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The Diagnostic Power Of IL-6 In the Diagnosis of Acute Cholecystitis

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ABSTRACT

Background: Cholecystitis is an inflammatory condition of the gallbladder that varies in severity and is associated with elevated inflammatory markers such as interleukin-6 (IL-6). Understanding the relationship between IL-6 levels and disease severity may improve diagnosis and management.

Methods:
This case–control study enrolled 68 patients aged 22 to 45 years diagnosed with cholecystitis at Nasiriyah Teaching Hospital, Thi-Qar City, Iraq, from March 2024 to February 2025. Patients were classified into mild, moderate, and severe groups based on clinical and imaging criteria. Forty healthy patients without gallbladder disease served as controls. Exclusion criteria included recent antimicrobial treatment, chronic illnesses, pregnancy, and lactation. Serum IL-6 levels were measured by ELISA following standardized protocols.

Results:
Mean serum IL-6 concentration was significantly higher in patients (85.2 ± 21.4 pg/ml) compared to controls (32.7 ± 12.6 pg/ml) ($p < 0.001$). IL-6 levels progressively increased with cholecystitis severity: mild (64.3 ± 12.8 pg/ml), moderate (83.7 ± 14.5 pg/ml), and severe (106.5 ± 18.2 pg/ml), with statistically significant differences among groups (ANOVA, $F = 18.46$, $p < 0.001$). Post hoc analysis confirmed that each severity group differed significantly in IL-6 levels. Receiver operating characteristic (ROC) curve analysis showed excellent diagnostic accuracy for IL-6 with an area under the curve of 0.914. At a cut-off value of 58.0 pg/ml, IL-6 achieved a sensitivity of 89.6% and specificity of 82.4% for distinguishing cholecystitis patients from healthy controls ($p < 0.001$).

Conclusions:
Serum IL-6 is markedly elevated in patients with cholecystitis and correlates strongly with disease severity. IL-6 demonstrates high diagnostic accuracy and may serve as a valuable biomarker for identifying and stratifying cholecystitis in clinical settings.

KEYWORDS

Interleukin-6, Cholecystitis, Sensitivity, Specificity.

Introduction

Acute cholecystitis is among the leading significant causes of acute abdominal pain and a common indication for emergency surgery all over the world. In most cases, it occurs as a consequence of gallstone blocking the cystic duct; then inflammation develops within the gallbladder, followed by ischemia and secondary bacterial infection (Pereira et al., 2020). The compilation of early accurate diagnosis for acute cholecystitis helps in guiding appropriate treatment decisions and preventing its associated complications such as empyema, gangrenous cholecystitis, or gallbladder perforation. However, with more advances made both in

imaging techniques and improvements toward uniformization regarding diagnostic criteria, an initial clinical assessment happens to be very challenging with even better-occurring atypical presentations among the elderly and immunocompromised (Yacoub et al., 2021).

At present, the diagnostic workup involves using a combination of physical examination and laboratory markers (e.g., white blood cell count, C-reactive proteins CRP), plus imaging-mostly ultrasonography. However, these tools might not be sensitive or specific enough for early and mild cases. In the past few years, more and more people have taken an increased interest in using cytokine biomarkers, especially interleukin-6 (IL-6), for improved diagnostics in inflammatory diseases; acute cholecystitis included (Salman et al., 2024).

IL-6 is a multiplicative pro-inflammatory cytokine secreted by monocytes, macrophages, and endothelial cells in response to tissue injury and infection. It plays a central role in the acute phase response because it stimulates the liver to synthesize CRP and fibrinogen as well as leukocyte activation (Tanaka et al., 2014). While CRP may take 12-24 hours to significantly increase, IL-6 levels do rise within hours of the onset of inflammation; thus, sensitivity-wise, it may be an earlier marker (Gabay & Kushner, 1999). Other studies placed levels for IL-6 as well significantly elevated for acute cholecystitis patients compared with other abdominal conditions; therefore, it could be useful in early differentiation and severity assessment (Akyurek et al., 2005). Though the findings are promising, in little time, IL-6 will be integrated into routine diagnostic algorithms. More importantly, variability in the design of studies, sample sizes, and cut-off values applied in different literatures has delayed its integration. There is a need to systematically evaluate the diagnostic performance of IL-6; that is, its sensitivity, specificity, and predictive values compared to conventional inflammatory markers.

