

## The correlation between immunoglobulin levels with cyst count in patients with and without surgery for hydatid disease

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### ABSTRACT

**Background:** Hydatid disease remains a major public health problem in all endemic areas due to *Echinococcus granulosus* infection. High immunoglobulin levels determine the immune response to hydatid cysts. Knowledge about the association of immunoglobulins with cyst pathogen burden thus helps understand disease activity and develop better therapeutic strategies.

**Aim of study:** To evaluate immunoglobulin levels (IgA, IgE, IgG) in relation to cyst number in patients with hydatid disease who underwent surgical removal of cysts and those who did not undergo surgery.

**Methodology:** Three groups of patients participated in the case control study divided into surgically treated patients with hydatid disease, patients who did not undergo surgery and control groups. Immunoglobulin measurements were performed by ELISA while cysts was confirmed by MRI.

**Results:** The levels of IgA along with IgE and IgG were elevated significantly in non-operated patients compared to operated patients when results were analyzed ( $p < 0.0001$ ). Non-operated patents showed a strong positive link between cyst count measurements and IgA ( $r = 0.777$ ,  $p < 0.0001$ ) as well as IgE ( $r = 0.655$ ,  $p < 0.0001$ ) and IgG ( $r = 0.713$ ,  $p < 0.0001$ ). Cyst count showed relationships that remained statistically significant for the operated patients although they were less strong with IgA ( $r = 0.391$ ,  $p = 0.033$ ) and IgE ( $r = 0.521$ ,  $p = 0.003$ ) and IgG ( $r = 0.465$ ,  $p = 0.010$ ).

**Conclusion:** Disease severity shows a meaningful relationship between cyst number and immunoglobulin levels.

**Keywords:** Hydatid disease, *Echinococcus granulosus*, Immunoglobulins, Immune response.

### 1. INTRODUCTION

Cystic hydatid disease (CHD) functions as hydatidosis or echinococcosis while existing as a cyclozoonotic infection through the entire world. Farm animals suffer from this significant parasitic disease because it originates from *Echinococcus* tapeworms during their larval phase. Herbivores and rodents make up the intermediate hosts according to Al-Jebory (2012).

CHD diagnostic progress has mainly targeted antibody production mechanisms along with immunological processes in CHD research. Scientific interest in hydatid cyst antigens has increased because of their potential value in serological testing. Current investigations show that hydatid cyst fluid demonstrates inconsistent properties for its usage as an antigen in diagnostic tests. Standardization becomes complicated because antigenic makeup along with immunogenic properties fluctuate when considering cyst position and host immunity together with infection development stages (Abu Jabel and Rogan, 2023).

IgE functions as the essential mediator for parasite-induced immune responses including the infection caused by CHD. The presence of high IgE levels indicates allergic reactions towards hydatid cyst antigens that demonstrate the continued immune response against the parasite. Diagnosing active infections depends heavily on this marker because it reveals both hypersensitivity and immune reactions toward cyst fluid antigens (Abu Jabel and Rogan, 2023).

Different studies of CHD have demonstrated IgG as the main laboratory marker used for diagnosing this condition. Research indicates that specific IgG subclass types IgG1 and IgG4 appear during the chronic phase of the disease because they represent adaptive immune system activity. An increased IgG measurement indicates patient contact with hydatid cyst antigens yet these antibodies can stay elevated independently from treatment outcomes thus affecting post-treatment program assessments (Maleki *et al.*, 2023).

IgA levels show limited study application in hydatid disease but they reveal their relationship to both mucosal defense mechanisms and entire-body immune tasks. Laboratory findings of IgA within CHD suggest the development of immune response activation near mucosal surfaces where cysts are present.

The diagnostic value of elevated IgA levels shows its best performance by combining measurements with other important indicators (Abu Jabel and Rogan, 2023).

Medical experts agree that surgery provides the main treatment for hydatid cysts yet the recovery of immunoglobulin levels following surgery remains unknown. Additional research has to examine the connection between cyst size and immunological reactions which stay after surgical procedures because some studies show antigens remain in the body following operations. Therefore, this research aimed to investigate the relationships between hydatid disease patient immunoglobulin levels (IgA, IgE, IgG) alongside cyst counts in operated patients (surgically treated) and non-operated patients (medically treated) only.

## 2. MATERIALS AND METHODS

### Study Design and Population

Case control study included 90 participants of three groups: non-operated patients (31) diagnosed with hydatid disease through imaging and serological tests, operated patients (30) who had undergone surgical removal of hydatid cysts, and control group (29) of healthy individuals was also included for comparative analysis.

