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Risk Factors for Border Malaria in a Malaria Elimination Setting: A Retrospective Case-Control Study in Yunnan, China

Jian-Wei Xu, Hui Liu,* Yu Zhang, Xiang-Rui Guo, and Jia-Zhi Wang

Yunnan Institute of Parasitic Diseases, Yunnan Provincial Center of Malaria Research, Yunnan Provincial Collaborative Innovation Center for Public Health and Disease Prevention and Control, Yunnan Provincial Key Laboratory of Vector-Borne Diseases Control and Research, Puer 665000, China; The Fourth Hospital of Baotou Municipality, Inner Mongolia, Baotou, China; Yingjiang County Center for Disease Control and Prevention, Yingjiang China; Tengchong County Center for Disease Control and Prevention, Tengchong, China

Abstract. A retrospective case-control study was conducted to identify risk factors for border malaria in a malaria elimination setting of Yunnan Province, China. The study comprised 214 cases and 428 controls. The controls were individually matched to the cases on the basis of residence, age, and gender. In addition, statistical associations are based on matched analyses. The frequencies of imported, male, adult, and vivax malaria cases were respectively 201 (93.9%), 194 (90.7%), 210 (98.1%), and 176 (82.2%). Overnight stay in Myanmar within the prior month was independently associated with malaria infection (odds ratio [OR] 159.5, 95% confidence interval [CI] 75.1–338.9). In particular, stays in lowland and foothill (OR 5.5, 95% CI 2.5–11.8) or mid-hill (OR 42.8, 95% CI 5.1–319.8) areas, or near streamlets (OR 15.3, 95% CI 4.3–55.2) or paddy field or pools (OR10.1, 95% CI 4.4–55.8) were found to be independently associated with malaria. Neither forest exposure nor use of vector control measures was associated with malaria. In conclusion, travel to lowland and foothill or mid-hill hyperendemic areas, especially along the waterside in Myanmar, was found to be the highest risk factor for malaria. In considering the limitations of the study, further investigations are needed to identify the major determinants of malaria risk and develop new strategies for malaria elimination on China-Myanmar border.

INTRODUCTION

Remarkable progress has been achieved in reducing malaria burden globally over the past 10 years.[1,2] Nowadays, there are 99 endemic countries; of these, 65 are controlling malaria and 34 are pursuing elimination. The 34 eliminating countries have declared a national policy for malaria elimination or are pursuing spatially progressive elimination within their borders.[2–4] Countries in the Asia Pacific region are making particularly strong progress toward eliminating malaria.[5] As one of countries with a great reduction in malaria incidence, China aims to eliminate malaria by 2020.[6]

In low transmission settings, malaria is increasingly imported, caused by *Plasmodium vivax*, and clustered demographically in adult men with shared epidemiological risk factors. Current malaria control interventions and strategies are not likely to be optimal, and novel strategies targeting high-risk groups are urgently needed. In high endemic, control settings, risk factors can be established through nationally representative cross-sectional surveys, such as malaria indicator surveys. However, in areas where transmission is very low and malaria infections are rare, these surveys are unlikely to adequately detect cases or identify risk factors. Furthermore, such large-scale surveys require substantial financial and operational resources.[7,8] Case-control analysis is a well-established method to study rare diseases and identify associated demographic, behavioral, and clinical risk factors, being particularly appropriate for rare diseases. As yet, this epidemiological tool has not to be extensively applied to malaria, which has traditionally been studied in high-endemic settings.[7,9–11]

In China, malaria has been eliminated from large parts of the country. The remaining at-risk areas can be characterized as low endemic and they are clustered in parts of central China, southern China, and Tibet. The southern province of Yunnan will be particularly challenging for elimination as it shares a 4,061 km border with malarious countries including Myanmar, Laos, and Vietnam.[12,13] The epidemiology of malaria in this area is presumed to be similar to other parts of Southeast Asia, where reported malaria incidence and parasite species have been identified. Malaria tends to concentrate among migrant workers on border regions and in forest areas. For example, men who travel into the deep forest for work become infected with bites from *Anopheles dirus* (the primary vector in the deep forest of Southeast Asia) and return to their home villages on the forest fringe where they become reservoirs for transmission of the parasites by *Anopheles minimus* (the primary vector on the forest fringe of Southeast Asia) to their young children.[14] However, these risk factors have not been evaluated in a controlled study. To improve understanding of risk factors of border malaria infection in Yunnan and to support the design and implementation of targeted interventions, we conducted a retrospective case-control study.

