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Original Research

Establishment and evaluation of different fever related syndromes for screening malaria patients

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Summary
Aim: Analyze the clinical symptoms of feverish population and select significant symptoms to establish fever related syndromes to screen malaria patients.
Method: A"Registration form for patients with fever" was designed to gather information about symptoms of feverish population and standard blood smear was made for each patient to do the microscope test. SPSS 17.0 was used to analyze the distribution of clinical symptoms between malaria patients and non-malaria patients. Then the significant symptoms were selected to establish different syndromes by manual combined method. Sensitivity, positive predictive value (PPV), likelihood ratio, Youden index and Kappa were used for selecting the optimal syndrome.
Result: 1508 forms were got and 241 of them were malaria patients. 12 symptoms had different distribution between malaria population and non-malaria population. 52 fever related syndromes were established by using the 12 symptoms. Finally, No.52 syndrome(body temperature above 39ºC, periodic onset of fever and no diarrhea) were selected as the optimal syndrome, its sensitivity and positive predictive value were 74.3% and 84.4%.
Conclusion: The optimal malaria related syndromes can be used as a screen tool to screen malaria patients, especially in the villages where equipment and professional staff were lack.

INTRODUCTION

Fever is a main symptom of malaria and a feverish patient has a high likelihood of being infected by malaria, especially in the malaria epidemic area [1]. We found most of the feverish patients (about 81.2% [2])—their first time to see a doctor is in the village clinics, so if the village doctors can effectively identify the probable and potential malaria patients from the feverish population, they can give them more pertinent suggestion and treatment. However, to the village clinics' doctors, there are two obstacles making them hard to identify and diagnose the suspect malaria patients quickly and effectively.

The first one is that most malaria patients' symptoms are atypical, making the doctors unable to distinguish them effectively. When we investigated the malaria patients in villages of Anhui province-a malaria epidemic area in mid-east of China, where the vivax malaria incidence would have a re-emergence in each year's warmer days[3], we found that just a small part of the patients, their first onset presented typical manifestation (cold, fever and onset periodically). Most of patients have been infected malaria repeatedly, they have got certain immunity and their symptoms are atypical, making the village doctors hard to identify them.

Another important reason is that the village doctors lack the necessary equipment and skills to diagnose a malaria patient. The gold standard for diagnosing a malaria patient is to examine the blood smear by microscope. The prerequisite of microscopy examination is that it needs special equipment and reagent and requires experienced professional staff.

However, in most malaria epidemic area of China, due to the limited medical and sanitary conditions, the microscopy examination only can be carried out in the township level hospital, rather than the village clinics. The village doctors have no tools and abilities to test the patients. That means they are the first to contact with the suspect malaria patients, however, they can't give them a clear diagnosis. They always treat them as common feverish ones, without treating them with Chloroquine and primaquine. This may delay the right treatment and prolong the propagation time of a malaria patient as a source of infection.

In order to help village doctors to identify the malaria patients efficiently and effectively, in this study, we collected the symptoms of feverish population in the malaria epidemic area, examined their blood smear by microscope, analyzed the relationship between the symptoms and the malaria infection, we selected some symptoms that have statistical significance with the infection of malaria, then we established different syndromes by combined different symptoms together. By comparing the sensitivity (SEN) and positive predict value (PPV) of each combined syndrome, we selected one optimal syndrome which have the high SEN and PPV for screening malaria patients from the feverish ones. Village doctors can use the selected syndrome to screen malaria patients from the feverish ones and give them suitable treatment in time.

METHODS

Study field

We selected the Xutong town and Banqiao town as the investigation spot to collect datum of the feverish population. The two towns lie in the north of Anhui Province, along the Huai River. They are both the representative vivax malaria epidemic area. The malaria incidence rates of the two towns were 13.5‰ and 10.4‰ respectively in 2007. The infection of the two towns was relative concentrated. They both have convenient traffic and their staff and technical conditions are suitable for carrying out study.

