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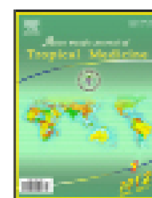


Document heading doi:

Immunodiagnostic efficacy of detection of *Schistosoma japonicum* human infections in China: a meta analysis

Wei Wang[1,2*], Youzi Li[1,2], Hongjun Li[1,2], Yuntian Xing[1,2], Guoli Qu[1,2], Jianrong Dai[1,2], Yousheng Liang [1,2*]

[1]*Jiangsu Institute of Parasitic Diseases, 117 Yangxiang, Meiyuan, Wuxi 214064, Jiangsu Province, People's Republic of China*
[2]*Key Laboratory on Technology for Parasitic Disease Prevention and Control, Ministry of Health, 117 Yangxiang, Meiyuan, Wuxi 214064, Jiangsu Province, People's Republic of China*

ARTICLE INFO

Article history:
Received 14 November 2011
Received in revised form 15 December 2011
Accepted 5 January 2012
Available online 20 January 2012

Keywords:
Schistosomiasis japonica
Immunodiagnosis
Indirect hemagglutination assay
Enzyme-link immunosorbent assay
Diagnostic efficacy
Meta-analysis

ABSTRACT

Objective: To assess the diagnostic efficacy of the currently most widely used indirect hemagglutination assay (IHA) and enzyme-linked immunosorbent assay (ELISA) for detection of *Schistosoma japonicum* human infections. **Methods:** A comprehensive search was undertaken from China National Knowledge Infrastructure, Wanfang Database, VIP Database, PubMed, Cochrane Library, Science Citation Index Expanded, Proquest, and the inclusion and exclusion criteria were strictly settled. The funnel plot was used to assess the publication bias, Cochran's Q test was employed to measure the homogeneity between studies, a summary receiver operating characteristic (SROC) curve was used to compare the diagnostic accuracy between the IHA and ELISA qualitatively by means of the Weighted Least Square method, the Ordinary Least Square method and the Robust regression method, and the diagnostic odds ratio (DOR) was drawn to compare the accuracy quantitatively. **Results:** Out of 785 publications, 19 papers were eventually selected for analysis. Literature quality assessment indicated that minor publication bias existed in studies pertaining IHA test, but no bias was found in literatures regarding ELISA test. The heterogeneity test showed a heterogeneity between studies was present (χ^2=466.07 and 34.67, both P values<0.0001). The areas under the SROC curves of IHA were all higher than that of ELISA test using the three methods (Weighted Least Square method: 0.766 *vs.* 0.695, Ordinary Least Square method: 0.826 *vs.* 0.741, Robust regression: 0.815 *vs.* 0.715). The TPR* values for IHA and ELISA were 0.710, 0.759, 0.749, and 0.650, 0.686 and 0.666, respectively, and *OR* values were 5.997, 9.937, 8.893, and 3.432, 4.784 and 3.959, respectively. The DOR of IHA was 9.41 (95% *CI*: 4.88-18.18), and 4.78 (95% *CI*: 3.21-7.13) for ELISA. **Conclusions:** All above results revealed that the diagnostic performance of IHA is better than that of ELISA. However, taking into account their unsatisfactory diagnostic value in areas with low infection intensity, a search for a better diagnostic test that can be applied in field situations in China should be given high priority.

1. Introduction

Schistosomiasis, one of the neglected tropical diseases[1], is still a major public health concern affecting over 207 million people in 76 countries, with a further 779 million people at risk of infection with one of the causative parasites[2]. Schistosomiasis japonica, caused by infection with *Schistosoma japonicum* (*S. japonicum*), was considered as one of the most serious parasitic diseases that were endemic in China[3-5]. Large-scale schistosomiasis control programs since the 1950s have dramatically reduced the number of the areas endemic for the parasite as well as the burden of disease among humans[6-12], and the control achievements were further consolidated by the World Bank Loan Project (WBLP) for Schistosomiasis Control initiated since 1992 in China[13-16]. Nevertheless, following the termination of the WBLP for Schistosomiasis Control in 2001, and the effects

*Corresponding author: Wei Wang and Yousheng Liang, Jiangsu Institute of Parasitic Diseases, Key Laboratory on Technology for Parasitic Disease Prevention and Control, Ministry of Health, 117 Yangxiang, Meiyuan, Wuxi 214064, Jiangsu Province, People's Republic of China.
E-mail: wangweijipd@yahoo.com.cn, wxliangyousheng@yahoo.cn

Foundation project: Supported by the National S & T Major Projects (2008ZX10004-011), the National Science & Technology Pillar Program of China (2009BAI78B06), the National Natural Science Foundation of China (81071379), the Natural Science Foundation of Jiangsu Province (BK2009076), the Jiangsu Provincial Scientific Foundation of Preventive Medicine (Y201031), Jiangsu Society for Editors of Scientific and Technical Periodicals (JKQJX006) and the Department of Health, Jiangsu Province (X200912).

of major floods along the Yangtze River valley and several other factors[17-26], schistosomiasis japonica was resurged in China[27-29], and currently the core endemic regions are mainly located in the lake regions of five provinces along the middle and lower reaches of the Yangtze River, and in some mountainous areas in the provinces of Sichuan and Yunnan, and over 0.7 million people living in China are thought to have the disease[30-33].

Diagnosis is central to the control of schistosomiasis[34,35]. It can be divided into direct parasitological techniques (detection of parasite eggs) like the Kato-Katz technique[36] and the miracidium hatching method[37], and indirect approaches (detection of antibody or circulating antigen in serum) including intradermal test, indirect hemagglutination assay (IHA), enzyme-linked immunosorbent assay (ELISA), circumoval precipitin test[38], dipstick dye immunoassay[39,40], *etc*. After the long-term implementation of national schistosomiasis control programs and large-scale praziquantel-based chemotherapy, both the prevalence and the intensity of infection of *S. japonicum* have declined dramatically, with the remaining majority of endemic foci in China characterized by a low intensity of infection independent of prevalence[41,42]. The problem of insensitivity of the parasitological techniques surfaced in China in terms of the low diagnostic accuracies in areas with low infection intensities. In addition, microscopy is time-consuming and labor-intensive[35].

Immunodiagnostic techniques, having high sensitivities, are easy to perform and are an excellent epidemiological tool for screening target populations for chemotherapy in endemic foci[34]. These assays are also useful for the surveillance of chemotherapy efficacy and for periodic control of transmission of the infection after it has been eliminated in an area[35]. Currently, ELISA and IHA are most widely used in China for immunodiagnosis of schistosomiasis japonica in the schistosome-endemic areas[35]. Many studies have been carried out to assess the diagnostic accuracies of different assays both in laboratory and in field settings in China. Due to the variation of experimental conditions, the values of the immunodiagnostic tests were vastly different, which would lead to the inaccurate estimates of the prevalence and the targets for chemotherapy. In addition, inaccurate evaluations impact the government decision-makers to formulate the disease control strategy[35,38]. Considering the fact that both ELISA and IHA tests were extensively used in China, a comprehensive and more accurate assessment of their diagnostic efficacies is of great importance for screening, epidemiological survey and control of schistosomiasis. We, therefore, conducted an integrated meta-analysis to assess the immunodiagnostic efficacies of the ELISA and IHA tests for detection of *S. japonicum* human infections in the field.

