

ORIGINAL ARTICLE

Clinical Value of IgG Antibody Test in Screening for *Clonorchis sinensis* Infection in High-Risk Population

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SUMMARY

Background: In areas where *C. sinensis* is endemic, early screening and diagnosis of *C. sinensis* infection is crucial to prevent complications and interrupt the chain of transmission. Testing for *C. sinensis* IgG antibodies is frequently employed as a screening method for detecting the disease. However, its effectiveness in populations with a high risk remains to be determined. This study aimed to evaluate the clinical value of IgG antibody testing for screening *C. sinensis* infection in high-risk populations.

Methods: Between October 2020 and September 2023, 1,080 participants from Liuzhou Municipal Liutie Central Hospital patients were recruited. All participants underwent enzyme-linked immunosorbent assay (ELISA) to detect IgG antibodies and fecal examination for *C. sinensis* eggs using the Kato-Katz technique. The study examined the diagnostic concordance between two methods by using inter-rater agreement evaluation (Kappa). The diagnostic effectiveness of IgG antibodies was assessed comprehensively and across different gender and age categories, with the outcomes of the parasite egg test serving as the benchmark for diagnosis.

Results: Out of the 1,080 participants, 48.0% (518/1,080) tested positive for *C. sinensis* eggs, and 46.9% (506/1,080) tested positive for IgG antibodies. The Kappa value of the two methods' diagnostic concordance was 0.599. The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of IgG antibody detection were 78.0%, 81.9%, 79.8%, 80.1%, and 80.0%, respectively, using *C. sinensis* eggs as the diagnostic criterion. Gender and age subgroup analyses revealed that diagnostic specificity, negative predictive value (NPV), and accuracy were higher in females than males ($p = 0.003$, 0.001 , and 0.049 , respectively). Sensitivity tended to decrease, while specificity tended to increase with age ($p = 0.007$ and 0.010 , respectively).

Conclusions: The technique for detecting Clonorchiasis IgG antibodies has a certain degree of accuracy in diagnosing *C. sinensis*, but its sensitivity is low, particularly in mild infections and in the elderly population. Diagnosis requires a combination of other assays or further optimization of the technique's performance.

(Clin. Lab. 2024;70:xx-xx. DOI: 10.7754/Clin.Lab.2024.240430)

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KEYWORDS

Clonorchis sinensis, *Clonorchis sinensis* IgG antibodies, *Clonorchis sinensis* eggs, sensitivity, specificity

INTRODUCTION

Clonorchiasis is a parasitic disease transmitted through the consumption of freshwater fish, such as sashimi, that contains infective cysticerci [1]. *Clonorchis sinensis* (*C. sinensis*) can survive in the human hepatobiliary system for up to 25 years after infection [2,3]. Chronic

infection can develop hepatobiliary diseases, including cholangitis, cholelithiasis, cholecystitis, pancreatitis, liver fibrosis, hepatocellular carcinoma, and cholangiocarcinoma (CCA) [4-6]. The risk of cholangiocarcinoma (CCA) is higher in areas where the liver fluke, *C. sinensis*, is endemic than in other areas [1,7]. In 2009, the International Agency for Research on Cancer (IARC), a part of the World Health Organization (WHO), classified *C. sinensis* as a class I carcinogen [8].

Guangxi, located in southwestern China, is renowned for its numerous rivers and abundant fishery resources. However, the rising trend of consuming raw fish in Guangxi is causing new food safety concerns [9]. Furthermore, economic development has improved trade and transportation channels, spreading infected fish and populations. As a result, *C. sinensis* has now expanded beyond villages near contaminated water bodies [10]. Environmental and socioeconomic factors have contributed to increased *C. sinensis* infection rates in Guangxi. According to the 2016 survey on the status of critical parasitic diseases in humans in China, the infection rate of *C. sinensis* in the Guangxi population was 6.65% [11]. As *C. sinensis* infection is often asymptomatic, most infected individuals are diagnosed incidentally during medical consultations for other conditions, which can delay treatment and increase the risk of complications [4,12]. The eggs of *C. sinensis* are released through the feces of individuals who have been infected. They can contaminate ponds and rivers, facilitating the life cycle of *C. sinensis* and exacerbating the epidemic [4]. Therefore, it is crucial to conduct early screening and diagnosis of *C. sinensis* infection in endemic areas, particularly among high-risk populations who consume raw fish, to prevent complications and interrupt the transmission chain.

