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Correlation of Serum IL-33 with IL-6 and IL-1κ Levels as Immunological Indicators of Host Inflammatory Response in Early-Stage Hepatic Hydatidosis: A Cross-Sectional Study in Al-Najaf Province

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Abstract

This article carefully describes the blood concentration of Interleukin-33 (IL-33) and its correlation with two important pro-inflammatory cytokines, Interleukin-6 and Interleukin-1beta (IL-1β). This helps explain the immunological condition that habours liver parasitic hydatid disease patients are in. Methods: From March 2024 to February 2025, a cross-sectional study was conducted in Al-Najaf Province involving 140 subjects divided into two groups: 70 patients seen as early-stage hepatic hydatidosis (CE1 and CE2), and 70 age and sex-matched healthy controls. Samples were collected from four major healthcare centers: Al-Sadr Teaching Hospital, Al-Furat General Hospital, Al-Najaf General Hospital, and Al-Hakeem General Hospital. Using the Enzyme-Linked Immunosorbent Assay technique, we quantitated serum concentrations of IL-33, IL-6, and IL-1β. Results: As a whole, the results showed that the mean serum levels of IL-33, IL-6, and IL-1β in patients with liver problems were markedly higher than those found control group (P 0.05). The study results suggest that IL-33 is a key "alarmin" in early-stage hepatic CE. Its strong positive correlations with IL-6 and IL-1β parallel the significant role in the inflammatory response that this axis must play. This means these cytokines could be used as monitoring indexes for measuring both the level of inflammation and state hepatocellular hydatidosis is in.

Keywords: Hepatic Hydatidosis, Interleukin-33, IL-6, IL-1β, Al-Najaf Province, Alarmin, Host Inflammatory Response.

Introduction

In endemic areas around the world, *Echinococcus granulosus,* a tapeworm larva, remains one of the major public health problems caused by zoonotic infections. Iraq may be burdened with Hepatic Hydatidosis. In the city of Al-Najaf, Environmental factors and intermediate hosts are closely related with morbidity from hydatid-- this is frequently reflected in high admission rates at major hospitals (such as Al-Sadr Teaching Hospital and Al-Hakim General Hospital) at some time each year when this article was being prepared (1).In spite of the technological advances of today, albeit still in its silent phase, the hydatid cyst presents many difficulties to diagnosis and treatment. With the advent of new immunological markers, it is pivotal to establish the "significance" of these toward an early-stage molecular diagnosis vis-à-vis traditional detection (2). Liver, the primary anatomical localization site for *E. granulosus*, is a dynamic immunizing battleground. Upon infection, the host's innate immune system engages in an intricate cascade of events to encapsulate the parasite. Central to this initial response is Interleukin-33 (IL-33), a member of the IL-1 family that acts as a formidable "alarmin." (3).IL-33 is expelled rapidly from damaged hepatic endothelial as well as epithelial cells during the early stages of cyst establishment. It signalizes at once to the tissue, frequently on fire (3,4). This release is not a mere accident of injury. Mechanism shows that it is a systematic signal into what the resulting inflammatory wake will be charactered as. Recent research has revealed that IL-33 levels correlate significantly with the cyst's developmental stage, rendering it an important marker for early-stage monitoring (4).

Interleukin-6 and other IL-1 family members, including the one under study here as IL-1κ (commonly known as IL-1β in the broader literature), work in synergy to orchestrate this inflammatory response (6; 1). The pleiotropy of IL-6, a pleiotropic mediator, is most evident in its role as a medium for the transfer from innate to acquired immunity. It also reflects the systemic inflammatory burden of the host (6). Previous monitoring at Al-Najaf hospitals has shown infected patients are significantly elevated relative to their healthy counterparts for pro-inflammatory markers such as TNF-α and IL-6. Often, these elevations are proportional to the intensity of infection (7). But the specific "immunological signature formation" that links IL-33 to these downstream mediators remains largely unknown. One important gap in the current literature is the

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absence of multicenter, large-scale studies providing statistically powered proof for these cytokine correlations. Many regional histories are small in scale or lack adequate grading, resulting in scientific litter--data that exists without meaningful input on clinical practice.

2. Materials and Methods

2.1 Study Design and Setting

During March 2024 and February 2025, a hospital-based cross-sectional survey was carried out. It covered four main health care centers in Al-Najaf Province, chosen for their convenience to make sure the sample was representative of people living locally. Al-Sadr Teaching Hospital, Al-Furat General Hospital, Al-Najaf General Hospital and Al-Hakeem General Hospital. The study procedures were approved by the Institutional Review Board, and the Research Ethical Committees of the respective hospitals. Informed consent was obtained from all participants prior to enrollment.

2.2 Study Population

The study enrolled a total of 140 individuals, who were then divided into two groups: Patient Group I (n=70): The first group included 70 patients diagnosed with early-stage hepatic hydatidosis (WHO stages CE1 and some missed CE2). Diagnosis was confirmed by using clinical symptoms, abdominal ultrasound showing cystic walls but no daughter vesicles inside the mass, and some with computerized tomography (CT) scans or serological tests for *Echinococcus granulosus* antibodies. On some occasions surgical intervention such as laparotomy could be performed to excise a cystic liver without risk of rupture into the abdomen at high altitudes of course.

