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Usefulness of clinical algorithm as screening process to detected malaria in low-to-moderate transmission areas of scarce health related resources

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Abstract

Introduction—In areas of low-to-moderate risk of malaria transmission, the World Health Organization recommends parasitic confirmation before treatment. Such areas have usually low budget for health care and malaria diagnosis is mostly based on clinical assumption. Algorithms have been developed to improve health care providers' identification of clinical malaria and could be used as screening to reduce the number of individuals requiring parasitic confirmation before treating.

Methods—Prospective clinical and parasitological data were collected from inhabitants of four villages from March 1984 through March 1985. Symptoms and signs recorded by physicians were used in multivariate models to test the best predictors of malaria. Sensitivity and specificity were calculated for various cut-offs of scores and compared to clinical diagnosis.

Results—A total of 8.941 individuals were evaluated during the 1-year period of data collection. The overall prevalence of malaria parasitemia was 19.7% (n = 1762). Of the 4280 people evaluated during the high season period, 24% (n = 1024) presented any parasitemia, 55.3% (566/1024) due to *Plasmodium falciparum*. The final clinical algorithm included history of fever, rigors, headache, absence of myalgia, backache or cough, nausea or vomiting, and splenomegaly on examination as predictable variables. At a cut-off score of 2.0, the sensitivity of the algorithm was higher for the entire sample (57% vs. 43%), for high season period (70% vs. 53%), for children less than 6 years of age (59% vs. 40%), for individuals with parasitemia due to *P. falciparum* (65% vs. 48%), and for high *P. falciparum* parasitemic individuals at high season (84% vs. 68%). However, specificity was usually lower unless a higher cut off was used, in which case the gain in sensitivity by using the algorithm was reduced.

Conclusion—In low-to-moderate transmission areas in which health related resources are scarce, a clinical algorithm increases the identification of real cases of malaria and could be used as screening for further parasitic identification.

1. Introduction

Microscopic review of Giemsa-stained blood films remains the standard method to confirm a clinical diagnosis of malaria. Unfortunately, in many areas of the developing world, laboratory support is not available and malaria diagnosis and treatment depends only on clinical suspicion (Font et al., 2001). Diagnosis of malaria-caused disease based only on clinical assumption varies in difficulty with the endemicity of infection. Repeated exposure tomalaria parasites build up premonition (parasitemia with no malaria symptoms). This generally occurs in geographic areas, e.g., the Sub-Saharan Africa, where the inhabitants are exposed to many

infectious mosquito bites (Beier et al., 1994; McElroy et al., 1994; Rogier et al., 2005). In such highly endemic areas usually only children have symptomatic clinical malaria and the World Health Organization (WHO) recommends antimalarial therapy of all children with fever or a history of fever and no other obvious cause (WHO, 2006).

Low and season exposure levels to malaria parasites create a different scenario in areas of low-to-moderate risk of malaria transmission. Clinical malaria occurs at all ages and at parasite densities well below those usually required to cause illness in the highly endemic Sub-Saharan Africa (McElroy et al., 1994; Beadle et al., 1995; Prybylski et al., 1999; Rogier et al., 2005). For that scenario, WHO recommends parasitic confirmation before treatment. However, for areas where malaria incidence is very low, the recommendation is that health workers should be trained to identify patients who have a risk of exposure to malaria before performing a parasitological test so that scarce resources can be better allocated (WHO, 2006).

Malaria continues to be a major public health problem in Pakistan (WHO, 2005). Although Pakistani national policy and planning has improved since the adoption of Roll BackMalaria control strategy in 1999, access to diagnosis and treatment remains inadequate (WHO, 2005). Both *Plasmodium falciparum* and *Plasmodium vivax* are prevalent, and in most parts of the country transmission occurs during and after the monsoon season (from July to December). The country has areas of low malaria transmission (Indian border) and areas of moderate transmission (Afghanistan border). The Punjab of Pakistan (Indian border), is classically described as having a seasonal and unstable malaria transmission (de Zulueta et al., 1980; Zafar-Latif et al., 1985).

Herein, we construct a clinical algorithm based on a score system created by using the best clinical predictors for malaria infection and compare its accuracy to the physician's ability to correctly identify malaria infection (clinical diagnosis). Our aim is to show if a clinical algorithm works better than clinical diagnosis to screen people that would benefit from parasitic confirmation.