Screening individuals for *C. sinensis* infection among high-risk groups is a significant challenge due to the need for rapid and accurate testing. While fecal parasite egg testing is considered the 'gold standard' for diagnosing *C. sinensis*, it can be affected by individual differences, the technical level of medical personnel, and their experience and responsibility [13]. During the early stages of infection, the number of eggs is typically low and difficult to detect, resulting in a high risk of missed or incorrect diagnosis [13]. Additionally, examining fecal parasite eggs is complex, time-consuming, and unsuitable for large-scale population screening [2]. PCR technology exhibits high specificity and sensitivity, enabling it to detect the presence of *C. sinensis* infection accurately [14,15]. However, sample contamination and high cost hinder its application in large-scale screening [16,17]. Imaging tests can help doctors observe changes in the liver and biliary system, such as cirrhosis and bile duct obstruction, which may suggest the presence of *C. sinensis* infection [18]. However, imaging tests lack sensitivity and specificity for diagnosing *C. sinensis* infection. Enzyme-linked immunosorbent assay (ELISA) is a commonly used immunological

technique for detecting IgG antibodies to *C. sinensis*. It has been applied to screen for *C. sinensis* infection due to its simplicity, rapidity, low cost, and good reproducibility. Previous studies have reported the effectiveness of serum IgG antibodies in diagnosing *C. sinensis* by testing clinically suspected patients and serum bank samples [19,20]. However, we need to be aware of any pre-published studies that evaluate the diagnostic performance of serum IgG antibodies by testing samples from high-risk groups. Therefore, this study aimed to assess the clinical value of serum IgG antibodies in screening for *C. sinensis* infection in a high-risk population.

MATERIALS AND METHODS

Participants

From October 2020 to September 2023, 1,080 participants were recruited. These individuals were long-term residents of Guangxi who had consumed raw fish for at least six months before the study. They attended the Liuzhou Municipal Liutie Central Hospital in Liuzhou, Guangxi, China. The study received approval from the Ethics Committee of the Liuzhou Liutie Central Hospital. In applicable cases, all participants or their guardians provided their written informed consent before participation.

Antibody tests

This study employed an ELISA clonorchiasis antibody kit manufactured by Shenzhen Huakang Bio-Biomedical Engineering Co. Ltd., utilizing a recombinant antigen derived from yeast. The optical density (OD) values were determined with a microplate reader. To accurately gauge the samples' values, the OD measurement of each specimen was adjusted by subtracting the OD value of the blank control. Additionally, before conducting laboratory tests, all participants involved in the research were trained in properly using ELISA reagents, interpreting results, and accurately reading OD values.

Examination of feces

Fecal samples were collected from all participants to detect *C. sinensis* eggs. The Kato-Katz method prepared three smears, which were examined microscopically by two experienced technicians. Results were recorded as positive for *C. sinensis* eggs if at least one technician found them and negative if neither technician found them.

Statistical analysis

Statistical calculations were performed using MedCalc Statistical Software version 19.1 (MedCalc Software, Ostend, Belgium). The study evaluated the agreement between *C. sinensis* IgG antibody detection and *C. sinensis* eggs microscopy by calculating the Kappa value through inter-scorer consistency evaluation. A higher Kappa value indicates better consistency between the

Table 1. Characteristics of the included 1,080 patients.