METHODS

Study site. The study was conducted in Tengchong and Yingjiang, two border counties at the Yunnan-Myanmar border (Figure 1). There are 39 health facilities that are required to report all suspected and laboratory-confirmed malaria cases through the China Information System for Disease Control and Prevention (CISDCP), the national internet-based disease reporting system. Basic demographic data and contact information are included in the reports. The epidemiology of malaria in this area has been described.[14–16] Briefly, these sites were selected because they are formerly hyper-endemic areas and the current hot spots of border malaria in China, as a result there were enough cases for the study.

Study design and data collection. The study was a retrospective case-control design and conducted from April to October 2012. The laboratory-confirmed cases were reported from all health facilities in Tengchong and Yingjiang from September 2010 to December 2011. Li and Fan[15] reported that 97.5% (2,556 of 3,646) of malaria patients were imported from

*Address correspondence to Hui Liu, Yunnan Institute of Parasitic Diseases, 6 Xiyuan Road, Puer, 665000, Yunnan, China. E-mail: liubible@126.com

FIGURE 1. Study Site, Yingjing and Tengchong, Yunnan Province, China.

Myanmar and most of them were male adults in Tengchong. To exclude the confounding effect of age and sex, controls were matched by age and sex. The goal of malaria elimination was to achieve zero incidence of locally contracted cases. It was important to identify the risk factors of local malaria infection,[17,18] therefore community of residence was also selected as one of matching criteria. Finally, the controls were matched two to one with cases on the basis of residence, age (±2 years), and gender.

First, blood smears from malaria cases reported from September 2010 to December 2011 were reread by an expert microscopist for secondary confirmation. Using contact information available in the case reporting system, the confirmed cases were then visited at their homes by study staff and approached for orally informed consent. A paper survey with 35 questions was administered in Mandarin to assess demographics and potential risk factors including housing condition, local ecology, socio-economic status, behavior, occupation, activities, travel, malaria awareness and knowledge, and use of malaria prevention measures. Information on activities, housing, use of personal protective measures, and local ecology was obtained on both the subject's home in Yunnan and at the locations where they had stayed 1 month before the date of malaria attack of case patients.

Controls were then recruited from adjoining households of cases.[13] Subjects matching the case by age (±2 years) and gender were invited to participate in the study. A finger prick was performed in consenting subjects to generate a blood slide for microscopy. Only subjects that were malaria free by microscopy were recruited as controls. The same questionnaire was then conducted with control subjects to collect data on potential risk factors.

Ethical approval was obtained from the Ethics Committee of Yunnan Institute of Parasitic Diseases, China. The Ethics Committee approved a verbal consent procedure as sufficient because the study was interview-based, and screening for malaria by microscopy is one of the malaria control components. Questionnaires were conducted by a team of seven trained interviewers.

Defining wealth tertiles. Details were recorded on principal components of housing characteristics (type of wall and roof), household appliances, and transport tools; and then were used to construct a wealth index. The wealth tertile was defined as 1) lowest tertile: soil and wood walls and terracotta roofs, only television sets or without any valuable electric items, only bikes or without any transport tools; 2) middle tertile: brick walls and terracotta roofs, television sets, motorcycles; 3) highest tertile: brick or reinforced concrete walls and roofs, television sets, and refrigerators, tractors or cars or trucks.[19–22]

Statistical analysis. Data were double entered and cleaned in EpiData 3.1 (EpiData Association, Odense, Denmark), and analyzed in Epi Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA). The statistical associations are based on matched analyses. For the case and the control group, the frequency and proportions of each predictor variable were calculated and compared using a χ^2 test. Variables likely associated with the outcome ($P < 0.25$) were selected as candidate variables for matched univariate and multivariate logistic regression.[23] Missing data were excluded from these analyses.

RESULTS

There were 214 malaria cases and 428 matched controls recruited to participate in the study. Of the 214 confirmed malaria case patients, 176 (82.2%) were vivax malaria and 38 (17.8%) were falciparum malaria. There were no mixed infections. Based on the CISDCP, 201 (93.9%) cases were imported from other countries, 12 (8.0%) locally acquired, and 1 could not be confirmed as imported or local. Among the 12 local cases, 4 were < 15 years of age, and the youngest one was only 3 years of age.