The present study aims to investigate the diagnostic power of IL-6 in acute cholecystitis. It can be useful as a reliable early biomarker for clinical practice.

Patients and Methods

This case–control study involved 68 patients who were diagnosed as having cholecystitis at Nasiriyah Teaching Hospital, Thi-Qar City, Iraq, from March 2024 to February 2025. Their ages ranged between 22 and 45 years. The patients were further subcategorized into three groups corresponding to the severity of their disease based on the standard clinical and imaging criteria for mild, moderate, and severe cholecystitis. Exclusion criteria included antimicrobial or vaginal treatment within the past month; chronic systemic diseases; pregnancy; and lactation.

A control group of 40 healthy subjects who had no history of gallbladder disease or cholecystitis was enrolled during the same period. All patients were subjected to a detailed clinical appraisal by surgical specialists to confirm the diagnosis and assess disease severity; this was supported by ultrasonography and pertinent laboratory tests.

About 3 mL of venous blood was taken from each participant into plain tubes with clot activators. The samples were spun at 3000 rpm for 10 minutes to separate serum; this was then kept at −20 °C until needed. The amounts of interleukin-17 (IL-17) in the serum were found using an enzyme-linked immunosorbent assay (ELISA) kit (Humacount, Germany), following the maker's steps.

All study procedures were approved by the hospital ethics committee. Written informed consent was obtained from all patients and control subjects. Patient selection, disease classification, and sampling were carried out under the supervision of qualified surgeons and laboratory personnel.

Statistical analysis

Data for this study were analyzed using SPSS software version 26. Descriptive statistics; mean ± standard deviation (mean ± SD) for continuous variables, to summarize the central tendency and variability, are presented. Categorical variables are presented in terms of frequencies and percentages. The chi-square (χ^2) test was used to evaluate the relationships and associations of categorical variables in the various study groups. It was applied to see if the differences in proportions that were observed were statistically significant.To compare the mean serum levels of IL-17 in patients based on the severity of cholecystitis (mild, moderate, severe), one-way analysis of variance (ANOVA) was applied. In case ANOVA showed significant differences, then also employed post hoc tests like Tukey's HSD to find out which specific groups were different from each other. The p-value was set at <0.05 for the threshold of statistical significance in all analyses undertaken in this study. Two-tailed statistical tests were used since differences in either direction were considered possible.

This analysis will try to see if there is a correlation between the concentration of IL-17 and the clinical severity of cholecystitis, along with other important clinical and demographic factors. (Al-Fahham, 2018).

Results

Table 1 shows the distribution of patients and controls according to age groups and gender. Of the 68 cholecystitis patients, the maximum frequency was observed in the age group 23–32 years (44.1%), followed by 33–42 years (36.8%). The lowest proportion of patients was recorded in the above 42 years category (19.1%). In turn, the control group showed a somewhat more even distribution between age groups, with the highest percentage in both 33–42 and >42 categories (37.5% each). Regarding gender, females constituted most of the cases among patients (82.4%). In controls, females also predominated but at a lower proportion (62.5%). The chi-square analysis indicates statistically significant differences at both age and gender distributions between patients and controls.

