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# A Study of Uric Acid Level as a Marker of Severity in Malaria

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**Abstract:**

**Context:** Malaria is an inflammatory condition triggered by the infection of parasite Plasmodium on erythrocytes. It is characterised by periodic fever with chills due to rupture of erythrocytes to release the progeny parasites. It is marked by release of variety of cytokines like IL-6, IL-12, IFN-Ɣ, TNF—α etc. Uric acid is one of the emerging inflammatory markers in malaria that demands attention. One of the proposed mechanisms is that there is accumulation of uric acid and its precursor, hypoxanthine in the infected erythrocytes. These are released into the blood on rupture of the schizont.

**Aim:** To find association of serum uric acid level with severity of malaria. Settings and Design: This was a hospital based longitudinal study conducted at a tertiary care centre in Kolkata, India.

**Materials and Methods:** We measured the plasma levels of uric acid and various inflammatory markers {Ferritin, C-reactive protein(CRP), LDH, C3, C4} in eighty eight patients admitted with microscopically proven malaria (severe or non-severe type). The levels of uric acid were compared with the disease severity and the inflammatory markers stated above.

**Statistical Analysis used:** The data was analyzed using MedCalc software and Microsoft Excel 2010 and further graphically plotted.

**Results:** The serum uric acid levels were raised in 18.51% of patients with severe malaria compared to only 4.91% with non-severe variety ($p= 0.04$). The uric acid levels demonstrated a positive correlation with CRP ($r=0.3334$, $p=0.0015$); procalcitonin & ferritn ($r=0.3701$, $p<0.0005$). However, it was negatively correlated with C3 ($r= -0.3780$, $p= 0.0003$) and C4 ($r=0.3180$, $p<0.005$). A univariate regression analysis supported our results to establish the correlation.

However, multiple logistic regression analysis demonstrated significant association between serum uric acid levels on day 1 and C3 decrement as a marker of disease severity.
**Conclusion:** Thus, it can be concluded that there is a definite association between the severity of malaria and plasma uric acid levels. Although, this study does not establish the causation, it acts as a cornerstone for further research into this field.
**Keywords:** malaria; uric acid; severity; other inflammatory markers
**Key Message:** This study established an association between severity of malaria and serum uric acid levels. Further, it depicted correlation between other known inflammatory marker and uric acid. Thus, attention shall be paid to serum uric acid levels as a new marker of disease severity in malaria.

## Introduction:

Malaria is an inflammatory condition characterized by cyclic, high-grade fever, shivering, headache, and nausea indicating the release of certain toxins into the bloodstream from ruptured erythrocytes. Molecules from the parasite and ruptured RBCs trigger host inflammatory responses [1]. The erythrocytic stage is marked by a spike in the release of inflammatory cytokines such as IL-1b, IL-6, IFN-g, TNF-a, and IL-12 [2, 3] that may lead to progressive inflammation if not controlled [4]. Specific parasitic molecular patterns are associated with host inflammatory responses including glycosylphosphatidylinositol (GPI) anchors, hemozoin, uric acid, and parasite DNA [5, 6, 7, 8].

In vitro studies showed the production of nitric oxide, TNF, and IL-1β by parasite GPI-anchors while synthetic and purified [9] Plasmodium GPI had immunogenic properties in vivo. Plasmodium species generate hemozoin as they detoxify heme in pRBCs. The hemozoin induces the production of IL-1β by immune cells such as monocytes and macrophages once secreted into circulation [10]. Hemozoin tends to activate the inflammasome protein complex [11, 12]. This was evident in the administration of parasite-derived hemozoin in disease-free mice that induced transcription of inflammatory genes [13]. Parasite DNA demonstrated induction of cytokine and chemokine responses by human plasmacytoid dendritic cells by activation of TLR9-MyD88 signaling pathway [14]. Despite the crucial role played by inflammation in malaria, the parasite-derived molecules that trigger it have not been identified.

On the release of phagolysosomal contents, parasite DNA is recognized in the cytoplasm by several cytosolic DNA sensors [15]. Uric acid derived from the parasite and the rupture of infected pRBCs have also been reported to induce strong inflammatory responses in patients [1]. In vitro studies show that uric acid derived from the parasite promotes the secretion of pro-inflammatory cytokines that include TNF, IL-1β, and IL-6 [16]. The uric acid levels are markedly elevated in periods correlating with infection [17, 18]. Apart from parasite-expressed inflammatory molecules, several host-derived molecules, such as damage-associated molecular patterns (DAMPs) are also involved in inducing the inflammatory response and cytokine release in severe malaria. They are nucleic acids, urate crystals, heme, and microvesicles derived from platelets, endothelial cells, and leukocytes [1, 19, 20, 21]. The total amount of uric acid present in infected erythrocytes is not increased [22]. This indicates that the activity of erythrocyte uric acid transporters [22] is unaffected by infection. However, high concentrations of hypoxanthine accumulate in infected erythrocytes [23, 24]. This is consistent with the lack of xanthine dehydrogenase activity in Plasmodium and erythrocytes [25] inferring that the infection

induces precipitation of prevalent uric acid pellets within the erythrocyte, but not the breakdown of hypoxanthine into uric acid. Thus, this study aims to find out the association between serum uric acid levels and severity of malaria.

