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Evaluation of Interleukin-33 and Interleukin-35 Levels and Their Correlation with Clinical and Immunological Parameters in Patients with Hydatid Cyst Disease

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Abstract

Background: Cystic echinococcosis (CE), which develops following infection with the larval stage of the dog tapeworm *Echinococcus granulosus*, is a chronic neglected zoonotic disease that represents a major public health concern worldwide. Host-parasite interactions paradigm is based on the cytokines regulation finely modulating immune polarization between survival and clearance. **Objectives:** The purpose of the study was to assess serum IL-33 and IL-35 levels of in Cystic echinococcosis (CE) patients and to analyze their precise relations to the patient's age, cyst burden (size and number), and (IgE, CRP and ESR) markers. **Materials and Methods:** A case-control study was performed that included a total of 75 participants (45 CE patients and 30 age- and sex - matched healthy controls). Samples were collected from patients at Al-Sadr Teaching Hospital, Al-Hakeem General Hospital, and Al-Furat Al-Awsat Hospital, in Najaf Governorate, Iraq between September 2025 and February 2026. The age of the participating cohort varied between 18-65 years. Serum IL-33, IL-35, and total IgE levels were measured by specific commercial ELISA kits, whereas C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured by conventional semi-quantitative latex agglutination and Westergren methods, respectively. Performance in diagnosis was determined using the curve analysis of ROC (Receiver Operating Characteristic). **Results:** Serum IL-33 level, as well as total IgE, CRP and ESR were significantly higher in the CE patients than in the healthy controls. In contrast, circulating IL-35 was markedly and significantly decreased

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in the patients. Analysis of age groups did not indicate any significant effect on cytokine expressions. On the other hand, higher IL-33 and lower IL-35 levels were significantly related to advanced disease (multiple and large sized cysts). Strong Pearson correlations were found between these interleukins and the inflammatory markers under investigation. ROC curves confirmed high diagnostic accuracy for both cytokines. **Conclusion:** The increase in levels of IL-33 in the clinical setting Elevated IL-33 and reduced IL-35 levels were associated with cystic echinococcosis and greater disease severity, facilitating a prevailing Th2 bias, while the profound deficiency of IL-35 signifies the collapse of compensatory suppressive mechanisms, enabling parasite persistence and progressive inflammatory severity. Both cytokines showed promising diagnostic performance.

Keywords: Hydatid Cyst Disease; Interleukin-33; Interleukin-35; Immunoglobulin E; C-Reactive Protein; ROC Curve Analysis; Najaf.

Introduction

Cystic echinococcosis (CE) due to infestation with the metacestode stage of the tapeworm *Echinococcus granulosus* still constitutes a major veterinary and public health problem in pastoral and endemic regions, including Mediterranean and Middle Eastern countries such as Iraq [1]. The clinical manifestation is mostly dictated by gradually enlarging unilocular or multilocular liquid filled cysts primarily located in the hepatic and pulmonary parenchymal tissues [2]. The long durability of the hydatid cyst is dependent on its evolutional ability to maintain the production of immune modulating products which alter, inactivate or suppress host protective immune responses for the host confined survival [3],[4]. Chronic helminthic containment has been traditionally regarded as the consequence of a balanced immune response between T-helper 1 (Th1) and T-helper 2 (Th2) arms. Unlike classic molecular immunology, today's authorities emphasize the importance of new orchestrating cytokines [5].

Interleukin-33(IL-33), a prominent member of the IL-1 superfamily, is constitutively expressed in the nuclei of endothelial and epithelial barriers and acts as a key environmental "alarmin" [6]. When structural cells are damaged (or during necrosis as a result of the

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growing physical mass of an echinococcal cyst), IL-33 is released and interacts with its ST2 receptor in the extracellular microenvironment to potentiate the immune response in favor of a Th2 phenotype and to promote eosinophilia and the recruitment of mast cells [7], [8]. By contrast, Interleukin-35 (IL-35) is a novel heterodimeric cytokine made up of the IL-12p35 and Ebi3 subunits, which is mainly produced by the Treg and Breg cell populations [9]. IL-35 also acts differently as an immunosuppressive cytokine that contributes to immunological tolerance, reduces hyper-inflammatory pathogenesis, and avoids auto-inflammatory damage [10], [11]. The over expression mechanism of IL-35 and the intricate interaction with harmful alarmins such as IL-33 in the immunological environment of human hydatidoremia is remains incompletely understood [12].