2. Materials and methods

2.1. Search strategy and data source

Electronic databases including China National Knowledge Infrastructure, Wanfang Database, VIP Database, PubMed, Cochrane Library, Science Citation Index Expanded, Proquest, and conference abstracts/hand searching were jointly employed for a comprehensive ascertainment to search data concerning the diagnostic efficacy of ELISA or IHA for schistosomiasis japonica in China. No restriction was applied to year of publication, because we did not want to miss any publications. All titles and abstracts were read carefully, and the full texts of the screened publications were reviewed.

2.2. Study selection

Both of the inclusion criteria and exclusion criteria for searching the publications were settled in the first stage of the meta-analysis. A text was included if it met all of the following criteria: (1) Sensitivity and specificity were reported or could be calculated; (2) IHA or ELISA test was used for immunodiagnosis on human infections; (3) The diagnostic value was identified by any gold standard methods of parasitological examinations such as Kato-Katz or the miracidium hatching test; (4) A schistosome-endemic region with intensity of infection was enrolled; (5) The full text was available for review. While the literatures failed to meet the criteria mentioned above or were unclear to inadequately present a certain term, then they were excluded.

2.3. Assessment of literature quality

The funnel plot was drawn to evaluate the literature quality using software Review Manager 4.2, and the funnel plot asymmetry indicated the emergence of publication bias.

2.4. Meta analysis

All data pertaining to IHA, ELISA, the gold standard used and the indicators of diagnostic accuracy including true positives (TP), false positives (FP), false negatives (FN) and true negatives (TN), sensitivity and specificity were initially extracted into a spreadsheet. Before merging the effect size, the heterogeneity test should be carried out to identify the homogeneity of the studies. We employed Cochran's Q test to measure the homogeneity between studies[43]. Following the heterogeneity test, the random effects model were used to estimate overall studies in order to take into account heterogeneity in the sources, and the sensitivity, specificity, likelihood ratio (LR) were merged. A summary receiver operating characteristic (SROC) curve was fit to compare the diagnostic accuracy between the IHA and ELISA qualitatively. Following a logit transformation, $D=\ln[(TP\times TN)/(FN\times FP)]$, $S=\ln[(TP\times FP)/(TN\times FN)]$. Where

D represents accuracy, namely a ln*OR* value of diagnostic tests; and S represents range of positive standard. Each indicator was added up 0.5 to avoid the emergence of 0. An SROC linear regression model was established between D and S, and the model is D=A+BS, namely $TPR=\{1+e^{-A/(1-B)}[(1-FPR)/FPR]^{(1+B)(1-B)}\}^{-1}$, while A and B represent the regression intercept and coefficient, respectively, which was calculated by the Weighted Least Square method, Ordinary Least Square method and Robust regression in this study. The sensitivity and specificity for the single test threshold identified for each study were used to plot an SROC curve, while the y axis represents TPR (sensitivity), and x axis for FPR (1–specificity). The area under curve (AUC) was calculated, and bigger AUC indicates better accuracy of the diagnostic tests. The odds ratios (*OR*s) of the two diagnostic tests were merged weightedly to compare the accuracy quantitatively, and the forest plot was drawn.

All statistical analyses and drawings were done in software Review Manager 4.2 and Meta–disc recommended by the Cochrane Collaboration.

3. Results

3.1. Literature searched

A total of 785 potentially related documents were identified. The flow chart in Figure 1 shows the steps of the process for the study selection, including the number of papers identified and number for exclusion of articles according to the criteria. Finally, a total of 19 papers were enrolled in the present study, among which 10 reported IHA, 5 reported ELISA and another 4 articles reported both. The diagnostic accuracy of both ELISA and IHA for schistosomiasis japonica presented a wide range of values. Among these studies, the sensitivity of IHA ranged from 37.6% (32.1%–43.3%) to 95.1% (83.5%–99.4%) and specificity from 35.7% (33.2%–38.2%) to 93.8% (91.6%–95.6%), while the sensitivity of ELISA spanned from 57.1% (42.2%–71.2%) to 97.3% (93.9%–99.1%) and specificity from 20.4% (16.5%–24.7%) to 84.3% (80.5%–87.5%). Details concerning the enrolled literatures are shown in Table 1[44–62].

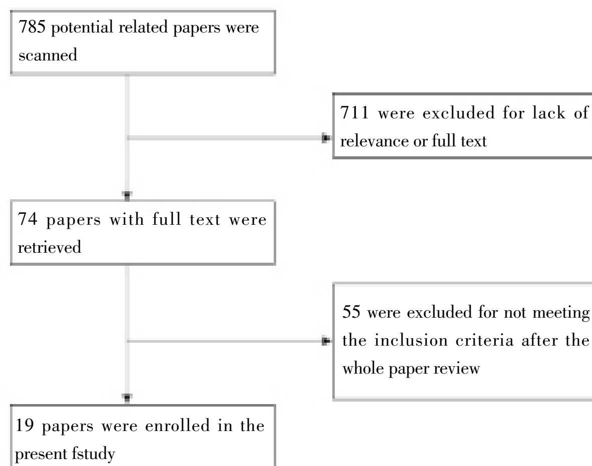


Figure 1. The flowchart of the process of study selection.

3.2. Literature quality assessment

According to the funnel graphs (Figure 2a and 2b), the plot pertaining to the diagnostic value of ELISA is almost symmetrical, with dense scattering dots, which suggests that there is no publication bias found. However, minor publication bias still exists in studies regarding the diagnostic efficacies of IHA according to the dots in the funnel graph.

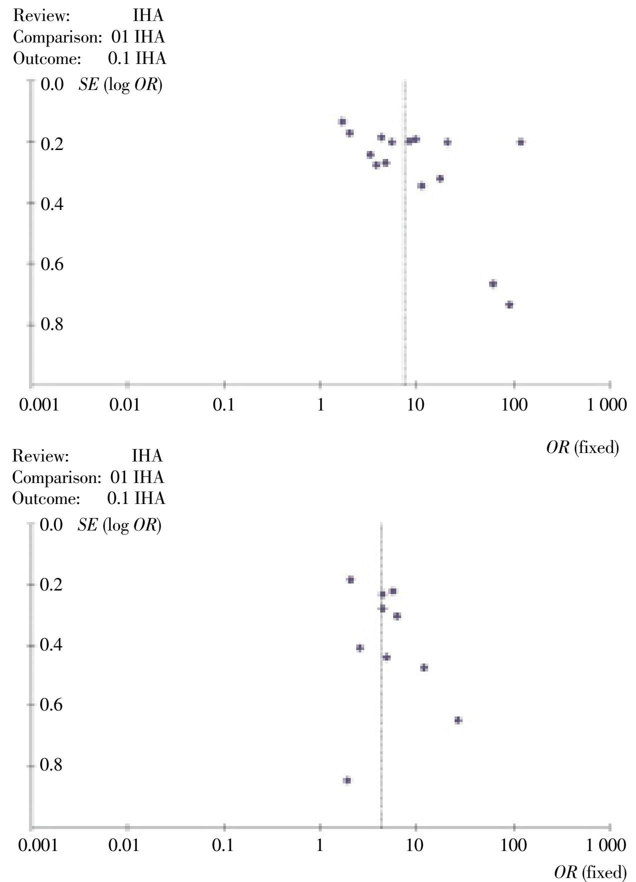


Figure 2. The funnel graphs for analysis of publication bias in studies pertaining to the diagnostic values of IHA (2a) and ELISA (2b).