2. Materials and methods

The study was approved by the Institutional Review Board (IRB) at University of Maryland, Baltimore. The IRB when this study was performed did not require that informed consent be obtained from the subjects since only clinical pertinent information was collected and no invasive procedures, including drawing venous blood, were performed. At the time our study was performed there were no constituted IRBs in Pakistan to evaluate the project. The questionnaires were used as outpatient data files and the blood films were used to diagnose malaria. For the purpose of data analysis for publication, subjects were coded as numbers, not by names.

2.1. Study area and population

Four villages having a high prevalence of both *P. falciparum* and *P. vivax* malaria were selected for cross-sectional and prospective study in the Kasur District of Punjab (Strickland et al., 1987). They are located on either side and within 20–200m of the Rohi drain, an irrigation drain with clear water and slow flow that supplies year-round breeding sites for anopheline mosquitoes, even during the dry season. During the rainy season, from mid-July to mid-September, standing ground water supplies additional breeding sites for the primary vector, *Anopheles culifacies.* The largest village, Khanke, had a population of 5500 people. The other villages ranged in population from 300 to 1300 people.

2.2. Data collection

Announced outpatient clinics were held in the communities every 2 weeks by 1–3 physicians and 3–5 paramedical personnel. The data were collected from March 1984 through March 1985. Every villager was eligible to visit the clinic. Each patient was registered, personal data were recorded, and the patient's temperature was taken. Clinical data was collected by young physicians hired and trained for this task. These were a selected group and their skill level for this task was advanced. They used a standard form listing the most common signs and symptoms, e.g., history of fever, rigors and headache. The accompanying adult, usually a parent or relative, was used to obtain demographic and clinical information for children less than 10 years of age. Physical examinations was limited to the patient's area of complaint with exception of children less than 10 years old who had abdominal examinations for detection of splenic and hepatic enlargement. Physicians were required to make a clinical diagnosis based upon their judgment before the results of the Giemsa-stained blood films were known, and appropriated therapy was dispensed. Finger-prick blood films were taken from every patient regardless of their complaints. The number of patients seen and blood films taken during each of these clinics usually ranged from 25 in the smallest village (Deoki) to 150 in the largest one (Khanke).

2.3. Processing of blood films

Thick and thin blood films were made on the same slide. The thin film was fixed with methanol and the whole slide was stained for 30min with 3% Giemsa diluted in a phosphate buffer solution of pH 7.2. The thick film was used to count parasites while the thin film was used to make the final species diagnosis. The number of asexual and sexual stages of *P. vivax* and *P. falciparum* were recorded per 500 white blood cells (WBC) with the exception of high parasitemias when only 100–200 WBC were counted. Three highly skilled, experienced, parasitology technicians were used in our study. They examined all blood films for at least 15min before recording them as negative. A senior technician randomly checked the slides to insure quality control. The density of parasitemia was estimated using 8000WBC/mm3 of blood as the standard value.

2.4. Statistical methods

Patients who had malaria parasites were defined as cases, regardless of parasite density, while those who had a negative blood film were defined as not having malaria. All signs and symptoms used in the score were defined as present or absent at examination, except fever that was defined as history of fever within the past 2 weeks. Seventeen of them were entered in a basic multivariate model at first: history of fever, headache, myalgia, backache, rigors, cough, diarrhea, fatigue, nausea or vomiting, weakness, abdominal pain, anorexia, "heart sink", palpitations, dizziness, splenomegaly (palpated below the left costal margin on inspiration vs. not) and hepatomegaly (palpated below the right costal margin on inspiration vs. not). Then, they were taken one by one off the model and the deviance of the two models was compared to check for the modeling fit. All variables were taken back to the model before excluding the next one. Only variables with p values equal or lower than 0.10 were kept in the final model. We used Generalized Estimate Equations to adjust for clustering by villages.

The final malaria score was calculated by summing the rounded up regression coefficients for the symptoms and signs present in the final multivariate model. The levels of score were defined by evaluating the distribution of the final continuous score. We anticipated that the score would vary according to the age of the patient and season of the year. Therefore, we tested the score in three subgroups of age (<6 years old, 6–14 years old, and >14 years old) and three subgroups of season: January–June: low malaria transmission; July–August: rainy season and high transmission for *P. vivax*, and September–December: high transmission season for *P. falciparum* (Prybylski et al., 1999). We also tested the score for those individuals presenting

isolated infection due to *P. falciparum* and for high parasitemic *P. falciparum* individuals, and for isolated infection due to *P. vivax*. Sensitivity and specificity for detection of any malaria parasitemia at different malaria score levels were calculated and compared to the reliability of the clinical diagnosis made by the physicians.