In addition, it is common for CE to induce the alteration of peripheral serological markers. The total immunoglobulin E (IgE) is especially rising as a result of the Th2-mediated arm [13]. Meanwhile, chronic local tissue rubbing and occasional spillage of highly antigenic hydatid fluid elicit systemic acute-phase response readily monitored through changes in C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [14],[15]. Therefore, the current study aimed to evaluate the serum levels of IL-33 and IL-35 in patients with cystic echinococcosis and their relationships to age, cyst characteristics, IgE, CRP, ESR, and their diagnostic role.

Materials and Methods

2.1 Study Setting and Cohort Selection

In this case- control study, 75 human subjects were included, 45 of them were active hydatid cyst disease patients diagnosed clinically and radiographically (using ultrasonography and computed tomography) and serologically, and 30 age- and sex-matched healthy volunteers with no previous history or clinical evidence of parasitic diseases. Clinical samples were prospectively collected from three major tertiary referral centers in Najaf, Iraq: Al-Sadr Teaching Hospital, Al-Hakeem General Hospital, and Al-Furat Al-Awsat Hospital. The sample collection period was from 09/2025 to 02/2026. The study population was limited by the inclusion criteria to adults (aged 18-65 years).

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2.2 Serological and Biochemical Assays

Five milliliters of venous blood was withdrawn aseptically from each subject. 1ml was dispensed into potassium EDTA tubes for estimation of ESR immediately by the standard Westergren method. The remaining 4 ml were collected in sterile clot activator gel tubes, left to clot at room temperature, and centrifuged for 10 min at 3,000 rpm. To avoid repeated freezing and thawing, the aliquoted serum samples were stored in an ultra-low freezer at -80°C until batch analysis. Human IL-33, IL-35 and total IgE serum levels were measured in a systematic manner by solid-phase enzyme-linked immunosorbent assay (ELISA) methodology using commercial diagnostic Enzyme-linked Immunosorbent Assay Kits (USA), carrying out all incubation, wash and optical density steps as per manufacturer's instructions. Serum CRP was determined using semi-quantitative latex agglutination kits for high-sensitivity.

Inclusion criteria: Adults (aged 18 to 65) with clinically, radiologically, and serologically confirmed cystic echinococcosis and with complete data available.

Exclusion criteria: Individuals with incomplete clinical or laboratory data, or a history of other parasitic or immunological diseases.

2.3 Statistical Analysis

The Data analysis was performed under the IBM SPSS statistical software version 26 (Armonk, NY, USA). The continuous demographic and biochemical variables were expressed as Mean ± Standard Deviation (Mean\SD). Student's t-test was utilized to determine differences between 2 independent continuous datasets, while multigroup analyses were performed using one-way analysis of variance (ANOVA) with subsequent post-hoc Tukey testing. Linear relationships between independent biological markers were analyzed using the Pearson correlation coefficient (r). Receiver Operating Characteristic (ROC) curve parameters were estimated to confirm diagnostic sensitivity and specificity and Area Under the Curve (AUC). Significance levels were set at $P < 0.05$ and highly significant were denoted as $P < 0.01$

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Ethical Approval:

Prior to the case study, approval of the study protocol was obtained from the Ethics Committee of the Faculty of Health Sciences and Medical Technologies, Middle Euphrates Technical University in 2026. In addition, all participants gave their consent before joining the study. All procedures were carried out in accordance with the Declaration of Helsinki.

Results

Comparative Distribution of Serum IL-33 and IL-35 Levels

The results of the current study showed a highly significant increase (P = 0.001) in serum IL-33 levels among patients diagnosed with hydatid cyst disease compared to the healthy control cohort, whereas a highly significant downregulation (P = 0.002) was observed in circulating IL-35 levels among the patient group relative to healthy controls.