Table 1. Age and residence distribution of investigated subjects with cholecystitis

Indicators		`Patients (No. = 68)		Control (No. = 40)		Chi Square	P value (Sig.)
		Freq.	%	Freq.	%		
Age/Years	23-32	30	44.10	10	25.00	6.72	0.034 (S)
	33-42	25	36.80	15	37.50		
	> 42	13	19.10	15	37.50		
Gender	Male	12	17.60	15	37.50	5.23	0.022 (S)
	Female	56	82.40	25	62.50		

S: significant at P<0.05

The bar chart gives the percentage distribution of cases of cholecystitis by levels of severity. In these 68 patients, the severe category accounts for the largest percentage at 44.1%, next is moderate severity at 33.8% and the mild form has the lowest percentage at 22.1%. There is a very clear demonstration in this pictorial representation that as severity of the condition increases, so does the frequency—emphasizing how much more advanced clinical presentations dominated in these particular cases (figure 1).

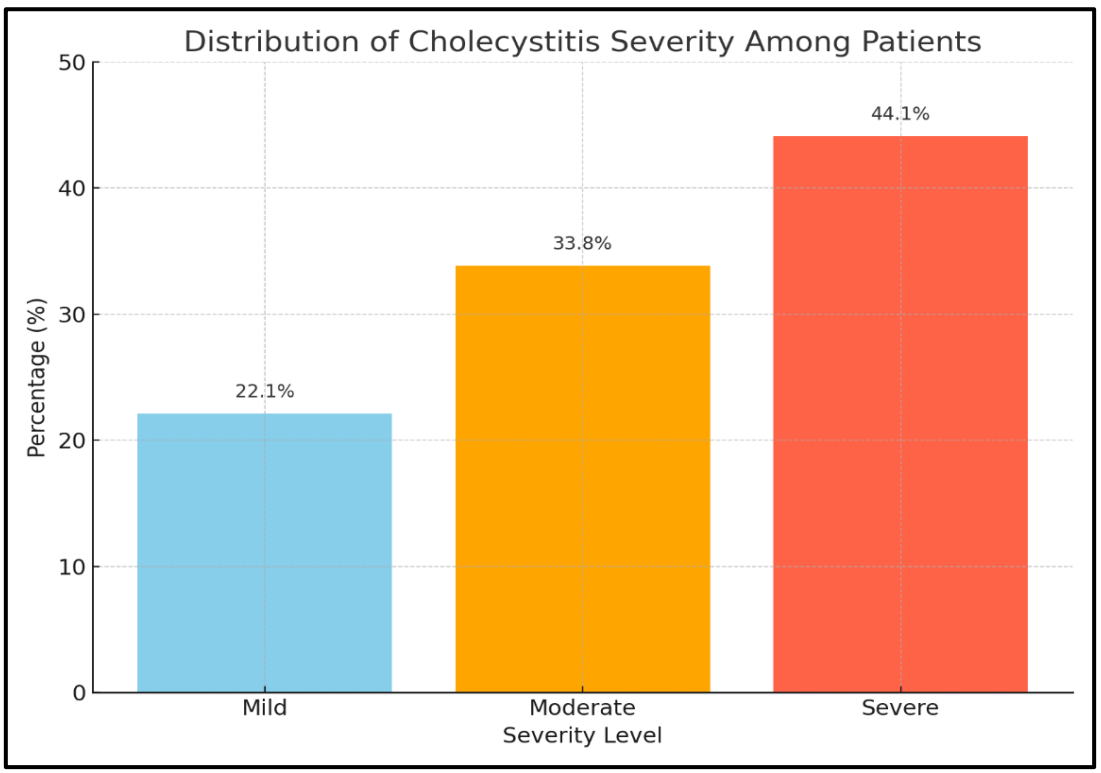

Figure 1. Distribution of cholecystitis according to severity of the disease

Table 2 illustrated the data on serum IL-6 levels in patients with cholecystitis as compared to healthy controls. Patients had a mean IL-6 concentration that was dramatically increased 85.2 ± 21.4 pg/ml versus 32.7 ± 12.6 pg/ml in controls. A p-value of <0.001 with an independent t-test indicates a highly significant difference between these two groups, meaning that IL-6 is greatly raised in the inflammatory condition of cholecystitis.

