Evaluation of Neutrophil Lymphocyte Ratio (NLR) in Sudanese Children with Falciparum Malaria

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Abstract: Severe falciparum malaria is one of the most world-wide infection among children leading to high mortality and morbidity especially in tropical regions. Neutrophil lymphocyte ratio (NLR) is prognostic and predictor factors indicative for inflammatory diseases, cancers, cardiovascular events, and in several types of infectious diseases such as falciparum malaria. The purpose of this study was to evaluate the neutrophil lymphocyte ratio (NLR) in Sudanese children with falciparum malaria. In addition to study association between NLR and malaria parasitemia and parasite count. A case control study was included 300 Sudanese children (100 severe falciparum malaria [with mean age 8.63 ± 3.40 years; 39% female], 100 uncomplicated falciparum malaria [with mean age 8.83± 4.20 years; 55% female] and 100 normal healthy children controls [with mean age 10.08 ± 3.58 years; 50% female]). The WBCs parameters measured using by Sysmex XP 300 N automated analyzer, and NLR counted by dividing absolute neutrophil count by the absolute lymphocytes count. The data were analyzed using SPSS software (V 20.0) and Stat disk software (V 13.0). Leukocytosis (34%) and increased NLR (30%) were observed in falciparum malaria cases. The mean of NLR in the falciparum malaria patients and control were $(3.47 \pm 3.51 \text{ and } 2.87 \pm 3.01 \text{ respectively})$ giving statistically significant difference in NLR between malaria cases and control (P value 0.000), while statistically insignificant differences in NLR between severe and mild malaria (P value 0.735). The study concluded that leukocytosis, increased NLR, absolute neutrophilia and absolute lymphocytopenia were observed as WBCs changes in falciparum malaria. Significant association was observed between development of severe falciparum malaria and absolute neutropenia. To improve management of severe malaria NLR may be recommended, along with others parameters, as predictive indicator for the disease severity among high risk groups.

Keywords— NLR, falciparum malaria, Sudanese children.

1. INTRODUCTION:

Falciparum malaria is one of the most world-wide infection leading to high mortality and morbidity especially in tropical regions. It was estimated that 99.7% of malaria cases is due to *P. falciparum*. According to World Health Organization, 285,000 children died before their fifth birthdays in Africa [1]. Furthermore, falciparum malaria cases among Sudanese patients was 87.6% [2].

Falciparum malaria associated with several hematological changes that affect the major blood cell lines such as red blood cells, white blood cells and platelets [3]. Among these changes lymphocytosis, lymphopenia and fluctuation in neutrophil count were frequently reported [4], which play a significant role in complication of malaria [5].

Neutrophil lymphocyte ratio (NLR) is a simple parameter to assess easily the inflammatory status of a subject. It is consider as strong prognostic and predictor factors for cancer and infectious diseases [6].

In the Sudan still a need for simple and readily available parameters for the early identification of patients at risk for severe or complicated malaria. The NLR data in malaria in Sudan are not yet available. Therefore, The present study report on assessment of NLR and it is role in falciparum malaria in Sudanese children.

2. METHODOLOGY:

The study was designed as case control study, conducted at Wad Medani Pediatric Hospital, Gezira State, Sudan on 300 Sudanese children. Samples were collected from 100 subjects previously diagnosed as severe *falciparum* malaria by blood film and WHO criteria [7]; 100 subjects previously diagnosed as uncomplicated *falciparum* malaria by blood film or ICT and 100 normal healthy controls according to inclusion and exclusion criteria.

All study procedures were approved by the Ethics Committees of Ministry of Health, Gezira State, Sudan. Informed consent was written from each participant parents.

A 2.5 ml venous blood samples were collected by clean venipuncture in K_3 EDTA containers. Thin and thick films were prepared immediately. Parasitemia and parasite count (%) was determined directly from thick and thin blood films respectively. White blood cells parameters were determined using the Sysmex XP 300 N automated hematology analyzer (Sysmex, Kobe, Japan). NLR was calculated by dividing absolute neutrophil count by the absolute lymphocytes count. The data were analyzed using SPSS software (V 20.0) and Stat disk software (V 13.0).

Leukocytopenia was defined as a leukocyte count of less than 3.5×10^9 /L and leukocytosis was defined as a leukocyte count exceeding 8.5×10^9 /L. Absolute neutropenia was defined as

absolute neutrophil count of less than 2.1×10^{9} /L and neutrophilia as absolute neutrophil count of more than 7.0×10^{9} /L. Absolute lymphocytopenia was defined as absolute lymphocyte count of less than 1.1×10^{9} /L and lymphocytosis as absolute lymphocyte count more than 3.0×10^{9} /L [8]. The Lower limit of neutrophil lymphocyte ratio was defined as NLR less than 0.78 and upper limit of neutrophil lymphocyte ratio was defined as NLR more than 3.53 [6].

