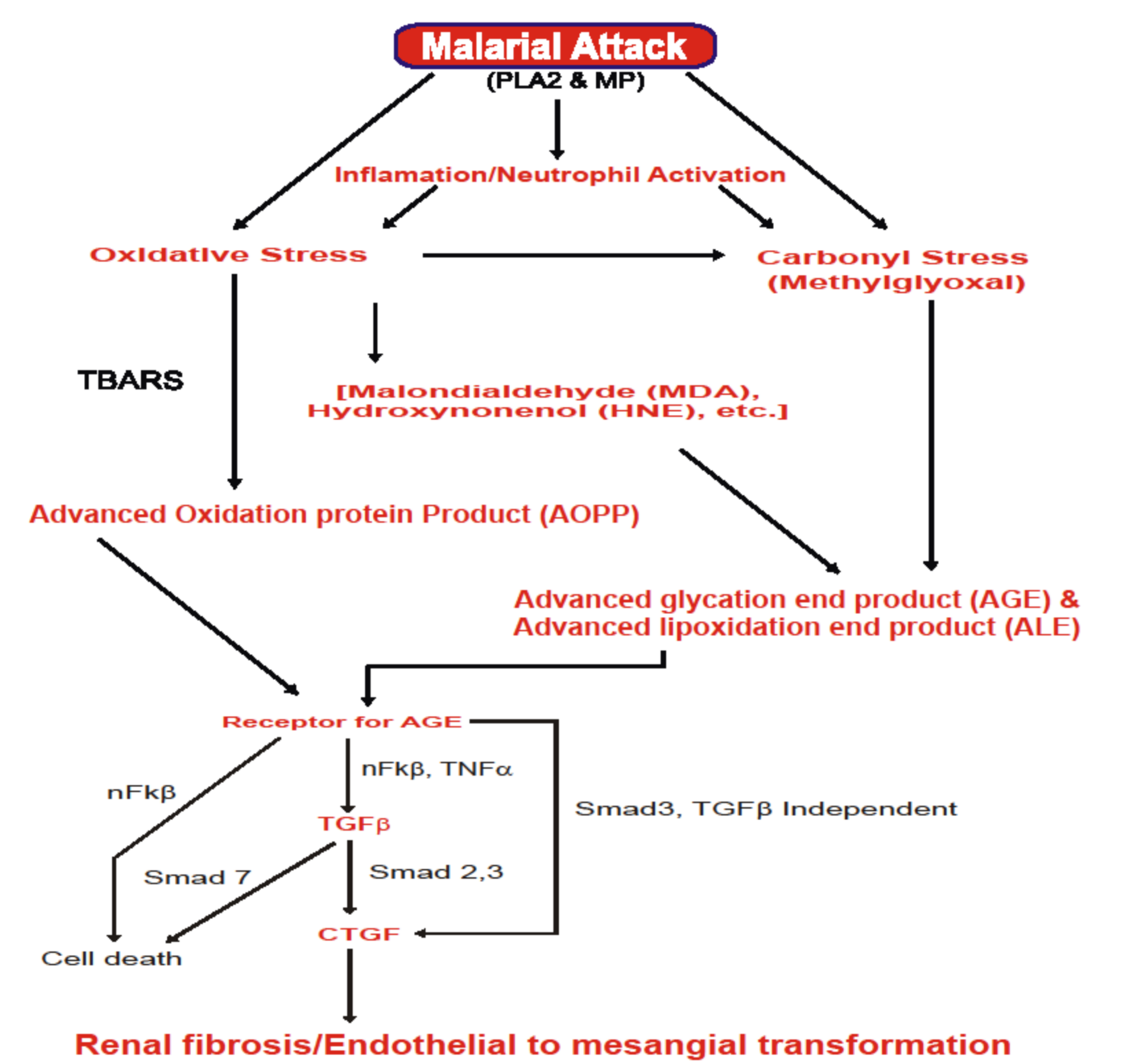
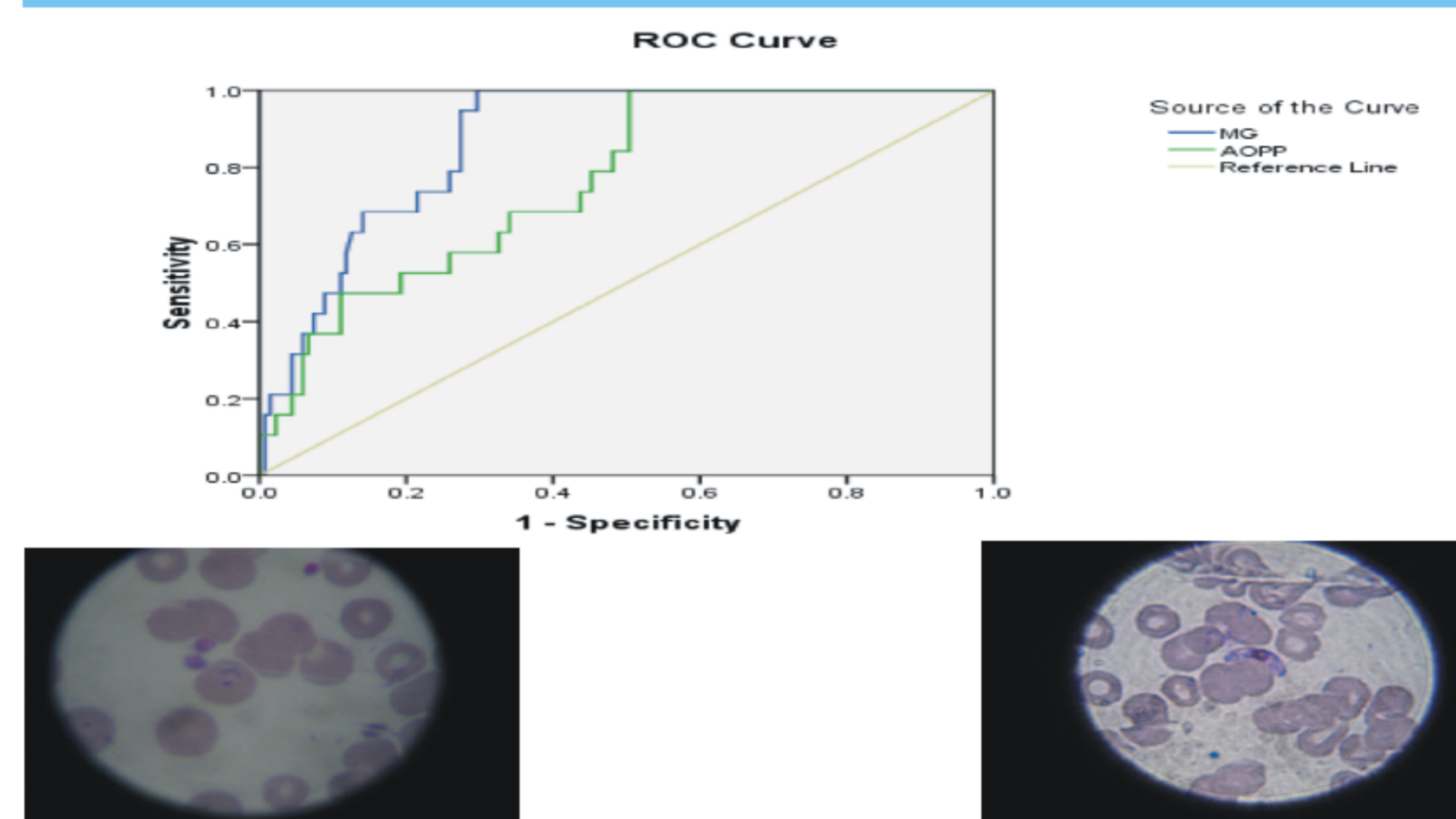