**Materials and Methodology** :

**Ethics Statement**

The study commenced after obtaining clearance from the Institutional Ethics Committee, Medical College Kolkata. Informed consent was taken from all the study subjects or their surrogate.

**Study Site and Population**

The study was conducted in a tertiary level setting of Medical College and Hospital, Kolkata. The patients were admitted to general medicine wards of the hospital. An observational longitudinal study was done for one and a half years. In this study sample size was calculated by using the method for repeat measure data analysis in GLIMMPSE website (free). Minimum sample size came as 88; taking uncomplicated and complicated case ratio as 10: 1. The transmission of malaria is seasonal and most intense during June-December. The data collection and intervention started in July 2018 and concluded in November 2019. The study group was aged 18-65 years, presented with fever, and had not received any antimicrobial for their condition. A detailed history was taken and a clinical evaluation was done. The parasite densities were confirmed using thick blood films and the ring-stage parasites were counted in the blood smear up to 200 leukocytes. The peripheral blood smear-positive and malaria antigen positive by MPDA kit was considered as positive for malaria. The study subjects were further divided into uncomplicated and complicated malaria.

Uncomplicated malaria is defined as laboratory-proven malaria with symptoms of fever with no complications like anemia, thrombocytopenia, acidosis, altered sensorium, hypovolemic shock, and jaundice. Complicated malaria has one of the decompensating features.

Any person with previously established chronic kidney disease, gout, carcinoma/leukemia, and nephropathy were excluded from the study. The presence of any other corresponding infection was also excluded. An alpha level of 5% was taken suggesting any p-value less than 0.05, significant. The power of the study was 80%.

**Study Variables and Methods**

The plasma sample of all the subjects was taken. The serum level of uric acid and various known inflammatory markers (CRP, Ferritin, Procalcitonin, LDH, C3, and C4) were measured and monitored for the first five days. Chest X-Ray, ABG, serum urea and creatinine, and routine urine examination were also done. Continuous variables were expressed as mean, median, and standard deviation and compared. Uric acid levels were compared with disease severity and with other known markers of severity and inflammation. Association between severity and inflammatory markers was determined through correlation. Regression analysis was done to check the strength of association.

The baseline uric acid level for a healthy person was 2.9 mg/dl; for uncomplicated malaria, it was 4.6mg/dl; for complicated malaria, it was 5.7mg/dl[26]. The data was analyzed using MetCalc software and Microsoft Excel 2010 and further graphically plotted. Significant charts are described in the results section.

**Results:**

It is known that the uric acid derived from parasites can stimulate the production of several inflammatory mediators from human PBMCs in vitro[27]. This study was done to find out whether this stimulation also occurs in vivo. The plasma uric acid levels, CRP, C3,

C4, ESR, and LDH were measured for this purpose among individuals who suffered from malaria. Out of 88 samples collected, 64 (72.7%) were men and 24 were women (27.3%). It was observed that 27(30.7%) patients developed severe malaria and 61(69.3%) developed non-severe malaria.[Table 1] Hypovolemic shock and bleeding manifestations were the most common finding in the severe variety. The hematological evaluation revealed profound thrombocytopenia (platelet <50,000/cumm) in 25% of the patients. The serum uric acid levels were raised in 18.51% of patients with severe malaria compared to only 4.91% with non-severe variety (p= 0.04). The severity of malaria was significantly associated with males compared to females (p=0.0056).

**Table 1: showing demographic data**

| Demograpic Profile | | Male | Female | Total |
|---|---|---|---|---|
| Age Distribution | <20 years | 4 | 1 | 5 |
| | 21-30 years | 14 | 6 | 20 |
| | 31-40 years | 9 | 4 | 13 |
| | 41-50 years | 12 | 4 | 16 |
| | 51-60 years | 10 | 3 | 13 |
| | >60 years | 15 | 6 | 21 |
| | Total | 64 | 24 | 88 |
| Type of Malaria | Vivax | 51 | 17 | 68 |
| | Falciparum | 9 | 5 | 14 |
| | Both | 4 | 2 | 6 |
| | Total | 64 | 24 | 88 |
| Severity of Malaria | Severe | 25 | 2 | 27 |
| | Non severe | 39 | 22 | 61 |
| | Total | 64 | 24 | 88 |

The serum uric acid levels were higher in the acute phase compared to those in the convalescent phase (p=0.0026) as shown in Box-Whisker plot [Figure 1]. The mean values of uric acid were compared to various inflammatory markers (CRP, Procalcitonin, Ferritin, C3,C4) for severe and non-severe malaria.

