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The Importance of Indirect Hemagglutination Test in the Diagnosis of Cystic Echinococcosis: Serological–Histopathological Correlation

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Abstract

Objective: We aimed to determine the reliability of indirect hemagglutination test and its relationship with cyst characteristics in cystic echinococcosis.

Methods: The study included 275 cases with indirect hemagglutination test requisition in Siirt; 23 of them were histopathologically examined and 17 of them were diagnosed as cystic echinococcosis. Indirect hemagglutination values (positive: ≥1/160 titrations) and patient and cyst characteristics were recorded. Accuracy rate, sensitivity, and specificity of the indirect hemagglutination test were calculated by comparing the histopathological diagnosis. The relationship between indirect hemagglutination titers and cyst characteristics was investigated.

Results: Seventeen cases had cystic echinococcosis diagnosis by indirect hemagglutination test and/or histopathology. Female : male ratio was 1.8 : 1 ($P < .003$), and mean age was higher in women (29.5) than in men (14.1) ($P < .031$). There was only 1 false-negative case in the indirect hemagglutination test. The accuracy rate, sensitivity, and specificity of the indirect hemagglutination test for detecting cystic echinococcosis were 96%, 94%, and 100%, respectively. The most common cyst localization was the liver (58.8%). Among indirect hemagglutination-positive cases, the largest cyst had the highest indirect hemagglutination titration. Liver-located cases had the highest titration level, while lung-located ones had the lowest. The lowest titration level was only seen in the cases with a single cyst, while most cases with the highest titration level had multiple cysts.

Conclusion: Cystic echinococcosis is a common public health problem especially in eastern Turkey. Indirect hemagglutination is a reliable, practical, and inexpensive method for both diagnosis and follow-up. We presented the first study that deals with the data of Siirt regarding cystic echinococcosis, but large-scale studies are needed for more information.

Keywords: Cystic echinococcosis, serology, indirect hemagglutination, histopathology

Introduction

Cystic echinococcosis (CE) is a zoonotic parasitic infection mostly seen in underdeveloped and developing countries caused by the larval stage of a cestode called *Echinococcus*.[1-3] It is one of the most important parasitic diseases in terms of both health and economy.[4] In Turkey, it is a public health problem predominantly in regions where animal husbandry is the main source of livelihood such as Eastern Anatolia Region.[4]

So far, 6 *Echinococcus* species have been described, 4 of which are pathogenic. *Echinococcus granulosus* is responsible for the vast majority of cases affecting humans presenting as CE.[5] *Echinococcus multilocularis* rarely affects humans and causes alveolar echinococcosis, which carries a worse prognosis.[6]

Definite hosts are dogs, intermediate hosts are farm animals such as sheep and goats, and humans are accidental intermediate hosts.[7] The parasite lives in hosts' small bowels, and eggs excreted in feces are ingested by intermediate hosts. Via the portal system, eggs reach the liver first and develop as a cyst. Sometimes it goes to other organs, mostly to the lungs of the intermediate hosts.[1,3,7] Human infection mainly results from contact with infected dogs or ingestion of products contaminated with parasite eggs.[8]

In humans, CE lesions most commonly involve the liver followed by the lungs; other organ involvements constitute up to 10% of infected cases.[5,6] Cystic echinococcosis is usually asymptomatic. Symptoms may occur over time, depending on the organ and size of the infection.[9,10]

The diagnosis of CE is made by clinical findings, radiologic techniques such as ultrasonography, computed tomography, magnetic resonance imaging, and serological tests such as indirect hemagglutination (IHA), indirect fluorescent antibody, enzyme-linked immunosorbent assay (ELISA), and western blot (WB).[9,11,12] In addition, protoscoleces may be detected by microscopic examination of the cyst fluid and histology.[12]

It has been reported that the sensitivity and specificity of serological tests depend on the structure, localization, viability and size of the cyst, the immune system of the person, the type and preparation of the antigen used, and the test's method.[1] Indirect hemagglutination test is a widely used serological technique which depends on the detection of specific *E. granulosus* antibodies at host serum and has high sensitivity and specificity compared with other serological methods. It is a reliable, easy-to-apply method, and the results can be obtained in a short time as an advantage.[8,12,13] It is also effective in asymptomatic cases.[1-3,11,13]

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In some cases, preoperative serologic results are verified with histopathologic examination.[1,2] Surgical methods are preferred for treatment depending on the cyst size and type.[12,14] Cystic echinococcosis is filled with clear and odorless cystic fluid, and it contains millions of structures called protoscolex. The cyst wall consists of the germinal membrane, laminar layer, and fibrovascular layer from the inside to out.[2]

In this study, CE cases with available IHA results and histopathologic diagnosis were examined in terms of patient age, gender, cyst characteristics (localization, number, and size), and IHA titers, and the relationship between various parameters was tried to be revealed.