Characteristic	Results
Gender	
Male	761 (70.5%)
Female	319 (29.5%)
Age (years)	55 (46 - 66), range of 9 to 97
< 46 years	264 (24.4%)
46 - 54 years	257 (23.8%)
55 - 65 years	279 (25.8%)
≥ 66 years	280 (25.9%)
<i>C. sinensis</i> eggs	
Positive	518 (48.0%)
Negative	562 (52.0%)
<i>C. sinensis</i> IgG antibodies	
Positive	506 (46.9%)
Negative	574 (53.1%)

Data are patients with percentages in parentheses. Age is medians (interquartile ranges, IQR).

two methods. The values range from -1 to 1 and are interpreted as < 0.2 for none to slight, 0.21 - 0.4 for fair, 0.41 - 0.6 for moderate, 0.61 - 0.8 for substantial, and 0.81 - 1.0 for almost perfect agreement [21]. The diagnostic performance of the IgG antibody test was evaluated by using a 2 x 2 list of diagnostic tests, with the *C. sinensis* egg result as the diagnostic gold standard. The evaluation included sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. Performance differences between genders (male and female) were compared by using the Pearson χ^2 test. According to age quartiles, patients were categorized into four age groups (< 46, 46 - 54, 55 - 65, and ≥ 66 years). The Cochran-Armitage χ^2 test for trend was used to compare performance differences between the groups. A p-value of < 0.05 was considered statistically significant.

RESULTS

Participants

A total of 1,080 patient encounters met the inclusion criteria. The median age was 55, and 70.5% (n = 761) were male. Out of the 1,080 patients, 518 were positive for *C. sinensis* eggs, and 562 were negative, resulting in a positivity rate of 48.0% (518/1,080). Additionally, 506 patients were positive for *C. sinensis* IgG antibodies, and 574 were negative, resulting in a positivity rate of 46.9% (506/1,080) (Table 1).

Overall diagnostic performance

Table 2 presents the diagnostic performance results for IgG antibodies. The IgG antibody test showed a moderate level of concordance with the egg test, with a diagnostic concordance Kappa value of 0.599 (95% CI: 0.551 - 0.647). Considering the use of *C. sinensis* egg detection as the definitive standard for diagnosis and using *C. sinensis* egg results as the gold standard for diagnosis, the IgG antibody test demonstrated a sensitivity of 78.0% (95% CI: 74.2 - 81.5), specificity of 81.9% (95% CI: 78.4 - 85.0), positive predictive value of 79.8% (95% CI: 76.8 - 82.6), negative predictive value of 80.1% (95% CI: 77.4 - 82.6), and accuracy of 80.1% (95% CI: 77.4 - 82.6).

Performance of *C. sinensis* IgG antibodies in diagnosing clonorchiasis

Tables 3 and 4 show IgG antibody performance in diagnosing Clonorchiasis by age and gender, using *C. sinensis* egg results as the gold standard. The diagnostic specificity, negative predictive value (NPV), and accuracy of IgG antibodies were higher in women than in men (p = 0.003, 0.001, and 0.049, respectively). There was no difference in sensitivity and positive predictive value (PPV) (p = 0.399 and 0.323, respectively). The results indicate that sensitivity tended to decrease while specificity tended to increase with age (p = 0.007 and 0.010, respectively) (Figure 1). However, there were no significant differences in PPV, NPV, and accuracy between the age groups (p = 0.088, 0.137, and > 0.999, respectively).

DISCUSSION

The consistency of two methods, serum *C. sinensis* IgG antibodies versus fecal *C. sinensis* eggs, was evaluated. The positivity rates for both methods were essentially the same: 48.0% for the egg test and 46.9% for the IgG antibody test. This was mainly because all study subjects had consumed raw fish, the most critical risk factor for *C. sinensis* infection [22,23]. Individuals who consumed raw fish were eight times more likely to be infected with *C. sinensis* compared to those who did not consume raw fish [24]. Additionally, a high frequency of raw fish consumption was associated with a high intensity of infection [25]. The concordance Kappa value of the IgG antibody test with worm egg detection was 0.599, indicating a moderate level of concordance, consistent with previous reports in the literature. To our knowledge, Han et al. were the only researchers to evaluate the concordance between serum *C. sinensis* IgG antibodies and fecal *C. sinensis* eggs. They recruited 2,359 patients with clinically suspected Clonorchiasis in Heilongjiang Province, China. Using the Kato-Katz method and ELISA, they tested the patients for *C. sinensis* eggs and IgG antibodies. The results showed moderate agreement between the Kato-Katz and IgG-ELISA methods (kappa value = 0.564) [19].

