CLINICAL CHARACTERISTICS, PARASITE DIAGNOSIS AND HEMATOLOGICAL PARAMETERS OF MALARIA IN SURAT THANI PROVINCE, THAILAND

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ABSTRACT:

Background: Malaria infection is still considered to be a major public health problem in Thailand where risk of infection is related to one or more of the *Plasmodium* species. In this study, a retrospective clinical and laboratory based data analysis of malaria patients at Phanom Hospital, Surat Thani Province, Thailand was collected and analyzed.

Methods: Data of patients with malaria infection during the period 2012-2015 were retrieved. This data included demographic details (age of patient, gender, and nationality), clinical characteristics, parasite diagnosis (days of fever, time of admission, diastolic pressure, body weight, and body mass index), and hematological parameters (hemoglobin, hematocrit, and Mean corpuscular hemoglobin concentration [MCHC]).

Results: A total of 395 malaria patients were recorded during the years 2012 to 2015. Most of them were admitted to Phanom Hospital during 2013 (215 cases, 54.4%). The mean age of patients was 30.6±17.1 years old. Most patients were male (253 cases, 64.1%) and of Thai nationality (349 cases, 88.4%). Mean days of fever before patients came to hospital was 4 days. Most patients (262 cases, 66.3%) came to hospital between 6 am-11.59 am. Three hundred and fifty-five patients with malaria (97.5%) were positive for *Plasmodium falciparum* infection. All three hematological parameters (hemoglobin, hematocrit and MCHC) were significantly lower (*P value*<0.05) in patients with *P.falciparum* compared to patients with *P.vivax*. Neutrophils count and Mean corpuscular volume (MCV) were significantly decreased in patients who came late to hospital (*P value*<0.05). In addition, lymphocyte and monocytes were significantly increased in patients who came late to hospital (*P value*<0.05)**.**

Conclusion: During the years of 2012 to 2015, patients infected with falciparum malaria was highest in the year 2013. Hemoglobin, hematocrit, and MCHC were significantly lower in patients with *P.vivax* compared to *P.falciparum*. Neutrophils, lymphocyte, monocytes, and MCV were significantly changed in patients who came late to hospital. This information would assist in understanding the pathogenesis and characteristic of malaria infection in Southern Thailand.

Keywords: Malaria; Clinical characteristic; Parasite ciagnosis; Hematological parameters; Thailand

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INTRODUCTION

Malaria infection is still a major public health problem in Thailand where the risk of infection related to one or more of the *Plasmodium* species. There are 5 species of *Plasmodium* that can infect humans, i.e., *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*

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and *Plasmodium knowlesi* [1]. In endemic areas, the most common symptom of malaria is fever, followed by nonspecific symptoms, including chills, headache, myalgia, nausea, and vomiting. Diarrhea, abdominal pain, and cough are occasionally seen [2]. Most patients with uncomplicated or non-severe infections have few abnormal physical symptoms other than fever, mild anemia, and, after several days, a palpable spleen. The liver can become enlarged, especially in young children, whereas mild jaundice is more likely in adults. In young children living in regions in which transmission is stable, recurrent infections cause chronic anemia and splenomegaly [3]. Currently, malaria diagnosis can be performed by clinical diagnosis and laboratory diagnosis.

Clinical diagnosis is the most commonly used, as well as the least expensive method. Clinical diagnosis is based on the patients' signs, symptoms, and on physical findings at examination. The earliest symptoms of malaria are very nonspecific and variable include fever, headache, weakness, myalgia, chills, dizziness, abdominal pain, diarrhea, nausea, vomiting, anorexia, and pruritus [4]. However, the similarity of malaria signs and symptoms with other tropical diseases impairs its specificity. Clinical diagnosis would lead to indiscriminate use of anti-malarial drugs for managing febrile conditions in endemic areas [5, 6]. In term of accuracy, a clinical diagnosis is varying with the level of malaria endemicity, season, and age group of patients which no single clinical algorithm is a universal predictor for malaria infection [7, 8].

