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ORIGINAL ARTICLE

Frequency of Malaria in neonatal sepsis.

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ABSTRACT… Objective: To determine the frequency of malaria in neonatal sepsis. **Study Design:** Cross-sectional study. **Setting:** Department of Neonatology, RTEH Hospital, Muzaffargarh, Pakistan. **Period:** July 2024 to December 2024. **Methods:** A total of 218 neonates presenting with suspected sepsis were analyzed. Demographical and clinical information was noted. Blood samples were collected and sent to laboratory for relevant investigations. Malaria parasite assessment was done using Acu-check Malaria P.f. / Pan Ag Rapid Test Device. Thin smear evaluation was be performed to identify the malarial parasite species. **Results:** In a total of 218 neonates, 112 (51.4%) were males. The mean age was 13.8±9.0 days. Hepatosplenomegaly, pallor, and jaundice were noted in 90 (41.3%), 107 (49.1%), and 53 (24.3%) neonates, respectively. Late-onset sepsis was the commonest type, found in 138 (63.3%) neonates. Malaria was present in 9 (4.1%) neonates, while P. falciparum, and P. vivax were identified in 4 (1.8%), and 5 (2.3%) neonates. Malaria in neonates with sepsis was found to have significant association with hepatosplenomegaly (100% vs. 38.8%, p<0.001), jaundice (77.8% vs. 22.2%, p<0.001), and higher temperature (38.9±0.3 vs. 37.4±1.3 ^{0}C, p<0.001), lower hemoglobin level (8.6±0.5 vs. 12.5±1.4 g/dl, p<0.001), and lower platelet levels (89.8±29.5 vs. 276.8±100.2 (10^9/L, p<0.001). **Conclusion:** Malaris should be considered in those neonates presenting with sepsis-like symptoms in endemic regions. The low prevalence (4.1%) observed reflects ongoing efforts to control malaria because of this life-threatening disease.

Key words: Hepatoseplenomegaly, Jaundice, Malaria, Neonate, Sepsis.

INTRODUCTION

Neonatal sepsis (NS) stands as a predominant cause of mortality on a global scale, particularly exhibiting higher prevalence and mortality rates in low and middle-income countries.[1] Local data reveals neonatal mortality rates of 42 per 1000 and these figures starkly contrast to those observed in developed countries.[2-4] The data highlights Pakistan's relative lag in achieving the goals outlined by the "Every Newborn Action Plan (ENAP)", aiming for 12 or fewer neonatal deaths by 2030.[5,6] Pakistan holds a significant position within the Group 3 countries of the Eastern Mediterranean Region, contributing to a staggering 95% of the total malaria burden in this regional context.[7] P. falciparum, the predominant malaria parasite, accounts for approximately 95% of malaria.[8,9] Despite being initially perceived as rare among newborns, there are emerging reports indicating an increasing incidence of malaria in this age group from various regions across the globe.[10,11]

Detecting malaria in neonates poses considerable challenges due to the non-specific and variable clinical features that often overlap with those of bacterial infections. Consequently, neonates presenting with fever are typically screened for sepsis and promptly administered antibiotics while awaiting blood culture results. A study done by Okechukwu et al analyzing 266 neonates found that 28.6% had malaria while 36.5% were having blood culture proven sepsis, and 4.5% neonates proven sepsis and malarial parasite.[12] Enyuma et al from Nigeria evaluating 150 febrile neonates noted that 2.9% neonates were having both malaria and NS.[10]

A thorough literature search exhibited that there is scarcity of knowledge about the prevalence

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of malaria in NS. The investigation into the prevalence of malaria in NS is critical for several reasons. Firstly, it addresses a knowledge gap regarding the simultaneous occurrence of these conditions, potentially guiding diagnostic and treatment strategies. Secondly, understanding this co-occurrence can aid in risk stratification, early identification, and targeted management of affected neonates, ultimately reducing mortality rates. This study was done to determine the frequency of malaria in NS.