3.3. Meta analysis

The heterogeneity test indicated the existence of heterogeneity between studies (For IHA, χ^2=466.07, P<0.0001; for ELISA, χ^2=34.67, P<0.0001), then the weighted merging sensitivity, specificity, LR and the corresponding 95% *CI* were calculated using random effects models and the results were presented in Table 2.

The SROC curves present a global summary of the performances of diagnostic tests. The SROC linear regression model fitting about IHA and ELISA were presented in Table 3, and the parameters in the SROC linear regression model calculated by the three methods (the Weighted Least Square method, Ordinary Least Square method and Robust regression) were shown in Table 4. Our findings showed that all TPR* of IHA were higher than that of ELISA, which suggests that the diagnostic accuracy of IHA for cases was higher than that of ELISA. In addition, all *OR* values for IHA test using the three statistical methods were higher than that of ELISA. The linear regression models of IHA and ELISA which were fit using the three methods were presented as follows, and then the SROC curve was drawn according to the

Table 1

Sensitivity, specificity, LR and corresponding 95% *CI* of IHA and ELISA in the enrolled studies.

	Author and year of publication	Sensitivity (%, 95% *CI*)	Specificity (%, 95% *CI*)	LR^+ (95% *CI*)	LR^- (95% *CI*)	Selection of golden standard
IHA	Li *et al*. 2003	82.8(71.3–91.1)	70.0(66.2–73.5)	2.756 (2.339–3.247)	0.246 (0.143–0.422)	Kato–Katz (3 slides for one fecal sample)
	Jin *et al*. 2005	37.6(32.1–43.3)	73.7(71.4–75.9)	1.429 (1.209–1.689)	0.847 (0.772–0.928)	Kato–Katz (3 slides for one fecal sample)
	Bao *et al*. 2006	40.7(32.5–49.3)	86.2(84.6–87.8)	2.959 (2.349–3.729)	0.687(0.599–0.790)	Miracidium hatching test (3 slides for 3 fecal samples)
	Liu *et al*. 2010	77.3(67.1–85.5)	58.1(54.0–62.1)	1.844 (1.591–2.137)	0.391 (0.265–0.578)	Kato–Katz (6 slides for 2 fecal samples)
	Xu *et al*. 2007 *	85.6(78.9–90.9)	35.7(33.2–38.2)	1.331 (1.232–1.437)	0.403 (0.270–0.603)	Kato–Katz or miracidium hatching test (3 slides for one fecal sample)
	Xu *et al*. 2007 **	76.0(68.3–82.7)	63.6(61.1–66.1)	2.090 (1.864–2.343)	0.377 (0.282–0.504)	Kato–Katz or miracidium hatching test (3 slides for one fecal sample)
	Lin *et al*. 2008	69.6(55.9–81.2)	88.4(85.5–90.9)	5.998 (4.515–7.966)	0.343 (0.231–0.511)	Kato–Katz (12 slides for 2 fecal samples)
	Zhao *et al*. 2007	95.1(83.5–99.4)	82.4(78.6–85.7)	5.390 (4.372–6.646)	0.059 (0.015–0.229)	Miracidium hatching test (3 slides for 3 fecal sample)
	Yuan *et al*. 2008	65.4(56.5–73.5)	81.5(79.1–83.6)	3.526 (2.969–4.188)	0.425 (0.335–0.539)	Miracidium hatching test (3 slides for one fecal sample)
	Yu *et al*. 2007	80.3(74.1–85.6)	48.4(37.7–59.1)	1.555 (1.260–1.919)	0.407 (0.286–0.579)	Kato–Katz (2 slides for one fecal samples)
	Zhou *et al*. 2007#	85.9(80.8–90.0)	61.2(58.7–63.6)	2.213 (2.042–2.398)	0.231 (0.168–0.316)	Kato–Katz (3 slides for one fecal sample)
	Guan *et al*. 1999	71.4(65.8–76.6)	44.4(39.1–49.7)	1.284 (1.140–1.446)	0.644 (0.518–0.802)	Miracidium hatching test (1 slide for 1 fecal sample) or Kato–Katz(2 slides for one fecal sample)
	Li *et al*. 2002	80.0(51.9–95.7)	93.8(91.6–95.6)	12.995 (8.695–19.421)	0.213 (0.077–0.587)	Kato–Katz (2 slides for one fecal samples)
	Wu *et al*. 2000	93.7(91.0–95.7)	89.0(88.1–90.0)	8.549 (7.815– 9.352)	0.071 (0.050–0.102)	Kato–Katz (3 slides for one fecal sample)
	Peng *et al*. 1982	91.3(87.7–94.2)	66.3(64.5–68.0)	2.709 (2.549– 2.880)	0.131 (0.092–0.186)	Miracidium hatching test (3 slides for 3 fecal sample)
ELISA	Chen *et al*. 2007	65.5(45.7–82.1)	57.5(51.9–62.9)	1.540 (1.149–2.064)	0.600 (0.360–1.000)	Kato–Katz (4 slides for one fecal sample)
	He *et al*. 2007	95.0(89.4–98.1)	20.4(16.5–24.7)	1.193 (1.118–1.273)	0.246 (0.110–0.549)	Kato–Katz (3 slides for one fecal sample)
	Bao *et al*. 2006	57.1(42.2–71.2)	82.4(79.8–84.8)	3.248 (2.453–4.301)	0.520 (0.376–0.720)	Miracidium hatching test (3 slides for 3 fecal samples)
	Wang *et al*. 2005	97.3(93.9–99.1)	24.5(19.9–29.7)	1.289 (1.205–1.379)	0.109 (0.045–0.265)	Kato–Katz (3 slides for 1 fecal sample) or miracidium hatching test (1 slide for 1 fecal sample)
	Xu *et al*. 2007	65.8(57.5–73.4)	51.7(49.0–54.3)	1.360 (1.196–1.547)	0.663 (0.526–0.835)	Kato–Katz or miracidium hatching test (3 slides for one fecal sample)
	Lin *et al*. 2008△	79.3(69.3–87.3)	53.5(49.2–57.6)	1.704 (1.483–1.958)	0.387 (0.255–0.588)	Kato–Katz or miracidium hatching test (3 slides for one fecal sample)
	Lin *et al*. 2008 △△	87.4(81.8–91.7)	38.9(35.6–42.3)	1.430 (1.325–1.544)	0.325 (0.221–0.476)	Kato–Katz (12 slides for 2 fecal samples)
	Zhou *et al*. 2007#	90.1(85.6–93.5)	38.4(36.0–40.8)	1.462 (1.380–1.548)	0.258 (0.176–0.380)	Miracidium hatching test (3 slides for 3 fecal sample)
	Yang *et al*.2007	75.0(34.9–96.8)	39.0(29.4–49.3)	1.230 (0.800–1.889)	0.641 (0.188–2.182)	Miracidium hatching test (3 slides for one fecal sample)
	Song *et al*. 2003	83.3(58.6–96.4)	84.3(80.5–87.5)	5.298 (3.932–7.138)	0.198 (0.070–0.556)	Kato–Katz (2 slides for one fecal samples)

