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Characteristics of Asymptomatic Malaria in Eastern Indonesia: A Cross-sectional Study

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Abstract

Background: Asymptomatic malaria predominates in the malaria-endemic region. Asymptomatic malaria is defined as an individual with confirmed-malaria test yet has no fever at the time of sample collection. Despite the absence of fever, other malaria-related symptoms can be present in an asymptomatic individual. The absence of fever leads to a low proportion of asymptomatic malaria case findings. Unfound and untreated asymptomatic malaria may lead to a decrease of hemoglobin level that progresses to anemia. It is necessary to find out those symptoms since it may aid asymptomatic malaria finding. This study was conducted to identify malaria-related symptoms other than fever and its potential contributing factors, as well as hemoglobin level in asymptomatic malaria subjects in eastern Indonesia.
Methods: This was a cross-sectional study using secondary random sampling data from the previous study in East Nusa Tenggara, Indonesia. Descriptive statistics, bivariate and multivariate analyses were carried out to analyze the data.
Results: 178 asymptomatic malaria data were included in the study. The most frequent symptoms were headache (18.8%), chills, and myalgia (12.4%). P. vivax was the most prevalent etiologic agent (52.5%). The risk of developing any symptom increased in P. vivax infection (OR =1.16, 95% CI=0.38-3.50), in the presence of anemia (OR=1.30, 95% CI=0.58-2.73), and in the presence of breeding sites (OR=1.04, 95% CI=0.40-2.66). Conclusion: malaria-related symptoms other than fever were found in asymptomatic malaria thus it may help the case finding and management as well as aid the malaria elimination program be easier to reach.

Keywords: asymptomatic malaria, hemoglobin level, malaria case finding, plasmodium

1. INTRODUCTION

Malaria is a vector-borne disease that endemic in various countries around the world, including Indonesia.[1] WHO reported 228 million malaria-confirmed cases that cause more than 405.000 death globally in 2018. In addition, The Ministry of Health of Indonesia reported 222.085 malaria-confirmed cases in 2018. The vast majority of malaria cases in Indonesia occurred in eastern Indonesia, particularly in Papua, West Papua, and East Nusa Tenggara provinces.[2]

The clinical status of malaria ranges from asymptomatic malaria, mild symptomatic malaria to severe symptomatic malaria.[3] This wide range of clinical status of malaria is influenced by various factors including the type of *Plasmodium*.[4] Clinically, asymptomatic malaria is defined as an individual with confirmed-malaria test yet has no fever at the time of sample collection.[5] Despite the increasing number of asymptomatic malaria studies, any malaria-related symptoms other than fever are not frequently involved or observed.[6] Previous study shows that several malaria-related clinical symptoms other than fever such as myalgia and headache can be present in asymptomatic malaria.[7]

The absence of fever in asymptomatic malaria can influence the malaria case finding in the malaria-endemic region.[7] The passive case finding starts with the presence of symptoms particularly fever and could be accompanied by other symptoms such as headache, nausea, vomit, diarrhea, and muscle soreness. Thus, individuals present with those symptoms will be tested to confirm malaria diagnosis using microscopic examination or rapid diagnostic test.[8] This algorithm cannot detect and find asymptomatic malaria cases because of the absence of fever in asymptomatic malaria. As a consequence, asymptomatic malaria cases are less likely to be found and treated. Therefore, malaria infection tends to persist and develop into a chronic infection.[7] A chronic untreated malaria infection has been shown to be associated with a decreased level of Hb so then anemia could be present in asymptomatic malaria as well. A large number of undetected asymptomatic malaria leads to the domination of asymptomatic malaria cases in the malaria-endemic regions.[7,9] In addition, undetected asymptomatic malaria cases could be the major source of malaria transmission and thus it complicates the malaria elimination program.[10] Since asymptomatic malaria tends to have a low level of parasitemia that allows it to be undetected by microscopic examination (submicroscopic asymptomatic malaria), therefore it is important to perform PCR examination in endemic areas where asymptomatic malaria predominates.[11] Further information regarding clinical symptoms of asymptomatic malaria is needed to improve its finding. Therefore, patients with asymptomatic malaria would be easier to found, treated, and they are less likely to develop complications due to chronic malaria infection. In addition, the malaria elimination program particularly in East Nusa Tenggara could be easier to reach because of the decreased level of source of transmission from asymptomatic malaria carriers.