Table 2. Measurement of IL-6 levels between patients with cholecystitis and control subjects

Groups	No.	IL-6 (pg/ml) Mean ± SD	T Test (P Value)
Patient	68	85.2 ± 21.4	< 0.001 (HS)
Control	40	32.7 ± 12.6	

HS: High significant at P<0.001

The data on IL-6 levels in patient sub-groups classified by varying severity of cholecystitis, reveals that the normal and mild cholecystitis patients reported to have the minimum mean levels of IL-6 at 64.3 ± 12.8 pg/ml, and the moderate and severe conditions were associated with higher values 83.7 ± 14.5 pg/ml and 106.5 ± 18.2 pg/ml respectively. Results of the ANOVA (F test =18.46) showed a statistically significant difference among the three severity groups (p value was less than 0,001). Therefore, one can infer that IL-6 levels are significantly associated with disease severity. Post hoc analysis (as indicated by different superscript letters in table 3) confirms that each group differs from the other groups in concentration level of IL-6 (table 3).

Table 3. ANOVA table foe the IL-6 levels in patients' groups according to severity of cholecystitis

Age Sub-groups	Freq.	IL-6 (pg/ml) Mean ± S.D	F test	T test P-value
Mild	30	64.3 ± 12.8 [a]	18.46	< 0.001 (HS)
Moderate	23	83.7 ± 14.5 [b]		
Severe	15	106.5 ± 18.2 [c]		

A, B, C indicate significant difference at p <0.05 ; HS: High significant at P<0.001

The table shows the diagnostic accuracy of IL-6 for cholecystitis. It gave a very impressive area under the ROC curve of 0.914, meaning overall, it has excellent accuracy. At an optimal cut-off value of 58.0 pg/ml, it can achieve a sensitivity of 89.6% and specificity of 82.4%, which means it can be used as an indicator to differentiate patients with cholecystitis from healthy people. The p-value (< 0.001) confirms the statistical significance of the diagnostic model (Table 4, figure 3).

Table 4. Receiver operating characteristic (ROC) analysis of IL-6 for the diagnosis of cholecystitis

Biomarker	(AUC)	Sig. p-value	Cut-off Point	Sensitivity (%)	Specificity (%)
IL-6	0.914	< 0.001	≥ 58 (pg/ml)	89.6	82.4