A correlation analysis between the increased uric acid and inflammatory markers like CRP, Ferritin, C3, C4 was performed to establish disease severity. A positive correlation was observed between the mean serum uric acid level and CRP level with r =0.3334 (p=0.0015) as shown in Figure 2.

Serum procalcitonin showed a stronger positive correlation with r= 0.3701 (p<0.0005) eliciting a greater association between uric acid levels on day 1 [Figure 3]. A similar analysis was seen for serum Ferritin (p<0.01) as shown in Figure 4.

The serum C3, C4 revealed strong negative correlation that was statistically significant (C4 r=-0.3750, p=0.0003; C3 r= -0.3180, p<0.005) as shown in Figure 5 and Figure 6. However, we did not find any significant association between serum LDH levels and uric acid.

Further, a univariate regression analysis was carried out to establish the correlation. It depicted a significant association between

disease severity and CRP ($p<0.0005$), Procalcitonin ($p<0.002$), Ferritin ($p<0.01$), C3 and C4. However, multiple logistic regression analysis had only established a significant association with serum uric acid on day 1 and C3 decrement as a marker of disease severity. [Table 2,3]

**Table 2: Multiple Logistic Regression Analysis ( co-effiecients and standard errors)**

| | |
|---|---|
| **Nullmodel-2LogLikelihood** | 108.509 |
| **Fullmodel-2LogLikelihood** | 44.517 |
| **Chi-squared** | 63.993 |
| **DF** | 9 |
| **Significancelevel** | P<0.0001 |
| **Cox&SnellR²** | 0.5167 |
| **NagelkerkeR²** | 0.7292 |

**Table 3: Multiple Logistic Regression Analysis (Showing overall model fit)**

| Variable | Coefficient | Std. Error | Wald | P |
|---|---|---|---|---|
| day1 | 2.17822 | 0.93554 | 5.4210 | 0.0199 |
| day3 | -0.37656 | 1.07921 | 0.1217 | 0.7271 |
| day5 | -0.73014 | 1.02655 | 0.5059 | 0.4769 |
| CRP | 0.011897 | 0.015563 | 0.5844 | 0.4446 |
| Serum ferritin | -0.00060762 | 0.0023982 | 0.06420 | 0.8000 |
| Procalcitonin | 0.075368 | 0.039112 | 3.7133 | 0.0540 |
| C3 | -0.068295 | 0.030455 | 5.0287 | 0.0249 |
| C4 | -0.10388 | 0.077569 | 1.7934 | 0.1805 |
| Constant | 4.53015 | 5.34825 | 0.7175 | 0.3970 |

As discussed above the multiple regression analysis tables of overall model fit and the co-efficients with standard errors are shown in Table 2 and 3.