### Sample Collection and Immunological Assays

Five ml of blood samples were collected from all participants in the current study to measure quantification of immunoglobulin (IgA, IgE, and IgG) levels using China kits (Shanghai YL Biotech) by ELISA. Samples collected from Iraq, Najaf city (Al-Sader Medical City, AL-Hakeem General Hospital, AL-Najaf Al-Ashraf Teaching Hospital, AL-Batool Private Hospital, Iraqi Private Hospital and Al-Hayat Private Hospital) at the time starting from 1 September 2024 to 31 December 2024.

## 3. INCLUSION AND EXCLUSION CRITERIA

### Inclusion Criteria

In this study, several inclusion criteria were applied. Participants included patients diagnosed with hydatid cysts based on ultrasound findings.

### Exclusion Criteria

Certain cases were excluded from this study based on specific criteria. Exclusion was applied to any case with incomplete information in the questionnaire. Additionally, individuals with cancer, autoimmune disease and chronic diseases were not included in the study.

### Ethical Standards

The current study received official approval from the Medical Laboratory Services Division of the College of Health and Medical Technologies, the Najaf Health Department, and the Training and Development Center (Approval No. 37907). In addition, informed written consent was obtained from all participants in all study groups.

### Statistical analysis

Pearson correlation analysis was used to determine associations between cyst count and immunoglobulin levels. Linear regression was performed to evaluate cyst count as an independent predictor of immune marker levels. A p-value < 0.05 was considered statistically significant.

## 4. RESULTS AND DISCUSSION

### Immunological markers levels in studied groups

Table (1) presents an entire analysis of immunological markers among non-operated patients, operated patients and healthy controls. The study presents immunology data through average measurements and standard deviation values of age alongside IgA, IgE and IgG immunoglobulin levels. The results display meaningful variation across all three tested groups which demonstrates an active involvement of these markers during *Echinococcus granulosus* infection scenarios within hydatid

disease patients.

**Table 1: Immunological markers levels in studied groups**

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Studied groups		Mean	Std. Deviation	Std. Error	Minimum	Maximum	p-value
Age (year)	Non-Operated	37.90	12.09	2.17	20	70	0.717 ns
	Operated patients	38.90	13.05	2.38	20	70	
	Control	40.62	13.85	2.57	24	70	
IgA mg/ml	Non-Operated	209.46	43.91	7.89	135.12	295.34	0.0001*
	Operated patients	71.76	6.36	1.16	60.34	80.12	
	Control	58.64	16.87	3.13	30.55	97.33	
IgE IU/ml	Non-Operated	1,223.71	220.67	39.63	900.00	1,600	0.0001*
	Operated patients	333.67	96.57	17.63	210.00	500	
	Control	120.09	40.22	7.47	73.00	200	
IgG mg/ml	Non-Operated	313.97	124.78	22.41	200.00	602.00	0.0001*
	Operated patients	96.11	16.77	3.06	60.00	120.00	
	Control	34.11	13.92	2.58	18.31	62.17	
Significant differences at p- value < 0.05.							

Non-operative patients exhibited significantly heightened immunological markers which reached IgA at  $209.46 \pm 23.11$  mg/ml and IgE at  $1223.71 \pm 56.45$  IU/ml and IgG at  $313.97 \pm 20.15$  mg/ml. *Echinococcus granulosus* evokes a strong immune response which occurs because of the active presence of hydatid cysts.

Studies support the findings that immunoglobulin levels increased after infection with *E. granulosus*. Zhang *et al.* (2012) stated that IgA functions as a key defense mechanism against parasitic infections at the mucosal barrier. According to Gottstein *et al.* (2017) elevated IgE levels indicate that patients experience strong allergic and immunologic responses to hydatid antigens. Chen *et al.* (2014) demonstrated that parasitized patients exhibit elevated IgG levels which corresponds to the findings of this study about ongoing adaptive immunity.

The operated patient group exhibited quantitative decreases in their total immunoglobulin levels across the board including IgA ( $71.76 \pm 4.15$  mg/ml) and IgE ( $333.67 \pm 11.11$  IU/ml) and IgG ( $96.01 \pm 7.15$  mg/ml). The procedure produces positive results by eliminating the antigen source which leads to decreased immune system activation. Successful surgical removal of hydatid cysts decreases immunological markers as described by Chen *et al.* (2014) in their research findings. Operation procedures lead to reduced levels of IgA, IgE and IgG thus indicating a restoration of normal immune response mechanisms because the active cysts no longer stimulate immunity.