Table 2. The performance of *C. sinensis* IgG antibodies for Clonorchiasis with *C. sinensis* eggs as a gold standard.

<i>C. sinensis</i> eggs	<i>C. sinensis</i> IgG antibodies		
	+	-	Total
+	404	114	518
-	102	460	562
Total	506	574	1,080
Kappa (95% CI)	0.599 (0.551 - 0.647)		
Sensitivity% (95% CI)	78.0 (74.2 - 81.5)		
Specificity% (95% CI)	81.9 (78.4 - 85.0)		
PPV% (95% CI)	79.8 (76.8 - 82.6)		
NPV% (95% CI)	80.1 (77.4 - 82.7)		
Accuracy% (95% CI)	80.0 (77.5 - 82.3)		

PPV - positive predictive value, NPV - negative predictive value.

Table 3. Test performance of *C. sinensis* IgG antibodies for males and females.

	Results (n)				Test performance (%)				
	TP	TN	FP	FN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
Male	323	274	77	87	78.8 (74.5 - 82.6)	78.1 (73.4 - 82.3)	80.8 (77.4 - 83.7)	75.9 (72.2 - 79.3)	78.5 (75.4 - 81.3)
Female	81	186	25	27	75.0 (65.7 - 82.8)	88.2 (83.0 - 92.2)	76.4 (68.8 - 82.6)	87.3 (83.2 - 90.6)	83.7 (79.2 - 87.6)
χ^2					0.710	9.013	0.976	10.965	3.868
p-value					0.399	0.003	0.323	0.001	0.049

TP - true-positive, TN - true-negative, FP - false-positive, FN - false-negative.

Table 4. Test performance of *C. sinensis* IgG antibodies for different age groups.

	Results (n)				Test performance (%)				
	TP	TN	FP	FN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
< 46 years	93	119	32	20	82.3 (74.0 - 88.8)	78.8 (71.4 - 85.0)	74.4 (67.9 - 80.0)	85.6 (79.9 - 89.9)	80.3 (75.0 - 84.9)
46 - 54 years	111	93	29	24	82.2 (74.7 - 88.3)	76.2 (67.7 - 83.5)	79.3 (73.4 - 84.2)	79.5 (72.7 - 84.9)	79.4 (73.9 - 84.2)
55 - 65 years	119	105	23	32	78.8 (71.4 - 85.0)	82.0 (74.3 - 88.3)	83.8 (78.0 - 88.3)	76.6 (70.5 - 81.9)	80.3 (75.1 - 84.8)
≥ 66 years	81	143	18	38	68.1 (58.9 - 76.3)	88.8 (82.9 - 93.2)	81.8 (74.1 - 87.6)	79.0 (74.2 - 83.1)	80.0 (74.8 - 84.5)
χ^2					7.301	6.551	2.902	2.21	< 0.001
p-value					0.007	0.010	0.088	0.137	> 0.999