LR^+: Positive likelihood ratio; LR^-: Negative likelihood ratio.

There were two IHA assays in the study conducted by Xu *et al*. * indicated the result of IHA–A, and ** indicated the result of IHA–B.

The study conducted by Lin *et al* was carried out in 2005 and 2006. △ indicated the result of 2005, and △△ indicated the result of 2006.

The data were the merged results of two study sites in the study.

Table 2

The merging sensitivity, specificity, positive and negative LR of the two diagnostic tests (%, 95% *CI*).

Diagnostic test	Sensitivity	Specificity	LR^+	LR^-
IHA	75.6 (73.9–77.3)	73.0 (72.4–73.7)	2.877 (2.106–3.931)	0.306 (0.196–0.480)
ELISA	84.9 (82.6–86.9)	50.4 (49.2–51.6)	1.666 (1.443–1.923)	0.367 (0.263–0.511)

Table 3

Characteristics of the SROC regression model fitting about IHA and ELISA.

Author and year of publication		TP	FP	FN	TN	TPR	FPR	Weight	D	S
IHA	Li *et al*. 2003	53	186	11	433	0.828	0.300	8.513	2.417	0.727
	Jin *et al*. 2005	115	401	191	1 124	0.376	0.263	57.754	0.523	–1.538
	Bao *et al*. 2006	57	246	83	1 542	0.407	0.138	29.150	1.460	–2.211
	Liu *et al*. 2010	68	251	20	348	0.773	0.419	13.974	1.551	0.897
	Xu *et al*. 2007 *	125	909	21	504	0.856	0.643	17.035	1.194	2.374
	Xu *et al*. 2007 **	111	514	35	899	0.760	0.364	24.607	1.713	0.595
	Lin *et al*. 2008	39	67	17	510	0.696	0.116	9.867	2.860	–1.199
	Zhao *et al*. 2007	39	81	2	378	0.951	0.176	1.850	4.511	1.430
	Yuan *et al*. 2008	85	224	45	984	0.654	0.185	25.337	2.116	–0.844
	Yu *et al*. 2001	159	47	39	44	0.803	0.516	13.169	1.339	1.471
	Zhou *et al*. 2007#	207	609	34	960	0.859	0.388	27.081	2.261	1.351
	Guan *et al*. 1999	200	197	80	157	0.714	0.556	34.548	0.689	1.143
	Li *et al*. 2002	12	37	3	564	0.800	0.062	2.245	4.110	–1.338
	Wu *et al*. 2000	413	458	28	3 723	0.937	0.110	24.638	4.787	0.596
	Peng *et al*. 1982	295	978	28	1 923	0.913	0.337	24.602	3.031	1.679
ELISA	Chen *et al*. 2007	19	137	10	185	0.655	0.425	6.048	0.942	0.341
	He *et al*. 2007	114	309	6	79	0.950	0.796	5.226	1.581	4.308
	Bao *et al*. 2006	28	158	21	740	0.571	0.176	10.987	1.832	–1.256
	Wang *et al*. 2005	182	237	5	77	0.973	0.755	4.490	2.470	4.719
	Xu *et al*. 2007	96	683	50	730	0.658	0.483	30.075	0.719	0.586
	Lin *et al*. 2008△	69	263	18	302	0.793	0.465	12.960	1.482	1.205
	Lin *et al*. 2008△△	166	510	24	325	0.874	0.611	18.965	1.483	2.385
	Zhou *et al*. 2007#	218	967	24	602	0.901	0.616	20.429	1.733	2.680
	Yang *et al*. 2007	6	61	2	39	0.750	0.610	1.411	0.651	1.546
	Song *et al*. 2003	15	70	3	375	0.833	0.157	2.398	3.288	–0.069

TPR: True positive rate; FPR: False positive rate; $D=\ln[(TP\times TN)/(FN\times FP)]$, $S=\ln[(TP\times FP)/(TN\times FN)]$.
There were two IHA assays in the study conducted by Xu *et al*. * indicated the result of IHA-A, and ** indicated the result of IHA-B.
The study conducted by Lin *et al* was carried out in 2005 and 2006. △indicated the result of 2005, and △△ indicated the result of 2006.
The data were the merged results of two study sites in the study.

Table 4

The regression parameters and accuracy of IHA and ELISA in the included studies.

Statistical method		A	*SE*(A)	95%*CI*	B	*SE*(B)	95%*CI*	TPR*	*SE*(TPR*)	*OR*
IHA	Weighted least square method	1.791	0.322	1.101–2.482	0.235	0.226	– 0.249 – 0.718	0.710	0.033	5.997
	Least square method	2.296	0.367	1.508–3.084	0.023	0.264	– 0.543 – 0.590	0.759	0.034	9.937
	Robust regression	2.185	–	–	0.052	–	–	0.749	–	8.893
ELISA	Weighted least square method	1.233	0.260	0.644–1.823	0.114	0.124	– 0. 166–0.393	0.650	0.030	3.432
	Least square method	1.565	0.364	0.743–2.388	0.032	0.149	– 0.305–0.369	0.686	0.039	4.784
	Robust regression	1.376	–	–	0.080	–	–	0.666	–	3.959

A: regression intercept, B: coefficient, *SE*: standard error, TPR*: diagnostic accuracy; *OR*: odds ratio.

models.

IHA:

$TPR_{WLS}=\{1+e^{-2.341}[(1-FPR)/FPR]^{1.614}\}^{-1}$;

$TPR_{OLS}=\{1+e^{-2.350}[(1-FPR)/FPR]^{1.047}\}^{-1}$;

$TPR_{Robust}=\{1+e^{-2.305}[(1-FPR)/FPR]^{1.110}\}^{-1}$.