Methods

Our study included 275 cases with a preliminary diagnosis of CE from different clinics and outpatient clinics in Siirt Training and Research Hospital between January 1, 2017, and March 20, 2022, for whom an IHA test was requested. Indirect hemagglutination values were obtained from the database of our hospital's microbiology laboratory. Ethical committee approval was received from the Ethics Committee of University of Amasya (Date: April 7, 2022, Number: 44). Informed consent was not obtained due to retrospective design of the study.

In this study, 23 of 275 patients were operated in our hospital, and the cyst materials were histopathologically diagnosed. Each patient was considered as a single case whether with a single or multiple cyst. The diagnosis of cystic material was recorded from the pathology reports. The accuracy rate, sensitivity, and specificity of the IHA test for detecting CE were calculated by comparing the IHA test results and the histopathological diagnoses.

In cases with CE diagnosis, age and gender characteristics of the patients and the frequency of cyst localization and cyst number (single or multiple) were determined. The mean cyst size was calculated by considering the largest cyst size in multiple cysts. It was investigated whether there was a statistically relationship between IHA titers and cyst characteristics.

Indirect Hemagglutination Test

In our routine practice, serum samples obtained from blood samples that came to the microbiology laboratory are kept at –20°C until the study was conducted. A kit operating on the principle of IHA (hydatidose, Fumouze Laboratories, Levallois-Perret, France) is applied to the serum samples. Serum dilutions are made in U-bottomed microplates. A suspension of erythrocyte with antigen is added to the microplates. After 2 hours of incubation at room temperature, if agglutination occurs and a reddish-brown film covers the well, there are anti-*E. granulosus* antibodies in the serum and the test is accepted as positive. In the absence of specific antibodies, agglutination does not occur, resulting in a ring-like deposit at the bottom of the well, and the test is accepted as negative. After the procedures are performed in accordance with the kit test procedure, titer ≥ 1/160 results are considered positive for *E. granulosus.*

Statistical Analysis

The data were analyzed using the Statistical Package for Social Sciences version 26.0 (IBM SPSS Corp.; Armonk, NY, USA) statistical program. While evaluating the data, descriptive statistics were presented as the number of cases and percentages in categorical variables. In the analysis of continuous variables, normality analyses were performed with the Shapiro–Wilk goodness of fit test. The *t*-test and 1-way analysis of variance in independent groups were used for the comparisons of the normally distributed variables of the data, the Mann–Whitney *U*-test was used for the comparisons of the non-normally distributed variables, and the chi-square test was used for the comparisons of the qualitative data. Fisher's exact test was applied in cases where the chi-square test could not be applied in 2 × 2 tables. Means were presented with their SDs. Statistical significance was evaluated as $P < .050$. Accuracy rate (true positive + true negative/true positive + false positive + true negative + false negative), sensitivity (true positive/true positive + false negative), and specificity (true negative/true negative + false positive) were manually calculated.

Results

Patients

A series of 275 cases included 155 female and 120 male patients (female : male; 1.3 : 1). The mean age was 35.6 ± 20.5 (1-80).

Ninety-three (33.8%) blood samples were seropositive and 182 (66.2%) were seronegative by IHA test. Sixteen of 93 (17%) seropositive and 7 of 182 (0.3%) seronegative (23 in total) cases underwent surgery in our hospital.

Comparison of Indirect Hemagglutination Test Results and Histopathological Diagnoses

Cystic echinococcosis diagnosis was verified histopathologically in all 16 seropositive cases (Figure 1). So, there was no false seropositivity. There was false seronegativity in only 1 case. In total, 17 cases had CE diagnosis with IHA test and/or histopathology. Remaining 6 seronegative cases had different histopathological diagnosis: 2 nonspecific pleural exudates, 1 pericardial coelomic cyst in the lung, 1 peritoneal inclusion cyst, and 2 nonspecific inflammation in the liver. Comparisons of IHA test results and histopathological diagnoses are summarized in Table 1.