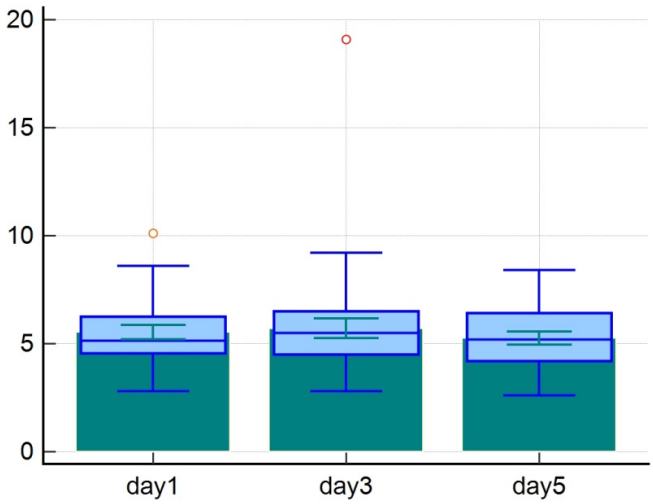


**Figure 1: Box Whisker Plot of repeated uric acid measurement (on day1, day3 and day5)**

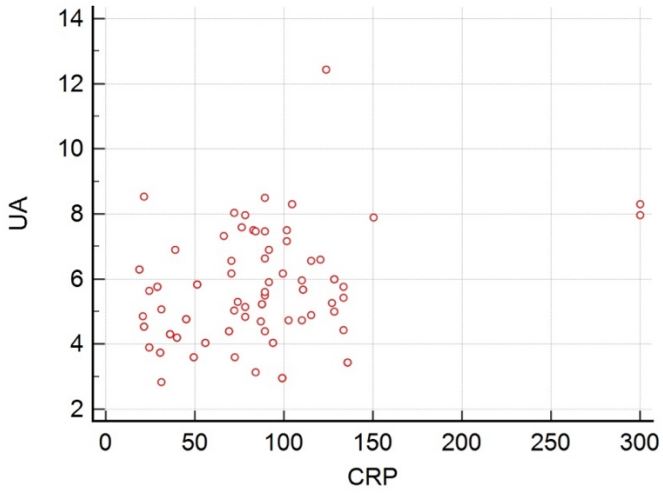


**Figure 2: Scatter Diagram showing correlation between serum CRP and uric acid**

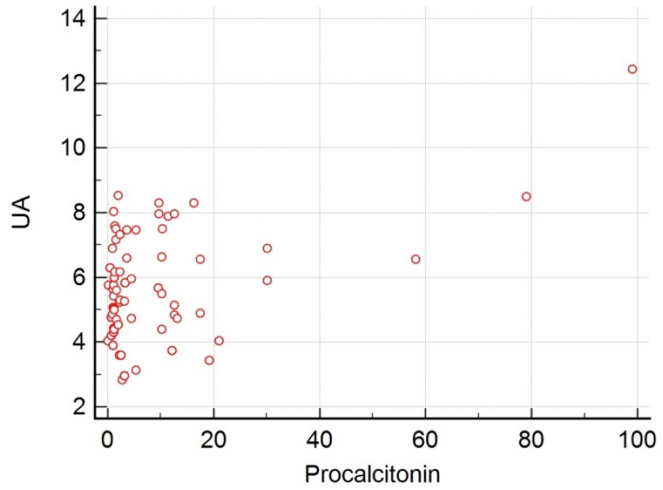


**Figure 3: Scatter Diagram showing Correlation between serum procalcitonin and uric acid**

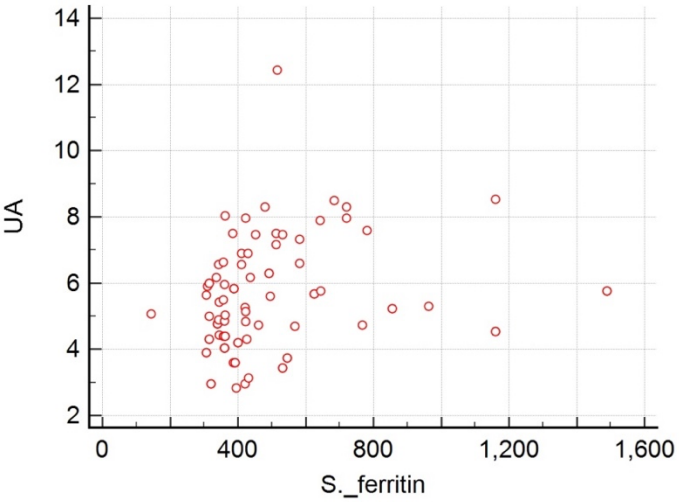


**Figure 4: Scatter Diagram showing Correlation between serum ferritin and uric acid**

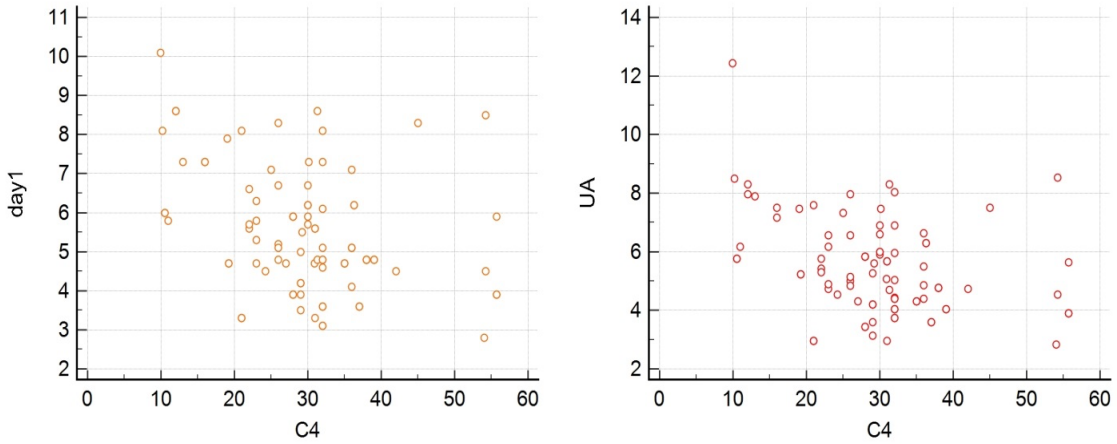


**Figure 5: Scatter Diagram showing correlation between serum C4 on day 1 and uric acid**

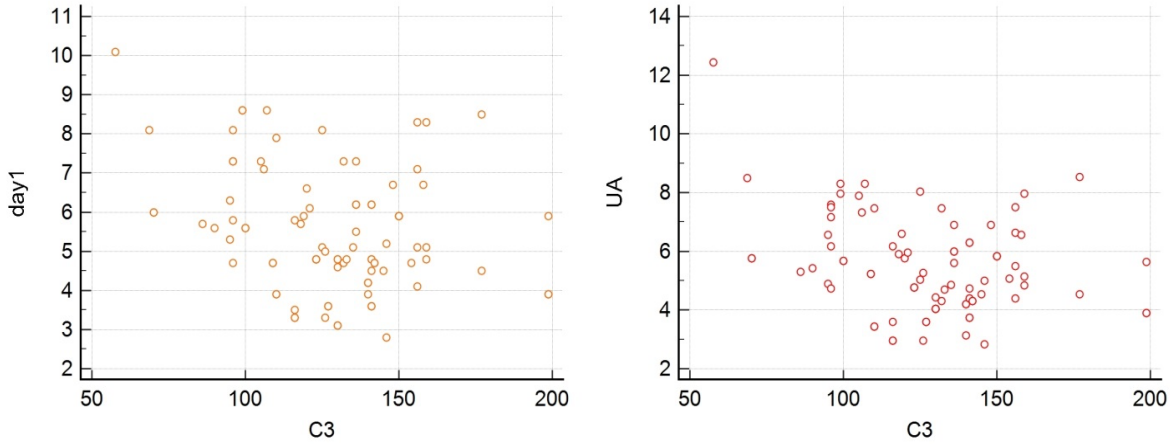


**Fig 6: Scatter Diagram showing correlation between serum C3 on day 1 and uric acid**

## Discussion:

Malaria is a significant cause of morbidity and mortality in tropical countries including India. The severity of the disease is unpredictable. Early diagnosis and treatment are necessary to prevent catastrophic outcomes. The study strives to find a cost-effective new marker to predict the disease severity from its early symptomatic days through serum uric acid levels.

Evaluation of the sex distribution revealed 72.73% males and 27.63% females. Among them, 39.06% of male patients had severe disease (P<0.0056, Chi-squared test, c2=7.662). In a study, A prospective study from south India to compare the severity of malaria caused by Plasmodium vivax, P. falciparum, and dual infection by Mitra S, Abhilash KPP et al, 111 out of 131 patients (84.73%) were males [28].

In this study, 27 (30.7%) patients developed severe malaria and 61 (69.3%) developed non-severe malaria. Significant severity was seen in patients with vivax, 19 (27.94%). Hypovolemic shock and bleeding manifestations were the most common finding in the severe variety. In a study by Limaye C S, Londhey V A et al, 31% with severe vivax mono-infection was manifested by thrombocytopenia, leukopenia, acute respiratory distress syndrome, hypotension, and mucosal bleeding as seen in falciparum and mixed malaria. Acute renal failure,

cerebral malaria, high bilirubin, anemia, metabolic acidosis. and death was less frequently observed than in falciparum and mixed malaria. [29]