The data were entered by the physicians and two data management specialists trained by EF. Data that had outliers were rechecked. We performed data analysis with SAS 9.1.2, SAS Institute Inc., Cary, NC, USA, 2003.

3. Results

Blood films were taken from 8941 outpatients during the 13 months. The median age was 10 years (ranging from a few months to 98 years) and 58% were female. The overall prevalence of malaria parasitemia was 19.7% ($n = 1762$). The prevalence of *P. falciparum* was 11.3% and prevalence of *P. vivax* was 9.3%. Coinfections were present in 4.9% ($n = 87$) of those having parasitemia (Table 1). Among the 649 malaria infections detected between September and December, *P. falciparum* accounted for approximately 80% ($n = 516$). In the period between July and August the most prevalent species was *P. vivax*, accounting for 77% (288 out of 375). Transmission was lower during the dry period from January through June and 52% ($n = 381$) of the infections at that time were due to *P. vivax*. The infecting malaria species were approximately evenly distributed in three of the villages. However, 62.7% of all malaria infections detected in Plair were due to *P. falciparum*. Of the 1675 individuals in whom only one infecting species was detected in the blood, 982 (58.6%) had levels of parasitemia between 1 and 1000 parasites/_l and 693 (41.4%) had levels above 1000 parasites/_l. Whereas only 29.2% of *P. vivax* infections had parasitemias above 1000 parasites/_l, 51.2% of *P. falciparum* infections had parasite densities at the higher level.

The best fitting multivariate model included history of fever, rigors, headache, absence of myalgia, backache or cough, nausea or vomiting, and splenomegaly on examination as predictable variables (Table 2). The final median score was 1.5 (ranging from 0 to 6). Based on that, we created four groups of dichotomous score levels for the accuracy analysis based on different cut-offs: (a) lower vs. equal or greater than 1.5; (b) lower vs. equal or greater than 2.0; (c) lower vs. equal or greater than 2.5; and (d) lower vs. equal or greater than 3.0. However, only the three latter groups were used in the analysis due to the small number in the first group.

Table 3 shows the comparison among clinical diagnosis and the three scores. Sensitivity was higher for a cut-off score of 2.0, although at lower level for individuals over 14 years old. However, specificity for the same score was lower than clinical diagnosis. A score of 2.5 presented slightly higher sensitivity but specificity similar to clinical diagnosis. A score of 3.0 had very low sensitivity. While the scores seemed to have worked better in all subgroups, clinical diagnosis had poorer result for the season in which *P. vivax* was more prevalent.

Table 4 shows the same comparison for individuals presenting isolated infection due to *P. falciparum*. Again, sensitivity was higher for a cut-off score of 2.0 but it was also slightly better for a cut-off score of 2.5. Specificity was lower than clinical diagnosis for the 2.0 score and similar for the 2.5 score. Both clinical diagnosis and clinical algorithm performed better for high parasitemic individuals (algorithm better than clinical diagnosis).

Finally, Table 5 shows the comparison for isolated infection due to *P. vivax*. In that case, both clinical diagnosis and clinical algorithm performed worse than in other cases, although the algorithm has proven better than clinical diagnosis with the exception of adults in whom neither the clinical diagnosis nor the score were very accurate. The score was particularly superior, at the expense of reduced specificity, to the clinical diagnosis in *P. vivax* infections in children.

4. Discussion

In general, sensitivity of the algorithm's diagnostic score in its lower cut-off of 2.0 was better than a diagnosis made by the physicians. This was true in different levels for any period of the year and for patients 14 years old or younger. Our data also showed that the algorithm worked better for individuals infected by *P. falciparum* and particularly the group with higher *P. falciparum* parasite densities. However, as sensitivity increased specificity usually was reduced unless a higher cut off score was used. As expected this gain in specificity usually resulted in reduced sensitivity.