When histopathological diagnosis was accepted as the definitive diagnosis, the accuracy rate, sensitivity, and specificity of the IHA test for detecting CE were calculated as 96%, 94%, and 100%, respectively.

Patient and Cyst Characteristics of Cystic Echinococcosis Cases

In the series of 17 CE cases, the female : male ratio was 1.8:1, and the mean age was 24.0 ± 16.5 (6-60).

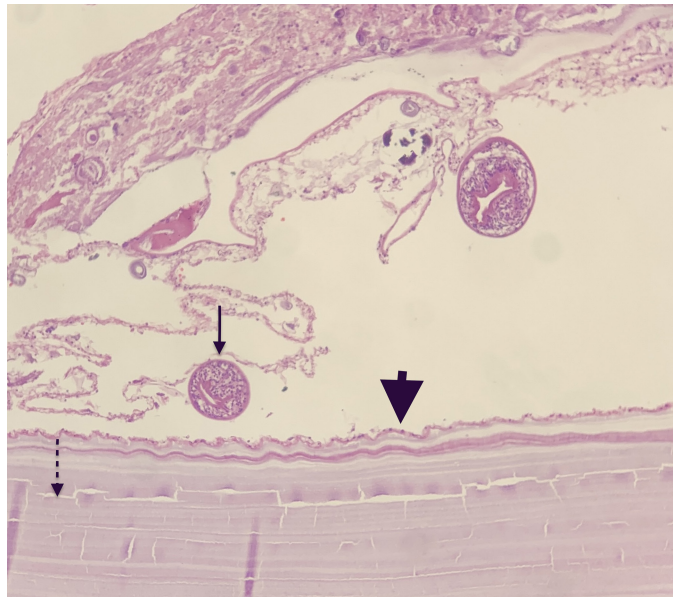

Figure 1. Scolex of *Echinococcus granulosus* (arrow) and laminar layer (striped arrow) and germinative layer (bold and short arrow) (hematoxylin ×200).

Table 1. General Patient and Cyst Characteristics in Cystic Echinococcosis Cases (n = 17)

		n	%
Age (years)	Mean ± SD (minimum-maximum)	24.0 ± 16.5 (6-60)	
	≤18	9	52.9
	19-39	5	29.5
	40-60	3	17.6
Gender	Female	11	64.7
	Male	6	35.3
Cyst localization	Liver	10	58.8
	Lung	6	35.3
	Abdomen	1	5.9
Cyst number	Single	9	52.9
	Multiple	8	47.1
Cyst size (cm)	Mean ± SD (minimum-maximum)	8.3 ± 2.7 (4-13)	
IHA titration	<1/160 (negative)	1	5.9
	1/160	2	11.8
	1/320	4	23.5
	1/640	2	11.8
	1/1280	2	11.8
	1/2560	6	35.2
	Total	**17**	**100**

IHA, indirect hemagglutination; SD, standard deviation.

Cyst localizations were as follows: 10 (58.8%) liver, 6 (35.3%) lung, and 1 (5.9%) abdomen. The cyst number varied between 1 and 4. Most (52.9%) cases had a single cyst. The mean cyst size was 8.3 ± 2.7 (4-13) cm.

Indirect hemagglutination titrations were as follows: 1/160 in 2, 1/320 in 4, 1/640 in 2, 1/1280 in 2, and 1/2560 in 6 cases. Remaining 1 case was seronegative. General patient and cyst characteristics of CE cases are summarized in Table 1.

Comparison of Patient Characteristics with Each Other

There were 11 (64.7%) female and 6 (35.3%) male patients, and women's dominance was statistically significant ($P < .003$). When gender and mean age were compared statistically, there was a significant difference ($P < .031$). The mean age was higher in women (29.5 ± 17.4) than in men (14.1 ± 9.1) (Table 2).

When the gender distribution according to age groups was analyzed, 55.6% of the cases in the ≤18 age group were male. This male rate decreased to 20% at 19-39 and to 0 in the 40-60 age group. So, the female rate was 100% in the 40-60 age group (Figure 2).

Comparison of Cyst Characteristics with Each Other

Cyst Localization and Number. Most (6 of 10) cases with liver localization had multiple cysts, while most (4 of 6) cases with lung localization had a single cyst. There was a single cyst in the case with abdominal CE. In the statistical analysis that included only the cases with liver and lung localizations, we could not find a relationship between cyst localization and number ($P = .606$) (Table 3).