ELISA:

$TPR_{WLS}=\{1+e^{-1.392}[(1-FPR)/FPR]^{1.257}\}^{-1}$;

$TPR_{OLS}=\{1+e^{-1.617}[(1-FPR)/FPR]^{1.066}\}^{-1}$;

$TPR_{Robust}=\{1+e^{-1.496}[(1-FPR)/FPR]^{1.174}\}^{-1}$.

The SROC curves of the diagnostic performances of IHA and ELISA were presented in Figures 3a and 3b. The areas under the SROC curves of IHA were all higher than that of ELISA test using the three methods (Weighted Least Square method: 0.766 *vs.* 0.695, Ordinary Least Square method: 0.826 *vs.* 0.741, Robust regression: 0.815 *vs.* 0.715). It is indicated that the diagnostic efficacy of IHA is better than that of ELISA, which is similar to the above results revealed by TPR* and *OR* values.

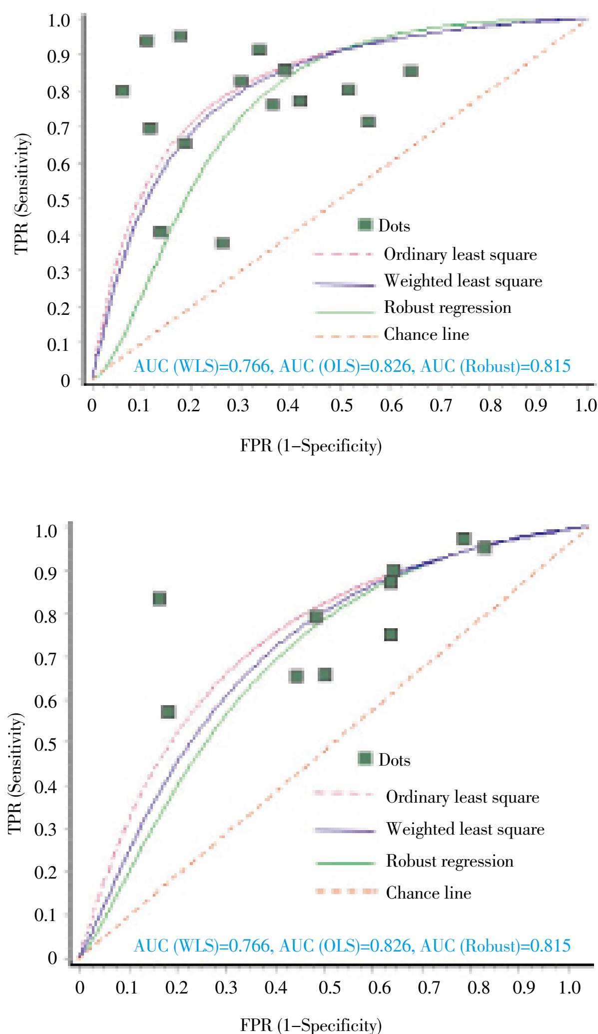


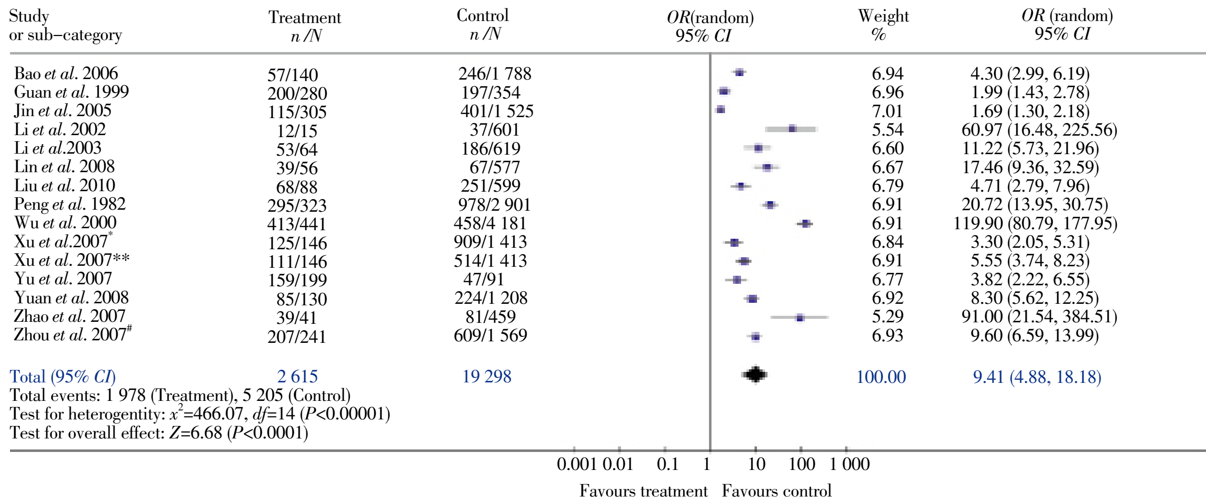
Figure 3. The SROC curves of diagnostic efficacies of IHA (3a) and ELISA (3b) in the enrolled studies.

In quantitative comparison, the *OR*s of IHA and ELISA were merged weightedly, the diagnostic odds ratio (DOR) of IHA was 9.41 (95% *CI*: 4.88-18.18), and 4.78 (95% *CI*: 3.21-7.13) for ELISA. It is indicated that IHA outperforms ELISA. Figures 4a and 4b show the forest plots of DOR for IHA and ELISA.

