ISSN: 0975-3583,0976-2833 VOL13, ISSUE 01, 2022

A Hospital Based Cross-Sectional Study to Assess Hyponatremia as a Predictor of Mortality among Patient with Severe Malaria

Sheikh Yasir Islam[1], Amit Kumar Sharma[2], S Nayyer[3]

[1]Associate Professor of Medicine, Department of Medicine, Lady Hardinge Medical College, New Delhi, India
[2]Associate Professor, Department of Medicine, LHMC & SSK Hospital, New Delhi, India.
[3]Consultant Medicine, Dr BSA Medical College and Hospital, Delhi, India.

Abstract

Background: In Asia, Malaria-related hyponatraemia incidence ranges between 37% to 57 percent and since the prevalence of malaria is high in India and hyponatremia is common yet unexplored complication associated with it, the present study was conducted with an aim to determine the prevalence of hyponatremia in severe malaria and its association with mortality.**Material and Methods:**The present cross-sectional study was carried for a duration of two years among 220 adult patients with severe malaria admitted to the wards and ICU in a tertiary care centre. Patient-specific information was collected in a structured schedule and blood sample was collected for laboratory investigations after obtaining written informed consent. The power of serum sodium levels in predicting the mortality was evaluated by Receiver Operating Characteristics (ROC) curve.**Results:**The malaria rapid test kits results showed that 57.3% of plasmodium species was only P. falciparum. The prevalence of hyponatraemia was higher among subjects with mixed infection (78.8%) as compared to P. falciparum group (52.4%). Also, the mortality rate was higher among subjects with mixed infection (14.9%) as compared to P. falciparum group (6.3%). The best cut-off for serum sodium in predicting mortality among severe malaria subjects, on charting the ROC was 126 mEq/L with sensitivity and specificity as 76.6% and 88.4% respectively.**Conclusion:**Present study shows that in severe malaria, hyponatremia is a common electrolyte imbalance. Mixed malaria infection is more frequently and severely associated with hyponatremia than isolated falciparum malaria. As a result of our findings, we suggest that serum electrolytes be measured in malaria patients of all ages.

Keywords: Hyponatremia, Malaria, Mortality.

Corresponding Author: Dr Amit Kumar Sharma, Associate Professor, Department of Medicine, LHMC & SSK Hospital, New Delhi, India, Email: dramitsharma1506@gmail.com

Introduction

Malaria is one of the most common infectious diseases that humans have ever encountered. It has impacted people in over 100 nations and wreaked havoc on the health-care systems of those countries. It is most common in Africa and Southeast Asia. Malaria caused an estimated 300-500 million morbidity and 2-3 million mortality each year.[1,2]

According to the 2018 World Malaria Report, 219 million cases of malaria were reported in 2017, up from 217 million cases in 2016. In 2017, the expected number of malaria deaths was 435,000, which was identical to the previous year. 3 Nigeria (25 percent), the Democratic Republic of the Congo (11 percent), Mozambique (5 percent), India (4 percent), and Uganda (four percent) accounted for nearly half of all malaria cases globally in 2017 (4 percent).[3]

According to the National Vector Borne Disease Control Program (NVBDCP) incidence records, the annual parasite incidence (API) in most of India was less than 2, with 2–5 API in scattered regions and > 5 API in Rajasthan, Karnataka, Southern Madhya Pradesh, Chhattisgarh, Gujarat, Jharkhand, Goa, and Orissa, as well as the north-eastern states.[4]

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 01, 2022

Malaria is a mosquito-borne disease that, while not endemic in Delhi, has a higher referral rate of severe cases from endemic regions such as Haryana and Uttar Pradesh. Plasmodium species are unicellular eukaryotic protozoan parasites that cause malaria. P.falciparum, P.vivax, P.ovale, P. malariae, and P. knowlesi are the five species that have been identified as having the capacity to infect people. The complicated epidemiology of malaria in India is due to the geographical, ethnic, and vast distribution of nine anopheles vectors that transmit three plasmodia vectors, namely P. falciparum, P. vivax, and P. malariae.[4]

Clinical signs and symptoms appear eight to twenty-five days after the parasite has infected you. Fever, headache, vomiting, hemolytic anaemia, jaundice, and other symptoms are common. Malaria, particularly falciparum malaria, can, nevertheless, cause a variety of complications affecting multiple physiological systems.