AUC: Area Under the curve

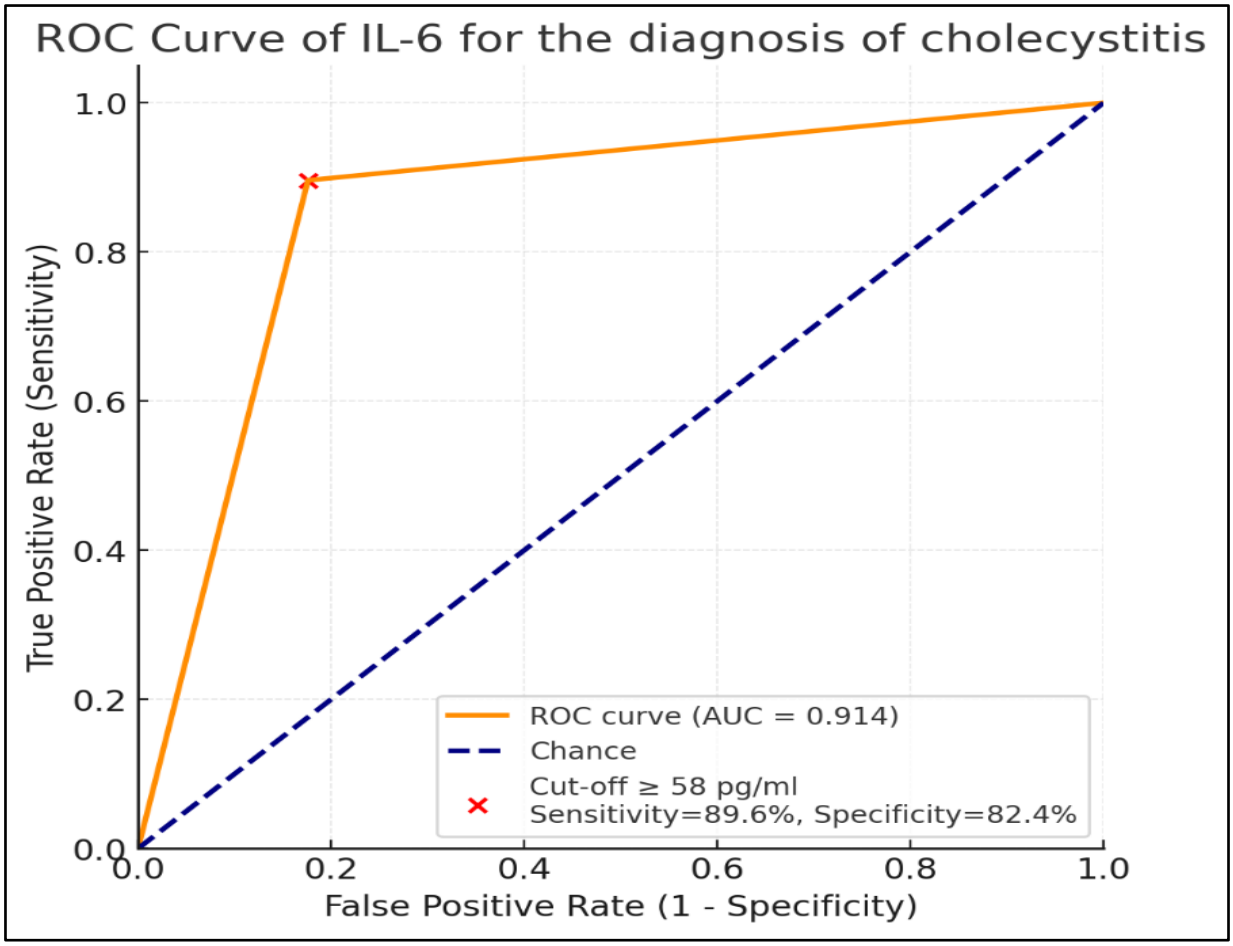

Figure 3. ROC Curve of Serum IL-6 Levels for Diagnosing Cholecystitis

Discussion

This study assessed the role of serum IL-6 in diagnosing cholecystitis and its correlation with the severity of disease. The present findings will bring to light strong evidence that levels of IL-6 are significantly raised in females diagnosed with cholecystitis as compared to healthy controls and that these levels increase further in accordance with the severity of disease. Besides, results from ROC curve analysis confirm that IL-6 has an excellent diagnostic accuracy, meaning it can have potential clinical utility.

Patients diagnosed with cholecystitis presented a mean serum IL-6 concentration of 85.2 ± 21.4 pg/ml, levels significantly greater than in healthy controls, which was 32.7 ± 12.6 pg/ml ($p < 0.001$). As an established view, this finding coincides with that of Tanaka et al., 2014 who described IL-6 as a pro-inflammatory cytokine synthesized in response to tissue injury and infection. This synthesis goes on to stimulate the liver production of acute-phase reactants such as C-reactive protein (CRP), which then has a central role in systemic inflammation. Our study has verified the marked elevation of IL-6, hence its usefulness as an inflammatory marker that mirrors gallbladder inflammation during cholecystitis.

The present study also opens avenues for further applicability since it has already been established that elevated IL-6 levels correlate with severity. In moderate and severe cholecystitis patients, the mean concentrations of IL-6 were 83.7 ± 14.5 pg/ml and 106.5 ± 18.2 pg/ml respectively as compared to 64.3 ± 12.8 pg/ml in normal/mild disease patients ANOVA yielded an F value of 18.46 for the three groups comparison at $p < 0.001$ The incremental increases observed here further support the hypothesis not only about levels identifying the presence of cholecystitis but that these may also signify how far along and severe the disease is.