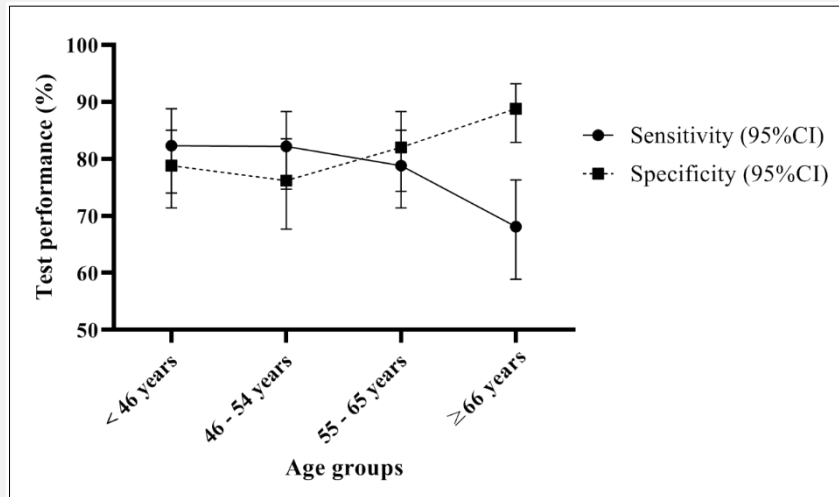


Figure 1. Changes in sensitivity and specificity in different age groups.

In addition to diagnostic consistency, it is essential to consider sensitivity and specificity as performance indicators, particularly in endemic areas requiring higher sensitivity to screen patients with *C. sinensis* infection. The diagnostic performance of the serum IgG antibody test was evaluated by using the fecal *C. sinensis* egg test results as the diagnostic gold standard. The sensitivity was 78.0%, specificity was 81.9%, positive predictive value was 79.8%, negative predictive value was 80.1%, and accuracy was 80.0%. These results suggest that the serum *C. sinensis* IgG antibody test is accurate and reliable in diagnosing *C. sinensis*. However, our study found a lower sensitivity of the IgG antibody test than other studies. For instance, Han et al. conducted a Bayesian analysis on 2,359 patients with clinically suspected Clonorchiasis. They reported a sensitivity of 98.7% for the diagnosis of *C. sinensis* by IgG-ELISA [19]. Similarly, Li et al. evaluated four immunodiagnostic kits for Clonorchiasis in China, and three of the IgG test kits had a sensitivity ranging from 81.51% to 99.16% [20].

This study found that the sensitivity of the IgG antibody test was insufficient for effectively screening for *C. sinensis* infection in at-risk populations in endemic areas. The sensitivity of the IgG antibody test was essentially the same in men and women, with no significant differences observed in subgroups. Notably, a pattern related to patient age was observed. As individuals age, the sensitivity of the IgG antibody test decreases while its specificity increases. This may be due to the natural decline in the immune system's ability to fight off infections, resulting in weaker antibodies in older adults, which are the body's defense mechanism [26]. Furthermore, it is worth noting that older adults tend to

visit the doctor more frequently and may have undergone therapeutic measures that could weaken the *C. sinensis* infection. Li's study also indicates a potential correlation between a patient's immune response and the severity of the disease. The IgG antibody assay exhibits higher sensitivity in severe infections but may produce more false-negative results in serum samples from less severely infected individuals [20]. These findings are more favorable than those of previous studies.

When comparing gender subgroups, it was discovered that IgG antibody testing had higher specificity, NPV, and accuracy in females than in males. This difference may be attributed to males having more opportunities to consume raw fish than females, leading to recurrent infections in the male population [23,25]. However, it should be noted that IgG antibody testing cannot differentiate between past and present infections [27].

There are limitations to this study. Firstly, it was conducted at a single center, which may introduce bias. Additionally, quantitative data on fecal worm eggs was not collected, making it unclear how well the IgG antibody test performs as a diagnostic tool in mildly infected populations.

CONCLUSION

In conclusion, detecting serum *Clonorchis sinensis* IgG antibodies demonstrates a sure accuracy in diagnosing Clonorchiasis. However, its sensitivity is relatively low, particularly in cases of mild infection and among the elderly. Therefore, when making a diagnosis, it may be necessary to combine other detection methods or further optimize the performance of this technology.

Acknowledgment:

The authors deeply appreciate the participants in this study and thank the clinical staff at all participating hospitals for their support and contribution to this project.

Source of Funds:

This work was supported by the Self-funded Health Commission of Guangxi Zhuang Autonomous Region (grant no. Z20200273).

Declaration of Interest:

The authors declare that they have no conflicts of interest.

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