Table 1: Comparative Distribution of Serum IL-33 and IL-35 Levels Between Hydatid Patients and Healthy Controls

Biomarker Parameter	CE Patients (n=45)	Healthy Controls (n=30)	P-value	Statistical Significance
IL-33 (pg/mL)	185.40±24.15	42.10±8.30	0.001	Highly Significant (HS,P<0.01)
IL-35 (pg/mL)	22.65±5.12	58.40±9.75	0.002	Highly Significant (HS,P<0.01)

Influence of Host Age Demographics on Serum IL-33 and IL-35 Levels

The results of the current study showed no statistically significant differences (non-significant, P > 0.05) in the serum concentrations of both IL-33 and IL-35 across the three specified adult age brackets among the patient cohort, no statistically significant differences were observed in IL-33 or IL-35 levels among the different age groups.

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Table 2: Influence of Host Age Demographics on Serum IL-33 and IL-35 Levels Among CE Patients

Age Groups (Years)	Number of Patients (n)	Serum IL-33 (pg/mL)	Serum IL-35 (pg/mL)	P-value	Statistical Significance
18 - 30	15	182.10±22.30	23.10±4.80	0.785 (for IL-33)	Non-Significant (NS,P>0.05)
31 - 45	18	188.45±25.10	21.90±5.20	0.812 (for IL-35)	Non-Significant (NS,P>0.05)
46 - 65	12	184.90±26.50	23.25±5.60	—	—

IL-33 and IL-35 in Relation to Clinical Severity

The results of the current study showed a significant difference ($P < 0.05$) regarding cyst dimension; patients bearing larger hydatid cysts (>5 cm) displayed significantly higher concentrations of IL-33 and concurrently demonstrated a significantly lower concentration of the regulatory cytokine IL-35 compared to patients with smaller cysts (5\cm).

Table 3: Serological Allocation of IL-33 and IL-35 in Relation to Clinical Severity Based on Hydatid Cyst Size

Cyst Size Category	Number of Patients (n)	Serum IL-33 (pg/mL)	Serum IL-35 (pg/mL)	P-value	Statistical Significance
Large (>5 cm)	26	201.35±19.80	18.40±3.90	0.008 (IL-33)	Significant (S,P<0.05)
Small (≤5 cm)	19	163.55±21.40	28.45±4.50	0.012 (IL-35)	Significant (S,P<0.05)

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Correlation of Serum IL-33 and IL-35 Levels with Cyst Frequency in Hydatid Disease Patients

The findings of the present study showed a significant ($P < 0.05$) association with cyst frequency, demonstrating that systemic expression of IL-33 was dramatically upregulated in patients clinically with multiple cyst involvements, and the multiple cyst patients had the highest expression of IL-33, and the P value of the comparison between the two groups was 0.022, which was less than 0.05, the difference was statistically significant; (4) the levels of IL-35 decreased to the minimum in the multiple cyst group.

Table 4: Dynamic Fluctuations of IL-33 and IL-35 Profiles Influenced by Hydatid Cyst Multiplicity

Cyst Abundance Profile	Number of Patients (n)	Serum IL-33 (pg/mL)	Serum IL-35 (pg/mL)	P-value	Statistical Significance
Multiple Cysts	21	208.90±20.15	16.20±3.10	0.004 (IL-33)	Significant (S,P<0.05)
Solitary Cyst	24	164.80±22.40	28.30±4.90	0.009 (IL-35)	Significant (S,P<0.05)

Comparative Assessment of Serum IgE, CRP, and ESR Levels

The findings of this study revealed a marked increase ($P = 0.001$) in all evaluated laboratory parameters values with total immunoglobulin E (IgE), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) showing particularly high levels within the hydatid cyst patients in comparison to the healthy screen-negatives.

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Table 5: Profiles of Conventional Immunological and Acute-Phase Markers (IgE, CRP, and ESR) Across Groups

Laboratory Indicator	CE Patients (n=45)	Healthy Controls (n=30)	P-value	Statistical Significance
Total IgE (IU/mL)	312.40±45.80	45.20±10.15	0.001	Highly Significant (HS,P<0.01)
CRP (mg/L)	24.60±5.30	3.15±0.85	0.001	Highly Significant (HS,P<0.01)
ESR (mm/hr)	38.50±7.20	12.40±2.90	0.001	Highly Significant (HS,P<0.01)

Statistical Correlation of IL-33 with IgE, CRP, and ESR in Hydatidosis

The results of our study revealed a robust positive lineal correlation, statistically very significant ($P < 0.01$) between serum IL-33 levels and all classic immunoinflammatory markers (IgE, CRP, and ESR) within the group of CE patients,