The control group exhibited IgA at  $58.64 \pm 6.45$  mg/ml together with IgE at  $120.09 \pm 2.15$  IU/ml, and IgG at  $34.11 \pm 1.15$  mg/ml as standard values for healthy subjects with no immune activation. Surgical intervention emerges as crucial because these research findings demonstrate the fundamental differences between the immune characteristics of untreated patients when compared to surgically treated patients.

The short levels of immunological markers in the control group confirm that these heightened responses in non-operated disease patients result specifically from hydatid pathology rather than natural interpersonal immune pattern diversity.

## 5. IMMUNOLOGICAL MARKERS LEVELS ACCORDING GENDER IN BOTH GROUPS OF PATIENTS

Table 2 shows the mean immunological marker levels that divide patients between female and male populations affected by human hydatid disease in non-operated and operated groups. Scientists analyzed three immunology markers which are IgA and IgE together with IgG. The research indicates male participants possess higher levels of all markers than female subjects but these results show no statistical significance ( $p > 0.05$ ).

**Table 2: Immunological markers levels according Gender in both groups of patients**

Gender			Mean	Std. Deviation	Std. Error	p-value
Non-Operated patients	IgA mg/ml	Male	217.19	38.80	10.37	0.382 ns
		Female	203.08	47.91	11.62	
	IgE IU/ml	Male	1,249.64	197.00	52.65	0.562 ns
		Female	1,202.35	242.27	58.76	
	IgG mg/ml	Male	331.86	137.63	36.78	0.478 ns
		Female	299.24	115.29	27.96	
Operated patients	IgA mg/ml	Male	72.78	5.70	1.34	0.288 ns
		Female	70.22	7.23	2.09	
	IgE IU/ml	Male	351.67	97.75	23.04	0.217 ns
		Female	306.67	92.15	26.60	
	IgG mg/ml	Male	98.58	13.80	3.25	0.332 ns
		Female	92.40	20.54	5.93	
Significant differences at p- value < 0.05. ns: non-significant between both male and female patients						

Among participants in the non-operative group males averaged higher amounts of IgA markers at  $217.19 \pm 38.80$  mg/ml than females at  $203.08 \pm 47.91$  mg/ml although the difference was not statistically important ( $p = 0.382$ ). The results showed that male participants displayed higher IgE levels at  $1,249.64 \pm 197.00$  IU/ml than female participants with levels at  $1,202.35 \pm 242.27$  IU/ml but the difference proved not statistically significant ( $p = 0.562$ ). düzenli measurements of IgG revealed a male mean level at  $331.86 \pm 137.63$  mg/ml which was not significantly different than the female mean level at  $299.24 \pm 115.29$  mg/ml ( $p = 0.478$ ).

The data confirms a regular pattern of increased immunological markers throughout male subjects in agreement with similar research conducted by Zhang et al. (2012) who observed that gender variations in cystic echinococcosis (CE) immune responses remained negligible. The study results show matching immunological responses between sexes because both genders develop IgA and IgG antibodies during early and prolonged infection stages according to Zhang et al. (2012). According to Chen et al. (2014) the removal of human cyst hydatid disease cysts through surgery could affect the immune markers present in the body since cyst extraction brings changes to the immune system. IgA and IgE showed slight elevations among male participants in this evaluation yet these results remained statistically insignificant according to data from Qasim and Yousif (2020). The researchers documented that post-surgical markers related to immunity including IgA and IgE levels changed but gender-related patterns between male and female patients did not clearly emerge during the post-operative period so the disease condition seems to determine immune system responses more than biological sex.

The operative group exhibited identical outcome results as the non-operative group yet presented lower total immunological markers levels. The evaluation of IgA concentrations found results of  $72.78 \pm 5.70$  mg/ml in male subjects and  $70.22 \pm 7.23$  mg/ml in female participants without statistical significance between groups ( $p = 0.288$ ). The study showed that male patients revealed IgE measurements at  $351.67 \pm 97.75$  IU/ml whereas female patients demonstrated  $306.67 \pm 92.15$  IU/ml but their difference was not significant based on the 0.217 p-value. Results from the IgG tests displayed an equivalent pattern showing  $98.58 \pm 13.80$  mg/ml in male participants and  $92.40 \pm 20.54$  mg/ml in female participants ( $p = 0.332$ ).

Sharma and Gupta (2021) established that surgical intervention and infection severity determine hydatid disease responses more strongly than patient gender because of their findings regarding post-surgical patients. The findings showed immune marker levels of IgG and IgA usually decrease following cyst removal surgery demonstrating the patient's recovery process.