TABLE 1
Characteristics of cases and controls, Yunnan, China, 2012

Characteristics	No. patient-cases (%) $N = 214$	No. controls (%) $N = 428$	P value
Demographics			
Male sex	194 (90.7)	388 (90.7)	1.000
Age (years)			
< 16	4 (1.9)	6 (1.4)	0.738
16–30	83 (38.8)	160 (37.4)	0.796
31–50	111 (51.9)	241 (56.3)	0.326
> 50	16 (7.5)	21 (4.9)	0.255
Ethnicity			
Han (Chinese)	174 (81.3)	349 (81.5)	0.943
Jingpo (Kachin)	16 (7.5)	36 (8.4)	0.682
Dai (Thai)	11 (5.1)	26 (6.1)	0.632
Lisu and others	13 (6.1)	17 (4.0)	0.321
Wealth index			
Lowest tertile	114 (53.3)	230 (53.7)	0.978
Middle tertile	77 (36.0)	161 (37.6)	0.751
Highest tertile	23 (10.7)	37 (8.6)	0.472
Major cash sources			
Working as day laborers	109 (50.9)	215 (50.2)	0.933
Farming and others	105 (49.1)	213 (49.8)	0.933
Education			
Illiterate and primary school	66 (30.8)	140 (32.7)	0.697
Secondary school and higher	148 (69.2)	288 (67.3)	0.697
Housing structure			
Armoured concrete	13 (6.1)	21 (4.9)	0.533
Brick and tile	77 (36.0)	169 (39.5)	0.389
Wood and earth	119 (55.6)	233 (53.4)	0.779
Others	5 (2.3)	5 (1.2)	0.430
Screened windows and doors	182 (85.4)	375 (87.6)	0.365
Vector control measures			
Use of measures against mosquito bite in home	171 (79.9)	281 (65.7)	0.0003
No any bed nets	65 (30.4)	195 (45.6)	0.0003
untreated nets	113 (52.8)	187 (43.7)	0.036
ITNs or LLINs	36 (16.8)	46 (10.7)	0.041
Sleeping under a net prior malaria attack	138 (64.5)	$N = 351$ 247 (70.4)	0.145
Local ecology			
Hill zone			
Lowland and foothill	101 (47.2)	197 (46.0)	0.845
Mid hill	56 (26.2)	114 (16.6)	0.899
Upper hill	57 (26.6)	117 (27.3)	0.851
Streamlets	76 (35.5)	135 (31.5)	0.312
Paddy field or pools	56 (26.2)	114 (26.6)	0.975
None water source	82 (38.3)	179 (41.8)	0.394
Proximity to vegetation			
Forest	26 (12.1)	49 (11.4)	0.794
Crops	141 (65.9)	301 (70.3)	0.252
Others	47 (22.0)	78 (18.2)	0.307
Overnight stay in Myanmar ≤ 1 month before malaria attack	201 (93.9)	$N = 419$ 74 (17.7)	< 0.0001
Knowledge			
Knowledge that malaria is caused by mosquitoes	$N = 213$ 127 (59.6)	$N = 427$ 252 (59.0)	0.883
Knowledge of malaria prevention measures, including:	$N = 213$	$N = 426$	
Chemoprophylaxis	115 (54.0)	196 (46.0)	0.057
Bed nets or repellents	60 (28.2)	140 (32.9)	0.228
No knowledge	38 (17.8)	90 (21.1)	0.328
Awareness of malaria prevention	$N = 213$ 68 (31.9)	$N = 425$ 137 (32.2)	0.937

For cases and controls, $N = 214$ and $N = 428$, respectively, unless otherwise indicated.
ITNs = insecticide-treated nets; LLINs = long-lasting insecticide nets.