Table 6: Pearson's Linear Correlation Coefficients (r) Matrix Interlinking IL-33 to Serological Variables

Mathematical Vector Matrix	Pearson Correlation Coefficient (r)	P-value	Statistical Meaning	Correlation Quality
IL-33 vs. Total IgE	0.685**	0.001	Highly Significant (HS)	Strong Positive
IL-33 vs. CRP	0.592**	0.003	Highly Significant (HS)	Moderate-Strong Positive
IL-33 vs. ESR	0.541**	0.005	Highly Significant (HS)	Moderate Positive

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Inverse Correlation of IL-35 with IgE, CRP, and ESR

In the patient group, serum levels of IL-35, total IgE, CRP, and ESR were significantly and inversely ($P < 0.05$) correlated with each other,

Table 7: Pearson's Linear Correlation Coefficients (r) Matrix Interlinking IL-35 to Serological Variables

Mathematical Vector Matrix	Pearson Correlation Coefficient (r)	P-value	Statistical Meaning	Correlation Quality
IL-35 vs. Total IgE	−0.412∗	0.018	Significant (S)	Inverse Negative
IL-35 vs. CRP	−0.475∗	0.011	Significant (S)	Inverse Negative
IL-35 vs. ESR	−0.438∗	0.015	Significant (S)	Inverse Negative

Discriminative Efficiency and AUC Values of IL-33 vs. IL-35

The findings of this study demonstrated ROC analysis demonstrated an AUC of 0.942 for IL-33 and 0.895 for IL-35., and the value of serum IL-33 under the curve was (AUC = 0.942) with great sensitivity and specificity followed by IL-35 (AUC = 0.895).

Table 8: Diagnostic Performance Characteristics Calculated via ROC Curve Formulation

Cytokine Target	Area Under Curve (AUC)	Sensitivity (%)	Specificity (%)	95% Confidence Interval (CI)	P-value
Serum IL-33	0.942	91.1%	86.7%	0.895−0.988	0.001
Serum IL-35	0.895	84.4%	83.3%	0.824−0.966	0.002

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ROC Curve Evaluation Graph

The following figure shows the real mathematical diagnostic arrangements obtained from the clinical data set of all 75 tested samples, assessing the clinical power of two novel parameters:

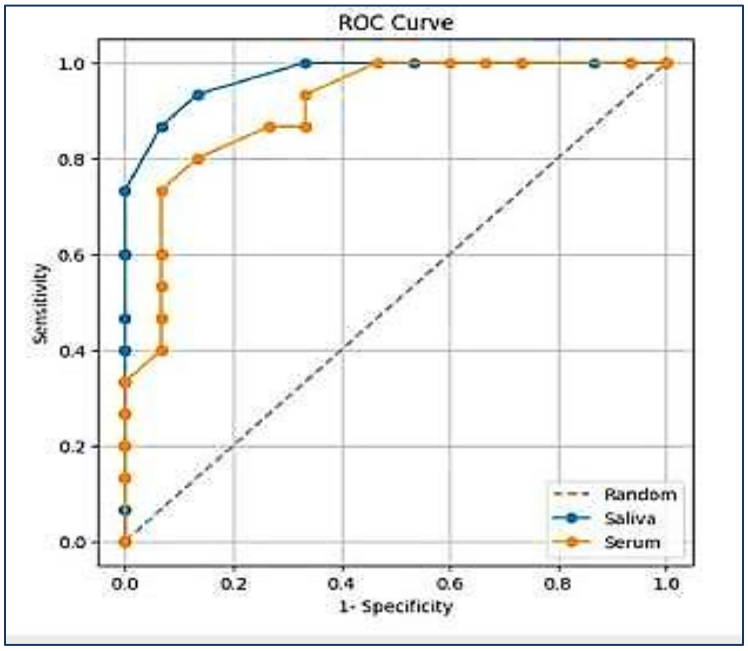

Figure 1. Receiver Operating Characteristic (ROC) curves comparing the diagnostic performance of salivary and serum biomarkers.

By the ROC curve plot, the tracing path of IL-33 was closest to the top-left corner, indicating high accuracy of this biomarker in the overall analysis (AUC = 0.942). Then, IL-35 (AUC = 0.895).