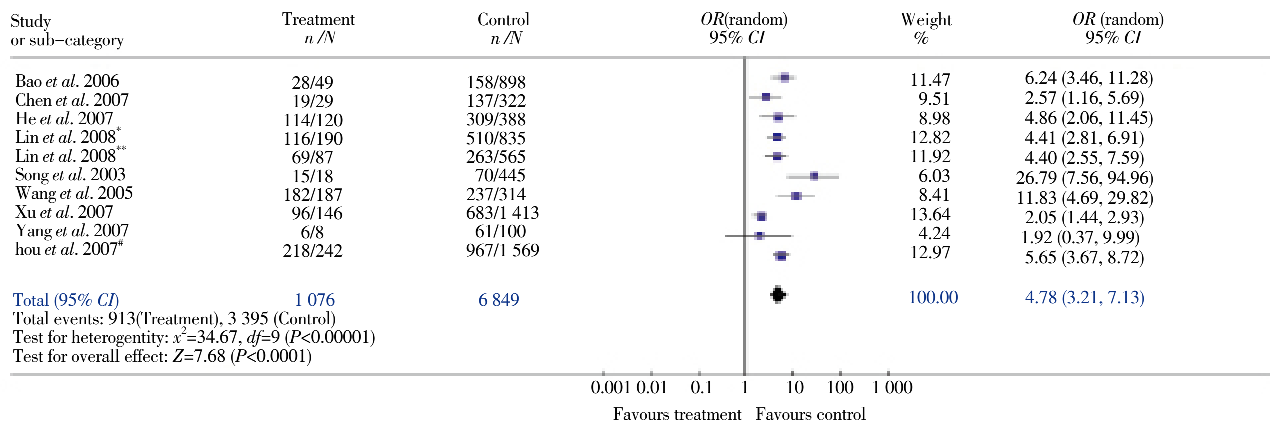
4. Discussion

Although great achievements were gained in the control of schistosomiasis japonica in China through more than 50-year efforts, the disease remains a major public-health problem in China currently[3-5]. The prevention and control of the disease need rapid and reliable diagnostic techniques to identify target populations accurately for treatment[34]. In this case, diagnosis, as central to schistosomiasis, at the levels of both individual and community is essential for the control program[35]. Diagnosis of schistosomiasis is usually performed by parasitological (microscopic detection of eggs), and/or immunological methods (antibody and antigen detection). The demonstration of parasite eggs in feces directly indicated the presence of the causative agent worms, but the disadvantages of this approach include a high fluctuation in eggs counts, easily missed low infections, a relatively time-consuming methodology and low compliance[34,35]. The immunodiagnostic technology, owing to its rapid, affordable and easily acceptable (high compliance) advantages over parasitological techniques, had been, in reality, integrated into the schistosomiasis control program in P.R. China as a way to improve the diagnostic record in identifying the target populations for treatment since early 1980s when the safe and effective drug praziquantel was introduced. Many immunodiagnostic assays have been developed and applied in China[38-40,63-65], among them, ELISA and IHA are mostly widely used for schistosomiasis diagnosis in field situations of China. However, the values of performance index of the immunodiagnostic tests varied greatly. It is, therefore, of great importance and essential to evaluate their diagnostic efficacies in a comprehensive and more accurate way.

Results of the current study showed that a large variety of the diagnostic efficacy of IHA and ELISA was estimated, the sensitivity of IHA ranged from 37.6% to 95.1%, and specificity from 35.7% to 93.8%, while the sensitivity of ELISA spanned from 57.1% to 97.3% and specificity from 20.4% to 84.3%. There are many factors that can contribute to such a large variation. Apart from the selection of the gold standard, some other potential causes for the inconsistence of the diagnostic value are listed as follows: (1) The pilot areas included in the studies have different environmental ecosystems. In terms of geographic characteristics, the schistosome-endemic areas in China can be divided into 3 major types, namely lake and marshland regions, plain regions with waterway networks and hilly and mountainous regions[30,66]. The diagnostic values of an immunodiagnostic reagent may be dissimilar in different types of endemic areas[34]; (2) Size of the detection samples; (3) The sensitivity and specificity vary with the prevalence and intensity of schistosome infection[44,48,49,56]; (4) Different diagnostic agents. For example, many antigens can be used to establish an ELISA technique. In addition, the assays are not supplied by the same manufacturer[48]; (5) Subjective factors of the operators[67]. In order to make a comprehensive and accuracy evaluation of the diagnostic value of an immunodiagnostic assay, all these potential factor that may



a



b

Figure 4. The forest plots of DOR for IHA (4a) and ELISA (4b) tests.

impact the diagnostic outcomes were taken into account. During the review and selection of the papers, the inclusion and exclusion criteria were strictly settled.

The funnel plots we drew indicated minor publication bias exist in the enrolled studies pertaining the diagnostic value of IHA. Publication bias is a widespread and particularly thorny issue in meta–analysis, which may seriously distort attempts to estimate the effect under investigation. There are numerous reasons responsible for the existence of the bias, including language bias, availability bias, cost bias, familiarity bias, outcome bias, and so on[68,69]. In the present study, the literatures included have been published in national or international journals, but those without publish were not collected. The publication bias, therefore, may emerge. In addition, due to the limitation of access to the literature resources, those paper with easy access to the full text and published in English and Chinese were selected, which may also lead to the existence of selection bias and language bias. Although those bias mentioned above may exist, the current study makes use of the limited citations to draw a conclusion that IHA is superior in diagnosis of schistosomiasis to ELISA, which has been identified by previous field trials[46,48,52].

Our meta–analysis identified that both of the two immunodiagnostic assays are suitable for the detection of *S. japonicum* infections in schistosomiasis control program which are revealed by the TPR* values, and IHA shows a better diagnostic efficacy in comparison with that that of ELISA, suggested by the results of TPR*, *OR* values as well as the AUC of the SROC curve. However, the result revealed by the statistical methods is a comprehensive analysis of both sensitivity and specificity. Actually, from the result of the included studies, we can find the sensitivity of ELISA is higher than that of IHA, but the specificity of ELISA is lower. Considering sensitivity is given priority in low endemic areas, it seems that ELISA test is more suitable for screening the target for chemotherapy as a primary approach to cover more cases. In addition, these assays proved to have an unsatisfactory sensitivity and specificity, especially in patients with light infections. Currently in China, in most

schistosome-endemic areas, the schistosome infection has been under control and infection intensities are usually low[30]. A search for a better immunodiagnostic test or novel molecular biological tools that can be applied in field situations in China is essential and should be given high priority.

Conflict of interest statement

We declare that we have no conflict of interest.

References

[1] WHO. *Scientific working group on schistosomiasis, meeting report. November 14-16, 2005*. Geneva: World Health Organization; 2006.

[2] Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J. Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. *Lancet Infect Dis* 2006; **6**: 411-425.

[3] Zhou XN, Wang TP, Wang LY, Guo JG, Yu Q, Xu J, et al. The current status of schistosomiasis epidemics in China. *Chin J Epidemiol* 2004; **25**: 555-558.

[4] Zhou XN. Epidemic characteristics and key points of scientific research of schistosomiasis in China. *Chin J Endemiol* 2006; **25**: 473-474.

[5] Zhou XN, Bergquist R, Leonardo L, Yang GJ, Yang K, Sudomo M, et al. Schistosomiasis japonica control and research needs. *Adv Parasitol* 2010; **72**: 145-148.

[6] Zhou XN, Wang LY, Chen MG, Wu XH, Jiang QW, Chen XY, et al. The public health significance and control of schistosomiasis in China-then and now. *Acta Trop* 2005; **96**: 97-105.

[7] Engels D, Wang LY, Palmer KL. Control of schistosomiasis in China. *Acta Trop* 2005; **96**: 67-68.

[8] Wang LD, Utzinger J, Zhou XN. Schistosomiasis control: experiences and lessons from China. *Lancet* 2008; **372**: 1793-1795.

[9] Jiang QW, Wang LY, Guo JG, Chen MG, Zhou XN, Engels D. Morbidity control of schistosomiasis in China. *Acta Trop* 2002; **82**: 115-125.

[10] Yuan H, Jiang Q, Zhao G, He N. Achievements of schistosomiasis control in China. *Mem Inst Oswaldo Cruz* 2002; **97**: 187-189.

[11] Zhao GM, Zhao Q, Jiang QW, Chen XY, Wang LY, Yuan HC. Surveillance for schistosomiasis japonica in China from 2000 to 2003. *Acta Trop* 2005; **96**: 288-295.