Laboratory diagnosis of malaria infection, thick and thin blood smears stained with Wright-Giemsa dye, is the most common procedure which used to of detecting malaria parasite. Currently, it still remains the standard method for diagnosing malaria [9]. In term of diagnostic accuracy, blood films examination relies on the quality of the blood smear and experience of laboratory personnel. In case of microscopic technique is not available, Rapid diagnostic test (RDT) is a choice for malaria detection. The RDT is a device that can detects malarial antigen in a small amount of blood by immune-chromatographic assay,, which could be completed within 5–20 min [10]. The commercial RDT dipsticks are available and frequently uses in routine diagnostic laboratory such as OptiMAL [11], ICT [12], Para-HIT-f [13], ParaScreen [14], SD Bioline [15], Paracheck [16]. Moreover, a molecular diagnostic method, such as polymerase chain reaction (PCR) are also developed with higher sensitivity when compared to the blood film examination [17]. However, disadvantages of PCR related to its cost-effectiveness.

Phanom Hospital is a primary hospital located in Phanom District (Amphoe) in the southwest of Surat Thani Province of southern Thailand. It is located within the hills of the Phuket mountain range, with around 60% of the area consisting of mountains and forests. These environments lead to transmission of malaria in this area. Surat Thani was the top 8 provinces in Thailand with high incidence of malaria infection in the recent year [18].

This study, a retrospective clinical and laboratory data of patients with malaria at Phanom Hospital in Surat Thani Province, Southern part of Thailand were investigated and analyzed.

MATERIAL AND METHODS

Ethical approval of research protocol was approved by the Ethical Committee of Surat Thani Provicial Health Office (EC code: STPHO2016-001; Approval date: April 19, 2016) and the Ethical Clearance Committee on Human Rights Related to Researches Involving Human Subjects of Walailak University (EC code: 16/019; Approval date: May 17, 2016). A retrospective data of patients who admitted and diagnosed with malaria infection during 2012-2015 at Phanom Hospital, Surat Thani province, Thailand, was under investigated. These data included demographic data, clinical characteristics, results of thick/thin film examination, and hematological parameters from automate blood cell analyzer. Demographic data included age of patients, gender, and nationality. Clinical characteristics included days of fever, time of patients admitted, diastolic pressure, body weight, and body mass index (BMI). Medical diagnosis (signs and symptoms) was firstly performed by on-duty physicians according to clinical presentations of patients. This medical diagnosis was as followed: Fever with unspecified, unspecified malaria, *P. falciparum* malaria with unspecified, *P. vivax* malaria without complications, *P. falciparum* with cerebral complications, Malaria due to simian plasmodia, *P. malariae* malaria without complication.

All patients were referred to the medical laboratory of Phanom Hospital for collecting blood for the detection of malaria parasite. The venous blood samples were drawn into EDTA tubes for

Table 1 Clinical data of malaria patients

Clinical data	Frequency (%), n=395
Year	
2012	29 (7.3)
2013	215 (54.4)
2014	122 (30.9)
2015	29 (7.3)
Age (mean±SD)	30.6±17.1
<20	111 (28.1)
20-29	90 (22.8)
30-39	76 (19.2)
40-49	63 (15.9)
≥ 50	55 (13.9)
Gender	
Male	253 (64.1)
Female	142 (35.9)
Nation	
Thai	349 (88.4)
Non-Thai	46 (11.6)
Fever	
Yes	354 (89.6)
No	41 (10.4)
Days of fever before admitted (mean±SD)	3.62±2.73
Time admitted	
6 am-11.59 am	262 (66.3)
12.00 am-5.59 pm	115 (29.1)
6.00 pm-11.59 pm	18 (4.6)
Diastolic pressure (mean±SD)	68.9 (10)
Body weight (mean±SD)	55.2 (11.5)
Body mass index (BMI) (mean±SD)	22.2 (4.64)

preparation of the thick and thin smears following by Wright-Giemsa stain. Laboratory confirmation of malaria parasite was based on the microscopic examination of stained thin and thick blood films. The results turned out as *Plasmodium* sp. with parasite density. Hematological parameters were obtained from Hematology Analyzer providing data on white blood cells (WBC) with five part differentials, red blood cells (RBC), platelets, red cell distribution width (RDW), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), and hemoglobin (Hb).