Cyst Localization and Size: Both the largest (13 cm) and the smallest (4 cm) cysts were located in the lung. The mean cyst size was 8.0 ± 3.6 cm in this localization. There was no statistically significant relationship between 2 parameters ($P = .926$) (Table 4).

Cyst Number and Size: Mean cyst size was 9.3 ± 2.6 cm in cases with a single cyst and 7.2 ± 2.4 cm in cases with multiple cysts. However, cyst number and size were not found to be statistically related ($P = .052$) (Table 4).

Table 2. Age and Gender Distribution in the Cases With Cystic Echinococcosis (n = 17)

	n	%	Test	*P*
Male	6	35.3	1 sample Chi-square	.003
Female	11	64.7		
Total	17	100		
	Mean age ± SD			
Male	14.1 ± 9.1		Independent *t*-test	.031
Female	29.5 ± 17.4			
Total	24.0 ± 16.5			

Comparison of Indirect Hemagglutination Results with Cyst Characteristics

Indirect Hemagglutination Results and Cyst Localization. Highest titration level (1/2560) was only seen in cases with liver localization, while the lowest titration level (1/160) was only seen in cases with lung localization. Cyst localization was also the lung in 1 false seronegative case. Since the number of variables was not suitable, statistical analyses could not be performed (Table 5).

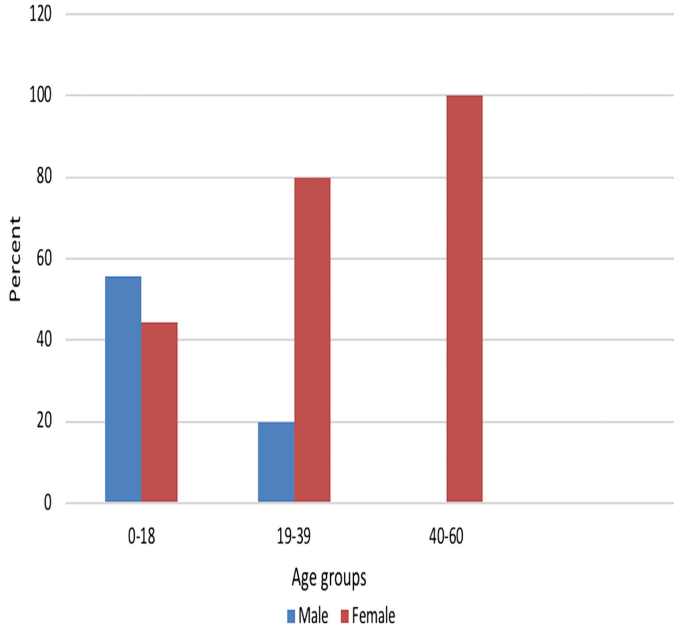

Figure 2. Distribution of cystic echinococcosis cases according to gender and age groups.

Table 3. Comparison of Cyst Localization and Number (n = 16)*

		Single		Multiple			
		n	%	n	%	Test	*P*
Localization	Liver	4	50.0	6	75.0	Fisher's exact test	.606
	Lung	4	50.0	2	25.0		
	Total	8	100	8	100		

*One case which had an abdomen-located single cyst was not included to the statistical analysis.

Indirect Hemagglutination Results and Cyst Number. Lowest titration level (1/160) was only seen in the cases with single cyst. In contrast, most (4 of 6) cases with highest titration level (1/2560) had multiple cysts. Since the number of variables was not suitable, statistical analyses could not be performed (Table 5).

Indirect Hemagglutination Results and Cyst Size. In our CE series, the case with the largest cyst (13 cm) was IHA negative. Among the IHA-positive group, the largest cyst was 12 cm in size, and this case had the highest titration level. In statistical analyses, there was no relationship between the IHA titration levels and cyst size ($P = .962$) (Table 6).

Table 4. Comparison of Cyst Localization and Cyst Number with Cyst Size (n = 17)

			Cyst Size (cm)					
		n	Mean	Median	Minimum	Maximum	Test	*P*
Cyst localization	Liver	10	8.5 ± 2.3	8.0	6.0	12.0	1-way ANOVA	.926
	Lung	6	8.0 ± 3.6	8.0	4.0	13.0		
	Abdomen	1	9.0 ± 0.0	9.0	9.0	9.0		
Cyst number	Single	9	9.3 ± 2.6	9.0	4.0	13.0	Mann–Whitney *U*-test	.052
	Multiple	8	7.2 ± 2.4	6.8	4.0	12.0		