TABLE 2
Activities, housing conditions, and local ecology in Myanmar, data from cases and controls that stayed overnight in Myanmar before the malaria attack in the case

Characteristics	No. patient-cases (%) $N = 201$	No. controls (%) $N = 74$	P value
Activities in Myanmar	$N = 198$		
Lumbering	135 (68.2)	64 (86.5)	0.04
Others	63 (31.8)	10 (13.5)	0.04
Housing conditions	$N = 198$		
Shelter huts	147 (73.1)	66 (89.2)	0.013
Houses	51 (25.8)	8 (1.8)	0.0008
Use of measures against mosquito bites	$N = 195$ 84 (43.1)	$N = 72$ 10 (13.9)	< 0.0001
Hill zone	$N = 198$		
Lowland and foothill	83 (41.9)	11 (14.9)	< 0.0001
Half hill	47 (23.7)	1 (1.4)	< 0.0001
Hill	68 (34.4)	62 (83.8)	< 0.0001
Mosquito breeding sites ≤ 100 m around staying site			
Streamlets	106 (52.7)	7 (9.5)	< 0.0001
Paddy field or pools	40 (19.9)	3 (4.1)	0.0025
None	55 (27.4)	64 (86.5)	< 0.0001
Vegetation nearby staying site	$N = 198$		
Forest	127 (63.2)	62 (83.8)	0.002
Crop	48 (23.9)	9 (12.2)	0.029
Others	23 (11.6)	3 (4.1)	0.098

For cases and controls, $N = 201$ and $N = 74$, respectively, unless otherwise indicated.

Characteristics of the cases versus controls are shown in Table 1. The cases were predominantly male (194 of 214 or 90.7%) and the 428 controls were matched by gender. Median age of cases and controls were 33.6 (range 3 to 62) and 33.8 (range 4 to 64) years. The case and control groups were similar in terms of ethnicity, household wealth index, main cash sources, education, housing structure, presence of screened windows and doors, hill zone, proximity to breeding sites and vegetation, and awareness on malaria prevention ($P > 0.25$). According to answers of participants to a specific knowledge question on methods for malaria prevention, 115 (54.0%) cases versus 196 (46.0%) controls knew of chemoprophylaxis, and 60 (28.2%) cases versus 140 (32.9%) controls knew of using bed nets or repellents for malaria prevention ($P < 0.25$). Cases were more likely to own bed nets including insecticide-treated nets (ITNs) or long-lasting insecticide nets (LLINs) and other measures against mosquito bites in the home than control group ($P < 0.05$). Most of the cases (93.9%) stayed overnight in Myanmar within 1 month of the malaria episode.

Characteristics of cases and controls that stayed at least 1 night in Myanmar in the 1 month before the malaria attack in the case are shown in Table 2. In Myanmar, lumbering activities, housing conditions, use of measures against mosquito bites, and local ecology were significantly different between case and control groups ($P < 0.05$). The hill zones of their staying sites were similar ($P = 0.464$).

Table 3 shows the results of matched univariate and multivariate logistic regression analyses. Independent risk factors associated with malaria infection were overnight in the hyperendemic areas of Myanmar, especially staying in lowland, foothill, and mid hill, and proximity of potential mosquito breeding sites such as streamlets and paddy fields or pools nearby their staying site. In both China and Myanmar, ownership of bed

TABLE 3
Risk factors for border malaria infection Yunnan, China, 2012

Factors	OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Features in home, China:				
Use of measures against mosquito bite	0.48 (0.32–0.72)	0.0003	0.69 (0.21–1.71)	0.3312
No any nets at home (vs. ITN or LLIN)	0.43 (0.25–0.74)	0.0017	0.64 (0.24–1.67)	0.3017
Own untreated nets (vs. ITN or LLIN)	0.77 (0.46–1.30)	0.3690	0.89 (0.36–1.80)	0.3690
No use of a net prior malaria attack	0.76 (0.52–1.12)	0.1728	0.92 (0.47–1.45)	0.3627
Overnight in Myanmar ≤ 1 month prior malaria attack	53.75 (29.94–97.67)	< 0.0001	159.5 (75.1–338.9)	< 0.0001
Features of staying site in Myanmar:				
Lumbering reported as an activity	0.33 (0.15–0.73)	0.0040	2.44 (0.36–16.76)	0.3652
Shelter hut vs. house	0.35 (0.14–0.82)	0.0125	0.71 (0.16–3.23)	0.6627
No use of measures against mosquito bites	0.21 (0.10–1.46)	< 0.7061	0.73 (0.15–1.75)	0.2807
Lowland and foothill (vs. upper)	6.88 (3.20–15.07)	< 0.0001	5.45 (2.52–11.80)	< 0.0001
Mid hill (vs. upper)	42.85 (6.07–860.16)	< 0.0001	42.82 (5.13–319.75)	0.0002
Streamlet within 100m	17.62 (7.17–45.27)	< 0.0001	15.30 (4.25–55.16)	< 0.0001
Paddy field or pools within 100m	15.52 (4.27–66.72)	< 0.0001	10.12 (4.36–55.76)	< 0.0001
Proximity to forest	0.27 (0.06–0.99)	0.0470	0.44 (0.08–2.36)	0.3402
Proximity to crops	0.70 (0.13–3.21)	0.7449	0.62 (0.14–2.61)	0.5271