Statistical analysis was performed to present frequency, proportion, data tendency, and also difference between groups of patients. For continuous variable, the normality of data was tested using Kolmogorov-Smirnov Test. Difference between groups was analyzed using The Mann-Whitney U Test. Categorical data were analyzed using Fisher's exact Test. All analysis was run using SPSS ver. 11.5 (SPSS Inc., Chicago, IL, USA) with *P value* less than 0.05 considered statistical significant.

RESULTS

Clinical characteristic of patients were shown in Table 1. Briefly, 395 patients with malaria were recorded. Most of patients admitted at Phanom Hospital in year 2013 with 215 cases (54.4%), followed by 122 cases (30.9%) in 2014, 29 cases (7.3%) in 2012, and 29 cases (7.3%) in 2014, respectively. Mean age of patients was 30.6±17.1 years old. Most of patients were male (253 cases, 64.1%) and Thai nation (349 cases, 88.4%). Three hundred fifty four patients (89.6%) got fever when admitted at the hospital, and 41 cases were patients with no fever. For patients with fever, mean days of fever in day of admission was about 4 days. Most of patients (262 cases, 66.3%) admitted at hospital during the morning hours (6 am-11.59 am) of the day, following by the afternoon hours (12.00 am-5.59 pm) of 115 cases (29.1%), and the evening hour (6.00 pm-11.59 pm) of 18 cases (4.6%), respectively.

Medical diagnosis according to sign and symptoms was firstly performed by on-duty physicians. Most of patients were diagnosed as *P. falciparum* malaria with unspecified (362 cases,

Table 2 First medical diagnosis according to clinical characteristic of patients

Parameters	Frequency (%), n=395
Plasmodium falciparum malaria, unspecified	362 (91.6)
Unspecified malaria	13 (3.3)
Plasmodium vivax malaria without complications	10 (2.5)
Plasmodium falciparum malaria with cerebral complications	5 (1.3)
Malaria due to simian plasmodia	1 (0.3)
Plasmodium malariae malaria without complication	1 (0.3)
Fever, unspecified	3 (0.8)

Table 3 Confirmatory diagnosis of malaria by hospital laboratory

Parameters	Frequency (%), n=395
***Plasmodium* spp.**	
P.falciparum	385 (97.5)
P.vivax	9 (2.28)
P.malariae	1 (0.25)
Parasite density (mean±SD)	0.07(0.14)

Table 4 Hematological parameters of infected cases

Parameters*	*P. falciparum* Mean±SD	*P. vivax* Mean±SD	*P value***
WBC ($x10^3/\mu L$)	5.56±1.75	6.01±2.42	0.602
Neutrophil ($x10^3/\mu L$)	3.87±2.53	4.27±2.23	0.764
Lymphocyte ($x10^3/\mu L$)	1.18±0.73	1.14±0.68	0.892
Monocyte ($x10^3/\mu L$)	0.45±0.25	0.47±0.23	0.473
Eosinophil ($x10^3/\mu L$)	0.11±0.14	0.07±0.08	0.107
Basophil ($x10^3/\mu L$)	0.05±0.05	0.05±0.04	0.438
RBC ($x10^6/\mu L$)	5.08±3.65	4.39±0.73	0.057
Hemoglobin (g/dL)	13.4±1.64	11.3±1.91	0.002
Hematocrit (%)	40.9±19.2	34.5±5.54	0.004
MCV (fL)	82.1±9.55	79.5±11.4	0.597
MCH (pg/cell)	27.5±3.13	26±4.1	0.359
MCHC (g/dL)	33.4±1.15	32.7±0.71	0.046
Platelet ($x10^3/\mu L$)	130.8±64.3	97.8±36.5	0.110

*no data of *P.malariae*

** *P value* by The Mann-Whitney U Test

91.6%), following by Unspecified malaria (13 cases, 3.3%), *P. vivax* malaria without complications (10 cases, 2.5%), *P. falciparum* malaria with cerebral complications (5 cases, 1.3%), Malaria due to simian plasmodia (1 cases, 0.3%), *P. malariae* malaria without complication (1 cases, 0.3%), and fever with unspecified symptom (3 cases, 0.8%) (Table 2).