Numerous studies have shown thrombocytopenia as a predictor of malaria. One such study by Shiraz Jamal Khan et al showed 121 out of 228 patients (53%) who presented with fever and thrombocytopenia were diagnosed with malaria.[30] This study resonances with other studies. In addition, it proposes that there is no significant association between disease severity and thrombocytopenia (P=0.0585). WHO has defined severe malaria to be associated with high mortality.[31] In this study, 22 patients (25%) had profound thrombocytopenia (platelet count <50000) with an overall prevalence of thrombocytopenia among 78 patients (88.6%). Among them, 24 out of 27 severe cases had thrombocytopenia however, this was not statistically significant (Chi-squared test; □2 =0.292, P = 0.0585). In a study done by Mohd Arif et al, out of 100 patients, 79% had thrombocytopenia but, only 22.79% also presented with severe disease.[32] These findings further help avoid unnecessary platelet transfusion in thrombocytopenic patients with malaria.

Here, the study assesses uric acid as a novel marker for the severity of malaria. Uric acid levels were measured on day 1, day 3, and day 5 of hospital admission. Mean (±SD) values of uric acid on respective days in patients with severe malaria were 5.5±1.54, 5.68±2.12 and 5.24±1.46 mg/dl, showing a peak at day 3. Repeated measures of ANOVA analytic test for subsequent uric acid analysis on three days showed a significant change in repeat measures of uric acid with a linear trend (P=0.0001)[Figure 1]. In a study done by Purna Chandra Karua and Manoj Kishan in Western Odisha, out of 55 patients, 17 (31%) had raised uric acid levels. Among them, 14 (82%) were complicated malaria and 3 (18%) were uncomplicated malaria. The mean value of uric acid in complicated malaria was 7.61 mg/dl.[33]

A correlational analysis showed association of multiple quantitative variables of inflammation and severity with uric acid levels. The analysis showed statistically significant correlation with positive correlation between uric acid level on day 1 with CRP (r=0.3334, P=0.0015) [Figure 2], Procalcitonin (r=0.3701, P=0.004) [Figure 3] and negative correlation with C3 (r=-0.2855, P=0.0070), C4 (r=-0.3507, P=0.0008). Also, there was statistically significant correlation with positive correlation between 'mean uric acid' level of three days with CRP (r=0.3159, P=0.0027), procalcitonin (r=0.4540, P=<0.0001) and negative correlation with C3 (r=-0.3180, P=0.0025) [Figure 6], C4(r=-0.3750, P=0.0003) [Figure 5].