ITNs = insecticide-treated nets; LLINs = long-lasting insecticide nets.

nets including ITNs or LLINs, using measures against mosquito bites including sleeping under a net did not differ significantly between case patients and matched controls. In Myanmar, activities and housing conditions of Chinese migrants, and vegetation nearby the staying site did not differ significantly between case patients and matched controls too.

DISCUSSION

The study revealed that most case-patients were imported from the neighboring districts of Myanmar (93.9%), male (90.7%) and 16–50 years of age (90.7%), and vivax malaria (82.2%). Independent risk factors associated with malaria infection were overnight in the lowland, foothill, and half-hill areas of Myanmar. This coincides with comments in the literature: malaria cases are increasingly male, adult, clustered geographically, imported among migrant and other hard-to-reach groups, and caused by *P. vivax* in eliminating settings.[7] This is also similar in Cambodia, the males and adults had an increased risk of *Plasmodium* spp. infection.[24] However, local malaria infection still exists, especially for patients < 15 years of age, and the youngest one only 3 years of age, who had never been in the neighboring districts of Myanmar, showed that local malaria transmission has not been interrupted completely.

In the Greater Mekong Subregion (GMS), forests are commonly considered as a major determinant of malaria risk.[14,25–29] In Vietnam a large proportion of all malaria cases and deaths occurred in the central mountainous and forested areas.[28] In Myanmar, about 60% of the total malaria cases occurred in forest or forest fringe areas; forest workers (loggers, gem miners, etc.) were at high risk of malaria.[29] The explanation is that forests and forest fringes are mountainous and hilly areas, difficult of access, sparsely inhabited by the ethnic minorities, and limited economic development and infrastructure. Men who travel into the deep forest for work become infected with bites from *An. dirus* and return to their home villages on the forest fringe where they become reservoirs for transmission of the parasites by *An. minimus* to their young children.[14,29] However, the study found that malaria was associated with Chinese migrants staying in the lowland and foothill or mid-hill areas, especially along the waterside. The study results showed that the border crossers of the control group reported staying in forests more often than that of the case group, and the percentage of loggers among controls (86.5%) was higher than that among case patients (68.2%). One of the reasons might be that the study site was next to Kachin State of Myanmar, where malaria burden is particularly high and malaria outbreaks occur frequently, the malaria-related mortality rate was as high as 7.8 deaths per 1,000 people in 2005[29–31]; Liu and others[32] reported a mean parasite rate 16.3% (95% confidence interval [CI]: 12.9–20.1%) among residents of Kachin State in 2010. In most parts of Southeast Asia, the year-round high rainfall and temperatures, and malaria vectors lead to persistent and intense malaria transmission.[25] However, in northern Myanmar the mountainous areas border with China, the high altitude leads to its difference from most parts of Southeast Asia; the hilly forested areas have low temperatures, fewer mosquito breeding sites, less malaria vector, and less parasite reservoirs caused by sparse population.

In theory, people who have a better knowledge of malaria transmission and methods of prevention, awareness and using measures for malaria prevention, should have reduced malaria infection. The reported investigation in the literature documented that use of bed nets provide useful protection against malaria infection.[33,34] However, the results of the study did not show that the knowledge of malaria transmission and prevention was associated with the reduced risk of malaria infection; furthermore, it was not documented that the ownership and the use of bed nets or repellents was related to the reduced risk of malaria infection. On the contrary, the percentage of case patients (54.0%) who knew chemoprophylaxis was higher than that of controls (46.0%); and the percentage of case patients (43.1%) who used measures of bed nets or repellents against mosquito bites in Myanmar was higher than that of controls (13.9%). When malaria is rare to see in the eliminating setting of China, the better knowledge and behavior might be attributable to malaria infection. People who had malaria attacks might have more experience with malaria and they might actively seek knowledge and take action for malaria prevention and control.