METHODS

This cross-sectional study was conducted at the department of neonatology, RTEH Hospital, Muzaffargarh, Pakistan, from July 2024 to December 2024. Approval from Institutional Ethical Committee was obtained (IHHN_IRB_2024_03_010, dated: 29-May-2025). Informed and written consents were taken from parents/guardians. A sample size of 218 was calculated using online EpiInfo sample size claculator taking the frequency of malaria in suspected NS cases as 28.6%[12], with 95% confidence level, and 6% margin of error. Inclusion criteria were neonates presenting with suspected sepsis. Exclusion criteria were neonates receiving anti-malarial drugs, or antibiotics (as per history and medical record) at least 1 weeks prior to enrollment. Neonates having congenital heart disease or congenital dysmorphism were also excluded. Parents or guardians of the neonates unwilling to participate in this study were also not included. Non-probability convenient sampling technique was adopted. NS was labeled as neonates presenting with any of the systemic manifestations like poor feeding, convulsions, drowsiness or unconsciousness, movement only when stimulated or no movement, fast breathing, grunting, severe chest in-drawing, abnormal body temperature, central cyanosis or severe jaundice, severe abdominal distension, or local infection.[13] Early-onset NS (EONS) was sepsis occurring within the first 3 days of life. Late-onset NS (LONS) was sepsis occurring in from the 4th to 28th day of life.[14]

Neonates fulfilling eligibility criteria were admitted, and demograhical along with clinical information was noted. Maternal history evaluation included maternal peripartum pyrexia, pre-labour rupture of membrane, antenatal care received (as per history and medical record), and mode of delivery. Blood samples were collected and sent to laboratory for relevant investigations including complete blood count, C-reactive protein, random blood sugar, renal parameters, and malaria parasite (Acu-check Malaria P.f. / Pan Ag Rapid Test Device) evaluation. Thin smear evaluation was be performed to identify the malarial parasite species as per standard laboratory procedures. Standard laboratory parameters were considered for the laboratory investigations. All the investigations were performed in the institutional laboratory. All the neonates were treated as per institutional protocols.

Data were analyzed using IBM-SPSS statistics, version 26.0. Qualitative data were shown as frequency and percentages. Quantitative data were represented as mean and standard deviation (SD). Effect modifiers were controlled through stratification. Post-stratification, chi-square test/fisher's exact test or independent sample t-test was applied taking $p<0.05$ as statistically significant.

RESULTS

In a total of 218 neonates, 112 (51.4%) were males, and 106 (48.6%) females. The mean age was 13.8±9.0 days, while 147 (66.4%) neonate were aged between 8 to 28 days. Gestational age evaluation revealed that 136 (62.4%) neonates were born pre-term. The mean duration of symptoms was 3.36±1.7 days. Hepatosplenomegaly, pallor, and jaundice were noted in 90 (41.3%), 107 (49.1%), and 53 (24.3%) neonates, respectively. Late-onset sepsis was the commonest type, found in 138 (63.3%) neonates. Malaria was present in 9 (4.1%) neonates. Among these 9 cases, P. falciparum, and P. vivax were identified in 4 (44.4%), and 5 (55.6%) neonates. Malaria in neonates with sepsis was found to have significant association with hepatosplenomegaly (100% vs. 38.8%, $p<0.001$), jaundice (77.8% vs. 22.2%, $p<0.001$), and higher temperature (38.9±0.3 vs. 37.4±1.3 ^{0}C, $p<0.001$), lower hemoglobin level (8.6±0.5 vs. 12.5±1.4 g/dl,

p<0.001), and lower platelet levels (89.8±29.5 vs. 276.8±100.2 10^9/L, p<0.001), and the details are shown in Table-I.

Evaluation of maternal aspects revealed the mean maternal age to be 31.3±7.8 years, while 104 (47.7%) mothers were aged ≤ 30 years. History of peripartum pyrexia, and PROM were present in 64 (29.4%), and 41 (18.8%) mothers. Antenatal care was received by 158 (72.5%) mothers. Mode of delivery was vaginal among 128 (58.7%) cases. Malaria in neonates with sepsis was not found to have significant association with any of the maternal characteristics (Table-II).