3. RESULTS:

300 Sudanese children were participated on the study and allocated into complicated *falciparum* malaria (100), uncomplicated *falciparum* malaria (100) and normal healthy

children controls (100). Their demographic characteristics were depicted in Table 1. The hyperparasitemia represented 72 % in severe malaria, 18 % in uncomplicated malaria. Furthermore, the average of parasite count for severe and uncomplicated malaria were $(0.88 \pm 0.42 \text{ and } 0.39 \pm 0.30 \text{ respectively})$ (Table 1).

As show in table (2), the mean of TWBCs, absolute neutrophil count, absolute lymphocyte count and NLR in falciparum malaria cases were $(7.14 \pm 3.24 \times 10^{9}/L, 4.52 \pm 2.85 \times 10^{9}/L, 1.78 \pm 1.03 \times 10^{9}/L$ and 3.47 ± 3.51 respectively). On the other hand, the high NLR, leukocytosis, absolute neutrophilia and absolute lymphocytopenia were determined (34 %, 29 %, 16.5 % and 19 % respectively) in falciparum malaria cases (Table 3).

| Factors | Severe malaria | Uncomplicated malaria | Falciparum malaria |
|--------------------------------|----------------|-----------------------|-----------------------------------|
| | (SM) - N = 100 | (UM) - N = 100 | $\mathbf{All} - \mathbf{N} = 200$ |
| Age (years) | | | |
| Mean \pm SD | 8.63 ± 3.40 | 8.83 ± 4.20 | 8.73 ± 3.81 |
| Age group (years) | | | |
| Less than 5 years | 19 (19 %) | 24 (24 %) | 43 (21.5 %) |
| 6-10 years | 47 (47 %) | 41 (41 %) | 88 (44 %) |
| 11 - 15 years | 33 (33 %) | 29 (29 %) | 62 (31 %) |
| More than 15 years | 1 (1 %) | 6 (6 %) | 7 (3.5 %) |
| Gender | | | |
| Male | 61 (61 %) | 45 (45 %) | 106 (53 %) |
| Female | 39 (39 %) | 55 (55 %) | 94 (47 %) |
| Parasitemia | | | |
| + | 4 (4 %) | 43 (43 %) | 47 (23.5 %) |
| ++ | 3 (3 %) | 25 (25 %) | 28 (14 %) |
| +++ | 21 (21 %) | 14 (14 %) | 33 (16.5 %) |
| ++++ | 72 (72 %) | 18 (18 %) | 90 (45 %) |
| Parasite count (%) (Mean ± SD) | 0.88 ± 0.42 | 0.39 ± 0.30 | 0.64 ± 0.44 |

| Table 1: Demographic | characteristics of | study participants: |
|----------------------|--------------------|---------------------|
| | | |

Table 2: Description of WBCs parameters:

| Factors | Severe malaria (SM) – N= 100 | Uncomplicated malaria (UM) – N = 100 | Falciparum malaria All – N = 200 |
|---|---------------------------------|---|-------------------------------------|
| TWBCs \times 10 ⁹ /L (Mean \pm SD) | 6.74 ± 3.49 | 7.54 ± 2.92 | 7.14 ± 3.24 |
| Absolute neutrophil count \times 10 ⁹ /L (Mean | 4.23 ± 3.21 | 4.81 ± 2.42 | 4.52 ± 2.85 |
| ± SD) | | | |
| Absolute lymphocytes count $	imes$ 10 ⁹ /L | 1.71 ± 1.00 | 1.84 ± 1.07 | 1.78 ± 1.03 |
| $(Mean \pm SD)$ | | | |
| NLR (Mean \pm SD) | 3.39 ± 3.91 | 3.56 ± 3.09 | 3.47 ± 3.51 |

Table 3: Frequency of WBCs parameters:

| Parameters | Low | Normal | High | |
|--|-------------|--------------|-------------|--|
| TWBCs \times 10 ⁹ /L | 13 (6.5 %) | 129 (64.5 %) | 58 (29 %) | |
| Absolute neutrophil count $	imes 10^9$ /L | 29 (14.5 %) | 138 (69 %) | 33 (16.5 %) | |
| Absolute lymphocytes count \times 10 ⁹ /L | 38 (19 %) | 148 (74 %) | 14 (7 %) | |
| NLR | 14 (7 %) | 118 (59 %) | 68 (34 %) | |