## 6. CORRELATIONS BETWEEN NUMBER OF CYST IMMUNOGLOBULINS IN BOTH OPERATED AND NON-OPERATED PATIENTS

Table (3) presents the relationship between cyst numbers and immunoglobulins level such as IgA, IgE, and IgG in patients who underwent surgical treatment along with those receiving only medical treatment. The study results reveal the relationship strength between cyst number and immune responses which provides understanding of hydatid cystic echinococcosis

pathogenesis.

**Table 3: Correlation of No. cysts with immunoglobulins in both two groups of patients**

Groups			No. cyst	IgA mg/ml	IgE IU/ml	IgG mg/ml
Non-Operated patients	No. cyst	R	1.	0.777**	0.713**	0.655**
		P		0.0001	0.0001	0.0001
	IgA mg/ml	R		1.	0.808**	0.832**
		P			0.0001	0.00011
	IgE IU/ml	R			1.	0.668**
		P				0.0001
	IgG mg/ml	r				1.
		p				
Operated patients	No. cyst	r	1.	0.391*	0.521**	0.465**
		p		0.033	0.003	0.010
	IgA mg/ml	r		1.	0.767**	0.774**
		p			0.0001	0.000
	IgE IU/ml	r			1.	0.825**
		p				0.0001
	IgG mg/ml	r				1.
		p				

Non-operated patients (No. = 31) displayed a very strong positive association between the cyst number counts and their IgA levels ( $r = 0.777$ ,  $p < 0.0001$ ). The immune response driven by IgA molecules intensifies in direct proportion to the number of cysts detected in non-operated patients since IgA functions as a fundamental component of mucosal defense and shows evidence of persistent antigen exposures. The relationships between IgA levels and other immune markers became statistically significant when measured against IgG ( $r = 0.832$ ) and IgE ( $r = 0.808$ ) while additional research by Zhang *et al.* (2012) as well as Gottstein *et al.* (2017) demonstrated that increased hydatid cyst loads enhance immunoreactive responses.

Research findings in operated patients (No. = 30) still demonstrated meaningful associations between IgA ( $r = 0.391$ ,  $p = 0.033$ ) while the relationship strength substantially decreased. Surgical cyst removal decreases the amount of exposed antigens which results in diminished immune system activation. Research by Chen *et al.* (2014) showed surgical procedures lead to decreased IgA levels thus indicating that immune system activation weakens after surgically removing antigen sources.

The number of cysts demonstrated significant correlation to IgE levels ( $r = 0.655$ ,  $p < 0.0001$ ) in patients who did not undergo surgery which showed increased IgE production depended on cyst count. Elevated levels of IgE indicate a Th2-type immune response that typically relates to allergic responses alongside parasitic infections according to (Gottstein *et al.*, 2017). IgE levels in operated patients displayed a significant yet reduced correlation with cyst number ( $r = 0.521$ ,  $p = 0.003$ ) indicating that surgical cyst removal decreases but not eradicates antigenic exposure from cysts. The remaining significant although weaker connection between IgG measurements and cyst burdens after surgery probably stems from continuous immune system activation that might result from leftover antigens or partially removed cysts (Hussien, 2023).

The non-operated patients exhibited persistent antibody responses through their elevated IgG levels which directly corresponded to cyst number ( $r = 0.713$ ,  $p < 0.0001$ ) in accordance with chronic parasitic infection patterns. Assessments showing elevated IgG indicate that the immune system maintains activity against hydatid cyst antigens (Ramadan *et al.*, 2021). Surgical intervention weakens the antibody level correlation ( $r = 0.465$ ,  $p = 0.010$ ) while the operated group maintains an existing relationship between antibodies and the number of cysts. According to Qasim & Yousif (2020) the immunological

response to antigens from hydatid cysts declines with reduced IgG levels due to decreased chronic inflammation and immune stimulation.

## 7. LINEAR REGRESSION ANALYSIS

Table (4) illustrates the findings from a linear regression analysis performed to measure the cyst number influence on multiple immunological factors for both non-operated and operated patient populations. The examination examines the immunological markers IgA together with IgE and IgG. The presented table displays regression coefficients (B) and t-values and p-values and 95% confidence intervals (95% CI) for each marker which illustrates the cyst number and immune response connection. Non-operated patient results indicate substantial increases in immune response activity that the operated patient data shows reduced the strength of immune system activities after patients received surgical treatment.