The extracellular fluid cation sodium (Na) regulates the normal distribution of water and osmotic pressure in a variety of body fluids. A change in normal serum sodium levels is associated with numerous health effects. Disturbances in electrolyte balance such as hyponatremia is a common complication of malaria. This electrolyte disturbances serve as a predictor of illness severity. Malaria-related hyponatraemia has long been recognised as a complication.[5] The occurrence of hyponatraemia in malaria has largely been studied in endemic areas, with an emphasis on children with severe Plasmodium falciparum malaria.[5-7] Adults in Asian countries have been reported to have an incidence of hyponatremia ranging from 37% to 57 percent.[8,9] However, few research in non-immune groups or patients infected with different Plasmodium species have been conducted. Although the pathogenesis of hyponatraemia in malaria is unexplained, some investigations have suggested that increased vasopressin secretion, whether properly or improperly, plays a role.[8,10] Despite the fact that a recent study revealed that individuals with malaria and hyponatraemia have a fair prognosis, cerebral oedema can still occur in rare circumstances.[8,11]

Since the prevalence of malaria is high in India and hyponatremia is common yet unexplored complication associated with it, the present study was conducted with an aim to determine the prevalence of hyponatremia in severe malaria and its association with mortality in a tertiary care hospital.

Material and Methods

Study setting and Design

The present cross-sectional study was carried for a duration of two years (May 2019 to April 2021) in the Department of Pulmonary Medicine of a tertiary care teaching and referral hospital, Delhi, India, after obtaining ethical approval from Institutional Ethics Committee (IEC/IRB No.; LHMC, Delhi).

Sample Size and study subjects

The sample size was calculated as 201 by using the prevalence of hyponatremia in severe malaria as 55% as mentioned in the studies by Charan et al., Naing et al., and Siwal et al., and taking absolute precision as 7%. Considering dropout rate of 8%, the final sample size was calculated as 220. Prior to enrolling of subjects into the study, written informed consent was obtained either from patient or relatives after explaining in detail regarding the purpose of study, and consecutive sampling method was used to enrol the study subjects till the calculated size was achieved.[12-14]

The present study included the patients (18 years or above) with severe malaria (smear positive or rapid card test positive for only Plasmodium falciparum or both Plasmodium falciparum and Plasmodium vivax [mixed infection]) admitted to the wards and ICU as study subjects. Patient with present history of diuretics and any other medication or disease which causes low sodium were excluded from the study. Defined criteria to consider the patient as having severe malaria was a Glasgow Coma Scale (GCS) score <11 (indicating cerebral

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 01, 2022

malaria); or Anaemia (haematocrit <0.20 L/L with parasite count >100.000/μL); or Jaundice (serum bilirubin >50 μmol/L with parasite count >100.000 μL); or Renal impairment (urine output <400 mL/24 h and serum creatinine >250 μmol/L); or Hypoglycaemia (blood glucose <2.2 mmol/L); or Hyperparasitaemia (>10% parasitaemia); or Shock (systolic blood pressure <80 mm Hg with cold extremities).[15,16]

Data and Sample collection

After admission, clinical history was taken and patient-specific and relevant information was collected in a structured data collection schedule through interviews. At the time of admission 10 mL of blood sample was collected from each patient for laboratory investigations such as blood glucose; complete blood counts (done by Pentra ES 60 [HORIBA MEDICAL] automated haematology analyser); serum electrolytes (done by 9180 electrolyte analyser [Roche]); renal and liver function tests (done by CobasIntegra- 400 [Roche] biochemical analyser); thick and thin smears (staining with Giemsa stain); and rapid card test (by using Plasmodium falciparum Histidine-Rich-Protein 2 and Plasmodium vivax lactate dehydrogenase screening [ICT Malaria, Binax]) for malaria parasite detection.

Statistical analysis

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 28. Results were analysed with baseline demographic and clinical, laboratory parameters of each group of study patients. Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD. Normality of data were tested by Kolmogorov-Smirnov test. If the normality was rejected, then non parametric test was used. Quantitative variables were compared using Unpaired t-test between the two groups. Qualitative variables were compared using Chi-Square test /Fisher's exact test. The power of serum sodium levels in predicting the mortality in severe malaria patients was evaluated by means of Receiver Operating Characteristics (ROC) curve. Optimal cut-off score to predict mortality was determined by visual inspection of the curve at a level that combined maximum sensitivity and optimal specificity. All tests were performed at a 5% level of significance; thus, an association was significant if the p value was less than 0.05.