Characteristics		Malaria		P-Value
		Yes (n=9)	No (n=209)	
Gender	Male	7 (77.8%)	105 (50.2%)	0.106
	Female	2 (22.2%)	104 (49.8%)	
Age (days)	≤7	2 (22.2%)	69 (33.0%)	0.499
	8-28	7 (77.8%)	140 (67.0%)	
Age (days)		16.0±9.4	13.7±8.9	0.445
Weight (kg)		2.6±0.8	2.5±0.8	0.712
Gestational age	Pre-term	4 (44.4%)	132 (63.2%)	0.256
	Term	5 (55.6%)	77 (36.8%)	
Residence	Rural	7 (77.8%)	130 (62.2%)	0.344
	Urban	2 (22.2%)	79 (37.8%)	
Duration of symptoms (days)		3.0±1.5	3.4±1.7	0.516
Clinical features	Hepatosplenomegaly	9 (100%)	81 (38.8%)	<0.001
	Pallor	9 (100%)	98 (46.9%)	
	Jaundice	7 (77.8%)	46 (22.2%)	<0.001
	Petechial hemorrhages	1 (11.1%)	20 (9.6%)	0.878
Type of sepsis	Early-onset	3 (33.3%)	77 (36.8%)	0.831
	Late-onset	6 (66.7%)	132 (63.2%)	
Laboratory parameters	Hemoglobin (g/dl)	8.6±0.5	12.5±1.4	<0.001
	Total leukocyte count (10^9/L)	8.8±1.3	12.5±1.4	0.873
	Platelets (10^9/L)	89.8±29.5	276.8±100.2	<0.001
	Serum creatinine (mg/dl)	1.3±0.4	1.2±0.4	0.813
	Urea (mg/dl)	43.4±9.2	35.1±14.1	0.082
	Random blood sugar (mg/dl)	92.6±10.8	82.2±29.6	0.295
	C-reactive protein (mg/L)	45.0±34.1	45.0±34.1	0.551

Table-I. Association of malaria with demographic, vital, and laboratory characteristic in neonates having sepsis (n=218)

Characteristics		Malaria		P-Value
		Yes (n=9)	No (n=209)	
Maternal age (years)		34.0±6.8	31.2±7.9	0.289
Peripartum pyrexia		1 (11.1%)	63 (30.1%)	0.220
Prelabour rupture of membranes		1 (11.1%)	40 (19.1%)	0.546
Antenatal care received		8 (88.9%)	150 (71.8%)	0.260
Mode of delivery	Vaginal delivery	6 (66.7%)	122 (58.4%)	0.621
	Cesarean section	3 (33.3%)	87 (41.6%)	

Table-II. Association of malaria with maternal characteristic in neonates having sepsis (n=218)

DISCUSSION

The findings of this study showed that elevated temperature, pallor, jaundice, hepatosplenomegaly, and thrombocytopenia have significant association of malaria in NS. The prevalence of hepatospelenomegaly was significantly higher in malaria then as compared to the clinically suspected NS (100% vs. 38.8%, $p<0.001$). Jaundice was more common in malaria-positive neonates (77.8% vs. 22.2%, $p<0.001$). These clinical features are consistent with findings by Enyuma et al.[15], who reported hepatosplenomegaly and jaundice as hallmark features of neonatal malaria. The mean hemoglobin level in malaria-positive neonates in this study was significantly lower (8.6 ± 0.5 g/dL) compared to malaria-negative neonates (12.5 ± 1.4 g/dL, $p<0.001$). These finding are consistent with studies that describe anemia as a key manifestation of malaria in neonates, often resulting from hemolysis and bone marrow suppression.[16] Platelet counts were markedly reduced in malaria-positive neonates (89.8 ± 29.5 vs. 276.8 ± 100.2 $\times109$/L, $p<0.001$), a feature attributed to malaria-induced platelet destruction and sequestration.[17]