Object of study

Objects in this study are people who visit village doctors with body temperature beyond 37.5℃ (body temp≥37.5℃).

Method

We designed "Registration form for patients with fever". Well-trained village doctors used this form to inquire the feverish patients (body temp≥37.5℃), gathered the patients' symptom information. Doctors made standard blood smear for each patient and examined the blood smear by microscopy to make a diagnosis. The results of the microscopy examination matched the registration form by a unique code. After the field work, we gathered all the registration forms, inputted them to computer to analyze.

We compared the symptoms' distribution between the malaria feverish patients and the non-malaria feverish patients, selected the symptoms which have a different distribution between the two groups. Then we established a series of fever related syndromes by combining different symptoms together and evaluated the value of each combined syndromes by using the index of sensitivity (SEN), Specificity (SPE), positive predictive value (PPV) etc. We used SPSS17.0 for statistical analysis and chi-square test to detect the symptoms' distribution.

RESULTS

From July 20, 2009 to Oct. 20, 2009, we collected 1736 questionnaires of the feverish population, after match the questionnaires' code with the blood smear's code, we excluded 228 invalid questionnaires and got 1508 effective questionnaires.

Totally, 17 symptoms were found in feverish people, they were: cold, chill, sweating, hand and face pale, hypodynamia, periodic attack of fever, persistent attack, irregular attack, muscle and joint sore, nasal obstruction and discharge, cough, throat sore, nausea or vomit, stomachache, diarrhea, headache, chest pain. Of the 1508 feverish patients, from high to low, their prevalence rates were as follows: hypodynamia 89.9%, irregular attack 62.5%, headache 53.6%, cough 49.6%, snuffle and discharge 45.3%, chill 37.1%, sweating 36.87%, periodic attack of fever 27.9%, nausea or vomit 27.3%, throat sore 24.6%, cold 23.8%, muscle-joint sore 21.5%, hand-face pale 20.1%, persistent attack 9.6%, diarrhea 7.1%, stomach 6.6%, chest pain 3.4%. The distribution of the 17 symptoms in the total feverish patients and in the malaria feverish patients was demonstrated in the figure-1 and figure-2.

By comparing the two figures, we found that the symptoms' distributions between the malaria feverish patients and the total feverish patients are discordant with each other. Some symptoms have high percentage in malaria feverish patients (such as chill, sweating, periodic attack of fever, nausea and headache) and some are high in the total feverish patients (such as irregular attack, snuffle and discharge, cough). This suggests that we can use some combined symptoms (we call it fever related syndromes) to screen the malaria feverish patients from the total feverish patients, even though the onset of malaria is atypical.