Results

In present study the mean age of study subjects was 41.1±6.5 years, so nearly half of subjects (48.2%, 106/220) belonged to age group of 40-49 years [Table 1]. Males were among three fifth of severe malaria patient (58.2%, 128/220). The malaria rapid test kits results showed that 57.3% (126/220) of plasmodium species was only P. falciparum whereas rest were of mixed species. The mortality rate among severe malaria subjects was 10.0% (22/220).

[Table 2] shows that mean age of subjects with P. falciparum infection was 40.2±6.1 years and it was 41.1±5.9 years for mixed infection. There was no difference ($p>0.05$) in male and female representation among two different groups (P. falciparum vs mixed infections). The serum sodium level in P. falciparum was 134.4±5.9 mEq/L and it was 126.5±6.8 mEq/L in mixed infections and this difference was statistically significant ($p<0.05$). Similarly, the prevalence of hyponatraemia was higher among subjects with mixed infection (78.8%) as compared to P. falciparum group (52.4%). Also, the mortality rate was higher among subjects with mixed infection (14.9%) as compared to P. falciparum group (6.3%).

The serum sodium level, specifically among patients with hyponatremia were significantly ($p<0.05$) reduced among subjects with mixed infection (125.7±4.7) as compared to subjects with P. falciparum infection (129.4±2.1). Similarly, serum sodium level, specifically among patients with hyponatremia were significantly ($p<0.05$) reduced among patient who died (123.4±4.2) as compared to those who got discharged (127.3±1.7).

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 01, 2022

[Figure 1] shows the ROC for serum sodium levels for predicting the mortality among study subjects. It shows that the discriminating ability was 0.857 (good). The best cut-off for serum sodium in predicting mortality among severe malaria subjects, on charting the ROC was 126 mEq/L with sensitivity and specificity as 76.6% and 88.4% respectively with a significant p value of <0.05.

Table 1: Demographic characteristics of study subjects (N=220).

Variables	Number (%)/ Mean±SD
Age (in years)	41.1±6.5
Age group (in years)	
18-29	40 (18.1)
30-39	62 (28.2)
40-49	106 (48.2)
50 or more	12 (5.5)
Gender	
Male	128 (58.2)
Female	92 (41.8)
Plasmodium species	
P. falciparum	126 (57.3)
Mixed infection	94 (42.7)
Outcome	
Discharged	198 (90.0)
Death	22 (10.0)

Table 2: Demographic, clinical profile and laboratory parameters of study subjects (N=220).

Variables	Total	P. falciparum (n=126)	Mixed infection (n=94)	p-value
Age (in years)	41.1±6.5	40.2±6.1	41.1±5.9	P=0.273
Gender				
Male	128 (58.2)	76 (60.3)	52 (55.3)	P=0.457
Female	92 (41.8)	50 (39.7)	42 (44.7)	
Clinical profile				
Pulse rate (bpm)	104.5±7.4	101.3±6.3	106.4±9.2	P<0.0001
Systolic BP (mm Hg)	108.9±11.2	109.4±12.3	107.8±10.2	P<0.306
Respiratory rate (rpm)	25.6±5.4	23.9±4.3	26.2±5.5	P<0.0006
Temperature (0C)	101.3±0.9	100.4±1.1	101.8±0.9	P<0.0001
GCS <11				
Yes	32 (14.5)	18 (14.3)	14 (14.9)	P=0.899
No	188 (85.5)	108 (85.7)	80 (85.1)	
Laboratory parameters				
Serum Sodium (mEq/L)	130.6±6.4	134.4±5.9	126.5±6.8	P<0.0001
Serum Potassium (mEq/L)	3.3±0.4	3.2±0.8	3.6±0.1	P<0.0001
Hyponatremia (<135 mEq/L)				
Yes	140 (63.6)	66 (52.4)	74 (78.8)	P<0.0001
No	80 (36.4)	60 (47.6	20 (21.2)	
Outcome				
Discharged	198 (90.0)	118 (93.7)	80 (85.1)	P=0.627
Death	22 (10.0)	8 (6.3)	4 (14.9)	

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 01, 2022

Table 3: Analysis of among study subjects with hyponatremia (N=140).