Raised uric acid levels on day 1 and mean uric acid level of 3 days was significantly associated with disease severity (p=0.0004 and p=0.0418). Univariate regression analysis showed a significant association between disease severity and CRP (P=0.0003), procalcitonin (P=0.0016), C3 (P<0.0001), C4 (P<0.0001), and ferritin (P=0.0096) [Figure 4]. However, when the variables were assessed by multiple logistic regression model, only 'uric acid on day 1' (P=0.0249) and 'C3' (P=0.0199) levels showed statistical significance in predicting disease severity. The uric acid levels on day 1 correlated well with disease severity. The consequent days' uric acid levels did not correlate well with disease severity. This disparity must have been grossly confounded by the effectiveness of therapy.

Raised CRP, ferritin, procalcitonin levels seen in univariate regression analysis suggests inflammatory response in malaria. Multiple logistic regression associates disease severity with C3 level decrement. All this suggests that the severity of malaria is due to inflammation likely induced by uric acid released from the ruptured red cells housing the parasite.

In the same study in Western Odisha, out of 55 patients, 30(55%) patients have raised serum CRP levels. Among them, 22 (73%) were complicated malaria.[34] In a different study by Castberg FC, ferritin levels were higher in patients with severe malaria (P = 0.002).[7] Similarly, a study by Hesselink, D.A et al showed a rise in another inflammatory marker, procalcitonin, in patients with severe P. falciparum infections.[35] A high level of C consumption was seen in children with severe malarial anemia compared to uncomplicated malaria in a study done by Nyakoe, Nancy & Taylor et al.[36]

A study from Nigeria, by Ade-serrano MD, Ejezie G. C. et al in Rural Nigerian School Children, shows the relationship between Plasmodium falciparum gametocytaemia and the complement components C3, C4, and C3b investigated in 141 ambulant rural Nigerian school children. Their findings suggest that C3b hypocomplementemia may be related to the advent of circulating P. falciparum gametocytes in children. Their study also confirmed C3 and C4 hypocomplementemia in acute malaria [37].

In a study, Plasma Uric Acid Levels Correlate with Inflammation and Disease Severity in Malian Children with Plasmodium falciparum Malaria, by LoperaMesa T M, Mita-Mendoza N K et al, proved elevated uric acid levels may contribute to the pathogenesis of P. falciparum malaria by activating immune cells to produce inflammatory cytokines in the pediatric population. Although this study cannot identify the cause of elevated uric acid levels, their association with parasite density and creatinine levels suggests that parasite-derived uric acid and renal function may be involved.[38]

In a study from India (2019), by Bhardwaj Nitin, Ahmed Z MD, Sharma S et al, shows the demographic, clinical, and laboratory parameters significantly altered in case group compared to healthy controls, (p-value<.05) except for gender, cholesterol, triglycerides, Gamma-GT and Cytochrome c.[39]

Therefore, uric acid is a marker of severity in malaria patients. The proper pathophysiology is not yet known. However, all the studies, including this, show a significant correlation and matter of interest for further studies and possible trials of uric acid lowering agents in the management of severe malaria.

## Conclusion

There has been significant progress towards the treatment of malaria that has resulted in a diminutive rate of mortality and number of hospitalizations due to severity of the disease. However, the severity and progression of the disease is unpredictable and has been less studied so far. Identification of certain biochemical markers can help us to identify the significant factors that can establish certain proclivity towards the severity of the disease. Ascertaining the statistically significant factors with the strongest correlation can help us to study the incidence, progression, variability and duration of severe malaria and predetermine strategies to counter the severity of the disease to improve the overall status during the treatment and duration of hospitalization.