Weighting the score in favor of the predictors presenting higher regression coefficients may have helped to increase the reliability of clinical-based algorithms. Interestingly, the absence of three symptoms, myalgia, back pain and cough, was related to malaria cases. Our subjects were patients who sought medical assistance in temporary community clinics for a variety of different illnesses, and the presence of these symptoms may indicate competing causes of morbidity. Also, the reliability of the algorithm varied according to variables, e.g., age (better for children) of the individual and species (better for *P. falciparum*), most likely because the signs and symptoms included in the final algorithm have a higher probability of being associated with malaria parasitemia in these subgroups. The score is more sensitive than the clinical diagnosis for *P. falciparum* with minimal loss of specificity (except at score of >2) for patients 14 years old or younger until the score is greater than 3. The poorer results for *P. vivax* indicate a lower level of parasitemia and symptoms related to infection with this species.

Our study is based upon data from outpatients from an endemic area in Punjab, Pakistan, with slightly more *P. falciparum* (53%) than *P. vivax* (47%) infections, considerable seasonal variation in intensity and species transmission related to the pattern of rain in the region, and slight variation of prevalence of both species among the different communities. Also, *P. falciparum* was responsible for the majority of high parasitemic cases (Prybylski et al., 1999). These results are representative of moderate seasonal transmission of malaria, and different from results from other areas, e.g., the Sub-Saharan Africa, were transmission is much more extensive (McElroy et al., 1994; Rogier et al., 2005). In the latter situation, malaria is likely to be the cause of febrile illness in children or in adults with higher parasitemias (Rougemont et al., 1991; McElroy et al., 1994). In areas of low-to-moderate malaria transmission, lesser numbers of exposures retards acquisition of immunity and results in people of all ages suffering from clinical illness when infected. This could progress to severe malaria if left untreated.

Despite the seasonal transmission of malaria in this area of the Punjab, premonition was surely present in many subjects, especially adults. This explains why the clinical algorithm was less reliable for adults. Also confounding the reliability of diagnosing malaria are competing causes of illness, such as upper respiratory infections, as shown by our index showing the value of an absence of certain symptoms. This issue goes back to the objective of our score that is to correctly identify malaria infection by using the algorithm to screen people that would benefit from blood films for parasite confirmation. The purpose of our study was to detect people with malaria infections by analyzing their symptoms. Clearly, many of our subjects had premonition since they had malaria infections without appropriate clinical symptoms.

Many studies have evaluated the feasibility of clinical algorithms in areas of different levels of malaria transmission (Genton et al., 1994; Gomes et al., 1994; Olaleye et al., 1998; Muhe et al., 1999; Bojang et al., 2000; Chandramohan et al., 2001; Anand et al., 2002; Hozhabri et al., 2002; Malik et al., 2005; Mwangi et al., 2005; Mogensen et al., 2006). They differ in the way scores are created, definition of malaria, age group studied, and level of malaria transmission, but they usually agree that, although a clinical algorithm can improve

identification of a case of malaria, a Giemsa-stained blood film reduces over-treatment and wastage of antimalarial drug during this era of increasing cost and widespread increase in parasite resistance to many available drugs (Chandramohan et al., 2002). Treatment of uncomplicated malaria in areas of low to-moderate transmission aims at avoiding disease progression to severe malaria, and the goal is to identify any person potentially having clinical malaria and treat them promptly. By relying only on diagnosis made by a health care provider, our data show that we would have missed several treatment opportunities, especially in children less than 14 years old. The clinical algorithm using a score of 2.0 increased by 26% the number of diagnosed patients with parasitemia, from 578 to 786, over a clinical diagnosis. Using a cut-off of 2.5 only increased the diagnostic sensitivity by 13%, from 578 to 666 individuals. If we use only a history of finding of fever at the clinical exam, we will have increase in real positives of 14% and in false negatives of 36% (data not shown). Our data suggest the clinical algorithm would be best for screening and the ideal score would depend upon the availability of stained blood films.

We have analyzed an old dataset that reflected malaria transmission of an area in Pakistan more than 20 years ago. Changes in environmental patterns can cause seasonal and annual variations in malaria transmission, infection and disease. However, we do not believe malaria has changed greatly in these four villages during the 20 years since our assessment was performed. Although features related to the malaria epidemic in the Punjab region of Pakistan have changed over the years (Klinkenberg et al., 2004), our data from almost 9000 clinic visits is probably the largest sample size among reports that addressed the utility of clinical algorithms in identifying malaria infection. Although these algorithms are site specific and may vary from year-to-year, following validation they can assist in the management of malaria in other areas that have similar transmission patterns. For instance, a study in the Sind region of Pakistan has reported a clinical algorithm based on fever greater than 3 days in duration and absence of cough or rigors as highly sensitive and modestly specific for detecting *P. falciparum* among children (Hozhabri et al., 2002).