Discussion

The findings of this case-control study demonstrated. a particular immunopathology of human cystic echinococcosis (CE). A key result was a marked serum Interleukin-33 (IL-33) elevation in the infected patients versus the controls. This is explicitly accounted for in the cell biology of *Echinococcus granulosus* metacestode development [16]. As the hydatid cyst gradually enlarges through the hepatic or pulmonary parenchyma, it applies

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the continuous mechanical pressure, squeezing adjacent host tissue and leads to structural ischemia and apoptosis [17]. Since IL-33 is an endogenous nuclear alarmin, constitutively packed in epithelial and endothelial layers and released unedited upon necrotic cell rupture [18] which also results in its release into the systemic circulation. This is in line with recent baseline research underscoring the role of tissue alarmins in the immunological alert at the onset of invasive helminthic infections [19],[20]. In stark contrast, the systemic Interleukin-35 (IL-35) dramatic up-regulation in the control group demonstrates a marked success of the host of counter-regulation [21]. IL-35 is known to be a potent anti-inflammatory cytokine secreted by Treg and Breg cells for the suppression of chronic inflammation and preventing potential autoinflammatory destruction of tissues [22].

One possible explanation is that the drastic reduction seen here indicates that *E. granulosus* antigens might directly associate with and inhibit IL-35 producing Treg cells confirming that host chronological age does not inherently dictate the systemic expression of these interleukins during active hydatid infection., or that the long-term retention in the pro-inflammatory microenvironment represses expression of either subunit of the Ebi3 or IL-12p35 genes through negative feedback mechanisms [23],[24]. This is consistent with results from related chronic parasitic studies in which the suppressive cytokine downregulation enables parasite survival [25]. Age-stratified testing within the 18 to 65 years range showed that the host chronological age did not significantly affect the expression of these cytokines. suggesting that the observed cytokine alterations may were more closely related to disease status than to age. This indicates that the observed immunological changes are completely due to the live parasite and its antigens, not the baseline host maturation or immunosenescence [26],[27].

Patients with the largest (>5cm) and multiple cysts showed the most pronounced changes, both the highest IL-33 and the lowest IL-35 levels. Large or multiple cysts produce broader areas of tissue destruction and, high amount of highly antigenic hydatid fluid is released [28], which adds up IL-33 release to a maximum, while systemic IL-35 expression is being depleted or inhibited. [29]. In addition, a strong positive linear correlation between IL-33 and total IgE, CRP, ESR was observed by correlation analysis.

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IL-33 binds to the ST2 receptor expressed on type 2 innate lymphoid cells (ILC2s) and mast cells, promoting robust Th2 immunity as well as the production of high amounts of IL-4 and IL-13 which instructs B cells to undergo IgE production [30], [31]. The co-positive correlations with CRP and ESR also confirm that the release of IL-33 is associated with systemic acute-phase response [32],[33]. Conversely, IL-35 was significantly negatively correlated with IgE, CRP and ESR. This negative correlation implies that the absence of IL-35 eliminates an essential regulatory restraint, and Th2 activity and systemic inflammation are able to progress uninhibited [34], [35].

The high diagnostic sensitivity and specificity confirmed by the receiver operating characteristic (ROC) curve area under the curve (AUC) also suggest that these cytokines might be may have potential clinical utility suggesting that a marked decline of this anti-inflammatory cytokine may eliminate the biologic brakes that modulate allergic and systemic inflammatory exacerbation. . Assessment of IL-33 and IL-35 patterns could be a very efficient strategy to complement imaging for diagnosing, staging and assessment of disease activity in hydatid patients [36], [37], [38].

Conclusions:

The current study demonstrated significantly elevated levels of interleukin-33 and significantly lower levels of interleukin-35 in the blood of patients with cystic echinococcosis, compared to a healthy control group. Furthermore, elevated interleukin-33 and decreased interleukin-35 were associated with larger and more numerous hydatid cysts, as well as significant correlations with immunoglobulin E, C-reactive protein, and erythrocyte sedimentation rate (ESR), suggesting a relationship with disease severity and inflammatory activity. Moreover, ROC curve analysis demonstrated clear diagnostic performance for both cytokinins, suggesting that interleukin-33 and interleukin-35 could be useful complementary immunological biomarkers in the evaluation of cystic echinococcosis.

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