[12] Utzinger J, Zhou XN, Chen MG, Bergquist R. Conquering schistosomiasis in China: the long march. *Acta Trop* 2005; **96**: 69-96.

[13] Zhou XN, Wang LY, Chen MG, Wang TP, Guo JG, Wu XH, et al. An economic evaluation of the national schistosomiasis control programme in China from 1992 to 2000. *Acta Trop* 2005; **76**: 255-265.

[14] Chen XY, Wang LY, Cai JM, Zhou XN, Zheng J, Guo JG, et al. Schistosomiasis control in China: the impact of a 10-year World Bank Loan Project (1992-2001). *Bull World Health Organ* 2005; **83**: 43-48.

[15] Zhang W, Wong CM. Evaluation of the 1992-1999 World Bank Schistosomiasis Control Project in China. *Acta Trop* 2003; **85**: 303-313.

[16] Sun CS, Yu BG, Liao HY, Dai YH, Xu X, Zhu HG, et al. Achievement of the World Bank loan project on schistosomiasis control (1992-2000) in Hubei province and the challenge in the future. *Acta Trop* 2002; **82**:169-174.

[17] Wu XH, Zhang SQ, Xu XJ, Huang YX, Steinmann P, Utzinger J, et al. Effect of floods on the transmission of schistosomiasis in the Yangtze River valley, People's Republic of China. *Parasitol Int* 2008; **57**: 271-276.

[18] Dudgeon D, Arthington AH, Gessner MO, Kawabata Z-I, Knowler DJ, Lévêque C, et al. Freshwater biodiversity: importance, threats, status and conservation challenges. *Biol Rev* 2005; **81**: 163-182.

[19] Seto EYW, Wu WP, Liu HY, Chen HG, Hubbard A, Holt A, et al. Impact of changing water levels and weather on *Oncomelania hupensis hupensis* populations, the snail host of *Schistosoma jaonicum*, downstream of the Three Gorges Dam. *Ecohealth* 2008; **5**:149-158.

[20] Zhu HM, Xiang S, Yang K, Wu XH, Zhou XN. Three Gorges Dam and its impact on the potential transmission of schistosomiasis in regions along the Yangtze River. *Ecohealth* 2008; **5**: 137-148.

[21] Huang YX, Rong GR, Cai G, Gao ZH, Zhou XN, Zhu YC. Effects of flood on snail distribution in marshland along Yangtze River in Jiangsu Province. *Chin J Schisto Control* 2000; **12**: 346-349.

[22] Yang GJ, Utzinger J, Lv S, Qian YJ, Li SZ, Wang Q, et al. The regional network for asian schistosomiasis and other helminth zoonoses (RNAS$^+$) target diseases in face of climate change. *Adv Parasitol* 2010; **73**: 101-135.

[23] Zhou XN, Yang GJ, Yang K, Wang XH, Hong QB, Sun LP, et al. Potential impact of climate change on schistosomiasis transmission in China. *Am J Trop Med Hyg* 2008; **78**: 188-194.

[24] Yang GJ, Vounatsou P, Zhou XN, Tanner M, Utzinger J. A potential impact of climate change and water resource development on the transmission of *Schistosoma japonicum* in China. *Parassitologia* 2005; **47**: 127-134.

[25] Zhou XN, Yang K, Hong QB, Sun LP, Yang GJ, Liang YS, et al. Prediction of the impact of climate warming on transmission of schistosomiasis in China. *Chin J Parasit Dis Parasitol* 2004; **22**: 262-265 (in Chinese).

[26] Liang S, Seto EY, Remais JV, Zhong B, Yang C, Hubbard A, et al. Environmental effects on parasitic disease transmission exemplified by schistosomiasis in western China. *Proc Natl Acad Sci USA* 2007; **104**: 7110-7115.

[27] Wang RB, Wang TP, Wang LY, Guo JG, Yu Q, Xu J, et al. Study on the re-emerging situation of schistosomiasis epidemics in areas already under control and interruption. *Chin J Epidemiol* 2004; **25**: 564-567.

[28] Hong QB, Sun LP, Huang YX, Li W, Yang K, Gao Y, et al. The third smapling survey of schistosomiasis in Jiangsu Province. *Chin J Schisto Control* 2005; **17**: 268-272.

[29] Liang S, Yang C, Zhong B, Qiu D. Re-emerging schistosomiasis in hilly and mountainous areas of Sichuan, China. *Bull World Health Organ* 2006; **84**: 139-144.

[30] Zhou XN, Guo JG, Wu XH, Jiang QW, Zheng J, Dang H, et al. Epidemiology of schistosomiasis in the People's Republic of China, 2004. *Emerg Infect Dis* 2007; **13**: 1470-1476.

[31] Li SZ, Luz A, Wang XH, Xu LL, Wang Q, Qian YJ, et al. Schistosomiasis in China: acute infections during 2005-2008. *Chin Med J (Engl)* 2009; **122**: 1009-1014.

[32] Hao Y, Zheng H, Zhu R, Guo JG, Wu XH, Wang LY, et al. Schistosomiasis situation in People's Republic of China in 2008. *Chin J Schisto Control* 2010; **21**: 451-456.

[33] Hao Y, Zheng H, Zhu R, Guo JG, Wang LY, Chen Z, et al. Schistosomiasis situation in People's Republic of China in 2009. *Chin J Schisto Control* 2010; **22**: 521-527.

[34] Wu G. A historical perspective on the immunodiagnosis of schistosomiasis in China. *Acta Trop* 2002; **82**:193-198.