The mean NLR, absolute neutrophil count and absolute lymphocyte count in falciparum malaria cases were $(3.47 \pm 3.51; 4.52 \pm 2.85 \times 10^{9}/L$, and $1.78 \pm 1.03 \times 10^{9}/L$ respectively) versus normal healthy control $(2.87 \pm 3.01, 3.65 \pm 1.38 \times 10^{9}/L$ and

 $2.29 \pm 0.69 \times 10^{9}$ /L respectively), giving statistically highly significant differences (P value 0.000, 0.004 and 0.000 respectively); while there was no significant difference in TWBCs between them (P value 0.330) (Table 4).

| Table 4: C | Comparison of | WBCs parameter | s between falcip | arum malaria | cases and control: |
|------------|---------------|-----------------------|------------------|--------------|--------------------|
| | | | | | |

| Parameters | Malaria (N=200) | Control (N=100) | P value * |
|--|-----------------|-----------------|-----------|
| | (Mean ± SD) | (Mean ± SD) | |
| TWBCs \times 10 ⁹ /L | 7.14 ± 3.24 | 6.79 ± 1.98 | 0.330 |
| Absolute neutrophil count \times 10 ⁹ /L | 4.52 ± 2.85 | 3.65 ± 1.38 | 0.004 |
| Absolute lymphocytes count \times 10 ⁹ /L | 1.78 ± 1.03 | 2.29 ± 0.69 | 0.000 |
| NLR | 3.47 ± 3.51 | 2.87 ± 3.01 | 0.000 |

* P value > 0.05

There were no significant differences in NLR, TWBCs, absolute neutrophil count and absolute lymphocyte count between severe malaria and uncomplicated malaria (P value 0.734, 0.080, 0.145 and 0.382 respectively) (Table 5).

The mean NLR in falciparum malaria parasitemia cases (+, +++, +++ and ++++) were $(2.53 \pm 2.62, 3.25 \pm 2.44, 4.82 \pm 4.99$ and

 3.52 ± 3.38 respectively) giving statistically significant differences between them (P value 0.032); while there was no significant differences in TWBCs, absolute neutrophil count and absolute lymphocytes count (P value 0.729, 0.414 and 0.050 respectively) (Table 6).

Table 5: Comparison of WBCs parameters between uncomplicated (UM) and severe falciparum malaria (SM):

| Parameters | UM (N=100) | SM (N=100) | P value * |
|--|-----------------|-----------------|-----------|
| | (Mean ± SD) | (Mean ± SD) | |
| TWBCs × 10 ⁹ /L | 7.54 ± 2.92 | 6.74 ± 3.49 | 0.080 |
| Absolute neutrophil count × 10 ⁹ /L | 4.81 ± 2.42 | 4.23 ± 3.21 | 0.145 |
| Absolute lymphocytes count $	imes 10^9$ /L | 1.84 ± 1.07 | 1.71 ± 1.00 | 0.382 |
| NLR | 3.56 ± 3.09 | 3.39 ± 3.91 | 0.734 |

* P value > 0.05

Table 6: Comparison of WBCs parameters between falciparum malaria parasitemia:

| Parameters | + | ++ | +++ | ++++ | P value * |
|--|-----------------|-----------------|-----------------|-----------------|-----------|
| | (N=47) | (N=28) | (N=35) | (N=90) | |
| TWBCs \times 10 ⁹ /L | 7.09 ± 2.66 | 6.99 ± 3.39 | 7.70 ± 3.64 | 6.99 ± 3.33 | 0.729 |
| Absolute neutrophil count × 10 ⁹ /L | 4.11 ± 2.17 | 4.49 ± 2.64 | 5.18 ± 3.30 | 4.49 ± 3.03 | 0.414 |
| Absolute lymphocytes count \times 10 ⁹ /L | 2.14 ± 1.02 | 1.59 ± 0.77 | 1.64 ± 1.24 | 1.70 ± 0.99 | 0.050 |
| NLR | 2.53 ± 2.62 | 3.25 ± 2.44 | 4.82 ± 4.99 | 3.52 ± 3.38 | 0.032 |

* P value > 0.05

NLR had no significant correlation within malaria parasitemia (P value 0.152), despite had statistically significant difference (P value 0.032). While, the absolute lymphocyte count had significant negative correlation within malaria parasitemia (P value 0.017; r -0.130), despite had statistically no significant difference (P value 0.050) (Table 7).