Table 5. Comparison of IHA Titration Levels With Cyst Localization and Cyst Number (n = 16)*

		Cyst Localization						Cyst Number			
		Liver		Lung		Abdomen		Single		Multiple	
		n	%	n	%	n	%	n	%	n	%
IHA titration	1/160	0	0	2	40.0	0	0	2	25.0	0	0
	1/320	2	20.0	1	20.0	1	100	2	25.0	2	25.0
	1/640	1	10.0	1	20.0	0	0	1	12.5	1	12.5
	1/1280	1	10.0	1	20.0	0	0	1	12.5	1	12.5
	1/2560	6	60.0	0	0	0	0	2	25.0	4	50.0
Total		10	100	5	100	1	100	8	100	8	100

*One case which was seronegative was not included in the table. In this case, the cyst was located in the lung and it was a singe cyst.
IHA, indirect hemagglutination.

Table 6. Comparison of IHA Titration Levels and Cyst Size (n = 16)*

			Cyst size (cm)					
		n	Mean ± SD	Median	Minimum	Maximum	Test	*P*
IHA titration	1/160	2	7.5 ± 5.0	7.5	4.0	11.0	1-way ANOVA	.962
	1/320	4	8.0 ± 1.4	8.5	6.0	9.0		
	1/640	2	7.0 ± 4.2	7.0	4.0	10.0		
	1/1280	2	8.0 ± 0.0	8.0	8.0	8.0		
	1/2560	6	8.6 ± 2.8	7.8	6.0	12.0		

*The largest cyst diagnosed as cystic echinococcosis was 13 cm in size. Since it was seronegative, it was not included in this table.
ANOVA, analysis of variance; IHA, indirect hemagglutination.

Discussion

Indirect hemagglutination is a widely used serological technique for the diagnosis of CE.[14-16] In our study, we detected 33.8% positivity in 275 cases who were requested for the IHA test, and all operated and histopathologically CE diagnosed cases were seropositive. Güreser et al[1] found a 12.7% seropositivity rate among 253 patients who were requested for IHA test in Çorum province. Eşgin et al[3] found 54.1% seropositivity in their study, including 85 cases who were requested for the IHA test in Ankara; and this rate was 78.3% among operated cases. Miman et al[2] investigated IHA positivity in their study, including 91 cases with histopathologic CE diagnosis. Only 50 of them also had IHA test results, and the seropositivity rate was 92%.

Miman et al[2] reported a false-negativity rate of IHA test of 8%. Bilge et al[16] found the sensitivity and the specificity of IHA test to be 75% and 100%, respectively. Akgün et al[11] reported the sensitivity and the specificity rates to be 89% and 95%. In our study, in total 23 (16 seropositive and 7 seronegative) cases underwent surgery. When IHA test results and histopathological diagnoses were compared, 17 cases had CE diagnosis by histopathology and 16 of them were also seropositive. So, there was no false seropositivity, but false seronegativity was seen in 1 case. Although the number of cases was limited in our study, accuracy rate, sensitivity, and specificity of IHA were found to be 96%, 94%, and 100%, respectively.

In the literature, female gender preponderance was reported in most studies.[11,14,15] However, there are few studies that find the rate of IHA height equal in both sexes or report male predominance.[13,17] In our study, there was a significant female gender predominance, in line with the general literature. Male and female gender dominance differences may be due to sociocultural differences.

Miman et al[2] reported the mean age as 36 (4-80) in cases with histopathological diagnosis of CE. Durmaz et al[18] found the mean age to be 53.5 (11-85) in their study. In our series including 17 CE cases, the age ranged from 6 to 60, and the mean age was 24. In addition, women had significantly higher mean age than that of men (29.5 and 14, respectively).

Çitil et al[19] found that 70% of the 111 IHA-positive cases were in the 20-60 age group. Kurt et al[20] reported that 54% of 106 CE cases were over 18 years old. Aslan et al[15] found that the number of CE cases detected by IHA was the highest (43%) in the 25-49 age group, while it was the least (11%) in the 0-14 age group. Akgün et al[11] reported that 55% of the IHA-positive cases (73) were in the 16-45 age group. These higher seropositivity rates in mid-adulthood may be due to the parasite eggs ingested in childhood giving symptoms at later ages.

Unlike these studies, when we divided our CE cases into ≤18 and 18-60 age groups, the positivity rate was higher (53%) in the first group rather than adulthood. When we analyzed both patient age and gender distribution, we observed that 55.6% of the cases in the ≤18 age group were male. This rate was decreasing to 20% in the 19-39 age group and it was 0 in older cases. So, all cases in the 40-60 age group were female.