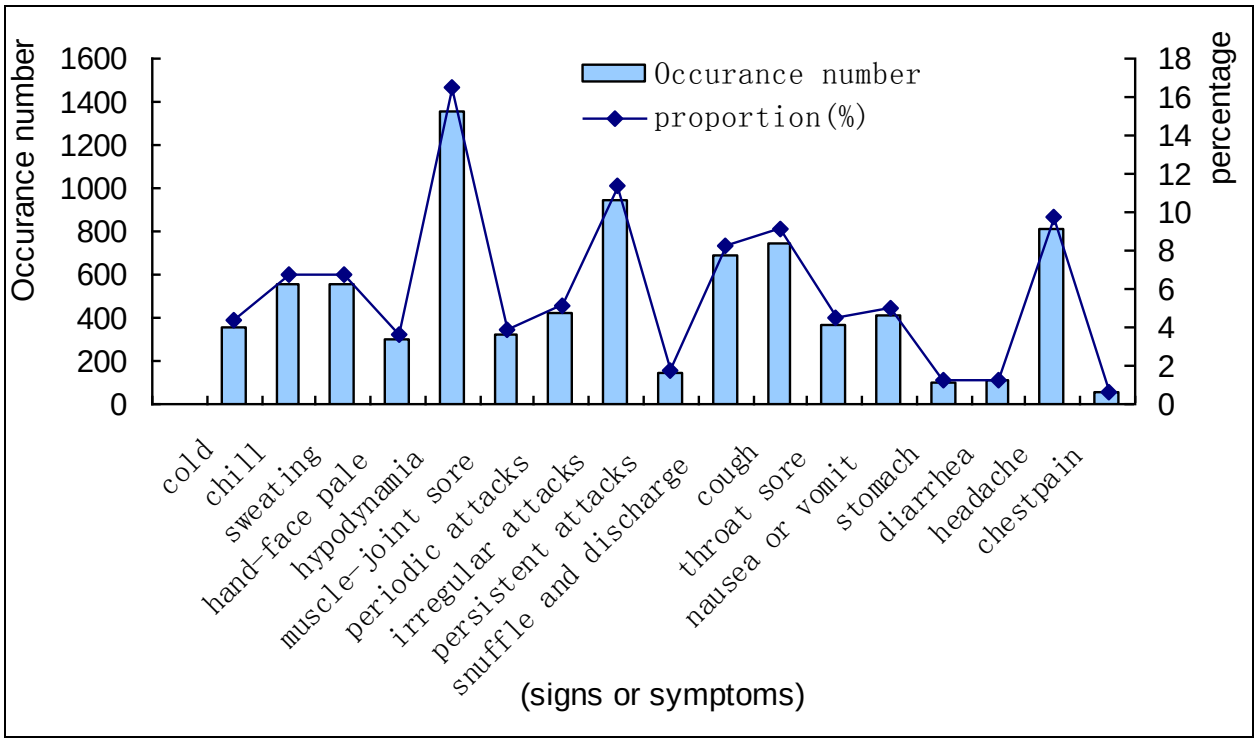

Figure 1. 17 symptoms' distribution in the total feverish patients

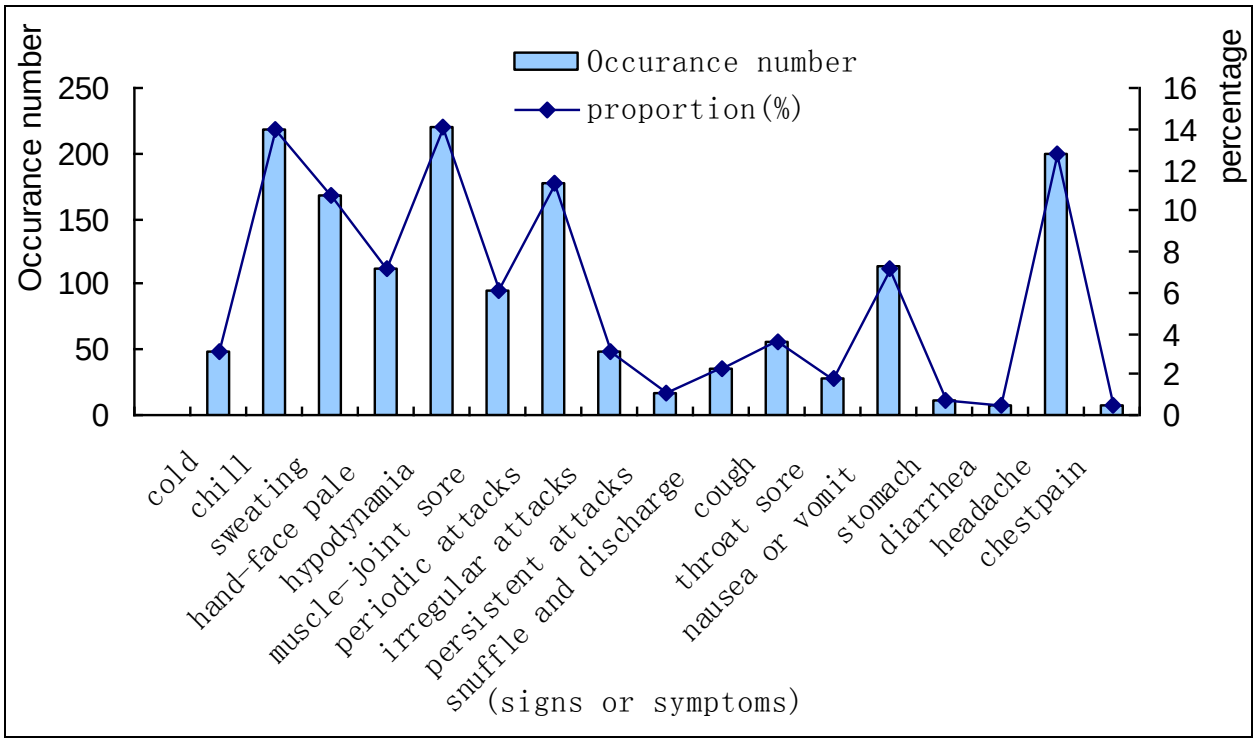

Figure 2. 17 symptoms' distribution in the malaria feverish patients

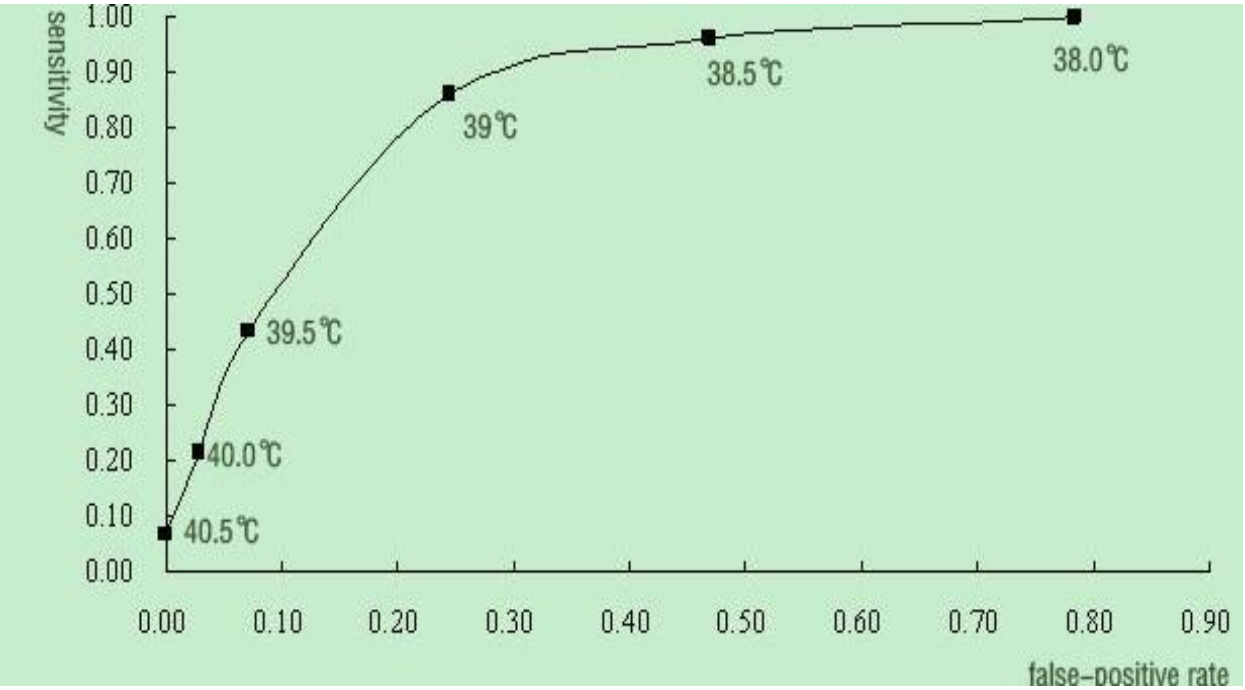

Figure 3. The ROC curve of body temperature

Cutoff point of body temperature

Body temperatures of the 1508 cases were in the range of 37.5℃～41.0℃. We got 6 body temperature values at the interval of 0.5℃. We counted the number of malaria patients below and above each body temperature value and calculated each value's sensitivity (SEN) and specificity (SPE).