Table 4: Linear regression analysis of No. cyst as independent factor for identified the risk markers in both groups of patients.					
Groups		B	t	p-value	95.0% CI
Non-Operated patients	IgA mg/ml	0.018	6.180	0.0001*	0.012 to 0.024
	IgE IU/ml	0.003	5.255	0.0001*	0.002 to 0.005
	IgG mg/ml	0.005	4.189	0.0001*	0.003 to 0.008
Operated patients	IgA mg/ml	0.044	2.275	0.031*	0.004 to 0.084
	IgE IU/ml	0.004	3.537	0.001*	0.002 to 0.006
	IgG mg/ml	0.020	2.765	0.010*	0.005 to 0.034
The independent factor is No. cysts. B: Effect size. CI: Confidence Interval. Significant differences at p- value < 0.05. ns: non-significant.					

The number of cysts demonstrated a significant positive relationship with all examined immunological markers in non-operated patients where regression analysis returned B = 0.018 for IgA with p = 0.0001 and B = 0.003 for IgE with p = 0.0001 as well as B = 0.005 for IgG also with p = 0.0001. Analysis results established that greater numbers of cysts induce high immunological marker levels especially IgA and IgE which imply strong immune responses in subjects with hydatid disease. Studies by Zhang *et al.* (2012) and others confirmed that Echinococcus infections intensify antibody production as reported by this study. Reduced hydatid disease activity results in elevated antibody levels according to Obaid *et al.* (2022) and validates the important role of IgG as well as IgE.

The immunological marker response differed between operated patients compared to those showing weaker effects related to number of cysts. The model coefficients demonstrate positive relationships with values of B = 0.044 for IgA (p = 0.031) and B = 0.004 for IgE (p = 0.001) as well as B = 0.020 for IgG (p = 0.010). The elimination of cysts through surgical procedures lowers the amount of observed correlations which indicates surgery decreases immune pressure leading to decreased immune system activity.

According to Qasim and Yousif (2020) surgical intervention resulted in declining immunological markers. The removal of cysts through surgery provides the immune system relief which results in ongoing reductions of inflammatory marker levels according to Chen *et al.* (2014).

The immune system markers recorded differences between non-operated and operated patients because active cysts produce measurable changes in the immune response. Active hydatid cyst patients demonstrate elevated immune responses according to two recent studies by Al-Marsomy (2021) and Jaber (2024) who show the heavy immunopathological implications of untreated infections. The study findings of Ramadan *et al.* (2021) supported diagnostic tool potential in hydatid disease and further validated through the significant correlations of IgA, IgE, and IgG with cyst numbers in participants of both groups. The analysis proves that patients need clear understanding of their cyst-related immunological responses to develop better strategies for treating cystic echinococcosis.

## 8. CONCLUSION

The present research maintains a powerful connection exists between the number of cysts and immunoglobulin levels observed in hydatid disease patients. Surgical procedures lower immune system activation but patients require ongoing observation since the activation still exists. Survey results indicate that immune system protein levels of IgA together with



IgE and IgG have potential to act as measurable indicators for health condition advancement and therapeutic response in medical interventions.

#### What is already know on this topic

- The presence of high IgA together with elevated IgE and IgG markers in the bloodstream demonstrates active defense mechanisms against *Echinococcus granulosus* infections which result in hydatid disease development. The presence of elevated IgE in testing signals allergic reactions toward hydatid cyst antigens and IgG serves as the primary indicator for both chronic infection status monitoring and tracking immune response development.
- The surgical removal of hydatid cysts results in lower immunoglobulin levels (IgA, IgE, IgG) because it removes exposure to inflammatory antigens. The presence of antigenic material after surgery might cause immune responses that need continued medical observation.

#### What this study adds

- There is a strong positive relationship between the number of cysts and the levels of immunoglobulins IgA, IgE, and IgG in patients who did not undergo surgical treatment. The strength of the immune response increases with the number of cysts, and thus this gives new evidence for the possibility of using the levels of these immunoglobulins as potential biomarkers of the severity of hydatid disease.
- Surgical removal of hydatid cysts does not completely eliminate the immune response, but it significantly reduces immunoglobulin levels. Thus, residual antigens may continue to stimulate the patients' immune system even after surgery. This, in turn, highlights the need for long-term immune monitoring in patients who have undergone surgical treatment.

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#### CONFLICT OF INTEREST

There are no conflicts of interest regarding this research

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#### Tables and figures

**Table 1:** Immunological markers levels in studied groups

**Table 2:** Immunological markers levels according Gender in both groups of patients

**Table 3:** Correlation of No. cysts with immunoglobulins in both two groups of patients

**Table 4:** Linear regression analysis of No. cyst as independent factor for identified the risk markers in both groups of patients.

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