The results of blood-smear samples showed that all patients were positive for *Plasmodium* spp. by microscopic examination under microscope. Three hundred and eighty-five patients (97.5%) were positive with *P. falciparum*, following by 9 cases (2.28%) with *P. vivax*, and 1 case (0.25%) with *P. malariae*. The mean parasite density was 0.07 percent (Table 3).

Comparison of hematological parameters between *P. falciparum* and *P. vivax* were shown in Table 4. Hemoglobin, hematocrit, and MCHC were significantly lower (*P value*<0.05) in patients with *P. vivax* compared to *P. falciparum.* Mean hemoglobin level of patients with *P. vivax* (13.4 g/dL) was lower than those with *P. falciparum* (11.3 g/dL). Mean hematocrit of patients with *P. vivax* (40.9%) was higher than those with *P. falciparum* (34.5%). Mean MCHC level of patients with *P. vivax* (33.4 g/dL) was lower than those with *P. falciparum* (32.7 g/dL). No significant change of WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophil, RBC, MCV, MCH, and platelet was found (*P value*>0.05). Hematological parameters of patient with *P. malariae* could not be obtained.

Table 5 Hematological parameters of infected cases with different day of fever

Parameters*	Fever ≤ 3days Mean±SD	Fever > 3days Mean±SD	*P value***
WBC (x10^3/µL)	5.56±1.74	5.62±1.81	0.842
Neutrophil (x10^3/µL)	4.17±3.21	3.66±1.51	0.026
Lymphocyte (x10^3/µL)	1.02±0.69	1.32±0.74	<0.001
Monocyte (x10^3/µL)	0.42±0.27	0.48±0.04	0.003
Eosinophil (x10^3/µL)	0.1±0.13	0.12±0.16	0.396
Basophil (x10^3/µL)	0.05±0.05	0.05±0.04	0.105
RBC (x10^6/µL)	4.87±0.63	5.35±5.67	0.663
Hemoglobin (g/dL)	13.4±1.72	13.1±1.68	0.268
Hematocrit (%)	40.1±5.04	41.5±29.5	0.174
MCV (fL)	82.9±9.1	80.3±10.1	0.032
MCH (pg/cell)	27.6±3.2	27.1±3.13	0.169
MCHC (g/dL)	33.3±1.16	33.5±1.12	0.085
Platelet (x10^3/µL)	130.4±72.2	129.7±54.4	0.806

*no data of *P.malariae*

***P value* by The Mann-Whitney U Test

Table 6 Parameters of infected cases with different time of admitted

Parameters*	Admitted time			*P value***
	6 am-11.59 am Mean±SD	12.00 am-5.59 pm Mean±SD	6.00 pm-11.59 pm Mean±SD	
Age	31.4±16.2	29.4±19	26.7±2.38	0.176
BPD	69±9.72	68.9±10.8	66.1±9.16	0.384
Body weight	56.7±16.7	52.4±19	51.5±17.1	0.075
BMI	22.5±4.49	22±4.75	20.7±5.93	0.427
WBC (x10^3/µL)	5.44±1.72	5.95±1.87	4.96±1.45	0.017
Neutrophil (x10^3/µL)	3.59±1.44	4.24±1.67	6.02±9.77	0.001
Lymphocyte (x10^3/µL)	1.24±0.73	1.09±0.73	0.78±0.35	0.002
Monocyte (x10^3/µL)	0.45±0.26	0.45±0.24	0.37±0.17	0.503
Eosinophil (x10^3/µL)	0.11±0.13	0.12±0.15	0.07±0.11	0.175
Basophil (x10^3/µL)	0.05±0.05	0.04±0.03	0.03±0.18	0.001
RBC (x10^6/µL)	4.89±0.63	5.48±6.62	4.9±0.63	0.963
Hemoglobin (g/dL)	13.4±1.65	13.2±1.79	13±1.38	0.401
Hematocrit (%)	40.1±4.93	42.7±34.4	39±4.13	0.511
MCV (fL)	82.4±9.41	81.3±10.3	80.1±6.68	0.264
MCH (pg/cell)	27.5±3.24	27.4±3.07	26.8±2.38	0.364
MCHC (g/dL)	33.4±1.1	33.4±1.25	33.4±1.19	0.88
Platelet (x10^3/µL)	130.5±67.9	131.8±56.9	111.3±43.97	0.609