The ROC (receiver operating characteristic curve) curve is a common tool for selecting the cutoff point. Usually the point which is closest to the upper left corner was identified as the optimal cutoff point [4, 5]. In this study, According to the SENs and false-positive rates in different body temperature values, we got the ROC curve of the temperature (figure-3). In the ROC curve of the temperature, the closest point to the upper left corner is 39℃, in this temperature point, the SEN and SPE is relative high and the false-positive rate is low. So we chose 39℃ as a cutoff point of body temperature for screening malaria feverish patients from the total feverish patients.

The SENs and SPEs of 17symptoms as indicator to screen malaria patients

We analyzed the 17 symptoms' frequency distribution in the malaria feverish patients and non-malaria feverish patients. Using each symptom as an indicator to screen malaria patients, we got the SEN、SPE、PPV and NPV of each symptom (Table 2).

Table 1. SENs and SPEs of each body temperature value for screening malaria

Body temp value	A	B	C	D	SEN	SPE	False positive rate
38.0℃	241	992	0	275	1.000	0.217	0.783
38.5℃	232	595	9	672	0.963	0.530	0.470
39.0℃	208	311	33	956	0.863	0.755	0.245
39.5℃	104	91	137	1176	0.432	0.928	0.072
40.0℃	52	35	189	1232	0.216	0.972	0.028
40.5℃	16	0	225	1267	0.066	1.000	0.000

Note A: The number of malaria patients in and above this temperature; B: The number of non malaria patients in and above this temperature; C: The number of malaria patients below this temperature; D: The number of non malaria patients below this temperature.