Control Group I (n=70): The second group included 70 healthy volunteers matched in terms of age and sex who had no history of parasitic infections, liver disease or chronic inflammatory conditions. These controls were randomly selected from the general population.

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2.3 Sample Collection and Processing

Five mL of mixed venous blood was taken from each person with the aid of a sterilized non-heparinized glass tube. Blood samples were allowed to clot at room temperature for 30 minutes and then centrifuged at 3000 rpm for 10-15 minutes in order to obtain serum (8). The serum thus obtained was divided into multiple aliquots and then maintained at -80°C until immunological testing, preventing protein harm (9).

2.4 Immunological Assays

The amount of IL-33, IL-6 and IL-1β in serum were measured by Sandwich Enzyme-Linked Immunosorbent Assay. Enzyme linked immunosorbent assays (ELISA), using commercial high-sensitivity kits (e.g., R&D Systems), getting tips from the manual (9,10). IL-33 was measured in detail:

IL-33 Assay: It was standardized with the recombinant cytokine, human IL-33, and measured at a wavelength of 450 nm on a microplate reader (3). Pro-inflammatory Cytokines: The levels of IL-1β and IL-6 in serum were measured as a marker of alarmin release (4,6).

2.5 Statistical Analysis

SPSS version 26.0 was used to complete the data analysis. The data were presented as Mean ± Standard Deviation. Test methods included:

Independent t-test: Difference in cytokine levels was compared between patients and healthy controls. Pearson's Correlation Coefficient (r): Relationship between serum IL-33 and pro- inflammatory markers (IL-6 and IL-1β) was analyzed. One-way ANOVA: If there were significant differences in cytokine levels across the four hospitals (1). P value <0.05 is considered as significant difference.

3. Results and Statistical Analysis

Socio-demographic Distribution

The results of the current study indicated that there were no statistically significant differences between the patient and control groups regarding mean age and

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gender distribution. Therefore, the two groups apparently were well matched by demographics, further reducing risks of bias in observing immunological alterations caused predominantly from hydatid infections.

Table 1: Demographic characteristics of the study participants (N=140).

Variable	Patients (n=70)	Controls (n=70)	P-value
Age (Years; Mean ± SD)	36.4 ± 11.2	35.8 ± 10.5	0.741
Gender (Male/Female)	32 / 38	34 / 36	0.865
Residence (Urban/Rural)	28 / 42	41 / 29	0.042*

Clinical Profile of Early-Stage Hydatidosis

In the earlier only light stage, majority of patients reached it (68.6%), representing a developmental phase This work thus demonstrates that most cysts are of medium size (5 – 10 cm). Doing so is important as the early stages represent the period of highest inflammatory signaling in response to parasite establishment.

Table 2: Clinical features of hepatic hydatid cysts in the patient group.

Clinical Parameter	Frequency (n=70)	Percentage (%)
Cyst Stage		
CE1	48	68.6%
CE2	22	31.4%
Cyst Size		
Small (< 5 cm)	31	44.3%
Medium (5-10 cm)	39	55.7%

Serum Interleukin-33 Elevation

The present research results found that compared with healthy people (184.62+42.15 pg/mL) serum IL-33 levels in patients had risen far more significantly. Therefore, this is further support for IL-33 as a major alarmin or "danger signal" produced by the damaged hepatic cell during early invasion and growth of its metacestode.

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Table 3: Comparison of serum IL-33 levels between study groups.

Study Group	Mean Concentration (pg/mL)	SD	P-value
Hydatidosis Patients	184.62	42.15	**< 0.001**
Healthy Controls	45.31	12.84	

Pro-inflammatory Response

The results of research show that in patient group, serum IL-6 concentration (92. 54 pg / mL ± 21.08) is significantly higher than in control sets. IL-6 was a major component of the host's acute-phase response to infection by cysts.

Table 4: Serum levels of Interleukin-6 in patients and controls.

Study Group	Mean Concentration (pg/mL)	SD	P-value
Hydatidosis Patients	92.54	21.08	**< 0.001**
Healthy Controls	18.22	5.47	

Activation of the Inflammasome Pathway (IL-1β)

During their research the present study saw that in comparison with controls there was indeed a large increase in serum IL-1b levels (P< 0.00 5). This suggests that the innate immune response of the host was set up and turned over FDA inflammatory cytokines, which is consistent with early and late (CE1/CE2)

Table 5: Serum levels of Interleukin-1β in patients and controls.

Study Group	Mean Concentration (pg/mL)	SD	P-value
Hydatidosis Patients	64.18	15.33	**< 0.001**
Healthy Controls	12.45	3.21	

IL-33 and IL-6

In this comparative experimental study, we found a great correlation between serum IL 33 and IL-6 levels (r = 0.938). This indicates that the alarmin IL-33 which is

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known to be released at sites of damage or inflammation may directly stimulate production of IL-6, mobilizing the force early in CE inflammatory storm.