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## References:

1. Gallego-Delgado J, Ty M, Orengo JM, van de Hoef D, Rodriguez A. A surprising role for uric acid: The inflammatory malaria response. Current Rheumatology Reports. 2014;16(2):401
2. Dinko B, Pradel G. Immune evasion by Plasmodium falciparum parasites:

Converting a host protection mechanism for the parasite's benefit. Advances in Infectious Disease. 2016;6(2):67759
3. Artavanis-Tsakonas K, Tongren JE, Riley EM. The war between the malaria parasite and the immune system: Immunity, immunoregulation and immunopathology. Clinical and Experimental Immunology. 2003;133:145-152
4. Dodoo D, Omer FM, Todd J, Akanmori BD, Koram K. Absolute levels and ratios of proinflammatory and anti-inflammatory cytokine production in vitro predict clinical immunity to Plasmodium falciparum malaria. The Journal of Infectious Diseases. 2002;185:971-979
5. Schofield L, Hackett F. Signal transduction in host cells by a glycosylphosphatidylinositol toxin of malaria parasites. The Journal of Experimental Medicine. 1993;177:145-153 [106] Griffith JW, Sun T, McIntosh MT, Bucala R. Pure hemozoin is inflammatory in vivo and activates the NALP3 inflammasome via release of uric acid. Journal of Immunology. 2009;183:5208-5220
6. Griffith JW, Sun T, McIntosh MT, Bucala R. Pure hemozoin is inflammatory in vivo and activates the NALP3 inflammasome via release of uric acid. Journal of Immunology. 2009;183:5208-5220
7. Sharma S, DeOliveira RB, Kalantari P. Innate immune recognition of an AT-rich stem-loop DNA motif in the Plasmodium falciparum genome. Immunity. 2011;35:194-207
8. Gowda NM, Wu X, Gowda DC. The nucleosome (histone-DNA complex) is the TLR9-specific immunostimulatory component of Plasmodium falciparum that activates DCs. PLoS One.
9. Naik RS, Branch OH, Woods AS. Glycosylphosphatidylinositol anchors of Plasmodium falciparum: Molecular characterization and naturally elicited antibody response that may provide immunity to malaria pathogenesis. The Journal of Experimental Medicine. 2000;192(11):1563-1576. DOI: 10.1084/ jem.192.11.1563
10. Olivier M, Van Den Ham K, Shio MT, Kassa FA, Fougeray S. Malarial pigment hemozoin and the innate inflammatory response. Frontiers in Immunology. 2014;5:25. DOI: 10.3389/ fimmu. 2014. 00025
11. Dostert C, Guarda G, Romero JF, Menu P, Gross O, Tardivel A. Malarial hemozoin is a Nalp3 inflammasome activating danger signal. PLoS One. 2009;4:e6510. DOI: 10.1371/journal.pone.0006510011;6:e203 98
12. Shio MT, Eisenbarth SC, Savaria M, Vinet AF, Bellemare MJ, Harder KW. Malarial hemozoin activates the NLRP3 inflammasome through Lyn and Syk kinases. PLoS Pathogens. 2009;5:e 1000559. DOI: 10.1371/journal.ppat. 1000559
13. Deroost K, Lays N, Pham T-T, Baci D, Van den Eynde K, Komuta M. Hemozoin induces hepatic inflammation in mice and is differentially associated with liver pathology depending on the Plasmodium strain. PLoS One. 2014;9(11):e113519. DOI: 10.1371/journal.pone.0113519
14. Pichyangkul S, Yongvanitchit K, Kum-arb U, Hemmi H, Akira S, Krieg AM. Malaria blood stage parasites activate human plasmacytoid dendritic cells and murine dendritic cells through toll-like receptor 9-dependent pathway. Journal of Immunology. 2004;172:4926-4933. DOI: 10.4049/jimmunol.172.8.4926
15. Gowda DC, Wu X. Parasite recognition and signaling mechanisms in innate immune responses to malaria. Frontiers in Immunology. 2018;9:3006. DOI: 10.3389/fimmu.2018.03006
16. Orengo JM, Leliwa-Sytek A, Evans JE. Uric acid is a mediator of the Plasmodium