Liver was defined as the dominant localization in former studies from different regions.[1,2,7,21] This may be a feature of CE depending on the life cycle of the parasite.[7] Our cases were dominantly (58.8%) located in the liver, and it was followed by the lung (35.3%), which is consistent with the former studies.[3,9-11,14,22] In our series, there was only 1 abdomen-located case (5.9%). Durmaz et al[18] found that the lung was a much rarer localization compared to splenic and mesenteric ones. However, they also stated that the absence of lung surgery in their center could be the explanation of this situation.

Miman et al[2] analyzed the relationship between cyst number and localization in their study including 91 histopathologically diagnosed CE cases. They found that cysts localized in the liver were disposed to be single and ones in the lung were disposed to be multiple, but they could not find a specific relationship. Contrary to their work, in our series, most (60%) cases with liver localization had multiple cysts, while most (66.7%) cases with lung localization had a single cyst. However, the results were not significant.

Miman et al[2] reported that cysts located in the liver were larger than the lung-located ones. In our study, both the largest (13 cm) and smallest (4 cm) cysts were located in the lung, and the mean cyst size was 8 cm in this localization. In statistical analysis, there was no relationship between cyst localization and size. Further studies with larger numbers may help to elucidate this relationship.

Lissandrin et al[23] reported a positive correlation between cyst number and size in a study including 171 hepatic CE cases which were diagnosed by IHA or ELISA. In our study, the mean cyst size was higher in single cysts (9.3 cm) than multiple ones (7.2 cm). However, this result was not statistically significant.

In the literature, it was reported that IHA titration percentages were lower in extrahepatic CEs.[1,21,24,25] Consistent with this information, we observed that the highest titration level (1/2560) was only in the cases with liver localization, while the lowest level (1/160) was only in cases with the lung localization. The cyst localization was also the lung in our false-negative case. Our intraabdominal CE case had 1/320 titration. Since our variables were not suitable, we could not perform statistical evaluation on this subject.

Lissandrin et al[23] studied on only liver cysts and found significant positive correlation between serology results and cyst number. Zarzosa et al[24] found no statistically significant difference between multiple and single CE cases in terms of IHA sensitivity or titers. In our series, which included both hepatic and extrahepatic cysts, the lowest titration level was seen only in cases with single cyst, while most (66.6%) cases with highest titration level had multiple cysts. However, statistical analyses could not be performed about this subject.

According to World Health Organization Informal Working Group Echinococcosis classification, according to ultrasonographic findings, CEs are classified in stages as active, transitional, and inactive.[14] Lissandrin et al[23] grouped the cysts by using this classification, and they found a positive relationship between cyst size and serologic status in only active cysts. In our study, we could not evaluate the radiological data; however, we compared the IHA titration levels and cyst size. The largest cyst (13 cm) of our series was seronegative. Among seropositive cases, the largest cyst was 12 cm in size and located in the liver. This case had the highest titration level (1/2560), while the case with the smallest (4 cm) cyst had the lowest (1/160) titration level. Moreover, the mean cyst size was higher (8.6 cm) in the cases with 1/2560 titration level than that of the other levels. However, no statistically significant relationship was found between 2 parameters.

Conclusion

Cystic echinococcosis is a common public health problem especially in the east of Turkey. This is the first study that deals with the data of Siirt province regarding this disease, apart from case reports. Indirect hemagglutination is a reliable, practical, and inexpensive method with a high accuracy rate, specificity, and sensitivity in the diagnosis of CE. Our results have suggested that high titration levels may be associated with liver localization, multiple

cysts, and larger cyst size. However large-scale studies are needed for more information.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of University of Amasya (Date: April 7, 2022, Number: 44).

Informed Consent: Informed consent was waived due to retrospective design of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Ö.Y.; Design – Y.G.B.; Supervision – H.D.; Resources – Ö.Y., Y.G.B.; Materials – Ö.Y., Y.G.B. ; Data Collection and/or Processing –Ö.Y., Y.G.B.; Analysis and/or Interpretation – H.D., Y.G.B.; Literature Search – Ö.Y., Y.G.B., H.D.; Writing Manuscript – Ö.Y.; Critical Review – H.D. ; Other – H.D.

Declaration of Interests: The authors have no conflict of interest to declare.

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