BPD=blood pressure diastolic, BMI=body mass index

*no data of *P.malariae; ** P value* by The Kruskal Wallis Test

Comparison of hematological parameters and days of fever before admission were shown in Table 5. Neutrophils, lymphocytes, and monocytes count were significantly changed when patients with fever ≤ 3days compared with patients with fever >3 days (*P value*<0.05). Mean of neutrophils count (3.66 x10^3/µL) in patients with fever >3 days were significantly lower than those with fever ≤ 3days (4.17 x10^3/µL), whereas, means of lymphocytes (1.32 x10^3/µL), and monocytes count (0.48 x10^3/µL) in patients with fever >3 days were significantly higher than those with fever ≤ 3days with lymphocytes (1.02 x10^3/µL), and monocytes (0.42x10^3/µL). Mean of MCV in patients with fever >3 days (80.3 fL) was significantly lower than those with fever ≤ 3days (82.9 fL).

Comparison of clinical characteristic and hematological parameters with time of admission was shown in Table 6. Neutrophils count was significantly raised in patients who admitted during 6.00 pm-11.59 pm (6.02 x10^3/µL) as compared to patients who admitted during 6 am-11.59 am (3.59

x10^3/µL) and during12.00 am-5.59 pm (4.24 x10^3/µL) (P value=0.001). Lymphocytes count was significantly lower in patients who admitted during 6.00 pm-11.59 pm (0.78x10^3/µL) as compared to patients who admitted during 6 am-11.59 am (1.24x10^3/µL) and during12.00 am-5.59 pm (1.09 x10^3/µL) (*P value*=0.002). Basophils count was significantly lower in patients who admitted during 6.00 pm-11.59 pm (0.03x10^3/µL) as compared to patients who admitted during 6 am-11.59 am (0.05x10^3/µL) and during 12.00 am-5.59 pm (0.04 x10^3/µL) (*P value*=0.002).

DISCUSSION

This study investigated the clinical characteristics, parasite diagnosis and hematological parameters of patients with malaria admitted at Phanom Hospital in Surat Thani Province, Southern of Thailand. From analysis of demographic data, most of patients were in adults of ≥30 years old) which slightly higher when compared to the previous study [19] which was reported in western Thailand (mean 26 years old). Age of patients was significantly associated with the risk for developing severe disease. This study found that patients with age <20 years old were frequency admitted at the hospital when compared to other age groups. This showed the trend of malaria infection was gradually decreasing with age. This trend was supported by a previous study reported that malaria incidence rose with age until the late teens, and either remained constant or decreased in young adults [20]. The possible cause of lower rate of malaria infection in adults was that some adults in high transmission areas are less susceptible to malaria attack due to the acquisition of some immunity early in life [20]. In endemic malaria areas, the peak of incidence at a much younger age is thought to be associated with the acquisition of clinical immunity due to intense challenge of the immune system early in life, when other protective mechanisms may still be operating [21]. In term of mortality rates due to malaria attack, a previous study [22] reported that the number of severe cases increased with age: 3.2% with patients <30 years old; 5.3% with patients 30–39 years old; 9.8% with patients 40-49 years old; and 23.5% with patients ≥ 50 years old. However, one study [23] indicated mortality from malaria was highest in the youngest (<2 years) and oldest age groups (>40 years). For an analysis of gender, male incidence was higher than female. When considered the gender of patients as a risk factor for malaria, it's always with conflicting results. The possible high incidence in male patients may cause by labour, leisure patterns, and sleeping arrangements may lead to different patterns of exposure to mosquitoes for men and women [24]. In some societies, men have a greater occupational risk contracting malaria than women if they work in mines, fields or forests at peak biting times, or migrate to areas of high endemicity for work [25]. Moreover, previous studies [26, 27] reported that the risk for disease severity and mortality was higher in female patients.