Table 3. 52 fever related syndromes

Serial number	Syndromes
1	Body Temp≥39℃, periodic attack of fever, chill, sweating, hand-face pale, muscle-joint sore, nausea or vomit, headache, no-diarrhea, no-cough, no snuff and discharge, no throat sore
2	Body Temp≥39℃, periodic attack of fever, chill, sweating, muscle-joint sore, nausea or vomit, headache, no-diarrhea , no-cough, no snuff and discharge, no throat sore
3	Body Temp≥39℃, periodic attack of fever, chill, sweating, nausea or vomit, headache, no-diarrhea, no-cough, no snuff and discharge, no throat sore
4	Body Temp≥39℃, periodic attack of fever, chill, sweating, headache, no-diarrhea, no-cough, no snuff and discharge, no throat sore
5	Body Temp≥39℃, chill, sweating, headache, no-diarrhea, no-cough, no snuff and discharge, no throat sore
6	chill, sweating, headache, no-diarrhea, no-cough, no snuff and discharge, no throat sore
7	sweating, headache, no-diarrhea, no-cough, no snuff and discharge, no throat sore
8	headache, no-diarrhea, no-cough, no snuff and discharge, no throat sore
9	no-diarrhea, no-cough, no snuff and discharge, no throat sore
10	no-diarrhea, no snuff and discharge, no throat sore
11	no-diarrhea, no throat sore
12	Body Temp≥39℃, muscle-joint sore, headache
13	Body Temp≥39℃,nausea or vomit
14	Body Temp≥39℃, no cough
15	Body Temp≥39℃, no snuff and discharge
16	Body Temp≥39℃, no throat sore
17	Body Temp≥39℃, periodic attack of fever
18	Body Temp≥39℃,chill
19	Body Temp≥39℃,chill,sweating
20	Body Temp≥39℃, chill, sweating, headache
21	Body Temp≥39℃, chill, sweating, headache, periodic attack of fever
22	Body Temp≥39℃, periodic attack of fever, chill
23	Body Temp≥39℃, chill, sweating, headache, periodic attack of fever, hand-face pale
24	chill, sweating, headache, periodic attack of fever, hand-face pale
25	chill, sweating, headache, periodic attack of fever,
26	Body Temp≥39℃, periodic attack of fever, no snuff and discharge
27	Body Temp≥39℃, periodic attack of fever, no cough
28	Body Temp≥39℃, periodic attack of fever, no throat sore
29	chill, sweating, periodic attack of fever
30	chill, sweating, headache, periodic attack of fever, hand-face pale, no diarrhea
31	chill, sweating, headache, periodic attack of fever, no diarrhea
32	chill, sweating, periodic attack of fever, no diarrhea
33	Body Temp≥39℃, no diarrhea
34	Chill, no diarrhea
35	periodic attack of fever, no diarrhea
36	chill, sweating, headache, periodic attack of fever, hand-face pale, no cough, no stuff and discharge, no throat sore
37	chill, sweating, headache, periodic attack of fever, no cough, no stuff and discharge, no throat sore
38	chill, sweating, periodic attack of fever, no cough, no stuff and discharge, no throat sore
39	Body Temp≥39℃, no cough, no stuff and discharge, no throat sore
40	Chill, no cough, no stuff and discharge, no throat sore
41	periodic attack of fever, no cough, no stuff and discharge, no throat sore
42	chill, sweating, headache, periodic attack of fever, hand-face pale, no diarrhea, no cough, no stuff and discharge, no throat sore
43	chill, sweating, headache, periodic attack of fever, no diarrhea, no cough, no stuff and discharge, no throat sore
44	chill, sweating, periodic attack of fever, no diarrhea, no cough, no stuff and discharge, no throat sore
45	Body Temp≥39℃, no diarrhea, no cough, no stuff and discharge, no throat sore
46	Chill, no diarrhea, no cough, no stuff and discharge, no throat sore
47	periodic attack of fever, no diarrhea, no cough, no stuff and discharge, no throat sore
48	periodic attack of fever, chill, no diarrhea,
49	periodic attack of fever, chill, no stuff and discharge
50	periodic attack of fever, chill, no cough
51	periodic attack of fever, chill, no throat sore
52	Body Temp≥39℃, periodic attack of fever, no diarrhea

There are 12 symptoms whose distribution are different in the two groups (according to α=0.05), they are: chill, sweating, hand-face pale, muscle-joint sore, periodical attack of fever, irregular attack, snuff and discharge, cough, throat sore, nausea or vomit, diarrhea, headache. The symptoms' incidence rates in the feverish patients were in the range of 8.0% ~ 92.9%. Their SENs were in the range of 13.7% ~ 96.7%. PPV of each symptom is not high, in the range of 16.6% ~ 42.1%. So if we use a single symptom as indicator to screen malaria, its PPV was too low to use. We need to combine some symptoms together as a syndrome and take the syndrome as a new indicator to screen malaria patients. So next step, we would combine the 12 symptoms in different ways, get different syndromes, and then evaluate each syndrome's SEN and PPV to select a better one.

The established syndromes

By consulting the previous literatures, combining the incidence rate of each symptom in the feverish patients, using stepwise decreasing method, we established 52 syndromes (table 3). The 52 syndromes' SEN and PPV were listed in the table 4.

An ideal syndrome for screening malaria patients should have both high SEN and PPV. So we summed each syndrome's SEN and PPV and calculated their mean values, listed in the table 4. We ranked the SENs of the syndromes in a rising sequence, presented the rising SENs and their PPVs and their means in the same coordinate, we got the figure-4.