2. METHODS

Study design and location

This was a cross-sectional study using secondary data from the previous malaria study that was held during 2013-2014 in 5 areas with diverse Annual Parasitic Incidence (API) in East Nusa Tenggara Province, Indonesia: Oenino (API <1), Panite (API 1-5), Batu Putih (API 1-5), Oinlasi (API >5), and Oe'ekam (API >5).[12]

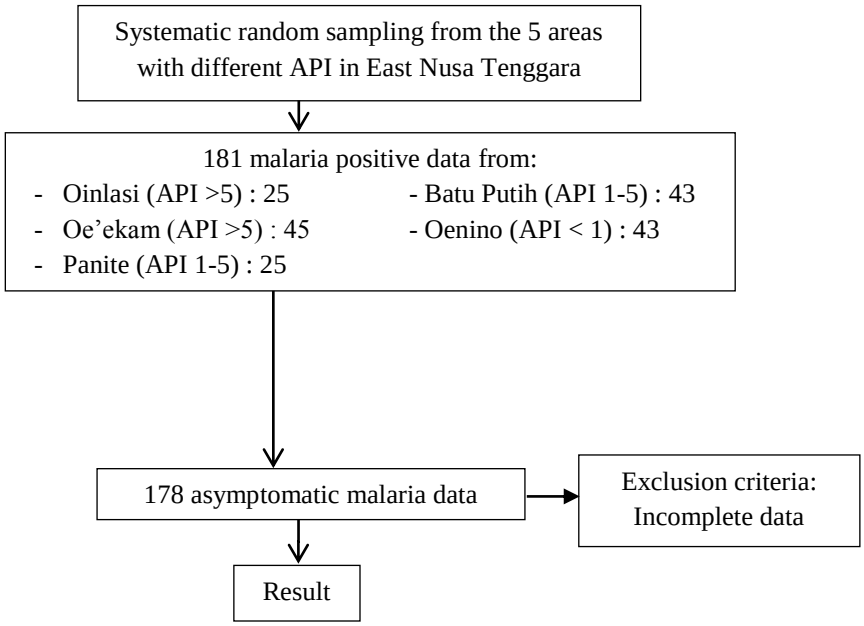
Data Sources and Participants

181 malaria-positive data were obtained by systematic random sampling using household data in each area from the previous study. Only asymptomatic malaria data that were included in the study, which defined as data of positive malaria diagnosis by nested polymerase chain reaction (PCR) method, did not complain fever at the time of sample collection and were confirmed by temperature examination using a thermometer (<37,5^{o} Celcius). Individu with incomplete data was excluded from the study.

Variables

Ten clinical symptoms data including chills, headache, anorexia, weakness, myalgia, nausea, vomit, abdominal pain, diarrhea, and cough, as well as the residence time in endemic region and the presence of vector breeding sites, were obtained from a standard questionnaire filled out by the medical doctor as local health officer. The ten clinical symptoms were defined as the presence of those symptoms in the study subjects during the time of the sample collection or the previous history of those symptoms during one month before the time of the sample collection and were confirmed using direct interview by the local health officer. Physical examinations then were carried out by the local health officer. To minimize the measurement bias, the medical doctor that carried out the examination was exchanged, which the doctor from primary health center A took turns to examine the patient from primary health center B, and vice versa.

Hemoglobin data were collected using a drop of a blood sample from the fingertip (1 µL) and were tested using Bene-Check Hemoglobin Test. Hemoglobin level was classified as anemia (Hb ≤11 mg/dL) and non-anemia (Hb >11 mg/dL) according to the WHO classification.[13] *Plasmodium* species data were determined by the nested-PCR method that followed the protocol Snounou et al.[14]



Inclusion criteria:
Malaria positive cases determined by PCR, did not complain fever at the time of sample collection and were confirmed by temperature examination (temperature <37,5^{o}C)

Figure 1. Research Flowchart

Data measurement and analysis

The data were processed and analyzed using IBM® SPSS® 25th version and Microsoft Excel® 2010 software. Bivariate analysis was used to analyze the association between the presence of any clinical symptom based on *Plasmodium* species, hemoglobin categories, duration of residency in endemic region, and the presence of vector breeding sites around the residence. Then, multivariate analysis was also carried out to identify the association between the four independent variables and dependent variable simultaneously. Statistical significance is achieved if the p-value <0,05. This study had received an ethical exemption from the Medical Research Ethical Committee, Faculty of Medicine, Padjadjaran University, with ethic license number 920/UN6.KEP/EC/2020.