Variables	Serum Sodium (mEq/L)	p value
Gender		
Male (n=81)	131.6±3.6	P=0.132
Female (n=59)	130.7±2.2	
Plasmodium species		
P. falciparum (n=80)	129.4±2.1	P<0.0001
Mixed infection (n=60)	125.7±4.7	
Outcome		
Discharged (n=126)	127.3±1.7	P<0.0001
Death (n=14)	123.4±4.2	

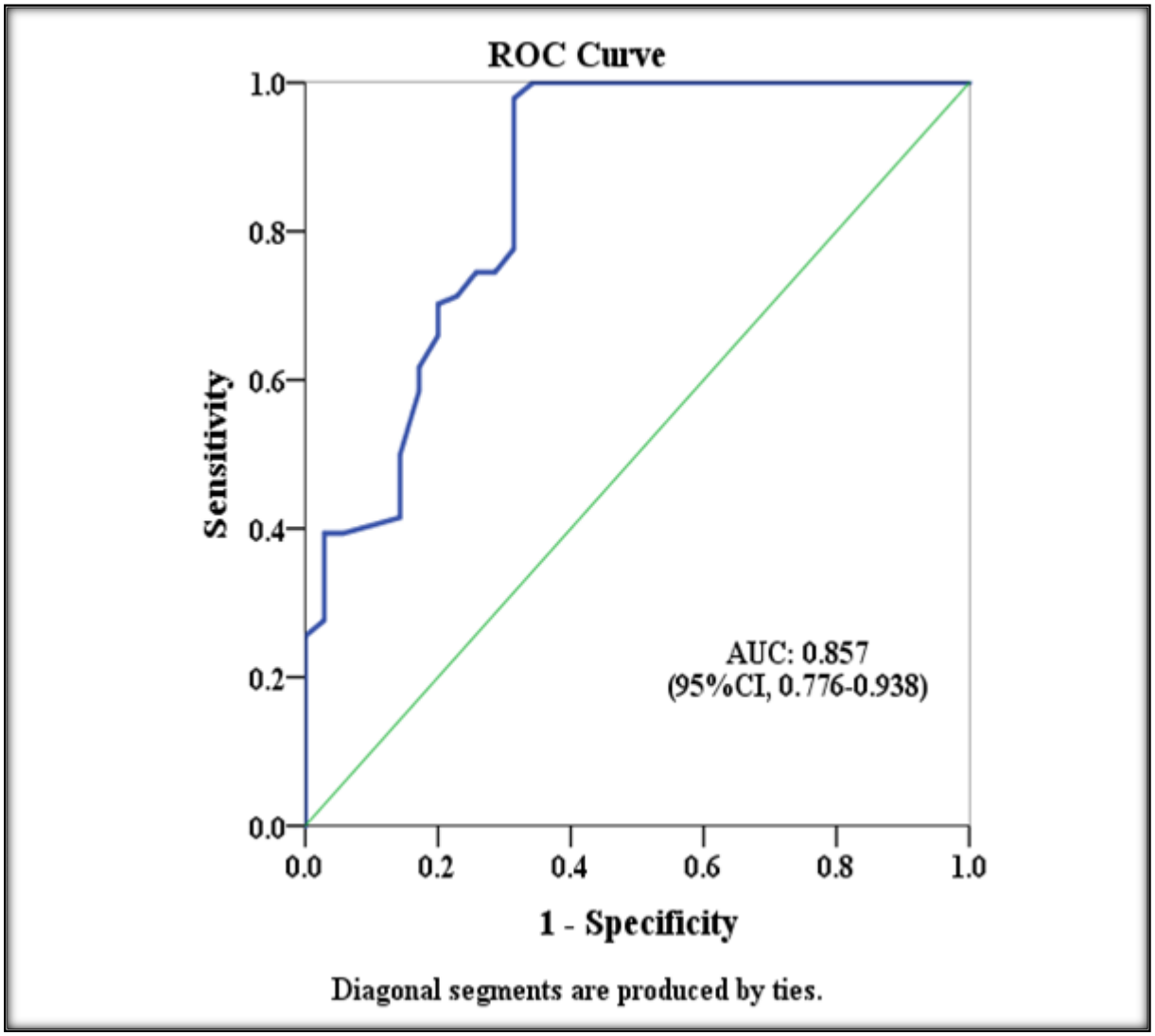

Figure 1: Receiver operating characteristics curve (ROC) for serum sodium for predicting the mortality among study subjects (N=220).