The ROC analysis we conducted further showed that IL-6 has great discriminative ability in the diagnosis of cholecystitis since it gave an AUC of 0.914. At a cut-off value of ≥58 pg/ml, IL-6 attained sensitivity and specificity values of 89.6% and 82.4%, respectively. This basically means that IL-6 can fairly differentiate those

individuals who have cholecystitis from healthy ones and thereby reduce diagnostic uncertainty in clinical practice.

Our findings resonate with the recently published studies, which indeed place IL-6 as a biomarker of promising nature for cholecystitis. For example, El-Molla et al., 2023 reported levels of IL-6 that were significantly raised in patients having acute cholecystitis (mean 79.8 ± 20.1 pg/ml) against healthy controls and also demonstrated an AUC of 0.902, quite close to 0.914 found in our study. Similarly, Al-Shamlan et al., 2022 showed IL-6 to be a reliable marker in the differential diagnosis of complicated cholecystitis with sensitivity and specificity values above 85% at cut-off levels close to 60 pg/ml.

In addition, study Khan et al. (2022) evaluated IL-6 in 70 patients acute cholecystitis found mean level 90.5 ± 23.6 pg/ml significantly higher controls ($p < 0.001$). Their ROC analysis yielded an AUC of 0.906, our results corroborating. Notably, they also observed significant association IL-6 levels disease severity, echoing our observations. Besides cholecystitis, IL-6 has been much tested as an inflammatory biomarker in other abdominal maladies. Liu et al. (2023) found IL-6 to be significantly higher in patients with acute appendicitis and peritonitis which further supports its role as a sensitive marker of intra-abdominal inflammation. These findings together with ours make the clinical relevance of IL-6 unassailable.

Increased IL-6 is biologically plausible in cholecystitis since gallstone obstruction usually causes this disease. These also explain the development of mucosal ischemia as well as bacterial colonization and an inflammatory cascade in cholecystitis characterized by cytokine release (Suzuki et al., 2021). This, in turn, makes macrophages, endothelial cells, and other immune cells produce more IL-6 which then acts on hepatocytes to synthesize acute-phase proteins thereby amplifying systemic inflammation (Tanaka et al., 2014). Just like in other studies where IL-6 levels were found to increase with disease severity, our study concerning complicated cholecystitis also depicts a similar pattern with progressively higher levels of this cytokine.

These findings have major clinical applications. The measurement of IL-6 could be used to supplement imaging modalities, particularly in patients whose presentation is not typical and in whom imaging results are inconclusive. Even though ultrasonography is the most commonly used modality, some limitations may exist with this method in the identification of complicated or gangrenous cholecystitis (Baharoon et al., 2023). A sensitive biomarker, like IL-6, could make an early alert for severe underlying inflammatory conditions and, therefore, need for early surgical intervention. Secondly, IL-6 may help as a stratification tool for risk. Those patients with levels greater than 100 pg/ml can be prioritized for urgent cholecystectomy while those patients with lower levels can also be managed conservatively. This is in line with the 2018 Tokyo Guidelines; the severe cholecystitis patient should be identified as soon as possible (Yokoe et al., 2018). Third, it could be possible to use IL-6 as part of multi-marker panels or scoring systems in order to make diagnosis more accurate. Its combination with traditional markers like CRP and WBC count could present an overall more comprehensive appraisal. For example, the study by Kim et al. (2022) showed that combining IL-6 and CRP improved the AUC to 0.938 compared to IL-6 alone.

Conclusion

It is shown that patients with cholecystitis have significantly elevated serum IL-6 levels, a correlation with the severity of disease. Strong diagnostic accuracy is demonstrated by IL-6, thus bringing forward its potential to be an effective biomarker for diagnosis as well as severity assessment. The testing for IL-6 should be accompanied by clinical and imaging evaluations; however, it may improve the preciseness of diagnostics and also treatment decisions. Further large-scale studies, along with standardized testing methods, are needed to confirm its routine clinical use.

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