3. RESULTS

1. Characteristics of the subjects

A total of 178 PCR confirmed-malaria subjects did not complain of fever at the time of sample collection and were confirmed by temperature examination (<37,5^{o} C). Therefore, asymptomatic malaria was found in 98,34% of all malaria positive cases. All of them were included in the study. Table 1 shows the distribution of clinical symptoms and the type of *Plasmodium*, as well as hemoglobin profile in the study subjects. The most frequent symptoms observed were headache (18,0%), chills and myalgia (12,4%), and weakness (11,2%), respectively. *Plasmodium vivax* was the most prevalent *Plasmodium* type observed in this study (53,4%). The mean

hemoglobin level was 11,25 g/dL, with the lowest and the highest hemoglobin level of 6 g/dL and 16 g/dL, respectively.

Table 1. Distribution of the Clinical Symptoms, *Plasmodium* species, and Hemoglobin profile

2. Bivariate analysis

Table 2 shows that there was no significant association found between the presence of any clinical symptom and the type of *Plasmodium* species, hemoglobin level, duration of stay in endemic region, as well as the presence of breeding sites around the residence.

Table 2. Bivariate Analysis

	Any Clinical Symptom		**Total**	**p-value**
	Yes	**No**		
***Plasmodium* species**				
P. falciparum	13	42	55	0,471
P. vivax	15	80	95	
Mix (*P. falciparum* + *P. vivax*)	6	22	28	
Hb level				
Non anemia (Hb >11 mg/dL)	21	82	103	0,609
Anemia (Hb ≤11 mg/dL)	13	62	75	
Duration of Recidency in Endemic Region				
>5 years	28	128	156	0,298
<5 years	6	16	22	
Breeding Places Around the Residence				
No	7	29	36	0,953
Yes	27	115	142	

3. Multivariate Analysis

Table 3 shows the result of multivariate analysis of the possible contributing factors to the presence of any malaria-related symptoms other than fever. The risk of developing any symptom increased in *P. vivax* infection (OR =1.16, 95% CI=0.38-3.50), in the presence of anemia (OR=1.30, 95% CI=0.58-2.73), and in the presence of breeding sites (OR=1.04, 95% CI=0.40-2.66), respectively.

Table 3. Multivariate Analysis

Variables	B	OR	p- value	95% CI	
				Lower	Upper
Constant	-.98	.38	.16		
***Plasmodium* species:**					
P. vivax	.14	1.16	.80	.38	3.50
Mix	-.38	.68	.48	.24	1.98
Hb level	.26	1.30	.51	.58	2.73
Duration of residency in endemic region	-.57	1.04	.28	.20	1.60
Breeding places around the residence	.04	1.04	.94	.40	2.66

4. DISCUSSION

From this study, we found 98,34% (178 of 181) asymptomatic malaria cases among all malaria confirmed cases that highlight the domination of asymptomatic malaria among all confirmed cases in the endemic region. This result is consistent with several studies regarding the domination of asymptomatic malaria that was conducted in other regions, including in Papua, Indonesia, and Dhaka, Bangladesh that found 97,7% and 77% asymptomatic malaria cases among all confirmed cases, respectively.[11,15] Because of the absence of fever, these individuals are less likely to seek medical help, therefore asymptomatic infections are less likely to be found and treated by passive case finding, and it eventually persists longer in a population.[7] The domination of asymptomatic individuals in the malaria-endemic region is thought to complicate the malaria elimination program because it may become a source of infection.[10,16] Gametocyte density is a critical factor in malaria transmission that determines if a mosquito develops an infection from an infective blood meal. Although the asymptomatic infection can be associated with lower gametocyte density, there is evidence that mosquitoes can become infected by blood meal from an individual that has gametocyte density as low as five gametocytes per microliter. A previous study has demonstrated that individuals with low or even undetectable gametocytaemia by microscopic examination contributed to almost 10% of the overall number of infected mosquitoes. Therefore, it may result in malaria transmission.[17,18]