Discussion

Even 105 years after Ross discovered the transmission route of malaria through malaria parasites, malaria remains the world's leading killer.[17] In present study, the mean age of study subjects was 41.1±6.5 years, and nearly half of subjects (48.2%, 106/220) belonged to age group of 40-49 years. These finding also correlates with the studies conducted by

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 01, 2022

Karlekar et al., and Sahar et al.[18,19] Malaria is more common in people under the age of 40, according to studies, although the severity of malaria worsens with age.[20,21]

In present study males were among three fifth of severe malaria patient (58.2%, 128/220). The above results were similar to studies conducted by Singh et al., and Karlekar et al.[18,21] Males have a higher malaria incidence than females, which can be explained by their movement across larger areas, which increases their chances of being bitten by mosquitos.[22]

The malaria rapid test kits results showed that 57.3% (126/220) of plasmodium species was only P. falciparum whereas rest were of mixed species and to some extent it was in accordance with the studies conducted in North India.[21,23,24] As a result of the foregoing, P. falciparum is the most common infection in Delhi and the NCR.

The severity of infection is indicated by electrolyte imbalance, which is thought to be a result of malaria with uncertain pathogenesis. According to the findings of this study, malaria induced hyponatremia in 63.6 percent of patients with severe malaria, which is consistent with prior studies from Uttarakhand (India), Bangladesh, the Netherlands, and Kenya.[8,17,25,26] Severe hyponatremia is linked to poor prognosis, extended stays in the hospital, neurological impairments, and mortality.[17]

In present study the serum sodium level in P. falciparum was 134.4±5.9 mEq/L and it was 126.5±6.8 mEq/L in mixed infections. In a study by Jasani et al., however, average serum sodium was found to be 127.76 mEq/L in P. falciparum patients and 132.37 mEq/L in P. vivax patients.[27] Rani et al., found no significant difference in serum sodium levels between P. falciparum and P. vivax infections, implying that hyponatremia was only a reflection of the disease's severity.[1]

In present study, the prevalence of hyponatraemia was higher among subjects with mixed infection (78.8%) as compared to P. falciparum group (52.4%). But it was in contrast to the studies by Dubey et al., and Jasmin et al., where prevalence of hyponatraemia was higher among subjects with P. falciparum as compared to mixed infection group.[27,28]

Hyponatremia was shown to be more severe and lethal in severe mixed malarial infection than in severe falciparum alone infection in the current study, which is consistent with previous researches.[17] We assume severe vomiting is a major cause of hyponatremia in individuals with mixed malarial illness because they have excessive vomiting and dehydration.

Hyponatremia with a cut-off of 126 mEq/L was found to predict mortality in severe malaria patients with 76.6 percent sensitivity and 88.4 percent specificity. This association has never been reported before, therefore it cannot be compared.

The study's limitation was that it was a single-centric study, and the findings may not be applicable to a broad population of patients, necessitating a large-scale cross sectional comparative study to validate the findings. Although the study focused on the most usually affected electrolyte, sodium, a full analysis of potassium, calcium, and magnesium would have provided a more complete picture of electrolyte imbalance in malaria.

Conclusion

In severe malaria, hyponatremia is a common electrolyte imbalance. Mixed malaria infection is more frequently and severely associated with hyponatremia than isolated falciparum malaria. Hyponatremia with a cut-off of 126 mEq/L predicted mortality with 76.6 percent sensitivity and 88.4 percent specificity. As a result of our findings, we suggest that serum electrolytes be measured in malaria patients of all ages. Electrolyte imbalance should be treated concurrently with the disease to avoid sequelae from electrolyte loss. More research into the pathophysiological basis of hyponatremia in malaria is needed.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 01, 2022