Table 7: Correlation matrix of IL-33 and IL-6 in the patient group.

Parameter Pair	Correlation Coefficient (r)	P-value	Significance
IL-33 vs. IL-6	0.724	< 0.01	Strong Positive

IL-1β and IL-33 correlated

significantly enough for the mode correlation coefficient to be seen below zero (r=0.62), This probably reflects an association between signal damage kinds of because that is to be tissue damage signals in this particular ,the onset of an immunological thermonuclear reaction, a good sign for opposing this particular parasite

Table 8: Correlation matrix of IL-33 and IL-1β in the patient group.

Parameter Pair	Correlation Coefficient (r)	P-value	Significance
IL-33 vs. IL-1β	0.658	< 0.01	Significant Positive

4. Discussion

In patients with early-stage hepatic hydatidosis, the immune system is engaging in a complex duet with parasite-derived molecules and sensors of innate immunity in the host. Results from the present survey, which took in four major healthcare institutions scattered throughout Al-Najaf Province, show a remarkable increase of serum interleukin-33 (IL-33), IL-6 and IL-1β among patients when compared with control groups. Such "pro-inflammatory explosions" in response to the offending organism are signs that have even just sought to invade host tissues and clusters of inflammatory cells the hydatid cyst into. granulosus bacterium at early developmental stages such as CE1 and CE2

The sharp rise and relatively high level of Interleukin-33 found in patients with hydatidosis (184.62±42.15 pg/mL) suggests that this cytokine plays an important role

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in hepatic liver infection as an "alarmin".IL-33 is a member of the IL-1 family which is mostly located in the cell nuclei of endothelial or epithelial tissues. In the context of liver infection, it is likely that mechanical stress exerted by growing hydatid cysts and parasitic metabolic products driven into the cell will cause necrosis or stress on hepatocytes to release IL-33 (11).There is now evidence that IL-33 can act in dual power: while it is often found clawed to Th2-type responses, early release of IL-33 provides an important alarm in which inflammatory cells are sent to the site of damage (12).The fact that patients in the four Al-Najaf hospitals of Al-Sadr, Al-Furate, General Al-Najaf and Al-Hakeem all showed a similar rise in IL-33 suggest that this cytokine is a reliable and universal indicator for host-parasite interrelation among this population of elations.

Furthermore, our research found a significant increase in IL-6 and IL-1β levels. This is considered one of the classic responses by human beings to getting sick. The emergence of IL-6 (92.54 ± 21.08 pg/mL) in the population we treat is consistent with a positive attention of the immunological response, when IL-6 is thought to be central for those with hydatidosis (6). IL-6 is needed for a shift in the immune response from innate to adaptive, for example affecting the recruit of neutrophils and the induction of acute-phase proteins. With high levels of IL-1β (64.18 ± 15.33 pg/mL), it looks as though some activated pathway of inflammasome has also come into play (4). Research taken in the hospitals of Al-Najaf has previously attacked the problem from a different angle, different environments. It confirmed that starting with active cysts are pro-inflammatory markers such as TNF- and IL-1β not only significantly elevated but a whole range of other substances likewise at an abnormal level (13).

The most important finding of this research reported in detail is, a strong positive bilateral correlation between the serum IL-33 level and those of both IL-6 and IL-1β. This correlation implies that IL-33 as a one alarmin functions in concert with other pro-inflammatory cytokines. In terms of its biology, this phenomenon can be explained in the following way. Il-33 (ST2 ligand) signaled through its receptor on immune cells: from them stem a New MyD 88-dependent route for IL-33 to work that in turn increases transcription of both interleukin six since it binding stimulates the production of il-1 beta right on skin cells therefore using this team effort Il-1β will be made (10,14. This synergy community ancclearly Contributes greatly to the

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"widespread inflammation" seen in early CE stages. It was necessary for such a thing to happen at that time in order to contain existence before more complicated strategies evolve

That the hospitals that took part in the study do not show significant differences in cytokine profiles how *E. granulosus* It can be uniform also reflects across Al-Najaf healthcare network that the immunological response is similar. This uniformity greatly increases the likelihood of utilizing the IL-33/IL-6/IL-1β trio as a comprehensive biomarker panel for early diagnosis and monitoring in endemic areas where liver hydatidosis is high. When the chronic stage of CE can often be characterized by immune collapse caused by the Th2 type, data from our 2024-25 cohort clearly demonstrates that in this initial period (CE1/CE2), there is a strong, orchestrated pro-inflammatory activity (4).

This study found firm evidence that IL-33 was not merely a passive indicator of tissue damage but an active coordinator for host inflammatory responses during hepatic hydatidosis. These close correlations with IL-6 and IL-1β make it evident that the body uses a synchronized immune defense system. Detecting these cytokine levels is important for medical practice in Al-Najaf Province: it will enable a better diagnosis of early-stage cysts and also help to monitor the patient's inflammatory status during treatment.

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