In conclusion, microscopic detection of malaria parasites is very important to detect people who require treatment for malaria. However, this simple procedure is frequently not available in malarious areas with limited resources. In low-to-moderate transmission areas where health-related resources are scarce, algorithms could be used for screening to reduce the number of patients requiring microscopic blood films (Chandramohan et al., 2002; WHO, 2006). The usefulness of this clinical algorithm as a screening process to detect malaria could be confirmed by repeating the evaluation in the Punjab or in other low-to-moderate transmission areas.

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Table 1

General characteristics of malaria transmission at the Kasur District of Punjab, Pakistan (n = 8941)

Characteristic	Number (%)
Gender	
Male	3778 (42)
Female	5163 (58)
Age (years)	
<6	2791 (31)
6–14	2614 (29)
>14	3536 (40)
Season of transmission	
January–June	4660 (52)
July–August	2264 (25)
September–December	2016 (23)
Village	
Baghiane	2201 (25)
Deoki	698 (8)
Khanke	4337 (48)
Plair	1705 (19)
Prevalence of parasitemia	
General	1762 (19.7)
Plasmodium falciparum	923 (10.3)
Plasmodium vivax	751 (8.4)
Co-infection	87 (1)

Table 2

Final multivariate model for the best predictors of malaria infection

Sign or symptom	Patients with symptom, *n* (%)[a]	Regression coefficient (rounded value)	95% Confidence interval
History of fever	865 (49)	0.755 (1.0)	0.532–0.977
Headache	330 (19)	0.100 (0.5)	−0.001 to 0.201[*]
Absence of myalgia	1500 (85)	0.238 (0.5)	0.009–0.467
Absence of back pain	1719 (98)	0.341 (0.5)	0.117–0.566
Rigors	503 (28)	0.726 (1.0)	0.576–0.876
Absence of cough	1292 (73)	0.259 (0.5)	0.224–0.294
Nausea or vomiting	210 (12)	0.353 (0.5)	0.216–0.491
Splenomegaly[b]	233 (13)	1.203 (1.5)	1.043–1.363

[a] Out of 1762 presenting any parasitemia.

[b] Splenomegaly was present when the spleen was palpated below the left costal margin on inspiration and was confirmed by percussion (reference: not palpated).

[*] *p*-Value = 0.052.

Table 3

Sensitivity and specificity of clinical diagnosis and clinical algorithm scores by season and age subgroups to detect malaria parasitemia

Characteristic	Sensitivity (%)	95% CI[a]	Specificity (%)	95% CI
General population (*n* = 8941; positive films = 1762)				
Clinical diagnosis Score[b]	43	40–45	84	83–85
≥2.0	57	54–59	71	70–72
≥2.5	47	45–50	83	82–84
≥3.0	36	34–38	89	88–90
January–June (*n* = 4660; positive films = 738)				
Clinical diagnosis Score	42	38–45	84	83–85
≥2.0	54	50–57	72	71–74
≥2.5	43	39–46	84	83–85
≥3.0	30	27–34	90	89–91
July–August (*n* = 2264; positive films = 375)				
Clinical diagnosis Score	27	22–31	87	86–89
≥2.0	40	35–45	77	75–79
≥2.5	34	29–39	84	82–86
≥3.0	24	20–29	91	89–92
September–December (*n* = 2016; positive films = 649)				
Clinical diagnosis Score	53	49–57	81	79–83
≥2.0	70	66–73	61	58–64
≥2.5	60	56–64	76	73–78
≥3.0	50	46–53	83	81–85
Less than 6 years old (*n* = 2791; positive films = 710)				
Clinical diagnosis Score	40	36–43	84	83–86
≥2.0	59	55–62	66	64–68
≥2.5	49	45–53	79	77–80
≥3.0	34	31–38	89	87–90
Between 6 and 14 years old (*n* = 2614; positive films = 631)				
Clinical diagnosis Score	47	43–51	79	77–80
≥2.0	58	54–62	65	63–67
≥2.5	51	47–54	76	74–78
≥3.0	41	37–45	84	82–86
More than 14 years old (*n* = 3536; positive films = 421)				
Clinical diagnosis Score	42	37–47	88	86–89
≥2.0	51	46–55	79	78–81
≥2.5	40	35–45	89	88–90
≥3.0	32	27–36	93	92–94

[a] CI: confidence interval.