References

1. Rani A, Akhtar S, Nawaz SK, Irfan S, Azam S, Arshad M. Electrolyte disturbance and the type of malarial infection. Iran J Public Health 2015;44(11):1492-7.
2. Mishra SK, Mohapatra S, Mohanty Patel NC, Mohapatra DN. Acute renal failure in falciparum malaria. Indian Acad Clin Med 2002;3(4):141-7.
3. World Health Organization. Malaria. Geneva: WHO; 2019. Available from: https://www.who.int/ news-room/fact-sheets/detail/malaria.
4. Kumar A, Valecha N, Jain T, Dash AP. Burden of malaria in India: retrospective and prospective view. Am J Trop Med Hyg 2007;77(6):69-78.
5. English MC, Waruiru C, Lightowler C, Murphy SA, Kirigha G, Marsh K. Hyponatraemia and dehydration in severe malaria. Arch Dis Child 1996;74:201-5.
6. Ladhani S, Patel VS, El Bashir H, Shingadia D. Changes in laboratory features of 192 children with imported falciparum malaria treated with quinine. Pediatr Infect Dis J 2005;24:1017-20.
7. Sowunmi A. Hyponatraemia in severe falciparum malaria: a clinical study of nineteen comatose African children. Afr J Med Med Sci 1996;25:47-52.
8. Hanson J, Hossain A, Charunwatthana P, Hassan MU, Davis TM, Lam SW, et al. Hyponatremia in severe malaria: evidence for an appropriate antidiuretic hormone response to hypovolemia. Am J Trop Med Hyg 2009;80:141-5.
9. Thanachartwet V, Krudsood S, Tangpukdee N, Phumratanaprapin W, Silachamroon U, Leowattana W, et al. Hyponatraemia and hypokalaemia in adults with uncomplicated malaria in Thailand. Trop Doct 2008;38:155-7.
10. Sowunmi A, Newton CR, Waruiru C, Lightman S, Dunger DB. Arginine vasopressin secretion in Kenyan children with severe malaria. J Trop Pediatr 2000;46:195-9.
11. Ustianowski A, Schwab U, Pasvol G. Case report: severe acute symptomatic hyponatraemia in falciparum malaria. Trans R Soc Trop Med Hyg 2002;96:647-8.
12. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian Journal of Psychological Medicine 2013;35(2):121.
13. Naing L, Winn T, Rusli BN. Practical issues in calculating the sample size for prevalence studies. Archives of Orofacial Sciences 2006;1:9-14.
14. Siwal N, Singh US, Dash M, Kar S, Rani S, Rawal C, et al. Malaria diagnosis by PCR revealed differential distribution of mono and mixed species infections by Plasmodium falciparum and P. vivax in India. PloS one 2018;13(3):e0193046.
15. Karnad DR, Nor MB, Richards GA, Baker T, Amin P. Intensive care in severe malaria: Report from the task force on tropical diseases by the World Federation of Societies of Intensive and Critical Care Medicine. J Crit Care 2018;43:356-60.
16. Shah MP, Briggs-Hagen M, Chinkhumba J, Bauleni A, Chalira A, Moyo D, et al. Adherence to national guidelines for the diagnosis and management of severe malaria: A nationwide, cross-sectional survey in Malawi, 2012. Malaria Journal 2016;15(1):369.
17. Ibinda F, Zarnack HC, Newton CR. Sodium disturbances in children admitted to a Kenyan hospital: Magnitude, outcome and associated factors. PloS One 2016;11(9):e0161320.
18. Karlekar SR, Deshpande MM, Andrew RJ. Prevalence of asymptomatic plasmodium vivax and plasmodium falciparum infections in tribal population of a village in Gadchiroli district of Maharashtra state, India. Biological Forum-An International J 2012;4(4):42-4.
19. Sahar S, Akhtar T, Bilal H, Rana MS. Prevalence of plasmodium falciparum, malarial parasite in Muzaffargarh district, Punjab-Pakistan: a two year study. Pakistan J Sci 2012; 64(2):64-6.

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 01, 2022

20. Schwartz E, Sadetzki S, Murad H, Raveh D. Age as a risk factor for severe Plasmodium falciparum malaria in nonimmune patients. Clin Infect Dis 2001;33(10):1774-7.
21. Singh G, Urhekar AD, Maheshwari U, Samant P. Malarial infection: effects on electrolytes parameters. Asian Acad Res J Multidisciplinary 2015;1(32);211-6
22. Reuben R. Women and malaria-special risks and appropriate control strategy. Soc Sci Med 1993;37(4):473-80.
23. Gupta NK, Bansal SB, Jain UC, Sahare K. Study of thrombocytopenia in patients of malaria. Trop Parasitol 2013;3:58-61.
24. Asma U, Taufiq F, Khan W. Prevalence and clinical manifestations of malaria in Aligarh, India. Korean J Parasitol 2014;52(6):621-9.
25. Jain A, Kaushik R, Kaushik RM. Malarial hepatopathy: clinical profile and association with other malarial complications. Actatropica 2016;159:95-105.
26. vanWolfswinkel ME, Hesselink DA, Zietse R, Hoorn EJ, van Genderen PJ. Hyponatraemia in imported malaria is common and associated with disease severity. Malar J 2010;9(1):140.
27. Jasani JH, Sancheti SM, Gheewala BS, Bhuva KV, Doctor VS, Vacchani AB.et.al. Association of the Electrolyte Disturbances (Na+, K+) with Type and Severity of Malarial Parasitic infection. J Clin Diagn Res 2012;6(4):678-81.
28. Dubey TN, Gupta N. Acid - Base imbalance and Dyselectrolytemia in Malaria. J Med Sci Clin Res 2017;5(6):23365-71.