Fig. : Proposed pathway of FMAKI. PLA2-Phospholipase A₂; Metallporroteinase;

Incidence of acute renal failure, oliguria and mortality

Study	ARF	Oliguria	Mortality Rate
Sitprija V et al (1970)	21%	---	10%
Stone et al (1972)	---	85.6%	28.9%
Habte B et al (1990)	33.3%	45%	29%
Present study (2012)	28.7%	72%	26%

Severity of AKI and Parasite Density

Severity of AKI	Parasite density <5%	Parasite density 5-10%	Parasite density >10%
Mild	12	5	4
Severe	9	8	12

Severity of AKI and Parasite Density

	Cases with oliguric AKI	Cases with non-oliguric AKI	Total No. of cases & Percentage
No. of cases	36	14	50
Survival	26(63.88%)	14(100%)	37 (74%)
Mortality	13(36.12%)	0	13 (26%)

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DISCUSSION

- The pathogenesis of malarial AKI is multifactorial. The role of oxidative and carbonyl stress is not well described. AOPP and MG the key marker of oxidative and carbonyl stress has definite link in final kidney injury. The probable hypothesis started from membrane lysis of RBC.
- Break down of RBC membranes following hemolysis released the threonine, fatty acids, MDA like compounds (by the breakdown of arachidonic acid of RBC membrane) and carbonyl derivatives are produced rapidly which may be the precursor of MG synthesis. Thus MG accumulates. Increase of MG may indicate the insufficient renal clearance and increased pathogenesis. Further studies are required to better understand whether the decrease of thiol concentration in FMAKI derives only from oxidative stress or from other non oxidative pathway and the occurs due to depleted GSH mediated detoxification only or malaria induced altered metabolic pathway is linked to it.

CONCLUSION

- High Parasitic index is surrogate predictor of FMAKI
- MG the carbonyl stress marker along with oxidative stress are significantly raised and possibly linked to the pathogenesis of AKI.

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