Overmatching may be one of the main limitations in this study. In the eliminating setting, malaria cases cluster on border areas, are increasingly male, adult, imported, among migrant and other hard-to-reach groups.[7] Li and Fan reported that 97.5% (2,556 of 3,646) of malaria patients were imported from Myanmar and most of them were male adults in the study site.[15] To exclude the confounding effect of age and sex, controls were matched by age and sex. The goal of malaria elimination was to interrupt local mosquito-borne malaria transmission in a defined geographical area, i.e., zero incidence of locally contracted cases; but imported cases will continue to occur, and continued intervention measures are required to prevent reintroduction.[17,18] Therefore, community of residence was also selected as one of the matching criteria to identify the risk factors of local malaria infection. One of the purposes of using age, gender, and community of residence as matching criteria was to explore methods for reduction of the confounding effect from age and gender, and to identify risk factors of local malaria infection. However, we could not ensure whether this design might lead to overmatching and limiting assessment on these as independent risk factors. The study results did not identify any risk factors of local malaria infection because of only 12 (8.0%) locally acquired cases, therefore the purpose has not been achieved by using residence as one of the matching criteria. This failure showed that use of residence as a matching criterion may be inappropriate in a malaria elimination setting. Despite among 214 case-patients, 194 (90.7%) were male and 210 (98.1%) adult (≥ 16 years), this study could not identify whether they are an independent risk or confounding factors because of using age and gender as the matching criteria.

The study also had several other limitations. The first was the potential bias in capture of case patients. The cases were from records of public health facilities. The malaria patients who sought treatment from the private sector were excluded from this study. Some Chinese migrants carry anti-malarial drugs with them for self-saving during staying in Myanmar; however, the case-patients were from parasite-based diagnosis in China. In cases where the self-medication cured their malaria infection, they might not seek diagnosis and treatment from the public health service in China, which led to exclusion of them from the study too. These might lead to selection bias. The second is that some people declined to answer certain questions that they thought of as sensitive, and might cause responding bias. The third is that the financial support for this study only permitted an operation period of < 1 year, unable to recruit enough case patients in such a short period, therefore a design of retrospective case-control study was used. A weakness of this design was that the data were collected after the fact, and there are major challenges with recall bias, particularly in the control subjects who would have a hard time remembering the time before a date that is not relevant to them.

In conclusion, imported malaria is particularly prominent, and most malaria patients are male, adult, and infection of *P. vivax* in the malaria elimination setting of Yunnan, China. The independent risk factors for malaria infection were staying in the lowland, foothill, and half hill, and availability of streamlets and paddy fields or pools nearby their staying sites of Myanmar. However, the study identified neither forest exposure nor use of vector control measures to be independently associated with malaria infection. In considering the limitations of the study, further research is needed to identify the major determinants of malaria risk on the China-Myanmar border, and to develop new strategies for malaria elimination; for example, how to promptly find and treat imported malaria infection in China, reduce malaria transmission and incidence in Myanmar through effective cooperation mechanism between China and Myanmar, and promote vigilance and use of personal protection among Chinese border crossers through effective behavior change in communication.

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Authors' addresses: Jian-Wei Xu and Hui Liu, Yunnan Institute of Parasitic Diseases, Malaria Division, Puer, China, E-mails: xjw426@163.com and liubible@126.com. Yu Zhang, The Fourth Hospital of Baotou Municipality, Clinical Laboratory, Baotou, China, E-mail: 905049522@qq.com. Xiang-Rui Guo, Yingjiang County Center for Disease Prevention and Control, Division of Parasitic Diseases, Yingjiang, China, E-mail: fangwenyan50537405@qq.com. Jia-Zhi Wang, Tengchong County Center for Disease Prevention and Control, Division of Parasitic Diseases, Division of Parasitic Diseases, Tengchong, China, E-mail: tcwangjiazhi@yahoo.com.cn.

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