Despite the increasing number of asymptomatic malaria studies, any malaria-related symptoms other than fever are not frequently involved or observed.[6] Our study found that individuals with asymptomatic malaria could have any malaria-related symptoms in the absence of fever, particularly headache, chills, and myalgia. A similar result has been reported in another study in Brazilia.[7] Typically, the recurrent episode of fever is present in malaria. This results from the erythrocyte rupture that releases schizont into circulation and therefore triggers an inflammatory response.[19] However, there are various factors that possibly influence the clinical expression of malaria, including naturally acquired clinical immunity, parasitic load and virulence, the

host's age, and genetic factors.[7] Individual with repeated and chronic exposure of *Plasmodium* infection as present in the moderate or high transmission setting appears to develop a partial immunity that reduces the intensity of clinical symptoms and functions as a protection against severe malaria. This eventually results in minimal symptomatic illness or even totally asymptomatic infection.[4,20] Therefore, the longer length of residency in the endemic region is frequently associated with the decreased risk of developing fever due to the increased amount of repeated and chronic exposure to *Plasmodium* that results in partial immunity. However, this study found that the duration of residency in the endemic regions above 5 years was more likely to experience any malaria-related symptoms other than fever. Another study in Brazilia found the similar finding which suggests that there are several symptoms that are more pronounced in populations with longer duration of stay in an endemic region, particularly abdominal pain, although fever is less likely to be found in that population.[7] The pathological mechanisms underlying the presence of these symptoms in the absence of fever were not assessed in our study. Despite the absence of fever, other malaria-related symptoms may also be inconvenient for the individuals and therefore should not be neglected in the process of malaria case finding and treatment, particularly in the high or moderate transmission setting where most of the population had acquired partial immunity.

P. vivax was the most prevalent etiologic agent in this study. In general, *P. vivax* is the second most prevalent *Plasmodium* causing malaria in Indonesia, with the *P. falciparum* in the first place.[21] Another study found a similar finding which shows that *P. vivax* was the most frequent etiologic agent in asymptomatic malaria.[22] Individuals with *P. vivax* infection are thought to develop immunity more quickly than individuals with *P. falciparum* infections and therefore are more likely to control parasitemia and subsequent clinical symptoms to a greater degree.[23] However, compared to the individuals with *P. falciparum* infection, our study found that infection with *P. vivax* was increased the risk of developing any malaria-related symptoms other than fever. This might result from the association between the several symptoms with the particular *Plasmodium* species. For example, chills or rigor was known to be associated with *P. vivax* infection.[24]

Anemia is a common finding in malaria that may result from the release of inflammatory mediators such as TNF-alpha and Il-10 that suppress erythropoiesis, increased phagocytic removal of the red blood cells, and impairment of iron homeostasis due to the increased production of hepcidin that reduces iron stores.[9,25] Numerous studies have found that the decrease level of Hb that progresses to anemia could also be present in asymptomatic malaria, particularly in children.[9,26] In addition, because asymptomatic individuals are less likely to seek medical help, anemia in asymptomatic malaria tends to be persistent and chronic due to the longer period of infection.[9] Our study found the hemoglobin level as low as 6 g/dL in asymptomatic individuals, with the average level 11,25 g/dL. In addition, our finding suggests that the individuals with anemia (hemoglobin level ≤11 mg/dL) were 1.30 times more likely to develop any malaria-related symptoms other than fever, compared to the individual with hemoglobin level >11 mg/dL. This study did not measure various factors that possibly influence

the hemoglobin level in malaria patients, however, other studies found that malnutrition is one of the contributing factors to anemia in malaria patients.[26,27]

The presence of vector breeding sites around the residence positively influences vector sustainability and malaria transmission.[22] Our study found that the presence of breeding sites increased the risk of developing malaria-related symptoms other than fever by 1.04 times. Similarly, another study in eastern India found the increased risk of developing malaria as much as 2.03 times in population with the presence of breeding sites around the residence, and asymptomatic malaria predominates among all infected individual in that study.[22]

This study has several limitations. Since this was a cross-sectional study, the follow-up event was not done. Follow-up is essential to measure whether asymptomatic individuals develop a fever as the course of illness continued. In addition, this study did not measure the various factors that may influence the hemoglobin levels, therefore the result of a decrease in hemoglobin levels in this study may also be caused by various factors other than malaria itself.

5. CONCLUSION

Several malaria-related symptoms other than fever are found in this study and it may help in the process of asymptomatic malaria screening and case finding. The infection with *P. vivax*, the presence of anemia, and the presence of breeding sites are all increasing the risk of developing any malaria symptom other than fever. Due to the contribution of asymptomatic malaria to the overall malaria transmission and its potential effect to cause chronic anemia, asymptomatic cases, as well as symptomatic cases, should be found and completely treated to minimize worse outcomes in individuals and help the malaria elimination program be easier to achieve.

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