Table 4. SENs and PPVs of the 52 syndromes

Syndrome	SEN	PPV	Mean	Syndrome	SEN	PPV	Mean
1	0.100	1.000	0.550	29	0.481	0.744	0.613
2	0.116	1.000	0.558	30	0.232	0.824	0.528
3	0.149	1.000	0.575	31	0.398	0.828	0.613
4	0.216	1.000	0.608	32	0.465	0.757	0.611
5	0.249	0.833	0.541	33	0.846	0.447	0.647
6	0.299	0.600	0.45	34	0.896	0.394	0.645
7	0.365	0.489	0.427	35	0.913	0.545	0.729
8	0.515	0.365	0.44	36	0.166	0.909	0.538
9	0.747	0.354	0.551	37	0.282	0.895	0.589
10	0.896	0.331	0.614	38	0.332	0.87	0.601
11	0.996	0.228	0.612	39	0.564	0.576	0.57
12	0.365	0.458	0.412	40	0.631	0.500	0.566
13	0.465	0.636	0.551	41	0.647	0.736	0.692
14	0.664	0.533	0.599	42	0.166	0.909	0.538
15	0.747	0.563	0.655	43	0.266	0.941	0.604
16	0.747	0.489	0.618	44	0.315	0.905	0.61
17	0.747	0.818	0.783	45	0.548	0.569	0.559
18	0.73	0.611	0.671	46	0.614	0.500	0.557
19	0.465	0.700	0.583	47	0.614	0.740	0.677
20	0.365	0.688	0.527	48	0.763	0.719	0.741
21	0.332	0.87	0.601	49	0.664	0.784	0.724
22	0.647	0.886	0.767	50	0.614	0.804	0.709
23	0.199	0.857	0.528	51	0.73	0.733	0.732
24	0.232	0.824	0.528	52	0.743	0.844	0.794
25	0.415	0.806	0.611				
26	0.631	0.905	0.768				
27	0.581	0.921	0.751				
28	0.647	0.867	0.757				