In this study, the prevalence of malaria in neonates with suspected sepsis was 4.1%. Among neonates having malaria ($n=9$), P. falciparum, and P. vivax were identified in 4 (44.4%), and 5 (55.6%) neonates. These findings also align with previous studies conducted in similar malaria-endemic regions. A study conducted by Diala et al.[18], in Nigeria reported a prevalence of neonatal malaria at 5.3%, with the majority of cases attributed to P. falciparum. Mwaniki et al.[19], in Kenya identified congenital malaria in 0.35% of neonatal admissions, but this lower prevalence was attributed to the implementation of robust malaria prevention strategies, including insecticide-treated bed nets (ITNs). Higher prevalence rates have been reported in certain regions like a study by Ekanem et al.[20], in Nigeria reported congenital malaria in 35% of neonates with suspected sepsis. The discrepancies in prevalence may stem from differences in the study population, diagnostic methods, and local malaria transmission intensity. While this study utilized rapid diagnostic tests (RDTs) supplemented by microscopy, the sensitivity of these tools might vary across settings.[21,22]

The findings of the present study highlight the need for heightened clinical suspicion for malaria in neonates presenting with sepsis in endemic areas. The overlapping clinical features of malaria and bacterial sepsis, such as fever and respiratory distress, necessitate comprehensive diagnostic workups, including malaria screening. In this study, maternal peripartum pyrexia was noted in 29.4% of cases, and PROM in 18.8%. These factors are consistent with findings from Nfor and Senyuy[23], who identified maternal fever and PROM as risk factors for vertical malaria transmission. Strengthening antenatal care services, including malaria prevention and treatment, could mitigate these risks. Future studies should explore outcomes of neonates with malaria and evaluate the effectiveness of integrated sepsis-malaria management protocols. Strengthening malaria prevention strategies during pregnancy and enhancing diagnostic capabilities in neonatal care units are imperative to reducing the burden of neonatal malaria and improving survival outcomes. The sickle cell gene has been shown to confer protection against severe P. falciparum malaria and has consequently reached a high prevalence in regions where malaria is endemic, largely due to natural selection. There is a lack of local data on this association in Pakistan, highlighting the need for further research in this area.[24] Although the overall frequency of malaria in neonatal sepsis was relatively low (4.1%), its presence was strongly associated with specific clinical features such as hepatosplenomegaly, jaundice, fever, anemia, and thrombocytopenia. Early detection and prompt treatment of malaria in septic neonates can significantly improve clinical outcomes and reduce mortality. Routine screening for malaria in neonates with suspected sepsis may be warranted in high-risk areas to avoid missed diagnoses and to ensure appropriate management.

The cross-sectional design in this study precludes causal inferences regarding the associations observed. The reliance on RDTs and

microscopy, while practical, may have limited sensitivity for detecting low-level parasitemia, potentially underestimating the true burden of neonatal malaria. Single center study setting may limit the generalizability to other settings with different malaria transmission dynamics. The non-probability sampling technique may have introduced selection bias.

CONCLUSION

Malaris should be considered in those neonates presenting with sepsis-like symptoms in endemic regions. The low prevalence (4.1%) observed reflects ongoing efforts to control malaria because of this life-threatening disease. The strong associations between malaria and clinical features such as hepatosplenomegaly, jaundice, anemia, and thrombocytopenia reinforce the importance of routine malaria screening in neonates with sepsis.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Muhammad Usman:** Data collection, drafting, responsible for data, approval for publication.
2	**Ather Razzaq:** concept, designing, proof reading, critical revisions.
3	**Ejaz Ahmad:** Data synthesis, data analysis, proof reading.
4	**Syed Hassan Ahmad:** Data collection, drafting, responsible for data.
5	**Wasif Ijaz:** Data synthesis, data analysis, proof reading.
6	**Muhammad Imran:** Proof reading, analysis.
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