

Proteinuria and malaria parasite counts in children

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Abstract

Background Malaria-induced proteinuria has been observed in severe cases of malaria. Few studies have been done to assess for an association between proteinuria and malaria parasite counts before the disease becomes severe.

Objective To investigate a possible association between proteinuria and malaria parasite counts in children.

Methods A cross-sectional study was conducted on school-aged children in Panyabungan, Mandailing Natal, between September to November 2010. Malaria was diagnosed by microscopic examination of peripheral blood smears. Children with malaria underwent proteinuria tests by urine dipstick method. An association between proteinuria and malaria parasite counts was analyzed using linear regression test.

Results Of 181 participants with *Plasmodium falciparum* malaria, 53.6% were female and had a mean age of 7.8 years. Subjects' nutritional status were as follows: 50.8% normoweight, 28.2% mild malnutrition, 3.3% moderate malnutrition, and 17.7% severe malnutrition. Clinical manifestations showed 36.5% suffered from subfebrile temperatures and 29.8% had pallor. Proteinuria occurred in 45.9% participants and there was a weak association between proteinuria and malaria parasite counts ($r = .261$, $P = .0001$).

Conclusion There is a weak association between proteinuria and malaria parasite counts in children.

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Keywords: proteinuria, malaria, *Plasmodium falciparum*, kidney involvement

Malaria, an infection caused by *Plasmodium* species, is one of the most common parasitic diseases causing morbidity and mortality in tropical regions.^{1,2} Its prevalence in Indonesia varies by region.³ The *Riset Kesehatan Dasar* (Basic Health Research) 2007 reported a 3% malarial prevalence in Sumatera Utara. The Mandailing Natal District was the second highest malaria-infested area in Indonesia, with the highest prevalence malaria was found in Panyabungan, Panyabungan Utara, and Siabu area.^{4,5}

Kidney involvement in malaria infections varies widely, from asymptomatic proteinuria to acute renal failure (ARF).¹ Only two malaria parasites, namely, *P. malariae* (quartan malaria) and *P. falciparum* (falciparum malaria), have been clearly associated with kidney diseases.⁶ Kidney complications may include glomerular endothelial activation and damage, as well as tubulointerstitial damage, leading to inadequate permeability and tubular reabsorption. These condi-

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tions ultimately lead to excessive protein expenditure.^{2,6-8} Some studies found no significant association between proteinuria and the degree of parasitemia,^{1,9} while there was a positive correlation between malaria infection and creatinine levels.¹ However, another study found a significant difference in proteinuria between patients with and without malaria, but no significant difference in creatinine levels between the two groups.¹⁰ The aim of this study was to assess for an association between proteinuria and malaria parasite counts in children.

Methods

We conducted a cross-sectional study on school-aged children in Panyabungan, Mandailing Natal, Sumatera Utara Province between September and November 2010. We recruited 181 children by consecutive sampling who were aged 6 to 15 years and had falciparum malaria parasites in their peripheral blood smears, and had parents or guardians who provided informed consent. We excluded subjects who had clinical heart or kidney diseases, edema, were active in sports, or had taken medicines that affected the kidneys. This study was approved by the Ethics Committee for Research of the Medical Faculty, University of Sumatera Utara.

Subjects underwent blood examinations for plasmodium identification after the taking of blood smears from their fingertips. This procedure was performed by trained laboratory technicians. Subjects with plasmodium in their blood smears underwent urine proteinuria examinations by dipstick method then were given anti-malarial medication.

Parasite counts was performed as the amount of malaria parasites found among 200 leucocytes, while proteinuria levels were expressed as negative, trace (equal to 0.15 g), positive + (equal to 0.30 g) and positive ++ (equal to 1.0 g).

Data was processed and analyzed with SPSS version 17.0, and presented in text, figures, and tables. An association between proteinuria and malaria parasite counts was analyzed using linear regression test. A P value of < 0.05 was considered to be statistically significant with a 95% confidence interval (95% CI).

Results

During the study periode there were 280 children with confirmed malaria parasites from peripheral blood smears and all were *Plasmodium falciparum*. Of these patients, 47 children did not provide urine specimens, 34 children did not return the questionnaire forms, and 18 children refused to participate. Hence, there were 181 subjects in our study, with a mean age of 7.8 (SD 1.43) years, more girls than boys, and most were well-nourished. Specific clinical symptoms for malaria such as fever and pallor were not significantly found. We obtained proteinuria in 45.9% of the subjects (Table 1).

We evaluated for an association between proteinuria and malaria parasite counts by linear regression test and found a weak association ($r = .261$, $P = .0001$) (Figure 1).