falciparum-induced inflammatory response. PLoS One. 2009;4:e5194
17. Lopera-Mesa TM, Mita-Mendoza NK, van de Hoef DL. Plasma uric acid levels correlate with inflammation and disease severity in Malian children with Plasmodium falciparum malaria. PLoS One. 2012;7:e46424
18. Mita-Mendoza NK, van de Hoef DL, Lopera-Mesa TM. A potential role for plasma uric acid in the endothelial pathology of Plasmodium falciparum malaria. PLoS One. 2013;8:e54481
19. Butt AN, Swaminathan R. Overview of circulating nucleic acids in plasma/serum: Update on potential prognostic and diagnostic value in diseases excluding fetal medicine and oncology. The Annals of the New York Academy of Sciences. 2008;1137(1):236-242
20. Figueiredo RT, Fernandez PL, Mourao-Sa DS, Porto BN, Dutra FF, Alves LS, et al. Characterization of heme as activator of Toll-like receptor 4. The Journal of Biological Chemistry. 2007;282(28):20221-20229
21. Mantel PY, Marti M. The role of extracellular vesicles in Plasmodium and other protozoan parasites. Cellular Microbiology. 2014;16(3):344-354
22. Van de Hoef DL, Coppens I, Holowka T, et al. Plasmodium falciparum-derived uric acid precipitates induce maturation of dendritic cells. PLoS One. 2013; 8:e55584. [PubMed: 23405174]
23. Orengo JM, Evans JE, Bettiol E, et al. Plasmodium-induced inflammation by uric acid. PLoS Pathog. 2008; 4:e1000013. [PubMed: 18369465]
24. Julio Gallego-Delgado, Maureen Ty, Jamie M. Orengo, Diana et al. a Surprising Role for Uric Acid: The Inflammatory Malaria Response. Curr Rheumatol Rep. 2014 February ; 16(2): 401. doi:10.1007/s11926-013-0401-8.
25. Reyes P, Rathod PK, Sanchez DJ, et al. Enzymes of purine and pyrimidine metabolism from the human malaria parasite, Plasmodium falciparum. Mol Biochem Parasitol. 1982; 5:275–290. [PubMed: 6285190]
26. Lopera-Mesa TM, Mita-Mendoza NK, van de Hoef DL, Doumbia S, Konate´ D, et al. (2012) Plasma Uric Acid Levels Correlate with Inflammation and Disease Severity in Malian Children with Plasmodium falciparum Malaria. PLoS ONE 7(10): e46424. doi:10.1371/journal.pone.0046424
27. Orengo JM, Leliwa-Sytek A, Evans JE, Evans B, van de Hoef D, et al. (2009) Uric acid is a mediator of the Plasmodium falciparum-induced inflammatory response. PLoS One 4: e5194
28. Mitra S, Abhilash K, Arora S, Miraclin A. A prospective study from south India to compare the severity of malaria caused by Plasmodium vivax, P. falciparum and dual infection. J Vector Borne Dis. 2015;52 (4):281-286
29. Limaye CS, Londhey VA, Nabar ST. The study of complications of vivax malaria in comparison with falciparum malaria in Mumbai. J Assoc Physicians India. 2012;60:15-18.
30. Shiraz Jamal Khan et al. Thrombocytopenia as an Indicator of Malaria in Adult Population. Hindawi Publishing Corporation Malaria Research and Treatment Volume 2012, Article ID 405981, 4 pages doi:10.1155/2012/405981https://downloads.hindawi.com/archive/2012/405981.pdf
31. WHO, Severe falciparum malaria, Transactions of the Royal Society of Tropical Medicine and Hygiene, vol. 94, Supplement 1, pp. S1–S90, 2000.
32. Mohd Arif, Shivcharan Jelia et al. A study of thrombocytopenia in malaria and its prognostic significance. International Journal of Research in Medical Sciences

Arif M et al. Int J Res Med Sci. 2016 Jun;4(6):2373-2378 www.msjonline.org DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20161817

33. Purna Chandra Karua, Manoj Kishan. Serum C-Reactive Protein And Serum Uric Acid As Prognostic Markers In Malaria At Western Odisha. International Journal of Scientific and Research Publications, Volume 10, Issue 9, September 2020DOI: 10.29322/IJSRP.10.09.2020.p10556
34. Castberg FC, Sarbah EW, Koram KA, et al. Malaria causes long-term effects on markers of iron status in children: a critical assessment of existing clinical and epidemiological tools. *Malar J*. 2018;17(1):464. Published 2018 Dec 11. doi:10.1186/s12936-018-2609-6
35. Hesselink, D.A., Burgerhart, JS., Bosmans-Timmerarends, H. *et al.* Procalcitonin as a biomarker for severe *Plasmodium falciparum* disease: a critical appraisal of a semi-quantitative point-of-care test in a cohort of travellers with imported malaria. *Malar J* **8,** 206 (2009). https://doi.org/10.1186/1475-2875-8-206
36. Nyakoe, Nancy & Taylor, Ronald & Makumi, Joseph & Waitumbi, John. (2009). Complement consumption in children with Plasmodium falciparum malaria. Malaria journal. 8. 7. 10.1186/1475-2875-8-7.
37. Ade-Serrano MA, Ejezie GC, Kassim OO. Correlation of Plasmodium falciparum gametocytemia with complement component titers in rural Nigerian school children. Journal of Clinical Microbiology. 1981 Jan;13(1):195-198. DOI: 10.1128/jcm.13.1.195-198.1981
38. Lopera-Mesa TM, Mita-Mendoza NK, van de Hoef DL, Doumbia S, Konate´ D, et al. (2012) Plasma Uric Acid Levels Correlate with Inflammation and Disease Severity in Malian Children with Plasmodium falciparum Malaria. PLoS ONE 7(10): e46424. doi:10.1371/journal.pone.0046424
39. Bhardwaj N, Ahmed MZ, Sharma S, Srivastava B, Pande V,Anvikar AR. Clinicopathological study of potential biomarkers of Plasmodium falciparum malaria severity and complications. Infect Genet Evol.2020;77:104046. doi:10.1016/ j.meegid.2019.10404