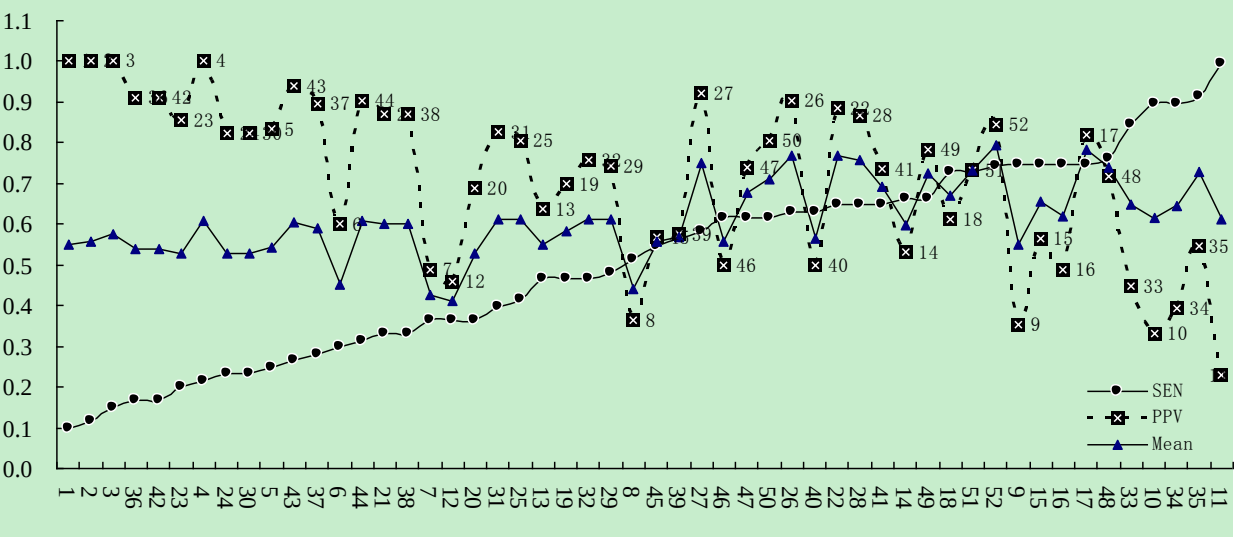

Figure 4. SENs of PPVs of the 52 syndromes

Figure 4 shows that, along with the rising of the SENs, the line of PPV has a big fluctuation and a descending trend. After the No.49 syndromes, the SEN have an evident ascend up to the 70%. After the No. 48, although the SENs climb up quickly, however, the PPVs have a big drop under the level of 50%. So the optimal syndrome was between the No.49 and No.48. By comparing the PPVs in this interval, we finally chose No. 52 as the optimal syndromes for it has relative high SEN(74.3%) and PPV(84.4%). The syndrome of No.52 includes the symptoms as follows: Body Temp≥39℃, periodic attack of fever and no diarrhea. Some comprehensive evaluation indexes of No.52 syndrome were listed in table 5. Its positive likelihood ratio is far high and negative likelihood ratio is very low; its Youden's index and Kappa value were both above 70%.

Table 5. the comprehensive evaluation index of the No.52 syndrome

No. syndrome	Positive likelihood ratio	Negative likelihood ratio	Youden's index	Kappa value
52	28.577	0.264	0.717	0.753

DISCUSSION

In this study, we used symptoms in feverish population to combine 52 different syndromes and finally the No.52 syndrome was selected as the best one for screening malaria patients, which includes "body temp≥39℃, periodic attack of fever of fever and no diarrhea". It's SEN and PPV were both far outweigh any single symptom'.

Some previous studies have tried to use symptoms as a tool to select targeted objects for blood smear test or for screening suspicious malaria patients to have a treat. Wang [6] had analyzed the symptom's composition of feverish people; at last he suggested that "chill and periodic attack of fever" can be used as a standard to screen feverish people for blood smear test. Bassert [7] investigated 280 local malaria patients in Zimbabwe and found that among these patients, 85.7% of them have the main complaint of headache, 79% about weak and 73.2% about high body temperature. He analyzed each single symptom's SEN and PPV and found that none single symptom' PPV was above 28%. So he got the conclusion that a single symptom or sign of the malaria can't be used to diagnose malaria. In Wang's study, he just analyzed the composition of each single symptom, not giving the SEN and PPV; although Bassert gave the SEN and PPV of each single symptom, he didn't consider combining some symptoms as syndrome. Our study combined some single symptom as syndromes to evaluate their SENs and PPVs. Comparing the previous studies, the syndromes have better SENs and PPVs for screening malaria patients.

Bruce-Chwatt [8] thinks that the basic clinical course of malaria is composed of a series of symptoms accompanied by an intermittent fever, which is one of the characteristics of the malaria different from other diseases. Fever is the most common symptom--about 99.4% malaria patients have fever [6]. So when we wanted to establish a syndrome for screening malaria patients, the feverish people was a preferred population. Feverish population has a broad range and

the accompany symptoms are various. Our study show that lots of feverish people accompany with alimentary canal symptoms and respiratory symptoms. However, we can't do blood smear test for all feverish ones, for doing that the cost is very high and the efficiency is quite low, especially in the area where the epidemic of malaria is in the period of elimination[9-11]. WHO critics [12]: in the elimination period of malaria surveillance, it would be a great waste of resource if we adopt the large-scale blood smear test method which was used in the control period.

A typical onset of malaria includes periodic chill, fever, sweating and fever reducing. However, in practice, many malaria patients' symptoms are atypical. Sha [9] analyzed the atypical symptoms of vivax malaria in the endemic area and found: the clinical manifestations are various; lots of patients have headache, dizziness and anorexia; partial patients have vomit and nausea; others have stuffy nose, cough and other respiratory symptoms. The results were consistent with our study. Some symptoms are rare in the malaria patients, so they can use as exclusion in screening malaria, such as diarrhea in the selected syndrome.

The selected syndrome can be used in the elimination period of malaria, to screen the suspicious patients to do blood smear test. And also, in the endemic area where laboratory equipment and personal skill are lack, the selected syndrome can be used for screening suspicious patients to have a treat.

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