Fever is the universal screening symptom for malaria. In this study, almost 90% of patients came to hospital with history of fever. For the clinical diagnosis in this study, most of patients (91.6%) were diagnosed as *P. falciparum* malaria with unspecified symptoms. Some patients (8.4%) were miss-diagnosed. This may due to, in part, associated with non-specific nature of the signs and symptoms. Following definitive diagnosis of malaria by microscopic method, patients with *P. falciparum* was the most frequency found (98%). This proportion was higher than a previous report in western Thailand (50%) [19]. Different countries reported different proportion such as the study in Brazil which found *P. falciparum* (70%) [28]; Ethiopia (82%) [29]; and China (55%) [30]. Falciparum malaria infection which cause severe malaria is associated with a 7-32% mortality rate depending on organ/systems involved [31].

For hematological parameters of infected cases, hemoglobin, hematocrit, and MCHC were significantly difference. Hemoglobin, hematocrit, and MCHC were higher in patients with falciparum malaria. This was contrast to another study which reported similar level of those parameters in Tak, western part of Thailand. However, only small number of patients with *P.vivax* (9 patients) were found in this study. When comparing between hematological parameters of infected cases and day of fever, neutrophils were significantly increased in patients with fever ≤ 3days and decreased in patients with fever > 3days. This was supported by one study [32] which reported that acutely falciparum infected children had a significant fall in the mean neutrophil count on Day 3. The underlying mechanisms include a shift in neutrophils from the circulatory to the marginal pool to sites of inflammation, splenic localisation, serum lymphotoxic factors which in turn cause lower neutrophil in the blood [33]. While, the lymphocytes were significant lower in patients with fever ≤ 3days. It can be explained that the

lymphocytes depletion in malaria infected patients during the acute phase of the disease were the sequestration of lymphocytes to lymph nodes or other body parts and abnormal cell death through apoptosis [34]. Monocytes were also significant higher in patients with fever > 3days. This may be due to ingestion of malaria pigment by monocytes or macrophages which were observed in blood and bone marrow of infected cases [32]. In addition, phagocytosis of infected and uninfected red cells by monocytes/macrophages had also been observed [35]. MCV of patients with fever > 3days were higher than those of with fever ≤ 3days. This may be supported by higher rate of erythrocyte production in the bone marrow and release young erythrocyte in the blood [36].

Our results also showed lowest neutrophils count in patients admitted at hospital in the morning. However, highest neutrophils count was found in patients who admitted at hospital in the evening. In contrast to neutrophil, lymphocyte and basophils were highest in patients admitted at hospital in the morning. Their levels were lowest in patients admitted at hospital in the evening. A previous study [37] reported fluctuations in the concentrations of peripheral blood immune cells that granulocyte levels were highest in the evening at 6 pm while lymphocyte levels either peaked in the evening or at midnight which as contrast to results of this study that lymphocyte levels were highest in the morning. This Abnormal fluctuation of lymphocyte may suggest their main role during malaria infection. However, further study need to validate this fluctuation in vivo and in vitro study.

CONCLUSION

During the year 2012 to 2015, the highest number of malaria cases was recorded in 2013. Most of patients came to hospital during the morning hours (6 am to 11.59 am). *P. falciparum* with uncomplicated symptoms were mostly found in those patients with malaria. Hemoglobin, hematocrit, and MCHC were significantly lower in patients with *P. vivax* compared to *P. falciparum*. Neutrophils count and MCV were significantly drops in patients came late to hospital. In contrast, lymphocyte and monocytes counts were significantly raised in patients came late to hospital. This information will guild to understanding pathogenesis and characteristic of malaria infection in Sothern Thailand.

LIMITATIONS

The hematological data of *P. malariae* could not be obtained. However, the results of this study still provide valuable information regarding clinical presentation, clinical diagnosis, and laboratory diagnosis of malaria in southern regions of Thailand.

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