[b] Score composed as described in the text.

Table 4

Sensitivity and specificity of clinical diagnosis and clinical algorithm subgrouped by season, age and level of parasitemia for detecting *Plasmodium falciparum* parasitemia (isolated infection)

Characteristic	Sensitivity (%)	95% CI[a]	Specificity (%)	95% CI
General population (*n* = 8102; *Plasmodium falciparum* = 923)				
Clinical diagnosis Score[b]	48	45–52	84	83–85
≥2.0	65	61–68	71	70–72
≥2.5	55	52–58	83	82–84
≥3.0	44	41–48	89	88–90
Higher season of transmission: September–December (*n*= 1847; *Plasmodium falciparum* = 480)				
Clinical diagnosis Score	55	50–59	81	79–83
≥2.0	72	67–76	61	58–64
≥2.5	63	58–67	76	73–78
≥3.0	53	48–57	83	81–85
Less than 6 years old (*n* = 2364; *Plasmodium falciparum* = 283)				
Clinical diagnosis Score	41	35–47	84	83–86
≥2.0	67	61–72	66	64–68
≥2.5	57	51–62	79	77–80
≥3.0	44	38–50	89	87–90
Between 6 and 14 years old (*n* = 2319; *Plasmodium falciparum* = 336)				
Clinical diagnosis Score	57	52–62	79	77–80
≥2.0	70	65–75	65	63–67
≥2.5	62	56–67	76	74–78
≥3.0	53	47–58	84	82–86
More than 14 years old (*n* = 3419; *Plasmodium falciparum* = 304)				
Clinical diagnosis Score	46	40–52	88	86–89
≥2.0	57	51–62	79	78–81
≥2.5	45	40–51	89	88–90
≥3.0	36	30–41	93	92–94
Higher season of transmission and parasitemia greater than 1000 μl^{-1} (*n* = 1663; *Plasmodium falciparum* = 296)				
Clinical diagnosis Score	68	62–73	81	79–83
≥2.0	84	79–88	61	58–64
≥2.5	76	70–80	76	73–78
≥3.0	65	59–71	83	81–85

[a] CI: confidence interval.

[b] Score composed as described in the text.

Table 5

Sensitivity and specificity of clinical diagnosis and clinical algorithm scores by season and age, for detecting *P lasmodium vivax* parasitemia (isolated infection)

Characteristic	Sensitivity (%)	95% CI[a]	Specificity (%)	95% CI
General population (*n* = 7930; *Plasmodium vivax* = 751)				
Clinical diagnosis Score[b]	35	32–39	84	83–85
≥2.0	46	43–50	71	70–72
≥2.5	37	34–41	83	82–84
≥3.0	25	22–29	89	88–90
Higher season of transmission: July–August (*n* = 2164; *Plasmodium vivax* = 275)				
Clinical diagnosis Score	22	17–28	87	86–89
≥2.0	35	29–41	77	75–79
≥2.5	28	23–34	84	82–86
≥3.0	17	13–23	91	89–92
Less than 6 years old (*n* = 2459; *Plasmodium vivax* = 378)				
Clinical diagnosis Score	38	33–43	84	83–86
≥2.0	52	47–57	66	64–68
≥2.5	43	38–48	79	77–80
≥3.0	27	23–32	89	87–90
Between 6 and 14 years old (*n* = 2252; *Plasmodium vivax* = 269)				
Clinical diagnosis Score	34	28–40	79	77–81
≥2.0	43	37–50	65	62–67
≥2.5	35	30–41	76	74–78
≥3.0	25	20–31	84	82–86
More than 14 years old (*n* = 3219; *Plasmodium vivax* = 104)				
Clinical diagnosis Score	31	22–41	88	86–89
≥2.0	34	25–44	79	78–81
≥2.5	25	17–35	89	88–90
≥3.0	21	14–30	93	92–94

[a] CI: confidence interval.

[b] Score composed as described in the text.