NLR, TWBCs, absolute neutrophil count and absolute lymphocyte count had no significant correlation within malaria parasite count (P value 0.808, 0.167, 0.173 and 0.270 respectively) (Table 7).

| Table 7. Correlation between which parameters and fattipar uni mataria parasitenna and parasite count. |
|--|
|--|

| Parameters | | TWBs | Absolute | Absolute | NLR |
|----------------|-------------------------|---------|------------|-------------|---------|
| | | | neutrophil | lymphocytes | |
| Parasitemia | Correlation coefficient | - 0.040 | - 0.002 | - 0.130 | 0.077 |
| | P value* | 0.454 | 0.972 | 0.017 | 0.152 |
| Parasite count | Correlation coefficient | - 0.067 | - 0.066 | - 0.055 | - 0.012 |

| | P value* | 0.167 | 0.173 | 0.270 | 0.808 |
|-----------------|----------|-------|-------|-------|-------|
| * P value > 0 | 0.05 | | | | |

22 % of severe malaria cases, had absolute neutropenia and 13 % had absolute neutrophilia. 7 % of uncomplicated malaria cases, had absolute neutropenia and 20 % had absolute neutrophilia; giving statistically difference between absolute neutrophil count frequency and malaria severity (P value 0.008) (Table 7). There were no significant differences between WBCs frequency, NLR frequency and absolute lymphocyte count among malaria severity.

| Table 8: Cross tabulation | between absolute neut | rophil frequency a | and falciparun | n malaria severity: |
|----------------------------------|-----------------------|--------------------|----------------|---------------------|
| | | - opini noquene, e | | |

| Parameters | UM | SM | Total | P value* |
|-----------------------|---------|---------|-------|----------|
| | (N=100) | (N=100) | | |
| Absolute neutropenia | 7 | 22 | 29 | 0.008 |
| Normal neutrophil | 73 | 65 | 138 | |
| Absolute neutrophilia | 13 | 20 | 33 | |
| Total | 100 | 100 | 200 | |

* P value > 0.05

4. DISCUSSION:

Falciparum malaria constitutes a major public health problem in Sudan, accounts 87.6%. Furthermore, 75% of population is at risk of developing falciparum malaria. The children are 3 times more likely to get malaria than adults.

The treatment outcome of malaria depends on appropriate early diagnosis and appropriate management with the recommended therapy to reduce deaths attributed to severe malaria.

The neutrophils and lymphocytes play vital role in induction of immune responses to falciparum malaria infection and their ratio (NLR) have been proven as predictors of malaria infection and its clinical severity.

High NLR, leukocytosis, absolute neutrophilia and absolute lymphocytopenia were observed (34 %, 29 %, 16.5 % and 19 % respectively) in falciparum malaria cases. The WBCs values (NLR, TWBCs and Absolute neutrophil count) were increased in falciparum malaria as compared to normal healthy control (P value 0.000, 0.330 and 0.004 respectively) except for absolute lymphocyte count (P value 0.000).

The increasing in TWBCs in malaria more than control may be due to an increase releasing of leukocytes at the initial stage of infection to fight against malaria infection and this related to the effective immune response to malaria in malaria endemic areas. Garba et al. reported the TWBCs was higher in falciparum malaria than controls [9]. In contrast disagree with Kini and Chandra study that showed the TWBCs was decrease in falciparum malaria than controls [10].

The increase in absolute neutrophil count in falciparum malaria could be due to a representation of early release of neutrophil from the bone marrow in response to the infection. Similar studies were showed increasing in neutrophil in falciparum malaria than control [10, 11].

In our patients was observed 19 % of patients had lymphopenia. Akhtar et al. reported that the 17 % of the patient had lymphopenia [4], furthermore Chaudry et al. reported that the 16.7 % of the patient had lymphopenia [12]; while Prasad et al. observed that the 11.1 % of the patient had lymphopenia [5]. These value was decreased in falciparum as compared with normal healthy control suggesting chronic stimulation of

lymphocytes by environmental microorganisms may be contributing through increased lymphocytes apoptosis that is also seen in healthy donors from endemic areas, or suggesting activated lymphocytes sequestering during malaria and this mechanism of lymphocyte depletion and sequestration are activated by plasmodium infection [13, 14], or is accompanied by an increase in neutrophil count which is usually considered as a sign of systemic inflammation [3, 15].