[35]Zhu YC. Immunodiagnosis and its role in schistosomiasis control in China: a review. *Acta Trop* 2005; **96**: 130–136.
[36]Katz N, Chaves A, Pellegrino J. A simple device for quantitative stool thick–smear techniques in schistosomiasis mansoni. *Rev Inst Med Trop Sao Paulo* 1972; **14**: 397–400.
[37]MOH. *Handbook of schistosomiasis control.* Shanghai: Shanghai Science & Technology Press; 2000.
[38]Li YH. *Immunology and immunodiagnosis of parasitic diseases.* Nanjing: Jiangsu Science & Technology Publishing House; 1991.
[39]Zhu Y, He W, Liang Y, Xu M, Yu C, Hua W, et al. Development of a rapid, simple dipstick dye immunoassay for schistosomiasis diagnosis. *J Immunol Methods* 2002; **266**: 1–5.
[40]Zhu YC, Socheat D, Bounlu K, Liang YS, Sinuon M, Insisiengmay S, et al. Application of dipstick dye immunoassay (DDIA) kit for the diagnosis of schistosomiasis mekongi. *Acta Trop* 2005; **96**: 137–141.
[41]Zheng J. Schistosomiasis control and its prospect in China. *Chin J Schisto Control* 2003; **15**: 1–2.
[42]Li YS, Zhao ZY, Ellis M, McManus DP. Applications and outcomes of periodic epidemiological surveys for schistosomiasis and related economic evaluation in the People's Republic of China. *Acta Trop* 2005; **96**: 266–275.
[43]Rosman AS, Korsten MA. Application of summary receiver operating characteristics (sROC) analysis to diagnostic clinical testing. *Adv Med Sci* 2007; **52**: 76–82.
[44]Li JH, Wang TP, Xiao X, Wu WD, Lv DB, Fang GR, et al. Cost–effectiveness of screening methods for determining the subjects of chemotherapy in areas with moderate endemic of schistosomiasis. *Chin J Schisto Control* 2003; **15**: 120–123.
[45]Jin J, Pan XP, An JS, Tang JM, Zhou SH, He LZ, et al. Study on the correlation of detectable rates for schistosomiasis between the techniques of IHA and Kato–Katz in different endemic areas. *J Trop Dis Parasitol* 2005; **3**: 204–206.
[46]Bao JG, Qiang GX, Deng YJ, Zhang R, Chen Y. Comparison of four examination methods for schistosomiasis in the field. *J Trop Dis Parasitol* 2006; **4**: 33–34.
[47]Liu YM, Lin DD, Hu F, Huang XH, Li JY, Li ZS, et al. Evaluation on application of common diagnosis methods for schistosomiasis japonica in endemic areas in China II Quantitive analysis of detection results for *S. japonicum* infection by IHA screening method and Kato–Katz technique. *Chin J Schisto Control* 2010; **22**: 126–131.
[48]Xu J, Chen NG, Feng T, Wang EM, Wu XH, Chen HG, et al. Effectiveness of routinely used assays for the diagnosis of schistosomiasis japonica in the field. *Chin J Parasitol Parasit Dis* 2007; **25**: 175–179.
[49]Lin DD, Liu YM, Hu F, Tao B, Wang XM, Zuo XX, et al. Evaluation on application of common diagnosis methods for schistosomiasis japonica in endemic areas in China I Evaluation on estimation of prevalence of *Schistosoma japonicum* infection by IHA screening method. *Chin J Schisto Control* 2008; **20**: 179–183.
[50]Zhao L, Zhu JJ, Wang J. Assessment of two immunodiagnostic kits for detection of schistosomiasis japonica in clinical application. *Prac Prev Med* 2007; **14**: 1912–1913.
[51]Yuan MZ, Wang JS, Peng XW, Chen LC, He J, Chen Y. Effect of IHA and NP30 for screening schistosomiasis. *Chin J Schisto Control* 2008; **20**: 76–77.
[52]Yu JM, de Vlas SJ, Jiang QW, Gryseels B. Comparison of the Kato–Katz technique, hatching test and indirect hemagglutination assay (IHA) for the diagnosis of *Schistosoma japonicum* infection in China. *Parasitol Int* 2007; **56**: 45–49.
[53]Zhou YB, Yang MX, Wang QZ, Zhao GM, Wei JG, Peng WX, et al. Field comparison of immunodiagnostic and parasitological techniques for the detection of schistosomiasis japonica in the People's Republic of China. *Am J Trop Med Hyg* 2007; **76**: 1138–1143.
[54]Guan WH, Yuan HC, Zhao GM, Yu JM, Yang QJ. Survey of schistosomiasis epidemic in dam–circle marsh region. *Chin Public Health* 1999; **15**: 686–688.
[55]Li JH, Wang TP, Xiao X, Wu WD, Lv DB, Fang GR, et al. Screening schemes for determining the subjects of chemotherapy in areas with moderate endemic of schistosomiasis. *Chin J Schisto Control* 2002; **14**: 418–421.
[56]Wu ZW, Liu ZC, Yang GF. Reliability of application of IHA method to determine chemotherapy targets of schistosomiasis in moderately endemic areas of lake region. *Chin J Schisto Control* 2000; 12: 21–23.
[57]Peng XH, Hou CS, Shi CC. Survey of application value of IHA for diagnosis of schistosomiasis japonica. *Sichuan Med* 1982; **3**: 75–76.
[58]Chen SR, Chen F, Zhou XN, Li HJ, Steinmann P, Yang Z, et al. Comparison of etiological and serological diagnosis methods in schistosomiasis mountainous endemic area. *Parasitol Infect Dis* 2007; **5**: 1–4.
[59]He W, Zhu YC, Liang YS, Dai JR, Xu M, Tang JX, et al. Comparison of stool examination and immunodiagnosis for schistosomiasis. *Chin J Schisto Control* 2007; **19**: 107–109.
[60]Wang SW, Yang Z, Yin GL, Li YL, Yang J, Zhao JB, et al. Applicable value of ELISA for detecting antibody of schistosomiasis in heavily endemic areas. *Parasitol Infect Dis* 2005; **3**: 79–80.
[61]Yang Z, Yin GL, Fan CZ, Luo BR, Liu YH, Duan YC, et al. Effect of dot immunogold filtration assay for diagnosis of schistosomiasis. *Parasitol Infect Dis* 2007; **5**: 97–98.
[62]Song HT, Liang YS, Dai JR, Li HJ, Ji CS, Shen XH, et al. Cost–effectiveness of three immuno–assays for diagnosis of schistosomiaisis in lower endemic areas. *Chin J Schisto Control* 2003; **15**: 301–302.
[63]Xiao X, Wang T, Ye H, Qiang G, Wei H, Tian Z. Field evaluation of a rapid, visually–read colloidal dye immunofiltration assay for *Schistosoma japonicum* for screening in areas of low transmission. *Bull World Health Organ* 2005; **83**: 526–533.
[64]Wen LY, Chen JH, Ding JZ, Zhang JF, Lu SH, Yu LL, et al. Evaluation on the applied value of the dot immunogold filtration assay (DIGFA) for rapid detection of anti–*Schistosoma japonicum* antibody. *Acta Trop* 2005; **96**: 142–147.
[65]Lei JH, Liu WQ, Sun CS, Tang CL, Li MJ, Chen YL, et al. Detection of circulating antigen in serum of mice infected with *Schistosoma japonicum* by immunomagnetic bead ELISA based on IgY. *Acta Trop* 2009; **111**: 39–43.
[66]Li YS, Sleigh AC, Ross AGP, Williams GM, Tanner M, McManus DP. Epidemiology of *Schistosoma japonicum* in China: morbidity and strategies for control in the Dongting Lake region. *Int J Parasitol* 2000; **30**: 273–281.
[67]Xu J, Feng T, Guo JG, Zheng H, Wang Q, Wu XH, et al. Comprehensive evaluation of several diagnosis agents of schistosomisis japonica in China. *Chin J Schisto Control* 2005; **17**: 116–119.
[68]Zhang J, Shang Z, Zhang X, Zhang Y. Modeling and analysis of Schistosoma argonaute protein molecular spatial conformation. *Asian Pac J Trop Biomed* 2011; **1**(4): 275–278.
[69]Song F, Khan KS, Dinnes J, Sutton AJ. Asymmetric funnel plots and publication bias in meta–analyses of diagnostic accuracy. *Int J Epidemiol* 2002; **31**: 88–95.