Table 1. Characteristics of subjects

Characteristics	n = 181
Mean age (SD), years	7.8 (1.43)
Gender, n (%)	
Male	84 (46.4)
Female	97 (53.6)
Nutritional status, n (%)	
Well-nourished	92 (50.8)
Mild malnutrition	51 (28.2)
Moderate malnutrition	6 (3.3)
Severe malnutrition	32 (17.7)
Subfebrile, n (%)	66 (36.5)
Pallor, n(%)	54 (29.8)
Malaria parasite count/200 leukocytes, n (%)	
<500	23 (12.7)
500-750	8 (4.42)
751-1000	29 (16.02)
1001-1250	50 (27.62)
1251-1500	63 (34.81)
>1500	8 (4.43)
Proteinuria, n (%)	
Negative	98 (54.1)
Trace (0.15 g)	53 (29.3)
1+ (0.3 g)	25 (13.8)
2+ (1.0 g)	5 (2.8)

Discussion

Clinically, symptoms of single malaria infections in non-immune patients consist of several bouts of fever in a certain interval (paroxysm), punctuated by a period free of fever (latent period).¹¹ Malarial symptoms differ

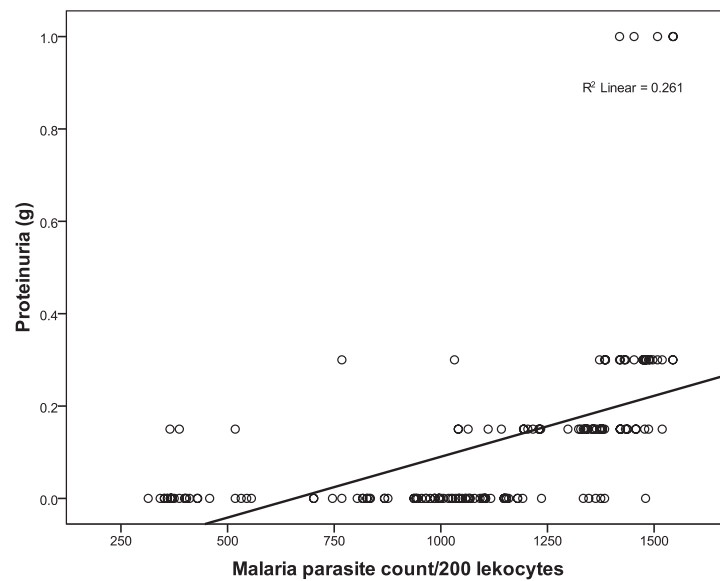


Figure 1. The association between proteinuria and malaria parasite counts

in people with partial and no immunity. For those with no immunity, such as tourists, parasitemia induces significant symptoms, and the magnitude of parasitemia has been associated with mortality and complications. However, people with partial immunity may have few or no symptoms.⁵

Our study was conducted in a malaria-endemic area. No significant specific symptoms, such as fever or pallor, were found in children with malarial infections, some even had no symptoms. Subfebrile temperature and pallor were found in 36.5% and 29.8% of the children, respectively. In contrast, previous studies reported that 92-100% of subjects had fever, and 91% of subjects had pallor.¹²⁻¹⁴

Falciparum malaria is a microvascular disease with a strong metabolic component, as infected erythrocytes have greater cytoadherence to endothelial capillaries, causing functional microvascular obstruction. Cytokines, such as tumor necrotizing factor (TNF)- α , have a role in increasing the molecular receptors of endothelial cells, leading to increased cytoadherence and obstruction. As such, subsequent tissue hypoxia and hypoglycemia may complicate brain, lung, and kidney function.²

Kidney involvement in malaria varies widely, from electrolyte abnormalities, or increased proteinuria to

acute renal failure (ARF).^{15,16} The incidence of ARF in these patients reportedly varied from 2.3-17.2%. Kidney dysfunction in the form of albuminuria has been seen in 20-90% of patients with *P. falciparum* infection.¹ A previous study found that malaria-associated renal failure was a common and serious complication of severe *Plasmodium falciparum* malaria.¹⁷ In addition, a retrospective study reported that 38% of malaria-induced acute renal failure patients had proteinuria more than 1 g/24 hours.¹³ A Nigerian study reported that mild proteinuria occurred in 40% of acute falciparum malaria patients, with no relationship between proteinuria and peripheral parasite density.¹⁸ However, other Nigerian studies showed positive correlations between proteinuria and malaria parasitemia.^{19,20}

In the 45.9% of subjects with proteinuria in our study, there was a positive association between proteinuria and malaria parasite counts. No leukocyturia cases were found among our subjects, that would suggest a concurrent presence of urinary tract infections. As such, we suggest that the proteinuria in these cases was malaria-induced proteinuria. We used a dipstick urine test for proteinuria because of it was sensitive, easy to use, inexpensive, and yielded quick results. Past studies found dipstick urinalysis to be a reliable

screening method, but not a good diagnostic method for detection of proteinuria, due to its excellent sensitivity but poor specificity.²¹⁻²³ As such, further investigations should be made on pediatric malaria patients using more specific tests for proteinuria.

In conclusion, we observe a weak association between proteinuria and malaria parasite counts in children. Further research by using a gold standard method for assessing proteinuria is required to explore this association.

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