NLR was high in falciparum malaria cases (3.47 ± 3.51) as compared to normal healthy control (2.87 ± 3.01) (P value 0.000). This finding agree with study done in Ghana (P value 0.001) [3], Thailand (P value 0.001) [16], Germany (P value 0.001) [15]. And possibly causes accompanied by an increase in neutrophil count which is usually considered as a sign of systemic inflammation and decrease in lymphocytes [3, 15].

Despite slightly increased average of NLR in uncomplicated as compared with severe falciparum malaria $(3.56 \pm 3.09 \text{ and } 3.39 \pm 3.91 \text{ respectively})$ giving statistically insignificant difference between them (P value 0.734). This finding consistence with Louis Dias and Sumanth (4.34 for uncomplicated and 4.66 for severe) [17] and Berens-Riha et al. (P value 0.279) [15].

The WBCs values (NLR, TWBCs, absolute neutrophil count and absolute lymphocytes count) were increased in uncomplicated falciparum malaria as compared severe, but statistically there were no significant differences (P value 0.734, 0.080, 0.145 and 0.382 respectively). Frimpong et al. observed WBCs values were higher in severe falciparum malaria [18]. In contrast, van Wolfswinkel et al. observed WBCs values were higher in severe falciparum malaria [13].

The interesting finding were NLR had no significant correlation within malaria parasitemia (P value 0.152), despite had statistically significant difference (P value 0.032). While, the absolute lymphocyte count had significant negative correlation within malaria parasitemia (P value 0.017; r -0.130), despite had statistically no significant difference (P value 0.050). Otherwise there were no significant correlation between malaria parasitemia and TWBCs or absolute neutrophil. Antwi-Baffour et al., reported significant negative correlations between malaria parasitemia and absolute lymphocyte count (P value 0.030) [3]. In contrast van Wolfswinkel et al. reported significant correlations between

parasitemia and total leukocyte count or NLR, in addition, no significant correlations between parasitemia and absolute lymphocyte or neutrophil counts [13]. Kotepui et al., also reported NRL was correlate with malaria parasitemia [16].

Leukocytopenia in present study represent 13 % of falciparum cases (76.9 % in severe malaria compared to uncomplicated malaria). Similar results from previous study showed the leukocytopenia was 11.5 % [19].

Decreased NLR was observed in 71.4 % in severe malaria compared to uncomplicated malaria (P value 0.000). From 68 patients with increased NLR; 52 (76.5 %) have hyperparasitemia. From 58 patients with leukocytosis 37 (63.8 %) have hyperparasitemia.

The NLR, TWBCs, absolute neutrophil count and absolute lymphocyte count had no significant correlation within malaria parasite count (P value 0.808, 0.167, 0.173 and 0.270 respectively). Conversely, van Wolfswinkel et al. reported significant correlations between NLR and parasite count [13].

Neutropenia and neutrophilia were observed in 75.6 % and 61.1 % in severe malaria compared to uncomplicated malaria (P value 0.008). From 29 patients with absolute neutropenia 22 (75.6 %) have severe malaria and 19 (65.5 %) have hyperparasitemia. While from 33 patients with absolute neutrophilia 23 (69.7%) have hyperparasitemia. Absolute neutrophilia was represented 20 % in uncomplicated falciparum malaria cases. Prasad et al. reported neutrophilic predominance in cases positive for plasmodium simple malaria [5]. This finding possibly accompanied by association of severe malaria and hyperparasitemia with failure of production, alteration of distribution or abnormality of neutrophil life span in manner analogous to the mechanism of malaria anemia and malaria thrombocytopenia. This finding explained an increasing the average of NLR in uncomplicated as compared with severe falciparum malaria.

Lymphocytopenia and lymphocytosis were observed in 76.3 % and 57.1 % in hyperparasitemia.

Finally the age group had significant negative correlation with TWBCs, Absolute neutrophil count and absolute lymphocyte count (P value 0.001, 0.032 and 0.001 respectively) while insignificant correlation with NLR (P value). Similar result observed in pervious study [20]. A gradual decline in WBC counts in association with increasing age is a normal feature in most populations.

5. CONCLUSION:

The study was concluded that high NLR, leukocytosis, absolute neutrophilia and absolute lymphocytopenia were major changes associated with falciparum malaria among children in Sudan. Furthermore, absolute lymphocyte count had significant negative correlation within malaria parasitemia. While, severe falciparum malaria associated with absolute neutropenia.

The high NLR in falciparum malaria may help to be recommend this hematological marker as prognostic tool to assess the disease severity and to improve the management of complicated malaria among patients at high risk for the disease.

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